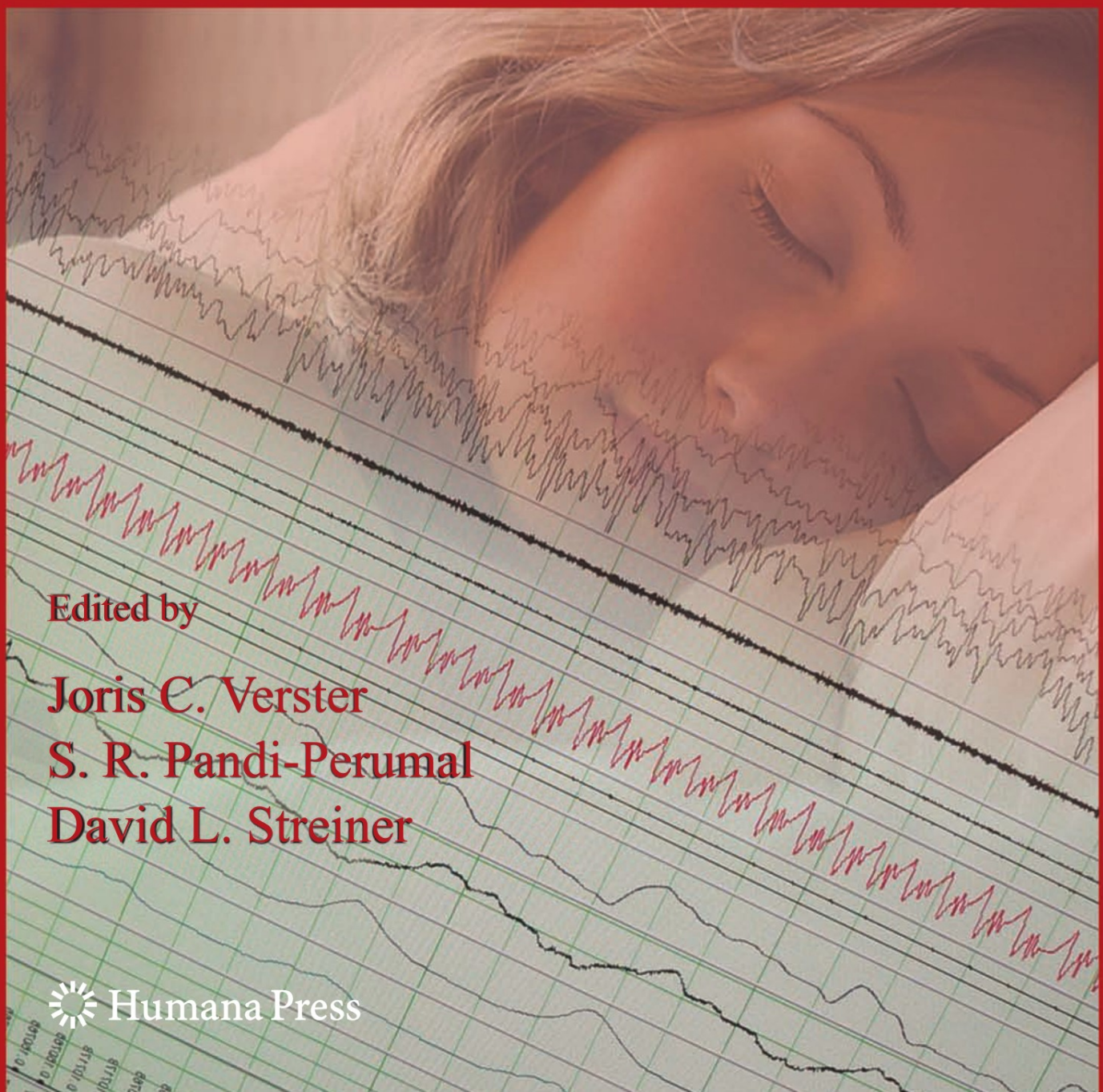
Sleep and Quality of Life in Medical Illness



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Humana Press

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To our families,
Who are the reasons for any of our accomplishments,
Who have taught and aided us
In much of what we know and do!

Preface

Had you looked up "quality of life" (QOL) in *Index Medicus* prior to 1975, your search would have been fruitless. Although the term was most likely first introduced by Karnofsky in 1949 within the realm of chemotherapy for cancer patients (1), it was not used as a key word in *Index Medicus* for another 26 years. Since that time, there has been an exponential growth in the number of articles about QOL. Figure 1 shows the number of unique articles cited each year in Medline and PsycInfo: 7 in 1970, 331 in 1980, not quite 1800 in 1990, slightly over 6000 in 2000, and nearly 11,000 in 2005. Once the domain of mainly medicine and psychology, QOL has found its way into every aspect of health care, including physiotherapy, occupational therapy, social work, nursing, and others. Consequently, if anything, these are likely underestimates of the actual number of relevant articles.

There are many factors that can account for this growth of interest in QOL. The first is probably the changing nature of the types of disorders seen by physicians. Although there have been occasional outbreaks of deadly infectious diseases (e.g., SARS and avian flu), the reality is that, for the past half century, an increasing share of interventions are aimed at improving the quality of patients' lives rather than preventing premature deaths. Procedures ranging from joint replacement and coronary bypass surgery to treatments for arthritis and sleep disturbances do little to increase longevity; rather, they make it easier for the person to function in his or her daily life. A cynical perspective would say that clinicians are now interested in QOL to justify their existence, as interventions such as hip replacement cannot be rationalized on the basis of preserving lives. However, as people live longer, they do in fact become more susceptible to disorders and conditions that interfere with activities of daily living and consequently decrease their QOL.

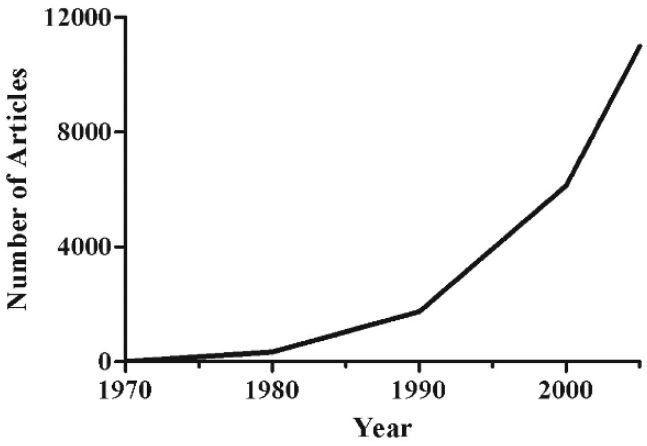

FIGURE 1. Number of articles in Medicine and PsycLit using "quality of life" as a keyword.

A second factor is the realization that QOL is not synonymous with the absence of symptoms: patients with serious chronic disorders may experience great satisfaction with life, and conversely, amelioration of patients' symptoms does not automatically translate into improved QOL. Albrecht and Devlieger (2) refer to the former phenomenon as the paradox of "high quality of life against all odds." They found that over half of the patients they interviewed with moderate to serious disabilities reported having excellent or good QOL; a finding that parallels ours with adolescents who had serious neurodevelopmental problems secondary to extremely low birth weight (i.e., under 1000 g) (3). Conversely, we have also found that pharmacological control of epileptic seizures in children did not necessarily result in an improvement in their QOL (4). Thus, understanding the effects of a disorder from the patient's perspective requires us to go beyond a simple enumeration of their symptoms and determine how they see their lives as a whole. This is reflected in the World Health Organization's *International Classification of Functioning, Disability and Health* (5), which differentiates between structural changes to the body, as opposed to what a person is able to do, given his or her circumstances. That is, it recognizes the fact that two people, with objectively similar degrees of disease, may function at very high levels because of a host of other factors including, for example, social support, intellectual capacity, and structural changes in the environment (e.g., ramps for mobility-impaired individuals).

At the same time, a third factor is that patients are requesting, if not demanding, treatments that can better their

QOL. Looming large in Canada, for example, is pressure from the public to reduce the wait times for cataract surgery, joint replacement surgery, and other such procedures. Although few people die from these conditions, patients are increasingly unwilling to live with them. Commissions have been struck to investigate the issue, and various provincial governments have poured millions of dollars into the health care system to reduce wait times. Again, the issue is not quantity of life but rather its quality.

Related to this, a fourth factor fueling interest in QOL is the fact that the practice of medicine has progressed beyond the days of paternalistic care predicated on the judgment of the physician regarding what is best for the patient. The public has become more assertive and sophisticated regarding their health care, demanding a shared role in decision-making. For example, although surgery leads to greater life expectancy following laryngeal cancer, patients are less satisfied with it than other forms of treatment that lead to shorter survival times but better preserve speech and eating (6). Thus, there is concern on the part of both clinicians and patients in documenting the effects of interventions on QOL.

Consequently, this book is a welcome addition and necessary reference for anyone interested in sleep and its effects on individuals. The first chapter, *Quality of Life in Clinical Medicine*, sets the stage in defining what is meant by QOL. The next two chapters are guides to helping the practitioner and researcher evaluate QOL instruments and by whom they should be completed. This is followed by chapters about sleep and sleep disorders in general and their effects on QOL. The bulk of the remaining chapters are devoted to detailed reviews of what is known about QOL in various medical and psychiatric disorders, including cancer, Parkinson's disease, pregnancy, schizophrenia, cardiovascular disease, and so forth.

Today, physicians and scientists have an impressive array of powerful tools and techniques for assessing and obtaining qualitative and quantitative health status. It is the editors' belief that the choice and effective use of such QOL instruments, which require an understanding of the fundamental principles upon which modern healthcare status are measured, are constructed. It is our hope that we have succeeded in producing a useful book. As usual, we welcome communications from our readers concerning our volume.

Joris C. Verster
S. R. Pandi-Perumal
David L. Streiner

Credits and Acknowledgments

We acknowledge with thanks the significant contributions of many individuals who played instrumental roles in the development and completion of this new volume, entitled *Sleep and Quality of Life in Clinical Medicine*. This book provides an introduction to the ever-expanding interface between sleep, quality of life, and various medical illnesses.

Firstly, we acknowledge with great thanks to our contributors. Without their involvement and dedication to the research they describe, this volume would not have been possible.

We were fortunate to experience a warm, professional, and highly enthusiastic support from Richard Lansing, Executive Editor of Humana Press. His commitment to excellence was a strong guiding force throughout the development of this volume. The wonderfully talented people at Humana Press/Springer made this project a pleasurable one. In particular, we wish to acknowledge the help of Amy Thau, Production Editor at Humana Press. Her candid comments and insights were invaluable.

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Finally, and most importantly, we express our gratitude to our friends and families for their patience and support. We appreciate their cheerful forbearance as we abandoned them for nights, weekends, and holidays for editing and for the support we needed to see this book through to its realization.

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1
Quality of Life in Clinical Medicine

Kathleen W. Wyrwich and Cynthia R. Gross

Summary Defining and measuring *quality of life* (QOL) is challenging and interdisciplinary, but nearly all can agree on the import role of health. The term *health-related quality of life* (HRQL) distinguishes the elements of health, function, and well-being that are experienced by people in the context of their health conditions and treatments from general QOL. HRQL measures usually incorporate at least three core domains of physical health, mental/emotional health, and social health in accordance with the 1947 World Health Organizations broadened definition of health. Many theoretical models attempt to describe how health affect QOL, but fall short, especially for describing sleep/wake symptoms or energy/fatigue because these facets of health have both a strong physical and mental health component. Wilson and Cleary's conceptual model of patient outcomes (1995) proposes a testable dynamic model of causal relationships, bridging the gap between biomedical models and psychosocial models of health. Explicit conceptual frameworks are needed for the use of any HRQL measure, which range from generic measures that can be used across a broad spectrum of the population to disease-specific measures that are tailored to a particular health condition. The family of HRQL measures also include clinimetric measures that rely on expert-driven disease attributes or indicators that "make sense" to the clinician, profile measures that provide an outline of several aspects of HRQL, indexes, and utility measures that represent a preference or value between 0 (death) and 1 (complete health), which can be useful in economic evaluations of health conditions and treatment. Recognizing how patients assess their HRQL when responding to HRQL items by use of the Rapkin–Schwartz Appraisal Model (2004) is useful for understanding HRQL responses, especially in longitudinal studies.

Keywords Quality of life · health-related quality of life · well-being · generic measures · disease-specific measures · clinimetric measures · utility measures · health status · Wilson–Cleary model · Rapkin–Schwartz Appraisal Model · WHOQOL · PROMIS

Learning objectives:

- Distinguish among the prominent definitions of quality of life (QOL) and assess the implications of using subjective and objective indicators to represent QOL.
- Contrast definitions of health-related quality of life (HRQL) and QOL and explain the rationale for addressing each concept in sleep/wake research.
- Compare major models of HRQL and the implications of each model for research.
- Classify HRQL measures according to target population, developmental perspective, and scoring and indicate the applications they are most suitable to address (e.g., economic analysis, clinical trials, epidemiological surveys).

Introduction

In 1993, The World Health Organization Quality of Life Group defined quality of life (QOL) as an "individual's perceptions of their position in life in the context of culture and value systems in which they live, and in relation to their goals, expectations, standards, and concerns" (1). Still others, like Professor Sam Salek of University of Wales, Cardiff, have taken a simpler approach and defined "quality of life" as the degree to which a person enjoys the important possibilities of his/her life (2).

Wikipedia, the collaboratively written global online encyclopedia, characterizes the complexity of "quality of life" with the following 2006 updated entry:

> The well-being or quality of life of a population is an important concern in economics and political science. There are many

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components to well-being. A large part is standard of living, the amount of money and access to goods and services that a person has; these numbers are fairly easily measured. Others like freedom, happiness, art, environmental health, and innovation are far harder to measure. This has created an inevitable imbalance as programs and policies are created to fit the easily available economic numbers while ignoring the other measures that are very difficult to plan for or assess.

Debate on quality of life is millennia-old, with Aristotle giving it much thought in his *Nicomachean Ethics* and eventually settling on the notion of eudaimonia, a Greek term often translated as happiness, as central. The neologism liveability (or livability), from the adjective *liv(e)able*, is an abstract noun now often applied to the built environment or a town or city, meaning its overall contribution to the quality of life of inhabitants.

Understanding quality of life is today particularly important in health care, where monetary measures do not readily apply. Decisions on what research or treatments to invest the most in are closely related to their effect or a patient's quality of life (3).

Clearly, these broad definitions for QOL are indicative of the many challenges in measuring this construct. First, QOL is multifaceted, encompassing culture, value systems, location, goals, expectations, standards of living, concerns, freedom, happiness, art, environment, innovation, spirituality, health, and more. Second, the study of QOL is interdisciplinary in nature and encompasses the disciplines of sociology, psychology, communications, political science, hospitality, housing, marketing, management, economics, education, public administration, health care, environmental sciences, medical sciences, and others (4). Third, although QOL is a universal concept and has a large influence on local, national, and regional agendas, it can have different meanings across the globe and from person to person.

Despite these challenges, most composite QOL indicators usually include in their scales at least some measurement of economic well-being, health, education, freedom, social participation, and self perceived well-being or satisfaction (5). Moreover, many composite QOL indicators, as well as specific aspects of QOL, are in tandem with each other. To illustrate this phenomenon, Shackman, Lui, and Wang (6) compared several international QOL indicators. They used public domain data sources of international QOL or well-being measured in the years 2000–2002 that included Estes World Indicator of Social Progress (WISP), Prescott-Allen's Human Well-being Index (HWI), and the United Nations' Development Program Human Development Index (HDI).

The WISP (7) was developed by Estes in the 1990s and yields a single score for each country based on 40 social indicators within ten categories: education, health, national economy, demography, natural environment, gender equality, social chaos, cultural diversity, military expenditures, and traditions of general welfare. The seven health indicators in the WISP's weighted QOL construct include life expectation at 1 year, infant mortality rate per 1000 liveborn, under 5 years of age child mortality rate, population in thousands per physician, per capita daily calorie supply as percent of requirement, percent children fully immunized (DPT) at age 1, and percent children fully immunized (measles) at age 1. Prescott-Allen's HWI (8) measures the sustainability of 180 countries by distilling 36 indicators of socioeconomic conditions that measure aspects of human well-being, such as longevity, stability of family size, wealth, knowledge, culture, community, and equity. HDI, developed by the United Nations Development Program (9) is perhaps the best-known composite index of well-being (10). First published in 1990, the HDI is based on three weighted indicators: (i) longevity, as measured by life expectancy at birth; (ii) educational attainment, as measured by a combination of adult literacy rate and combined gross (school) enrollment ratio; and (iii) standard of living, as measured by real gross domestic product (GDP) per capita in purchasing power parity (PPP) terms. Health has clearly been identified as a fundamental component of QOL, present in each global indicator. Health is incorporated into the WISP index through seven detailed nation-level indicators, while in the HDI and WHI, health is represented by life expectancy.

TABLE 1.1. Correlations among global quality of life indices (6).

	WISP	HWI
HWI	0.95	
HDI	0.93	0.90

WISP, Estes World Indicator of Social Progress; HWI, Prescott-Allen's Human Well-being Index; and HDI, United Nation's Development Program—Human Development Index.

In data collected from over 100 countries across the globe, all three measures are highly correlated with each other and can explain over 80% the variation in any one of these indices using any one of the other measures—much more than one might expect given the limited overlap in content (Table 1.1). However, not all measured aspects of QOL are equally as correlated. Shackman et al. further examined some of the QOL indicators used to calculate these global indices (6) and found that several QOL indicators (in bold face in Table 1.2) did not achieve a moderate level of correlation or $|r| > 0.5$.

Table 1.2 demonstrates two additional issues in the measurement of QOL. First, we see that these specific QOL indicators include objective measures, such as infant mortality rates and GDP, as well as subjective measures, like perceptions of voting fairness and life satisfaction. Second, it is the subjective measurements that display the lowest correlations with the global QOL indices (HDI, WISP, and HWI). Hence, although developed nations may have lower infant mortality rates and higher GDP, which are significant predictors of improved life quality as measured by the global indices, life satisfaction scores are less predictable for these countries. Indeed, mean life satisfaction scores on a 1- to 10-point scale are greater in Colombia and Iceland than in either the US or Great Britain (11).

TABLE 1.2. Correlations between global quality of life indices and specific quality of life indicators (6).

	HDI	WISP	HWI
Infant mortality rate	–0.89	–0.85	–0.80
Phone lines per capita	0.80	0.85	0.86
Literacy rate	0.83	0.84	0.72
Gross domestic product per capita	0.73	0.77	0.80
Internet users per 1000	0.72	0.75	0.82
Under nutrition	–0.72	–0.68	–0.69
Freedom (political rights and civil liberties)	**–0.50**	–0.65	–0.72
Contestation (voting fairness rating)	**0.34**	0.51	0.56
Life Satisfaction*	**0.50**	**0.41**	0.54

*All things considered, how satisfied are you with your life-as-a-whole these days? (1–10).

Definitions of QOL and Health

There is general consensus that patients' QOL should be an important consideration in treatment decisions, health policy, and research (1), but less consensus on what QOL is. The term QOL is often used to denote all aspects of life and health when judged from the patient's and caregiver/family's perspectives. The lack of a distinct and unique meaning has lead to inconsistency and confusion in the literature (12). Therefore, when selecting measures or interpreting the literature, it is essential to reflect upon the conceptual framework posed by the work and distinguish among measures that all purport to assess QOL but are based on different frameworks and definitions. As demonstrated above, QOL is often perceived to be very abstract and universal, and definitions include happiness, satisfaction with life, and an imagined "gap between aspiration and achievement" (13). Even with these abstract definitions, QOL may be assessed from a societal perspective relative to cultural values and societal norms about what is important in life (1, 14, 15) or from a highly individualized "what does quality of life mean for you?" perspective (16). Thus, some definitions lead to measures that consist of a standard list of important areas of life (e.g., health, income, and neighborhood safety) to be rated as being satisfactory or not, whereas other definitions lead to open-ended interviews that elicit evaluations of a highly personal list of what is important (e.g., ability to go fishing and relationship with pets). There is growing consensus that in either case, the resulting data should not be derived from factors objectively weighed or counted by clinicians or external raters but be subjective judgments made by the respondent. Thus, QOL measures are considered to be patient-reported outcomes (PROs) (1, 17). Indeed, QOL measurement perspectives that reflect only objective physical "disease burden" and impairment, oblivious to social contributions and life satisfactions, have been harshly criticized as ignoring the essence of life's value in valuing QOL (18).

Moreover, for individuals, these objective societal health indicators may not be personally relevant measures of QOL and, in fact, can flow in opposition. Consider the real trade-off that can exist between length of life and QOL for patients with human immunodeficiency virus (HIV) infection being treated with anti-viral agents (19). Early 1990s trials of zidovudine for mildly symptomatic HIV infection showed that the drug increased progression-free survival by an average of 0.9 months. Yet, when trialists examined the survival data using the "Quality-Adjusted: Time Without Symptoms or Toxicity" (Q-TWIST) process that incorporates disease progression and severe adverse events, patients treated with zidovudine faired poorly (20). Hence, longevity and HRQL results contradicted one another, making such treatment decisions more complex for both patients and their clinicians.

Health-Related Quality of Life

Several decades ago, the term health-related quality of life (HRQL) was introduced to further distinguish between QOL as used in general conversation and those elements of health, function, and well-being that are experienced by people, in the context of their health conditions and treatments (21, 22). Models of HRQL are typically descriptions of key components or domains, usually along the lines of the original WHO definition of health as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" (23). Such models regularly include at least three core domains: physical health, mental/emotional health, and social health. These core domains are typically defined in terms of function, well-being, and satisfaction, and then subdivided into dimensions or facets. For example, the mental/emotion health domain typically has a diverse range of facets, such as depression, cognition and self esteem. A recent US National Institute of Health (NIH) HRQL model along these lines was proposed by the Patient Reported Outcomes Measurement Information System (PROMIS) network (24), an NIH-funded collaborative whose goals are to develop and disseminate item banks, short forms, and computerized adaptive testing software for NIH researchers and others to evaluate patient-reported outcomes (Figure 1.1).

The WHOQOL group, an international collaborative established to define and develop QOL measures for cross-cultural comparisons, came to consensual agreement on six core domains, including the three domains listed above—physical, psychological and social relationships—plus three additional domains—level of independence, environment, and spirituality/religion/personal belief (1). While the latter three domains are generally beyond the purview of health care treatment plans, their content reflects the breadth of factors that impact an individual's QOL and could be influenced by major public health initiatives. For example, in the environment domain, the WHOQOL group includes facets such as freedom and physical safety, access and quality of health care and social care, opportunities for recreation and environmental pollution. Notable features of the WHOQOL Group's conceptualization of QOL are a strong emphasis on subjective evaluations (e.g., perceptions of subjective conditions, such as

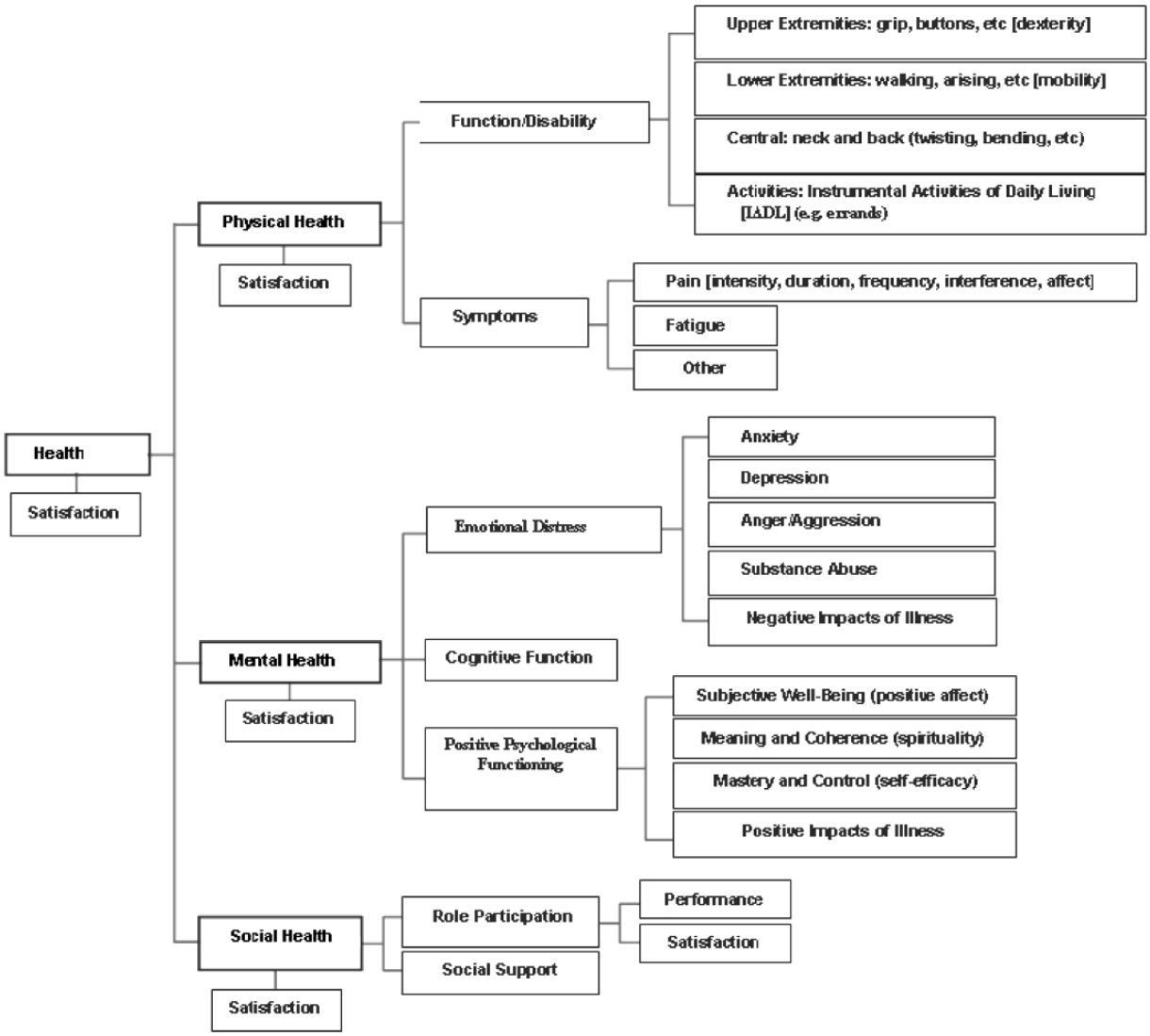
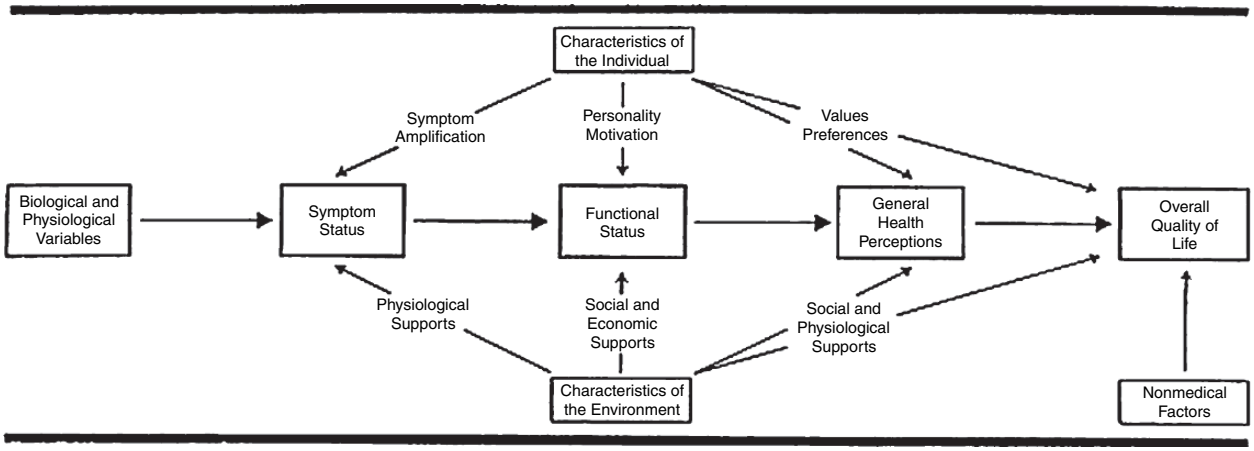


FIGURE 1.1. Patient Reported Outcomes Measurement Information System (PROMIS) domains of health-related quality of life (HRQL) (reprinted with permission of the PROMIS Cooperative Group).

satisfaction with sleep) that are distinct from perceptions of more objective conditions or functioning (e.g., ability to walk a specified distance) and inclusion of positive dimensions of well-being. The WHOQOL domains evolved from a health perspective where "consideration of the patients' viewpoint is paramount" and the resulting measures are intended for use by health professionals and researchers, so it is reasonable to include the WHOQOL along with models of HRQL. If one envisions a continuum from the most broadly defined to the most narrowly defined HRQL models, the WHOQOL model would definitely be placed on the broadly defined end.

There are at least two shortcomings of component models of HRQL, such as that proposed by the PROMIS network. First, by adopting a strict hierarchical structure, facets like sleep/wake symptoms or energy/fatigue, that have both physical and mental components, cannot be included in a single location. Second, and perhaps most importantly, component models do not lend themselves to hypothesis generation or suggest interventions to enhance HRQL or QOL. In contrast, the dynamic and inclusive model of HRQL proposed by Wilson and Cleary (25) (Figure 1.2) was developed specifically to propose a series of testable causal relationships to inform clinical interventions aimed at improving health outcomes. The Wilson and Cleary model explicitly depicts aspects of HRQL inter-related and linked in a causal chain of increasing complexity from biologic measures to health perceptions and overall QOL. It attempts to bridge the gap between biomedical models of disease causation and psychosocial QOL models that emphasize perception, function, and well-being. The model is simplified, with arrows depicting what the authors propose are the dominant causal associations, and they provide examples of the evidence to support these associations. Counter examples, such as the weak or absent associations between some biologic or



Relationships among measures of patient outcome in a health-related quality of life conceptual model.

FIGURE 1.2. Wilson and Cleary model (reprinted with permission of *Journal of American Medical Association*).

physiologic abnormalities and symptoms (e.g., asymptomatic conditions), and evidence of reciprocal or bi-directional causal pathways are also noted. The authors define symptoms as "patient's perception of an abnormal physical, emotional or cognitive state", function as "the ability of an individual to perform particular defined tasks" and health perceptions as "the integration of all the health concepts" (implying symptoms, function, and mental health), which is important because health perceptions predict use of health care services, morbidity, and mortality. While the authors distinguish among these HRQL concepts, they found that they were unable to fully show how emotional or psychological factors interact with the other HRQL concepts and outcomes. Using depression as an example, the authors find no clear demarcation between physiology/function/perception and relationships that are generally bi-directional (e.g., chronic pain leads to depression, depression can worsen pain). Noting that overall QOL, variously defined as happiness or satisfaction, is often not closely related to either objective life circumstances or aspects of HRQL, the authors comment that expectations and aspirations change as individuals adapt to their circumstances (issues considered later in the this chapter under HRQL appraisals) and posit that researchers will find questions about satisfaction with specific aspects of health to be more responsive to therapeutic interventions.

While component models, like PROMIS and WHOQOL, are useful frameworks for developing measures, dynamic models like that of Wilson and Cleary are important for framing hypotheses for research. Therefore, it is advisable to keep both types of models in mind when evaluating the domains and facets of HRQL to measure, and it is strongly recommended that researchers be explicit about the conceptual framework that underlies their choice of measures, as advocated in a recent guidance issued by the US Food and Drug Administration for PROs (17).

Measures of HRQL

Generic Measures

There are literally hundreds of HRQL measures, so it is helpful to classify them into types. Perhaps the most basic distinction is between measures that are generic and those that are specific. A generic measure is valid and useful across a broad segment of the population, regardless of their current state of health, gender, race, or other personal characteristics. Consequently, generic measures can be used in epidemiologic population surveys where respondents may be healthy adults or persons with extremely compromised health states. Generic measures can also be used to longitudinally track changes in health states where the respondents may be severely ill at one point in time, but in average or even optimal states of health at another time. The Short Form-36 (SF-36) is the most widely used generic measure of HRQL (26).

Specific Measures

A prime disadvantage of generic measures is, in fact, their essential commonness. There is no "hook" or particularly important and interesting set of items that pique the interest of the respondents and motivate them to answer the questions. In contrast, specific HRQL measures are tailored to a particular health condition or segment of the population, and therefore the questions are innately more interesting and important to the respondents, having direct relevance to the respondents' current condition or personal characteristics. Content of specific HRQL measures may include symptoms or side effects of therapy that are otherwise exceedingly rare in the population (e.g., uncontrollable vomiting, loss of pigmentation, and facial swelling) but of prime importance to the target group. The PedsQOL is an example of a specific measure,

designed for just children (27), while the Functional Assessment of Cancer Therapy—General version (FACT-G) is an example of a measure developed exclusively for persons with cancer (28). There are also HRQL measures specific to a particular facet of health, such as fatigue, for persons in a particular location or living situation, such as the nursing home or ICU, and those undertaking a specific role, like caregiving. While specific measures are often viewed as inappropriate for the general population, common symptoms, like depression or fatigue, are so ubiquitous that specific HRQL measures for these facets of health can be completed by the general population and provide a meaningfully broad range of responses.

Profiles

Another way to classify HRQL measures is to distinguish between those that are scored to provide a profile and those scored to create an index. A HRQL profile covers several domains or multiple facets of health and for each, provides a score, all scaled to the same metric. Thus, the profile is like a school report card and can be used to substantively identify particular facets where an individual has the best health and functioning and where they have limitations or impairments to health. The SF-36 is a profile, providing eight multi-item subscales measuring physical functioning, role limitation due to physical health problems, bodily pain, social functioning, general mental health (psychological distress and psychological well-being), role limitations because of emotional problems, vitality (energy/fatigue), and general health perceptions. In addition, the SF-36 provides two summary scores, one for physical health and one for mental health. Table 1.3 shows what subscales scores reflect (26, 29).

Another well-known profile is the Sickness Impact Profile or SIP (30). The SIP covers 12 facets of health and well-being: ambulation, movement and mobility, body care, social interaction, communication, alertness, emotional behavior, sleep, eating, work, household management, recreation, and also provides overall summary scores for physical (ambulation, body care, and movement and mobility) and psychosocial (emotional behavior, social interaction, alertness, and communication) functioning (30). The SIP may also be reported as a total score (all facets), giving it attributes of an index. Both the SF-36 and SIP have been translated into multiple languages and have extensive implementation manuals with directions for their proper use and interpretation.

Indices

An index is a single number, akin to class rank for academic accomplishment, and like a class rank, it lacks the details to distinguish among persons based on areas of poor or optimal function. A HRQL index may be obtained from a single question (“how would you rate your health overall?”) or derived from many items that cover a wide array of health facets. However, in contrast to a profile, regardless of the number of questions, a HRQL index is scored to provide a single value, generally scaled from 0 to 1 or from 0 to 100. While an index measure alone does not provide HRQL results that identify clinical problems or targets for therapy, the single number index can be a useful summary for comparing groups, and a particular type of index, termed a utility (described further below), is essential for economic analyses for comparing therapies to support policy and health care decision making.

Psychometric Measures

HRQL measures may also be classified according to the approach or discipline that guided their development. Types of development approaches include psychometric, clinimetric, and utility. The psychometric approach commonly begins with an in-depth exploration of the experiences of the target population, often using qualitative techniques such as interviews and focus groups and by obtaining expert opinions and literature reviews. For example, hundreds of patients were interviewed in the process of item creation for the SIP (30). This provides a reasonable pool of candidate items that are judged to provide ample coverage of the designated health domains or facets. The final stages of development invariably include pilot testing and, in optimal circumstances, multiple investigations in a variety of populations and using several administration modalities.

The psychometric approach is the dominant methodology for HRQL measurement development, and it is based on a rich history of scale construction for measures of personality and attitudes based on self-reports. Classical test theory (31), heavily dependent on statistical methods such as correlation and factor analysis and statistics, such as Cronbach’s alpha coefficient for assessing internal consistency, guided test construction throughout the latter part of the twentieth century. At the present time, these methods are increasingly augmented by newer approaches, such as Rasch scaling and item response theory (32) to order items by their level of difficulty or severity on a single “ruler” to optimally assess a unidimensional domain or facet of HRQL. Both the classic and newer techniques are computationally intensive, and rely heavily on statistical considerations for forming the final scale. The psychometric approach is also the main source of criteria for evaluating scales.

Clinimetric Measures

The clinimetric approach, a term coined by Alvin Feinstein, is a form of scale creation that relies on expert-defined critical attributes and causal indicators (33). Thus, the final clinimetric scale is expected to be congruent with the prevailing theory of disease etiology and progression, be sensitive to clinically meaningful improvements or worsenings, and most of all, “make sense” to clinicians (34). It would not be appropriate to use statistics like Cronbach’s alpha to eliminate

TABLE 1.3. SF-36, number of items and interpretation of the eight subscales.

Concepts	No. of items	Score interpretation Low scores	High scores
Physical functioning (PF)	10	Limited a lot in physical activities	Performs all types of physical activities without limitations due to health
Role physical (RP)	4	Problems with work/daily activities due to physical health	No problems with work/daily activities due to physical health
Social function (SF)	2	Extreme/frequent interference with normal social activities due to physical/emotional problems	Performs normal social activities without interference due to physical/emotional problems
Bodily pain	2	Problems associated with body pain interfering with daily activities	No interference with daily activities from body pain.
Mental health (MH)	5	Feelings of nervousness and depression all of the time	Feels peaceful, happy, and calm all of the time
Role emotional (RE)	3	Problems with work/daily activities due to emotional problems	No problems with work/daily activities due to emotional problems
Vitality (VT)	4	Feels tired and worn out all of the time	Feels full of energy and pep all of the time
General health (GH)	5	Believes personal health is poor and likely to worsen	Believes personal health is excellent

Adapted from (29).

any of the expert-selected indicators, even if the correlation between that indicator and other attributes is low. While many clinimetric scales are observer-rated examinations (e.g., APGAR, Glasgow Coma Scale), others, like those that operationalize assessment of symptoms and conditions using interviews based on DSM-IV criteria (35), are self-reports and can be grouped with HRQL measures as PROs (17). The evaluation of the quality of scales developed from the clinimetric perspective may rely on factors outside the standard psychometric criteria for scale evaluation (described below) and often hinge on issues such as the ability to screen for a particular condition with high sensitivity and specificity against a criterion (e.g., pathology report, imaging study, and diagnostic work-up) or to predict future morbidity or mortality with a useful level of accuracy.

Utility Measurements

Economics, specifically utility theory, provides the third framework for HRQL measure development. Health utilities are a particular type of HRQL index, notable because they are obtained through a process consistent with economic theory of decision making under risk. Each utility represents a preference or value placed on a state of health, ranging from 0 equals death to 1 equals complete health. Utility values are used to adjust duration of survival by quality of survival, so that living 1 year in full health is equivalent to living 2 years in a state valued as half of complete health (36). The gold standard method of assessing utilities is called the standard gamble, but other techniques that do not invoke risk are often used to obtain HRQL preferences for economic analysis. Alternatives are needed because the standard gamble can be a challenging cognitive task, difficult for anyone who is uncomfortable with numbers, percentages or the concept of risk. One alternative is to use statistical approaches to convert profiles like the SF-36 into a pseudo-utility (37, 38) although these approaches can give divergent results (39). Another alternative is to use multi-attribute utility systems. In these systems, respondents can complete straight-forward, relative simple questions about their health, and the "system" links their response choices to results from prior population studies to map the responses on to the 0 to 1 utility metric. The EQ-5D is a particularly appealing multi-attribute utility measure, consisting of five self-report questions and that can be easily completed through mail or Internet survey (40). Moreover, the EQ-5D is freely available to researchers working at academic centers or non-profit trusts, has US and UK norms, and has been translated into several languages.

HRQL Appraisals

Equally important to understanding types of HRQL instruments is an appreciation of how an individual discerns and reports aspects of HRQL. Consideration of the appraisal process is rooted in an often-speculated phenomenon of *response shift* that arises in longitudinal HRQL assessments. A response shift occurs when patients change their internal standards, values, and/or the conceptualization of HRQL during the disease trajectory and treatment (41). Shifting internal criteria, values, or conceptualization of QOL may make assessments over time incomparable. Moreover, differences in HRQL across treatment arms may be jeopardized when response shift affects the treatment groups differently and is more likely to occur as a result of adaptation to deteriorating or improving health.

Consider a woman who has just been diagnosed with breast cancer. Her HRQL may be quite low at this time (baseline) if mastectomy is considered her best survival option. However, after reflecting with her family and supportive husband on the treatment outcomes, her HRQL may greatly improve by the time of her next clinical encounter. Her internal criteria

on the importance of her physical image or her value of that image or the way she conceptualizes what is most important to her may change as she adapts to her diagnosis. Therefore, her HRQL assessment at the second clinical encounter is not directly comparable to the baseline measurement due to response shift.

Although response shift is difficult to empirically detect, consideration of this phenomenon requires an understanding how HRQL assessments are made. In response to this need, Bruce Rapkin and Carolyn Schwartz developed a model to address the "broader QOL assessment paradigm of self appraisal and meaning" (42, p. 5). Their model contains four components applied in consecutive order when patients report their HRQL: frame of reference, sampling strategy, standards of comparison, and combinatory algorithm. First, consider the common self-rated health item: "In general, how would you rate your health—excellent, very good, good, fair or poor?" To reply, respondents must first select their *frame of reference* or the experiences they deem important to consider. This frame of reference could be the intensity or duration of physical activities over the past day or week, or they may focus on recent periods of mental or emotional frailties. Once a frame of reference is selected, specific experiences are pulled from memory determining *the sampling strategy*. It is not possible to recall all events within the frame of reference, but certain relevant events are entered into the sampling frame. Once selected, each event is then judged against some *standard(s) of comparison*, whether it is the activities that were accomplished at a younger age or by another person, or observed coping behaviors seen in others deemed worthy to serve as a standard of comparison. Finally, after this comparison is made, a *combinatory algorithm* is applied to summarize the comparison, as well as internal values placed on possible options (i.e., excellent, very good, good, fair or poor), to yield an item response.

The Rapkin–Schwartz HRQL Appraisal Model provides a means to identify and organize the underlying HRQL response process. By knowing the components used by respondents, as well as change over time in any components, identification of response shift is somewhat simplified. More importantly, understanding the model allows clinicians the opportunity to structure one-to-one interviews to elicit descriptions of the patient's specific model components (frame of reference, sampling scheme, standards of comparison, and combinatory algorithms) when patient-perceived HRQL assessments are not congruent with healthcare providers' perceptions (43).

Issues that need to be addressed by future research:

- Theoretical models of health-related quality of life and appraisals need empirical testing to assess their value
- Existing health-related quality of life measures need to be fully evaluated to assure that important patient needs are expressed and measured, not just those of clinician experts
- Existing health-related quality of life measures need to be fully evaluated to assure that each reflect a valid conceptual framework

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2
Patient Versus Proxy Ratings of Quality of Life

Naresh M. Punjabi

Summary Over the past few decades, the concept of health-related quality of life has evolved as a multi-dimensional and subjective construct that includes a person's physical, psychological, social, and spiritual well-being. With the increasing availability of new and aggressive treatments that can lengthen survival, health-related quality of life is being recognized as an essential outcome in clinical practice and research. Great strides have been made in the development of several generic and disease-specific quality of life measures. While it is generally accepted that health-related quality of life should be directly ascertained from the patient, there are situations where self-report is not a viable option. Population subsets such as very young children, the elderly, patients with severe underlying disease, or those with cognitive disability may not be able to provide information regarding their health status. In such situations, proxiess which include close family members or health care professionals can provide the necessary information on behalf of the patient. The subject of patient–proxy agreement is reviewed in this chapter with a brief consideration of various factors that can influence the level of inter-rater agreement. Specific issues related to the use of proxies are presented for pediatric and adult samples. Finally, the application of proxy assessments of health status in sleep disorders medicine is discussed.

Keywords Proxy assessments · patient–proxy differences · inter-rater agreement.

Learning objectives:

- Assessment of health status or health-related quality of life through proxy reports is an alternative means of characterizing patient's health status when self-reports are not practical or feasible.
- Proxies can provide reasonably accurate assessments of patients' health status.
- Patient–proxy discrepancies are due to proxies reporting more functional limitations than patients themselves
- Patient–proxy agreement is greatest for ratings on directly observable domains of health status (e.g., physical functioning).
- The level of patient–proxy agreement is influenced by the degree of patient impairment, the proximity of the patient–proxy relationship, and the proxy's own health status.

Introduction

The patient interview constitutes a central component of the day-to-day practice in clinical medicine. The medical history is the cornerstone for establishing clinical diagnoses and is an invaluable component in guiding the physical examination and selecting diagnostic tests (1). It also provides the means by which a therapeutic bond is formed between the patient and physician. Effective physician–patient communication is essential in fostering health promotion and is directly correlated with improved patient outcomes (2). For the most part, health care delivery is largely focused on a specific problem with the primary goal of cure and restoration of normal function. However, over the past two decades there is a growing recognition that a patient's subjective assessment of health is equally important as objective physiologic outcomes. A major factor driving the increased interest is the awareness that traditional measures such as disease-free survival are inadequate in assessing the overall impact of a disease and its treatment on the patient's daily life. Furthermore, the need to estimate the public health burden associated with a disease and the need to compare different diseases have also contributed to

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the growing significance of quality of life. In fact, interest in assessing quality of life has continued to increase in recent years with the acknowledgement by clinicians and researchers alike that such indicators are essential not only for diagnostic or therapeutic decisions but also for assessing health care quality, allocating health care resources, and capturing a holistic view of health status.

Although there is still much debate in the literature regarding the definition of quality of life, there is a general agreement that it is a subjective concept that refers to how an individual perceives his or her level of daily functioning (3,4). Quality of life is a multi-dimensional construct that represents a sum of a person's physical, emotional, psychological, and social well-being. The term health-related quality of life is a subset of the overall concept of quality of life and is used as a means for characterizing the patient's subjective experience of health and disease. The science of measuring health-related quality of life has advanced sufficiently and new instruments are constantly added to the already existing armamentarium of available measures. Health status instruments can be classified either generic or disease-specific (5). Generic health-related quality of life instruments are designed to quantify the impairments in various dimensions of health status imposed by a disease process. Advantages of such instruments include their broad scope, the availability of normative data, and the ability to compare different conditions. Potential disadvantages include the lack of items that are of clinical relevance for a specific disease and the insensitivity to treatment-related change. In contrast, disease-specific instruments are designed to characterize the impairments associated with a particular disease and thus arguably are more responsive to therapeutic interventions. Potential disadvantages of disease specific instruments include the inability to compare across disease groups and limited number of assessments on reliability and validity. Irrespective of the type of approach used, the prevailing ethos with any health status instrument is that the assessments provide an unbiased estimate of the patient's rating of their health. However, there are many situations in which it is impossible or impractical to directly acquire the information from the respondents because they are unavailable or incapable. Patients who are illiterate, very young or old, cognitively impaired, or severely ill cannot be expected to reliably provide health-related information. In such circumstances, other informants or proxies can be used as alternative sources of information on the patient's behalf (6). Examples of proxies include family members, caregivers, or health care professionals. Using proxies as a substitute for the patient avoids the systematic exclusion of patient subgroups that can lead to biased estimates of disease burden. Because proxy judgments of health status can have implications for the type of care selected and associated benefits experienced, it is essential to know whether proxy responses accurately reflect the experiences and desires of the patient. Thus, the purpose of this chapter is to provide a brief overview of available literature on the use of proxies as surrogate raters for patients' health status. Within the context of this non-exhaustive review, topics such as the concordance between patient and proxy responses on health status and the influence of patient–proxy characteristics on response patterns will be highlighted.

Patient–Proxy Ratings in Pediatric Populations

Assessing health status in children poses a number of unique challenges that are not encountered with adult samples. Above and beyond the controversy of selecting a specific health status measure, children may lack the necessary language skills or the cognitive development to comprehend the abstract concepts embedded within questions on health status. Moreover, the inherent heterogeneity of pediatric samples due to varying age gives rise to the additional dilemma that health status changes with increasing age. For example, Cadman and Goldsmith have shown that a health status index that is useful for 3-year-old children cannot be applied to 5 year olds (7). Such findings are not surprising given the rapid biological and psychological changes that occur throughout childhood and adolescence. These changes make it particularly challenging to determine whether longitudinal improvements (or decrements) in health status are related to the underlying disease, the associated treatment, or the developmental changes that are inevitable over time. Despite these difficulties, it is imperative that health status be examined in children of all ages to further our understanding of the effects of illnesses. Thus, when possible, children should be allowed to assess their health status, especially if reliable and age-appropriate instruments are available. Collecting self-reported data is highly relevant particularly in older children (e.g., adolescents) given their cognitive competencies and ability to reflect on topics such as school performance, relationships with peers and family, and social aspects of life (8). However, parental or caregiver assessments can complement or substitute for the child's own assessment when self-reported data are limited or unavailable.

A fundamental issue here and throughout this chapter is whether proxies are able to provide an accurate appraisal of a person's health status. Certainly, given the crucial role that parents, family members, and other caregivers have in a child's life, understanding the proxy-perspective is of significant value irrespective of any potential discrepancies. Evidence on the level of inter-rater agreement in pediatric samples comes from numerous studies with parallel parent and child assessments of the child's health status. A consistent observation across some of these studies is the low to modest degree of correlation between concurrent inquiries on various health issues ranging from psychiatric symptoms to health status (9–15). However, not all of the available data point to a poor concordance between parent and child assessments. Several studies have reported a modest to high

level of agreement (16, 17) that is determined, in part, by the specific health-related domain under investigation (18). For example, parents and their children tend to agree more on the overt physical attributes of the child's health (10, 14, 15, 18) compared to social or emotional attributes (19). In addition, there is also evidence to suggest that inter-rater agreement is less if the child is chronically ill with the parent often underestimating the child's health status (i.e., reporting poorer health compared to the child's own assessment) (11,18). Interestingly, the opposite has been observed in healthy children with the parents often overestimating the child's health status (11, 20, 21). Other characteristics such as age, gender, temporary illness, and socioeconomic and demographic factors can also contribute to the degree of parent–child agreement (16). In fact, Waters et al. have shown that mothers with poor self-reported health status are likely to report lower health status scores for their children (22). Finally, it should also be recognized that the child's condition itself can have a negative impact on the proxy and thus influence the proxy ratings of the child (23). Although such problems would argue against the use of proxies, understanding the response of family members to an illness is critical as it can alter the child's own perspective of the disease. Future research will undoubtedly have to address existing gaps in the use of proxy ratings in pediatric medicine including other determinants of validity and utility of such measures. Furthermore, it will be critical to determine whether acquiring a family perspective of the child's health can favorably impact long-term clinical outcomes.

Patient–Proxy Ratings in Adult Populations

As with pediatric samples, inquires of health status in select adult patient samples also may not be feasible. Individuals with limited cognitive or communicative ability, severe physical or emotional distress, or subjects who are unable or unwilling to comply pose a challenge in the assessments of their health status. Patients with dementia (24), stroke (25), and elderly subjects (26) fall into this category where reliable ascertainment of health-related experiences may be burdensome, logistically difficult, or fraught with incompleteness. Even in the presence of relatively mild deficits, some patients may find it difficult to distinguish between different responses despite full comprehension of individual questionnaire items. Thus, investigations on the population prevalence of impaired health status in adults with varying degrees of cognitive dysfunction or a serious illness are likely to produce biased results as the least affected are apt to provide the most informative data. Similarly, in the context of clinical practice, a severe physical or cognitive disability can seriously hamper the use of self-reported health status measures which increasingly are being utilized to monitor treatment-related changes, identify or uncover issues previously overlooked, and improve patient–physician communication. Thus, the use of a proxy respondent (e.g., a family member or a caregiver) provides an alternative source of information and can partially resolve the problem of excluding patients with limited self-reporting capabilities. However, as in pediatric patients, an implicit assumption with the use of a proxy-rater in adults is that the respondent possesses sufficient knowledge about the patient to provide a meaningful assessment on various dimensions of their health.

Considerable research has been undertaken to evaluate the level of patient–proxy agreement on health status in adults. A comprehensive exposition of this topic and its associated determinants in different patient sub-groups is beyond the scope of this chapter but has been thoroughly reviewed by others (27–30). A consistent finding across these reviews is that despite moderate to good patient–proxy agreement (correlations ranging from 0.42 to 0.78) (28), proxies tend to rate patients' health status lower than the patients themselves (27). Such underestimation by proxies has been found across diverse study samples, including the elderly (31–34) and patients with disabilities (35–37), chronic medical conditions (27, 28), dementia (38–42), stroke (25, 43–45), and cancer (46–48). Systematic differences between the patient and proxy have been attributed to number of factors including patient and proxy demographics, the patient–proxy relationship, the degree of patient impairment, and caregiver burden (29). In addition, the complexity of the questionnaire, the context of the assessment, and the period which the assessment encompasses are also important determinants (29).

Currently, the data are sparse on whether specific patient or proxy characteristics (e.g., age, gender, race, or education) have any bearing on the patient–proxy agreement. Indirect evidence from studies related to perception of pain suggests that age and gender may influence the degree of patient–proxy agreement (49, 50). However, other studies on the effects of demographic factors on proxies' ratings of patients' health status have yielded conflicting results (32, 51–53). Thus, definitive conclusions on whether patient or proxy characteristics modify the extent of inter-rater agreement will have to wait until future studies are able to provide empirical evidence on such associations.

Selection of the most appropriate person as a proxy respondent has also been the topic of much debate. In one of the earliest studies, it was noted that the level of agreement between patients and health care providers was poor (54). While it would seem reasonable to speculate that patient reports would be more congruent with those obtained from a family member, this may not necessarily be the case. Laden with methodological limitations, most studies have had included small sample sizes and often have not simultaneously compared agreement statistics derived from family members and health care providers. When direct three-way comparisons (i.e., between the patient, family member, and health care provider) have been made, the level of agreement between patients and physicians approximates or is slightly lower than the agreement between patients and their family members (55–57). It can be easily argued, however, that due

to the infrequency of encounters, health care providers are not as aware of the patients' functional impairments as family members. In fact, Wilson et al. (47) have shown that patients are more concordant with their relatives than with physicians. Not surprisingly, the frequency of interactions between the two raters is an important factor with the highest level of agreement occurring in those patient–proxy pairs that cohabitate (51, 52). Collectively, the body of available data suggests that, while a health care provider may be able to reasonably estimate a patient's health status, every effort should be made to select a proxy who has the most contact with the patient but is not responsible for the patient's daily care.

There is also evidence to indicate that the severity of illness and the associated burden imposed on the caregiver can further temper the level of patient–proxy agreement. Several studies (45, 46) have shown that differences between patient and proxy ratings become larger as disease-related impairment increases. Although others have been unable to replicate those findings (32, 53), there is now an evolving notion that perhaps the most divergent patient–proxy ratings are in those with moderate degrees of functional impairment (57, 58). Specifically, proxies are able to more accurately estimate the patient's subjective level of impairment when the patient's functional status is either very good or very poor. Thus, proxies and patients are more congruent in answering questions of health when disease-associated symptomatology is greatest or nonexistent. Finally, caregiver burden and proxies' own health status have also been shown to be important determinants of the level of patient–proxy agreement (35, 58, 59).

Another recurrent finding across most, if not all studies, is that discrepancies between patient and proxy vary as a function of the health status dimension under investigation (27–30). For example, agreement is better on those aspects that are concrete and directly observable such as physical functioning. In contrast, agreement is somewhat limited when more subjective aspects such as social and emotional health are assessed (27). Furthermore, it should not be surprising that the content of the health status assessment itself can also affect the validity of proxy reports. Measures that are comprised of questions on aspects of health status that are readily visible to the proxy will lead to greater degrees of patient–proxy agreement compared to measures that require reporting of patients' subjective experience.

A central issue that has not been discussed thus far is that, by definition, analyses of patient and proxy ratings agreement require that both respondents complete the same assessments. However, concurrent ratings may always not be possible because those patients for whom the proxy ratings are most relevant cannot complete the assessments due to their functional disability. Thus, determination of the patient–proxy agreement in situations where it is most needed has to be based on sufficiently large study samples that allow for inferences from mild and moderate disease. Unfortunately, there is a dearth of studies with large enough sample sizes to allow for such projections. Future research is clearly warranted to address such methodological weaknesses and understand when and how to utilize proxies to gain insight into the impact of chronic diseases and associated treatments on the daily lives of patients when self-reported data are unavailable.

Patient–Proxy Ratings in Sleep Medicine

Sleep medicine is a relatively new subspecialty that has rapidly evolved over the last two decades. The National Commission on Sleep Disorders Research in 1993 estimated that approximately 40 million people in the USA suffer from chronic disorders of sleep (60). Serial polls by the National Sleep Foundation have shown that since 2001 there has been a downward trend in the percentage of adults reporting eight or more hours of sleep from 61% in 2001 to 52% in 2002 and 49% in 2005 (61). Furthermore, approximately one-third of the respondents surveyed in 2005 were found to be at risk for insomnia, sleep apnea, and restless legs syndrome. The consequences of sleep-related disorders are enormous and include decreased daytime alertness, excessive sleepiness, depressed mood, automobile and work-related accidents, impaired quality of life, obesity, hypertension, glucose intolerance, type 2 diabetes mellitus, and cardiovascular disease (62).

As with other chronic diseases, assessment of health status in sleep medicine honors the primacy of the patient as the "gold-standard." However, independent observer reports are of considerable importance in sleep medicine because many of the signs and symptoms associated with sleep disorders, such as fatigue, inadvertent dozing, loud snoring, and witnessed apneas often are not apparent to the patient or are considered socially undesirable. Thus, patients may either deny or disown those aspects that may, in fact, help establish the clinical diagnosis and disease-related impairment. While major cognitive impairments are not a typical finding in a majority of sleep disorders, measuring only the patients' view of their own health status may be suboptimal. Clinical experience suggests that an independent observer (e.g., a family member or spouse) can often provide crucial information on nocturnal sleep behavior and daytime sleep tendency that is invaluable in the diagnostic evaluation. In fact, patient and proxy interviews on symptoms of snoring and sleepiness show that while there is a modest degree of agreement, there is added value in questioning a proxy (63). Despite the obvious concern that patients with sleep disorders may not provide accurate information on health status, characterizing differences in patient and proxy reports in sleep disorders has not been an area of active investigation. In the only report available, Breugelmans et al. interviewed a sample of patients with sleep apnea and their bed partners on health status (64). Consistent with the literature from other chronic diseases, bed partners of patients with sleep apnea have a tendency to report lower functional status on behalf of the patient than the patients themselves. Patient's age and severity

of sleep apnea in that study did not correlate with magnitude of the patient–proxy disagreement. Interestingly, patient gender was an important determinant of the directionality of patient–proxy agreement. Male patients with sleep apnea had higher self-reported vitality and social functioning scores on the Medial Outcomes Study Short Form-36 (65) compared with their female proxies. In contrast, female patients had lower self-reported scores in those domains compared with their male proxies.

Given the above findings, it would be reasonable to speculate that symptoms of sleepiness, fatigue, and irritability in sleep disorders may impose a certain amount of burden on family members who may then unknowingly exaggerate the impairment in reporting the patient's health. At least for sleep apnea, one of the most common conditions in sleep medicine, bed partners have been observed to have diminished objective sleep quality (66) and are more likely to report insomnia, morning headaches, excessive sleepiness, and fatigue (67). With appropriate treatment, these bed partners experience improvements in sleep quality, daytime alertness, mood, and quality of life. However, caregiver burden does not appear to influence the level of patient–proxy disagreement in sleep apnea (64). Without doubt, the topic of patient–proxy agreement on health status is a relatively unexplored area in sleep medicine and deserves close scrutiny. Empirical studies aimed at evaluating patient and proxy perspectives are greatly needed in sleep medicine to determine whether proxies provide information that assists in the diagnosis and management of patients with sleep disorders.

Conclusions

Patient–proxy agreement on the patient' health status is determined by a broad array of factors such as patient and proxy demographics, the nature of the patient–proxy relationship, type and severity of medical condition, amount of caregiver burden, and the content of the assessments. Despite the fact that health status is a subjective construct, for some patients the proxy, at times, may be the only source of information and may actually provide data that is more reliable and valid. Proxy-derived information is invaluable in quantifying disease-related impairment if the disease process is associated with disabilities making inquiries of health from some patients difficult. Furthermore, disorders associated with progressive decline in cognitive function would significantly benefit from incorporation of proxy ratings to prevent potential loss of information on health status over time. The obvious challenge that lies ahead is to collect the empirical evidence that will allow for a better understanding of the different contexts where proxy reports are acceptable and, more importantly, the degree to which proxy reports are able to have a positive impact on clinical outcomes. These questions are worthy of further investigation especially in relation disorders of sleep where misperception or denial of symptoms is pervasive and proxies familiar with the patient provide a possible source of supplemental data.

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Issues that need to be addressed by future research:

- Determine the level of agreement between self-reported and proxy-reported health status in sleep disorders such as insomnia, narcolepsy, and restless legs syndrome.
- Establish how patient–proxy discrepancies vary with the overall health of the patient, socioeconomic and demographic factors, type of health status assessment, and caregiver burden.
- Develop standardized health status questionnaires that are specific to the proxy perspective.
- Examine changes in patient–proxy agreement on health status over time in sleep disorders and other medical conditions.
- Investigate whether the proxy perspective can direct clinical decisions to improve quality of care and patient outcomes.

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3
Criteria for Evaluating Quality of Life Measurement Tools

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Summary Selecting the best health-related quality of life (HRQL) measures for sleep/wake research requires evaluation of congruity between each measure's conceptual framework and the proposed research study's hypotheses, design, and sample. As a first step, the study team works to identify the most salient HRQL concepts, often with the help of focus groups and patient interviews. Next, a brief review of anthologies and electronic resources may be sufficient to find candidate measures addressing the relevant concepts. Judging the relative merits of the candidate HRQL measures requires careful analysis. A comprehensive and systematic approach for comparing the quality and suitability of candidate HRQL measures based on literature is recommended. Considerations and criteria for assessing the psychometric evidence of measurement quality, including validity, reliability, responsiveness to change, and sensitivity to group differences, are presented. Also discussed are useful attributes such as population norms and precedents for determining the minimally important difference (MID). To insure successful implementation, pilot testing of the chosen measures with the target population is encouraged. This chapter also provides an overview of a new and exciting methodology, item response theory (IRT), that is leading to the refinement of HRQL measures. IRT also enables computer-adaptive testing (CAT), where concept indicators (e.g., individual questions about a concept such as daytime sleepiness) are successively selected from an item bank and shown to each patient in an order tailored to that of patient's previous response choices. The results rapidly and accurately estimate that patient's true score while yielding scores that can be grouped across patients or followed over time. This chapter ends with a list of practical issues like the patient burden, costs, and copyright that impact the choice of HRQL tools, along with a list of resources for locating measures.

Keywords Quality of life · health-related quality of life · validity · reliability · item response theory · compute-adaptive testing · sensitivity to change · minimal important difference · measurement · patient burden · patient-reported outcomes measurement information system.

Learning objectives:

- Distinguish among psychometric attributes of content, criterion and construct validity, and evaluate the strength of the evidence for validity when studies of these attributes are presented in the literature.
- Explain reliability, responsiveness to change, sensitivity to differences, and minimally important differences and apply standard criteria for judging these properties when selecting health-related quality of life (HRQL) measures.
- Identify a comprehensive list of practical considerations (e.g., administration costs and reading level) tailored to a specific research context and articulate a strategy for balancing these considerations with psychometric quality.
- Explain how item response theory provides for improving static HRQL measure and paves the way for computer-adaptive testing of HRQL constructs.

Introduction

Sleep/wake disorders have been linked to serious and distressful health consequences including reduced quality of life (QOL) (1, 2) and have major economic consequences (3–5). For many researchers, the evaluation of the impact of therapy on patients' QOL has become a standard component of treatment efficacy and cost effectiveness analyses, while in clinical practice, there is increasing interest in QOL assessment as it may improve communication, increase adherence,

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and optimize real-world treatment effectiveness (6). While sleep researchers and clinicians are often eager to evaluate the impact of their therapies on patients' QOL, there are a multitude of such measures and relatively few guidelines for selecting the best measures for sleep patients (7). The purpose of this chapter is to provide recommendations for evaluating the content and quality of QOL measures to provide guidance in selecting measures and interpreting QOL results in the literature. This chapter describes the criteria for evaluating QOL measures and offers suggestions for finding and selecting QOL measures for sleep research.

Criteria for Evaluating HRQL Measures

There are many issues to consider when evaluating the HRQL literature or selecting measures for research or practice. The most fundamental issue is the match between intention and execution. Congruity between the conceptual framework, study design, sample, hypotheses, and the measures is essential. For example, a measure that asks about symptom frequency (e.g., How often is the symptom experienced?—every day, 4–6 days a week, etc.) will provide quite different information than a measure that asks about symptom impact (e.g., How much does the symptom interfere with your day-to-day functioning?—not at all, a little, etc.), and while both are symptom scales, data from these two measures may exhibit strikingly different relationships with other outcomes. A determination of the appropriateness of a HRQL measure rests on congruity and on the quality of measurement. What constitutes high-quality measurement properties is discussed below.

Psychometric Properties

There are several key principles and rules of thumb that provide practical guidance for those without specialized training in the science of measurement, a field known as psychometrics. For those desiring more than the brief summary presented here, we recommend chapters 1 and 2 in McDowell's anthology of HRQL measures (8) and the text on measurement by Streiner and Norman (9). A comprehensive reference is the text by Nunnally and Bernstein (10). With the disclaimer that what follows is not comprehensive, we begin this section with an overview of the psychometric properties of validity and reliability, the essential underpinnings of measurement. The end of the section describes two additional aspects of measurement, responsiveness to change and sensitivity to group differences.

Validity

Validity refers to the appropriateness and meaningfulness of the information that is derived from a measure and the usefulness of this information to address questions in research and practice. The validity of a HRQL measure is context specific, as what is meaningful and useful in one context may have little or no usefulness in another. Utilities are a classic example of HRQL measures that can be valid, but only for a very specific purpose. The process of validation for a HRQL measure is not a simple or finite task but is instead a building of evidence based on a series of investigations to assess meaning and usefulness. These investigations are sometimes classified as demonstrations of specific aspects of validity, such as coverage of relevant content (content validation) or ability to predict a particular criterion (criterion validation). Validity is not proven but should be supported by the weight of the evidence across a series of validation studies.

Content Validation

To be valid, a HRQL measure should be supported by a consensus or at least a convincing rationale, that the measure reflects the full range of elements (attitudes, symptoms, behaviors, etc.) that constitute the domain of interest and does not have items that are irrelevant to the domain. Patient interviews or focus groups, supplemented by expert opinion, are typically used to generate relevant content to cover the domain of interest. Later in the development process, expert review and pilot studies with the target population are conducted to evaluate the completeness and relevance of the final or near-final version(s) of the measure. Procedures have been devised to enhance the rigor of content validation procedures (11). Supplemental support for the content validation process can be inferred from statistical evaluation using factor analysis and measures of internal consistency.

An aspect of validity closely related to a measure's content is its general appearance, an attribute commonly referred to as face validity. Face validity is the impression a HRQL measure makes, primarily as judged by members of the target population (i.e., respondents). Respondents may be unwilling to devote time to completing assessments that do not look meaningful or appropriate to their stated purpose. While conveying a valid first impression to respondents does not insure a measure's accuracy, it can influence the completeness of data collection and therefore be instrumental to obtaining high-quality results.

Criterion Validation

A criterion is a benchmark or standard for comparison. Criterion validation is the process of evaluating the pattern and strength of the relationship between a new measure and a known benchmark. Criterion validation studies may be concurrent or predictive. When a new HRQL measure and the relevant criterion are measured at the same time, concurrence provides evidence of validity. When the new measure is shown to accurately predict the value of a criterion assessed at a future point in time, prediction is convincing evidence of validity. For most HRQL domains, there are no concrete

standards (i.e., no scale to weigh symptoms of fatigue and no ruler for self-esteem). Therefore, new HRQL measures are often compared to older HRQL measures for the same domain that already have an established base of evidence for validity. As factors like positive mood and social desirability can bias responses to HRQL measures assessed at the same point in time and make the resulting data more highly correlated than the underlying phenomena might truly be, the most compelling evidence from a criterion validation study is prediction of a performance-based outcome (e.g., 6-min walk), expert evaluation, clinical diagnosis, or other criterion that is not a patient-reported outcome (PRO).

Construct Validity

Construct validity is an over-arching expectation that valid measures will provide appropriate and meaningful results. Many hold the view that all forms of validity, in their essence, are aspects of construct validity. Building the case for construct validity is process of devising and testing hypotheses about how a valid measure should relate to other valid measures, where there is prior knowledge to predict the form of these relationships. For example, a measure of depression symptoms that purports to deliver higher scores for those with more depression symptoms should find significant mean differences among samples of the general population, patients with schizophrenia, and patients diagnosed with major depression, termed a test of extreme groups (9). Furthermore, the depression measure should yield symptom scores that are positively related to measures of insomnia or anxiety symptoms (convergent validation), negatively related to measures of optimism and positive affect, and not be particularly related to height or bone density (divergent or discriminant validation). Criterion validation studies are similarly predicated upon a priori expectations of what results constitute evidence of validity. Thus, construct validity is dependent on the existence of a relevant theoretical framework or model of disease etiology and progression to establish what is, and is not, meaningful, appropriate, and useful (12). Because validity is context specific, prior validation studies in a different population (e.g., college students) do not assure that a measure will be valid in the target sample (e.g., elderly). Clearly, construct validation in the patient population in which the final measure will be employed is the most convincing evidence.

Reliability

A measure that is valid is not useful unless it is also reliable. While validity is akin to accuracy, reliability is consistency. On repeated assessment, a reliable measure will give the same result, except for random errors of measurement, as long as the respondent's true state is unchanged. The classic manner in which reliability is assessed is to administer a HRQL measure on two occasions, over a time period sufficiently short to support the assumption that the health status of the respondents has not changed. For generally stable health states, a week or two may be an appropriate interval. Data from the repeated assessments are then correlated (using Pearson's correlation) or tested for agreement (using an intraclass correlation coefficient or chance-corrected agreement statistic, kappa) to obtain a reliability coefficient (9). The reliability coefficient is an estimate of the proportion of observed variance that is due to true differences among respondents on the HRQL domain. While the observed variance includes measurement error, the variance due to true differences does not. If there were no measurement error, the reliability coefficient would be 1.0. In practice, a high correlation (.8 or above) or high kappa (.7 or above) is interpreted as evidence of reliability.

When a multi-item HRQL measure that is scaled to assess a unidimensional domain or facet is administered only once, an indication of the reliability of that measure can be gleaned from the consistency of the responses to the items that comprise the measure. If the items are internally consistent, assessed by a statistic called Cronbach's alpha coefficient that quantifies the extent of inter-correlations among the items, there is evidence that the measure is reliable. A rule of thumb is that a reliable HRQL measure should produce alpha values between .7 and .9 if the measure is intended to compare groups, such as arms in a clinical trial (10, 13). If a HRQL profile covers several domains or facets, each subscale should demonstrate this same level of internal consistency. Alpha is sensitive to the length (number of items) of a measure. Values of alpha over .9 suggest that a shortened version of the measure could be developed. Experts caution that investigators should never trade increased reliability for reduced validity and emphasize that reliabilities around .8 may provide optimal balance between respondent burden and reliability for research (10).

In clinical practice, where decisions are to be made for a patient, informed by that patient's observed score on a HRQL measure, it is important that the measure used is very precise. The precision of a single HRQL score is represented by the width of its 95% confidence interval. The confidence interval around the patient's observed score is expected to contain the patient's true score 95% of the time. The width of this confidence interval is a function of the reliability of the HRQL measure and the standard deviation of the measure (obtained from normative samples). Unless the reliability is high (alpha values of .9 or above), this confidence interval will be too wide relative to the score and not sufficiently precise to be useful.

Responsiveness to Change

Responsiveness is the ability of a HRQL measure to detect change, when the underlying domain or facet has been changed, as by an effective treatment. While several established valid and reliable HRQL measures may exist for a particular domain, they may not be equally responsive to change. Measures that have few items to distinguish among

persons at the highest (or lowest) levels of health may lack responsiveness and be unable to detect further improvement (or worsening), issues termed floor and ceiling effects.

Responsiveness is important because randomized clinical trials with responsive outcome measures will require smaller sample sizes to detect change than trials with less responsive outcomes. When several HRQL measures are assessed before and after an intervention, the responsiveness of competing measures, quantified as effect sizes, can be compared. An effect size for responsiveness can be formed in several ways, including mean change divided by the standard deviation at baseline and as mean change divided by the standard deviation of change, a ratio called the standardized response mean (13, 14).

What constitutes a clinically meaningful change or minimally important difference (MID) in response to treatment will differ from measure to measure. For some measures, such as the St. George Respiratory Questionnaire, the developer has established criteria for meaningful change (15). Where such guidance is not available, many researchers will rely on the rule of thumb proposed by Cohen for effect sizes in the context of power: .2–.5, small; .5–.8, medium; and >.8, large (16). The work by Norman et al. (17) suggests that a .5-effect size is a reasonable criterion for meaningful change in HRQL measures of persons with chronic disease conditions when a HRQL measure lacks a pre-specified MID for comparing groups. In practice, what constitutes a meaningful response for a single patient may be based on a diagnostic cut off, with a meaningful response considered a change from a baseline score in the poor functioning range to a follow-up score in the normal range. Methods for using this approach and accounting for measurement error have been proposed (9).

Sensitivity to Differences

Sensitivity is closely related to responsiveness but emphasizes cross-sectional discrimination not longitudinal change. Sensitivity to differences is the ability of a HRQL measure to distinguish among groups that differ with respect to the measured domain or facet. One way to compare the sensitivity of a set of two or more HRQL measures is to administer all measures at the same time to a sample containing several subsamples or patient groups known to differ on the domain of interest. Analysis of variance is then used to compare the group means for every measure in the set. The statistic for evaluating sensitivity is the relative validity, RV, the ratio of the *F*-statistics for two measures (13). By convention, the smallest *F*-statistic is placed on the bottom for all comparisons. The HRQL measure with the largest *F*-statistic will have the biggest RV and be the most sensitive measure in the set.

Some measures can be sensitive but lack responsiveness. For example, a measure of sleep-related breathing problems might include items like "need to sleep with extra pillows." While this item might be useful to distinguish between patient groups with and without breathing problems (sensitivity), it would not capture worsening (responsiveness) for those who needed extra pillows at baseline.

Classical test theory (CTT) is central to the methods described earlier in the chapter for evaluating the validity and reliability of a HRQL measure. However, increasingly HRQL researchers are turning to item response theory (IRT) to assist HRQL measurement creation, refinement, and evaluation. IRT is also key to linking HRQL measures, determining whether different groups interpret and/or respond to an item differently (differential item functioning), and the development of item banks to support computer-adaptive testing (CAT). CAT administration of HRQL measures is a process of tailoring the sequence of questions presented to each participant based on their prior responses and thereby giving each participant the most appropriate and least number of items to accurately and precisely estimate their true score in a HRQL domain.

What is Item Response Theory?

CTT is built from the model of $x = t + e$, where x is an individual's response to an item in the domain y, t is the true score for the individual on that item, and e is the error that gets added (or subtracted) to t when producing x. Moreover, when summing responses from scale items, under CTT all items are assumed to be equally strong representatives of the domain y.

In comparison, IRT centers on the likelihood of a particular response, given an individual's ability level, named theta (θ), for the underlying construct. In very simple terms, consider the following four participants in a pain study (Table 3.1). Each is asked four questions (items 1–4) about activities that may cause pain, and the dichotomous response choices are simply "Yes, I have pain when I do that" or "No pain when I do that," which are coded 1 and 0, respectively.

There are several things that we immediately learn about the items and the participants in this study: Dan has the most instances of pain and Amy the least; item 1 is an activity that rarely causes pain, whereas item 4 is likely to cause almost everyone to hurt. Rough item characteristic curves (ICCs) can be constructed for each of these items. An ICC uses the probability of an item being endorsed for the y-axis's scale and the underlying latent construct, θ, for the x-axis. The resulting curve reflects the increasing likelihood of endorsing an item as θ grows larger (Figure 3.1). We can also derive a more judicious scoring mechanism for these participants that reflects the difficulty in responding.

TABLE 3.1. Visualizing item response theory's item characteristic curves.

	Amy	Bert	Carol	Dan
Item 1	0	0	0	1
Item 2	0	0	1	1
Item 3	0	1	1	1
Item 4	1	1	1	1

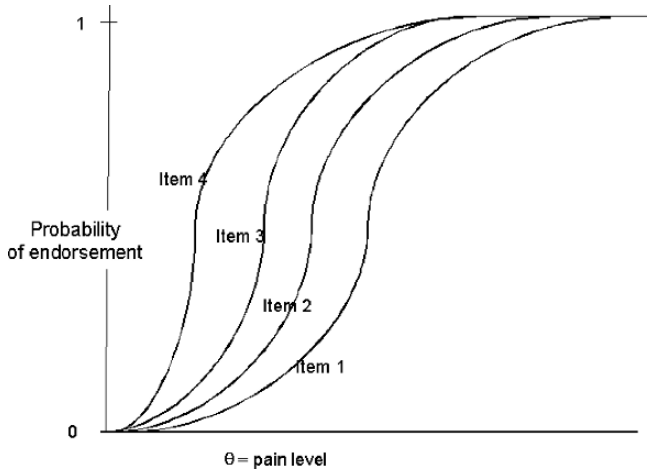

FIGURE 3.1. Item characteristic curves (ICCs).

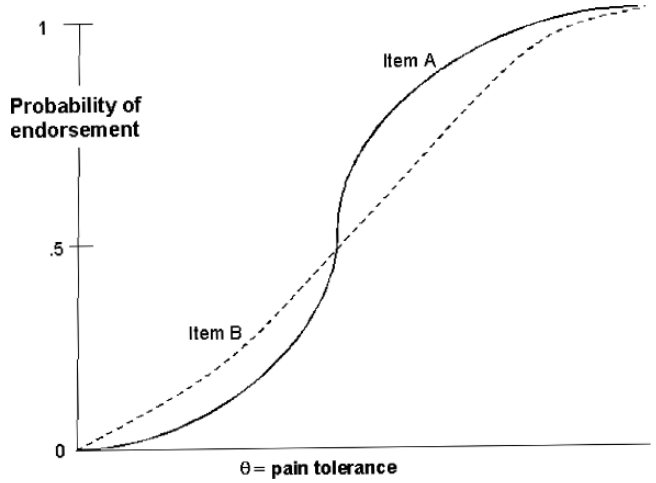

FIGURE 3.2. Two-parameter item characteristic curves (ICCs) with the same difficulty but differing discriminations.

As the shape of the ICCs in Figure 3.1 implies, the trace lines employ a logistic model expressed as

$$P(\theta) = \frac{e_{\mathrm{i}}^{(\theta - b_{\mathrm{i}})}}{1 + e_{\mathrm{i}}^{(\theta - b_{\mathrm{i}})}},$$

where b_i denotes the difficulty parameter of item i.

The difficulty parameter in this model, b_i, indicated the θ level where the probability of endorsement is exactly 50% and is also called the item's threshold. Difficult to endorse items like "Do you have pain when you blink?" has very high difficulty parameters, and in the case of our data, only Dan would have endorsed this item if it was item 1 (Table 3.1). However, items that are easily endorsed, such as "Do you have pain when struck by a boulder?," has a very low threshold in that most, if not all, participants would respond "yes" to this question (item 4).

The equation above represents the one-parameter logistic model and is the basis of Rasch IRT models. A two-parameter model incorporating both difficulty (b_{i}) and each item's discrimination (d_{i}) has also been developed and is designated as

$$P(\theta) = \frac{e_{\mathrm{i}}^{d(\theta - b_{\mathrm{i}})}}{1 + e_{\mathrm{i}}^{d(\theta - b_{\mathrm{i}})}},$$

where b_{i} denotes the difficulty parameter of item i and d_{i} denotes the discrimination parameter of item i.

The advantage of the two-parameter model over the previous model is that the slope of the ICC can also be modeled. That is, two items may have the same or nearly the same difficulty but one of those items may steeply increase near the difficulty level indicating that responders within a narrow θ range quickly distinguish themselves as endorsers or not of the item (Figure 3.2). This property identifies that the steeper sloped item (item A) is generally more desirable than item B for measurement in the specific θ range (middle) that corresponds with the item's difficulty threshold.

These IRT models for one and two parameter dichotomous items can also be extended for use with polytomous response data. Although various polytomous IRT models exist (18), the simplest of these to describe is the one parameter Graded Response Model. Consider the self-rated health items "In general, how would you rate your health—excellent, very good, good, fair or poor?" If we number these five ordered response choices as k = 5, 4, 3, 2, and 1, respectively, the logic behind this model starts with ICCs for the likelihood of responding with 1 (poor) or higher, $P(k \geq 1)$. This probability is obviously 1 for all values of θ because all responses are only 1 or higher and yields an initial ICC trace that looks like a horizontal line at $y = 1$. Similarly, we can create dichotomous ICCs for the likelihood of endorsing this item at the level of 2 or higher, $P(k \geq 2)$, with a response of poor being considered a non-response (0) and all other responses an endorsement (1). This process of developing initial dichotomous ICC traces can continue for 3 or higher (vs. 1 = poor or 2 = fair), 4 or higher (vs. 1, 2, or 3), and finally, the likelihood of responding with a 5 (excellent) compared to all other choices. These initial traces would look similar to the four ICCs depicted in Figure 3.1.

The initial ICCs can now be subtracted from each other in succession to produce response-specific ICC traces for this item. For example, when the ICC for the probability of responding with 2 or higher, $P(k \geq 2)$ is subtracted from the probability of 1 or higher, $P(k \geq 1)$ at each level of θ, the resulting ICC represents the probability of giving a response of 1 or poor to the self-rated item, $k = 1$. Similarly, when each subsequent adjacent ICC is subtracted from the next lower level, that is, $P(k \geq 2) - P(k \geq 3)$ yields $P(k = 2)$, $P(k \geq 3) - P(k \geq 4) = P(k = 3)$, $P(k \geq 4) - P(k \geq 5) = P(k = 4)$, these four traces yield ICCs for the specific response levels. Finally, the

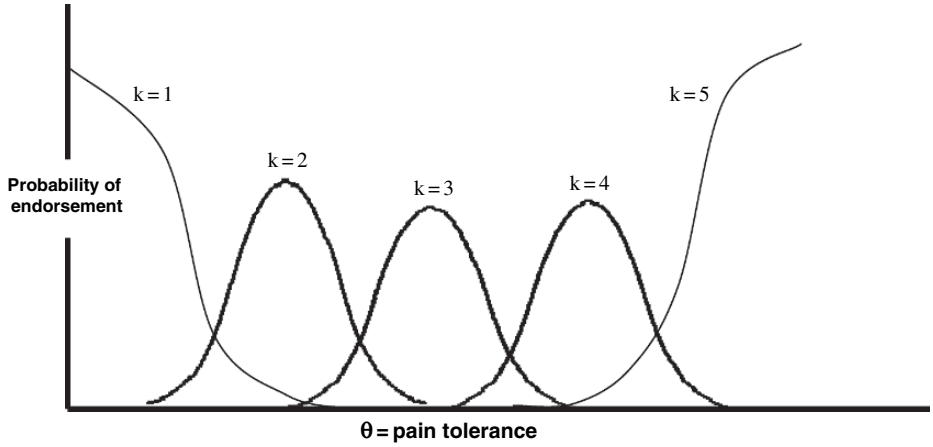

FIGURE 3.3. Item characteristic curves (ICCs) for a polytomous item.

initial $P(k \geq 5)$ is the ICC for $P(k = 5)$ given that there are no other responses greater than 5 (Figure 3.3).

The astonishing power of IRT to specify these ICCs does come with a significant, but not insurmountable, set of limitations. First, there are several model assumptions to be met, including monotonicity, unidimensionality, and local independence of each construct. Monotonicity implies that, apart from sampling fluctuation, the proportion of people passing each step on the response scale should be larger for those with a higher scale score (correcting for item overlap with the scale score). A violation of monotonicity occurs if the predicted order is reversed (19). Unidimensionality indicates that the scale items measure a single common construct. We cannot apply IRT models to latent construct data if the scales are not unidimensional enough to allow for the unbiased scaling of respondents on a common latent trait (20). Tests of local independence indicate whether proposed construct items are uncorrelated (weak local independence) or completely independent (strong local independence) after the common latent trait or traits have been controlled for. Violations of the local independence assumption arise primarily from two or more items that share variance even after extracting a common dimension (21). For example, items like "I generally feel that my life is out of my control" and "My life is generally out of my control" can cause a local dependency problem for a fatalism measure because these two items are correlated greater than what the common trait predicts.

Beyond these modeling assumptions, IRT software can be challenging to execute and comprehend given the multiple aspects of model fit examined. Moreover, the needed sample sizes to carry out two-parameter modeling for operational use can be staggering ($n > 1000$), yet Rasch models can confidently be run with smaller samples ($n \leq 150$) (22). A listing of free and for cost software options to run Rasch or two-parameter models can be accessed at http://www.winsteps.com/rasch.htm.

IRT Use for Evaluating and Improving HRQL Measures

Despite the challenges above, knowing the parameters of an item's ICCs can assist researchers creating and evaluating HRQL measures in several important ways. First, static surveys given with all of the same items in the same order at each administration can be reduced in length if some items appear to have the very similar difficulty (and discrimination if using the two-parameter model). The reduced measure saves time, as well as respondent and data entry burden without decreasing measurement quality. Better yet, CAT from a bank of items known to tap a latent construct, like sleep quality or pain, uses an initial item's response to give a general range of the respondent's ability (θ). By administering subsequent items that measure well and more precisely in that initial range, each subsequent question can further narrow in on the respondent's θ range to a desired level of accuracy before halting the testing process. Hence, precise measurement occurs with the administration of few items that are selected in real time based on initial responses, known difficulties and discriminations of banked items, and the added information learned from subsequent item responses (18).

Currently, The patient-reported outcomes measurement information system (PROMIS) initiative, funded by the US National Institutes of Health (NIH), has established a collaborative relationship between NIH and individual research teams to

- Develop and test a large bank of items measuring PROs.
- Create a CAT system that allows for efficient, psychometrically robust assessment of PROs in clinical research involving a wide range of chronic diseases.
- Create a publicly available system that can be added to and modified periodically and that allows clinical researchers to access a common repository of items and computerized adaptive tests (23).

The network will collaborate on the collection of self-reported data from diverse populations of individuals with a variety of chronic diseases, using agreed-upon methods, modes, and questionnaires. Specifically, under the leadership of Paul Pilkonis, MD, at University of Pittsburgh, a sleep/wake functioning item bank is being developed and tested for future use to help standardize assessments of sleep/wake functioning across research studies and clinical care (24).

In addition, IRT has also been used to handle missing data by constructing informed missing data responses. If other item responses in a domain or construct of interest are known, these answered items can be mapped back to the most like θ level of the responder. This θ level can then be directly linked to the most likely response on the unanswered item to provide an informed datum. The linkage of specific responses to a most likely ability level can also flag unlikely response patterns that may indicate inconsistency by a respondent or data entry problems (25). Likewise, alternative forms that measure the same construct can be linked to "translate" the scores from one measure into scores from a second measure using the same θ yardstick for the construct (26).

When the probabilities of responding in different categories to a specific item differ by population for the same underlying level of the attribute, this item displays differential item functioning (DIF). That is, if an item intended to measure functional ability in older adults, like "Do you prepare your own meals?," is endorsed less often by men than women with the same overall functional ability, this item is not measuring the underlying ability (θ) as much as it is differentiating that women in the household are more likely to prepare meals than men. DIF is an undesirable characteristic limiting the validity and the generalizability of an item and a measure. IRT methods allow for the evaluation of DIF by contrasting a model's difficulty and slope (discrimination) parameters between two or more groups to elucidate item(s) that bias resulting measurements and better inform the HRQL evaluation process (27). Within the field, however, there is still debate on how much DIF is clinically meaningful and important to recognize over detectable DIF that may be an artifact of differences found given the very large samples needed to run these analyses (28, 29).

Tips for Selecting HRQL Measures

There is no simple answer to what are the best HRQL measures for a study, but a systematic approach to identifying and defining the relevant conceptual domains and facets of HRQL is the best starting point. Often prior work, meta analyses, and other reviews will be adequate to elucidate what the relevant concepts are. Where such information is lacking, pilot studies such as focus groups with patients and providers, surveys, consensus panels of experts, or combinations of these approaches may be needed to establish the set of relevant domains and facets. Once the relevant HRQL concepts are identified, it can be useful to list each domain and facet along with its study definition and to circulate the list among the co-investigators to confirm that there is consensus on meaning and to facilitate the process of identifying potentially appropriate HRQL measures. The books and websites listed at the end of this chapter may help investigators compile an initial list of potential HRQL measures for each concept. When a preliminary review identifies two or more HRQL measures that match the investigator's concept definition and initial evaluation suggests they are of high quality, a systematic and in-depth comparison should follow. A table format is useful for this comparison. For each domain or facet, an evaluation table constructed with a column for each competing measure and rows for the developer's definition, key details of the evidence of psychometric merit in the areas of validity, reliability and responsiveness, and pragmatic considerations (e.g., respondent burden, reading level, ease of administration and scoring, availability of published norms, clinical cutoffs, and recommended MIDs and costs). Depending on the study scope, additional rows may address issues such as availability of validated translations and adaptations for disabled respondents. A recommended list of questions to address is given in Table 3.2. Once the relative merits of the candidate HRQL measures have been documented, a strong rationale for selecting the final measures can usually be made, both to the study team and in grant proposals to potential funders. This systematic approach does not obviate the need for pilot testing, however, as each study may have unique aspects that can impact the quality of the data collection.

While a study may have targeted a small set of HRQL domains or facets in the study primary and secondary hypotheses, a common technique is to insert these measures in a battery consisting of a generic core with a profile such as the SF-36 (30) and a utility measure such as the EQ-5D (31). The addition of these generic measures will insure that the study sample(s) can be compared to norms and results are amenable to economic analyses. Furthermore, if unanticipated positive or negative impacts on HRQL exist, these generic measures are likely to detect them.

This chapter has not addressed how to proceed when investigators are unable to locate valid and reliable HRQL measures for relevant concepts. That is the time when it is essential to obtain expert consultation, as construction of high-quality HRQL measures is a complex, time-consuming, and challenging process.

Below is a list of sources for locating HRQL measures:

Books

1. McDowell I. *Measuring Health: A Guide to Rating Scales and Questionnaires*, 3rd ed. New York: Oxford University Press, 2006.

TABLE 3.2. Questions to guide selection of HRQL measures.

Psychometrics	1. Does the developer's definition match the investigator's definition? 2. What is the quality of the evidence for validity? 3. Has validity been investigated in a population similar to the proposed study sample? 4. What is the quality of the evidence for reliability? Is there a short form that is sufficiently reliable for the study purpose? 5. What is the quality of the evidence for responsiveness and sensitivity?
Analysis considerations	1. What form do the results take? Are results likely to be skewed or have major floor or ceiling effects? 2. Are there relevant norms, clinical cutoffs, MIDs? 3. Is there a single score or a series of subcale scores? Can you use the subscales individually (i.e., are they reliable?) 4. What response rates have been obtained using the instrument? 5. What level of responsiveness is likely to occur and would that be statistically significant in this study, with the sample size planned? 6. Does the manual (or prior publications) address handling missing data?
Participant burden	1. What is the respondent burden? How long does it take to complete? 2. Is the measure culturally appropriate? Age appropriate? 3. Can the measure be used by those with limitations due to education (e.g., reading level and knowledge of numbers), dexterity, intellect, vision, etc.? 4. Is the cognitive task challenging? Frustrating? 5. Are the questions very personal, intrusive? (e.g., Are some items or questions frequently skipped? Do subjects find the scale annoying or demeaning?—these issues may be revealed in pilot testing) 6. Are there valid versions in each language needed?
Costs and practical considerations	1. Must forms be purchased? Do you need permission for use of the instrument? What are the copyright and licensing requirements? 2. Is special training or certification needed for administering the instrument, to score, or interpret the results? 3. How long does it take to score? 4. Is a manual available to explain the procedures for administration and scoring? Is it clearly written? Is software or programming code included? 5. Can it be (or has it been) mailed, self-administered, used over the phone, or via the Internet? Dillman (2007) encourages the use of "unimode" development, so measures can be used in a variety of administration formats, such as mail, phone, and Internet, with the results merged for analysis. 6. Can the assessment be repeated? How often—every day, week, month, etc.? 7. Is this version the current version, or will there be an updated and improved version soon to be published? (an email to the developer may answer this question)

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Websites

1. http://www.euroqol.org: The homepage for the EQ-5D, multi-attribute utility system consisting of a five-item descriptive profile that generates a single index value for health status. The developers indicate that they have not current plans to revise the three-level, five-dimensional format of the EQ-5D.
2. http://www.bath.ac.uk: This is the homepage for the Bath Field Center of the World Health Organization Quality of Life (WHOQOL) Group. The WHOQOL-100 is a 100-item measure of perceived QOL that emphasizes the effects of disease and treatment interventions on QOL. There is also a shorter measure called the WHO Quality of Life-BREF (WHOQOL-BREF) that addresses the same domains. The WHOQOL-Bref has 26 items that measure the following domains: physical health, psychological health, social relationships, and environment. These measures were developed collaboratively by 15 diverse sites around the globe to be international cross-culturally comparable. These are now available in over 40 language versions.
3. http://www.outcomes-trust.org: The Medical Outcomes Trust is a not for profit organization that supports QOL research and facilitates distribution of HRQL measures including the SIP, St. George's Respiratory Questionnaire, and SF-36. Their site lists the measures, copyright requirements, and fees along with the materials (manuals, software, etc.) that come with the instruments. The SF-36 and

related measures can also be accessed through their homepage http://www.SF-36.org.

4. http://mapi-research.fr: The homepage of the Mapi Research Institute and Mapi Research Trust. The Trust makes instruments available, including the PedsQL and Minnesota Living with Heart Failure Questionnaire, and the site lists the conditions for use, fees, and so on.
5. http://www.ISOQOL.org: The homepage of the International Society for Quality of Life Research contains a variety of resources for health researchers including an annotated bibliography and recommendations for best practices. The journal for this society is *Quality of Life Research*.
6. http://www.ISQOLS.org: The homepage of the International Society for Quality of Life Studies has a variety of resources for QOL researchers. This society has links to several journals, including *Social Indicators Research*, *Journal of Happiness Studies*, and *Applied Research in Quality of Life*.

Issues that need to be addressed by future research:

- Software for use of item response theory needs to be simplified and streamlined for use by more investigators.
- Standards for determining differential item functioning need clearer guidance.
- Standards for identifying when the IRT model "fits well" for a HRQL measure need clarification for increased acceptance.

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4
Human Sleep

An Overview

Jaime M. Monti and Daniel Monti

Summary The Rechtschaffen and Kales system for scoring sleep states distinguishes a waking state, nonrapid eye movement (NREM) sleep, and rapid eye movement (REM) sleep. From the polysomnographic point of view, four stages are conventionally distinguished during NREM sleep. The young adult spends 20–28% of a night's sleep in REM sleep, 4–5% in stage 1, 46–50% in stage 2, 6–8% in stage 3, and 10–16% in stage 4. A range of differences in average sleep length has been established in young adults. In this respect, subjects have been characterized who sleep significantly less (short sleepers) or more (long sleepers) relative to a group norm. Short sleepers spend less time in stages 1, 2, and 3 sleep, whereas long sleepers spend more time in stage 2 sleep and REM sleep. On the basis of behavioral and polysomnographic aspects, three sleep states have been defined in the newborn infant: quiet sleep (the precursor of adult NREM sleep), active-REM sleep (the precursor of adult REM sleep), and indeterminate sleep. Total sleep time attains its highest levels in neonates and young infants (16–17 h). The fastest decrease in sleep length is observed in the 6-month-old infant (13–14 h) and is mainly related to the diminution of REM sleep during daytime. Compared to the infancy, changes of sleep duration during early childhood occur at a slower pace. The total amount of sleep decreases to 12 h by 4 years and to 8–10 h by 10 years. A series of neural structures involved in the occurrence of waking, NREM sleep, and REM sleep have been characterized in the central nervous system (CNS). In addition, a number of neurotransmitters have been described that function to promote waking (acetylcholine, noradrenaline, dopamine, serotonin, histamine, glutamate, and orexin), NREM sleep (γ-aminobutyric acid, gallanin, and adenosine), and REM sleep (acetylcholine).

Keywords Human sleep · young adults · short and long sleepers · newborn infants · regulation of sleep.

Learning objectives:

- The young adult spends 20–28% of a night's sleep in REM sleep and 72–80% in NREM sleep.
- Subjects have been characterized who sleep significantly less (short sleepers) or more (long sleepers) relative to a group norm.
- In addition to sleep duration, two other variables—slow wave sleep and REM sleep—undergo profound changes from infancy to maturity and old age.

Introduction

Sleep is closely related to every facet of daily life. In this respect, disturbed sleep affects not only our health and well-being but also our quality of life.

The introduction of a number of new techniques during the past few decades, including polysomnographic surface measurements of central nervous system (CNS) activity, eye movements, and muscle activity, has allowed sleep to be described in electrophysiological terms (1). In addition, functional neuroimaging studies have revealed changes in CNS cortical and subcortical areas during sleep and waking (2).

Sleep in the Young Adult

Sleep in the normal adult is accomplished when a number of changes in the CNS bring about a set of behavioral, physiological, and psychological changes. The sleep–wakefulness cycle can be characterized by the polysomnographic recording of three basic parameters: the electroencephalogram (EEG), electro-oculogram (EOG), and electromyogram (EMG). The Dement and Kleitman system for scoring sleep stages (3) modified by Rechtschaffen and Kales (4) distinguishes a

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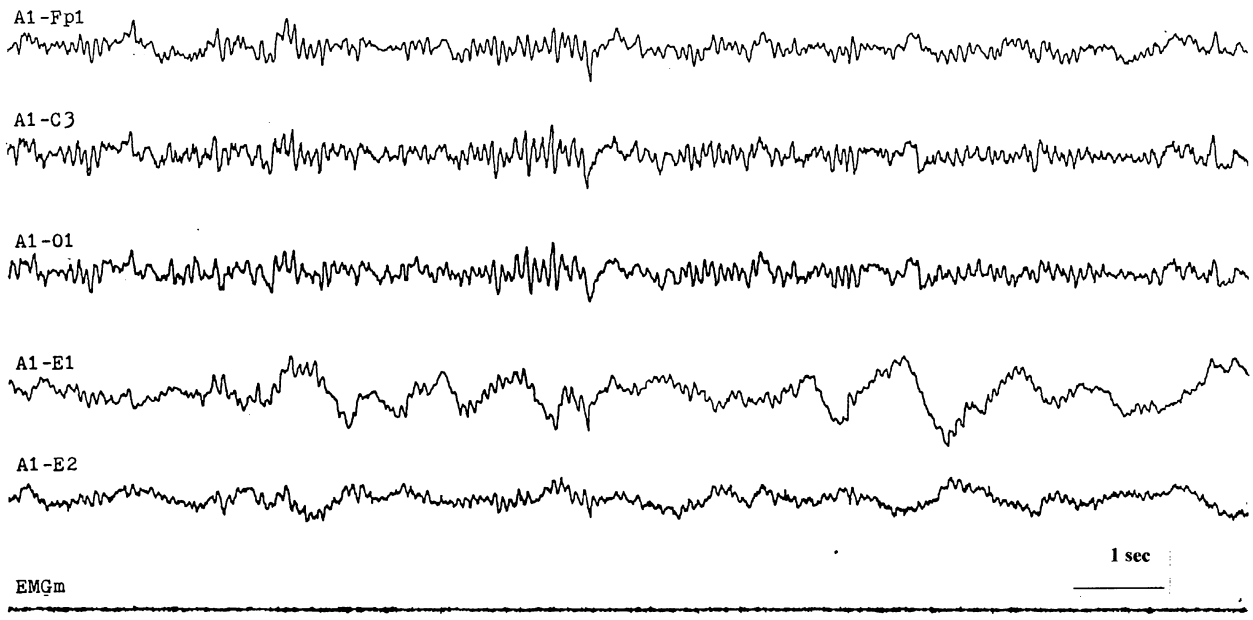

FIGURE 4.1. Patterns of electroencephalogram (EEG) activity during quiet waking in the young adult. A1–Fp1, frontal cortex; A1–C3, central cortex; A1–O1, occipital cortex; A1–E1, right electro-oculogram; A1–E2, left electro-oculogram; EMGm, chin electromyogram. Time in seconds.

waking state, nonrapid eye movement (NREM) sleep, and rapid eye movement (REM) sleep.

Relaxed wakefulness is characterized by an EEG with sinusoidal waves (alpha activity, 8–12 Hz) intermixed with lower amplitude irregular beta waves (13–35 Hz), slow or rapid EOG activity (recorded as out-of-phase or in-phase deflections), eyelid blinks, a relatively high tonic EMG, and movement artifacts (Figure 4.1).

During NREM sleep, the subject is lying down motionless, their eyes are closed, and a given sensory input (light and noise) no longer induces a behavioral response. From the polysomnographic point of view, four stages are conventionally distinguished: (i) stage 1: as the subject falls asleep, his antigravitation muscles markedly relax and EOG leads record slow and predominantly horizontal eye movements. At the EEG level, alpha activity is substituted by relatively low-voltage waves (50–70 μV) with a prominence of activity in the theta range (4–7 Hz). Vertex spike-like waves of up to 200 μV in amplitude occur sporadically during this stage (Figure 4.2). When the subject is left undisturbed, stage 1 sleep lasts only a few minutes during a night's sleep. However, it can reappear following sensory stimulation. (ii) Stage 2: this stage is defined by the presence of sleep spindles and K-complexes. Sleep spindles show as brief bursts of rhythmic waves (spindle shaped) with a frequency of 12–14 Hz and a duration of at least 0.5 s. They can be recorded as isolated events or in close temporal relation to a K-complex. K-complexes are relatively high-amplitude potentials with a negative sharp wave immediately followed by a positive component and a total duration exceeding 0.5 s (Figure 4.3). They usually occur spontaneously but can also be elicited by external stimuli of all sensory modalities. Sporadic slow waves can be recorded during stage 2 as well. (iii) Stages 3 and 4 are characterized by the presence of slow high-amplitude waves (delta waves with a frequency of 1–2 Hz or slower and an amplitude of 75 μV or greater). When at least 20% but no more than 50% of the scoring epoch consists of delta wave activity, it is classified as stage 3 (Figure 4.4). If more than 50% of the epoch contains delta waves, sleep is classified as stage 4. Stages 3 and 4 are also referred as slow wave sleep (Figure 4.5).

During REM sleep, the subject is flaccid and even more unresponsive than during NREM sleep. Periodically, his eyes move rapidly under closed lids. If the subject is waken up, he might actually say that he was dreaming. The polysomnogram is characterized by the presence of low voltage mixed frequency EEG activity that closely resembles that of stage 1. On this background, saw-tooth waves (theta activity, 4–7 Hz) are often observed in conjunction with bursts of REMs. In contrast, muscles are completely relaxed. However, the flat EMG tracing is periodically interrupted by muscle twitches (Figure 4.6). Discontinuous events such as muscle twitches and REMs that occur in REM sleep are known as phasic events, whereas continuous processes such as desynchronized EEG and muscle hypotonia are tonic events.

The young adult spends 20–28% of a night's sleep (7–8 h) in REM sleep, 4–5% in stage 1, 46–50% in stage 2, 6–8% in stage 3, and 10–16% in stage 4 (5–7). Sleep stage amounts for males and females within the same age range are not significantly different (8).

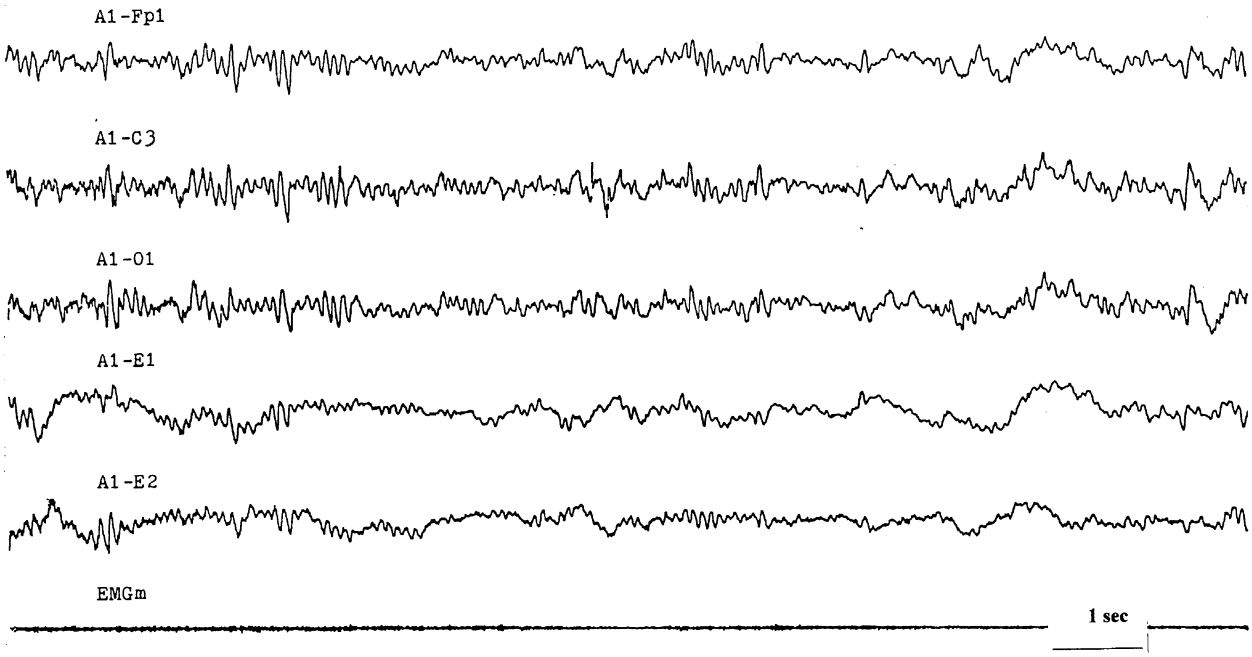

FIGURE 4.2. Patterns of electroencephalogram (EEG) activity during stage 1 sleep in the young adult.

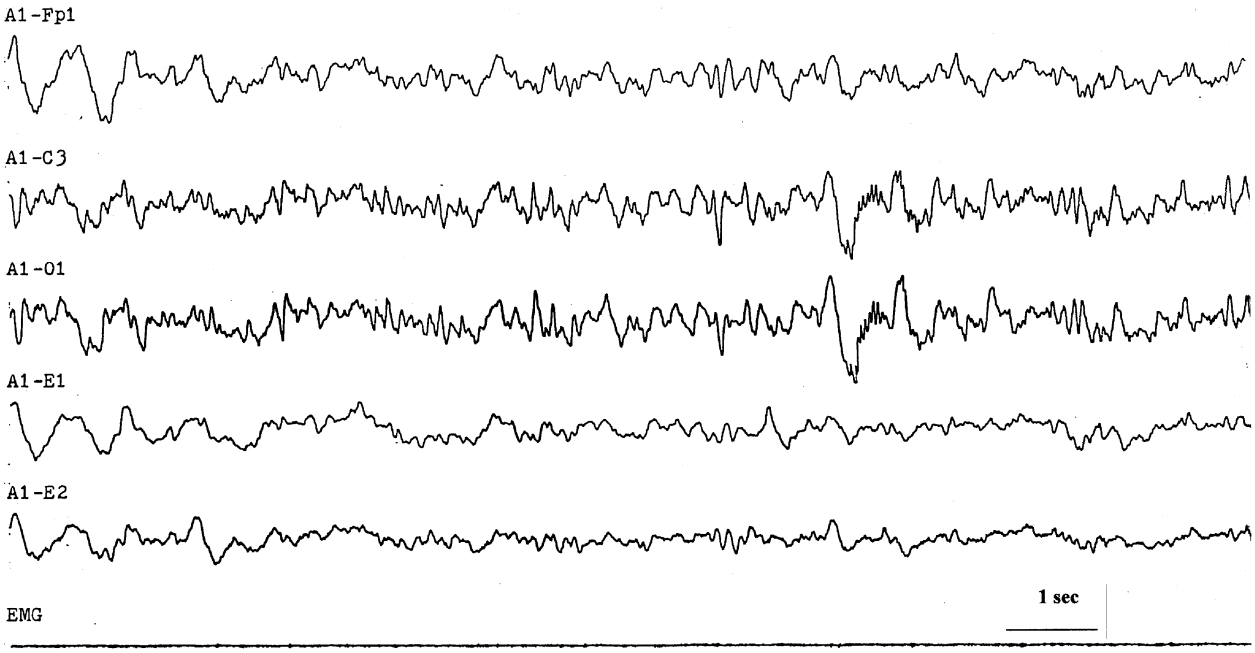

FIGURE 4.3. Patterns of electroencephalogram (EEG) activity during stage 2 sleep in the young adult.

Temporal Aspects of the Sleep Cycle in the Young Adult

The sleep of the young adult shows a highly consistent pattern from night to night. However, the percentage of time each subject spends in a given sleep stage and the number of sleep stage changes vary widely among individuals. Williams et al. (9, 10) and Agnew et al. (11) studied the sequence in which one sleep stage appeared after another during NREM sleep. When NREM sleep started deepening, a progression of only one stage at a time (from stage 1 to 4) was usually observed.

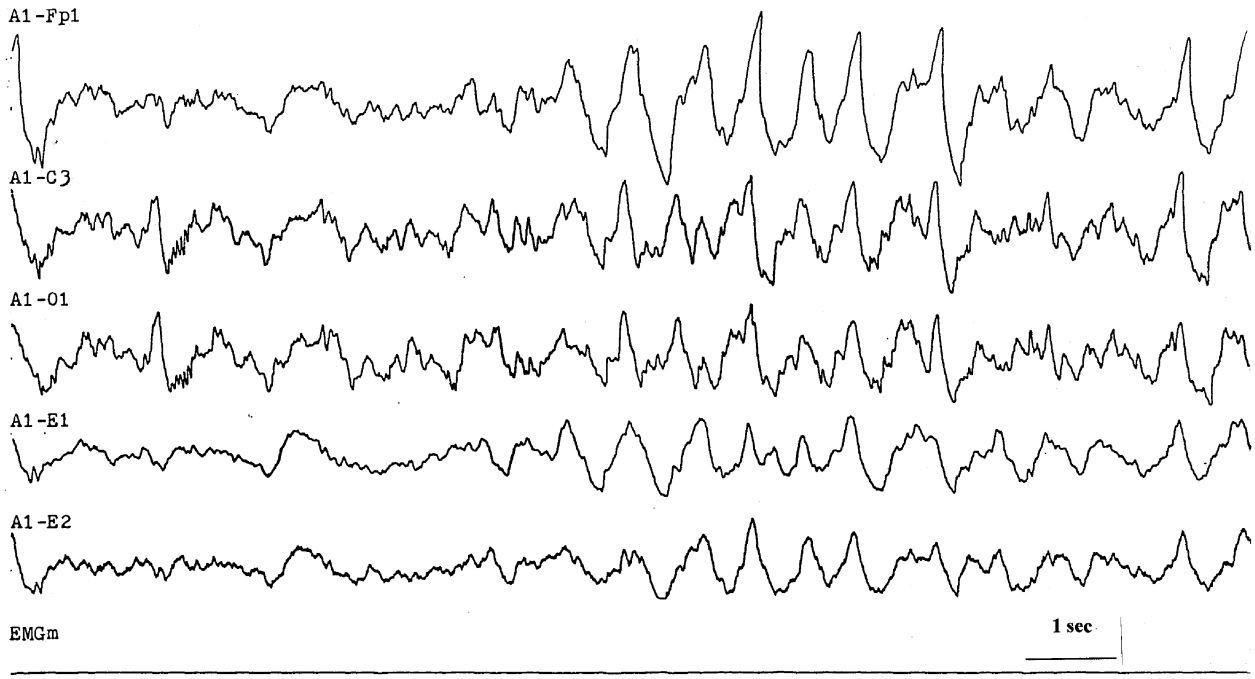

FIGURE 4.4. Patterns of electroencephalogram (EEG) activity during stage 3 sleep in the young adult.

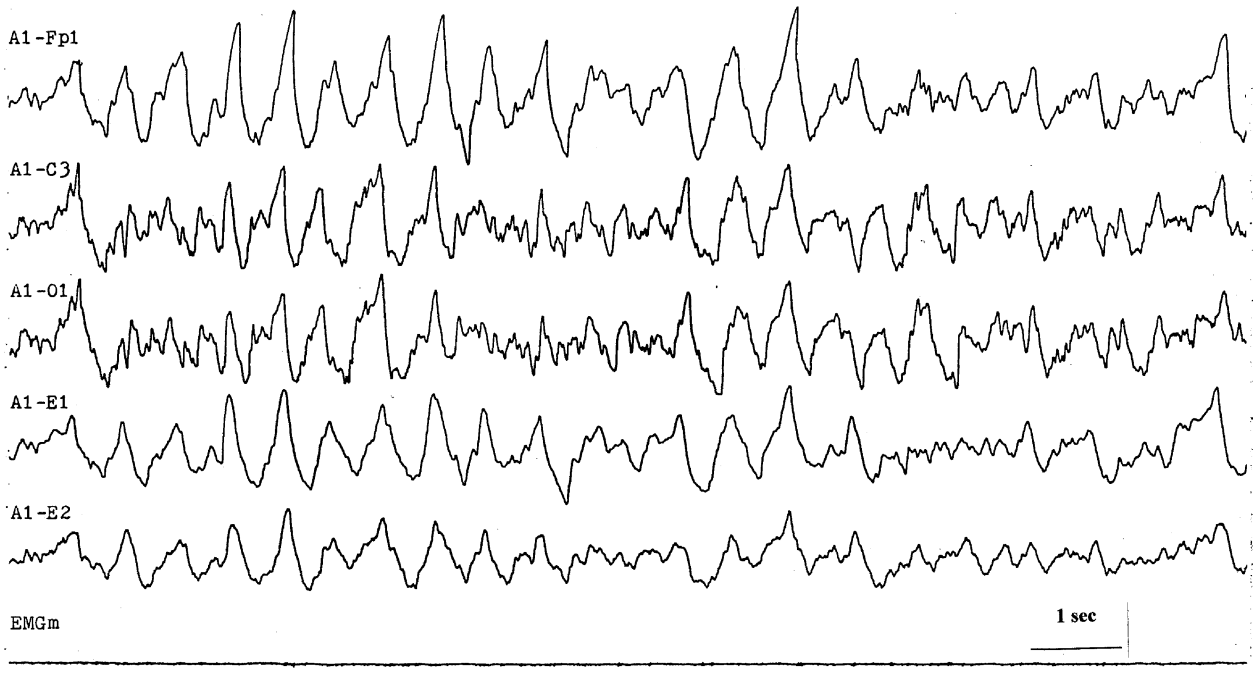

FIGURE 4.5. Patterns of electroencephalogram (EEG) activity during stage 4 sleep in the young adult.

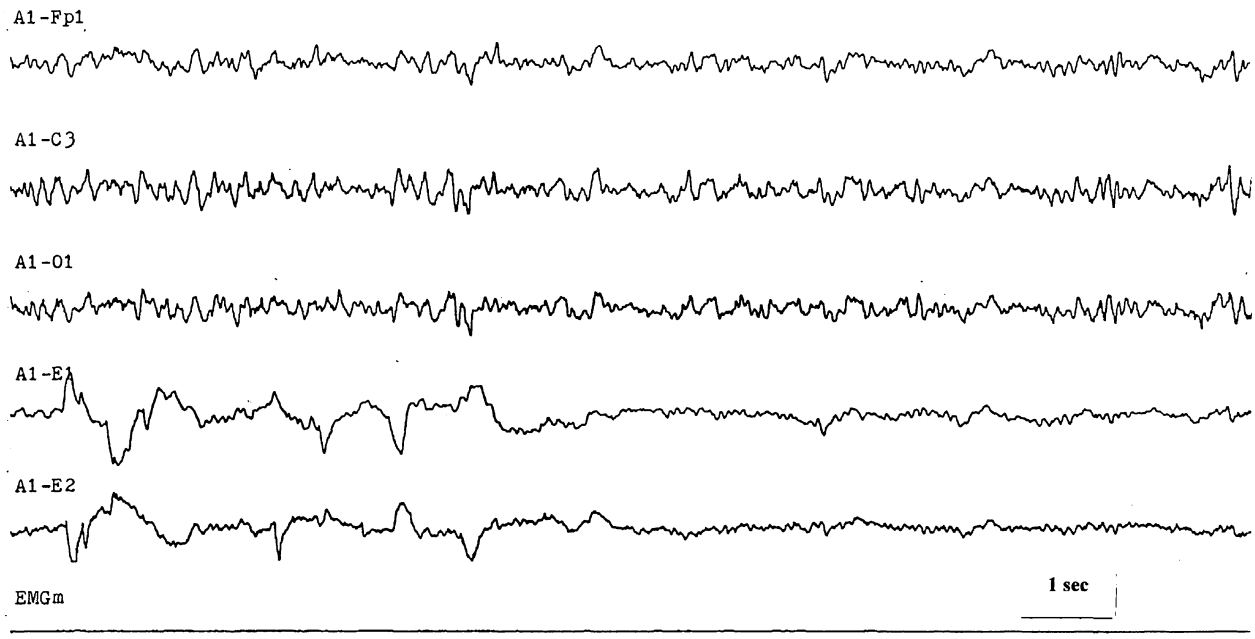

FIGURE 4.6. Patterns of electroencephalogram (EEG) activity during stage REM sleep in the young adult.

When sleep was moving out of stage 4, stage by stage changes were also observed. However, comparatively higher amounts of abrupt shifts were evident.

REM sleep follows a course independent of the NREM sleep stages (5). The first REM period appears about 90 min after falling asleep. NREM sleep preceding the first dream period distinctively shows large amounts of slow wave sleep. During a typical 8-h sleeping night, five to six REM periods occur at intervals of 80–100 min, with the duration of each period generally increasing over the night. They are usually preceded and followed by stage 2 sleep. Stage 4 and REM sleep are differently distributed during the night. Stage 4 predominates during the early part of the night and REM sleep in the latter part (8, 12). The interval from the beginning of one REM period to the beginning of the next is conventionally defined as a sleep cycle.

Stages of Sleep and EEG Spectra

As was mentioned previously, the sleep EEG consists of an irregular pattern of both slow and rapid waves. In this respect, it has been shown that spectral analysis of the night's EEG provides data on the predominance of low- or high-frequency waves at any given moment (13). As expected, spectral patterns corresponding to the alpha rhythm (8–12 Hz) of relaxed wakefulness are present before the onset of NREM sleep. On the other hand, EEG activity in the low-frequency bands (1–4 Hz—stages 3 and 4) predominates during the first 2-h interval of NREMS, whereas EEG activity in the 12–16 Hz bands (sleep spindles) shows high levels during stage 2 sleep (Figure 4.7).

Short and Long Sleepers

Several reports have established a range of differences in average sleep length of young adults. On the basis of physiological and psychological studies, subjects have been characterized as who sleep significantly less (short sleepers) or more (long sleepers) relative to a group norm (14). Compared with an age-matched control group, short sleepers are persons who sleep 6 h or less but have no complaint. They spend less time in light sleep (stage 1) and stages 2 and 3 and as much time in stage 4 and REM sleep as the control group (15). Concerning the kind of person, daytime activity and style that is associated with that differing sleep need, it has been proposed that short sleepers are efficient, hardworking, and somewhat hypomanic (15, 16). On the other hand, long sleepers spend more than 9 h sleeping every night. Their sleep pattern is characterized by a marked increase in stage 2 sleep and REM sleep. However, it does not differ from either the control group or the short sleep group in stage 4 sleep (15). Long sleepers tend to be anxious, depressed, and withdrawn (16, 17).

Sleep in Newborn Infants

During the newborn period, the polysomnographic recording of the EEG, EOG, and EMG does not readily allow to define NREM sleep and REM sleep. Four patterns of EEG activity have been described during the full-term neonate's sleep (18). They comprise (i) a low voltage and predominantly fast activity pattern; (ii) a tracé alternant pattern characterized by bursts of high-voltage slow waves with the occasional occurrence of both rapid low-voltage and sharp waves; (iii) a

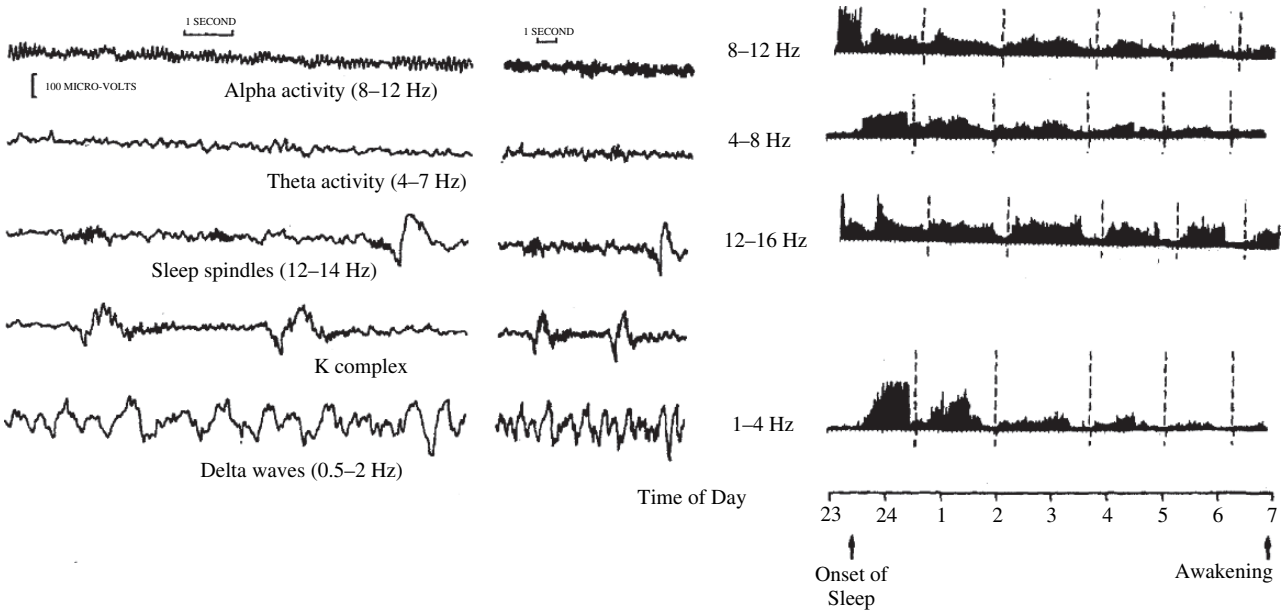

FIGURE 4.7. Patterns of electrical waves and electroencephalogram (EEG) spectra observed in the young adult. Left column, electrical waves recorded from the scalp; right column, EEG spectra of changes occurring in the brain during sleep and waking. [Modified from: F. Snyder. Psychophysiology of human sleep, *Clin Neurosurg* **18** (1971), pp. 503–536 and A. Borbély, *Secrets of Sleep*. Basic Books Inc, New York (1986).].

high-voltage slow pattern; and (iv) a mixed pattern that includes both high-voltage slow and low-voltage polyrhythmic components. On the basis of behavioral and polysomnographic aspects, Anders et al. (18) have defined three sleep states: quiet sleep, active-REM sleep, and indeterminate sleep.

Quiet sleep, the precursor of adult NREM sleep, is characterized by behavioral quiescence and closed eyes. Although any of the sleep patterns described above can be seen during quiet sleep, only the tracé alternant is exclusive of this sleep state. At term, quiet sleep occupies 35–45% of total sleep time. By 2 months of age, the tracé alternant is progressively replaced by an EEG pattern that resembles NREM sleep.

Active-REM sleep, the precursor of adult REM sleep, is distinguished by considerable behavioral activity. In this respect, facial (fine twitches, tremors, grimaces, and smiles) or limb movements are interspersed with gross body writhing. REMs, either singly or in bursts, are usually recorded together with a low-amplitude EMG. The EEG shows a low-voltage irregular or mixed pattern. At term, active-REM sleep occupies 45–50% of total sleep time.

At times, the polysomnogram of young, term infants do not meet the above quiet sleep and active-REM sleep criteria. It has been proposed that these epochs correspond to a state of poorly organized sleep and should be scored as indeterminate sleep (19, 20).

Wakefulness in the neonate is best characterized by behavioral observation. During waking, the infant shows either gross body movements, vocalizations, and grunting or is relatively inactive and with eyes open.

Total sleep time attains its highest levels in neonates and infants. Moreover, the fastest decrease in sleep length is observed during this period (from 16–17 h in the newborn to 13–14 h in the 6-month-old infant) and is mainly related to the diminution of REM sleep during daytime. In addition, the number of sleep onset REM periods is significantly reduced (21). By 3 months of age, quiet sleep EEG patterns can begin to be subclassified into NREM sleep stages (22).

Sleep and wakefulness are evenly distributed between day and night in the newborn (23). As the infant grows, the polyphasic pattern tends to be substituted by periods of consolidated sleep and wakefulness. By 3 months of age, sleep is predominantly observed during the nocturnal hours (24).

Compared to the infancy, changes of sleep variables during early childhood occur at a slower pace. The total amount of sleep decreases to 12 h by 4 years, and NREM sleep is seen in most sleep onsets. In addition, slow wave sleep onset tends to predominate during the first third of the night. At 5 years of age, REM sleep percentage of total sleep time tends to approach values observed in the young adult and to predominate during the last part of the night.

At 10 years of age (school-aged children), total sleep time amounts to 8–10 h.

It should be stressed that in addition to sleep duration, two other variables, slow wave sleep (mainly stage 4 sleep) and REM sleep, undergo profound changes during development. REM sleep (expressed in minutes) decreases steadily during early childhood. The decline tends to ease during late childhood and then after a plateau during adolescence and

young adult years continues to diminish through maturity and old age.

Stage 4 sleep amounts to 17% of total sleep time at age 2.6 years. This sleep stage decreases continuously throughout the life span, amounting to 4.5% of total sleep time at mean age 80 (25).

Neural Structures and Neurotransmitters Involved in the Regulation of Sleep and Waking

The neural structures involved in the promotion of waking are located in (i) the brain stem [dorsal raphe and median raphe nuclei (DRN, MRN), locus coeruleus (LC), laterodorsal and pedunculopontine tegmental nuclei (LDT/PPT), and medialpontine reticular formation (mPRF)], (ii) the hypothalamus [tuberomammillary nucleus (TMN) and lateral hypothalamus (LH)], (iii) the basal forebrain (BFB) (medial septal area and nucleus basalis of Maynert), and (iv) the midbrain ventral tegmental area (VTA) and substantia nigra zona compacta (SNc) (26).

The following neurotransmitters function to promote waking: (i) acetylcholine (ACh—LDT/PPT, BFB), (ii) noradrenaline (NA—LC), (iii) serotonin (5-HT—DRN, MRN), (iv) histamine (HA—TMN), (v) glutamate (GLU—mPRF), (vi) orexin (LH), and (vii) dopamine (DA—VTA, SNc) (27). The NA-, 5-HT-, and HA-containing neurons send long ascending projections to the forebrain including the cerebral cortex and subcortical structures. Moreover, the DA-containing cells project into the basal ganglia and frontal cortex. Cholinergic neurons from the midbrain tegmentum (wake/REM-on) project to the thalamus (ventro-medial, intralaminar, and midline nuclei) and BFB, whereas cholinergic BFB neurons have widespread rostral projections to the cerebral cortex and hippocampus. Orexin-containing neurons from the LH project to the entire forebrain and brainstem arousal systems. Glutamatergic neurons comprise the projection neurons of the mPRF, thalamus, and cerebral cortex (28).

The ascending projections into the forebrain follow a dorsal and a ventral route (29). The dorsal route terminates in the nonspecific thalamic nuclei, which in turn project to the cerebral cortex. Glutamate is involved in this step. The ventral route passes through the hypothalamus and continues into the basal forebrain where cells in turn project to the cerebral cortex and hippocampus. Acetylcholine participates in this step. In addition, many of the neural structures so far described send descending projections to the spinal cord that modulates muscle tone.

Neurons in the BFB, preoptic area, and anterior hypothalamus constitute a sleep-inducing system. Electrical stimulation of the preoptic area, including the horizontal limb of the diagonal band of Broca, leads to sleep with electrocortical synchronization (30). In contrast, lesions involving these structures disrupt slow wave sleep and REM sleep (31). Recording of single-cell activity in the preoptic/anterior hypothalamic area of several species allowed the identification of neurons that increase their discharge rates during slow wave sleep (32). All these neurons contain γ-aminobutyric acid (GABA) and gallanin, two inhibitory neurotransmitters, and project to brainstem and hypothalamic areas involved in the promotion of waking. Thus, the GABA/gallanin-containing cells in the preoptic/anterior hypothalamic area could in part promote sleep by inhibiting 5-HT, NA, HA, and ACh neurons.

Adenosine has been proposed to induce sleep by inhibiting cholinergic neurons on the BFB and brainstem. In this respect, adenosine and the adenosine transport inhibitor NBTI [s-(p-nitrobenzyl)-6-thioinosine] decreases the discharge rate of BFB neurons during waking, whereas the adenosine A_1 receptor antagonist CPDX (8-cyclopentyl-1-1,3-dimethylxantine) induces the opposite effect (33, 34).

Cholinergic neurons in the LDT and the PPT act to promote REM sleep. The predominantly glutamatergic neurons of the REMS-induction region of the mPRF are in turn activated by cholinergic cells that results in the occurrence of tonic and phasic components of REM sleep. All these neurons are inhibited by serotonergic (DRN), noradrenergic (LC), histaminergic (HA), and dopaminergic (VTA) cells. Two types of neurons have been characterized in the LDT and PPT. One type of neuron has higher firing rates during waking and REM sleep (wake/REM-on cells) than during NREM sleep, whereas the other type of cell increases its firing rate from waking to NREM sleep and still more during REM sleep (REM-on neurons). The release of 5-HT, NA, HA, and ACh in areas relevant for REM sleep is high during waking, whereas during REM sleep only ACh is released at a significant rate. The release of all neurotransmitters is reduced during slow wave sleep (29, 35).

Issues that need to be addressed by future research:

- New methods are needed to study in more detail the dynamic structure of sleep
- Additional research is needed to examine the cellular mechanisms underlying the involvement of central nervous system structures in sleep occurrence
- Additional studies are warranted to identify the brain circuitry that controls sleep–wake transitions

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5
Sleep Disorders

An Overview

Geneviève St-Jean and Célyne H. Bastien

Summary This chapter introduces the reader to the different classifications of sleep disorders. This chapter comprises nine general sections of main sleep disorders encountered in the general population: insomnia, sleep apnea, narcolepsy, hypersomnias, periodic limb movement disorder, restless leg syndrome, REM-related parasomnias, non-REM-related parasomnias, and circadian rhythm disorders. Each section provides a general definition/description of the disorder, diagnosis pointers, main consequences associated with the disorder as well as some treatment options. When available, prevalence and incidence data are provided. Two short clinical vignettes illustrate main complaints of insomnia and apnea. These vignettes also report some daily consequences of the unrefreshing and disturbed sleep experienced by the sleepers. Although most sleep disorders are diagnosed and treated, the present chapter also highlights that some of them nonetheless may go unnoticed to the suffering individuals but not to his/her bed partner/significant other. Furthermore, daily consequences associated with sleep disorders are various, and a thorough examination of all side effects shall be taken into consideration during evaluation and when treatment is initiated. Sleep medicine is a growing field and the common goal of all clinicians and researchers is by far to alleviate sleep disorders' sometimes disastrous consequences and increase the quality of life of suffering individuals.

Keywords Sleep disorders · vignettes · diagnosis · consequences · treatment · quality of life

Learning objectives:

- General definition of major sleep disorders.
- An overview of consequences associated with sleep disorders.
- One or two treatment options for each defined disorder.

Introduction

It is today widely recognized that at least 15% of the general population suffer from a sleep disorder. All age groups, from early years through middle and late years of life, can be afflicted. Furthermore, this percentage can be tripled in psychiatric settings. Primary or secondary to either a psychopathology, medical illness, medication intake, or another sleep disorder, when one does not sleep or perceives not to sleep adequately; his/her quality of life is undeniably affected. This chapter is devoted to a general overview of the different sleep disorders either reported by an individual or, as also encountered in general practice, reported by a significant other.

Classification and Diagnosis

> We have created a new clinical specialty, sleep disorders medicine, whose task is to watch over all of us while we are asleep. —William Dement (1985)

In recent years, the American Sleep Disorders Association and the different tasks forces devoted to the study and diagnosis of sleep disorders (such as NIMH and associated professional associations) have made genuine progresses in the recognizance of sleep disorders in the general population as well as in clinical settings. In sleep disorders medicine practice, the *International Classification of Sleep Disorders* (ICSD; 1) now proposes four general sections of sleep disorders: dysosmias, parasomnias, sleep disorders associated with medical/psychiatric disorders, and other proposed sleep disorders. In addition, the diagnostic classification of sleep and arousal disorders are grouped under four different

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coding: DIMS (disorders of initiating and maintaining sleep—insomnias); DOES (disorders of excessive somnolence); disorders of the sleep wake schedule, and dysfunctions associated with sleep, sleep stages or partial arousals (parasomnias). On the other hand, 18 different disorders associated with insomnia or hypersomnia can be found in *The Diagnostic and Statistical Manual of Mental Disorders* (4th ed., 2).

Examples of Sleep Disorders

The venue of sophisticated technologies, such as polysomnography, has enhanced our understanding of sleep disorders. In addition, the development and validation of questionnaires now provide good insights and pointers of the impact of sleep disorders on one's well-being and daily functioning. Although we have learned through sleep deprivation studies that sleep loss diminishes daytime performance, increases sleepiness, and affects mood, these same observations are also the result of various sleep disorders. If you are not convinced, consider the following two case illustrations:

1. After tossing around for what seemed an eternity, Geraldine turns to the bedside. Three a.m. says the red light on the alarm clock. "Oh no, not tonight again…I can't sleep…" Geraldine thinks: "I have that big meeting tomorrow…. How am I going to be able to deliver that talk effectively if I don't have a good night's sleep…?"
2. "Leon, we have to do something about this gasping and snoring at night. Don't you hear yourself? I can't take this anymore! I will make an appointment with Doctor Zacks right this morning. There must be something we can do about this. At the same time, maybe you can discuss with him the fact that you are falling asleep everywhere, even behind the wheel?"

There is no doubt that the most prevalent sleep disorder is insomnia as depicted in case 1. Although not always confirmed by objective measures, it remains nonetheless a puzzling disorder that heavily burdens the suffering individual as well as society, as billions of dollars derive from its consequences everyday, albeit be in work absenteeism, loss of performance, or health care systems use. On the other hand, and not less psychologically/cognitively costly for the individual, sleep apnea, as depicted in case 2, if left undiagnosed, can lead to serious consequences such as cardiovascular diseases and even death.

Major Sleep Disorders

Insomnia

As approximately 30% of the general population experience insomnia symptoms, 10% suffer from insomnia syndrome (3,4). Insomnia, as a symptom, is a diagnosis criterion of other mental disorders (e.g., depression) and as a syndrome, may be secondary or comorbide to another disease. DSM-IV (2) qualifies *chronic primary insomnia* as a complaint of difficulty initiating or maintaining sleep or of a sleep of poor quality for a period of at least a month. In addition, daytime functioning must be impaired or distress must be presented. Moreover, sleep difficulties should not be due to another health or mental disorder or to substance consumption. According to the International Classification of Diseases (ICD-10, 5) and the ICSD, insomnia should last at least 6 months to be qualified as chronic. Female gender, as well as increasing in age are a risk factor associated with the disorder (3, 4).

ICSD adds sub-classifications to the diagnosis of insomnia. In some cases, complaints of sleep difficulties are objectively observable, in other cases, they are not. In other words, a patient may complain of sleep difficulties while objective polysomnographic recordings are normal, or there may be constant and important gap between objective and subjective measures of sleep (6). In fact, depending on the diagnosis criteria used, as much as 50% of individuals suffering from primary insomnia could be poor estimators of their sleep length and, consequently, classified as suffering from *paradoxical insomnia*, sleep state misperception or subjective insomnia (7). All three terms are found in the scientific literature to qualify this condition. While paradoxical insomnia sufferers and good sleepers seem to be equivalent on measures of sleep macroarchitecture, there may be subtle and finer differences in the microarchitecture characterizing both groups (8).

Among insomnia sufferers estimating their sleep accurately, and therefore presenting real deficits in the initiation or continuity of sleep, are found patients suffering from *psychophysiological insomnia*. The patients are assumed to be conditioned by sleep-related stimuli of the environment (e.g., bedroom) or bedtime routine, which are then associated in the patient's mind with the anxiety, fear, or frustration of having trouble to sleep (9–11). Consequently, their level of arousal is increased, preventing them from a good night sleep. Moreover, when awake in bed, they report rumination, excessive worrying, and catastrophic thinking on consequences of sleep loss.

A third form of primary insomnia, less common but still acknowledged, is *idiopathic* or *childhood-onset insomnia*. In this case, insomnia is reported since early childhood, typically before the age of 10 if not since birth and has always been relentless. A genetic disposition may explain a proportion of the idiopathic insomnia cases but not all. Also, a higher rate of difficult and premature deliveries is found in the idiopathic insomnia population compared to the general population (12, 13).

Consequences related to insomnia are multiple: fatigue, sleepiness, mood disruption (14), and reported impaired attention and memorization are frequent complaints (15). In addition, falling asleep in inappropriate places (i.e., at work, theater, reading, or driving an automobile) is problematic. Moreover, irritability and avoidance of certain activities may be isolating. Sleep aids, increased medical visits, and

absenteeism from work imply important costs for the patient as well as society (16, 17). There are evidence of the efficacy of several psychological treatments for insomnia such as stimulus control therapy, relaxation, paradoxical intention, sleep restriction, and cognitive behavior therapy (18). In addition, effective pharmacologic therapies, including benzodiazepine and newer non-benzodiazepine hypnotics, improve sleep maintenance although side effects are possible (19).

Sleep Apnea

Obstructive, central, and mixed sleep apneas are conditions where the breathing is repeatedly disrupted during sleep. Obstructive apnea, which affects 4% of men and 2% of women in the middle age (20), causes the soft tissues of the rear of the throat to collapse, consequently blocking the airway. This disorder may be the result of an airway malformation, such as maxillomandibular malformation or adenotonsillar enlargement, an excess of fatty tissues in the airway, or the relaxation and collapsing of the muscles during sleep; therefore, it is most common in middle-aged and overweight men. Typically, obstructive apnea creates loud snoring followed by 20–30 s of silence. Central apnea appears in cases of neuromuscular pathologies or brain stem lesions where the brain fails to signal the breathing. Accordingly, breathing efforts as well as airflow are interrupted. Mixed sleep apnea refers to both obstructive and central problems.

Consequences of sleep apnea are found during sleep and daytime as well (20). As the patient inhales after a breathing failure, microarousals and body movements occur and affect sleep quality which causes daytime sleepiness. Sometimes, arousals following obstructive events are associated with chest discomfort, suffocation, choking, or intense anxiety. Cardiac arrhythmias associated with apnea events are at the origin of the increase risk of sudden death during sleep. Typically, patients report severe dryness of the mouth along with the feeling of being unrefreshed in the morning. Concentration and memory problems generally result from oxygen desaturation as well as from sleepiness associated with the disturbed sleep. About 20% of patients complain of morning headache although it is not specific to sleep apnea. A decrease of testosterone attributable to the reduced oxygen saturation may also decrease libido. Complaints of excessive sleepiness are usual but can vary amongst sleep apnea sufferers. Sleepiness is most evident in relaxing situations although in active ones, sleepiness can result in accidents, job loss, or family problems. Secondary depression, anxiety, irritability, and despair are common. Therefore, the treatment of sleep apnea should address daytime sleepiness, the suppression of apneas, and the restoration of normal oxygenation during sleep (21). Weight loss may be indicated in some cases. Nasal continuous positive air pressure (N-CPAP) is actually the most prescribed treatment for obstructive sleep apnea (22).

Narcolepsy

The diagnosis of narcolepsy affects 20–60 persons per 100,000 and has a peak incidence between the ages of 15 and 35 years (23). The excessive sleepiness that characterizes narcolepsy is usually illustrated by multiple refreshing naps during the day, of about 10–20 min, after what sleepiness increases again until another nap is needed 2–3 h later. Sleep may occur during calm activities such as traveling, listening to music, watching television, and reading, but it can also happen in sleep-incompatible situations: eating, talking, or even driving. Sleepiness can be tolerated with much effort, but eventually, sleep attacks are inevitable. In fact, signs of drowsiness are found on electroencephalographic daytime recordings. Multiple sleep latency test (MSLT) sleep onset measures are often below 5 min and contain two or more REM periods (24). Night PSG reveals an increased number of awakenings as well as an increased amount of stage 1 (25). Sometimes, hypnagogic hallucinations or sleep paralysis are reported. Over the years, sleepiness can improve due to coping strategies of the patient or worsen and be associated with the development of periodic limb movement or sleep apnea. Naps or amphetamine-like drugs may help to reduce daytime sleepiness (26).

Cataplexy is the second characteristic symptom of narcolepsy for which onset occurs either simultaneously or after the onset of sleepiness symptoms. It is defined by a sudden loss of muscular tone for a few seconds or minutes caused by a strong, pleasant, or exciting emotion. While consciousness, memory, and respiration remain intact, selected bilateral muscles or all skeletal-muscle groups are affected by the loss of tone. The intensity of cataplectic episodes may vary, for example, when the intensity is mild, the weakness may not be discernible to others. The frequency of cataplectic events varies from one individual to another: one may suffer from several episodes during a day as another may only have a few per year. In patients with severe and frequent cataplectic episodes, tricyclic antidepressant medications are indicated to reduce the symptoms (27) and patients may learn how to avoid attacks in the long run. However, the frequency of events generally decreases over time.

Because of sleepiness and cataplexy, individuals suffering from narcolepsy are at higher risk of having accidents in home and work environments as well as on the road. In addition, education, occupation, and social relations may be affected by the disorder and therefore affect the patient's quality of life.

Hypersomnia

ICSD distinguishes recurrent hypersomnia, idiopathic hypersomnia, and post-traumatic hypersomnia. All forms are characterized by a complaint of excessive daytime sleepiness and/or a prolonged nocturnal sleep period and daily sleep periods.

Recurrent Hypersomnia

Prevalence data for recurrent hypersomnia are still unknown. The onset is most frequent in adolescence although it also occurs through adulthood. It is believed to affect more men than women although the true sex ratio has not yet been identified. Recurrent hypersomnia consists of episodes of severe sleepiness often precipitated by acute febrile episodes and severe somatic stress. Somnolence must last at least 18 h a day during a period of 3 days to 3 weeks. These periods must also occur at least one to two times a year. In Klein–Levin syndrome (28), the best known form of recurrent hypersomnia, patients may sleep for up to 18–20 h a day, waking only to rapidly consume large amount of food and void. A monosymptomatic type of the disorder is also described without the binge eating but includes possible disorientation, forgetfulness, depression, depersonalization, and occasional hallucinations as well as behavior changes (irritability, aggression, and impulsive behaviors). Following somnolence episodes, transient dysphoria, insomnia, elation, restlessness, or sexual hyperactivity may be observed. All presented symptoms severely affect the patient's social and occupational life; yet, in between episodes of hypersomnia, sleep returns to normal and patients seem medically and mentally healthy. Lithium is a good prophylactic choice when the frequency of hypersomnia episodes is high (29).

Idiopathic Hypersomnia

The complaint of a constant or recurrent sleepiness during the day, daytime sleep episodes, or prolonged night sleep occurring before the age of 25 refers to idiopathic hypersomnia. Complaints of difficulty waking up, disorientation after awakening, sleep attacks preceded by drowsiness, and unrefreshing short naps may also be present. The prevalence of this rare disorder is still unknown. The course of the disorder is progressive but stabilizes and lasts lifelong. Stimulant drugs are the most prescribed treatment although morning sleep drunkenness is difficult to treat (30).

Post-Traumatic Hypersomnia

Post-traumatic hypersomnia implies the complaint of excessive sleepiness and the occurrence of frequent daily sleep episodes for which the onset is associated with a head trauma. Therefore, the patient's sleep pattern differs from pre-trauma to post-trauma. Headache, fatigue, difficulty to concentrate, and impaired memory can be associated with the disorder. Typically, the sleepiness resolves itself over weeks or months.

Periodic Limb Movement Disorder

Periodic limb movement disorder (PLMD) affects 4–11% of the general population (31). Up to 17% of patients with insomnia may be affected with PLMD (32), and it is most common in patients with narcolepsy (33) and obstructive sleep apnea (34) than in the general population. It can be induced or aggravated by the use of monoamine oxydase inhibitors and tricyclic antidepressants or the withdrawal of anticonvulsivants, benzodiazepines, barbiturates, and others. PLMD consists of periodic episodes of limb movements which can appear from the onset of stage 1 sleep. Movements are frequent in stage 2 sleep, decrease in stages 3 and 4, and are usually absent during REM sleep. The movement is characterized by an extension of the big toe with partial flexion of the ankle, knee, and sometimes hip, followed by a period where the legs are still. Upper limb movements are also probable. Movements can be observed on one or both legs but not necessarily simultaneously or symmetrically. PSG recordings showing a minimum of four repetitive contractions of 0.5–5 s at the anterior tibialis electromyogram (EMG) separated by a 20- to 40-s interval constitute an episode for the calculation of the periodic limb movement index (PLM index) which represents the number of episodes per hour of total sleep time. Movements can be present for few minutes, few hours, or can occur throughout the entire night. In severe cases, movements during wake can also occur. A K-complex, arousal, or awakening is generally associated with the movement. While a PLM index of at least five occurrences associated with an EEG arousal or awakening is considered as mild, a severe diagnosis would exceed an index of 20. Thus, PLMD is associated with fragmented sleep, restless sleep, complaints of insomnia, and/or excessive daytime sleepiness. Anxiety and depression may be correlated to the chronicity of the disorder. In some cases, the bed partners' sleep may also be disrupted by the PLM of the patient, without the patient being aware himself/herself of the limb movements. L-dopa and dopamine agonists are actual pharmacologic treatments used for PLMD although there is still a need for controlled randomized studies assessing both PLMD and subjective sleep parameter (31).

Restless Legs Syndrome

Restless legs syndrome (RLS) is most common amongst women (35). About 11% of the general population suffer from RLS (35) and it has been identified in 26% of pregnant women (36) and 18% of uremic patients (37). Symptoms consist of unpleasant sensations, ache and discomfort, pulling, or itching in the legs at night that cause an urge to move the legs. RLS is also characterized by the partial or complete relief when legs are moving and the recurrence of the sensations as movements stop. The symptoms are usually felt between the ankle and the knee but may also include the thighs, feet, and, more rarely, arms. Rest or long seated periods may cause symptoms lasting from a few minutes to several hours. Most RLS patients also show PLMD during sleep, and when both syndromes are diagnosed, involuntary limb movements during wake may occur. The disorder may last several years with periods of increasing and declining symptoms. RLS typically interferes with sleep onset. Severe insomnia may be a consequence to RLS. Moreover, patients may present symptoms of anxiety or depression as well as psychosocial dysfunction. Various treatments are now offered for RLS (38). Behavioral and counter

stimuli interventions—such as mental and physical activities, massages, or hot bath—and the avoidance of RLS possible exacerbators (caffeine, alcohol, nicotine, and some medications) can ameliorate symptoms. As iron deficiency is thought to play a role in RLS, iron replacement is a potential cure. Pharmacotherapies for RLS include dopaminergic agents, opiates, benzodiazepine receptor agonists, and antiepileptics.

REM-Related Parasomnias

Sleep disorders occurring specifically in REM sleep include a total of six different pathologies. As the objective of this section is to briefly present REM-sleep parasomnias, only nightmares, sleep paralysis, and REM-sleep behavior disorder will be discussed. Note that REM-related parasomnias also include other disorders: impaired sleep-related penile erections, which is defined by a weakened penile tumescence during sleep that would not be sufficient to engage in sexual intercourse, sleep-related painful erections, a condition where penile erections are painful only during sleep and may cause awakenings from REM sleep, and REM-sleep-related sinus arrest, a cardiac rhythm disorder in otherwise healthy persons.

Nightmares

The nightmare is defined by a long and complicated dream with structured sequences of images and a content that becomes increasingly threatening to the dreamer. It occurs during REM sleep on the second half of the night and is followed by an awakening that can be delayed, but even so, there is a recall of a frightening dream. Upon awakening, full alertness occurs immediately with a little confusion or disorientation and the return to sleep is delayed. Nightmares affect 10–50% of children between the age of 3 and 6. Less common in adults, 50% of the population report having occasional nightmares and approximately 1% have at least one per week (39). In various personality disorders, namely schizotypal personality, borderline personality and schizoid personality, and in schizophrenia, the presence of frequent nightmares is increased as it is the case for individuals presenting some features of these disorders. Stressful life periods or traumatic events tend to increase the frequency and severity of nightmares. Desensitization techniques might be helpful in adults to overcome nightmares (40).

Sleep Paralysis

Patients who experience or suffer from sleep paralysis report an inability to execute voluntary movements, usually for periods of time lasting from 1–7 min, at sleep onset or upon awakening. While ocular and respiratory movements are possible, limb, trunk, and head are typically immobile. A sensation of difficulty breathing may be present and contribute to the frightening character of the situation. Threatening hypnagogic imagery or dreamlike mentation may also be present. Sleep paralysis ceases spontaneously by mean of touch and movement induced by another person, by repeated efforts to move, or by vigorous eye movements. Appearing in an isolated or a familial form, sleep paralysis may also be a symptom of narcolepsy. The latter two forms tend to be more chronic while the former is associates with predisposing factors. Such factors often include irregular sleep habits, sleep deprivation, shift work, or jet lag. Other factors that might also induce sleep paralysis are mental stress, overtiredness, and sleeping in the supine position. The cause of sleep paralysis is thought to be a microstructural change, a neurochemical or neuroimmunologic dysfunction in the mechanism controlling the normal motor paralysis of the REM sleep stage. Six percent of the general population report a chronic complaint of sleep paralysis while another 6% experience at least one episode in their lifetime (41). In some cases, episodes may cause chronic anxiety or depression, but the disorder is usually without complications.

REM Sleep Behavior Disorder

REM sleep behavior disorder (RBD) is characterized by elaborate movements correlated with dream mentation during REM sleep. This condition contrasts with the electromyographic atonia normally found in this sleep stage. Punching, kicking, leaping, and diving out of bed occurring without an awakening are examples of reported movements associated with the content of dreams (42). RBD usually appears after a minimum of 90 min of sleep, and the frequency of episodes is variable, for instance, violent ones may occur from once a week to several times a night. PSG confirms a persistent muscle tone in REM sleep, excessive limb or body jerking and complex, vigorous or violent behaviors. Strong movements may harm the patient or the bed partner and cause significant social consequences. RBD is rare and affects more men than women. It usually begins progressively after the age of 50 but may start at any time (43, 44). At the onset of the disorder, dreams may become more vivid, unpleasant, violent, or active. Clonazepam reduces the number and intensity of behaviors during REM sleep (45).

Non-REM-Related Parasomnias: Arousal Disorders, Sleep–Wake Transition Disorders, and Other Parasomnias

Non-REM-related parasomnias comprise a variety of sleep disorders which, by nature, are undesirable physical phenomena associated with sleep. Some of them usually affect children, such as sleep enuresis, infant sleep apnea, congenital central hypoventilation syndrome, sudden infant death syndrome, and benign neonatal sleep myoclonus. Other non-REM sleep parasomnias are relatively rare like sleep-related abnormal swallowing, nocturnal paroxysmal dystonia, and sudden unexplained nocturnal death syndrome. As sleep bruxism (8.1), primary snoring, confusional arousals, sleepwalking, and sleep terrors are widespread, explicit definitions are given below.

Sleep Bruxism

Teeth-grinding or teeth-clenching occurring in sleep characterizes sleep bruxism. Such sleep disorder may be very unpleasant due to loud sound created by teeth-grinding and teeth-clenching as well as to jaw muscle discomfort it produces. It may also cause abnormal teeth ware or periodontal tissue damage (46), atypical facial pain, or headache. PSG recordings demonstrate that events of bruxism can be coupled with short arousals and are most frequent in stage 2 sleep; nonetheless, they can take place in all sleep stages (47). Predisposing factors of bruxism are minor dental, mandibular or maxillary pathologies, anxiety, cerebral palsy, and mental retardation in children. Lifetime prevalence of teeth-grinding is as high as 85–90% in the general population. However, it is severe enough to represent a clinical condition in only 15–22% of them (47). Generally, beginning between 10 and 20 years of age, the course of sleep bruxism may vary according to perceived stress or otherwise may be chronic. Possible treatments include occlusal adjustment and splints, psychotherapy, medications, physical therapy, muscle relaxants (such as diazepam), and suggestive hypnotherapy (47, 48).

Primary Snoring

Most prevalent in the middle age and overweight men, primary snoring lasting half of the night affects 22% of individuals (mostly men) between 40 and 65 years old (49). It is diagnosed by an observer noticing a loud sound produced by the vibration of pharyngeal tissues during inspiration or expiration, without evidence of apnea, hypoventilation, complaint of insomnia, or excessive daytime sleepiness. Typically, the snoring is continuous and occurs while the sleeper is in a supine position. The patient is not always aware of the snoring but may experience dry mouth which might force him to wake up to drink water. The use of central nervous system depressants, nasal congestion or obstruction, and obesity are main factors predisposing to primary snoring. Furthermore, primary snoring predisposes to obstructive sleep apnea. Hypertension, ischemic heart disease, and cerebrovascular disease are possible medical complications of snoring.

Confusional Arousals

Before the age of 5 years, almost every child will have experienced confusional arousals. This condition affecting only 4% of adults (50) is described as a state of confusion during and following an awakening generally from deep sleep, in the first third of the night. More precisely, the patient experiences disorientation in time and in space, inappropriate behavior and slow speech, mentation, and response to questions during several minutes to several hours. Predisposing factors are young age, recovery from sleep deprivation, circadian rhythm sleep disorders, the use of central nervous system depressants, hypersomnia, sleep apnea syndrome, sleep terrors, sleepwalking, and sometimes excessive exercises. Episodes of confusional arousals can be induced by forced awakenings. There are risks of personal injuries, and patients may become aggressive if they are restrained as they awake.

Sleepwalking

Sleepwalking is diagnosed by ambulation occurring in sleep, difficult arousal of the patient, and amnesia of the episode. PSG recordings indicate that it occurs in sleep stages 3 or 4 and mostly at the end of the first or second episode of slow wave sleep. Sleepwalking episodes can occur several times a week or only in presence of precipitating factors such as obstructive sleep apnea or other sleep disorders disrupting slow wave sleep, as well as internal or external stimuli. Most prevalent between 4 and 8 years of age, it generally disappears in adolescence and is rare in adults (50). In folk wisdom, sleepwalking has often been associated with inappropriate and dangerous behaviors. In fact, physical injuries, falls, and attempts to escape are possible risks associated with the disorder. Violent behaviors are more common in males experiencing stressors and abusing of caffeinated beverages and drugs (51). In children particularly, this condition can result in embarrassment or social isolation associated with the avoidance of sleeping elsewhere. Providing a safe sleep environment, closing doors and windows is appropriate for children. In severe adult cases of sleepwalking, benzodiazepines may be indicated (52).

Sleep Terrors

Sleep terrors are another disorder inducing awakening from slow wave sleep. Complaining of a sudden episode of intense terror during sleep, usually in the first third of the night, patients also experience partial or total amnesia of the event. During an episode of sleep terror, an autonomic discharge occurs including, for example, tachycardia, tachypnea, blushing of the skin, and diaphoresis. If patients awake before the end of the autonomic discharge, they may be conscious of this activation and report vague, brief and vivid dream images, or hallucinations. Sometimes, they may also try to escape from bed, fight, cry, or scream. It may be precipitated by fever, sleep deprivation, or the use of central nervous system depressant medications. Affecting 3% of children (53) and 4–5% of adults (54), sleep terrors are most often observed in children between 4 and 12 years of age and usually resolves itself during adolescence. In adults, psychopathologies may be associated with the disorder. However, such association should not be supposed in the case where children suffer from sleep terrors nor do children have a higher incidence of psychopathology than the general population. Sleep terrors may have negative consequences such as potential harm of patient or others and social embarrassment in relation to the disorder.

Circadian Rhythm Disorders

Circadian rhythm disorders refer to a desynchronization of the sleep during the 24-h day due to a problem of eliciting sleep when needed, desired, or expected. Other sleep disorders such as insomnia or narcolepsy may affect sleep timing, but in those cases, the primary diagnosis would be retained. A circadian rhythm disorder diagnosis should be made only when sleep timing is the primary cause of the sleep problem and when it does not encounter societal norms in that matter. Environmental factors dependent of the individual may induce some circadian rhythm disorders. For instance, in time zone change syndrome, the rapid travel across time zones causes difficulties of initiation and maintenance of sleep at the new time zone hour, excessive sleepiness during daytime, diminished subjective alertness and performance, and somatic symptoms. In shift work sleep disorder, transient symptoms of insomnia and sleepiness appear as the worker changes his work schedule including in it his habitual sleep period. Other circadian sleep disorders may have a more intrinsic or extrinsic nature, as the ones described below.

Irregular Sleep–Wake Pattern

Often presented as a complaint of difficulties initiating or maintaining sleep, irregular sleep–wake pattern is defined by at least three fragmented sleep periods during the 24-h day. Although the sum of the sleep periods corresponds to the norms according to the age of the patient, no sleep period is of normal length and sleep patterns are unpredictable as reported in the sleep logs (55). This condition is most common in patients with severe congenital or developmental brain dysfunction, in the elderly suffering from degenerative brain dysfunction, but may also occur in otherwise healthy patients. Other predisposing factors are a lack of regular daily routine, frequent naps, spending excessive time in bed, or bed rest for medical reasons and chronic depression. This rare condition predisposes patients to drug dependency, subjective cognitive impairment, and sleepiness. Daytime functioning and consolidation of sleep cycles can be improved by increasing exposure to bright light and structured social and physical activities (55).

Delayed Sleep-Phase Syndrome

Presented as a complaint of an inability to fall asleep and wake at the desired times, or of excessive sleepiness, delayed sleep-phase syndrome (DSPS) corresponds to a phase delay of the major sleep episode compared with the desired time for sleep (56). In patients with DSPS, as well as in normal individuals, night-shift work, late-night studying, or mental illness may induce a transient phase delay. However, patients with DSPS are thought to have weaknesses in the ability to synchronize their circadian systems with environmental time cues and therefore postpone their sleep phase (57). When there are no obligations to follow a normal schedule, patients have a sleep period of normal quality and duration, awake spontaneously, and keep a regular 24-h pattern of delayed sleep. The prevalence in the general population is unknown but could affect 5–10% of patients complaining of insomnia in sleep clinics (58). The onset of DSPS usually happens in adolescence (59); nevertheless, it can occur in children but is rare in adults over the age of 30. Complications such as absenteeism, chronic tardiness, or judgments by others (of laziness, for example) may occur at school, work, or in social activities. Chronotherapy, consisting in a supplementary sleep onset delay of 3 h a day until the desired time for sleep is reached, may help if the patient keeps a stable routine afterward. Phototherapy advances sleep time by the exposition in the morning to a 2500 lux light (60). Melatonine and vitamin B12 have also suggested interesting results in the treatment of DSPS (61, 62).

Advance Sleep-Phase Syndrome

Contrary to DSPS, advance sleep-phase syndrome is described by an advance of the sleep episode in comparison to the desired clock time. Complaints of terminal insomnia and inability to stay awake in the evening while having a sufficient amount of sleep may be reported. Sleep onset occurs typically between 6 p.m. and 8 p.m.; consequently, the last awakening happens between 1 a.m. and 3 a.m. An explanation of the disorder mentions a possible oversensitive phase advance capability or an altered ability of phase delay in the patient (55). This rare condition is theoretically most associated with elderly than other age groups. Negative consequences of advance sleep-phase disorder may be evening somnolence or sleep onset occurrence while attending social activities or driving. Chronic sleep deprivation and daytime sleepiness may also occur if obligations in the evening repeatedly postpone the sleep onset period. Preferred treatment options for advance sleep-phase syndrome are chronotherapy, timed bright light exposure in the evening, and hypnotics to maintain sleep until morning (55).

Non-24-h Sleep–Wake Syndrome

In individuals suffering from non-24-h sleep–wake syndrome, the sleep–wake rhythm has a 1- to 2-h delay in sleep onset and awakening each day despite the environmental and social cues. As a result, sleep onset and offset are progressively delayed, until at some point, the delay reaches 24 h and the sleep schedule returns to normal. Therefore, at times patients are “in phase” with the conventional social hours for sleep period, feeling alert and not complaining of sleeping difficulties. At other times, when there is a phase delay, patients complain of difficulties to fall asleep and to stay awake in the daytime. Consequently, scheduling activities or work becomes difficult and psychosocial functioning may be impaired. This rare disorder seems to be most prevalent in blind individuals (63). It is also seen, although less frequently,

in patients suffering from severe schizoid or avoidant personality disorder. Sometimes, behavioral intervention consisting of a strict sleep–wake schedule including strong social time cues may work. Hypnotic drugs do not seem to help but melatonin and vitamin B12 have shown some interesting effects in the treatment of the non-24-h sleep–wake syndrome (61, 64).

Conclusion

Sleep disorders are very prevalent in the general population. Although their presence may sometimes remain unnoticed for a fair period of time (e.g., apnea or PLMD), the repercussions on daily functioning are often noticeable, for the individual and his/her family and colleagues. Quality of life is so diminished and impaired in some sufferers that it translates in loss of work and even, at worst, family disintegration (e.g., divorce). The risk factors and the extent of side effects of sleep disorders are still understudied, and the routine use of questionnaires offering a closer look at the individual's global functioning are more than needed. Fortunately, research in sleep medicine is very active, and everyday, new and better treatments are developed and applied to relieve sufferers and consequently, offer better daily living.

Issues that need to be addressed by future research:

- Routine use of quality of life and global functioning questionnaires for diagnosis and treatment of sleep disorders.
- Additional epidemiological studies including risk factors.
- Consensus on questionnaires used in epidemiological studies.

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6
Sleep and Quality of Life in Insomnia

Damien Leger

Summary Purpose: Insomnia is highly prevalent in the general population, and most of the insomniacs complain of daily consequences the day following a poor night. However, it is very difficult to assess objectively this daytime impact. Quality of life (QOL) may be the most accurate way to understand the consequences of insomnia on the daily lives of patients. Subjects and Methods: Based on two keywords, insomnia and quality of life in Medline Pubmed, we reviewed articles on the subject from 1989 to 2006 and we retained those specifically focussed on QOL of insomniacs and some devoted to the impact of poor sleep on the QOL of subjects with other chronic illness. Results: We found very few studies focussed on the QOL of insomniacs. Many surveys were oriented on the QOL and sleep of patients with cancer or other chronic diseases. Conclusion: Insomnia is commonly linked to a worse quality of life status. QOL instruments may be powerful in showing the impact of poor sleep on the daily lives of patients by itself or during other associated chronic diseases. Specific QOL focussed on insomnia has to be developed to better assess the impact of insomnia on daytime functioning and to appreciate the efficacy of sleep treatments.

Keywords Insomnia · quality of life

Learning objectives:

- Quality of life is constantly impaired in chronic insomnia.
- The more severe the insomnia, the worse the quality of life.
- Sleep quality is a major issue in the quality of life of patients with chronic diseases.

Introduction

Insomnia is a complaint characterized by difficulty initiating or maintaining sleep, or non-restorative sleep, for at least 1 month with consequences on daytime functioning. These consequences are, however, difficult to define. The International Classification of Sleep disorders (ICSD) classification (1) only evoke "decrease functioning during wakefulness". The Diagnostic and statistical manual of mental disorders-4th edition (DSM-IV) (2) is more precise, "insomnia is serious enough to induce severe fatigue or signs attributable to insomnia and marked by symptoms such as irritability or disability in daytime functioning" or "is frequently accompanied by non-specific symptoms such as mood disorders, memory troubles, or lack of concentration." When clinicians or psychologists interview severe insomniacs, they often received very large witnesses about the impact of insomnia on domestic life, professional behavior, leisure and holidays, driving, social and familial relationship (3). However, there is no objective instruments to assess this impact. Quality of life (QOL) may be the way to better reflect the feeling of patients and to help sleep professionals in the objective evaluation of the impact of insomnia. QOL is a complex and multidimensional term that has been defined as "a concept encompassing a broad range of physical and psychological characteristics and limitations which describe an individual's ability to function and to derive satisfaction from doing so" (4). QOL has been widely studied in the last decades in evaluating the impact of chronic diseases. There are now confident instruments like the Sf36 (5) performed in many pathologies, and it is more easy than before to compare one group of patients to another one.

Recognition and Diagnosis of Insomnia

In terms of clinical practice and of epidemiology, chronic insomnia is usually defined based on the criteria of the DSM-IV (2) or of the ICSD (1) which are as follows:

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- A difficulty in falling asleep (sleep initiating insomnia), the occurrence of nocturnal awakenings with difficulties getting back to sleep (sleep maintenance insomnia), an early morning awakening (sleep offset insomnia), or a non-refreshing or non-restorative sleep, and often some of a combination thereof.
- At least three times a week for at least 1 month.
- Insomnia produces clinically significant distress or impairment in social, occupational, or other important areas of daytime functioning.

Insomnia may be primary or secondary to a variety of disorders, environmental factors and/or co-morbidities. Identifying and treating potential underlying conditions are priorities in the management of insomnia. Otherwise, insomnia will remain unresolved.

Primary Insomnia

Primary insomnia is an intrinsic sleep disorder that is characterized by the presence of insomnia that:

- Does not occur exclusively during the course of another sleep disorder: sleep disordered breathing, periodic limb movements, restless leg syndrome, or circadian rhythm disorder.
- Does not occur exclusively in the course of another mental disorder.
- Is not due to the direct physiological effect of a general medical condition, a substance or treatment, or a physical environmental factor.

A common mechanism of persistency of insomnia is conditioned (learned or psychophysiological) insomnia. It begins usually by an episode of acute situational insomnia, secondary to a stress, jet-lag, pain, illness, medication,... (insomnia precipitating factors). Then, the patient associates bed and non-sleeping and becomes hyperaroused at night and develops strategy of coping that perpetuates insomnia (insomnia perpetuating factors) (6). Individual differences in the vulnerability to sleep disturbances may constitute a continuum from vulnerability to transient or episodic insomnia through overt chronic primary insomnia (7). Ruminating about not being able to sleep plays a major role.

Secondary Insomnia

Insomnia is frequently associated with numerous other conditions: sleep disorders, mental or physical disorders, toxicological or environmental factors, and this is the role of the practitioner to carefully check all these conditions before considering insomnia as a primary disorder.

Almost all other sleep disorders are disturbing sleep seriously enough to induce a complaint of insomnia or poor sleep. Sleep apnea affects 5–10% of the general population. It increases with age and with the body mass index (BMI). It causes arousals and awakenings during all stages of sleep. Patients usually complain of non-restorative sleep rather than of real insomnia. Restless leg syndrome may affect sleep initiating and sleep maintaining, it concerns between 5–10% of the general population and may be associated to apnea. Circadian rhythms disorders are linked to a dysfunction of the biological clock due to an internal condition (delayed or advanced phase syndromes) or secondary to the under-exposure of the retina to light (blind people) or misalignement between external and endogenous rhythms (shift workers and jet-lag). They may induce sleep onset insomnia, early morning awakening, frequent arousals, and daytime sleepiness.

Mental disorders or co-morbidities are commonly associated with insomnia. In a survey made in the general population, it was found that prior consultations for anxiety symptoms were reported by 30.1% of the insomniacs and prior consultations for depression by 23% (8). Similarly in primary care patients with severe insomnia, a high prevalence of psychiatric diagnoses was found: 21.7% of severe insomniacs had depression, 7.2% neurosis/personality disorders, 10.2% acute psychological distress, 4.6% alcohol or drug abuse, 5.6% psychosomatic disorders, and 1% psychosis (9).

A variety of medical disorders may impact on sleep and awaken patients: central nervous system disorders, cardiorespiratory troubles, musculoskeletal disorders, and pain. Studies of specific populations reveal strong correlation between pain and complaints of sleep disturbances (10). Several endocrine and gastrointestinal disorders are also associated with sleep disruption, for example, nocturnal gastrointestinal reflux episodes may arise during sleep and induce abrupt arousals (11). A large number of medications and toxics (alcohol and drugs) also have an impact of sleep continuity.

Environmental factors may also induce sleep disruption and fragmentation even in good sleepers. Noise is one of the most common. Recently, the WHO office of environment and health has considered insomnia as one of the major health effects of noise exposure (12). Low or high temperature, altitude, and light also have an influence on sleep continuity.

Transient or Chronic

The duration of a patient's complaint has important implications. The ICSD defines acute or transient insomnia as persisting for no longer than 1 week and sub-acute or short term insomnia as lasting from 1 week to 3 months (1). Both are considered as adjustment sleep disorders, which are associated with a reaction to an identifiable stressor. Transient insomnia usually disappears with the reduction or the adaptation to the stressor. However, it may also be the foundation of a long-term condition. The individual's emotional and behavioral response to the first episodes of transient insomnia seems to play an important role in the course of the disease (6, 7, 13). Therefore, early identification and management of

insomnia may play a role in the prevention of long-term insomnia. Insomnia is considered as chronic if it lasts for more than 1–3 months (1, 2). In our experience, we believe that 1 month is a reasonable period to begin to talk of "chronic insomnia." Retrospective studies indicate that about 80% of severe insomniacs have had the problem for longer than 1 year with approximately 40% reporting longer than 5-year duration (8, 14). Longitudinal studies suggest that 30–80% of moderate to severe insomniacs show no significant remission over time (14, 15).

Severity

There is no clear consensus on the definition of severe insomnia. It seems insufficient to find it on the witnesses of patients. Many studies have observed that a large number of the so-called severe insomniacs did not consult any practitioner for years about their sleep problem. Chronic duration or nightly frequency may be criteria of severity. The magnitude of the impaired daytime functioning is also a good argument to assess severe insomnia. In several studies focussed on the daytime consequences of insomnia, we have considered severe insomniacs as subjects reporting at least two symptoms of poor sleep according to the DSM-IV definition of insomnia (3, 15).

Epidemiology

Many studies in the past decade have used the clinical criteria of insomnia to assess the prevalence of insomnia in the general population and in some subgroups of adults (8, 16, 17).They found a median prevalence for all insomnia of about 15% with a range of 10–25%. Prevalence increases with age, and insomnia is usually more common in women than in men. These studies, with few exceptions, do not attempt to identify etiologies of insomnia.

Method of Research

The selection of data began with a Medline PubMed search for articles published from 1990 to the present. Using keywords "Insomnia" and "Quality of life," we obtained 185 articles. Based on abstract content, we selected the 117 more relevant and up-to-date studies. We eliminated articles relating therapeutic trials in non-insomniacs patients. We also discarded non-original studies on insomnia (review articles).

There were very few articles specifically designed to assess the impact of insomnia on QOL. Most of the articles were devoted to the impact of sleep disorders on the quality of life of patients suffering from cancer. Some were exploring QOL in relation to sleep in diabetes, depression, Parkinson, chronic renal diseases with hemodialysis, patients with HIV, or chronic psychiatric diseases. QOL is also sometimes used to evaluate pharmacological and non-pharmacological treatments of insomnia.

Results

Using Quality of Life in the Assessment of the Daytime Consequences of Insomnia

The World Health Consensus report on sleep and health heavily recommends more studies on the QOL of insomniacs (4). Surprisingly, we found relatively few works specifically devoted to the subject (18–22). Four of them used the Short Form-36 (SF-36) (18, 19, 21, 22), a very widely used scale in QOL (23).

- The SF-36 was first used in insomnia in a survey designed to document the prevalence of insomnia and its impact on QOL (17). They showed that individuals with insomnia reported lower QOL scores. This association remained significant after controlling for demographic variables and comorbid conditions.
- Zamitt et al. (22) used several instruments to evaluate the impact of insomnia on QOL in a sample of 261 insomniacs compared to a control group of 101 good sleepers. Insomniacs were recruited by advertisements and fulfilled the DSM criteria for insomnia. Individuals with criteria of irregular sleep patterns, sleep apnea, restless leg syndrome, periodic limb movement disorders, history of psychiatric illness, alcohol or substance abuse, epilepsy, and HIV positive were excluded from the study. They used the SF-36 and the QOL inventory, a 31-item questionnaire specifically designed for the study and including aspects related to sleep, cognitive function, daytime performance, social and family relationships, and health. The authors showed a significant difference between the two groups ($p < 0.0001$, MANOVA) on all eight SF-36 subscales. Insomniacs reported more health concerns that limit physical activity, greater interference by physical or emotional problems with normal social activities, more bodily pain, poorer general health, less vitality, more emotional difficulties, and more mental health problems than the good sleepers' group. Using the QOL inventory, they also found a significant impact on the QOL of insomniacs. The authors suggested that the SF-36 can be used to assess differences between subject with insomnia and healthy controls and that the SF-36 may have clinical utility as a measure of impairment associated with insomnia.
- Leger et al. (3) so used the SF-36 to evaluate the quality of life of three matched groups of 240 severe insomniacs, 422 mild insomniacs and 391 good sleepers selected from the general population. They eliminated from the original group those with DSM-IV criteria for anxiety and depression. They found that severe insomniacs had lower scores in eight dimensions of the SF-36 than mild insomniacs and good sleepers. Mild insomniacs also had lower scores in the same eight dimensions than good sleepers. No dimension was more altered than the other. However, the mental health status and the emotional state were worse in severe and mild insomniacs than in good sleepers. This result demonstrates a clear interrelation between insomnia

and emotional state despite the fact that we had eliminated the subjects with DSM-IV criteria of anxiety. The authors concluded that SF-36 was sensitive to the severity of insomnia and seemed to be a reliable instrument to assess the impact of insomnia on QOL.

- Shubert et al. (5) have found the same kind of relationship between the severity of insomnia and the decreased quality of life in a group of 2800 elderly (aged from 53 to 97 years). It was a telephone interview, part of a 5-year follow-up examination of the Epidemiology of Hearing Loss Study. Participants were asked about symptoms of poor sleep. A response of "often" or "almost always" was coded as positive for an insomnia trait. The SF-36 was administrated to assess QOL of these subjects. Twenty six percent of the population reported one insomnia trait, 13% reported two, and 10% reported three. The eight domains of the SF-36 were significantly decreased as the number of insomnia traits increased. The authors concluded that insomnia is common among older adults and is associated with a decreased QOL.
- Idzikowski (18) discussed the concept of QOL applied to sleep and introduced the fact that short sleep is not necessarily deleterious but that abnormally shortened or fragmented sleep can reduce an individual's QOL. Smith and Shneerson (19) have used the SF-36 in a sample of 223 subjects explored for snoring or daytime somnolence. They showed that the SF-36 score is sensitive to sleep disruption.
- Katz and McHorney (24) finally demonstrated that insomnia acts by itself on the quality of life of patients suffering from chronic illness. Insomnia was severe in 16% and mild in 34% of these patients. Differences between patients with mild insomnia versus no insomnia showed small to medium decrements across SF-36 subscales ranging from 4.1 to 9.3 points (on a scale of 100) and for severe insomnia from 12.0 to 23.9 points. Insomnia appeared in this study as an independent factor of a worsened QOL to almost the same extent as chronic conditions such as congestive heart failure and clinical depression.

Poor Sleep Affect Quality of Life in Other Co-Morbid Patients

As it has been demonstrated in the previous study (24), there is a close relationship between insomnia and chronic illness, and it is therefore difficult to understand which is acting first on the QOL of patients. Leger et al. (20) found that the general health status was worse in severe and mild insomniacs than in good sleepers. However, they could conclude only that insomnia was related to a worse health status and not whether it was a cause or a consequence of the worse health status. One interesting finding of the study was illustrated by the relationship between insomnia and bodily pain. Bodily pain, caused by various illnesses, may also result in insomnia and poorer QOL; however, it is also possible that poor sleep increases the sensitivity of subjects to pain.

In patients suffering from cancer, the quality of sleep has been recognized as a powerful factor acting on the QOL (10). In a sample of 263 cancer patients undergoing chemotherapy, it was found that insomnia was negatively correlated to the QOL, probably by the way of depression. Insomnia explained only 4% of the variance of QOL and depression 47%. Stark et al. (25) also reported in 178 cancer subjects that insomnia was significantly and independently associated with a deficit of QOL. They recommended to interview the subjects with cancer about sleep to better discriminate subjects with anxiety. Lindley et al. (26) considered insomnia as a good reflect of QOL in the following adjuvant therapy for early-stage breast cancer.

In other chronic illness, several studies have shown that insomnia influences the QOL of patients, in Parkinson (27), in Hemodialysis patients (19) or in patients with anxiety and depression (28). In HIV disease, Nokes and Kendrew (29) also found that there was a correlation between sleep quality (assessed by the Pittsburgh Sleep Quality Index) and positive general well-being.

QOL in the Treatment of Insomnia

We found four studies evaluating the impact of treatments of insomnia on QOL. Goldenberg et al. (30) and Leger et al. (20) have shown the effect of Zopiclone in improving the quality of life of insomniacs explored by questionnaires (on professional, relational, sentimental, domestic, leisure, and safety aspects) that appear to be not significantly different from the good sleepers' one. Baca et al. (31) also showed that zolpidem improved patients QOL assessed by a questionnaire including four factors: social support, general satisfaction, physical and psychological well-being, and absence of work overload/free time. However, there is in our knowledge no extensive survey comparing the effects of several hypnotics with well-validated QOL instruments regarding non-pharmacologic. Quesnel et al. (32) have shown the efficacy of cognitive-behavioral therapy in insomnia in 10 women treated for non-metastatic breast cancer. They found an improvement of sleep assessed by polysomnography and at the global and cognitive subscales of the QLQ-C30.

Conclusion

Insomnia affects the daily lives of patients. However, it is often difficult to evaluate this impact and the efficacy of treatments on it. QOL seems to be a good means to better understand the complaints of insomniacs regarding their day to day functioning. Several studies have shown the sensitivity of the SF-326 in evaluating the impact of insomnia by itself or in relation with other associated chronic diseases. We also recommend the development of more accurate QOL tools specifically designed for insomnia.

Issues that need to be addressed by future research:

- Quality of life in sleep maintenance insomnia.
- Specific instruments are needed to assess impaired quality of life due to insomnia.
- There is a need for data regarding the effects of hypnotics on the quality of life of insomniacs.

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7
Effects of Hypnotics on Sleep and Quality of Life in Insomnia

Chris Alford and Sue Wilson

Summary This chapter provides an overview of the effects of hypnotics on sleep and quality of life (QOL). In the 1970s it was accepted that a consequence of taking longer acting benzodiazepine hypnotics was a residual hangover next day, producing feelings of sedation and impaired performance. The realization during the 1980s that insomnia was not just a subjective complaint of poor sleep, but in itself resulted in impaired functioning with increased accident risk, led to studies evaluating the effects of sleep medication on both sleep and waking function including QOL. The potentially impairing effects of hypnotic treatment therefore need to be weighed up against the costs and consequences of untreated insomnia. The emergence of the newer benzodiazepine receptor agonists (BzRAs) zopiclone, zolpidem and zaleplon (Z drugs) with their shorter half-lives and reduced levels of residual impairment, tolerance and dependency, particularly for zolpidem and zaleplon, shift the balance in favour of safer hypnotic treatment, so that insomnia should no longer go unrecognized and untreated in so many. Guidelines for limiting hypnotic prescriptions to a few weeks resulted from the association of long-term benzodiazepine use with tolerance and therefore lack of treatment benefit, as well as the associated risks of dependence occurring with some compounds. These guidelines are at odds with the significant number of chronic insomniacs, often elderly patients, who require long-term treatments. There is now limited evidence that newer formulations and different treatment schedules, including intermittent use, can sustain hypnotic efficacy with the Z drugs over longer periods, enhancing QOL and waking function, and without rebound insomnia following withdrawal. Similarly, behavioural and psychological approaches may be beneficial in the long term for some, though possible treatment limitations amongst different types of patients have still to be defined.

Keywords Benzodiazepines · residual effects · accidents · newer benzodiazepine receptor agonist (Z-drugs) · improved waking function · behavioural and psychological treatments

Learning objectives:

- Benzodiazepine hypnotics, particularly the longer acting ones, are associated with residual impairments of waking function next day.
- The elderly, in whom insomnia is more prevalent, are more vulnerable to the impairing effects of benzodiazepines and are at greater risk of accidents and falls as a result.
- Withdrawal of benzodiazepine and Z-drug hypnotics can produce rebound insomnia.
- Benzodiazepine use can be associated with dependency.
- Withdrawal from chronic benzodiazepine hypnotic use can be associated with improved waking function and quality of life.
- Behavioural and psychological treatments are useful for the treatment of chronic insomnia and withdrawal from long-term benzodiazepine use.
- The newer benzodiazepine receptor agonists or 'Z-drugs' have shorter half-lives and are associated with reduced residual effects, particularly zaleplon and zolpidem which are the shortest acting. However, they may not be so effective for sleep maintenance problems.
- Newer formulations of the Z-drugs (eszopiclone and zolpidem-MR) may be effective for both sleep initiation and maintenance problems, as well as having reduced residual effects.
- The Z-drugs are associated with improved waking function and quality of life in patients with insomnia.

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Introduction

Looking back over the last 30 years to when the authors first began in sleep research provides an interesting perspective with which to evaluate the use and effectiveness of hypnotics in the treatment of insomnia and their impact on quality of life (QOL). Whilst earlier studies dating from the 1950s had focussed on effects of these drugs on sleep, studies from the 1970s began to include assessment of residual effects next day (1).

Research from the beginning of this period included assessments of the then newer benzodiazepines, perhaps comparing them to the older barbiturates. Studies typically involved normally sleeping participants with sleep assessment largely based on subjective measures and a variety of daytime performance tests borrowed from the psychology laboratory to see whether the sedative drugs were still impairing performance next day (1–4). The view at this time was that residual impairment may be a necessary result of effective hypnotic treatment (2). Whilst benzodiazepines replaced the barbiturates for safety reasons, shorter acting benzodiazepines such as triazolam were then introduced in an attempt to limit the morning 'hangover'. Concerns over dependency, tolerance and the search for shorter acting drugs producing less or no residual impairments next day have resulted in the emergence of the 'Z' drugs also described as the newer benzodiazepine receptor agonists (BzRAs). The first was zopiclone, followed by zolpidem and then zaleplon, each with a shorter half-life. With zaleplon, a half-life of around 1 h means that this drug can be taken during the night, up to 4 h before waking, without detectable residual impairments (5, 6). This provides the opportunity for responsive treatment as required rather than prophylactic administration 'in case' of a bad night. We have also seen the arrival of the first 'non-scheduled' hypnotic in the USA, ramelteon, which is a melatonin receptor agonist for use in sleep onset insomnia, and developments continue with other GABAergic drugs which do not act through the benzodiazepine receptor such as gaboxadol (7) and tiagabine (8).

Has this evolution in hypnotic drugs met the needs of insomniacs and the needs of physicians treating their patients? If sleep can be improved has this solved any QOL problems that may ensue as a result of poor sleep? Recent publications indicate that the antidepressant trazodone is the most widely prescribed drug used for the treatment of insomnia in the USA and that hypnotic prescriptions have been falling over the last decade (9, 10). This evidence alone suggests that the needs of patients and physicians have not yet been met with the 'perfect' hypnotic as outlined by Bartholini nearly 20 years ago (11).

This chapter provides an overview of the current situation regarding hypnotic treatment for insomnia, focusing on health-related QOL aspects. A brief comparative review of selected papers that look at the effect of hypnotics on the sleep and waking performance in insomniacs is included. The final sections look at the treatment of insomnia with hypnotics and emerging alternative treatments, with a view to optimizing QOL.

Who are the Patients?

Whilst most studies of hypnotics have employed 'normal' male volunteers, as is frequently the case in central nervous system (CNS) drug development, insomniac patients complain of problems sleeping, or poor sleep quality and unrefreshing sleep, together with fatigue and tiredness and impaired functioning during the day. In fact, impairment of daytime function and impairment of related QOL aspects has been used to aid assessment of severity and the decision to treat this essentially 'subjective' complaint (12). Similarly, the majority of insomniacs are women (13–15) with the prevalence increasing with advancing age (16–18), with up to a quarter or a half of those aged 65 and older having insomnia (18–20) although normative data indicate a median sleep duration of 7 h in the elderly (21). It is also worth noting that the elderly are more affected by sleep maintenance problems whilst the young suffer more from sleep initiation difficulties (19) and this too has implications for hypnotic treatment. Regrettably, the focus of hypnotic studies has not been on the elderly or women rather than men. Epidemiological studies suggest that somewhere around 10–15% of the population have persistent or chronic insomnia (22–24). Figures for insomnia and related sleep problems often suggest higher figures of 30–40% (25–27) but may well reflect variability in the criteria used to assess this condition where even a chronic insomniac may not have problems sleeping every night. This lack of a standardized definition has had a negative impact when trying to compare studies of both pharmacological and non-pharmacological treatment approaches though standardized criteria have now been proposed and this should benefit future research (28, 29).

What we do know is that hypnotic use reflects the greater prevalence of insomnia in women rather than men and in older rather than young adults (19, 30–38). Frighetto et al. (17) reported that a third of patients, who were mostly in their eighth decade, admitted to hospital had received antidepressants or hypnotics prior to hospital admission in their Canadian study. Further, the elderly may have a greater need for long-term treatment and may well be more vulnerable to the impairing effects of sedative hypnotics drugs (16, 39, 40). Whilst clinical guidelines generally indicate limited periods for prescriptions (e.g. 2–4 weeks depending on the country), 14–35% of patients may have used them nightly over the previous year (41).

It is also important to recognize that nearly everyone will experience some sleep disturbance in the course of a year and some will continue to have sleeping difficulties for months or years afterwards. When we carried out a local survey of university employees with sleep problems, it indicated that

approximately half of these respondents had their problem for up to 6 months whilst the rest had a lasting problem, some up to 20 years. The Europe-wide SOFRES study found a median duration of 2–6 years (42). The long durations reported for insomnia led Epstein and Bootzin (43) to proclaim that these long suffering patients were 'in dire need of treatment'. This raises further questions of why should insomnia persist so long in those who develop chronic insomnia and are hypnotics of any use for long-term treatment?

Several authors have pointed out that patients, including the elderly, may not report their insomnia to their healthcare providers, and consequently the condition may not be recognized and will go untreated (18, 31, 44, 45). Sateia et al. (46) reported that between 30 and 80% of patients show no significant remission over time and that 70% of patients do not discuss their problem, a finding supported by Kageyama et al. (31), who suggested that 80% of Japanese insomniacs were untreated. Having witnessed the concern over benzodiazepine dependency in the 1980s, including public demonstrations in Europe, it was hardly surprising to see that hypnotic prescriptions fell from 1970 to 1989 reflecting these concerns and those of the prescribing physicians (47) although higher rates may be seen in some countries. Byles and colleagues report that in Australia half of their sample of older women with sleeping problems were receiving medication in the last month (30). These concerns and the resulting limitations imposed on treatment duration may partially explain why prescription hypnotics are not the most used or prescribed treatments for insomnia and why the antidepressant trazodone is the most widely prescribed 'hypnotic' in the USA (9) despite a relative lack of appropriate studies demonstrating efficacy (9, 10, 40). This in itself is remarkable given the sedative nature of this drug and its impairing effects on performance and impairment of sexual function (48, 49).

The association between insomnia and depression may in part help to account for the widespread use of trazodone although the use of sub-therapeutic doses of antidepressants as hypnotics may also result from the reluctance to use benzodiazepines long term although studies of their efficacy are more limited (10, 24, 40, 50–52). Thase (10) points out that ideally monotherapy would be used to treat both insomnia and depression, although at present no suitable drug exists. The close links between mental disorders such as anxiety and depression and insomnia emphasizes the need for appropriate treatment; half of patients with chronic insomnia have a primary psychiatric disorder such as anxiety or depression (10, 53). Insomnia has been considered as a possible prodromal phase for depression and although authors stop short of claiming that insomnia causes depression, the fact that untreated insomnia increases the likelihood of developing clinical depression is clearly established (54–57). Similarly, improvement in depression may parallel improvements in insomnia (10, 58–60) though this may reflect a negative cognitive bias associated with depression itself (61, 62). Subjective sleep improvement has also been linked to phase-shifts in sleep for these patients (63). However, these links should be considered when evaluating the effects of hypnotics on QOL and the relative merits of hypnotic treatment.

Before looking at the specific effects of hypnotics on relevant QOL aspects including mood and performance, it is useful to briefly consider the effects of insomnia itself on QOL, though fully described elsewhere in this volume, to provide a comparison. If hypnotics have negative effects, then is it worth using them or would it be better to leave insomnia untreated? Following on are the questions of whether all hypnotics are the same and how do they compare to other treatments?

What are the Costs and Consequences of Insomnia?

Whilst early studies of benzodiazepines focussed on their potential to improve sleep and possibly their effects on waking performance next day, there was a shift in research during the last decade recognizing the importance of health-related QOL and its relevance when considering insomnia and disturbed sleep (64, 65). The wake up call probably came in 1988 when Damien Leger published figures suggesting that of the US accident costs for 1988 ($50 billion) around a third may be sleep related (66). This helped to focus attention on the wider significance of sleep disorders as well as their treatment. There have been a range of estimates for the annual costs of insomnia including $14 billion direct costs and $80 billion for indirect costs (67, 68), and $30–35 billion by Chilcott and Shapiro (69) comprising direct costs (health care provision) and indirect costs such as absenteeism and accidents (70, 71). Consequently, there is now the realization that there is a critical duration of sleep needed to ensure health and safety (72, 73).

These figures alone show that it is important to treat insomnia as the cost to both patients and society will in turn affect QOL through reducing available resources. Further, the finding that falls in the elderly are related to insomnia and tiredness is important to bear in mind when considering the relative merits of hypnotic treatment (74). General costs and consequences include increased daytime sleepiness and fatigue leading to cognitive impairment and poor work performance and absenteeism in addition to increased accident risk including driving, increased risk of new or recurrent psychiatric disorder and increased substance use, poorer prognosis, increased healthcare-related financial burden and poorer social functioning at work and at home (10, 13, 22, 24, 55, 66, 68, 70, 75–77).

Apart from the more drastic consequences of insomnia with daytime sleepiness and fatigue resulting in impaired performance and accidents, recent research has indicated the role of sleep in memory consolidation (78), and this may partially explain the association of disturbed and insufficient sleep with poorer academic performance (79, 80). Recently, two groups

have shown a relative impairment in memory consolidation for insomniacs in comparison to normal sleepers (81, 82).

The 'SF-36' is perhaps the most well-known questionnaire-based QOL measure used in insomnia research though several exist including a specific 'quality of life in insomnia' (QOLI) scale (83). However, Buysse and colleagues recently described the use of the SF36 as 'essential' for insomnia research (28). The SF36 comprises eight dimensions: physical functioning, social functioning, role physical, role emotional, mental health, energy/fatigue, pain, general health perceptions. The authors were involved in evaluating the findings of the Europe-wide SOFRES study (42, 84), which indicated reductions for role physical, energy, vitality and mental health. These reductions fell outside the normal ranges established for the SF36 (85). These findings were supported by the significant reductions in emotional, social and physical domains found by Zammit et al. (86). Several studies have found reductions in QOL dimensions associated with insomnia, including greater reductions in SF36 with increased severity of insomnia for physical and social functioning, energy/vitality, mental health and general health perceptions (24, 87). This increased reduction in QOL with increased severity of sleep problems has also been observed for older women insomniacs (30), the patient group in whom insomnia is most prevalent. Research with other instruments has indicated increased functional impairment and healthcare costs in insomnia (88) and associated reductions in QOL (25, 45). A reduced QOL in the elderly with insomnia has also been reported (34, 36).

Taken together, these findings show that insomniacs are not just troubled by inadequate or un-refreshing sleep, with consequent feelings of tiredness and fatigue during the day, but that this in turn translates into significant health risks and costs, with poorer life performance affecting both work and home. Further, there is a significant financial burden attached as well as increased injury and mortality as a result of accidents. It is then remarkable that insomnia frequently goes unreported or untreated.

Do Hypnotics Improve Waking Function?

Given the above, there is a clear imperative to treat insomniac patients, whether they are primary insomniacs or whether their insomnia is related to another illness or associated with a mental health problem.

The earlier studies investigating benzodiazepines clearly established the residual effects associated with benzodiazepine use, particularly for the longer acting compounds or those with long-acting metabolites. Not only did the morning 'hangover' affect mood and subjective feelings of alertness but aspects of performance including speed of psychomotor response as well as memory were impaired (89–94). These findings, presented in numerous publications, together with concerns over dependency and tolerance associated with some chronic benzodiazepine usage and the realization that their continuous use did not improve the sleep of insomniacs and that withdrawal may itself produce insomnia and related adverse effects (95–103) led to the development of the newer benzodiazepine receptor agonists or BzRAs, zopiclone, zolpidem and zaleplon by the pharmaceutical industry (104–107). In comparison to the traditional benzodiazepines, these compounds are associated with a more natural sleep profile, e.g. without the reductions in slow wave sleep seen with benzodiazepines (50) and generally associated with a lower abuse potential and less residual effects, particularly zolpidem and zaleplon (23, 44, 108–111), leading to improvements in insomnia management (112).

Accidents and Car Driving

Laboratory performance assessments provide useful direct comparisons and models of every day life with which to compare a therapeutic class of compounds such as hypnotics. However, possible real life dangers associated with hypnotic consumption may be reflected in accident figures and driving assessment. Increased traffic accident risks have been associated with benzodiazepine use and an increased risk has also been found with zopiclone. Similarly, increased falls and associated injuries as well as increased traffic accidents have been linked to benzodiazepine use in the elderly (113–122).

The increasingly shorter half-lives for zopiclone (over 4 h), zolpidem (2 h) and zaleplon (1 h) have been reflected in their relative degree of residual impairment. The traditional benzodiazepines, particularly those with longer half-lives and longer acting metabolites are associated with greater impairment and sustained residual effects (23, 123–125). However, reviews also indicate that some of the shorter acting compounds are not associated with the same degree of impairment. For example, Puca et al. (126) reported improved sleep and QOL and no residual effects with triazolam given to shift-work syndrome patients.

The elderly are more vulnerable to the impairing effects of sedative drugs, particularly the longer acting ones, yet they receive more benzodiazepines and with more chronic use (35, 36–38, 39), and this is also reflected in falls and related injuries. Stein and Barrett-Connor (127) reported a reduction in QOL in the elderly associated with the use of medication including hypnotics that went beyond the impact of the comorbid illness. On the other hand, Ring (18) reviewed chronic insomnia in the elderly and noted that early recognition and treatment of insomnia would increase QOL, particularly as the condition is under-recognized in these patients.

When compared with the lower incidence of side effects in general for the Z-drugs and substantial lack of residual effects for zaleplon and zolpidem in particular, then a clear distinction can be made (23, 128–130). Recent reviews of driving studies have shown that both zaleplon and zolpidem lack residual effects when assessed with both simulated and on the road driving (131, 132). Given the clear association between insomnia, increased tiredness, sleep loss and driving

accidents (75, 77, 133), the lack of residual impairments in driving performance next day is an important indicator of the potential benefits of zaleplon and zolpidem on functional aspects of QOL.

The introduction of the newer BzRAs or Z-drugs has therefore provided something of a watershed in relation to pharmacotherapy for insomnia. The older benzodiazepines were frequently associated with residual impairments next day, which had a negative impact on QOL affecting waking mood, work performance and accident risks. The elderly in whom insomnia and benzodiazepine use is increased are most vulnerable here, with reduced hepatic clearance and other age-related impairments potentially exacerbating residual effects.

Studies of the effects of the Z-drugs on sleep, daytime alertness and performance, or related QOL aspects in insomniacs show that they are not associated with the degree of impairment seen with the benzodiazepines. Goldenberg et al. (134) reported significantly improved QOL in insomniacs after 2 weeks zopiclone in comparison to placebo. Leger, Quera-Salva and Philip (135) looked at both short- and long-term administration of zopiclone in insomniacs. Both sleep and QOL were improved at 8 weeks against placebo. No significant differences were found for patients who had been taking zopiclone for 12 months when compared to controls without sleep problems on nearly all QOL measures, suggesting that QOL can be normalized in insomniacs given appropriate hypnotics.

An investigation of eszopiclone, the (S)-isomer of racemic zopiclone, in elderly insomniacs revealed improved sleep, increased daytime alertness, physical well-being and other QOL variables, in addition to reduced napping (136). This contrasts with reductions in QOL found in insomniacs with increased daytime sleepiness and napping (25), demonstrating the ability of Z-drugs to promote a functional increase in daytime alertness when given to insomniacs. Soares et al. (137) found that eszopiclone improved both subjective sleep and QOL in women insomniacs. These brief examples demonstrate the ability of Z-drugs to both improve sleep and improve waking function when given to insomniac patients, including both short and long-term administration.

The results of systematic reviews of sleep, performance and related QOL measures with strict inclusion criteria, contrasting traditional benzodiazepines and the newer Z-drugs in carefully controlled patient trials have not been able to make firm conclusions due to the limited number of studies compared (138).

Studies of daytime function using psychomotor performance tests in healthy volunteers after hypnotic drug administration have been very useful in indicating behavioural toxicity, as seen above, and impairments have been seen after single doses of even short-acting agents. However, similar measures in insomniac patients have been less conclusive. Table 7.1 summarizes controlled studies of hypnotic drug effects on performance in patients. This includes some traditional benzodiazepines, the newer Z-drug hypnotics, as well as single examples for the GABA agonist tiagabine and melatonin agonist ramelteon. The studies in the table reflect the general findings from past research where the benzodiazepine flurazepam was deliberately chosen as a comparator for newer compounds as it is has the longest half-life (up to 250 h) and can serve as a positive control. Flurazepam reliably impairs performance next day whilst the Z-drugs or short-acting benzodiazepines may not although simulated driving performance was impaired by zopiclone as mentioned earlier. Whilst reliable deficits were seen with flurazepam other findings are less consistent than those in healthy volunteers. One explanation may be that these patients differ markedly from controls at baseline, in that they complain of fatigue, diminished motivation, cognitive dysfunction including reduced vigilance, memory and concentration, low mood and various physical complaints so that impairing effects of drugs may be less obvious. It may be that as these patients had been taking the treatment for some days or weeks, early impairment may have worn off by the time of testing.

Though limited in number, these studies endorse the conclusions made above that the newer Z-drugs are less impairing than older long-acting compounds, favouring their use over the older benzodiazepines with their related dependency, tolerance and withdrawal problems. To date, studies with the newer agonists tiagabine and ramelteon have been too few to draw specific conclusions.

Sleep Initiation and Maintenance

Given the variability in both the frequency of occurrence of disturbed sleep, as well as patient differences relating to problems in initiating sleep, maintaining sleep or waking early, it is important to consider which hypnotics are most suited to aiding sleep onset and which can also maintain sleep. With the benzodiazepines, longer acting compounds produced consistent residual impairment leading to the search for shorter acting but less impairing compounds on waking performance next day (139). This has been reflected in the development of the Z-drugs with even shorter half-lives. Whilst they produce less residual impairment, there is a trade-off resulting in reduced efficacy of the shorter acting zaleplon (1 h half-life) and zolpidem (2 h half-life) with regard to sleep maintenance. On the other hand, zopiclone (>4 h half-life) may produce significant waking impairment but is more appropriate for sleep maintenance problems (10, 40). The newer derivatives may be a response to this. Eszopiclone may promote sleep maintenance but with reduced potential for impairment, whereas modified release zolpidem (zolpidem-MR) may also increase sleep duration though studies are currently limited (136,140–142). The limitation of the shortest acting Z-drugs zaleplon and zolpidem in treating sleep maintenance problems is a potentially significant drawback to their use. It is also worth reflecting that more sleep onset insomnia

TABLE 7.1. Controlled studies of hypnotic drugs in insomnia.

Reference	Design	Patients	N	Drug	No. of nights	Improved sleep?	Test time (hours after dosing)	Tests	Performance results
175	DB II group	3/12 insomnia	30	Zopiclone 7.5 mg, flurazepam 30 mg, placebo	10	Y (subj)	11	DSST immediate and delayed, recall, movement	Flurazepam impaired movement
176	DB II group	Elderly insomniacs	36	Brotizolam 0.25 mg, flurazepam 30 mg	14	Y (subj)	12	DSST immediate and delayed, recall, movement	Both drugs impaired all. Impairment recovery proportional to half-life
177	Single-blind	Chronic insomnia (all had past hypnotics)	6	Placebo run-in, zolpidem 10 mg	14	Y	8.5	Memory, manual dexterity, maze, DSST	No impairment
178, 179	DB II group	Chronic insomnia, recruited by advertisement	107	Placebo run-in flurazepam 15 mg, 20 mg midazolam 15 mg	14	Y	9	DSST, vigilance, divided attention, mood	Flurazepam 20 mg impaired all, slight impairment with 15 mg, none with midazolam
180	DB PC II group	Insomnia, unable to sleep without medication	26	Zopiclone 7.5 mg or flurazepam 30 mg or placebo	35	Y	Not stated	CFF, CRT, digit span	CRT and digit span impaired by flurazepam
181	DB 5-way II group	Age 65+ DSMIIIR insomnia with TST < 5 hr and/or #w > 3 for 3 months	45	Temazepam 15 and 30 mg, triazolam 125 and 250 μg, placebo	Single dose	Not stated	12	Wechsler verbal memory tasks, DSST, trail-making, finger-tapping on mornings before and after dose night	Significant impairment word pair recall with high doses, significant improvement trail-making after low dose, high dose no change

TABLE 7.1. Continued

Reference	Design	Patients	N	Drug	No. of nights	Improved sleep?	Test time (hours after dosing)	Tests	Performance results
182	DB PC II group	3/12 insomnia	68	Zolpidem 10 mg and 15 mg, placebo	35	Y	Not stated	DSST	No effects (very little subjective effect, small objective effect on sleep)
134	DB PC II group	Recruited through market research organization, TST < 6 h, SOL > 30 min	231/227	Zopiclone 7.5 mg, placebo	14	Y	NA	QOL, subjective sleep	QOL improved both groups, significantly more in zopiclone group, in daily activities, social and professional subscales
183	DB PC CO	Primary insomnia (very similar to DSM IV criteria)	23 F	Zolpidem 10 mg, temazepam 20 mg, placebo at 02.00	30	Not stated	5.5	Driving simulator 07.30 followed by immediate recall memory test	No sig diffs although a few individual subjects' driving affected badly by both drugs—may be especially vulnerable people? No effect on memory tests
184	DB PC II group	DSM-IV primary insomnia, TST < 7h, SOL > 20 min	308	Eszopiclone 2, 3 mg, placebo	44	Y (3 mg)	1–1.5 h after wakening	DSST	No sig effect
132	DB PC 4-way CO	DSM-IV primary insomnia, recruited by advertisement	23	Zolpidem 10 mg, zopiclone 7.5 mg, lormetazepam 1 mg, placebo	7	Y	2 h after waking	Driving simulation	Lormetazepam-impaired speed deviation and speed limit deviation. Zopiclone increased number of collisions
8	DB PC CO	DSM-IV primary insomnia, recruited by advertisement	232	Tiagabine 4, 8, 12, 16 mg, placebo	2	N	About an hour after waking	DSST and Rey auditory learning test	DSST impaired by 8 and 16 mg
185	DB PC CO	Treatment seeking plus advertisement	107	Ramelteon 4, 8, 16, 32 mg, placebo	26	Y	Not stated	DSST, word-list immediate and delayed recall	No effects

#w, number of awakenings; CFF, critical flicker fusion frequency; CO, crossover; CRT, choice reaction time; DB, double blind; DSST, digit symbol substitution test; II group, parallel group; PC, placebo controlled; RT, reaction time; SOL, sleep onset latency; TST, total sleep time.

is seen in younger insomniacs whilst sleep maintenance problems are more prevalent in the elderly who in turn are more vulnerable to the effects of impairing drugs (19).

Treatment Regimens

Concerns over dependency and loss of efficacy after continuous treatment with benzodiazepines led regulatory authorities to impose clinical guidelines limiting prescriptions. Given the epidemiological data indicating that 10–15% of the population suffer from chronic insomnia and the need of some, including elderly patients for prolonged treatment, treatment guidelines are clearly at odds with patient needs. The development of the newer BzRAs, with a more favourable side effects profile, including reduced dependency potential for some compounds, suggests that guidelines predicated on the benzodiazepines may now be out of date and that longer treatment periods should be considered (14, 24, 143). Sadly, the duration of most controlled studies is relatively short, one meta analysis found a median treatment duration of just 7 days, whereas chronic insomniac patients sometimes use hypnotics for months to years (144, 145). Although few in number, some longer term treatment studies have been undertaken. Patient studies with zolpidem have revealed overall improvements (146–149). In a 17-week study of zopiclone, Fleming, Bourgouin and Hamilton (150) failed to find evidence of tolerance, whereas a study of eszopiclone in chronic insomniacs (141) revealed both sustained sleep improvements as well increased alertness and functioning during the day, but without adverse side effects or tolerance over the 6-month study period. A 12-month extension of the study showed comparable efficacy and safety (151). A shorter 5-week assessment of zaleplon (152) found that sleep latency was reduced across treatment weeks, although consistent increases in total sleep time were not seen. There was no evidence of tolerance or rebound insomnia seen on initial withdrawal.

Intermittent treatment has also shown promising results. Intermittent treatment with the benzodiazepine triazolam found reduced self-administration when compared to nightly or as needed treatment regimens (153). Although an 8-week comparison of zolpidem against placebo found improved sleep but failed to reveal significant differences for QOL, a multi-centre 2-week comparison of nightly against 5 out of 7 nights dosing revealed marked QOL improvements in both chronic insomniac treatment groups (154, 155). A more recent review of six patient studies with intermittent zolpidem administration found that sleep improved without adverse effects and hypnotic consumption was not increased. Some studies recorded improvements in QOL measures (44). Studies with zaleplon have indicated the lack of impairment next day with zaleplon when administered during the night, and this might also offer a new treatment regimen where patients can use the drug not only intermittently but on a symptomatic rather than prophylactic basis, waiting to see whether they can fall asleep naturally before taking a hypnotic (5, 6, 23).

Taken together, these studies of long-term and intermittent treatment regimens with the newer BZRAs or Z-drugs suggest that not only can the sleep of chronic insomniacs be improved for sustained periods but waking function and related QOL measures may also be improved. The lack of evidence for dependency or tolerance in these studies implies clinical guidelines might be updated supporting longer administration with associated benefits in QOL. This would help meet the needs of patients who require long-term treatment (10, 40).

Other Treatments for Insomnia

Prescription hypnotics are in a minority when compared to the range of treatments used by insomniacs. The widespread use of trazodone and antidepressants as 'hypnotics' has been mentioned. Other popular pharmacologically based treatments include over-the-counter (OTC) antihistamines, herbal remedies, L-tryptophan, melatonin and aromatherapy (9, 10, 40, 108) although alcohol is also popularly self-administered in the West despite cost, tolerance and toxicity (156). There are also a wide variety of other methods employed including psychological and behavioural therapies, bright light and relaxation therapy as examples. Whilst a fuller evaluation of these cannot be included here, a brief mention is appropriate.

There is limited evidence that OTC antihistamines work although recently some benefits have been reported for diphenhydramine (157). More profound effects on sleep have been reported for both promethazine and hydroxyzine although neither are available as OTC hypnotics (158–160). A recent review of melatonin shows promise for its use for circadian and sleep-phase disorders including shift work (161) although evidence for its use in insomnia is less positive (162).

Several herbal remedies have been investigated, and interest in these compounds is growing though published studies are few (163). Valerian or valerian and hops are popular in some herbal OTC remedies but findings are varied with Morin et al. (157) observing benefits in mild insomnia with valerian and hops whilst Diaper and Hindmarch (164) failed to find significant effect on sleep and performance with valerian alone. A recent review of 16 studies suggested that valerian might improve sleep quality without concomitant side effects (165). Similarly, there is some evidence emerging that aromatherapy may be useful, for example a study by Goel et al. (166) found that lavender not only improved sleep but also increased slow wave sleep which may be of particular benefit to the elderly whose slow wave sleep is reduced. Lewith et al. (167) have found that lavender oil reduced mild insomnia, and Komori et al. (168) found mixed fragrance assisted withdrawal from long-term benzodiazepine use in insomniacs.

Whilst more controlled studies are required for these alternative or complementary remedies, if efficacious, they may offer some advantages. Unlike many prescription medications, they may have reduced side effects and residual impairments next day. This is of particular importance for the elderly who may require longer treatment and who frequently suffer from other illnesses that may require medicines. Therapies that are free from adverse side effects, and possible drug interactions, may be of particular benefit and significantly improve not only sleep but resulting QOL.

Cognitive and behavioural therapies (CBT) are worth particular mention as there benefits are being increasingly recognized although they may not be suitable for all insomniac patients (10, 40). The negative effects of long-term benzodiazepine treatment, particularly in the elderly, has been outlined. Withdrawing patients can therefore provide benefits. In a study of elderly long-term benzodiazepine users in whom over 60% had continuously used their hypnotics for over 10 years, 80% were successfully withdrawn from their treatment at 6 months after tapering their dose. The withdrawers showed improved waking performance in comparison to the continuers but showed little by way of sleep differences or withdrawal problems (95).

Studies using CBT have also been successful in helping withdraw long-term benzodiazepine users from treatment and in maintaining improved sleep. Dixon, Morgan and colleagues noted decreased QOL at baseline in long-term hypnotic users, although the decrement reduced with advancing age (169, 170). At 3 and 6 months, sleep and QOL were improved, with sleep improvements and reduced hypnotic use maintained at 12 months follow-up. Reviews by Morin and colleagues have emphasized the reliable and durable effects that can result from behavioural treatments (171, 172), with Epstein and Bootzin (43) emphasizing that non-pharmacological treatments can make a substantial contribution to QOL for insomniacs. Authors have pointed out that the psychological and behavioural treatment approach takes time, as well as significant resources which may balance over long-term treatment, so that efficacy is delayed in comparison to drugs that may be more appropriate for short-term treatments. Further, not all patients may be suitable for CBT approaches, Morgan and colleagues found that patients with higher levels of distress at onset had poorer outcomes (10, 16, 40, 170, 173). Similarly, McCrae et al. (174) found that sleep hygiene practices did not differ between good and poor elderly sleepers suggesting this approach may have limitations in the elderly.

Conclusion

The current interest in medicinal treatments and QOL reflects developments in psychopharmacology. Where as past treatments were focussed on reducing deficits, present research looks more toward optimizing function and even enhancing performance. Thirty years ago, it may have been sufficient to treat disturbed sleep and insomnia with a sedative hypnotic compound and accept residual impairments next day as a consequence of improving sleep. Newer hypnotic compounds including the Z-drugs provide us with important treatment options when weighing up the cost benefit ratio for a particular patient. We know that prolonged and untreated insomnia is associated with impaired QOL as well as substantial costs to society as a result of direct health costs and indirect costs through accidents and absenteeism. Although the shortest acting of the Z-drugs may not be suitable for treating sleep maintenance problems, they show significantly reduced side effects and residual impairments, with improved QOL, and should be promoted over the older benzodiazepines as appropriate drug treatments for insomnia (113). The emerging hypnotics and newer formulations for the Z-drugs (eszopiclone and zolpidem-MR) hold promise for treating both sleep onset and sleep maintenance problems without compromising QOL, and prolonged treatment may now be acceptable.

Where possible, long-term drug treatment for insomnia should be avoided, with cognitive and behavioural therapies providing useful alternatives and aiding withdrawal from long-term benzodiazepine use resulting in improved sleep and QOL. However, the range of application and possible treatment limitations of these treatment approaches needs to be further explored. Similarly, studies of alternative and complementary therapies need progressing to establish the efficacy and range of application for treatments such as herbals and aromatherapy.

With the current range of hypnotic treatments, there is no longer an excuse for insomnia to go unreported and unrecognized and untreated in so many patients including the elderly. Further, shorter-term insomnia should be treated to help prevent the transition to chronic insomnia with its associated marked impairments in quality of life.

Issues that need to be addressed by future research:

- Further studies are required to assess the impact of long-term administration of the Z-drug hypnotics on sleep and waking function in chronic insomniacs, including the elderly.
- The range of patients and types of insomniacs that are effectively treated with behavioural and psychological therapies needs to be established.
- The effectiveness of alternative therapies including aromatherapy and herbal remedies needs to be established but may provide useful alternatives to prescribed hypnotics.

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8
Melatonin and Quality of Life

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Summary There is substantial evidence that fragmented sleep, delayed sleep phase syndrome (DSPS), insomnia, and impaired daytime alertness are the result of disorders in brain functioning that are closely linked to disruptions in the regulation of circadian rhythms. In children suffering from neurodevelopmental disabilities, such as attention deficit hyperactivity disorder (ADHD) and epilepsy, sleep disturbance and behavioral problems are significant correlated symptoms. There is also evidence that by addressing these problems directly, significant improvements can be made in the quality of life (QOL) experienced by the affected individuals. Children with ADHD exhibit impairments in the circadian pacemaker as shown by studies confirming an associated delay in the peak melatonin output under dim light conditions. Therapy involving melatonin administration to these children not only improves their sleep onset and efficiency but also improves their health status and QOL. The QOL of young adults who suffer from DSPS is significantly impaired by the resulting symptoms of insomnia and tiredness. Treatment of DSPS patients with melatonin has been reported to improve QOL dimensions such as physical functioning, mental health, and emotional well-being, as well as social functioning and general health. In patients suffering from chronic fatigue syndrome, melatonin improved QOL by enhancing vitality and energy and by reducing pain perception and fatigue. Melatonin has also been demonstrated to improve the quality of sleep of elderly insomniacs. Strategically timed administration of melatonin is useful for reducing the symptoms of jet-lag in intercontinental travelers. Additionally, melatonin has been found to enhance the nighttime alertness of shift workers and to improve their sleep during the daytime. Melatonin has a promising role in cancer patients not only as an oncostatic drug but also in promoting their general physical health and well-being. Meditation, besides improving QOL, coincidentally enhances the secretion of melatonin from the pineal gland, thus suggesting that melatonin may be an important physical mediator of the meditation experience.

Keywords Melatonin · attention deficit hyperactivity disorder · chronic fatigue syndrome · epilepsy · jet-lag · shift work · quality of life · cancer · meditation

Learning objectives:

- To understand how melatonin is linked to quality of life in normal physiology.
- To examine the association of melatonin dysregulation to various medical and mental disorders.
- To assess the potential application of melatonin to improve quality of life in various clinical conditions.

Introduction

Technological advancements such as rapid forms of transportation and the use of a 24-h lighting system have not only increased day to day comfort but have also created a number of health problems for modern man. For example, physical activity no longer needs to coincide with daylight hours and extends to the whole 24-h period (i.e. the "24-hour/7 days Society"). From an evolutionary perspective, this is an abrupt "environmental mutation." In such conditions, the brain loses its capability to sense internal and external rhythms, as reflected by the increased incidence of sleep/wake cycle disorders. As a result, people around the world often suffer from sleep problems, tension, and anxiety and mood disorders.

The technological impact of modern life has increased mean life expectancy, which in turn has increased the size of the elderly population (over the age of 60). The increased number of elderly persons has also resulted in increased incidence of persons suffering from chronic insomnia, age-related

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neurodegenerative disorders, such as Alzheimer's disease (AD) or Parkinsonism, cancer, and cardiovascular disease (1–4). There is thus an urgent need to develop therapeutic agents that improve the quality of life (QOL) not only in young individuals who are forced to work both night and day or who undertake rapid travel across different time zones, but also in elderly persons who suffer from sleep disturbances, neurodegenerative disorders, or cancer. Inasmuch as melatonin is a neurohormone that is critically involved in the regulation of sleep and circadian rhythms generally, it has been suggested that this biological agent can make a significant contribution to public health (5–11).

In recent years, it has been increasingly recognized that children with neurodevelopmental disorders such as attention deficit hyperactivity disorder (ADHD) and epilepsy also suffer from behavioral problems and sleep disorders and that these difficulties may be due to disruptions in circadian rhythms. Several clinical studies have now shown that melatonin significantly improves the QOL in those children (12–18).

Melatonin Biosynthesis and its Regulation

Melatonin is primarily secreted by the pineal gland of all mammals, including humans. In addition, melatonin synthesis occurs in other organs and tissues such as the eye (19), the gastrointestinal tract (20), lymphocytes (21), and skin (22). Melatonin biosynthesis starts by the conversion of tryptophan to 5-hydroxytryptophan and then to 5-hydroxytryptamine (5-HT, serotonin). 5-HT is acetylated to form *N*-acetylserotonin by the rate-limiting enzyme aryl alkylamine *N*-acetyltransferase. *N*-acetylserotonin is then converted into melatonin by the enzyme hydroxyindole-*O*-methyl transferase (HIOMT) (23).

Pineal melatonin synthesis has a circadian rhythm with a peak synthesis occurring during the night and followed by lower output levels during the day. This circadian rhythm in the secretion of pineal melatonin is generated by the central circadian pacemaker located in the suprachiasmatic nuclei (SCN) of the hypothalamus and is synchronized to a 24-h day–night cycle by environmental light acting through the retinohypothalamic tract (24). Special retinal ganglion cells containing melanopsin are involved as the photoreceptive elements in this pathway (25).

The melatonin rhythm normally develops in humans during the third to fourth month of life and reaches its highest amplitude at around 4–7 years of age (26, 27). Inasmuch as elderly individuals have lower melatonin levels than young individuals, the decline in melatonin production during old age may be a primary reason for the associated decline in sleep quality and changes of sleep/wake rhythm. Additionally, as evidence cited below suggests, reduced melatonin output may possibly be a contributing factor to the increased incidence of neurodegenerative diseases seen in the elderly (9, 28).

Circulating melatonin is metabolized mainly in the liver where it is first hydroxylated in the C6 position by cytochrome P_{450} monooxygenases (isoenzymes CYP1A2, and CYP1A1) and thereafter conjugated with sulfate to be excreted as 6-sulfatoxymelatonin (aMT6s) (29). Its clearance from the peripheral circulation is biphasic with half lives of about 3 and 45 min (30). Melatonin is also metabolized non-enzymatically in many cells and also extracellularly by free radicals and by few oxidants. For example, through this pathway, it is converted into cyclic 3-hydroxymelatonin by a direct scavenging of two hydroxyl radicals (24). In addition, melatonin is metabolized in the brain to form N^1-acetyl-N^2-formyl-5-methoxykynuramine (AFMK) and N^1-acetyl-5-methoxykynuramine (AMK) (25), two compounds with important antoxidant properties (29).

Melatonin Receptors

Inasmuch as melatonin easily diffuses through biological membranes, it can influence processes in almost every cell in the body. Some of its effects are receptor-mediated while others are receptor-independent. Melatonin is involved in various physiological functions such as sleep propensity (31, 32), control of sleep/wake rhythm (33), blood pressure regulation (34, 35), immune function (36–38), circadian rhythm regulation (6, 39), retinal functions (19, 40), detoxification of free radicals (29, 41), control of tumor growth (42, 43), bone protection (44), and the regulation of bicarbonate secretion in the gastrointestinal tract (20).

Melatonin action involves interaction with specific receptors in the cell membrane (45), with nuclear receptors (46) and with intracellular proteins such as calmodulin (47), dihydronicotinamide riboside : quinone reductase 2 (48), or tubulin-associated proteins (49). In addition, melatonin is a potent antioxidant acting as a free radical scavenger as well as thorugh induction of antioxidant enzymes, down-regulation of pro-oxidant enzymes, or stabilization of mitochondrial membranes (29, 41, 50).

Several major actions of melatonin are mediated by the membrane receptors MT_1 and MT_2 (45). They belong to the superfamily of G-protein-coupled receptors containing the typical seven transmembrane domains. These receptors are responsible for chronobiological effects at the SCN, the circadian pacemaker. MT_2 mainly acts by inducing phase shifts and MT_1 by suppressing neuronal firing activity in the SCN. MT_1 and MT_2 are also expressed in peripheral organs and cells and contribute, for example to several immunological actions or to vasomotor control (45).

A third binding site, initially described as MT_3, has now been characterized as the enzyme quinone reductase 2 (51). Quinone reductases participate in the protection against oxidative stress by preventing electron transfer reactions of quinones (52). Melatonin also binds to nuclear receptors of the retinoic acid receptor family, RORα1, RORα2, and RZRβ

(46). RORα1 and RORα2 seem to be involved in some aspects of immune modulation, whereas RZRβ is expressed in the central nervous system, including the pineal gland. Direct inhibition of the mitochondrial permeability transition pore by melatonin (53) indicates that another mitochondrial binding site is involved.

Melatonin and Age-Associated Sleep Disorders in the Elderly

Sleep disturbances are common complaints among the elderly. It has been estimated that nearly 40–70% of older people suffer from an inability to fall asleep, frequent nocturnal awakenings, and/or early awakenings (54). Persistent insomnia is estimated to occur in 10–25% of the elderly (55). As a result of this, elderly individuals suffer from deterioration of general physical health, which in turn is associated with decline in mental health. This leads to poor cognitive, psychological, and social functioning, and thereby results in a reduced QOL (56).

That the core problem in all of these difficulties may be the reduction in melatonin output that occurs in advancing age has been suggested by an investigation of the correlation between sleep disturbance and urinary aMT6s concentrations. In a study undertaken on 517 subjects aged 55 years and above, a significant reduction was found in the excretion of aMT6s in the urine of insomniac patients (9.0 μg of aMT6s excreted per night as compared to 18 μg in normal subjects of the same age group, 57).

Disturbed sleep, poor sleep quality, and trouble in falling asleep were all reported in postmenopausal women, the sleep complaints being associated with low mood (58). Abnormal melatonin secretion in postmenopausal women reporting sleep complaints has been described (59), and a diminished nighttime melatonin secretion was suggested as a cause for the deterioration in sleep maintenance in elderly females (60). Moreover, low-melatonin levels have been linked to bone loss (a major problem in perimenopausal women) at least in experimental animals (44).

These findings have been a major impetus to efforts for using melatonin to improve QOL in elderly insomniacs (7,61, 62). In most studies, early nighttime administration of melatonin, in doses ranging from 0.3 to 5.0 mg, was found to improve both the subjective and objective sleep parameters of sleep quality in patients suffering from insomnia (33, 63, 64). Melatonin in doses of 3 mg administered for a period of 6 months to insomnia patients as an add-on to a hypnotic (benzodiazepine) not only improved sleep quality, duration, and sleep latency but also significantly enhanced day time functioning, thus supporting the conclusion that melatonin improves physical well-being and hence the QOL (61). It is significant that even physiological doses of melatonin (0.3 mg) that raised the plasma melatonin levels to the normal range (60–200 pg/ml) improved sleep in subjects suffering from age-related insomnia (65). Collectively, these studies support the conclusion that melatonin is of significant value for the treatment of age-associated sleep disorders.

Melatonin Use and QOL in Children with Neurological Disabilities

The critical importance of exogenous melatonin treatment for children suffering from neurological disabilities such as ADHD, Smith–Magenis syndrome, epilepsy, and other pediatric disorders has become increasingly recognized inasmuch as these disorders cause not only sleep disturbances but also a number of behavioral problems resulting in impairments in cognitive and social skills. Children with ADHD have a delayed endogenous pacemaker as manifested by a delay in sleep onset, in dim light melatonin onset (DLMO), and in the time of awakening (12, 14, 16, 18). In several studies, the administration of melatonin was found to reduce sleep onset latency and to improve overall sleep quality, thus resulting in an enhancement of health status and QOL (14, 16, 66, 67). In one study (14), FS-II questionnaire and RAND-GHRI scales (scales that measure general functional, physical, physiological and social behaviors, and illness-specific scores) were administered to 79 children who were suffering from chronic sleep onset insomnia. Four weeks of melatonin treatment (5 mg/day) was effective in reducing sleep disturbances and improving the health status of the affected children when compared to placebo (14).

The mechanisms by which melatonin improves health status in children with ADHD are not completely understood. Although exogenous melatonin therapy was found to normalize the delays in the sleep–wake rhythm often seen in ADHD, with a resulting enhancement of the children's overall health status, in one study improvements in sleep quality following melatonin administration were associated with very few effects on QOL in ADHD children (68).

In epileptic children, many cognitive and social skills are affected. As antiepileptic drugs have been shown to affect the QOL due to their important side effects, melatonin was tried as an adjuvant to improve QOL in epileptic children subjected to valproate monotherapy (15). A questionnaire assessing the physical function, emotional well-being, cognitive function, social function, behavior, and general health was administered to those children. Significant improvements in QOL with melatonin use were seen in these children when compared to those receiving placebo (15).

Melatonin and QOL in Patients with Delayed Sleep Onset and Related Disorders

Delayed sleep phase syndrome (DSPS) is defined as the persistent inability to fall asleep at conventional bedtimes and marked difficulty in arising in the morning despite the occurrence of normal sleep architecture, quality, and duration

(69). It is seen mainly in young individuals. DSPS is often associated with severely disrupted work or social functioning and is more resistant to treatment than other sleep disorders (70). In a study of the impact of DSPS on QOL, 43 patients (15 men, 28 women, with a mean age of 34 years), all suffering from DSPS, were given the Medical Outcomes Study questionnaire (Short Form-36, MOS SF-36) for measuring physical, mental, and social health (71). A higher aggregate score on this instrument is associated with a greater quality of overall health (72). The findings confirmed that the QOL of DSPS patients is very much impaired (71). The principal complaints of DSPS patients in the study were insomnia and tiredness, both associated with a decrease in QOL dimensions "vitality" and "social functioning" (73). Taken together, these findings support the conclusion that DSPS is a sleep disorder that can severely impair the QOL of affected individuals.

Efforts to treat DSPS have emphasized the efficacy of melatonin treatment (74,75). In the above-mentioned study of QOL in DSPS patients (71), the participants received melatonin at a dose of 5 mg/day for 2–9 months, with the effects on QOL inferred from responses on the MOS SF-36 questionnaire that was administered just before and after melatonin treatment. Melatonin therapy was associated with improvements in all QOL dimensions including physical functioning, social functioning, emotional well-being, mental health, general health and bodily pain. The effect of melatonin on "role-physical," "vitality," and "health change" was noteworthy (71). Scores before and after melatonin treatment (mean ± SD) were 37.8 ± 22.7 and 66.9 ± 24.2 ("health change"), 38.1 ± 17.7 and 51.5 ± 18.9 ("vitality"), and 27.3 ± 40.8 and 51.7 ± 42.4 ("role-physical"). After melatonin administration, a significant improvement in physical functioning was found (p = 0.001). On social functioning, the score before and after melatonin treatment was 54.9 ± 26.2 and 67.2 ± 19.9 (p = 0.003). Whether the effects of melatonin were attributed to a direct action or to changes in some other substance(s) altered by melatonin treatment remains to be determined (71).

Another group of patients suffering from chronic fatigue syndrome and treated with melatonin was evaluated (13). A total of 38 patients (27 women and 11 men) completed the study. In these patients, QOL scores were significantly lower than those of healthy subjects and were similar to those found in patients with DSPS (13). The patients exhibited persistent fatigue sufficient to impair daily activities for at least 1 year, and their DLMO occurred later than 21:30 h. A QOL questionnaire (MOS SF-36) was administered to these patients before and after melatonin treatment. Melatonin was given in a dose of 5 mg 5 h before individual DLMO. Following melatonin treatment, scale measures of "physical functioning," "energy/vitality," "body pain," and "general health perception" dimensions increased significantly showing thereby that melatonin is effective in improving the QOL in patients with chronic fatigue syndrome (13). Similar results were reported in patients with fibromyalgia (76, 77). These studies are consistent with earlier findings demonstrating melatonin's capacity to inhibit cyclooxygenase inhibitors in experimental animals and support suggestions that melatonin can be considered to be an endogenous non-steroidal antiinflammatory substance (78).

In another study including 29 patients (24 women and 5 men) with chronic fatigue syndrome and late DLMO, the effect of a 5-mg dose of melatonin on fatigue severity was evaluated (79). During melatonin treatment, the score of specific questionnaire on chronic fatigue changed significantly in the affected group when compared to healthy controls, indicating that melatonin treatment improved QOL in those patients (79).

Chronic whiplash syndrome (CWS) is a poorly defined clinical entity in which complex symptoms develop after a forceful flexion and extension trauma of the cervical spine ("whiplash") and that is present for longer than 6 months after trauma. Symptoms include insomnia, impaired concentration and memory, increased fatigue, neck pain, and headache and are often so pronounced that many CWS patients cannot resume their daily activities (80). In a study of CWS patients who exhibited a delayed DLMO, the effect of melatonin treatment on QOL score was evaluated. Melatonin administration (5 mg/day) for a period of 4 weeks did not affect QOL in these patients (81). To what extent this negative results can be attributed to the short-treatment period with melatonin employed merits further investigation.

Melatonin and Alleviations of Symptoms of Jet-Lag

Rapid travel across time zones causes transient insomnia, poor performance, and reductions in the general sense of well-being (82). The duration and severity of jet-lag depend upon the number of time zones crossed and direction of travel. The primary reason for jet-lag is the desynchronization of circadian rhythms and the associated sleep disturbances. Any agent capable of accelerating the resynchronization of bodily rhythms would thus have significant value in minimizing the symptoms of jet-lag and in improving health and well-being of the individuals undertaking transmeridian travel (6).

A number of studies have investigated melatonin's potential for alleviating the symptoms of jet-lag. Melatonin was effective in placebo-controlled studies for reducing the subjective symptoms of jet-lag such as sleepiness, impaired alertness (83), and behavioral changes may be construed as the signs of improvement in general mental and physical health and hence in QOL.

The most severe health effects of jet-lag occur following eastbound flights, as this requires a phase advancement of the biological clock. In one study addressing this issue, phase advancement after melatonin administration (3-mg doses just before bedtime) occurred in all 11 subjects traveling from Tokyo to Los Angeles as well as faster resynchronization compared to controls (84). Melatonin increased the phase shift from about 1.1–1.4 h/day causing complete entrainment of 7–8 h after 5 days of melatonin intake. Melatonin has been found

to promote a 50% reduction in subjective assessment of jet-lag symptoms in 474 subjects taking 5 mg fast release tablets (83) . Therefore, with few exceptions, most of the evidence on the subject indicates that melatonin is useful for ameliorating "jet-lag" symptoms in air travelers (see meta-analysis at Cochrane Data Base, 85).

One of us examined the timely use of three factors (melatonin treatment, exposure to light, physical exercise) to hasten the resynchronization of circadian rhythms in a group of elite sports competitors after a transmeridian flight across 12 time zones (86). Participants in the study took melatonin at the local bedtime and effects on the circadian oscillator, that is, adjustment to the local time environment, were subsequently assessed. Individual actograms derived from sleep log data showed that all subjects became synchronized in their sleep to the local time in 24–48 h, well in advance of what would have been expected in the absence of treatment. More recently, a retrospective analysis of the data obtained from 134 normal volunteers flying the Buenos Aires – Sydney transpolar route over a period of 9 years was published (6). The mean resynchronization rate for this transmeridian flight across 13 time zones was 2.27 $\pm$ 1.1 days for eastbound flights and 2.54 $\pm$ 1.3 days for westbound flights.

Melatonin's Role in Night Shift Worker's Health

Nearly 15–20% of the work force is permanently engaged in night or rotating shift work created by the "24 hour/7 days Society" (87). The increasing demands of modern day life have seen the emergence of "around the clock" work shifts in hospitals, industries, nuclear power plants, and air and railroad transport systems. When individuals are forced to forego their normal sleep/wake and light–dark cycles, they experience a misalignment in timing of their altered sleep–wake schedules, thereby causing an internal desynchronization of bodily rhythms. The inversion of sleep–wake schedules has a variety of disruptive effects on the life styles, sleep, and general health of night shift workers. These include gastrointestinal, cardiovascular, and metabolic disturbances that can manifest as diabetes mellitus, peptic ulcer, hypertension, myocardial infarction, and other disorders (88, 89). A positive association between long periods of night shift work and increased risk of breast cancer has also been documented (90). It has been postulated that this finding, documented in women nurses working on night shifts, may be attributed to the suppression of melatonin secretion following continuous exposure to nighttime lighting. Adaptation to the reversal of day and night is essential for the maintenance of general health and QOL in night shift workers. It has been noted that a worker's ability to phase shift his or her body's endogenous melatonin rhythm is associated with improved shift work tolerance as inferred from neurobehavioral performance measures (memory test, reaction time, etc.) (91).

Accumulating evidence strongly suggests that it is the desynchronization and disruption of circadian rhythms associated with the reversal of sleep–wake time what accounts for the generally adverse health status seen in night shift workers (88, 89). Some studies have shown that the administration of melatonin can cause a rapid adaptation of night shift workers to inverted work schedules and further can improve sleep during daytime and increased alertness during night working hours (92, 93). Definite conclusions on this subject have yet to be drawn inasmuch as not all studies support a significant improvement in either mood or day time sleep in melatonin-treated night workers (94).

Melatonin for Improvement of QOL in Alzheimer's Disease

The general cognitive decline and increased memory impairment seen in AD patients is accompanied by disruptions in the circadian timing system as manifested by a greater incidence of sleep–wake rhythm disorders in this patient group (95). The disturbed sleep–wake rhythms in AD patients are also associated with a higher degree of irregularities of melatonin secretion (96). The decrease in melatonin secretion correlates well with abnormalities of the rest activity cycle (97). Moreover, it has been suggested that a decrease in cerebrospinal fluid (CSF) melatonin levels is an early event in the development of AD (98).

AD patients exhibit a chronobiological phenomenon known as "sundowning" (99). The symptoms of sundowning include a reduced ability to maintain attention to external stimuli, disorganized thinking and speech, and a variety of motor disturbances including agitation, wandering and repetitious physical behaviors, and emotional disturbances. These symptoms are prevalent during the late afternoon and early evening hours (99).

The first attempt to use melatonin as a sleep-promoting agent in AD was carried out in a small non-homogenous group of elderly demented patients with primary insomnia (100). Seven out of 10 demented patients treated with melatonin (3 mg p.o. for 21 days) showed a significant decrease in sundowning and reduced variability of sleep onset time. In another study, the administration of 6 mg of melatonin to 10 individuals with mild cognitive impairment improved sleep, mood, and memory (101). The efficacy of 3 mg melatonin/day at bedtime in improving the sleep and alleviating sundowning was shown in 11 elderly AD patients (102) and in 7 patients of another study (103). Melatonin (in a dose of 6–9 mg) was administered over a 2–3 year period to 14 AD patients who had symptoms of sleep disorders and sundowning agitation and was found to improve the patients' sundowning and quality of sleep (104). Another study on 45 AD patients with symptoms of sleep disturbance, and to whom 6 mg of melatonin was given daily for 4 months, demonstrated improvements in sleep and suppression of sundowning (105). In addition to these symptomatic improvements, which in

themselves added significantly to the patients' QOL, additional consequences of treatment included a reduction in the burden to the caregivers as well as an apparent arrest or slowing of the cognitive decline among patients in the melatonin group as compared to AD patients not receiving melatonin (104).

Melatonin efficacy in AD patients was confirmed in a double-blind study, with regard to amelioration of sleep–wake dysrhythmia and improvement of cognitive and non-cognitive functions (106). In a large multicenter, randomized, placebo-controlled clinical trial, the effects of two dose formulations of oral melatonin were investigated. A group of 157 subjects with AD and nighttime sleep disturbance was randomly assigned to one of three treatments: (i) placebo, (ii) 2.5 mg slow-release melatonin, or (iii) 10 mg melatonin given daily for 2 months (107). Melatonin facilitated sleep in a certain number of individuals, but collectively, the increase in nocturnal total sleep time and decreased wake after sleep onset as determined by actigraphic measures were only apparent as trends in the melatonin-treated groups. On subjective measures, however, caregiver rating of sleep quality showed significant improvement in the 2.5 mg sustained-release melatonin group relative to placebo (107).

Large interindividual differences between patients suffering from a neurodegenerative disease are not uncommon. As the circadian oscillator system is obviously affected in AD patients showing severe sleep disturbances, the efficacy of melatonin should be expected to also depend on disease progression. Overall, these studies support the use of melatonin in improving the general health and sleep quality of AD patients (11).

Melatonin and QOL in Patients with Mood Disorders

Mood disorders consist of major depressive disorder, bipolar affective disorder, and seasonal affective disorder (SAD). Some of these mood disorders are cyclic in nature and are often linked to the disrupted functioning of the circadian time-keeping system (108). Sleep loss or insomnia is a major risk factor for the occurrence of mania (109) and is often a prominent co-morbility of depression (110). SAD usually occurs in winter and remits in spring and summer. SAD includes depressive symptoms such as fatigue, social withdrawal, oversleeping, overeating, and weight gain (111). These symptoms are in contrast to those of insomnia, early morning awakening, poor appetite, and agitation that often occur in non-seasonal depression. Patients with SAD exhibit delayed circadian rhythms and the phase delay of the circadian pacemaker relative to the timing of the sleep–wake cycle may underlie the pathophysiology of SAD (112). Patients with SAD display a delayed melatonin secretion (113). The duration of melatonin secretion in SAD patients is shorter during summer when compared to healthy controls (8.5 ± 1.4 h vs. 9.3 ± 1.2 h) (114). As the amplitude of melatonin secretion rhythm is altered in patients with major depressive disorder, bipolar patients, or patients with SAD (59), it has been suggested that the timing and duration of melatonin secretion play an important mediating role in the pathophysiology of mood disorders (108).

A study to evaluate the effectiveness of melatonin in improving the QOL in healthy subjects ($n = 58$) exhibiting subsyndromal SAD was undertaken in Finland (115). A sustained release preparation of 2 mg of melatonin or placebo was administered 1–2 h before desired bedtime for a period of 3 weeks. Melatonin was also administered for the same period to people who suffered from weather-associated syndrome. Sleep quality, sleepiness after waking, atypical depressive symptoms, and health-related QOL were measured at the baseline and after melatonin treatment. Melatonin administration significantly improved the quality of sleep ($p = 0.03$) and vitality ($p = 0.02$) in subjects with subsyndromal SAD but not in subjects with weather-associated syndrome. These findings suggest that melatonin's effects are specific to disorders connected to the photoperiod rather than to the weather-related aspects of season (115).

Meditation, Melatonin, and QOL in Healthy Subjects and Cancer Patients

The practice of meditation is said to have immunoenhancing, anticancer, and antiaging effects (116). A number of parallels between the reported effects of meditation and of melatonin administration suggested a possible connection between the two therapeutic practices (117, 118). In a study conducted on 15 healthy men aged 25–35 years, the subjects were asked to perform Hatha yoga for 15 min and Omkar meditation for 30 min daily during 3 months (119). Serial blood samples were drawn at various time intervals to study the effects of these practices on melatonin levels. Heart rate, blood pressure, respiratory rate, peak expiratory flow rate, and psychological well-being also were measured before and 3 months of treatment. Plasma melatonin levels increased significantly after yogic practices and meditation and additionally correlated with a scaled measure of well-being ($p < 0.05$). These findings suggest that meditation acts as a psychophysiologic stimulus to increase endogenous melatonin secretion that in turn can promote an improved sense of well-being (119).

The effect on QOL of a meditation technique called mindfulness-based stress reduction (MBSR) was investigated in a study of 59 patients with breast cancer and 10 patients with prostate cancer (120). Forty-two patients completed both pre- and post- intervention questionnaires, and changes were noted on the overall global QOL score ($t = 2.23$, $p < 0.05$), indicating a greater overall QOL. Melatonin levels in this study did not change significantly after MBSR (120).

Earlier studies in meditators have indicated that individuals using the technique consistently produce higher melatonin

levels as compared to non-meditators (117). Acute increases in plasma melatonin levels have been reported following the practice of meditation, higher plasma melatonin levels being suggested to mediate the health-promoting effect (118).

In a large multisite study coordinated by the University of Massachusetts Medical Center (UMMC), the effects of a stress reduction and relaxation program on breast cancer were investigated. Women aged 20–65 years who had received a diagnosis of stage I or stage II breast cancer within 2 years of the study were surveyed before and after 4 months of participation in the program. Psychological and physiological factors including QOL, coping methods, anxiety, depression, melatonin, interleukin-4, and interferon-γ were measured. An assessment of 84 women was carried out at baseline and then 4 months later. Among program participants who completed questionnaires both at baseline and at the 4th month assessment point (30 subjects), there was a mean before–after increase of 1.58 μg/24 h of MT6s excretion, the principal melatonin metabolite (baseline aMT6s: 9.83 μg, after 4-month intervention: 11.41 μg/24 h). Inasmuch as the increases in the output of the melatonin metabolite paralleled the improvements in psychological factors, it was suggested that melatonin could be a relevant outcome variable in assessing psychosocial interventions, particularly for subjects with cancer.

Several studies have attempted to elucidate melatonin's cellular mechanism of action in breast cancer. There is evidence that melatonin acts as a selective estrogen receptor modulator (121). In particular, melatonin has been shown to inhibit the growth of estrogen-responsive breast cancer by modulating the cell's estrogen signaling pathway (42). Melatonin is also known to affect cell growth in breast cancer cells by modulating estradiol receptor-α transcriptional activity (122). Taken together, these findings suggest that melatonin has the potential as a safe and effective drug not only for exerting its oncostatic effect in cancer patients but also for improving the general health, vitality, physical functioning, and QOL in cancer patients.

Melatonin Activity on QOL in Patients with Irritable Bowel Syndrome

In a study of patients suffering from irritable bowel syndrome, the effect of melatonin administration (3 mg) on symptoms of abdominal pain, abdominal distension, frequency of defecation, stool type, abnormal sensation of defecation, QOL, and total bowel symptom score was evaluated before and after 2 weeks of treatment (123). Compared to placebo, significant reductions ($p < 0.001$) in the abdominal pain score were recorded following melatonin administration. Additionally, total bowel symptoms also decreased with melatonin treatment. However, no statistical differences were found as far as stool type, abnormal sensation of defecation, or QOL between the melatonin and the placebo groups. These findings supported the suggestion that melatonin's beneficial effect was due to amelioration of rectal sensitivity to pain and urgency. To what extent the lack of effect on QOL is related to the short period of treatment (2 weeks) deserves further investigation. While not all the symptoms studied showed reductions following melatonin administration, the finding that melatonin alleviated abdominal pain suggests that it can have value for improving health in patients with irritable bowel syndrome.

Conclusions

Melatonin has been found effective for improving sleep onset, health status and QOL in children with ADHD and for those suffering from chronic sleep onset insomnia. Melatonin improves the QOL of epileptic children by improving their cognitive functioning, emotional well-being, and other aspects of general health. In adult patients suffering from DSPS, melatonin improved a number of QOL dimensions including physical functioning, emotional well-being, bodily pain, and general health. In a study on patients with chronic fatigue syndrome, melatonin improved QOL by enhancing physical functioning, energy, and vitality and reducing the body pain. In addition to these specific conditions, melatonin has been found effective in enhancing QOL in elderly insomniacs by improving the quality of sleep. Melatonin is effective not only in inhibiting cancer growth but also in improving the QOL. Other conditions such as irritable bowel syndrome may be positively affected by melatonin.

Issues that need to be addressed by future research:

- Assessment of QOL should be included as a regular clinical practice.
- More evidence-based research is warranted to establish the exact directionality of the relationship between melatonin and chronic illnesses.
- Future studies need to focus on the therapeutic use of melatonin in various chronic disorders.

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9
Sleep and Quality of Life in Sleep Apnea

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Summary Health-related quality of life (HRQOL) is increasingly recognized as an important parameter in the assessment of the morbidity associated with obstructive sleep apnea (OSA). Generic and sleep disorder-specific instruments consistently demonstrate impairment in multiple domains of HRQOL in OSA, particularly in the domains of sleep, energy, fatigue, and vigilance. Sleep disorder-specific tools are potentially more sensitive than generic tools in describing HRQOL impairment in untreated OSA and treatment effects of continuous positive airway pressure (CPAP) and are increasingly being employed in clinical trials of OSA treatment. Severe OSA is generally associated with severe HRQOL impairment; however, studies do not consistently demonstrate a linear relationship between physiologic measures of OSA severity and measures of severity of HRQOL impairment. Excessive sleepiness, cognitive dysfunction, and psychological impairment are common measurable components of HRQOL impairment in OSA, particularly severe OSA, but the interactions among these and quality of life impairments measured by standard HRQOL instruments are not well studied. Therapeutic CPAP appears to broadly improve HRQOL domains in OSA, but substantial placebo effect has been demonstrated, suggesting that HRQOL impairment in OSA may be mediated by aspects of the disorder other than the physiologic effects of the OSA. Further randomized controlled trials should better elucidate the associations between physiologic impairment in OSA and HRQOL measures of interest to clinicians and researchers in this field.

Keywords Obstructive sleep apnea · health-related quality of life · excessive sleepiness · cognitive dysfunction · depression · health status · continuous positive airway pressure

Learning objectives:

- HRQOL is impaired in patients with obstructive sleep apnea.
- Patients with obstructive sleep apnea may be troubled by excessive sleepiness, cognitive dysfunction, and/or impairment, impairments that may be best assessed in addition to, and in association with, HRQOL instruments.
- Therapeutic CPAP is associated with improvement of HRQOL in patients with a broad degree of OSA severity, although significant placebo effect, noted in multiple studies, and lack of a consistent relationship between physiological measures of OSA severity and HRQOL impairment, suggests that factors other than physiological perturbations of OSA play a role in HRQOL impairment in this disorder.

Introduction

Patients' experience of their illnesses as assessed by health-related quality of life (HRQOL) indices is increasingly recognized as an important component of the disease process, with respect to initial presentation, diagnosis, and treatment success (1). Taking into account the different cultural and personal expectations regarding health and coping ability that each patient possesses, HRQOL can differ markedly among patients with the same severity of disease, thus offering a nuanced portrait of a patient's illness (2). Given the high prevalence of obstructive sleep apnea (OSA) in diverse populations and the adverse cardiovascular, cognitive, and psychological sequelae associated with it, it is not surprising that there has been considerable interest in assessing HRQOL in patients with this disorder.

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HRQOL Instruments and Measured HRQOL in OSA

Generic HRQOL Instruments

HRQOL encompasses such domains as physiology, physical function, social interaction, cognition, emotion, sleep and rest, energy and vitality, health perception, and general life satisfaction (3). Numerous generic instruments have been used to assess HRQOL in patients with OSA, most notably the Medical Outcomes Study (MOS) Core Survey and a subset of that survey, the Short Form-36 (SF-36), the Sickness Impact Profile (SIP), the Functional Limitations Profile (FLP), the Nottingham Health Profile (NHP), and the EuroQOL (EQ-5D) (1,4–8). The MOS Core Survey, developed by the RAND Corporation for use in its landmark 2-year study of chronic health conditions, consists of 116 items in multiple domains, broadly defined as physical health, mental health, and general health and has been used infrequently to study HRQOL in OSA (4, 9). However, a subset of the MOS Core Survey, the SF-36 (4) is perhaps the most extensively used HRQOL instrument and consists of a self-reported 36-item questionnaire addressing eight health concepts, commonly referred to as domains, dimensions, or subscales: (i) limitations in physical activities because of health problems (physical functioning); (ii) limitations in social activities because of physical or emotional problems (social functioning); (iii) limitations in usual role activities because of physical health problems (role-physical); (iv) bodily pain; (v) general mental health (psychological distress and well-being); (vi) limitations in usual role activities because of emotional problems (role-emotional); (vii) vitality (energy and fatigue); and (viii) general health perceptions (4). For each domain, the item scores are totaled and transformed onto a scale ranging from 0 (worst possible health) to 100 (best possible health) (10). Two summary scores of physical (physical component summary, or PCS) and psychological (mental component summary, or MCS) health status can also be calculated and have been used as surrogates for the results of the eight domains of the SF-36 (10). The SIP is a 136-item questionnaire assessing the impact that sickness has had on a patient's life and behavior (7). Twelve domains are grouped into three separate subscales: physical (ambulation, mobility, and body care), psychosocial (social interaction, communication, alertness, and emotional behavior), and other (eating, work, sleep/rest, home management, and recreational pastimes). The FLP, a measure of sickness-related behavioral dysfunction, was adapted from the SIP for use in a British population (6, 11). It incorporates essentially the same 136 items in the same 12 domains, with wording and valuations modified to better fit British, rather than American, valuations of the severity of impaired health status (6). Possible scores range from 0 (best possible health) to 100 (worst possible health) (6). Two summary scores, the physical dimension score and the psychosocial dimension score, can also be calculated by adding together a subset of the items (6). The NHP is another British-developed instrument used to assess HRQOL in OSA (1). This tool measures the domains of physical mobility, pain, social isolation, emotional reactions, energy, and sleep. Each domain encompasses a series of statements, with which the subject can agree or disagree; these statements are weighted to produce a scoring system ranging from 0 (no perceived distress) to 100 (maximum perceived distress) (12). Small to moderate correlations between the NHP and SF-36 subscales have been found in general and disease-specific population studies (13–15). Developed by European researchers, the EQ-5D is a five-item instrument assessing mobility, self-care, usual activities, pain/discomfort, and anxiety/depression using a three-item Likert scale response system (no problems, some problems, and inability/extreme problems); 243 combinations are possible (8).

HRQOL Impairment in OSA as Assessed by Generic Instruments

Numerous data using generic HRQOL instruments have identified impaired HRQOL in OSA patients relative to the general population. Smith and Shneerson (16) assessed 223 subjects referred for OSA evaluation, finding that all dimensions of the SF-36 were impaired compared to data from the general population, presumably some of which included patients with OSA, with the largest differences occurring in vitality and social functioning. Similarly, in 108 OSA patients with more than 10 episodes per hour of a greater than 4% fall in arterial oxygen saturation during sleep, Jenkinson and colleagues (11) found impaired HRQOL in all domains of the SF-36 compared to previously published population data in British working age adults (17). Particularly severe impairment was noted in the vitality domain, and the PCS and MCS were each 1 standard deviation (SD) below the mean score of the population. Bennett and colleagues (18), studying 51 OSA patients drawn from a community referral center with a median apnea + hyponea index (AHI) of 25/h, found that the domains of vitality and role-physical were significantly impaired relative to the same general population of British working-age adults as in the above-noted study. Sin and coworkers (19), analyzing HRQOL in a group of 365 Canadian patients with moderate to severe OSA (mean AHI 65.5/h) and 358 patients with mild OSA (mean AHI 5.1/h), found significant HRQOL impairments in the PCS and MCS scores of the SF-36: the PCS scores were over 1 SD below data reported for 45- to 54-year-old Canadians (20), and the MCS scores were nearly 1 SD below. Role-physical, physical functioning, general health perceptions, and social functioning were all approximately 1 SD below the Canadian general population data, whereas the vitality scores were 1.7 SD below.

Lloberes and coworkers (21) found significant impairment of NHP scores in Spanish patients compared with previously published data for the 50–59 year old range group of the general population of Barcelona (22) in 88 patients

with severe OSA (mean AHI 62.5/h). The domains of energy, emotional reactions, and sleep were most affected, with scores in the energy domain almost four times more impaired than those of the general population. In another study utilizing the NHP, all domains except emotions were significantly more impaired in 103 OSA patients (mean AHI 38/h) than 40 non-snoring control subjects (23). FLP data have also demonstrated substantially greater degrees of impaired HRQOL compared with the general working-age population in 108 patients with OSA referred for initiation of CPAP therapy (11). The domains most affected were alertness, sleep and rest, recreations and pastimes, and social interactions, all with scores substantially greater than zero.

Even patients with mild OSA have been found to have impaired HRQOL as measured by the SF-36 relative to control subjects. Measuring HRQOL with the SIP, Gall and co-workers (24) found that behavioral impairments in the areas of alertness, sleep, recreation, and work were significantly more common in mild OSA patients (mean AHI 8.7/h) than in control subjects: 15.5% of OSA patients reported impairment of alertness versus 1.4% of normal subjects, 21.6% of OSA patients reported impaired sleep versus 7% of normal subjects, 13.5% of OSA patients experienced impairment in the recreation domain versus 1.5% of normal subjects, and 16.4% of OSA patients reported impaired work function compared with 2.2% of normal subjects (24).

While the clinic-based studies described above are subject to some degree of selection bias, data from a population-based study found similar decrements in six of eight SF-36 domains in OSA patients (25).

Not all generic HRQOL tools have elicited depressed scores in OSA patients, however. Barbe and colleagues (26) found that 55 patients with severe OSA (mean AHI 55.4/h) reported SF-36 PCS and MCS scores in the normal range. Their scores on the Functional Outcomes of Sleep Questionnaire (FOSQ), a sleep-specific instrument (see below), were also in the normal range. However, this population was selected on the basis of absence of pathologic sleepiness, as defined by an Epworth Sleepiness Scale (ESS) score of 10 or less, whereas all of the other studies have been performed in patients with a high degree of subjective or objective sleepiness. In a study of untreated OSA patients selected for disabling symptoms attributable to their OSA, the EQ-5D failed to show more than minimal impairment of HRQOL in the OSA patients, whereas marked impairment was documented with the SF-36 and FLP (11). The authors suggested that the domains covered by the EQ-5D (mobility, self care, usual activities, pain/discomfort, and anxiety/depression) do not adequately assess areas that are particularly affected by OSA, including sleep, tiredness, and social interactions and so do not accurately characterize the impairments due to OSA. Similarly, Monasterio and colleagues (27) found NHP scores to be within the normal range in 142 patients with mild OSA (mean AHI 20/h). Hunt and coworkers (1) have suggested that this instrument was designed to assess severe disease to limit large numbers of false positive responses and thus may not detect HRQOL abnormalities in milder forms of disease.

HRQOL Impairment in OSA as Assessed by Sleep Disorder-Specific Instruments

HRQOL instruments have been designed to specifically measure response to treatment of OSA and, as such, to be more sensitive than generic instruments to clinically important within-subjects effects in OSA (28). Such instruments include the Calgary Sleep Apnea Quality of Life Instrument (SAQLI), the Functional Outcomes of Sleep Questionnaire (FOSQ), and the Quebec Sleep Questionnaire (QSQ) (29–31).

The Calgary SAQLI, which must be administered by an interviewer, has 35 questions arranged in four domains: daily functioning, social interactions, emotional functioning, and symptoms; a fifth domain, treatment-related symptoms, can be added for research purposes to assess possible negative consequences of treatment (29). The possible scores in each domain range from one (poor quality of life) to seven (excellent quality of life). A total score is also calculated, which has been shown to have moderate to strong correlations with all SF-36 domains (r = 0.39–0.65) in patients with OSA, with the strongest correlations occurring with the SF-36 vitality, social functioning, and mental health domains (32). Independent validation of the SAQLI similarly showed moderate to strong correlations between individual domain of the SAQLI and the SF-36, particularly between the SF-36 vitality domain and the SAQLI domains daily-life activities (r = 0.88) and symptoms (r = 0.76) and between the SF-36 social functioning domain and the SAQLI domain social interactions (r = 0.66) (33). Assessing the treatment effect of 4 weeks of CPAP therapy in 90 patients with severe OSA (mean RDI 53.8/h), Flemons and Reimer (32) found that all SAQLI domains showed a large effect size, whereas only the vitality domain of the SF-36 showed a similarly large effect. Before treatment, the SAQLI symptoms domain was most severely depressed (32). Thus, the SAQLI appears to be generally more sensitive to treatment effects than the SF-36 while performing at least as well in detecting HRQOL impairment in untreated OSA. Mok and coworkers (34), validating the SAQLI in a Cantonese population of 106 patients with severe OSA (AHI 30.9/h), similarly found that the symptoms domain was the most impaired. The FOSQ, which is specifically designed to assess the impact of excessive sleepiness on activities of daily living, is a self-administered questionnaire containing five domains (general productivity, social outcome, activity level, vigilance, and intimate relationships and sexual activity), as well as a global score (30). The FOSQ global score, general productivity domain, and activity domain have each been correlated with the SIP overall score (30) in patients with OSA. The FOSQ activity level subscale has also shown a moderate correlation with the SF-36 physical functioning domain, whereas the FOSQ global score and general productivity, social outcome, and activity level dimensions have been

correlated with the SF-36 role-emotional domain (30). The FOSQ social outcome score is further correlated with both the social function and mental health domains of the SF-36 (30). In a study of 42 patients with mild OSA (mean AHI 12.9/h), 72% reported abnormally low FOSQ scores across all measured domains (35). The most recently developed tool, the QSQ, is a 32-item self-reported OSA-specific questionnaire developed primarily for use as an outcome measure in clinical trials (31). It covers five domains, including daytime sleepiness, diurnal symptoms, nocturnal symptoms, emotions, and social interactions. As part of its validation, 60 consecutive adult patients with recently diagnosed OSA (mean AHI 29/h) who were awaiting treatment completed the questionnaire before and after definitive treatment. QSQ domains were correlated with many SF-36 domains, with the strongest correlations between diurnal symptoms and the vitality domain of the SF-36 (r = 0.85). Diurnal symptoms were also strongly correlated with role-physical (r = 0.72), and emotions were strongly correlated with mental health (r = 0.80) (31).

Relationship Between OSA Severity and Severity of HRQOL Impairment

Although the current HRQOL data as noted above span a wide range of OSA severity, no consistent or strong relationship between severity of the OSA, as measured by AHI and/or degree of nocturnal oxygen desaturation, and severity of HRQOL instrument impairment has become evident. Finn and coworkers (25) reported a significant relationship between OSA severity as assessed by AHI and impairment in six of eight SF-36 domains; only pain and role-emotional showed no linear relationship. Further, they noted that the difference in HRQOL impairment in mild obstructive sleep apnea hypopnea syndrome, or OSAHS, (AHI = 5/h) and moderate OSAHS (AHI = 15/h) was of clinical significance (25). Moore and coworkers (9) correlated polysomnographic (PSG) measures of sleep quality with HRQOL score, as measured by the MOS Core Survey, in 39 patients with moderate to severe OSA (mean respiratory disturbance index, RDI, 45/h). After controlling for age and gender, they found that RDI and number of arousals were significantly, although weakly, correlated with the MOS domain health distress (r = 0.399–0.481) and that RDI was further correlated with energy/fatigue and social functioning. Investigating the relationship between AHI and SF-36 domain scores in 135 men with severe OSA and daytime sleepiness, Goncalves and colleagues (36) found only weak, although significant, correlations between the domains of physical functioning and general health perceptions, and PSG severity indices of OSA. Weak correlations were also noted between the arousal index and impairment in physical functioning and role-physical, and nadir oxygen saturation and bodily pain (36). In the largest trial to date assessing the relationship between PSG measures of OSA and HRQOL indices, 5816 participants in the Sleep Heart Health Study were assessed using the SF-36 (37). Although most SF-36 domains were significantly impaired in the severe OSA subjects compared with U.S. normative data, only the domain of vitality demonstrated a linear relationship with severity of OSA as categorized by RDI 4%. Severe OSA (RDI 4% > 30 h), however, was significantly and negatively associated with the domains of general health perceptions, physical functioning, and social functioning, as well as vitality.

In contrast to the above, Fornas and colleagues (23), as cited above, performed nocturnal PSG and administered the Spanish language version of the NHP to 103 patients referred for evaluation of suspected OSA and to 40 non-snoring controls. Although there were significant differences between the OSA subjects and the controls in all NHP domains except emotions, there were no differences in these indices among the OSA patients grouped by severity of their OSA as assessed by AHI. D'Ambrosio and colleagues (38), in a prospective evaluation of 29 patients referred for possible sleep-disordered breathing, found no significant correlation between any domain score of the SF-36 and the respiratory disturbance index or arousal index.

Summary of HRQOL Impairment in Untreated OSA

In summary, virtually every domain of HRQOL assessed by generic and sleep disorder-specific instruments appears to be adversely affected in OSA, with an impressive consistency across a broad array of HRQOL domains and instruments. The most consistent impairments appear to be found in the domains of sleep and vitality/energy. Patients with OSA of all degrees of PSG severity report more impaired generic and OSA-specific HRQOL scores than normal controls and/or normative data, but significant variability exists when the current literature has sought to correlate PSG severity indices of OSA with severity indices of impaired HRQOL domains. The most consistent associations between PSG indices of OSA severity and severity of HRQOL impairment have been demonstrated in those patients with PSG evidence of severe OSA. Much of the foregoing data documenting impairment of HRQOL have been obtained in clinic-based studies of patients with severe OSA, although more recent treatment trials in patients with less severe OSA also have consistently demonstrated HRQOL impairment [see CPAP and HRQOL in OSA below]. Numerous possible confounders regarding the interpretation of these data remain relatively unaddressed in the current literature, including the possible roles of socioeconomic and cultural differences. Although there is significantly more experience with generic instruments, particularly the SF-36, OSA-specific tools have been well validated against these generic instruments and are potentially more sensitive measures of HRQOL in OSA, particularly when applied to trials measuring responses in HRQOL to treatment (see CPAP and HRQOL in OSA, below).

Excessive Sleepiness, OSA, and HRQOL

Relationship of Excessive Sleepiness to OSA

Excessive sleepiness (ES) during normal awake hours has been documented in patients with OSA in multiple studies and may be considered a HRQOL issue of particular relevance in OSA. For example, the Wisconsin Sleep Cohort Study, a random sampling of middle-aged workers, found that 22.6% of women and 15.5% of men who had an AHI > 5 reported experiencing frequent unrefreshing sleep and uncontrollable sleepiness that interfered with life (39). ES, however, has not been generally assessed as a specific domain in the currently used HRQOL instruments (excepting the QSQ, as noted above) and has accrued its own separate instruments of measurement. As with HRQOL indices, attempts to predict either objective or subjective ES from PSG measures of OSA severity have met with incomplete success (40). A higher Respiratory Disturbance Index (RDI) has been correlated with increasing levels of self-reported sleepiness (41). In contrast, Goncalves and colleagues (36), studying 135 men referred for OSA evaluation (mean AHI 48.7/h), found only a weak correlation between subjective sleepiness, as assessed by the ESS, and the arousal index ($r = 0.3$), the AHI ($r = 0.338$), and the nadir oxygen saturation ($r = –0.379$). In a study of 466 OSA patients (mean RDI 59/h), Roehrs and colleagues (42) found that objective sleepiness, as assessed by the Multiple Sleep Latency Test (MSLT), was significantly correlated with the RDI and that this correlation was stronger than that for the frequency of oxygen saturation decreases below 85%. Bennett and coworkers (43) found that numerous EEG and non-EEG markers of sleep fragmentation, including arousal index, micro-arousal index, autonomic arousal index, and movement event index, were correlated with subjective (ESS) and objective (Oxford Sleep Resistance Test, OSLER test) measures of daytime sleepiness. These correlations, however, were of only modest strength (43). The seemingly most important clinical association of ES, that of risk of motor vehicle accident (MVA), has also evaded strong correlation with measures of OSA severity, and current data suggesting an increased risk of MVA in OSA are particularly strong primarily in patients with PSG measures of severe OSA (44, 45). Multiple factors commonly present in OSA patients, including mood disorder; use of drugs such as sedative-hypnotics, anti-depressants, stimulants, ethanol, and caffeine; reduced activity levels; adverse cardiopulmonary status; and sleep hygiene perturbations, may all impact upon the presence and severity of disrupted sleep and daytime sleepiness, and likely confound the association between objective measures of OSA severity and subjective and objective measures of ES (46, 47).

Impact of Excessive Sleepiness on HRQOL Measurement in OSA

Few studies have investigated the relationship between subjective and objective daytime sleepiness of OSA and specific indices of HRQOL. One cross-sectional study of 129 men and women with mild OSA (mean RDI 8/h) and no significant co-morbidities found that ESS scores correlated negatively and significantly with the SF-36 domains of general health perceptions, vitality, and role-emotional although the correlations were weak ($r = 0.25–0.41$) (48). MSLT was significantly, although weakly, correlated with the vitality dimension only (48). Regression analysis showed that the subjective sleepiness experienced by these OSA patients explained only 6% of the decline in the summary measure of well-being and 3% of the decline in the summary measure of functional status (48). In another study, the relationship of subjective (ESS) and objective (OSLER test) measures of sleepiness to SF-36 indices was investigated in 51 OSA patients (median AHI 25/h) selected from a sleep clinic population on the basis of PSG to demonstrate a full spectrum of sleep-disordered breathing (18). ESS scores and the SF-36 vitality and role-physical domains, PCS, and MCS were significantly and negatively correlated, whereas the OSLER test was less strongly correlated with vitality and the PCS. As noted above, patients with untreated OSA and no measured ES have shown no impairment in SF-36-measured HRQOL. In two recent studies, subjective sleepiness (measured by the ESS) was significantly but weakly correlated (49) with the SF-36 total score in one study, explaining 5% of total variance, but not correlated with any SF-36 domain in the other (50). These data in their entirety suggest that ES is a related but measurably separate component of perturbations in HRQOL characteristically found in patients with OSA.

Cognitive Dysfunction, OSA, and HRQOL

Relationship of Cognitive Dysfunction to OSA

During the process of generating a disease-specific HRQOL instrument for OSA, Lacasse and colleagues (51) found that OSA patients complained of impairments in memory, concentration and work performance, somatic pain, irritability, mood disorders, and troubled social relationships with similar degrees of frequency and importance as ES. Cognitive dysfunction appears to be another major impaired component of quality of life that is not specifically assessed by HRQOL tools. Further, in contrast to the relationship between HRQOL and ES, there are no studies up to the present time, to our knowledge, directly comparing HRQOL indices with measures of cognitive dysfunction in patients with OSA. Work performance difficulty, including impaired concentration, and learning and performance of new tasks have been found in OSA patients compared with control subjects (52). Global cognitive impairment has been

described in patients with severe OSA and hypoxemia (mean apnea index 48/h, mean nadir oxygen saturation 67.7%) compared to sleepy but non-apneic control subjects and to non-sleepy normal subjects (53). Hypoxemia was specifically associated with impairments in motor speed, assessed by grooved pegboard testing, and perceptual-organizational ability, assessed by block design (53). Patients with severe OSA (mean RDI 41/h) have also been found to have impaired verbal and visual learning (assessed with the verbal-span and visual-span tests), reduced memory and attention (assessed with the Stroop color test, digit recall in inverse order, and the verbal and visual span tests), and a proclivity for perseverative errors (assessed with the Wisconsin card sorting test) compared with normal controls (54). Multiple logistic regression analysis demonstrated a positive relationship between the AHI and deficits of memory, whereas increasing severity of hypoxemia was associated with increasing impairment of frontal-lobe, or executive, functioning (54).

The relationship between cognitive deficits and OSA was also studied in 841 middle-aged patients enrolled in the Wisconsin Sleep Cohort Study (55). A significant negative association was found between the logarithmic transformation of the AHI and the psychomotor efficiency score (a measure of the ability to efficiently coordinate fine visual-motor control and information, which requires sustained attention and concentration) but not the memory score. Even relatively mild sleep-disordered breathing was associated with impairment: an AHI of 15/h was estimated to be equivalent to the decrement in psychomotor efficiency seen with five additional years of age or half of the decrement associated with sedative-hypnotic use (55). Redline and coworkers (56) similarly found impairments in vigilance and working memory, as assessed by the Wechsler adult intelligence scale-revised (WAIS-R) digits backward test and the continuous performance test (CPT) in 32 patients with mild OSA (mean RDI 17/h and no objective or subjective sleepiness) compared to control subjects. Among the OSA patients, performance on the CPT declined in the final 2 minutes of the test, suggesting an inability to sustain attention over a period of time. There was also a trend toward a significant difference in the Wisconsin card sorting test (WCST), with OSA patients tending to commit more perseverative errors (56). In contrast to the above, no significant impairment of cognitive function was found in 142 patients with untreated mild to moderate OSA (AHI 20/h) enrolled in a trial of CPAP efficacy (27). In the study by Redline and colleagues noted above (56), a broad range of cognitive testing was not different between OSA patients and the normal subjects, including digit-symbol substitution, Talland letter cancellation, perceptual sensitivity, California verbal learning test, digits backward test, WCST, and the trailmaking B test.

The Role of Excessive Sleepiness in Cognitive Dysfunction Associated with OSA

It is not clear to what extent cognitive dysfunction in OSA may be a function of ES itself and/or associated impaired vigilance. Engleman and Douglas (57) have noted that the effect sizes of cognitive dysfunction in OSA are generally smaller than those of sleepiness, suggesting that at least some of the measured impairment in cognitive function may be attributable to sleepiness. Conversely, analysis of cognitive-evoked potentials in OSA patients suggests that cognitive impairment in OSA is not necessarily a function of excessive sleepiness. Prolonged P300 latency, a validated marker of abnormal cognitive processing (58), has been utilized in a study of 143 consecutive severe OSA patients (RDI > 40/h) with and without objective sleepiness as measured by MSLT and 40 age-matched normal subjects (59). The OSA patients had longer visual P300 latency than controls, regardless of the presence of objective sleepiness. Similarly, P300 latency failed to normalize in 40 patients with severe OSA (mean RDI 77.4/h) following 2–4 months of CPAP therapy despite significant improvement in RDI, objective sleepiness, and desaturation index (58). Repeated assessment of 20 patients with optimally treated OSA withdrawn from CPAP therapy for 1 week demonstrated a trend to impairment only in the domain of vigilance despite the recurrence of severe OSA (mean AHI 50/h) and significant subjective sleepiness (ESS 14) (60). Taken together, these findings suggest a significant divergence between excessive sleepiness and cognitive impairment in patients with OSA, both treated and untreated.

The Role of Hypoxemia in Cognitive Dysfunction Associated with OSA

The contribution of hypoxemia to cognitive impairment has been specifically studied in patients referred for evaluation of OSA (61). Patients with awake and nocturnal hypoxemia demonstrated significantly poorer function in the domains of attention, concentration, complex problem solving, and short-term recall of verbal and spatial information than OSA patients without hypoxemia, assessed by the Trailmaking B test, paced auditory serial additional task (PASAT), and Wechsler memory scale stories. Attention, executive function, motor speed, and psychomotor processing speed were tested in 67 OSA patients (AHI > 10/h) and 74 normal subjects participating in the Sleep Heart Health Study; no significant differences between the two groups were found (62). However, subanalysis of the contribution of hypoxemia, comparing the top quartile of time spent with oxygen saturation below 85% to the lower three quartiles, revealed impairment of motor speed, assessed by the grooved pegboard test, in the patients with OSA. Further, multiple regression analysis showed severity of nocturnal oxygen desaturation to be predictive of poorer performance in the domains of motor

speed and psychomotor processing, a composite of performance on the digit symbol coding and symbol search tests (62). In experimental animals, intermittent hypoxemia similar to that occurring in OSA has been shown to cause spatial learning and retention deficits (63). Amelioration of many of these deficits with administration of an experimental antioxidant suggests that oxidative stress from repeated hypoxic–reoxygenation cycles may underlie these cognitive impairments of intermittent hypoxemia (63). In contrast, functional magnetic resonance imaging has demonstrated slowing of working memory speed, assessed with the *n*-back test, and absence of dorsolateral prefrontal cortex activation when compared to normal subjects regardless of the presence or absence of hypoxemia (64). Following 8 weeks of CPAP therapy, six of the 16 patients were re-imaged, and persistent absence of prefrontal activation, only partial recovery of posterior parietal activation, and continued impairment of behavioral performance were found, again suggesting a dissociation between the respiratory perturbations of OSA and cognitive function.

Summary of Cognitive Dysfunction and HRQOL Impairment in OSA

Cognitive dysfunction, as assessed by numerous performance and imaging studies, is a frequent although not consistent parameter of impaired QOL in patients with OSA. Such dysfunction has not been specifically studied in relation to impairment in standard HRQOL domains. Varying grades of OSA severity can be associated with significant cognitive dysfunction, and the severity of OSA as assessed by PSG appears to show some correlation with the degree of cognitive deficit. The contribution of excessive sleepiness and hypoxemia to the measured cognitive dysfunction of OSA remains to be better defined.

Psychological Dysfunction, OSA, and HRQOL

Relationship of Psychological Dysfunction to OSA

Psychological morbidity, including depression, anxiety, irritability, and strained interpersonal relationships, is frequently described in association with OSA (65–70). As with excessive sleepiness and cognitive dysfunction, such morbidity represents a major component of impaired quality of life in patients with OSA and has been assessed with tools other than those included as domains within specific HRQOL instruments. In 1977, Guilleminault and Dement (65) reported that 24% of a series of OSA patients had visited psychiatric professionals for symptoms of anxiety and depression and that 28% had elevated depression scales on the Minnesota Multiphasic Personality Inventory (MMPI), a frequently used personality test designed to identify personal, social, and behavioral problems (71). Beutler and co-investigators (67) subsequently analyzed 20 sleep apnea patients and 10 control subjects with the MMPI and the profiles of mood states (POMS) concluding that, relative to the control subjects, OSA patients tended to manifest hypochondriacal, hysterical, and depressed characteristics. A study of 25 men with sleep apnea (apnea index 33/h), 21 of whom had OSA, found that 40% met criteria for a psychiatric disorder: 20% met criteria for past major depression or chronic intermittent depression, 16% met criteria for alcohol abuse, and 49% met criteria for cyclothymia (66). The patients rated themselves overall as mildly to moderately depressed; those reporting higher depression scores also tended to complain of more daytime sleepiness, whereas those with lower depression scores tended to complain of insomnia. A retrospective review of 55 OSA patients (mean RDI 57/h) at a sleep clinic found that 45% of patients reported Zung Self-Rating Depression Scale (SDS) scores in the depressed range (70). Barnes and coworkers (35), studying mood in patients with mild OSA (mean AHI 12.9/h), found that 16% of patients reported a Beck Depression Inventory (BDI) score suggestive of moderate to severe clinical depression. A large retrospective review of the Veterans Health Administration database, searching for International Classification of Diseases, 9th edition, Clinical Modification codes indicating OSA and co-morbid psychiatric disorders, revealed an OSA prevalence of 2.91% and a high degree of psychiatric co-morbidity (72). Twenty-two percent of the OSA patients carried a diagnosis of depression, 16.7% had anxiety disorder, 11.9% suffered from PTSD, 5.1% were diagnosed with a psychotic disorder, and 3.3% had bipolar disorder. When compared with patients in the database not diagnosed with OSA, the OSA patients had a significantly greater prevalence of mood disorders, anxiety, PTSD, psychosis, and dementia (72).

The relationship between depression and OSA is complex and may be reciprocal. In a telephone survey of 18,980 randomly selected subjects, Ohayon (73) found that 18% of individuals who reported a major depressive diagnosis also reported a breathing-related sleep disorder diagnosis. Deldin and coworkers (74) performed home PSG in 19 depressed patients, unselected with respect to sleep-disordered breathing, and 15 non-depressed age-matched control subjects and found that 25% of the depressed patients experienced five or greater flow limitation events per hour. Sleep-related respiratory variables accurately distinguished between depressed and non-depressed patients 80% of the time.

Correlation of Severity of Psychological Impairment with Severity of OSA

As with other major entities discussed above that appear to impair quality of life in patients with OSA, the degree of psychological impairment in these patients has not been convincingly correlated with PSG indices of OSA severity.

Linear regression analysis of SDS data culled from 55 untreated OSA patients showed no significant correlation between baseline SDS score and such PSG measures of severity as nadir oxygen saturation or RDI (70). However, significantly higher RDIs were found in the group of patients determined to be depressed as compared with the non-depressed group (70). Pillar and Lavie (69) similarly found no significant association between RDI and depression, as measured by the Symptoms Checklist-90 Symptom Self-Report Inventory (SCL-90), in 1977 men referred for evaluation of OSA. However, higher depression and anxiety scores, assessed by the SCL-90, were found in the 120 women with severe OSA (RDI > 30/h) compared with the 174 women with mild OSA (RDI 10–30/h) in the same population of OSA patients (69). In a study of 20 OSA patients with a mean RDI of 48.8/h, depressive symptoms, assessed by the Center for Epidemiologic Studies Depression Scale (CES-D), accounted for 10 times the variance in the profile of mood states (POMS) fatigue scale score as did RDI and oxygen saturation (68). These findings were replicated in a follow-up study of 56 OSA patients with a mean RDI of 62.7/h (47). In a large epidemiological study enrolling 1408 patients from the Wisconsin Sleep Cohort Study, Peppard and coworkers (75) did find evidence of a dose–response relationship between severity of OSA by class ($0 < \text{AHI} < 5$; $5 \leq \text{AHI} < 15$; $\text{AHI} \geq 15$) and risk of depression, defined by an SDS score of 50 or greater. The fully adjusted model showed an odds ratio (OR) for development of depression of 1.6 for subjects with minimal OSA, an OR of 2 for mild OSA, and an OR of 2.6 for subjects with moderate or worse OSA.

Relationship between Psychological Impairment and HRQOL Instrument Assessment in OSA

Akashiba and colleagues (49) offered the first direct evidence of an association between OSA, depression, and HRQOL indices in a case–control study of 34 patients with severe OSA (AHI 51.6/h) and 34 normal subjects. Stepwise regression analysis demonstrated that SDS score (partial $R^2 = 0.505$), nadir oxygen saturation (partial $R^2 = 0.053$), and ESS score (partial $R^2 = 0.053$) explained 62.2% of the variance in the SF-36 total score. Strong correlations between the SDS score and SF-36 domains were specifically found with the general health perceptions, vitality, role-emotional and mental health domains. Subsequently, Kawahara and co-investigators (50) found that pretreatment SDS scores correlated negatively with the SF-36 domains of physical functioning, bodily pain, general health perceptions, vitality, social functioning and role-emotional in 132 OSA patients with severe OSA (mean AHI 59.4/h).

Summary of Psychologcial Dysfunction in OSA

Taken together and representing a wide array of psychological scales, these data suggest that psychological dysfunction is commonly reported and/or diagnosed in patients with OSA prior to treatment of the breathing disorder, with specific associations among psychological impairment and OSA severity indices becoming more robust as the severity of OSA increases. Such data, however, do not address causality in this setting. Impairment in specific HRQOL domains have been increasingly found to correlate with separate depression indices in this disorder.

Other Quality of Life Issues in OSA

In addition to the quality of life morbidities associated with OSA discussed above, marital satisfaction and erectile dysfunction (ED) have also been studied as major elements of impaired quality of life that are not specifically contained in standard HRQOL tools. Using the Evaluation and Nurturing Relationship Issues, Communication and Happiness (ENRICH) behavioral questionnaire, decreased marital satisfaction was found at baseline in 69 patient/partner couples awaiting CPAP therapy in the United Kingdom (76). Following 3 months of CPAP therapy, ENRICH scores significantly improved, compared to conservative therapy, with a moderate effect size (see below, CPAP and HRQOL in OSA). When SF-36 scores of 28 OSA patients with ED were compared to 98 OSA patients without ED, it was found that the ED patients reported lower HRQOL in five of the eight SF-36 dimensions. (77). The patients with ED had a higher mean AHI, lower nadir oxygen saturation and lower mean oxygen saturation. However, when the authors re-analyzed the HRQOL scores on the basis of nadir oxygen saturation less than or greater than 80%, no difference was found in any SF-36 dimension between more or less severely hypoxemic patients, suggesting that the impairment in the HRQOL scores was not due primarily to the severity of hypoxemia related to the OSA. Resolution of ED with CPAP is associated with significant improvements in HRQOL (77).

CPAP and HRQOL in OSA

HRQOL assessment following OSA treatment provides additional evidence for impaired quality of life in patients with OSA, as well as helps define the potential for improvement of these parameters. The subsequent section will specifically address this.

Background of CPAP Use in OSA

CPAP functions as a pneumatic splint to prevent pharyngeal collapse in patients with OSA, thereby decreasing the number of arousals and allowing for a night of improved sleep consolidation (78). It is the mainstay of physiologic and medical therapy for OSA, and numerous studies have demonstrated

a salutary effect of therapeutic CPAP on daytime sleepiness, sleep architecture, and OSA-associated cardiovascular perturbations including daytime and nighttime blood pressure, cardiac dysrhythmias, and left ventricular function (79–83).

Effects of CPAP on HRQOL in OSA

Multiple uncontrolled studies have demonstrated an improvement in HRQOL parameters in patients with OSA following use of CPAP. Smith and Shneerson (16) found that treatment with CPAP for 6 months improved all domain scores of the SF-36, with the vitality domain returning to a normal level. Following 5 weeks of CPAP therapy, patients with OSA showed significant improvement in multiple domains of the SF-36, with medium or large effect sizes (84) in vitality, social functioning, role-emotional, PCS, and MCS in the study by Jenkinson and colleagues described above (11). Bennett and colleagues (18) showed normalization of before-treatment impairment in the domains of vitality and role-physical in the above-mentioned study of 51 patients with moderate to severe OSA (AHI > 25/h) and daytime sleepiness. D'Ambrosio and co-workers (38), in the above-noted prospective evaluation of patients referred for polysomnography, found that all patients, regardless of severity of OSA, showed significant improvements in the domains of vitality, social functioning, and mental health. Patients with the lowest HRQOL scores at baseline appeared to improve the most with nasal CPAP treatment. Sin and coworkers (19), in the above-mentioned trial analyzing the short- and long-term effects of CPAP therapy on HRQOL in 365 patients with severe OSA (mean AHI 65.5/h) compared with 358 untreated patients with mild OSA (mean AHI 5.1/h), found that, although both patient groups had similar HRQOL impairments at baseline, the CPAP-treated patients reported higher MCS scores by 3 months of treatment. Improvement was greatest in the vitality domain and was sustained following 12 months of therapy (19). Kawahara and colleagues (50) studying 132 OSA patients with generally severe OSA (mean AHI 59.4/h), as noted in a preceding section of this chapter, found that each dimension of the SF-36 improved significantly following 8 weeks of CPAP treatment. Zung Self-Reporting Depression Scale (SDS) scores were also significantly improved, and the magnitude of improvement in five of the SF-36 domains (physical functioning, general health perceptions, vitality, social functioning, and mental health) was significantly correlated with the magnitude of improvement in SDS scores. As noted above, the work of McFadyen and colleagues (76) regarding marital satisfaction showed that 3 months of CPAP therapy was associated with significantly improved ENRICH scores compared to conservative therapy. Goncalves and colleagues (77), as cited above in the preceding section, compared 17 OSA patients with ED who successfully used CPAP with 17 age- and BMI-matched OSA control patients after 4 weeks of CPAP treatment. ED resolved in 13 of the 17 subjects and HRQOL scores rose, with statistically significant improvements in role-physical, general health perceptions, role-emotional, and mental health (77). Interestingly, the OSA patients without ED also showed improvement following CPAP treatment in the dimensions of general health perceptions and mental health.

Controlled trials of CPAP efficacy in OSA have also demonstrated HRQOL improvements with CPAP. Engleman and colleagues (85) assessed the effect of four weeks of CPAP treatment on sleepiness and HRQOL, compared with oral placebo, in 34 patients with mild OSA (mean AHI 10/h) through a randomized crossover design trial. In the setting of a significant reduction in subjective (ESS) but not objective (Maintenance of Wakefulness Test) measures of sleepiness, no significant improvement in HRQOL was elicited with the NHP, but five of nine SF-36 subscales (health transition, role-physical, bodily pain, social function, and energy/vitality) showed significant improvements with CPAP treatment, and the mental health subscale showed a trend toward improvement ($p = 0.09$). Notably, CPAP utilization in this trial was fairly low, with CPAP use averaging 2.8 ± 2.1 h per night. When the data were analyzed according to use of CPAP for more or less than 2.5 h per night, those in the higher-use group evidenced significantly larger improvements in NHP scores and the SF-36 dimensions of social function and vitality compared with placebo users. Redline and coworkers (86) compared 8 weeks of CPAP treatment with use of a nasal dilator strip in 97 patients with mild OSA (mean RDI 13.3/h and absence of pathological sleepiness). Compliance with CPAP, assessed by accessing the CPAP machine's internal compliance monitor, was poor, with measured CPAP use for only 44% of estimated sleep time, translating to approximately 3.1 h per night. Fifty percent of subjects randomized to CPAP used CPAP for at least 40% of estimated sleep time. Subjective (ESS) but not objective (MSLT) sleepiness was improved with CPAP therapy; neither improved with conservative therapy. A composite score of outcomes was assessed, including the SF-36 domains of vitality, general health perceptions, role-emotional, role-physical, and social functioning; the fatigue sub-score of the POMS; and the Positive and Negative Affect Scale (PANAS) score, which assesses positive and negative emotional states (87). The odds ratio of experiencing a favorable treatment response was 2.72 for the CPAP users as compared with those using nasal dilator strips (86). Post hoc analysis revealed that the only individual measurement of the composite score that improved significantly more with CPAP therapy than with conservative therapy was the SF-36 vitality domain (effect size 0.52). A study of 142 patients with mild to moderate OSA (mean AHI 20/h), randomized to either CPAP or conservative therapy for 6 months, showed normal HRQOL score ranges in all patients during initial assessment with both the FOSQ and the NHP (27). Despite this, the group treated with CPAP showed a trend toward improvement in the FOSQ domain of vigilance ($p = 0.06$) at 6 months. Notably, CPAP compliance was markedly higher than in other studies, with patients averaging 4.8 h of CPAP use per night. Forty-eight patients with moderate OSA (median AHI 22/h and mean ESS score

14) were randomized to 8 weeks of therapy with CPAP or a mandibular repositioning device (88). Relatively high CPAP compliance (4.9 h/night) was reported, and significant, although clinically modest, improvements were seen in the SF-36 PCS and MCS scores (effect sizes 0.35 and 0.34, respectively). Another study of 48 patients with moderate to severe OSA (mean AHI 54/h) randomized to 6 weeks of therapeutic versus sham CPAP showed significantly greater improvements in subjective sleepiness (ESS) and the FOSQ domains of general productivity and vigilance with therapeutic CPAP compared with placebo (89). Placebo effect was evident, as sham CPAP conferred significant HRQOL benefits, relative to pretreatment baseline, in the SF-36 domains of bodily pain, social functioning, and role-emotional, and in the MCS. There were no differences in overall treatment effect, measured by the SF-36, between therapeutic and sham CPAP.

Placebo effect is evident in other controlled trials of CPAP and HRQOL as well. Studying patients with severe OSA, Jenkinson and colleagues (90) performed a placebo-controlled, double-blind, randomized trial comparing therapeutic to sham CPAP in 101 patients with an oxygen desaturation index 4% (number of times per hour that oxygen saturation falls by 4%) of 30.7/h. OSA patients who used therapeutic CPAP therapy reported significant improvements in all SF-36 domains, with moderate or large effect sizes in general health, social functioning, physical role, mental role, mental health, vitality, and MCS. A small but significant placebo effect was noted in subjective sleepiness, mental health, and the two SF-36 summary scores (PCS and MCS); however, a large placebo effect was seen with the vitality score. Therapeutic CPAP use was associated with significantly larger improvements in each of these domains than placebo. Placebo effect on HRQOL indices is also evident in the data of Barnes and co-workers (35), who used an oral placebo to assess the effect of CPAP treatment in patients with mild OSA (mean AHI 12.9/h and no severe oxygen desaturation). With a reduction in the mean AHI to 4.24/h and measured CPAP compliance of 3.53 h per night, HRQOL as assessed by the FOSQ and SF-36 improved from pre-treatment scores in numerous domains, including general productivity, social outcome, activity level, and vigilance (FOSQ) and physical functioning, role-emotional, mental health, and vitality (SF-36). However, these improvements were no greater than those seen in the placebo group, with a strong trend toward a significant difference ($p = 0.06$) only for the FOSQ domain vigilance. It is possible that a CPAP carryover effect was present, which confounded these results. A follow-up study by the same investigators (91), comparing the efficacy of CPAP, mandibular advancement device, and oral placebo, found that placebo use significantly improved HRQOL as measured by the FOSQ mean score and the general productivity, activity, and vigilance domains. CPAP use conferred a benefit beyond that of placebo therapy in the same FOSQ domains, excepting vigilance and a composite of the SF-36 domains mental health, vitality, and bodily pain. Pre-specified post hoc analysis showed that this HRQOL improvement due to CPAP was also present for patients with mild OSA (baseline AHI of 15/h or less).

Summary of HRQOL in Untreated and Treated OSA

As documented in the above data regarding HRQOL in OSA and treatment with CPAP, numerous studies suggest that therapeutic CPAP therapy appears to be efficacious in improving HRQOL parameters in patients with OSA. Patients with more severe PSG parameters of OSA tend to show the greatest benefit. Among those patients with mild OSA, the HRQOL benefits of CPAP appear to accrue primarily in the domains of vigilance, vitality, physical function, and general health, which conclusion is supported by a recent Cochrane review of the clinical effectiveness of CPAP in the treatment of OSA (92). These CPAP efficacy data, assessing the characteristically most effective physiologic treatment of OSA, also support a large body of evidence that HRQOL is impaired in untreated OSA with respect to specific domains such as vigilance and vitality. However, placebo effect seen in some of the randomized controlled trials to date raises the possibility that HRQOL impairment in OSA, as assessed by the current tools in general use, accrues from aspects of the disorder other than the physiologic effects of the OSA itself, a notion further strengthened by the lack of consistent correlation between physiologic indices of OSA severity and HRQOL scores. The noted data also suggest that there are significant differences in sensitivity and specificity among the various tools currently employed to assess HRQOL in OSA and that further investigation is necessary regarding which HRQOL tools will ultimately bring the greatest degree of consensus regarding HRQOL impairment in different groups of patients with untreated OSA and the effects of successful OSA treatment on such impairment. Further randomized controlled trials are necessary to better elucidate the associations between physiologic impairment in OSA and the specific HRQOL measures of interest to clinicians and researchers in this field.

Issues that need to be addressed by future research:

- Randomized controlled trials are necessary to determine the contribution of socioeconomic status, cultural concerns, and factors other than the physiologic effects of OSA in the assessment of HRQOL in untreated OSA, and the treatment effect of CPAP.
- Further research is necessary to determine the optimal instruments and combination of instruments to identify and measure of HRQOL impairment in OSA before and after treatment.
- The relationships among specific HRQOL domain impairments and excessive sleepiness, cognitive

dysfunction, and psychological impairment in OSA remain to be better elucidated.
- The success of long-term treatment of OSA in improving HRQOL impairment requires further investigation.

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10
Sleep and Quality of Life in Narcolepsy

Meeta Goswami

Summary With an increase in the older segment of the population and a concurrent increase in the prevalence of chronic illnesses, interest in quality of life (QOL) has gained increasing significance. This presentation discusses the significance and theoretical constructs in the definition and measurement of QOL. Furthermore, a review of studies shows that narcolepsy has a profound negative social, psychological, and economic impact on the lives of affected individuals. New management strategies comprising comprehensive, multidisciplinary patient management approach including psychosocial treatment and social support are needed to improve patients' functional status. Educational programs about the wide ramifications of having narcolepsy are needed. Also, the operational definition of the symptoms of narcolepsy and indicators of health-related quality of life (HRQOL) are often not consistent and need standardization to make comparison of studies on the impact of narcolepsy more meaningful.

Keywords Narcolepsy quality of life · health-related quality of life · social support

Learning objectives:

- Narcolepsy has a profound negative social, psychological, and economic impact on the lives of affected individuals, and pharmacological treatment is neither optimal nor sufficient.
- New management strategies are needed, including patient's perspectives on illness, its impact and meaning.
- A comprehensive, multidisciplinary patient management approach, including pharmacological and psychosocial treatment and support group participation, is ideal for the management of narcolepsy.

Dynamics of Change

With technological advances in the field of health, the life expectancy of individuals has increased with a concurrent increase in the older segment of the population and, consequently, the rate of chronic illnesses. People not only want to live longer, but they also want to reduce levels of disability and discomfort and increase general satisfaction with their lives. Thus, both quantity and quality of life (QOL) have gained significance.

The increasing importance of the study of QOL in health/medicine is reflected in an increase in the number of articles in this area. A Medline computer search for publications on QOL, using keywords *quality of life*, showed an increase from 16 articles between 1966 and 1974 to 1,436 articles between 1975 and 1989 to 19,220 articles between 1990 and 2006 (November). Although publications on QOL in medical disorders continue to proliferate, the literature on QOL in sleep disorders and narcolepsy remains scant. A Medline computer search with keywords *quality of life* and *sleep disorders* revealed only three articles between 1975 and 1989 followed by 187 publications between 1990 and 2006. This compares with three articles between 1975 and 1989 and 11 articles between 1990 and 2006 using the keywords *quality of life* and *narcolepsy*.

This chapter discusses the significance and definition of QOL in health and methodological considerations in the development of QOL instruments followed by a review of literature on QOL in narcolepsy and implications for patient care and research.

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Significance of Quality of Life

Data gathered from QOL studies are useful at the governmental level for planning and policy. At the agency level, studies on QOL are important in conducting cost-benefit analyses, evaluating health programs, making appropriate changes in program development, and justifying funding. At the clinical level, studies on QOL provide valuable information for evaluating health outcomes, identifying problems and needs, and tailoring the management plan to suit patients' needs. Thus, QOL studies generate data that may be applied to enhance communication between patient and professional and improve overall quality of care for patients.

Additionally, results of such studies could be valuable for family members who care for the disabled in helping them to understand the patient's disability and provide an effective support system.

Definition of Quality of Life and its Measurement

For the scientific study of QOL, a theoretical model or construct must be delineated with a rationale for selecting the instrument. Persons may be viewed as aspiring to live a life that has a purpose, integrating various dimensions of life into a meaningful whole for optimal personal sense of peace and fulfillment. Health, including the physical, mental, social, and spiritual aspects, would be an important dimension for overall well-being. Impediments to personal fulfillment would be disease/illness and its impact, such as fear and pain, reduced energy and mobility, loss of job or relationships, and isolation. Another way of examining the QOL paradigm is by assessing the differences in a person's expectations, achievements, reactions, and reality. This gap may be reduced and, therefore, the QOL improved by enhancing functions with treatment, reducing expectations, accepting limitations of the disease (1–4), and improving interpersonal relations and satisfaction with life by appropriate counseling and social support.

The definition of QOL is elusive and constantly changing. The World Health Organization defines QOL as individuals' perception of their position in life in the context of the culture and value system in which they live and in relation to their goals, expectations, standards, and concerns (4). There is broad agreement in the consideration of five areas comprised of physical (including pain), emotional state (including concentration and memory), performance of social roles, intellectual function, and general feelings of well-being or life satisfaction (5–7). Others have proposed subjective well-being, health, and welfare (8) and social performance and social well-being, which are further specified in terms of social support and social adjustment (9) as important domains. Health status and QOL are separate concepts, as people with disabilities may assess their QOL highly despite having a disorder or disability depending on their attitudes toward pain and disability, their coping strategies, and social networks. Often, health status has been described as QOL (10–12).

Methodological Considerations in Development of QOL Instruments

Purpose

The instrument (questionnaire) should be suitable to the impairment/disease/condition under study. Generic instruments have a wider scope than disease-specific ones and are designed to make comparisons across a wide range of conditions and different health interventions and across demographic and cultural subgroups. They fail to capture domains that are salient to the individual and are not person-centered to capture the meaning of the illness to the patient. There is a call to develop individualized measures that are sensitive to the subtle social and personal lives of patients (12). When the goal is to measure clinically important changes of health interventions in specific conditions, diagnostic categories, or special populations, a disease-specific instrument is more suitable (13, 14).

Comprehensiveness

A combination of generic and disease-specific measures would ensure comprehensiveness and scope without losing specific clinical information (15). Biomedical measures based on laboratory tests and radiographs are objective and easy to quantify and analyze; however, they do not represent patients' perspectives, the impact of the illness on their lives, and their social functions (16, 17). It would be productive to measure subjective well-being because health and subjective well-being are inextricably interrelated (18), and self-perceived health status is shown to be predictive of mortality and disability (19). Some researchers support individual self-assessment (20–22). Subjective measures need not be "soft" if scientific consideration is given to the development of the instrument.

Sensitivity

The instrument should measure change over time. It should have the discriminative power to differentiate among and within respondents at a given point of time and predict future outcomes (23, 24).

Reliability

This is the extent to which a measuring instrument is reproducible and stable. Does the instrument yield the same results on independent repeated trials under the same conditions?

(25) Internal consistency, another measure of reliability, is the extent to which the items in an instrument measure the same concept (26).

Validity

To what extent does the instrument measure what it intends to measure? Face validity measures what we say it measures. Content validity depends on the extent to which a measurement reflects the full domain relevant to the particular measurement situation (25). Construct validity depends on making logical predictions about relationships between QOL and other variables and then checking whether these predictions hold when the instrument is used (26). Validity may also be established by consensus of experts or by using an instrument for which effectiveness has been established in a similar situation in the past. The instrument should be applicable to other populations and must be pretested on the population under study.

Administration

The instrument should be as brief as possible without sacrificing validity and relevant information so that patients can complete it in a reasonable amount of time without getting tired or bored. Selection biases, including institutional and self-selection, in recruiting subjects for surveys must be identified. The method of recruiting—personal interviews, telephone, or mail—and the order of items in the questionnaire, as well as the type of instrument, will affect responses. The generic instrument should be administered prior to the disease-specific instrument to reduce bias. Floor and ceiling effects are other important considerations (27). The field of functional health is rapidly evolving, and topics addressed include a new formulation of the structure of health status, the use of item response, theory, and computerized dynamic health assessment (28).

Health-Related Quality of Life Instruments

Health-related quality of life (HRQOL) instruments used in sleep research have been reviewed (27, 29). Here, we present selected instruments to measure QOL in narcolepsy.

The Short Form-36

The most commonly used generic measures developed from the Medical Outcomes Study are Short Form-36 (SF-36), SF-12, and SF-8. The SF-36 is the most comprehensive (30, 31) and has been tested extensively in the USA and other countries and has been translated into many languages. It is considered the current acceptable standard measure for HRQOL with high reliability and validity. The instrument measures eight dimensions: physical functioning, role functioning-physical, role functioning-emotional, mental health, social functioning, vitality, bodily pain, and general health. It does not ask questions about sleep and uses vitality as a proxy—a term that can be misinterpreted by the respondent. Vitality is included in the mental health summary score but correlates significantly with both mental and physical health (32). Shorter versions of the SF-36, that is, SF-12 and SF-8, are available to ensure easy administration in less time (33). The SF-36 version 2, a new modification, has improved wording and instructions, better internal consistency and reliability, and reduced floor and ceiling effects compared to the older version, thus improving its sensitivity to change and its precision (differentiation among groups) (27, 34).

Functional Outcomes of Sleep Questionnaire

The Functional Outcomes of Sleep Questionnaire (FOSQ) is a disease-specific, 35-item instrument that assesses the impact of excessive daytime sleepiness in physical, mental, and social functioning in daily activities. It measures activity level, vigilance, intimacy and sexual relationships, general productivity, and social outcome. The instrument is reported to have content validity, internal consistency, test–retest reliability, construct validity with the Epworth Sleepiness Scale as well as concurrent validity with the Sickness Impact Profile (SIP) and SF-36 (35). A Norwegian version showed satisfactory internal consistency, test–retest reliability, and construct validity (36). It is not as comprehensive as the SIP or the SF-36 as it does not include burden of symptoms and overall well-being (27). It could serve as an adjunct with the SF-36 to assess HRQOL in narcolepsy.

Quality of Life in Narcolepsy

The impact of narcolepsy and the QOL issues have been reviewed and documented (37–42), showing that narcolepsy has profound and varied effects on work, education, recreation, sexual life, interpersonal relations, memory, personality, and marital life. A study in Germany illustrated the high economic costs of having narcolepsy (43). Narcolepsy patients have poor driving records and high rates of automobile accidents (44, 45). Depression is a common feature in narcolepsy (42, 46–48). Psychopathology was noted by Kales and Krishnan (46, 47). However, a recent study in UK found that narcolepsy is not associated with psychiatric disorders or with diagnosable depressive disorders. These unexpected findings could be due to effects of medications, differences in sample size, lack of standardized measures of symptoms, selection bias, and confusing hypnagogic hallucinations of narcolepsy, especially auditory hallucinations, with schizophrenia (49). Rieger et al. found that attentional impairments in narcolepsy were not due to slowness and variability of performance alone. In addition to impairment in

the vigilance attention network, results showed impairment in the executive attention network in narcolepsy (50). Other issues are high divorce and unemployment rates in comparison with US rates. Pervasive feelings of tiredness, low levels of energy and motivation, and an apathetic demeanor were reported (51).

QOL in narcolepsy may also be affected in more subtle ways. For instance, the symptoms of narcolepsy are not visible and do not cause physical disfigurement or a discernible handicap; therefore, it is often not known that narcolepsy is classified legally by the United States Federal and State governments as a disability and in New York State as a developmental disability (52). Because of this lack of visibility of symptoms, patients are perceived by others as being normal and much is expected of them. Inability to fulfill role obligations in a highly competitive society causes them to feel socially isolated and have low self-esteem. They often report feeling vulnerable to accidents, job loss, loss of relationships, and economic loss with subsequent sense of insecurity. Procrastination, difficulty getting things done, punctuality, and planning and organizing time are areas of concern to these patients. Many tend to lack focus or concentration on tasks and vacillate when it comes to making decisions.

Health-Related Quality of Life

HRQOL was examined in a national investigation concerning the effects of modafinil on wakefulness (53).

Data were collected in two similar 9-week double-blind studies. Subjects (558) from 38 centers were randomized into one of three groups: placebo, 200 mg modafinil, or 400 mg modafinil. A questionnaire comprised of the SF-36 and supplemental narcolepsy-specific scales was administered to assess QOL changes with treatment**.** These two instruments were pretested on narcolepsy patients in two sleep centers (54). Compared to the general population, people with narcolepsy (PWN) were more affected in vitality, social functioning, and ability to perform usual activities due to physical and emotional problems. PWN experienced HRQOL effects as bad as or worse than those with Parkinson's disease and epilepsy in several HRQOL areas. HRQOL effects were worse among PWN than among those with migraine headaches with one exception: bodily pain.

In the UK (48), treated PWN had significantly lower scores than treated obstructive sleep apnea hypopnea syndrome (OSAHS) patients for mental health and general health as measured by the SF-36. When compared with untreated OSAHS patients, no significant differences were found in the eight domains of the SF-36, indicating a poor functional status in both conditions. Treated PWN were sleepier than untreated OSAHS patients with a greater impact on activities of daily living. PWN had difficulties in relation to leisure activities, subjects reported falling asleep in class (50%), at work (67%), and losing or leaving a job because of narcolepsy (52%).

In a study in Italy, following a psychometric analysis, the SF-36 was found to be a reliable outcome measure for hypersomniac disorders. Narcolepsy patients were compared with idiopathic hypersomnia and sleep apnea patients. All domains, except bodily pain, scored lower than the Italian norm. Some of the variance was explained by EDS (inverse relation) and disease duration (direct relation, probably due to adaptation) (55). The SF-36 was self-administered.

The FOSQ was used in a randomized trial with 285 patients with narcolepsy to study the effectiveness of sodium oxybate on HRQOL in these patients. Sodium oxybate produced significant dose-related improvements in the Total Functional Outcomes of Sleep Questionnaire score from baseline. Similar improvements were observed in the Activity Level, General Productivity, Vigilance, and Social Outcomes subscales ($p < .01$). Intimacy and Sexual Relationships subscale was not affected (56).

A survey of 129 members of the Australian Narcolepsy Support Group, using the Psychosocial Adjustment of Illness Subscale-Self Report (PAIS-SR) total score, showed more adjustment problems for men than for women. Younger people had more vocational adjustment problems than older PWN, probably due to the older group's better acceptance and management of their condition. Significant differences were found among the three medication status groups. The stimulant medication group was better adjusted than the no medication group and the stimulants + tricyclics group. The no medication group was the least adjusted in terms of social environment. PWN in this study reported more adjustment problems in comparison to cardiac, mixed cancers, and diabetes patients (57). The results of this study are difficult to compare with other studies because of the self-selected sample and different measuring instruments.

Similarly, in a mailed questionnaire survey of 305 members of the United Kingdom Association of Narcolepsy (UKAN), respondents scored significantly lower on all domains of the SF-36 than age- and sex-matched normative data and particularly poorly in the physical, energy/vitality, and social functioning domains. The psychosocial questions developed for this study showed that narcolepsy affected education, work, relationships, activities of daily living, and leisure activities. Respondents reported avoiding situations that could be embarrassing or hurtful if they were to have cataplexy or fall asleep inappropriately. The Beck Depression Inventory (BDI) indicated that 56.9% of subjects had some degree of depression. There was no difference among groups receiving different medications. Even those who were on medication did not show normal health status. These results suggest that the pharmacological management of narcolepsy is inadequate (58). This study was done on self-selected members, and diagnosis of narcolepsy was not clearly established.

A cross-sectional study of 77 respondents with a diagnosis of narcolepsy with cataplexy and membership in the

Norwegian Association for Sleep Disorder (NASD) showed that respondents had significantly lower scores on all domains of the scale of the SF-36, with the exception of the vitality domain, when compared with the normal population. The SF-36 was mailed to the respondents. Receiving medication for narcolepsy did not affect any domain in the study. The authors attribute differences in results from other studies to a difference in mindset or public education in Norway or to membership in the NASD (59).

Our literature review of studies on HRQOL in narcolepsy in the USA and Europe documents the extensive negative effects of narcolepsy on the lives of affected individuals in the areas of physical, mental, and social health. Despite differences in methodology, an overall pattern of decrement in functioning is illustrated. This high level of impact on activities of daily living indicates that treatment and management of narcolepsy are not optimal and that new treatment modalities are needed.

The improvement of QOL in narcolepsy depends on effective management of clinical symptoms of this syndrome, their effects, and subjective complaints of the patient. The biomedical symptoms of excessive daytime sleepiness, cataplexy, hypnagogic hallucinations, sleep paralysis, automatic behavior, and disturbed nocturnal sleep are ameliorated by appropriate pharmacological and behavioral management. Successful management of objective and observable clinical features may be affected by other complaints of narcolepsy patients, such as low level of energy and fatigue, problems with memory, depressed mood, and perception of lack of security in the environment. These complaints may be alleviated in some patients with pharmacological treatment and individual and family counseling.

Social factors play an important role in QOL as they are inextricably involved with health status (60–62). Social network variables have a direct relationship with mortality rates (61), and some significantly affect overall health status of patients with chronic diseases (63, 64). People who are more socially embedded function better than those with few social ties (65–68). Social support gratifies emotional needs (affection, sympathy, understanding, acceptance, and esteem from significant others) or instrumental needs (advice, information, assistance with responsibilities, and economic help) (69). In a qualitative study, narcolepsy patients reported several benefits of attending support groups: emotional support and strength from other peoples' experiences and valuable information on medications, diet, organizing tasks, and learning to keep awake. Support groups provide a forum for information exchange, acceptance and understanding by peers who are similarly affected, and access to pertinent resources in a supportive and caring environment. Patients feel reassured and develop confidence and hope (70). Thus, counseling and support are important in the comprehensive management of narcolepsy.

Conclusions

QOL and sleep medicine are emerging disciplines in the field of health and sleep disorders and will gain increasing significance in view of the changes in the delivery of health care in the USA.

A review of studies in the USA, Canada, Europe, and Australia shows that narcolepsy has a profound negative social, psychological, and economic impact on the lives of affected individuals. Pharmacological management is neither optimal nor sufficient. New management strategies are needed to improve patients' functional status and productivity. Timely diagnosis and treatment, not only of the clinical symptoms but also of the impact of narcolepsy and its treatment, are crucial for improving the QOL of patients. A comprehensive, multidisciplinary patient management approach, including pharmacological and psychosocial treatment and support group participation, is ideal for the management of narcolepsy. It is important to consider the patient's definition of illness and its impact and meaning to the patient. Patients' sense of vulnerability, safety, isolation, satisfaction with treatment, and overall satisfaction with life need sensitive consideration. Information on subtle life changes, often unknown to the patient, can be elicited with a short screening instrument to assess needs and make an appropriate referral for psychosocial management and support group participation. Public education programs about the wide ramifications of having narcolepsy must be directed toward physicians, nurses, counselors, social workers, school teachers, and pharmacists.

Lastly, considerable variation exists in the operational definition of the symptoms of narcolepsy and indicators of QOL. A combination of generic and disease-specific measures as well as subjective and objective measures will provide a comprehensive picture of the patient's well-being. The effects of demographic variables such as gender, social class, and ethnic backgrounds in HRQOL must be addressed so that management and educational activities can be fine-tuned to suit the specific needs of patients. Stratifying patients by medication status will likely eliminate some of the confounding effects of side reactions of medications in assessing the impact of narcolepsy. Effects of daytime sleepiness and tiredness, common complaints of PWN, on patients' responses are important considerations in analyzing data.

An international and multidisciplinary approach to develop a standardized, sensitive, reliable, and valid QOL instrument for narcolepsy will make national and cross-cultural comparison of studies on the impact of narcolepsy more meaningful.

Issues that need to be addressed by future research:

- Standardized, reliable, and valid instruments are needed to assess clinical symptoms and HRQOL in narcolepsy.

- A combination of generic and disease-specific measures as well as subjective and objective measures will provide a comprehensive picture of the patient's well-being.
- The effects of demographic variables, such as gender, social class, and ethnic backgrounds, and the role of medication status on HRQOL in narcolepsy need further investigation.
- Research is needed on the role of support groups on patients' well-being and their mechanism of action.

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Sleep and Quality of Life in Restless Legs Syndrome

Marco Zucconi and Mauro Manconi

Summary Restless legs syndrome (RLS) is a sensory-motor disorder characterized by uncomfortable and disagreeable sensations at lower limbs, urge to move them and peaking during rest periods and at evening/night, with impact on sleep, causing insomnia and sleep fragmentation. Both severity of the sensory symptoms and periodic legs movements during sleep (PLMS) contribute to sleep impairment and, consequently, to a reduced quality of life (QoL). Measurement of RLS impact on QoL is made, both in clinical and epidemiological studies, by means of a Short Form-36 (SF-36) of health survey questionnaire and by validated and disease-specific QoL scales (RLSQoL and Hopkins RLSQoL). Both types of measures indicated a significant impact of RLS on QoL in different clinical and prevalence studies and showed good reliability, reproducibility and responsiveness. Moreover, QoL significantly improved, both in short-term studies and in recently published long-term protocols, with dopaminergic treatment in comparison to placebo. In what measure RLS per se, some disease-specific symptoms as restlessness and bad sleep or other co-morbidity factors, contribute to the impairment of QoL remain to be further investigated.

Keywords Restless legs syndrome · periodic leg movements · quality of life · sleep · insomnia · therapy

Learning objectives:

- Quality of Life (QoL) is impaired in moderate to severe restless legs syndrome (RLS).
- Validated and disease-specific QoL scales showed good reliability, reproducibility and responsiveness.
- QoL is significantly improved by dopaminergic RLS treatment.

Introduction

Restless legs syndrome (RLS) is a common, often underdiagnosed, sensorimotor disorder characterized by an uncomfortable and disagreeable sensation in the legs, and sometimes also in the arms, which provokes an urge to move them (1). The appearance or worsening of the symptoms during rest periods with complete or partial improvement by movements, and the circadian trend of the symptoms occurring or intensifying in the evening or at night with difficulty to fall or stay asleep constitute the main symptoms of the syndrome. Moreover, because of the impact on sleep period, an effect on sleep structure with sleep loss and/or sleep fragmentation, the latter caused by periodic leg movements during sleep (PLMS), is one of the major finding of RLS (2). Thus, RLS, although not involving stereotyped movements during sleep per se, is classified in the sleep-related movement disorders section of the recent International Classification of Sleep Disorders (International Classification of Sleep Disorders-2, 2005) because of its close relationship with PLMS. Notwithstanding RLS does not increase the risk of mortality or of serious morbidity, sleep disruption at night and sensory problems involving discomfort and sometimes pain during the day have an impact on quality of life (QoL) and may lead to possible cognitive impairment (3, 4). As indicators coming from epidemiological and clinical population studies, sleep and daytime complaints may be or may not be of clinical relevance and, therefore, we have to measure the impact of such symptoms on normal daily living to justify the efforts for RLS treatment. The major problem of QoL research in RLS consists in the multi-facet character of the RLS disease. Impact of RLS is readily apparent in terms of distressing symptoms, sleep disturbance, social deprivations, depressive or anxious mood, and side effects of treatments. The measurement of QoL consequences of RLS by means of adequate, sensible and disease-specific approaches and tools may clarify the importance of the RLS impact and give better indications for treatment.

After a brief description of the RLS diagnostic criteria and of the impact of the syndrome on sleep, this chapter will

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examine the evaluation of health-related QoL status analyzing the impact of RLS on Short Form-36 (SF-36) health survey questionnaire and on disease-specific QoL scales (RLSQoL and Hopkins RLSQoL). Finally, the treatment effect and benefit on QoL will be discussed.

Impact of RLS on Sleep

Sleep is usually favoured by rest and nighttime, these two conditions are unfortunately the same which exacerbate RLS symptoms. On the other hand, the methods to relieve symptoms keep patients from sleeping. Therefore, in most of RLS patients, symptoms interfere with the onset and maintenance of sleep, generating insomnia, especially during the first part of the night (5). Despite not mandatory for the diagnosis, sleep disturbance is cited among the diagnostic criteria as a common associated feature of RLS, representing one of the major morbidity for RLS patients, which requires special consideration in planning treatment. Sleep disruption generally depends on RLS severity. When RLS symptoms are severe, insomnia often becomes the primary reason the patient seeks medical attention. In this case, insomnia should be intended as a subjective experience of disrupted sleep, which not always agrees with objective polysomnographic findings (6). When subjective complains correspond to instrumental results, a reduction in sleep efficiency, mainly due to increasing of sleep latency and sleep fragmentation, represents the most important finding in sleep report (7, 8). In mild RLS forms or in patients with an advanced peak of symptoms during evening and not bedtime, sleep impairment may be rare or absent. The prevalence of insomnia in RLS population is still unclear, but almost all patients who require a pharmacological treatment present some degree of sleep disturbance (5). Chronic insomnia, secondary to RLS, may even persist after symptoms resolution (6).

Another possible, but still discussed, cause of sleep disruption is represented by PLMS, which can be demonstrated in about 80–90% of RLS patients (9, 10). PLMS are repetitive leg jerks characterized by a triple flexion movement at ankle, knee and hip, which arise from sleep, especially during NREM stages 1 and 2 and from relaxing awake (PLMW, periodic legs movements during wake) (11). Leg movements are easily detected by placing two electrodes over each tibials anterior muscles during a standard polysomnography (12). PLMS is often associated with cortical arousals and awakenings, insomnia and excessive daytime sleepiness, but it is controversial whether they cause a sleep disorder by themselves (13–15). They probably contribute to RLS with the sleep fragmentation. The quantification of the number of PLMS associated with arousals (PLMS arousal index) are the most accepted method to measure the sleep RLS impact. An index (number of PLMS in an hour) greater than 15 for the whole night is considered pathologic. Periodic limb movements of sleep also occur frequently in several other sleep and neurological disorders or in subjects without sleep complaints, especially the elderly (16).

Sleep disruption is one of the main cause of reducing QoL in RLS patients (3). As there is a good correlation between the severity of sleep disruption and one of the symptoms, it is important to measure accurately and by a reliable method the RLS severity. The RLS rating scale (IRLSRS) has been validated by the International RLS Study Group for this purpose (17). It consists in a self-administered 10-item questionnaire which takes into account the burden of different aspects such as sensitive symptoms, motor component, frequency of symptoms occurrence, sleep disturbance, daytime sleepiness and the impact of the disease on the common daily activities. The final score ranges between 0 and 40 and classifies the RLS as mild (1–10), moderate (11–20), severe (21–30) and very severe (31–40). The RLS scale assessing may be useful also to verify the effectiveness of a treatment.

General Health-Related Quality of Life Impact of RLS

Firstly from epidemiological studies, the impact of RLS on QoL has been limited to an association with daytime fatigue, excessive daytime sleepiness, more physical and mental health problems, anxiety and depression symptoms, generally based on answers to self-reported questions included in the studies or depicted by anxiety–depression scales (18–21). Only more recently, specific measurements as SF-12 mental health score, SF-12 physical health score, Mini-Mental State Examination, SF-36 medical outcome score have been added to epidemiological questionnaire or, separately, investigated in population with RLS and compared with controls or across a range of patient populations with different medical conditions.

Overall, the SF-36, becoming the most commonly used general scale for the evaluation of health-related QoL, has been mostly evaluated in RLS population both in prevalence and clinical studies (3, 22, 23).

The MOS 36-item SF-36 health survey evaluates eight domains of health-related QoL: physical functioning, physical limitations on normal role activities, bodily pain, general health, energy/vitality, social functioning, emotional limitations on normal role activities and mental health (24). In the REST study (25), members of the RLS cohort had lower QoL scores for all domains than the normal population, with energy/vitality, physical and bodily pain the area mostly impacted. Moreover, a comparison of the US data with results from patients with other medical conditions in US populations showed that QoL in the RLS cohort was comparable with that in conditions such as type-2 diabetes, chronic obstructive pulmonary disorder, depression, hypertension and osteoarthritis. Similar results were observed in a further study (3), in which QoL was measured by means of the SF-36 in 85 patients with RLS and compared with data from a normative

population of 2474 people. Patients with RLS showed significant deficit on physical functioning, bodily pain, role functioning, mental health, general health and vitality domains compared with the general population. The greatest impairments in QoL were seen in patients with the most severe RLS. Moreover, patients with RLS had lower scores in a majority of SF-36 domains compared with patients with other cardiovascular disorders or type-2 diabetes (26). These results show that moderate to severe RLS has a substantial impact on both the physical and the mental health dimensions of QoL and disturbs the life of patients as much as other more frequent and known medical disorders.

However, some of these studies did not consider the co-morbidities associated with RLS. Thus, the question is whether the production of reduced QoL is due fully or mostly to RLS per se or to other factors associated with the syndrome. In the recent study of McCrink et al. (23), the authors analyzed data from the REST study and examined different RLS-related factors to explore which ones were associated with the detrimental impact on health-related QoL. Distress, symptom frequency, the use of prescribed medications for RLS, age, number of co-morbidities and number of physician visits correlated with reduced QoL at the SF-36 score or sometimes (in European samples rather than in US people) with improvement of QoL. This study indicates, as previously suggested (27), that the magnitude of impairment in QoL is also related to some co-morbidities such as anaemia, diabetes mellitus and reduced renal function. However, the study did not clarify an important issue, i.e. the impact of sleep loss and sleep-related modifications on the reduced QoL in RLS patients. The SF-36 does not include aspect and score for such factors, as insomnia, unsatisfactory sleep or daytime sleepiness.

In conclusion from the analysis of different domains of the SF-36, RLS, when moderate to severe, seems to have a detrimental effect on all the scales measuring QoL. In particular, the more pronounced deficit occurs for measures of vitality/energy and limitation of work and activities (limitation for physical problems and vitality domains), as we can expect with a sleep-related movement disorder, suggesting a major decrease in the level of alertness and energetic engagement with daily function.

Whether RLS per se, some disease-specific symptoms as restlessness and short sleep or co-morbidity factors may all contribute, and in what measure, to the impairment of QoL remain to be further investigated.

RLS Quality of Life Questionnaire

Sleep loss and sensitive symptoms are the two major causes of reducing QoL in RLS patients (23). Impairment in mental daytime activity and depression are the main consequences of insomnia, whereas problems in sedentary tasks (job and social activity) appear to be secondary to leg discomfort. For the peculiarity of RLS symptomatology, physical mobility or functioning are supposed to be less impacted compared to sleep and daily activities (3). Therefore, a RLS-specific scale better evaluates the range of life troubles and possible effects of treatment in their improvement. For this purpose, RLS-specific QoL questionnaire was created (28), which has been demonstrated as a reliable tool to assess more particularly RLS impact on daily activities. The RLS QoL questionnaire (RLSQoL) was developed by clinicians expert in sleep medicine with the help of patients affected by RLS and was validated on a cohort of 85 subjects with primary RLS. The instrument demonstrated a good internal reliability, as well as an appropriate reproducibility (test-retest reliability) over a 2-week period. Analyzing the same population with the more general SF-36 questionnaire, a significant correlation was found between the RLSQoL summary scale and the SF-36 mental components summary (3, 28). As expected for the low impact of RLS in limiting mobility, the correlation between RLSQoL summary and SF-36 physical components summary is not significant. The RLSQoL scale also well discriminates among groups with different RLS severity.

The RLSQoL consists in a 18-item self-administered questionnaire that takes into consideration the following areas: severity of RLS symptoms, evening activities, impact on morning activities regarding job or non-job appointments, concentrating in afternoon/evening sexual activities. The final summary score ranges from 0 to 100, with a lower score indicating worse QoL. The entire version of the RLSQoL questionnaire and the rules to calculate its final score are shown in Appendix 1.

Abetz et al. demonstrated the reliability and the responsiveness of the RLSQoL also in a large clinical trial setting (22). In this study, the questionnaire showed a solid correlation with the severity of symptoms assessed by the IRLSRS and by the Clinical Global Impression, measured at baseline and after a 12-week treatment by ropinirole.

Further studies are warranted to confirm the validity of the questionnaire in other than English languages and in symptomatic RLS forms.

Treatment Effect on Quality of Life of RLS

Drug treatment generally ameliorates sensory symptoms and reduces motor component both during wakefulness and sleep (29). At the same time, considering the impact of RLS on QoL, it is expected that treatment should improve QoL of RLS patients. There are numerous studies reporting the positive effect of L-dopa and dopaminergic agonists (DAs) on RLS symptoms and also on daytime consequences and complaints of RLS (19, 22, 30–32). Most of the studies are short-term in duration (less than 3 months) and this may lead not yet evident the effect on QoL, because, even though the maximum average efficacy is achieved after 4 to 8 weeks of treatment, the benefit on daytime effect, daily function and modification of life style may request a longer period of time,

i.e. several weeks. Recently, long-term studies on the effectiveness of DAs on RLS have been published indicating with more emphasis the effect on QoL as an important end-point for the maintenance of the drug efficacy (33, 34).

Different short-term double-blind placebo-controlled studies evaluating some DAs (ropinirole, pramipexole and cabergoline) showed statistically significant improvement in QoL by the Hopkins RLSQoL and the QoL RLS questionnaire (31, 35–37). Ropinirole demonstrated a 25% greater improvement on QoL compared with placebo in two multicentre European and US studies (35,36). Pramipexole showed a persistent effect through 12 weeks on QoL for both lower (0.25 mg) and higher (0.50–0.75 mg) doses, but it failed to modify SF-36 Health Scale as a whole but improved the social functioning subscale after a 3-week treatment period in another study (38). Also cabergoline determined a significant improvement in QoL-RLS after 5 weeks of administration in comparison to placebo (31). Analysis of SF-36 scales did not show results as much as positive as disease-related questionnaire: one study did not show significant difference in QoL between placebo and ropinirole treatment whilst the other one demonstrated improvement in mental health, social functioning and vitality (35, 36). These data confirm that the brief duration of short-term studies does not allow the general effects of QoL to be sensible to significant modifications and indicate the usefulness of disease-specific questionnaires rather than general health scales (39).

Concerning the few data on long-term studies with DAs, ropinirole showed statistically significant differences (improvement) both on RLSQoL questionnaire and SF-36 Health Survey (physical health problems and social functioning) during a 36-week study compared with placebo (34). A similar effect has been recently documented in a controlled withdrawal study of pramipexole after 6 months of open label treatment: at 9 months, QoL measured by the John Hopkins RLSQoL questionnaire persisted improved with respect to placebo, indicating a better health status in the pramipexole group after 9 months of therapy (40). Also in a long-term study with pergolide, although not measured by specific but generic scales (life satisfaction, negative feelings and complaints), the authors showed a significant effect, persisting at 1-year follow-up (32). In summary, dopaminergic treatment seems to significantly improve QoL both in short-term studies and apparently also in long-term follow-up observations in RLS patients.

Appendix 1

The following are some questions on how your RLS might affect your QoL. Answer each of the items below in relation to your life experience in the past 4 weeks. Please mark only one answer for each question. In the past four weeks (28):

1. How distressing to you were your restless legs?
   _ Not at all _ A little _ Some _ Quite a bit _ A lot
2. How often in the past 4 weeks did your restless legs disrupt your routine evening activities?
   _ Never _ A few times _ Sometimes _ Most of the time _ All the time
3. How often in the past 4 weeks did restless legs keep you from attending your evening social activities?
   _ Never _ A few times _ Sometimes _ Most of the time _ All the time
4. In the past 4 weeks how much trouble did you have getting up in the morning due to restless legs?
   _ None _ A little _ Some _ Quite a bit _ A lot
5. In the past 4 weeks how often were you late for work or your first appointments of the day due to restless legs?
   _ Never _ A few times _ Sometimes _ Most of the time _ All the time
6. How many days in the past 4 weeks were you late for work or your first appointments of the day due to restless legs?
   Write in number of days: __
7. How often in the past 4 weeks did you have trouble concentrating in the afternoon?
   _ Never _ A few times _ Sometimes _ Most of the time _ All the time
8. How often in the past 4 weeks did you have trouble concentrating in the evening?
   _ Never _ A few times _ Sometimes _ Most of the time _ All the time
9. In the past 4 weeks how much was your ability to make good decisions affected by sleep problems?
   _ None _ A little _ Some _ Quite a bit _ A lot
10. How often in the past 4 weeks would you have avoided traveling when the trip would have lasted more than two hours?
    _ Never _ A few times _ Sometimes _ Most of the time _ All the time
11. In the past 4 weeks how much interest did you have in sexual activity?
    _ None _ A little _ Some _ Quite a bit _ A lot
    _ Prefer not to answer
12. How much did restless legs disturb or reduce your sexual activities?
    _ None _ A little _ Some _ Quite a bit _ A lot
    _ Prefer not to answer
13. In the past 4 weeks how much did your restless legs disturb your ability to carry out your daily activities, for example carrying out a satisfactory family, home, social, school or work life?
    _ Not at all _ A little _ Some _ Quite a bit _ A lot
14. Do you currently work full or part time (paid work, unpaid or volunteer)? (mark one box)
    _ YES If Yes please answer questions #15 through #18
    _ NO, because of my RLS – Please go to the next page
    _ NO, due to other reasons – Please go to the next page
15. How often did restless legs make it difficult for you to work a full day in the past 4 weeks?

_ Never _ A few times _ Sometimes _ Most of the time _ All the time

16. How many days in the past 4 weeks did you work less than you would like due to restless legs?
    Write in number of days: __
17. On the average, how many hours did you work in the past 4 weeks?
    Write in number of hours per day: __
18. On days you worked less than you would like, on average about how many hours less did you work due to your restless legs.
    Write in number of hours per day: __

Scoring

A summary score can be calculated for the RLSQoL questionnaire based on the following items: 1–5, 7–10 and 13. All items must be recoded such that 1 equals most severe and 5 equals least severe, so that lower scores indicate worse QoL. The score is then transformed to a 0–100 score using the following algorithm: [(Actual raw score – lowest possible raw score)/possible raw score range] × 100. If more than two items are missing from the summary scale, the summary scale score cannot be calculated and is set to missing. If one or two items from the summary scale are missing, then a person-specific estimate is substituted for that missing item. This person-specific estimate is the average score, across the completed items in the summary scale, for that respondent.

Items 6 and 16–18 are scored as continuous variables, as written by the patient. For items 6 and 16, the minimum number of days is 0 and the maximum number of days is 28. For items 17 and 18, the minimum number is 0 h and the maximum number is 24 h. If the response to one of these items is missing or out of range, than that item is set to missing. Items 14–18 are work-related items, thus if patients reply "2" or "3" to item 14, they are not expected to reply to items 15–18. Thus, the missing data rates for items 15–18 will be artificially inflated. Items 11, 12 and 15 should be scored as categorical variables. Finally, item 14 can also be treated as a categorical variable as follows: 'yes' = 1, 'no, because of my RLS' = 2 and 'no, because of other reasons' = 3. If a response to one of these items is missing, then no score can be calculated for that item.

Issues that need to be addressed in future research:

- To discriminate changes in QoL that are due to the symptoms of RLS from those that come from concomitant or subsequent sleep disturbances, daytime tiredness or psychopathological symptoms.
- Further research on health-related QoL is needed to demonstrate the clinical relevance of RLS itself and to address special domains of quality of life like cognitive deficits or daytime tiredness and use methods other than questionnaires.
- Long-term effects of drug-treatment on QoL should be examined and verified for the different medications.

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12
Quality of Life in Excessive Daytime Sleepiness and Hypersomnia

Henry J. Moller and Shirley Lam

Summary The ability to be aware of and to interact with the external environment is a basic evolutionary requirement of all higher organisms requiring intact alertness. Hypersomnia and excessive daytime sleepiness (EDS) relate to the inability to maintain an alert state during the major waking periods of the day. Up until recently, somnolence arising due to sleep pathology was misunderstood as a sign of laziness or even malingering by many medical practitioners and society-at-large. The discovery of the orexin/hypocretin receptor system as a key mediator in abnormal daytime sleepiness as well as growing interest in the daytime cognitive impact of common sleep disorders have played important roles in improving scientific and public awareness of hypersomnia as a clinical entity. Hypersomnia, EDS and fatigue are among the most common manifestations of sleep disorders affecting quality of life (QOL) and productivity. In an increasingly interconnected global economy where workload and productivity have shifted towards cognitive as opposed to physical labour, research is now focusing more than ever on the impact of disorders causing somnolence during desired wake time. Similarly, scholastic/academic motivation and performance deficits are being noted in children and adolescents, in part due to the increased 24/7 availability of technology and entertainment options, usually at the expense of sufficient sleep. Other important implications of somnolence include the direct and indirect consequences of transport and occupational accidents, as well as disruption of family and social relationships. Clinical conditions causing this condition include obstructive sleep apnea (OSA), narcolepsy, idiopathic hypersomnia (IH), circadian disturbances and most commonly, self-imposed insufficient sleep syndrome. In conditions such as insomnia, restless legs syndrome (RLS) and periodic limb movements in sleep (PLMS), the association with frank daytime somnolence is more controversial although patients do complain of impaired daytime cognitive function. As the 'baby-boom' generation approaches old age, senescence-related deterioration of sleep quality and quantity is increasingly recognized as an important factor impacting QOL by affecting memory, cognitive function and vitality in activities of daily living (ADLs) including driving. Somnolence can be a serious and even life-threatening impairment. Often there is a gap between the subjective complaints of patients regarding the impact of hypersomnia/EDS on QOL and the ability to reliably measure this dysfunction. An important area of current research involves clarifying the nosology of daytime EDS symptoms, ranging from somnolence to fatigue or neurocognitive impairment. Improvements in diagnostic instruments assessing daytime function and ergonomic activities in relation to both healthy and pathological sleep processes will aid in better delineating these subjective and objective parameters.

Keywords Excessive daytime sleepiness · hypersomnia · sleep disorders · quality of life · road safety · public health · cognitive function

Learning objectives:

- EDS and hypersomnia occur in a number of pathological sleep conditions, both clinical/intrinsic and behavioural/self-imposed.
- EDS can present with a wide spectrum of symptoms, ranging form frank somnolence to fatigue and neurocognitive impairment.
- Because of its clinical heterogeneity and pervasive effect on daily function, EDS can greatly decrease QOL by decreasing work/scholastic performance, social/family functioning and increasing risk of errors and accidents.
- Death and injury due to road/industrial accidents have direct and indirect impacts on QOL.

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- Psychiatric disturbances such as mood and cognitive disorders are often comorbid with EDS.
- EDS is becoming a global issue with socioeconomic consequences that need to be addressed.

Introduction

Sleep can be described as a reversible behavioural state of perceptual disengagement from and unresponsiveness to the environment (1). Control of sleep and wakefulness is a complex process involving a wide range of neurochemicals including melatonin, hypocretin/orexin, dopamine and other biogenic amines, GABA, galanin, adenosine, histamine as well as various cytokines (2–5). Probably, the most classic recognized sleep disorder causing excessive daytime sleepiness (EDS) is narcolepsy, which results in sudden attacks of sleep occurring at inappropriate situations and times (4). Other common disorders causing EDS include sleep-related breathing disorders, idiopathic hypersomnia (IH), possibly certain subtypes of insomnia and nocturnal movement disorders, circadian rhythm disorders and somnolence as a component of the aging process or neurodegenerative conditions (1,2,4). As sleep is a basic physiological requirement (1,2,6), it is useful to distinguish underlying pathological sleep disorders requiring treatment from common causes of self-imposed sleep deprivation (1, 2). It is important, however, to recognize that sleep loss/debt is probably the single most important determinant of human sleepiness, and this is typically caused by self-imposed behaviours occurring in contemporary socioeconomic contexts.

Excessive Daytime Sleepiness, Hypersomnia and its Variants

Although EDS is becoming a more widespread problem in today's 24/7 society, affecting up to 12% of the population (1, 7), it has been estimated that as many as 95% of affected individuals are neither treated nor properly diagnosed (8). In today's society, sleeping is still considered by many as a waste of time, and by extension, somnolence is viewed as a symbol of laziness. Most of the time, patients suffering from EDS and other sleep disorders do not see themselves as requiring medical attention (2, 8). The aetiology of EDS varies from intrinsic sleep disorders such as narcolepsy to extrinsic sleep disorders including sleep deprivation, drugs, jet lag, shift work and other life-style causes (1,7,9).

Unlike sleepiness, which is as a normal biological function manifested by an increased likelihood of falling asleep when given an opportunity (7, 8), excessive sleepiness or hypersomnia is defined as an increased propensity to fall asleep and a subjective compulsion to sleep, as well as a tendency to take involuntary naps or suffer sleep attacks when sleep is not desired (10–12). Frequently, subjective symptom descriptions may confuse inexperienced or skeptical clinicians. In the assessment of sleep disorders, for example, patients may complain of excessive sleepiness, impaired alertness or debilitating fatigue, often confounding the clinician's attempt to formulate a diagnosis and treatment plan. It is nosologically important to distinguish excessive sleepiness from syndromes such as fatigue and apathy, which relate to different forms of physical and mental illness (11–13). 'Fatigue', typically described in the context of decreased ability for sustained performance on a physical or mental task, refers to tiredness, lack of energy and exhaustion (11); EDS is typically referred to in non-ergonomic terms as a homeostatic measure of where the individual is on the sleep–wake continuum in the absence of affective and motivational factors (11, 12). If non-pathological, temporary fatigue and EDS states may be respectively relieved by rest or sleep. By contrast, the dysfunction occurring in pathologic and/or chronic contexts is more enduring and refractory, thus requiring further assessment and treatment as quality of life (QOL) becomes negatively affected.

It is also nosologically useful to distinguish between hypersomnia of central and non-central origins. While the first edition of the International Classification for Sleep Disorders (14) had grouped most disorders of hypersomnolence as dyssomnias, along with obstructive sleep apnea (OSA) and restless leg syndrome, the recently published second edition (15) separated hypersomnias of central nervous system (CNS) origin from those of non-central origin. Through this distinction, it was hoped that improved understanding of the pathophysiologic mechanisms might be achieved, recognizing that there are a variety of causes to a final common pathway of hypersomnia.

Narcolepsy

Narcolepsy is a rare neurologic disorder associated with dysregulation of REM sleep, with an estimated frequency of 0.2–5.9 per thousand individuals and an elevated incidence among those of age 18–25 (16, 17). As only 11–14% of patients display all of the classical signs and symptoms (18) (which include EDS, cataplexy, hallucinations and/or sleep paralysis in sleep transition states), diagnoses of narcoleptic patients can be difficult (6, 7, 9, 19). Even though the origin of narcolepsy is unknown, it appears to have a genetic predisposition (20–22). Approximately 85–90% of narcoleptic patients have the HLA DQB1*0602 allele, and most of these patients have a highly significant hypothalamic deficiency of hypocretin/orexin which, as mentioned previously, is a key neurotransmitter for wakefulness (23, 24). Unlike in normal sleep, where the first REM period occurs about 90 min after sleep onset, narcoleptic patients display a pathognomonic pattern of premature REM sleep onset even on daytime naps, as evidenced on multiple sleep latency testing

(MSLT) (25). The implication of this is that there is a tendency of 'REM-pressure' in addition to EDS, which may occur both in pure narcolepsy and secondary narcolepsy-like states such as sleep deprivation and severe untreated OSA (2). This type of somnolence is typically severe and relieved by brief naps, from which patients are difficult to rouse (26). Aside from irresistible sleep episodes, patients manifest significant EDS during other periods of the day, even if the activity they are involved in is not monotonous; this often results in memory deficits, poor performance at work or other vocational activities, and in some cases, automatic behaviours (17).

Obstructive Sleep Apnea/Hypopnea Syndrome

As discussed earlier in this book, this is a fairly common syndrome, affecting up to 5% of adults in Western countries, especially over-weight males older than 40 years (27–29). OSA is most typically caused by recurrent episodes of upper airway obstruction during sleep due to pharyngeal collapse; this results in sleep fragmentation, hypoxia and, in cases of prolonged events, hypercapnia (2, 7, 27–30). This airway obstruction can be partial, resulting in obstructive sleep hypopnea syndrome; when there are episodes of total upper airway obstruction, it will result in OSA (7). One of the major co-morbidities of OSA is obesity in children as well as in adults, making this an increasing concern in light of current demographic trends in the developed world. Other contributing factors include retrognathia, macroglossia, nasal obstruction, older age and use of CNS depressants causing pharyngeal muscle relaxation (31–33).

Comparative studies of OSA patients and healthy individuals suggest a significantly higher rate of affective disorders in the former group, with associated QOL implications (34–36). It is thought that emotional and cognitive disturbance in EDS are an artifact of both disturbances in the restful restorative function of sleep and neuropsychiatric disturbance due to hypoxic CNS damage (31–35). Fatigue and EDS in OSA is also hypothesized to relate to the increased mental effort required for cognitive faculties such as attention, short-term memory and executive function (36–41). These deficits may result in increased error-proneneness, decreased work efficiency, as well as family or social conflicts (36–38).

Idiopathic Hypersomnia

Sometimes also described as idiopathic CNS hypersomnia, early descriptions of IH-symptoms overlapped with descriptions of von Economo encephalitis and classic narcolepsy (42); subclassifications of IH have been proposed based on immunologic stratifications such as presence of the HLA Cω2 antigen and sequelae of specific neuroimmune insults such as mononucleosis or Guillan–Barré syndrome (43, 44). As its name implies, IH describes patients who have EDS of unclear aetiology and is therefore typically a diagnosis of exclusion made by eliminating other diagnosable syndromes (2, 45, 46). Differential diagnosis includes somnolence due to a history of physical head trauma (47), mood disorders such as atypical depression (48) and subsyndromal undiagnosed breathing disturbances such as upper airway resistance syndrome (49). IH is similar to narcolepsy in that they are both currently incurable, and most clinicians see the EDS caused by IH as more treatment refractory (45, 46). Unlike narcolepsy, patients with IH do not suffer from cataplexy, hypnagogic hallucination and sleep paralysis. Patients display a relatively normal polysomnograph, with some increased propensity towards slow wave sleep (SWS), and reduced sleep onset latency on daytime MSLT testing without REM sleep onset. Patients are typically described as 'abnormally deep sleepers', prone to significant sleep inertia upon awakening, and unlike narcolepsy patients, find daytime naps unrefreshing (45, 46). Mood disturbances such as irritability and neurocognitive dysfunction may be noted by family or employers; frank aggressiveness or bizarre automatic behaviours may occur if individuals are forced out of the so-called sleep-drunken state by occupational/social demands, causing embarrassment and other social repercussions. Unlike OSA or narcolepsy, theories regarding the cause of the underlying cognitive impairment in CNS are inconsistent, likely due to the heterogeneous nature of this diagnostic category (45, 46, 50).

Insomnia and Circadian Rhythms Disorders

Insomnia describes a wide range of complaints relating to disorders of sleep and is usually a subjective complaint of dissatisfaction with sleep with decreased sleep quality, decreased sleep quantity, trouble getting to sleep and trouble maintaining sleep (50, 51). Insomnia will sometimes lead to acute or chronic sleep deprivation, and it has been shown that the amount of sleep loss is directly proportional to the increase in daytime sleepiness (35). Other reasons for sleep deprivation may include voluntary and/or pathological lifestyle reasons to stay up late, job-related consequences of working night shifts or poor sleep hygiene (1). Although increased risk of accidents and daytime impairment caused by acute sleep deprivation states and disorders such as OSA clearly associated with EDS is now well established (40, 41, 52, 53), far less research has been done on the analogous impact of chronic insomnia (CI) on daytime functioning. Research generally suggests that although patients with insomnia may not experience frank somnolence (12, 13, 54, 55), these patients do manifest reduced alertness on many tasks of daily living. A recent French epidemiological study found a threefold greater risk of automobile crashes in patients with CI, as well as lower self-esteem, satisfaction and efficiency at work compared with good sleepers (56). Given the clinical reality of the high prevalence of this condition in North America (51, 52) and the growing recognition that insomnia is more often a chronic than temporary source of sleep disturbance, the phenomenology of daytime impairment due to CI requires further study.

One of the major causes for EDS restricted to morning hours is the circadian-based disorder delayed sleep phase syndrome (DSPS), where an individual's internal circadian pacemaker is not entrained with the external or environmental time. It is characterized by a delay in timing of activities related to the sleep–wake cycle, but the sleep architecture of DSPS patients is otherwise normal (57, 58). Incidence of DSPS in the general population varies ranging from 0.2% in middle-aged adults to more than 7% in adolescents and young adults (58–62). Conversely, in advanced sleep phase syndrome (ASPS), more common in elderly individuals, irresistible sleepiness in the afternoon or early evening may cause disruption in social/vocational function (63–65). When EDS co-occurs with insomnia, comorbid circadian rhythm disorders should be considered (66). Other common examples of circadian rhythm alterations include jet lag and shift work (67–71). Similar to DSPS, patients suffering from jet lag and shift work-related somnolence demonstrate a non-synchronization of individual with their environment (2, 67, 68). Shift workers are estimated to account for approximately 20% of the global urban workforce (68, 69).

While shift work was previously associated with specific industrial and occupational sectors such as the military, healthcare, law-enforcement or the manufacturing sector, trends in economic globalization have created a workforce with both more flexibility and work-periods outside of traditional 8:00–17:00 h in occupations (67, 68). The health impact of a 24/7 society has been described as an environmental challenge that outstrips our biological adaptation to a 24-h light–dark cycle (67). Although shift work and circadian disorders are discussed in separate chapters of this book, there is a growing appreciation of these as causes of EDS and hypersomnia, with analogous implications on QOL issues (2, 69, 71). With the widespread shift towards automation and cognitive over physical labour, this trend will continue to escalate in the future, particularly as more people conduct vigilance-based activities at times other than traditional daytime work hours (72).

Drugs

As the importance of sleep health on QOL is increasingly appreciated, more attention is also being paid to how drugs affect sleep and wakefulness. Many medications have a marked effect on sleep architecture, either as the desired or adverse effects of the drug, these include hypnotics, anticonvulsants, antidepressants, antihistamines, lithium, antipsychotics, anti-Parkinsonian drugs and cardiovascular drugs (2–4, 9, 40, 73–81). A detailed review of drugs that cause somnolence is beyond the scope of this chapter although it is important to remember that most CNS-acting medications may disrupt wakefulness either directly or by affecting overnight sleep.

Prolonged use of stimulants, particularly if long-acting, can paradoxically increase sleepiness and cause decrements in the ability to maintain wakefulness by causing iatrogenic insomnia: paradoxically, attention and concentration problems may be augmented by decreasing the nocturnal total sleep time (82–85). Short-acting stimulants are also commonly abused, with daytime somnolence occurring as a withdrawal symptom (86).

Caffeine can be found widely in different food products, such as tea, chocolate and soft drinks (87–89). As caffeine has stimulating properties, it can lead to insomnia and sleep disruption that in turn can result in EDS and increased need of caffeine the following day. Caffeine can also result in drug–drug pharmacokinetic interactions with a variety of medication classes (89). Excessive use of stimulant drugs can lead to apparent short-term gain, but have negative consequences on sleep pattern and EDS, although the evidence is surprisingly anecdotal, disputed by some (84, 89), and overall is not well-described in the literature.

The use of sedative/hypnotics to treat daytime sleepiness by improving sleep quality and quantity has been described as a 'paradoxical treatment' of EDS (90). As discussed, this relates to treatment of insomnia symptoms such as undesired nocturnal wakefulness or sleep fragmentation (66, 91). Overuse of sedative agents, or use of over-sedating drugs, including those taken at bedtime with residual 'hangover sedation' are an important cause of EDS and reduced daytime performance (92, 93). Most, but not all antidepressants influence sleep architecture by suppressing REM and increasing REM latency (79–81). Antipsychotics affect sleep and can contribute to daytime sedation by blocking important neurotransmitters related to the wakefulness such as dopamine and histamine (94). Currently, there is intense clinical interest in the use of modafinil as a wakefulness-promoting agent with a more favourable risk–benefit profile compared to traditional stimulants (95–98). Use of any drug that may have consequences on wakefulness should be considered in the light of potential therapeutic and iatrogenic/adverse effects, immediate and long-term consequences and the pathophysiology of the underlying medical condition being treated.

Restless Legs Syndrome/Periodic Limb Movements in Sleep

The effect of restless legs syndrome (RLS)/periodic limb movements in sleep (PLMS) on QOL is currently under scrutiny, as this often-comorbid diagnostic entity has been shown to demonstrate daytime impairment though the contribution of fatigue versus sleepiness affecting QOL remains under debate (11, 12, 99–102). The most definitive recent international epidemiological study (103) has estimated the prevalence of PLMD at 3.9% and RLS at 5.5%, with a higher prevalence for both conditions in women and an increasing prevalence in RLS with age. On clinical presentation, about 80% of patients with RLS manifest PLMS, but only a minority of individuals with PLMS display symptoms of RLS (104). PLMS may co-occur in other sleep pathologies such as narcolepsy, OSA, REM-behavior disorder and

insomnia and in special medical conditions such as renal failure, diabetes mellitus and iron-deficiency anemia (102). The exact burden of daytime impairment remains unclear, with one recent Canadian study noting comparable daytime impairment to insomnia but significantly less than in OSA or narcolepsy patients (12). Patel argues that most EDS in RLS/PLMD is limited to patients with underlying OSA or end-stage renal disease (105), and in fact, RLS symptoms as well as daytime fatigue/EDS have been shown to respond favourably to CPAP in patients with comorbid OSA and RLS (106). In younger patients, a diagnosis of narcolepsy should also be considered, as up to 50% of adults with narcolepsy have PLMS (107) and as frank somnolence is probably rare in children or adults with PLMD (12, 99, 108, 109).

Consequences of EDS on QOL

Our mental functioning is totally integrated, and therefore, if there is a loss of any one function, performance in other spheres of functioning will also be affected. EDS not only affects an individual's sleep/wake cycle but has a more global effect on the patient's psychosocial function, cognitive performance, social relationships and safety, which can lead to great personal and public economical loss (2, 9, 38, 39, 53, 56, 57). These functions are all interrelated and therefore a deficit in one will readily lead to decrements in others.

Cognitive Performance

Deficits and neurocognitive performance are core features of almost all major disorders affecting brain functioning; they are highly relevant to a patient's subjective level of disability and QOL, yet difficult to objectively define in an ergonomic context for the treating clinician. EDS can lead to alterations in different aspects of cognitive performance, including executive function, attention and concentration, working memory and long-term memory impairment, decrease in the ability to plan strategically, mild fine motor skill loss (affecting agility and precision), difficulty in controlling impulses and impaired judgment. Cognitive dysfunction can result in difficulties at work and reduction in work capacity and efficiency (110).

Although this can be seen across the lifespan (110–112) in individuals with reduced cognitive reserve due to various conditions, EDS is most likely to unmask impairment relevant to QOL (113–115). Experimental chronic partial sleep deprivation, designed to replicate sleep loss in society, suggests that significant neurocognitive deficits accumulate over time in the face of subjective adaptation to the sensation of sleepiness (116–118). Although some authors have linked neurocognitive dysfunction to intrusion of microsleep episodes into waking consciousness (119, 120), the mechanism of impairment may be more subtle and therefore difficult to measure using neurophysiologic methods (118, 121). There is a growing need to develop quantifiable monitoring tools of cognitive performance with the ability to reliably characterize burden of impairment, to track treatments and to develop interventions relevant to actual activities of daily living (ADLs).

Road Safety

The degree of neurocognitive dysfunction impairment secondary to sleepiness has been described as comparable to alcohol intoxication (122), and while the experimental literature supports this (120–124), public awareness still lags behind (122, 123). The most current National Highway Traffic Safety Administration (NHTSA) report has suggested drowsy driving as the next public health and public awareness frontier beyond drinking and seat belt use (125). Numerous recent studies concerning sleepiness and motor accidents have been published, which have drawn attention to this issue (126–136). A survey in Brazil conducted by Mello et al. (129) found that 16% of bus drivers admitted to falling asleep while driving and that more than half of those drivers interviewed knew other bus drivers who have fallen asleep while driving. DePinho et al. in a cross-sectional study of 300 truck drivers found a mean reported sleep length of 5.6 h and reported poor sleep quality in 46% of drivers (130). In particular, younger drivers were likely to report hypersomnolence, with the chief cause being insufficient sleep. Adolescents and young adults are typically involved in motor accidents that occur at night and involve a young male driver going off the road (131–134); crashes in older adults usually occur during the mid-afternoon, implying a possible connection to circadian factors, as well as age-dependent sleep disorders such as OSA (135, 136). Other studies point to the concern that along with the actual psychomotor impairment, awareness impairment due to sleepiness is reduced (137), resulting in poor insight and judgment though this is disputed by some (138).

Without appropriate action, road-traffic injuries are predicted to escalate from the ninth leading contributor to the global burden of disease to the third by 2020 (122). As data continues to emerge regarding the contribution of drowsiness, inattention and impaired vigilance, sleep researchers and clinicians could contribute to reducing the public health burden of this very preventable problem (122, 123). The treatment of sleep disorders and implementation of educational programs, particularly targeting younger drivers and promoting increased awareness of the deleterious effects of sleep loss and work overload, may help to reduce accidents due to sleepiness (139, 140).

Economic and Public Heath

EDS diminishes an individual's ability to interact normally with his or her environment, which results in personal, economical and public heath problems (2, 139–143). Patients suffering from EDS tend to have lower economic income, poorer perceived of personal health, increased chance of having psychiatric disease, marital conflicts and impaired work performance, which in turn can have a more negative result in their already lower perceived QOL (56, 100, 101). As mentioned previously, the cost of sleepiness-related accidents from EDS and other sleep disorders varies widely, but

even with conservative estimation, it is over billions of dollars annually in North America alone (142). The 2002 Sleep in America Poll showed that 37% of adults reported that EDS interfered significantly with ADLs (143). Aside from driving-related issues, judgment errors in an occupational/operational environment can compromise the safety of others. In industrial settings, of particular concern are work environments such as the medical or military sector that demands high levels of responsibility and periodic sleep loss and/or shift work (121, 144, 145). A recent elegant study by Arnedt et al. using computerized cognitive and driving simulator testing demonstrated sleep-loss-related impairment comparable to alcohol intoxication in medical residents following a heavy night of on-call duties (144).

The reciprocal relationship of some sleep disorders (especially, but not limited to OSA) with obesity and the metabolic syndrome is another growing concern in the developed world, as there are cardiovascular, endocrine and mental health consequences (146, 147). EDS is a significant perpetuating factor in obesity, as it reduces ability to participate in exercise and other health-promoting ADLs (148). Somnolence has been linked to craving of carbohydrate-containing foods that further perpetuate the metabolic syndrome and all its associated negative health consequences (147, 149).

Behavior and mood changes

There is an obvious overlap between many symptoms of mood and sleep disorders, and this creates a treatment challenge for clinicians (80, 150). Major depressive disorder (MDD), for example, can include the symptom of hypersomnia, as well as symptoms such as fatigue/energy loss, disturbed concentration and diminished motivation (48, 151, 152). Yet, any of these symptoms may also be secondary to a primary sleep disorder (152, 153). As EDS and other manifestations of sleep disorders are not widely recognized by the general public, most patients with these conditions feel that others do not understand or tolerate their symptoms, which can lead to disruptions and arguments in family life and interpersonal relationships. It has been noted that hypersomnia is more likely to be reported than early morning awakening in younger patients with melancholia and bipolar disorder, but with age, early morning wakening becomes the dominant pattern (154). Hypersomnia may be one of the main remission-limiting factors in treatment of mood disorders, with light therapy and activating antidepressants such as bupropion and venlafaxine having shown to be effective treatments (80, 155, 156). Modafinil also appears to be a useful treatment adjunct for depressive symptoms with prominent fatigue and EDS (9, 157–160), although when using stimulant treatment, initial screening for underlying sleep disorders such as OSA or narcolepsy may be indicated (150, 161).

Broughton et al. found that two thirds of patients suffering from sleep disorders displayed symptoms of major depression within the previous 5 years and that half of narcoleptic patients had recurrent depression (162). Depressive symptoms are dramatically and independently associated with fatigue in depressive symptoms in OSA (163), and use of QOL ratings scales such as the SF-36 before and after treatment has substantiated this (164). With effective management of the primary sleep disorder causing EDS and secondary mood disturbance, QOL can be improved significantly (157–161). Although EDS is not intuitively linked to major depression symptomatology by most mental health clinicians, conditions such as OSA or narcolepsy may contribute to or exacerbate the condition of someone predisposed to MDD and their treatment may ameliorate or possibly prevent depressive symptoms (162–166).

As described below, research in adolescents has shown that sleep problems and associated EDS can cause increased difficulty in mood regulation (57, 58, 166–169). In the elderly, where cognitive and/or mood changes due to hypersomnia are often overlooked, and lack of treatment of underlying sleep disorders may result in inappropriate pharmacotherapy or premature institutionalization (63, 112, 116, 170).

Academic/School Performance

Patients with EDS often show reduced productivity at school, resulting in poorer grades than their school peers. Of particular interest in this population are DSPS (57, 58), narcolepsy (16, 17, 61, 62), insomnia (171–174) and due to the current 'obesity epidemic' increasingly, OSA (167, 175, 176). A major concern is the negative effect of the combination of sleep disorders with comorbid mood and attention problems is that it can create a 'negative spiral' both in school and social functioning as outlined Figure 12.1, demonstrating the interconnectedness of sleep and wakefulness with domains of social and vocational well-being. Survey studies of children and adolescents indicated that children with shorter total sleep time and sleep problems, such as OSA, have lower academic achievement than their healthy classmates (169, 176). These students are more likely to experience grade retention, inability to maintain concentration and tend to have less classroom interest (169, 171, 177–179).

In addition, these patients are more likely to perform below expected level academically as rated by teachers (180, 181). As EDS often manifests atypically in the pediatric population, attention deficit hyperactivity disorder (ADHD) or mood disorders may be misdiagnosed (168) or children may be labeled as 'problem students' (82). This can result in reduced self-esteem, secondary problems such as oppositional behaviours, aggressiveness or school failure (175–183). As processes of attention regulation and sleep–wake regulation share common neurobiologic mechanisms (184, 185), especially children undergoing evaluation for ADHD should be systematically assessed for sleep disturbances because treatment of sleep disorders is often associated with improved symptomatology, improved scholastic functioning and QOL (168, 184).

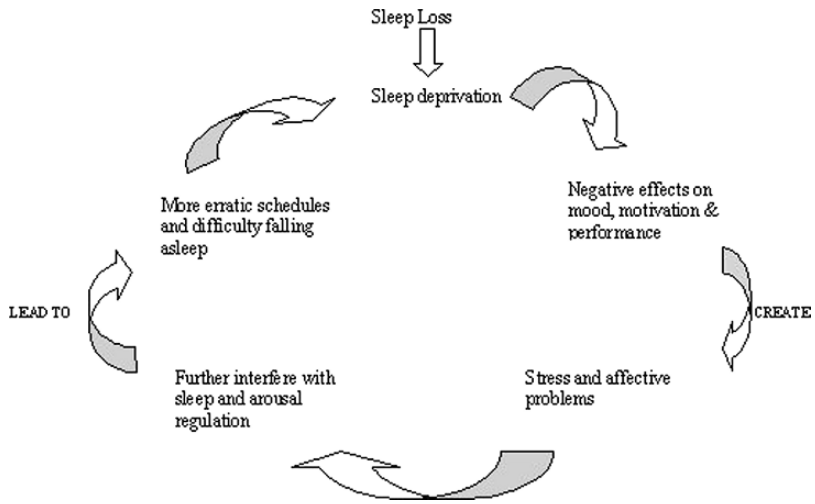

FIGURE 12.1. 'Negative spiral'. Sleep loss, whether self-imposed or due to sleep disorder can lead to stress and deterioration in circadian system. This will further worsen the symptoms of sleep deprivation and EDS, which will lead to more negative effects on function in the academic work and social domains

Summary: Overall QOL and Future Research and Policy Issues

Any experienced clinician or sufferer of a chronic sleep disorder is likely aware that *quality* of sleep is probably more desirable than *quantity*; and while recent research has focused on prolonging quantity of life with appropriate sleep health measures (185), QOL is what makes this quantity truly worth living. The World Health Organization's constitution defines 'health' as a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity (186). This chapter has summarized the complex and often overlapping aetiology of what is both a subjective state of disease perceived by an individual and increasingly, an ergonomically measurable neurobiological construct. QOL research in this area is an important avenue to bridge these areas. Ultimately, treatment of symptoms in isolation without consideration of an individual's more global health functioning does not adequately address overall well-being.

A number of specific sleep disorders causing the EDS/hypersomnia syndrome have been described in terms of phenomenology, etiology and prevalence, with specific attention to aspects of each disorder's contribution to QOL issues. Controversies regarding the spectrum of impairment from frank somnolence to fatigue and more subtle neurocognitive dysfunction have been addressed, as well as co-morbidity issues both between sleep and psychiatric disorders. The important issue of public health implications of sleepiness, both due to primary sleep disorders and due to changes in the global economic workforce has been raised and is also further addressed in the chapter on shift work and QOL.

There is an ongoing need for researchers to educate the public and policymakers of the potential consequences and hazards of EDS and thus increase the social awareness of this problem. This is perhaps most obvious with respect to the preventable public health threat of drowsy driving but also needs to be taken seriously by policymakers, employers and educators with an interest in the areas of economic productivity, academic achievements and social well-being.

Issues that need to be addressed by future research:

- Improved understanding of the complex co-morbidity of medical, psychiatric and sleep disorders causing EDS/ hypersomnia.
- Better understanding of impact of EDS in ergonomic/occupational setting.
- Clarification of the influence of sleep disorders without clear EDS, such as chronic insomnia or RLS/PLMS on QOL.
- Prevalence and co-morbidity of EDS in child and adolescents with respect to QOL in scholastic settings.
- Continued research on developing standardized screening and measuring tools for EDS and impaired alertness in ergonomic contexts such as driving and industrial settings.
- Better understanding of socioeconomic influences on EDS, including influences of trends like shifts towards technology and globalization.
- Development of consistent guidelines to manage EDS with respect to QOL.
- Attempt to establish consistent regulations, guidelines globally for patients suffering from EDS on acquiring driver's license.

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13
Sleep and Quality of Life in REM Sleep Parasomnia

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Summary Parasomnias are abnormal behavioral or physiological events that intrude into the sleep process disrupting its continuity. Parasomnia associated to REM sleep include REM sleep behavior disorder, nightmare disorders, recurrent isolated sleep paralysis (SP), and sleep-related painful erections. The quality of life of patients suffering from parasomnias may vary according to the disorder. REM sleep behavior disorder patients experience recurrent vivid and violent dreams and frequent sleep-related injuries for themselves or bed partners, with possible impacts on personal, couple, and social life. Despite the possible awakening from REM sleep, sleep architecture is usually preserved in RBD. Idiopathic RBD may often precede a neurodegenerative disease, and its diagnosis might imply a psychological burden for patients and their family. The increased risk for neurodegenerative illnesses poses the ethical dilemma whether the patient should or should not be told about, especially in view of the current lack of effective neuroprotective strategies and the lack of knowledge about the precise extent of this risk. Nightmares are intensely disturbing dreams involving a variety of dysphoric emotions, most often fear and anxiety. Nightmares have been correlated to various measures of psychopathology, namely neuroticism, anxiety, depression, but not all studies support this relationship. Personality factors, such as nightmare frequency, nightmare distress (ND), and coping style, appear to be important in modulating the clinical severity of nightmare disorder. Parasomnias, especially nightmare and SP, can lead to postawakening anxiety with difficulty returning to sleep, sleep avoidance, and sleep deprivation, with subsequent insomnia, daytime sleepiness, and intensification of the parasomnia REM-rebound related.

Keywords Parasomnia, quality of life · REM sleep · REM sleep behavior disorder · nightmare · sleep paralysis

Learning objectives:

- Parasomnias associated to REM sleep are abnormal behavioral or physiological events that intrude into the sleep process, disrupting its continuity, and include REM sleep behavior disorder (RBD), nightmare disorders, and recurrent isolated sleep paralysis.
- Patients with RBD experience recurrent vivid dreams associated to complex and violent behaviors, potentially injurious for them, or their bed partners, with impact on their personal, couple, and social life.
- Parasomnias, especially nightmare and sleep paralysis, are associated to various degrees of psychological distress. They may lead to postawakening anxiety with difficulty resuming sleep, sleep avoidance, and sleep deprivation. The latter may cause daytime sleepiness and/or parasomnia intensification related to the REM sleep rebound.

Introduction

Parasomnias are abnormal behavioral or physiological events that intrude into the sleep process, disrupting its continuity. Parasomnias are classified according to the type of sleep in which they occur, namely arousal disorders (from non-rapid eye movement, NREM) and parasomnia usually associated to REM sleep (1). The latter include REM sleep behavior disorder, recurrent isolated sleep paralysis (SP), and nightmare disorders. Sleep-related painful erections, formerly considered as REM sleep parasomnias, are currently not included in this group.

Quality of life can be defined as the overall state of well-being experienced by the subject, as assessed by subjective and objective measures of functioning, health, and satisfaction with the important dimensions of its life (2). The quantity and quality of sleep are strongly associated with quality of life, because they have an impact on energy levels, symptoms of fatigue, daytime sleepiness, mental and physical functioning, family relationships, and even bodily pain.

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REM Sleep Behavior Disorder

Clinical Picture

REM sleep behavior disorder is characterized by complex and often violent motor behaviors that emerge from REM sleep and that are associated with dream mentation (3). Patients typically seem to enact their dreams: they may talk, scream, gesture, move the arms often grasping, punching or kicking a virtual object, and sometimes jump out of the bed. Spontaneous awakening from episodes is not usual, but when occurs, arousal is rapid and usually followed by a recall of a dream that generally matches the observed behavior. For reasons not yet fully clarified, dreams of these patients tend to be unpleasant, stereotypical, action-filled, and violent in nature (3, 4). Video-polysomnographic (PSG) monitoring reveals a complete or intermittent loss of the physiological REM sleep muscle atonia, as measured by surface electromyography (EMG) of the chin muscle and an excessive EMG phasic activity during this stage.

Clinical Forms

Experimental animal models of RBD indicate that lesion of several regions of the brainstem are responsible for the emergence of the behaviors during REM sleep (5).

RBD can occur in two forms: acute and chronic. The acute RBD has been observed in drug abusers (particularly with tryciclic antidepressants, mono-amine inhibitors, or serotonin selective reuptake inhibitors) as well as during withdrawal from several substances (namely, alcohol, meprobamate, nitrazepam, and pentazocine) (3). The chronic form may be either idiopathic or secondary to various neurological disorders. Secondary RBD may be potentially triggered by any lesions involving the brain structures responsible for REM sleep atonia, mostly located in the brainstem. RBD has been actually observed in cerebro-vascular diseases, brainstem tumors, Guillain–Barré syndrome, multiple sclerosis, and Machado–Joseph disease (5). Very recently, RBD has been observed in association with limbic encephalitis (6) and with Morvan's syndrome (7), two disorders not related to brainstem impairment. However, the most frequent association of RBD is with a group of neurodegenerative diseases called alpha-synuchleinopathies that include Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA) (8). In PD, muscle tone abnormalities during REM sleep are frequent. Abnormalities in REM sleep muscle atonia, regardless to the history of behavioral manifestations, was found in 58% of PD patients, whereas full RBD is present in approximately one-third of patients (9). RBD may be also encountered in demented patients who show the clinical and neuropsychological features of DLB (10). Indeed, RBD has been recently included, as a suggestive feature, within the diagnostic criteria for DLB (11). RBD is also extremely frequent in patients with MSA, being present in about 90% of them (12). When no neurological signs or central nervous system (CNS) lesions are found, RBD is currently defined as "idiopathic." This form accounts for up to 60% of the cases described in the literature. However, one prospective study performed on idiopathic RBD showed that 38% male RBD patients developed a Parkinsonian syndrome within 4 years from the RBD diagnosis. The study has been recently updated, showing that up to 65% of idiopathic RBD patients eventually developed a Parkinsonian disorder and/or a dementia without Parkinsonism, about 13 years after the RBD onset (13, 14). On the other hand, in nearly 35% of patients, RBD remained idiopathic after a mean of 20 years. Therefore, the condition of idiopathic RBD is receiving increasing attention, as a possible prodrome in the development of a full-blown neurodegenerative disease (15). Recent studies found several slight abnormalities associated to the motor dyscontrol during REM sleep. The latter include slowing of the electroencephalographic rhythm in both wakefulness and REM sleep (16), neuropsychological abnormalities in specific functions, such as visuo-spatial constructional abilities and visuo-spatial learning (17), signs of autonomic impairment (18), olfactory deficit (19,20), subtle motor signs, and decreased color vision discrimination (21). It is not known whether these deficits will progress over time or whether they are simple epiphenomena, but the whole body of observations strengthen the notion of idiopathic RBD as a possible prodrome of a more pervasive neurodegenerative disease.

The increased risk of developing a neurodegenerative disease poses the ethical dilemma whether the patient should or should not be told about this risk, especially in view of the current lack of effective neuroprotective strategies. Specialist's attitudes are various, reflecting individual sensibility and experience, but most agree in carefully following these patients over the years to detect as soon as possible the eventual occurrence of neurological disease. Indeed, it should be noted that the exact extent of this risk, for example, the relative risk and the risk factors, for a patient newly diagnosed with idiopathic RBD, is not known at the moment, as large cohorts longitudinal studies are lacking. Given the current status of knowledge, some specialists find therefore unethical to create an excessive and unmotivated alarm in the patient and his family.

Consequences, Quality of Life, Dreams, and Sleep Pattern in RBD

Besides the psychological burden of possibly having a neurodegenerative disorder in its preclinical phase, idiopathic REM sleep behavior disorder per se represents a condition potentially harmful, and this one is usually the main reason for patients to seek medical attention. Indeed, injuries during sleep are reported by more than 75% of patients or bed partners (5) and they may include ecchymoses, lacerations, bone

fractures, and even sub-dural haematomas (21, 22). Frequent and, obviously, unintentional injuries to the bed partners raise important medico-legal issues. Is not uncommon that the patient's spouse seeks medical attention for traumatic lesions that occurred during sleep. Inconveniences may occur when the health workers are not fully aware of this condition. Furthermore, the disorder may have a significant impact on the couple life, as spouses often choose to sleep in separate rooms for obvious safety reasons. Sometimes, a psychiatric condition may be erroneously suspected and inappropriate treatments may be initiated, with an obvious impact on the patient and his family life. Other times, psychological factors are suspected while the disorder is thought to be exquisitely neurologic.

Regardless the extent of the sleep motor behaviors, patients with RBD experience frequent vivid and unpleasant dreams. Indeed, the vast majority of dreams tend to be stereotypical, action-filled, and often violent in nature. Patients with RBD very commonly report dreams in which they are attacked by unfamiliar people or animals and they would either fight back in self-defense or attempt to flee (5). Typical dreams may include an unfamiliar person entering the dreamer's house, a stranger threatening the dreamer or their relatives, or being attacked by animals. Fear and anger are the most commonly reported emotions associated to these dreams.

One study has recently assessed the dream content and its relationship with the daytime aggressiveness in RBD (4). This study included 49 patients with PSG-confirmed RBD and 71 healthy controls volunteers matched for age, gender, and education. Subjects were asked to recall one or more recent dreams according to the Hall and Van De Castle method, and dreams that occurred within 1 year from the interview were included. The study found that a higher proportion of subjects in the RBD group (83.7%) were able to recall at least one dream compared to same-age healthy subjects (49.3%). Ninety-eight (RBD) and 69 (controls) dreams were finally collected and analyzed. Compared to controls, patients with RBD reported a striking frequency of aggression, expressed by various indicators, namely a higher percentage of *dreams with at least one aggression* (66 vs. 15%), an increased *aggression/friendliness interactions* ratio (86 vs. 44%), and an increased aggressions/characters (A/C) ratio (0.81 vs. 0.12). Further analysis of data showed that in both RBD and controls, the dreamer was personally involved in the aggression in about 90% of cases while he or she was a witness in about 10% of cases. The characters involved in the aggression were largely males (96% males vs. 4% females) in the RBD group, whereas an equal representation of males and females was seen in the control group (55% males vs. 45% females). Physical aggression was the type of aggression far more represented in RBD dreams compared to controls dreams (29.3% vs. 3.8%). Furthermore, dreams of RBD patients showed an overall higher percent of physical activities and a reduced frequency of visual activity than dreams of controls (23). Another typical feature of RBD dreams is the very high frequency of animal characters (19 vs. 4%), almost invariably involved in aggressive interactions. Interestingly, none of the patients with RBD had a "dream with at least one element of sexuality" in contrast to what observed in control subjects (0% in RBD vs. 9% in controls). The latter is concordant with the observation that appetitive behaviors, such as feeding or sexual, have never been observed as a manifestation of RBD either in humans or in the animal model.

Despite the increased aggressiveness in their dreams, patients with RBD do not show an increased daytime aggressiveness. No differences in daytime aggressiveness, as assessed by the total Aggression Questionnaire (AQ) scores, were found between RBD patients and controls. When looking at the subtypes of daytime aggressiveness, patients with RBD showed even lesser "physical aggressiveness" than control subjects (16.5 vs. 20.4) and no difference on verbal aggressiveness, anger, and hostility. This result corroborates early observations of a discrepancy between the aggressiveness displayed in dreams and the frequent placid and mild-mannered temperament in patients with RBD (24).

According to the principle of continuity between dream content and waking mentation, dream subjects and emotions are in general continuous with the general level of well-being and with past or present emotional preoccupations and interests of the dreamers (25, 26). In children dream studies, it was found that children with more violence in their waking fantasies had more aggressive interactions in their dreams (27). Interestingly, in RBD patients, the amount of aggressiveness in dreams was found to inversely correlate with the measures of aggressiveness during the day. Indicators such as the percentage of "dreams with at least one aggression," the ratio "total aggressions/total characters," and the ratio "aggression/friendliness" were inversely correlated to the measures of daytime hostility, meaning that more the patients had dreams with aggression, the less they showed hostility during daytime. The inverse correlation found in RBD between aggression in dreams and measures of daytime aggressiveness, in particular the level of hostility, could somewhat corroborate early theories of a compensatory nature of dreams, in which aspects of the personality neglected in waking life would be highlighted in dreams (28).Yet, the relationships between recurrent aggressive dreams and psychological measures in RBD patients have not been assessed. However, RBD patients show a high stereotypic dream content, namely a high occurrence of a human or animal aggressor threatening the dreamer or his entourage, in front of a variety of psychological profile. The repetitive nature of dream content may suggest several linkages between dream content and the neural network for dreaming (29), and this could be particularly true in the case of RBD patients. According to the activation-synthesis model of dream generation, phasic discharges from brainstem generators activate either motor than perceptual, affective, and cognitive pathways, and these impulses are subsequently synthesized into

dreams by the forebrain (30). Thus, it may be hypothesized that such phasic motor activation induced by brainstem locomotor pattern generators, would be preferentially translated by the cortical imagery generators, in activities such as fighting or running rather than more static ones (23).

Although parasomnias are phenomena disrupting sleep continuity, sleep architecture in REM sleep behavior disorder is usually preserved. Awakenings from episode are generally brief and immediately followed by resumption of sleep. Therefore, sleep, latency, total sleep time, and sleep efficiency do not differ from those observed in normal controls (31, 32). On the other hand, slow wave sleep (SWS) percentage appear to be even increased in RBD compared to same-age population (3,32,33). Furthermore, one study using quantitative EEG analysis found an increased delta power during non-REM sleep in iRBD compared to age and sex-matched controls (32). It has been hypothesized that the increased amounts of SWS seen in RBD may represent an adaptive epiphenomenon resulting in energy conservation, with the clinical consequence of being fully rested upon arising and not fatigued during the day (5). Some authors postulated that the impairment of dopaminergic system observed in RBD would lead to an overactivity of the adenosine system resulting in an increased production of SWS (32). RBD is frequently associated to other type of motor activity during sleep, especially to periodic leg movements during sleep (PLMS) (31). Those are stereotyped and recurring movements of the lower limbs, characterized by the extension of the big toe and dorsiflexion of ankle, with occasional flexion of knee and hip. PLMS occurs typically every 20–30 s during sleep, and they may or may not to be associated to sudden and brief changes of the EEG called microarousals (MAs). These EEG events may be isolated or associated to a PLMS that they may precede, accompany, or follow. The index of MA (number per hour) is considered a sensitive measure of sleep instability, and a high MA index is thought to be associated to a non-restorative sleep. In RBD, the percentage of PLMS associated to MA was found to be reduced compared to other conditions (e.g., restless legs syndrome) (31). Cardiac activation associated to every PLMS (e.g., a brief tachycardia followed by bradicardia) is also blunted in RBD (31), and on the other hand, a lack of tachycardia is usually observed during the dream-enactment behavior despite the highly emotional content and the often violent nature of the motor behavior (3). Those findings suggest a possible impairment in the cortical and autonomical reactivity to internal stimuli in RBD, and it may explain the common restorative nature of nocturnal sleep in RBD patients and the usual lack of complaints about excessive daytime sleepiness or fatigue.

Treatment of RBD

Maximizing the safety of the sleeping environment, by removing bed tables or hurtful objects from the vicinity of the bed and replacing them with pillows, must be considered as the first action. Pharmacological treatment is mostly based on clonazepam, a benzodiazepine administered at bedtime in doses ranging from 0.5 to 2 mg that significantly controls both the behavioral manifestations of RBD and the disturbed dream content. Its efficacy and safety has been reported in about 90% of patients in all the three largest series of cases in literature (22, 34, 35). However, possible loss of efficacy over time may sometimes require to increase the dose, and daytime sedation is the most common unwanted side effects. Recently, other treatment have been evaluated, namely melatonin and pramipexole. The first, administered in doses ranging between 3 and 9 mg at bedtime, was found to be effective in controlling both behavior and dream disturbances in RBD. In symptomatic RBD patients, melatonin has been administered alone or in association with clonazepam. Melatonin is generally well tolerated, with side effects represented by occasional headache and dizziness. Some authors then believes that melatonin can be considered as sole or add-on therapy for treatment of RBD, when other factors limit the use of clonazepam (36, 37). Levodopa was reported to improve subjective symptoms of RBD in three patients with PD (38). Pramipexole, at the dose ranging from 0.5 to 1 mg at bedtime, induced a sustained reduction in sleep motor behaviors in five over eight iRBD patients, as confirmed by video recording. However, the mechanism of its therapeutic effect is unclear, as pramipexole does not seem to change the PSG features of RBD (39).

Nightmare Disorder

Clinical Picture

According to the recently reviewed International Classification of Sleep Disorder-2 (ICSD-2) (1), nightmares are disturbing mental experiences that generally occur during REM sleep and that often result in awakening. Emotions usually involve anxiety, fear, or terror but frequently also anger, sadness, embarrassment, disgust, and other negative feelings. Dream content is often represented by imminent physical danger to the individual, but it may also involve distressing themes. Upon awakening, full alertness is commonly observed, and the subject is usually able to report the nightmare content. Nightmares typically, but not exclusively, arise during REM sleep; multiple nightmares within a single night may occur and may bear similar themes. Nightmare is very common during childhood: it is estimated that 10–50% of children aged 3–5 years have nightmares severe enough to disturb their parents. Sporadic nightmares are very common also in adulthood: approximately 50–85% of adults report having at least an occasional nightmare. Nightmare disorder, for example, frequent nightmares causing a certain degree of distress, is estimated to affect approximately 2–8% of the general population. Children show an equal sex ratio distribution in reporting nightmare. Adolescent and adult females report nightmares more frequently than do their male

counterpart although women have a general higher dream recall as well, which necessarily leads to a higher recall of nightmares. Nightmare can be idiopathic or arise either immediately following a trauma (as acute stress disorder or ASD) or 1 month or more after a trauma (posttraumatic stress disorder, PTSD). Posttraumatic nightmares may take the form of a realistic rehearsal of a traumatic event or depict only some of its elements.

Sleep, Quality of Life, Distress, and Psychopathological Correlates of Nightmare

Nightmares may disrupt sleep continuity causing awakening although this is not a rule. Indeed, in the past ICSD (40) as well as in the current Diagnostic and Statistical Manual for Mental Disorders, edition IV-TR (DSM-IV) (41), nightmare was defined as an extremely frightening dream that wakes up the subject, as opposed to bad dream that is not intense enough to induce an awakening. The definition has been recently modified in the last ICSD, and the awakening criterion has been omitted (1). In fact, the presence of awakening seems not to be correlated to the ND. One study suggested that nightmare may be more intense, but bad dreams and nightmare share the same negative emotional tone, finding that the frequency of dreams with negative effect (bad dreams) is a better index of low well-being than nightmare frequency (42).

Sleep PSG pattern in nightmare disorder has been poorly investigated. In fact, polysomnography recording in the sleep laboratory is often unsuccessful because nightmare tends to occur less often there than at home (43). Even more, very few PSG studies have focused on sleep characteristics of idiopathic nightmares while almost all studies focused on posttraumatic nightmares, namely patients with PTSD. As PTSD is characterized by highly disrupted sleep (44), PSG characteristic of PTSD patients may differ from those of idiopathic nightmare sufferers. Indeed, one recent study assessed the sleep pattern of patients suffering from idiopathic nightmare, PTSD nightmares, and healthy controls, finding no difference in terms of total sleep time, sleep latency, REM latency, REM efficiency, REM density, REM percentage, SWS percentage, and the number of MAs (45). However, both type of nightmares were associated with an elevated number of periodic limb movements during sleep. Furthermore, subjects with PTSD nightmare experienced more and longer nocturnal awakening than idiopathic nightmare sufferers and healthy controls and a consequent lower sleep efficiency (46). Thus, insomnia seems to be associated with PTSD, possibly representing a symptom of posttraumatic stress. A difference between the two types of nightmare has also been reported in terms of nighttime occurrence: the posttraumatic ones tend to take place earlier in the night than the idiopathic ones (46). Results on autonomic activation associated to the nightmare are conflicting. One laboratory study of nightmare indicates moderate arousal, namely an increase of heart and respiration rates, only during some nightmare, with low arousal in most others (43). However, this study was conducted in a heterogeneous sample, including patients with various psychiatric condition and with PTSD. Other authors (47) recorded autonomic parameters during REM sleep period associated or not to a nightmare, finding a moderate level of sympathetic arousal in the latter. A significant acceleration of the heart rate was observed in the 3 min of REM sleep before the awakening associated to the nightmare, whereas no acceleration was observed in the absence of nightmare. Respiration rate, however, appears to be only slightly increased during nightmare.

Nightmares have been correlated to various measures of psychopathology, namely neuroticism (42, 48, 49), anxiety (48, 50, 51), and depression (52, 53), but not all studies support this relationship and results are controversial. For instance, several studies have indicated that neuroticism, a personality factor, is associated with nightmares although some studies have not (54). It has been suggested that the method of measurement (e.g., retrospective vs. prospective recall of nightmares) may explain discrepancies in results, as subjects scoring high on neuroticism are more likely to remember their nightmares when asked to report them retrospectively than do non-neurotic subjects (55). It has been also shown that state anxiety, which represents an indicator of current levels of stress, may be a mediating variable between neuroticism and nightmare as persons with high scores on neuroticism experience more stress, and stress is known to increases the frequency of negative emotion in dreams and therefore the frequency of bad dreams (56). To better elucidate, such as complex relationship between nightmares and psychopathological measures, other mediating factors have been suggested, namely the frequency of nightmare, the ND, and the coping style. Frequency of nightmare has been shown to be only moderately correlated to general waking distress (52, 57). Subjects with moderately frequent nightmares may have higher levels of ND than subjects with numerous nightmares. Therefore, the measure of ND (e.g., the impact of nightmares on daily functioning), rather than frequency, seems to be more significantly related to psychological complaints, appearing as a mediating factor between nightmares and psychopathology. ND is currently measured by the Nightmare Distress Scale (57) and is a trait-like variable that correlated with trait – but not state– anxiety (52), neuroticism (58), physical complaints (58), and stress-related symptoms (48). One study showed that, when controlling for ND, neither retrospective nor prospective nightmare frequency was related to any psychopathological measures or personality factor (42). However, some criticisms have been moved to this result. It was actually suggested that the peculiar response format of the ND scale, which is based upon frequencies of the distress, instead of intensity (e.g., the response to the answer: “do your nightmares affect your well-being?” can be “never, rarely, sometimes, often, always”), is likely to be confounded by the nightmare frequency (56). The authors suggested that the original ND scale by Belicki may

generate a measure too highly correlated with the nightmare frequency and therefore "it is not surprising that controlling for ND reduced the correlation between nightmare frequency and neuroticism" (54–56). The role of ND needs to be further assessed: it is not clear whether it represents a specific complaint or a personality trait and, above all, whether it is correctly measured. However, given its strong relationships with all well-being measures and despite the fact that it is not included among the diagnostic criteria of neither the DSM-IV or the ICSD-II, ND must be evaluated in the clinical setting to define nightmare as a clinical problem. Coping style, for example, the personal ability to cope with stress, is also considered a mediating factor, involved in perpetuating the nightmare-related distress, and therefore the nightmare disorder. Dysfunctional coping strategy, reported in nightmare sufferers compared to non-nightmare subjects, may exacerbate both nightmare frequency and distress (47).

Cognitive and behavioral consequences of nightmare disorder are important. Postawakening anxiety and difficulty returning to sleep are often present. Nightmare disorder can lead to avoid to go to sleep and the subjects may then become sleep deprived, with the results to have more intense nightmares, besides insomnia and daytime sleepiness (1–54). Nightmare associated to ASD and PTSD can develop at any age after physical and emotional trauma. Individuals with PTSD are at risk for developing mood disorder and depression, social and employment consequences, self-destructive and impulsive behavior, and substance abuse; it is not clear to what extent the nightmare contributes to these complications in PTSD.

Treatment of Nightmare

Data on effective pharmacotherapeutic treatment are poor. Prazosin, an alpha-1 adrenergic antagonist, is the only treatment reported to reduce PTSD nightmare frequency in a placebo-controlled trial (59), but further studies are necessary to confirm this result. Cognitive-behavioral treatment is currently the treatment of choice for nightmare. Strategies include exposure techniques, imagery rehearsal therapy (IRT), and lucid dreaming. With the IRT, patient is invited to visualize the recurrent nightmare with changing the end of the usual storyline in a more pleasant way (54, 60). Mastery of nightmare produces a reduction in the frequency and intensity of nightmare. The same may be obtained also with lucid dream techniques. Through daily exercises, the patients are instructed to become lucid during their nightmares and to realize that is only a dream (61). Lucidity decreases the level of anxiety and subjects can also perform actions to change the storyline, changing the negative emotional tone of the dream.

Recurrent Isolated Sleep Paralysis

Clinical Picture

Formerly included in the sleep–wake transition parasomnia, SP is now considered as REM sleep-related parasomnia (1). They are characterized by the inability to perform voluntary movements that the subject may experience prior to falling asleep (hypnopompic) or upon waking (hypnagogic). The subject is awake and conscious of the environment but unable to speak and move except to open his eye. Respiration is not affected. The phenomenon may last from few seconds to minutes and it usually resolves spontaneously, but it can be interrupted by sensory stimulation, such as being touched. Full recall of the episode follows.

A greater number of individuals reported SP in the supine position than all other positions combined (62). Hallucinatory experiences may be associated in a large proportion of cases, including auditory, visual, tactile, vestibular-motor, or a sense of presence.

Estimates of prevalence of SP vary depending on the studied sample. A very large-scale survey in Germany and Italy suggested an overall rate of 6.2% in the general population (63). A study of 254 households in Pennsylvania (64) found that 17% of individuals reported episodes of isolated SP.

Quality of Life and Distress in Sleep Paralysis

Especially during the first episodes, SP is associated to intense anxiety. The events can be emotionally profound and leave a lasting memory that patients vividly recall years later (65). The nature and intensity of imagery generation in both wakefulness and sleep seems to play a role in the occurrence and frequency of SP. Imaginativeness and vividness of nighttime imagery are two personality factors found to be most predictive of SP frequency in a large study of college students (66). Hallucinations, such as sensing presence of others, feeling external pressure on the chest, and hearing footsteps or odd sounds, often accompany the SP episodes (67). These experiences may cause fear and be interpreted as a supernatural experience in a culturally distinct manner (68), including "being ridden by the witch" among some African Americans in the USA, "Kokma" in the West Indies, and "Kanashibari" in Japan (68).

There are also studies suggesting a link between rates of SP and panic disorders. High rates of SP have been found in patients with panic disorder in comparison to other anxiety disorders or no disorders (69, 70). A recent study in a large sample of outpatients seeking treatment for anxiety disorders (68) found a near 20% rate of SP with no significant difference among patients with a primary diagnosis of panic disorder, social anxiety disorder, or generalized anxiety disorder. SP episodes could be evoked by the periods of sleep disruptions that have been documented in patients with anxiety disorders

(68). Given prevalence of SP within anxiety samples, assessment of SP symptoms as part of regular clinical practice may benefit patients by normalizing these often-frightening experiences (71).

Issues that need to be addressed by future research:

- The actual prevalence of idiopathic RBD need to be assessed by means of large epidemiological studies.
- The relationships between stereotypical and unpleasant dream content in RBD and both polysomnographic characteristics and daytime psychological measures need to be better assessed.
- The reciprocal relationships between nightmares, nightmare's distress, and psychopathology need to be further explored.
- Idiopathic nightmares, posttraumatic nightmares, and bad dreams need to be better characterized in terms of polysomnographic features.

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14
Sleep and Quality of Life in Non-REM-Related Parasomnias

Mark R. Pressman

Summary Undesirable behaviors occurring during non-rapid eye movement (NREM) sleep have been reported to be associated with injuries to self and others ranging from bruises and lacerations to paralysis to death. During sleepwalking, confusional arousals and sleep terrors complex motor behaviors may occur while cognitive functions that usually control or modify our actions are limited or absent. Dangerous behaviors such as falling down, jumping out of windows, and sleep driving have been reported.

Keywords NREM parasomnias · disorders of arousal · sleepwalking · injuries · suicide · sleep deprivation · stress · death · paralysis

Learning objectives:

- Sleepwalking and related disorders are not always benign.
- Sleep deprivation and stress my be associated with onset of sleepwalking and related disorders.
- Violent behavior directed at other individuals may occur during sleepwalking and related disorder.

General Description of NREM Parasomnias

Parasomnias are events, usually undesirable, that accompany sleep (1). Parasomnias are generally divided into events that come out of rapid eye movement (REM) sleep or non-rapid eye movement (NREM) sleep. In NREM sleep, parasomnias are most often noted to occur during sleep stages 3 and 4 or slow wave sleep (SWS).

The most common NREM parasomnias are sleepwalking, confusional arousals, and sleep terrors. The occurrence of these NREM parasomnias depends on predisposing, priming, and precipitating factors (2, 3). Predisposition is based on genetic susceptibility and familial patterns (4). The presence of one or more of these disorders in a first degree relative is reported to increase the probability of these disorders by a factor of 10 (5). The occurrence of these disorders is most often primed by factors that increase the quantity of SWS or increase the arousal threshold (3). Acute sleep deprivation is the most common priming factor along with situational stress. An acutely sleep-deprived and genetically susceptible individual will still most often require a proximal trigger to set the parasomnia in motion. Proximal triggers include snores and other types of sleep disordered breathing, leg movements, noises, and touch. The proximal trigger produces an arousal that in most normal individuals would result in complete wakefulness. However, in a patient with a common NREM parasomnia, the trigger only results in a partial awakening showing signs in the brain of both sleep and wakefulness. This brain state typically lasts for some minutes although much longer periods have been reported. While in this unusual brain state, the parasomnic has limited or absent executive brain functions including attention, planning, memory, and social skills. Despite the absence of these higher cognitive functions, complex motor behaviors may occur.

Sleepwalking, confusional arousals, and sleep terrors are all initiated by an incomplete arousal from SWS sleep. For this reason, they are grouped together and called disorders or arousal (6). A confusional arousal differs from sleepwalking in that the individual in the midst of a confusional state does not leave the bed. On the other hand, sleepwalking starts as a confusional behavior but becomes sleepwalking once the individual puts foot to floor and starts moving around. A sleep terror also starts with an incomplete arousal from sleep but is often associated with a frightening image and autonomic nervous system activation. To the observer, the sleep terror most often begins with a scream and agitated behavior. The

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individual with sleep terrors may leave the bed in agitated state and run. Once the individual leaves the bed, it is considered to be sleepwalking.

All episodes of sleepwalking, confusional arousal, and sleep terrors occur with eyes open. Individuals in the midst of these disorders when in familiar environments may be able to navigate around objects. However, mistakes are common. In an unfamiliar environment, mistakes are inevitable.

It is estimated that 20% of children have had at least one episode of sleepwalking or related disorders. The frequency of disorders of arousal declines with age so that by early adulthood the frequency of these disorders is 1–4% (7, 8).

Sleep and Disorders of Arousal

Acute Sleep Deprivation

Disorders of Arousal are most often reported to follow acute sleep deprivation. Four studies have recently tested this assumption (9–12). After periods of total sleep deprivation ranging from 24–38 h, three of four studies reported that complex behaviors during recovery SWS increased significantly. However, in the fourth study following 38 h of sleep deprivation, the authors report that the number of complex behaviors decreased. This suggests that a certain quantity of acute sleep deprivation may increase complex behaviors during SWS. However, at the higher limits of sleep deprivation, the change in the arousal threshold may be so great as to not permit arousals (2).

Case 1: A 25-year-old woman decided to return to university after several years to finish her undergraduate degree. To finance her education, she continued to work fulltime during the day and attended classes at night. To both work fulltime and study fulltime, she reduced her sleep time from 8 h to 5 h. Within 3 days, she began to experience both confusional arousals and sleepwalking episodes. Upon reflection, these episodes were a result of both the acute sleep deprivation and added situational stress of working and studying fulltime. When she scaled back her study time so that she could sleep 8 h again, sleepwalking episodes ceased.

The sudden appearance or reappearance of NREM parasomnias may be an indication of insufficient sleep and/or increased stress.

Disruption of Families Sleep

The families of patients with disorders of arousal may find their own sleep disrupted in a number of ways. By the far, the most common are episodes of sleep terrors in young children. A typical scenario is that parents are awakened by a "blood curdling" scream from the next room. They rush to the next room to find their young child sitting up in bed. Signs of autonomic arousal may be evident, rapid respiratory rate, flushed face, and occasionally signs of agitated movement. The parents speak to the child but receive no answer. The child looks confused and does not acknowledge the parents presence. After a few minutes, the parents induce the child to lay back down and the child quickly returns to sleep. The next morning the child has no memory of the episode, but the parents remain upset and disturbed.

In cases of frequent sleepwalking, family members may remain awake until after the usual time of onset, resulting in their own sleep deprivation. In other cases, family members may place alarms etc. to alert them to their family member's nocturnal wandering.

Injuries

Injuries during sleepwalking or episodes of sleep terrors are commonly reported although no epidemiological data exists on its frequency. Schenck and colleagues (13) conducted a major review of sleep-related injuries in 100 adult patients. Of the 100 patients, 54 had a final diagnosis of sleepwalking or night terrors. The authors report that of these 54 patients

1. Twenty-nine (53.7%) had repeated episodes of running directly into walls or furniture or falling out of bed.
2. Ten (18.5%) had jumped out of a window.
3. Ten (18.5%) had left their homes, driven cars, walked directly into lakes, or climbed ladders.
4. Four (7.4%) had handled loaded weapons.

In the entire group of 54 patients with sleep terrors and/or sleepwalking, 98.1% presented with bruises, 18.5% with lacerations, and 5.6% with fractures. The episodes resulted in lacerations often requiring large numbers of sutures. Fractures included fingers, toes, legs, and cervical vertebra requiring neurosurgery.

In addition to Schenck et al., reports of falling or jumping out of windows has been noted in a number of other journal articles . Nevsimalova and colleagues report on four patients who jumped out of windows. Two of the window jumpers suffered serious injuries with paraplegia of the lower limbs and the other two escaped permanent injury (14).

Other case reports include the following:

Case 2: A 17-year-old man fell out of the window of his sixth floor apartment at approximately 3 a.m. (15). He survived the fall and left the hospital 6 weeks later. Patient had childhood history of sleepwalking and history of enuresis until the present day. Patient had amnesia for the event. In his first week of hospitalization, the patient was noted on two occasions to get out of bed and stand up in an apparent state of sleepwalking.

Missing from the history are data on his typical duration of sleep and sleep schedule during the week prior to this episode. No information was presented on his stress levels or family history of sleepwalking.
Case 3: A 16-year-old world-ranked Canadian junior tennis player jumped or fell out of his third floor window of his hotel in Mexico city during a tennis tournament (16). This episode occurred at 12:30 a.m. He was severely injured, but survived. The fall from the window was preceded by a frightening image of an attacker with a knife. He went to the window to escape only to find it closed. He broke the window and fell out of it. The description of the episode is most compatible with a sleep terror following by sleepwalking. Not reported was any information on his sleeping habits or stress. It seems likely he might have been sleep deprived due to his travel schedule and feeling stress due to his tennis matches.

Several reports of severe injuries to sleepwalkers have been initially reported as suicide attempts.

Case 4: A 12-year-old female awoke to find a deep cut to her neck and no memory of how it occurred. Initially considered to be a suicide attempt, she was admitted to an inpatient psychiatric unit. After a 2-week hospitalization she was released with a diagnosis of a NREM parasomnia. In support of this diagnosis was a personal and family history of sleepwalking. Additionally, she was sleep deprived the day before the episode (17).

Parasomnia-related behaviors sometimes are associated with catastrophic accidental injuries and even deaths to others.

Case 5: A traveling salesman pulled off a Boston expressway that has a rest stop between the east- and west-bound lanes. He took a nap in his car. He was disturbed and started his car. He pulled into the expressway in the wrong direction against traffic. Oncoming cars described him with eyes open with a glazed look on his face. Other drivers honked their horns and flashed their light without effect. After several minutes he crashed into an oncoming car killing three people. He survived. Patient had past personal and family history of sleepwalking. Patient admitted to drinking alcohol in the hour before the accident (18).

Occasionally, deaths have been improperly attributed to accidents when they in fact occurred during sleepwalking episodes.

Case 6: A 21-year-old university student left his house in 30°F weather dressed only in his underpants. He walked six blocks to a local highway and then from behind bridge supports suddenly ran out onto the highway where he was hit by a large truck. He sustained a severe head injury and did not survive. His death was determined to be a suicide by the local coroner. His family members did not believe this death was a suicide. An investigation by the authors of this case report noted a frequent personal and family history of NREM parasomnias. He had been sleep deprived prior to the episode, and according to family and friends, he was extremely modest and would never leave his room in an undressed state. With this information in hand, the coroner was convinced to change the cause.

Violence

Disorders of arousal have been associated with violent behavior for several centuries. Murders, attempted murders, assaults, and rapes have been reported to occur during these disorders (19, 20). Violent behavior during sleepwalking usually occurs when the sleepwalking is grabbed, blocked, or touched. Occasionally, close proximity to the sleep walker is sufficient to trigger a violent episode. Violent behavior during confusional arousals almost always occurs when a sleeping individual is touched or aroused in some other way. The arousal and the violent behavior appear to occur simultaneously. Sleep terrors differs from sleepwalking and confusional arousals. It is reported to begin with a frightening image such as a fire or armed attackers in the bedroom. This frightening image is most often followed by agitated and confused behavior that results in out of bed sleepwalking behavior. If the agitated sleepwalker encounters another individual, violent behavior may result.

Sexual behavior during sleep (21, 22) as well as bizarre eating behaviors (23) may also occur during sleepwalking episodes. Sexual behavior during sleep may result in martial problems and even in criminal charges. Sleep eating behaviors may result in weight gain and in injuries from improper use of kitchen equipment.

NREM parasomnias are a risk factor for minor to severe injuries. An increased risk may be present in individuals who have a genetic susceptibility to NREM parasomnias following acute sleep deprivation and situational stress.

Issues that need to be addressed by future research:

- How can injurious or violent behaviors be predicted?
- How can injurious or violent behaviors be prevented?

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15
Sleep and Quality of Life in Older People

Alia Khan-Hudson and Cathy A. Alessi

Summary Sleep disturbance is common with advancing age due to age-related changes in sleep and an increased prevalence of certain sleep disorders, in addition to health conditions, psychosocial issues, medication effects and a variety of other factors that impact sleep. The evidence that insomnia and other sleep problems have negative effects on health and quality of life (QOL) across the lifespan is convincing, and data suggest that this relationship is even stronger as people age. Several population-based studies have demonstrated an association between impaired sleep and worse performance on global measures and specific individual domains of QOL in the older adult. In addition, among older people, excessive daytime sleeping may be associated with an increased risk in mortality and morbidity and increased risk of falls. With advanced age, sleep disturbance is also associated with declines in functional status and social functioning, in addition to memory and other cognitive impairments. There is also evidence that sleeping problems can interfere with an older person's ability to carry out healthy and stable relationships with their spouse, other family and friends, which likely further impairs their QOL. In general, people with sleep disturbances have poor health-related self-perception, which may be related to inability to cope with daily activities. Taken together, research evidence is convincing among older adults that the cumulative effects of sleep disturbance can significantly impair their well-being and QOL.

Keywords Elderly · insomnia · quality of life · health-related quality of life

Learning objectives:

- In the older person, the effects of health status on quality of life are as important, and in some situations may be even more important, than effects on survival.
- Sleep disturbance is common with advanced age and is associated with impairments in both global measures of quality of life and specific domains generally considered key aspects of health-related quality of life.
- The relationship between sleep disturbance and health-related quality of life is stronger among older compared to younger adults and is as significant as quality of life effects of other serious comorbid conditions (such as depression, congestive heart failure and other chronic health conditions).

Introduction

The ability to maintain a satisfying quality of life (QOL) is an important aspect of aging successfully. Unfortunately, sleep problems increase in prevalence with advancing age due to a variety of factors, such as age-associated changes in sleep and an increased occurrence of many sleep disorders. Research suggests that these sleep problems can negatively impact QOL in the older adult, particularly mood, cognition, and functional status. In fact, the effects of sleep on QOL may be even more important in older versus younger adults, and several population-based studies have demonstrated an association between impaired sleep and worse performance on global measures of QOL in the older adult. Recently, interventional studies on sleep problems in older people increasingly include outcome measures that address selected aspects or global measures of QOL, in addition to traditional sleep outcomes. These and other studies will help clarify whether

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improvement in sleep disturbance can improve QOL in older people.

Measuring Quality of Life in Older People

There is general consensus in the gerontology literature that with advancing age, the effects of health status on QOL are as important and in some situations perhaps, even more important than effects of health on duration of life (i.e. survival). Put simply, many experts believe and older people often report that 'living well' is even more important than 'living long'. Many studies have used multi-item, health-related QOL questionnaires or other measures to study multiple domains of QOL. Although there is no clear agreement among experts as to how to best define and measure QOL in older people, most commonly used QOL scales have significant overlap in the domains assessed (1). Most global QOL measures address multiple domains, including (but not limited to) health, physical functioning, and psychological and social functioning of the individual. In addition, other factors are often included and may be even more important with advanced age, such as the physical living environment, the individual's autonomy, how time is used and satisfaction with care. QOL measures usually include both measures of physical function and measures of emotional well-being and comfort (e.g. affect, pain and discomfort). Unfortunately, although many multi-dimensional QOL measures are available, relatively few were specifically developed for use in an older population (1).

Here, we will frequently use the concept of health-related QOL, which focuses on domains such as health, physical, psychological and social functioning, which is believed to be more likely to respond to health-related interventions. In addition, the concept of quality-adjusted life years (QALYs) is also commonly used in research involving older people. QALYs combine assessment of life expectancy (survival) over a set period of time and health, generally weighted by consumer (i.e. the individual's) preferences for various health states. Although the relationship between sleep and health-related QOL in older people has been addressed in several studies, there is little use of the concept of QALYs in sleep research involving older people.

Interestingly, some global QOL scales include sleep as a domain to be measured in assessing QOL. For example, the Sickness Impact Profile includes an item on sleeping or napping during the day (2). People who do not sleep well often do not feel well, so it seems reasonable to consider sleep itself an important aspect of QOL. However, our goal here is to understand how and to what extent sleep problems affect other measurable health domains (besides sleep itself) commonly included in the assessment of QOL in the older adult.

Sleep Problems in Older People

Extensive literature suggests that sleep problems are more common with advancing age (3–6). The aetiology of sleep complaints in older adults is often multi-factorial. Common causes include medical (e.g. cardiac, pulmonary, gastrointestinal and musculoskeletal problems) or psychiatric (e.g. depression and generalized anxiety disorder) conditions, medication effects (e.g. diuretics and psychotropic agents), psychosocial effects (e.g. bereavement and lifestyle or living location changes with retirement or declining health) and problems with the sleeping/bedroom environment (e.g. uncomfortable room temperature and noise and light disruption in the nursing home setting). Common sleep disorders include circadian rhythm problems, sleep-related breathing disorders, and sleep-related movement disorders such as restless legs syndrome and periodic limb movement disorder. In addition, when insomnia becomes chronic, it may worsen medical and/or psychiatric illnesses and can lead to excessive daytime napping, which may be associated with impaired intellect, decreased cognition, confusion and psychomotor retardation. All of these factors can have a negative impact on QOL.

Research also suggests that some of the sleep disturbance seen in older people is due to age-related changes in sleep (7). In a meta-analysis conducted by Ohayon and colleagues, the bulk of the change in sleep across the lifespan is seen between early to middle adulthood, beginning at age 19 through age 60 (8). In this meta-analysis, the most consistent age-related changes in sleep included decreases in total sleep time, sleep efficiency and slow wave sleep, in addition to increases in wake after sleep onset. As sleep disturbance is so common with advanced age, understanding the relationship between sleep and QOL at this stage of life is extremely important. In Figure 15.1, we provide a simple theoretical framework for understanding the possible inter-relationships between sleep and selected domains of QOL in older people.

Sleep, Health and Quality of Life in Older People

Several studies have demonstrated an association between sleep disturbance and health-related QOL in older adults (Table 15.1) (9–13). At least two studies used data from the Medical Outcomes Study (MOS, a cross-sectional survey of functional health and well-being) to address the association between sleep complaints and health-related QOL (9–10). First, Manocchia et al. analyzed data from over 3400 participants (aged 18–65+ years) from the MOS to evaluate the relationship between sleep complaints and health-related QOL (using the Medical Outcomes Study Short Form Health Survey, SF-36) (10). The SF-36 is a 36-item scale of function, well-being, disability and physical and mental health that can be reported as a global score, or physical and mental component summary scores. Sleep was assessed using one item ('How much of the time did you get the amount of sleep needed?', with six possible responses ranging from 'all of the time' to 'none of the time') selected from several MOS sleep items based on item performance characteristics. The authors found that increasing frequency of this sleep complaint was

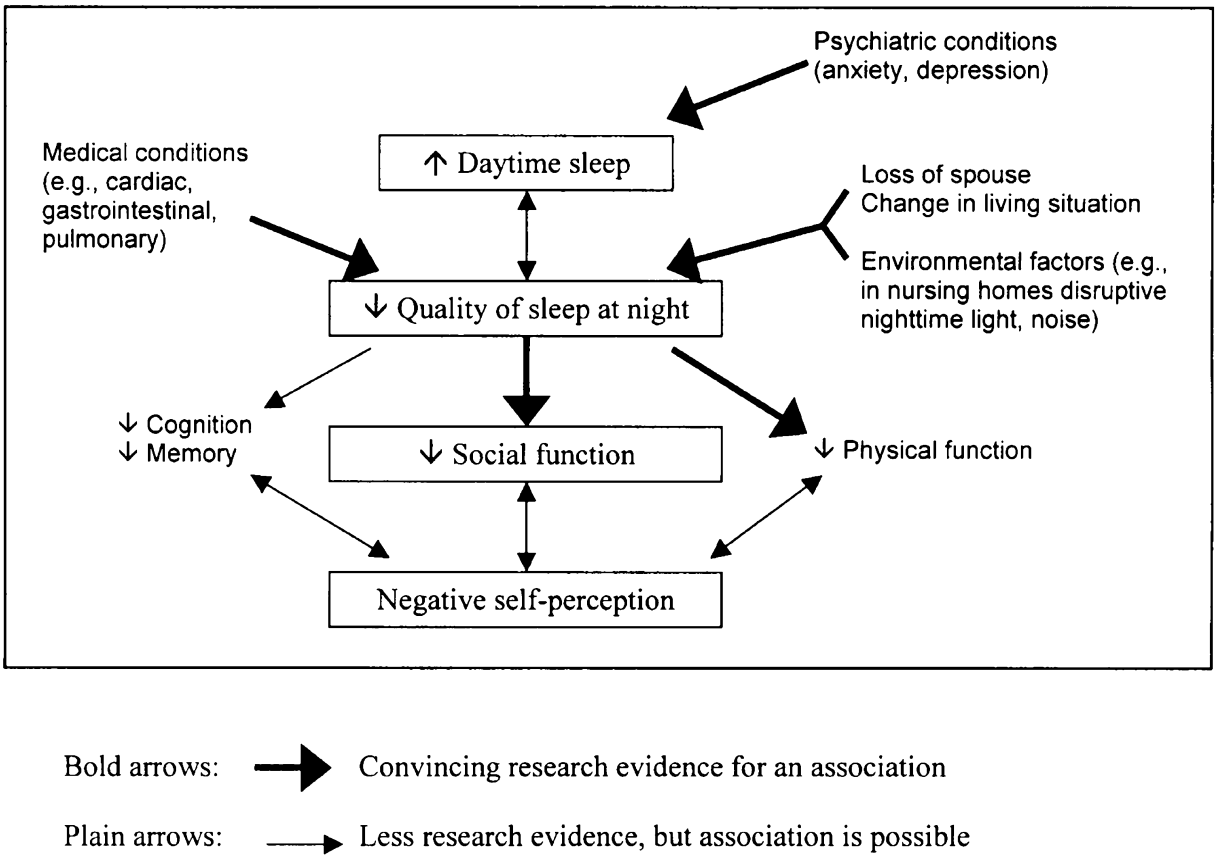

FIGURE 15.1. Possible interactions between sleep disturbance and the domains of quality of life among older adults.

associated with worse SF-36 scores, less work productivity and work quality, and increased health care utilization in the total sample and within multiple subgroups with chronic health conditions. Unfortunately, although 30% of the sample was aged ≥65 years, the specific associations between age and both sleep and health-related QOL were not reported. In a second study using MOS data, Katz et al. (described in more detail below) found that an insomnia complaint (defined as difficulty initiating or maintaining sleep) was independently associated with worse health-related qualify of life that was almost as severe as the association between QOL and several serious chronic comorbid conditions (e.g. congestive heart failure and clinical depression) (9).

In analysis of data collected from interviews in 2800 adults (aged 53–97 years) from a population-based study of hearing loss in Beaver Dam, Wisconsin, Schubert et al. reported findings on the prevalence of sleep problems and QOL in this older sample (12). Participants were asked three questions about their sleep, including to what extent did the participant (i) have difficulty getting to sleep, (ii) wake up and have a hard time getting back to sleep and (iii) wake up repeatedly. For each sleep question, a participant was considered to be positive for an 'insomnia trait' if they responded 'often' or 'almost always'. Health-related QOL was assessed with the SF-36. The authors found that the reported prevalence of waking repeatedly during the night increased significantly with age in both men and women, and the prevalence of waking and having a hard time getting back to sleep increased significantly with age in men but not women. In analyses adjusting for multiple other factors (such as age, number of chronic diseases and education), participants who reported 'often' or 'almost always' to any of the three insomnia questions had worse health-related QOL (both physical and mental component summary scores of the SF-36), with no single question having a stronger association with these summary scores. Further, there was evidence of a 'dose–response' in the relationship between insomnia traits and health-related QOL, with a significant decrease in both the physical and mental component summary scores and every domain of the SF-36 with increasing number of insomnia traits (adjusted for multiple confounders). When separated by gender, the greatest decrease in health-related QOL by insomnia trait was in the role-physical domain for men and the role-emotional domain for women. These domains address whether a person's physical health (for role-physical domain) or emotional problems (for role-emotional domain) have caused them to cut down, accomplish less or limit them in their work or activities.

TABLE 15.1. Selected studies that assessed sleep disturbance and quality of life in older people.

Study	Quality of life measure(s)	Sleep measure(s) used	Sample (N = sample size, percent women, mean age and/or age range in years)	Findings
Katz 2002 (9)	SF-36	Two MOS items (insomnia-defined responses indicating difficulty initiating or maintaining sleep over the prior 4 weeks)	*N* = 344556, 65 and 73% female for participants with no, mild or severe insomnia, respectivelyAge range 18–65+ years in the MOS studyMean ages 53.8, 54.8 and 53.1 for participants with no, mild or severe insomnia, respectively	Insomnia complaint was independently associated with worse health-related QOL (even after controlling for chronic medical co-morbidities), and decrements in QOL (SF-36 global and subscale scores) were almost as severe with insomnia as with chronic conditions such as congestive heart failure and clinical depression
Manocchia 2001 (10)	SF-36	Single item (getting amount of sleep needed) chosen from 12-item index from the MOS	*N* = 348461.8% femaleAge range 18–65+, 30.1% aged ≥65 years	Increasing level of sleep problem was associated with worse SF-36 scores, less work productivity and work quality, and increased health care utilization in the total sample and within multiple subgroups with chronic health conditions. Association with age not reported
Ohayon 2005 (11)	IADL	Sleep-EVAL System (telephone survey)	*N* = 102659% femaleAged ¿60 years (33.2% were ≥75 years)	Loss of autonomy (independence) in activities in daily living was associated with both early and late bedtime, and early and late wake-up time
Schubert 2002 (12)	SF-36	Three survey questions on insomnia traits (difficulty getting to sleep, wake up and hard to get back to sleep, waking repeatedly)	*N* = 2800Aged 53–97 years, mean age 69.3 years58.6% female	Positive insomnia questions were associated with worse SF-36 physical and mental component summary scores and more insomnia questions positive were associated with worse SF-36 scores (both component summary scores and every domain)
Stewart 2006 (13)	SF-12	CIS-R	*N* = 858055.1% femaleAge range = 16–74 years	Insomnia was of longer reported duration and more strongly associated with worse physical health-related QOL (SF-12, physical subscale) in older age groups
Zammit 1999 (14)	SF-36, Quality of Life Inventory, Work and Daily Activities Inventory, Zung Depression Scale, Zung Anxiety Scale	Sleep Assessment (QOL-SA, a 12-item sleep questionnaire), Stanford Sleepiness Scale	*N* = 36260.8% femaleAge range = 18–75 years, mean age = 44.4 years in the insomnia group and 37.1 years in the control group	Compared to controls, participants in the insomnia group had worse scores on all SF-36 subscales, more depression and anxiety, and greater impairments on the Quality of Life Inventory and the Work and Daily Activities Inventory (also more daytime sleepiness on the Stanford Sleepiness Scale). Within the insomnia group, there were no significant differences in health-related quality of life between those who were or were not treated, and between types of insomnia treatments used

CIS-R = revised Clinical Interview Schedule defined insomnia; IADL, Instrumental Activities of Daily Living Scale; MOS, Medical Outcome Study; QOL, quality of life; SF-12 = Short Form 12 Health Survey (12-item version); SF-36, Short Form-36 Health Survey (36-item version).

Daytime Sleeping and Quality of Life in Older People

The potential relationship between daytime sleeping and health-related outcomes (including QOL) among older people is under considerable debate. A study by Gooneratne et al. found that older adults who reported daytime sleepiness had functional limitations related to that sleepiness (14). However, as mentioned above, chronic insomnia can lead to daytime napping, and several studies have found that excessive daytime sleeping is related to an increased risk of mortality. For example, in a large prospective cohort study of over 3900 adults with an age range of 65–101 years, Hays et al. found that frequent daytime nappers had higher mortality risk compared to infrequent nappers (15). In another prospective cohort study of nearly 6000 participants with a mean age of 73 years, Newman et al. found that daytime sleeping was associated with not only increased mortality but also increased cardiovascular disease risk among both men and women after controlling for other known cardiovascular risk factors (17). In addition, in a descriptive study of over 1500 participants with an age range of 64–99 years, Brassington et al. demonstrated that daytime sleeping and napping is associated with an increased risk of falls (18). Finally, Ohayon

and colleagues found that older adults who reported excessive daytime sleeping were more likely to report cognitive impairments after controlling for other known cognitive risk factors (19). As these findings are largely correlational in nature, additional research is needed to fully understand whether there is a cause and effect relationship between daytime sleeping and health. In addition, large population studies may miss the individual beneficial effects of a restorative nap in some people.

An alternative view on the issue of daytime sleeping suggests that prescribed napping can be beneficial in patients with sleep complaints if it is properly timed and short in duration. Most nap studies involve younger adults, shift workers and long-distance drivers, which have shown some benefits that could be considered important to QOL, such as performance, neurobehavioral improvements, alertness and mood (20). Campbell et al. studied 32 healthy older adults and found that a short afternoon nap (mean nap duration of 81 min) improved cognitive and psychomotor performance immediately after the nap and throughout the next day (21). Tamaki et al. also found that among older adults, a short afternoon nap (30 min) may increase alertness and decrease fatigue (22). Additional research is needed to understand the relationship between daytime sleeping and QOL in older people.

Sleep and Psychosocial Aspects of Quality of Life in Older Adults

In addition to research demonstrating an association between sleep and markers of health and health-related QOL described above, other studies suggest a relationship between sleep and psychosocial aspects of QOL in older people. For example, using data from the 1991 National Sleep Foundation survey, Roth and Ancoli-Israel studied 1000 participants who were classified as chronic insomniacs (i.e. difficulty sleeping on a frequent basis), occasional insomniacs (i.e. difficulty sleeping under stressful circumstances) or no insomnia (i.e. never had difficulty sleeping) (23). These participants were asked to rate their QOL as a measure of ability to cope with minor problems, physical wellness, ability to accomplish tasks, enjoyment of life and general QOL. In this study, 70% of chronic insomniacs reported excellent or good QOL versus 81% of occasional insomniacs and 96% of non-insomniacs. In addition, 70% of chronic and occasional insomniacs reported excellent or good relationships with their spouse versus 81% in the non-insomniacs. Finally, 87% of chronic insomniacs reported excellent or good relationships with family and friends versus 91% of occasional insomniacs and 96% of non-insomniacs.

The 2003 National Sleep Foundation (NSF) Sleep in America poll provide additional important information on the relationship between sleep and QOL. The 2003 NSF Sleep in America poll surveyed 1506 community-dwelling older people (aged 55–84 years) and among other findings, reported an association between sleep and key psychosocial aspects of QOL, including mood, outlook and lifestyle (24). For example, in the 2003 NSF poll, insomnia symptoms (e.g. difficulty falling asleep, waking a lot during the night, waking too early and cannot get back to sleep and waking up feeling unrefreshed), daytime sleepiness and having a self-reported sleep problem were associated with whether or not the respondents reported feeling down, depressed or hopeless at least once a week. In addition, many of these sleep complaints were also more likely in respondents who rated their memory as fair or poor compared to those who rated their memory as excellent or very good. Several sleep complaints were also more common among those who reported finding it difficult to find a family member or friend to talk to when needed.

Other evidence demonstrating the relationship between sleep and psychosocial aspects of QOL is available. In a study comparing 100 patients (including 39 women with mean age 52 years and 61 men with mean age 53 years) with disturbed sleep referred to a sleep laboratory with 100 normal healthy adults, Saletu et al. (25) assessed sleep (by polysomnography and subjective report) and QOL using the QOL Index (26). The authors found that health-related QOL was significantly reduced in sleep disorders, with a more pronounced reduction in QOL with ‘nonorganic’ versus ‘organic’ sleep disorders. Out of 10 health-related QOL components, 7 were worse in patients with sleep disorders, including physical well-being, psychological well-being, self-care and independent functioning, occupational functioning, interpersonal functioning, personal fulfilment and overall QOL.

Older people increasingly remain in the work force as they age. Research suggests that psychosocial factors (e.g. social network) in the working environment are associated with sleep, particularly in women. Negative psychosocial factors in the work environment are associated with poor sleep, whereas positive psychosocial factors are associated with fewer sleep problems. In addition, Williams et al. (2006) recently demonstrated that positive family–work relationships are associated with better sleep quality (25). The relationship between the work environment and sleep is likely bidirectional, in that a poor working environment can negatively impact sleep, and poor sleeping can be contribute to a negative working experience and environment. The extent that these relationships effect QOL in the older worker is unknown.

Extensive literature also demonstrates a relationship between sleep and cognition, an important component of the psychosocial domain of QOL. Several studies have demonstrated that sleep problems impact cognition in older adults. A study by Zammit et al. (1999) studied insomnia symptoms and QOL in 362 people ranging in age from 18–75 years (27). Insomnia was identified by a 12-item Sleep Assessment (QOL-SA) questionnaire, where participants assigned to the insomnia group reported insomnia at least three times per week for at least 1 month (with at least two of the following: sleep latency $\geq$30 min, $\geq$3 awakenings per night, $\geq$1 awakening with difficulty returning to sleep, totalsleep time

≤6.5 h). The authors found that participants in the insomnia group had worse cognitive scores (Medical Outcomes Study Cognitive Scale), including poorer attention, concentration, memory, reasoning and problem solving and reaction time, compared to controls without insomnia.

Sleep, Activity Level and Activities of Daily Living in Older Adults

Across the lifespan, activity level and the ability to fulfil and maintain independence in activities of daily living is an important aspect of QOL. This is particularly true in the older adult, where the older person's ability to perform activities of daily living is recognized as an essential aspect of their QOL. Put simply, activities of daily living are things that a person needs to perform in their daily life. Measures of activities of daily living vary considerably, depending on the level of daily functioning being assessed. For example, measures can assess basic activities of daily living (e.g. eating, dressing, bathing, toileting, transferring in and out of bed), intermediate or instrumental activities of daily living (e.g. shopping, housework, local travel, handling finances and handling medications) or advanced activities of daily living (e.g. vigorous physical activity and long-distance travel). Most global QOL scales include some measure(s) of the level of independence in activities of daily living.

Most research that addresses the possible relationship between sleep disturbance and daily functioning in older adults have used global measures of QOL that include some items related to daily functioning. These and other studies suggest that sleep problems are associated with activity level and activities of daily living in older adults, but it is not clear whether limited activity results in poor sleep or poor sleep leads to limitations in activity. In addition, less physical activity during the daytime and more daytime napping may contribute to sleep disturbance at night and can negatively impact QOL, perhaps related to an increase in mood disorders and decreased ability to concentrate (9, 10, 12, 27).

Ohayon et al. performed a cross-sectional telephone survey of over 1000 participants aged 60 years or older in the metropolitan area of Paris, France, to determine normative data on sleep, cognitive function and activities of daily living (11). The survey included the Sleep-EVAL System to assess sleep variables and the 8-item Instrumental Activities of Daily Living Scale in addition to other measures. The authors tested for factors associated with long sleep duration, short sleep duration, early bedtime, late bedtime, early wake-up time and late wake-up time. They found that loss of autonomy (independence) in activities in daily living was associated with both early (9 p.m. or earlier) and late (1 a.m. or later) bedtime, and early (5 a.m. or earlier) and late (9 a.m. and later) wake-up time. The authors also found that older people who did not exercise were more likely to be long sleepers or short sleepers.

In a cross-sectional national mental health survey of 8580 adults (aged 16–74 years) living in private households in England, Scotland and Wales, Stewart et al. found that any insomnia (defined by the Clinical Interview Schedule) was reported by 37% of the sample (13). Insomnia categories were more likely to be of longer (2 years or more) reported duration and were more strongly associated with worse physical health-related QOL (physical subscale of the SF-12) in the older compared to younger age groups. Insomnia was also associated with reported fatigue across all age groups, with a stronger association in older age groups. All associations were adjusted for gender, education, physical illness and common mental disorders. In addition, older people were more likely to be taking benzodiazepine hypnotic medications.

Chronic Illness, Medication Use and Quality of Life in Older Adults

The degree to which the relationship between sleep disturbance and QOL among older people is impacted, at least in part, by other chronic illnesses and medication use is not clearly understood. Many (but not all) of the studies summarized above included some measure of chronic illness and medication use in their analyses. In the study by Katz et al. (mentioned above) that used data from the Medical Outcomes Study, the results of the SF-36 were compared among 3445 participants (aged 18–65+ years) with or without an insomnia complaint (defined as the complaint of difficulty initiating or maintaining sleep) (9). This analysis found that insomnia complaint was independently associated with worse health-related qualify of life, and decrements in health-related QOL (SF-36 global and subscale scores) were almost as severe with insomnia as with chronic conditions such as congestive heart failure and clinical depression.

In a cross-sectional survey of over 1300 older people (median age 75 years, 61% female), Stein et al. compared QOL (using SF-36) between participants who were and were not taking medications for depression, anxiety and/or insomnia (27). In their analyses, they found that participants who took a psychotropic medication for anxiety, depression or sleep were more likely to perceive themselves as ill. In adjusted analyses (adjusting for comorbid physical illness), use of these medications significantly predicted lower scores on both the physical and mental component scales of the SF-36 in women; this trend was not significant in men. The direction of a potential cause and effect relationship between psychotropic medications and health-related QOL could not be determined in this study and measures of sleep were not addressed.

The study by Zammit et al. (1999) mentioned above tested for differences in SF-36 results within the group of participants with insomnia comparing those insomnia participants who did and those who did not report using a treatment for insomnia (14). There were no statistically significant between-group (treatment versus no treatment, and type of treatment) differences in health-related QOL (SF-36 global or subscales) and no differences between participants treated for insomnia

between those who used a prescription sleeping medication daily, a prescription medication less than daily, an over-the-counter preparation daily and over-the-counter preparation less than daily. Differences across age categories in these comparisons were not reported.

Conclusions

The ability to maintain a satisfying QOL is an important aspect of aging successfully. Sleep problems increase in prevalence with advancing age due to a variety of factors, and research is convincing that sleep disturbance can negatively impact QOL among older adults. Several population-based studies suggest that the effects of sleep on QOL may be even more important in older versus younger adults. These and other studies provide strong evidence that sleep is associated with multiple domains of QOL, including health, physical, psychological and social functioning. Further research is needed to determine whether and to what extent interventions to improve sleep will also lead to beneficial effects on QOL in the older adult.

Issues that need to be addressed by future research:

- Consensus is needed in how to best measure quality of life in studies of sleep in older adults to allow comparison of findings across studies of different populations, age categories and health conditions.
- Further research is needed as to understand how quality of life is associated with different specific sleep disorders and what mechanisms underlie the relationships between sleep and quality of life in the older adult.
- Studies of pharmacological, non-pharmacological and other interventions on sleep among older people need to include global and/or specific measures of quality of life to determine whether quality of life can also improve with these interventions and to help define the balance in risks and benefits of intervening on sleep in the older adult.

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16
Sleep and Quality of Life in Children

Ron B. Mitchell and James Kelly

Summary Sleep disorders are known to have a dramatic effect on the quality of life of children. They may present very differently from infancy through adolescence, which makes diagnosis and treatment of these conditions both challenging and complex. Pediatric sleep disorders constitute a variety of conditions including central apnea, acute life-threatening events (ALTEs), sudden infant death syndrome (SIDS), and narcolepsy. However, the most common diagnosis is sleep-disordered breathing (SDB). SDB is associated with adenotonsillar hypertrophy and usually resolves after adenotonsillectomy. Children with SDB have scores on a global quality of life measure that are worse than those of children with asthma or juvenile rheumatoid arthritis. Fortunately, dramatic improvements in quality of life scores for SDB have been shown in a number of studies after adenotonsillectomy. The improvements are comprehensive and include all domains of quality of life. Caregivers report improvements in sleep disturbance, physical suffering, emotional distress, and daytime problems in their children. These improvements in quality of life are maintained up to 18 months after surgery and are dramatic regardless of the severity of SDB. The prevalence of SDB in children with obesity, neuromuscular or craniofacial disorders, Down syndrome or mucopolysaccharidoses is higher than in the general pediatric population and is widely underestimated. Unfortunately, few studies on quality of life have included these "high-risk" children or children with sleep disorders other than SDB. In future studies of quality of life and sleep disorders in children there is a need to quantify the diagnosis of the sleep disorder on the basis of data from polysomnography so that selection criteria might be standardized, to include appropriate control groups in the study design, and to assess the impact of co-morbidities.

Keywords Quality of life · behavior · child · sleep · sleep apnea · sleep-disordered breathing · polysomnography · tonsils

Learning objectives:

- Sleep disorders in children are common, underestimated, and have a large impact on quality of life.
- Sleep-disordered breathing (SDB) is the most common sleep disorder seen in children. It is associated with behavioral problems that include hyperactivity, reduced attention, somatic complaints, anxiety and depression.
- The quality of life of children with SDB is similar to that of children with chronic conditions such as asthma and juvenile rheumatoid arthritis.
- Adenotonsillectomy is known to lead to a dramatic improvement in quality of life that affects sleep disturbance, physical suffering, emotional distress, daytime problems, and caregiver concerns.
- The prevalence of SDB in 'high-risk' children, those with obesity, neuromuscular or craniofacial disorders, Down syndrome, or mucopolysaccharidoses, is higher than in the general pediatric population and is widely underestimated.
- A multidisciplinary approach is necessary for the diagnosis and treatment of sleep disorders in children.

Introduction

Over the last 20 years, there has been increasing recognition of the negative impact that sleep disorders have on a child's health. The known effects of poor sleep on behavior (1), school performance (2) and quality of life (3–5) have been shown to be significant and have led to a major public health concern. Pediatric sleep medicine has consequently grown dramatically into a multidisciplinary specialty that involves

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pulmonology, otolaryngology, neurology, psychology, and psychiatry. However, despite increasing knowledge in this field, sleep disorders remain obscure for many health care providers who treat children. This is in part a result of the fact that sleep disorders may present very differently from infancy through adolescence, and this makes the diagnosis and treatment of these conditions both challenging and complex. Nonetheless, there are now an increasing number of sleep centers that are dedicated to the evaluation, diagnosis, and treatment of children with sleep disorders.

Pediatric sleep disorders include a variety of medical conditions such as apnea, acute life-threatening events (ALTEs), sudden infant death syndrome (SIDS), and narcolepsy (6). However, the most common diagnosis is sleep-disordered breathing (SDB). SDB in children is a spectrum of disorders ranging in severity from primary snoring through upper airway resistance syndrome to obstructive sleep apnea (OSA) (7). It is possible to diagnose and to quantify SDB using full-night polysomnography (8). Primary snoring is the principal symptom of mild SDB, whereas obstructive apnea and hypopnea characterize severe SDB. Children with primary snoring have no evidence of changes in alveolar ventilation or sleep architecture. Upper airway resistance syndrome is characterized by increased respiratory effort and sleep fragmentation without episodes of hypopnea or apnea (9, 10). OSA is characterized by intermittent upper airway obstruction that disrupts normal ventilation and sleep patterns. OSA is a severe form of SDB that may cause cardiorespiratory complications if left untreated (11).

The estimated prevalence of OSA in 4-year-old children is 3%, whereas up to 10% of children have simple snoring (12). Adenotonsillar hypertrophy is the most common etiology of SDB in children, and adenotonsillectomy is known to be an effective therapy for this sleep disorder. In children with polysomnography-proven SDB who undergo adenotonsillectomy, resolution of SDB after surgery, determined by repeated polysomnography, ranges from 78 to 100% (5,13,14). Indeed, adenotonsillectomy, one of the most common surgical procedures in childhood, is increasingly performed for SDB rather than for recurrent throat infections (15).

Quality of life assessment is increasingly recognized as an important health outcome measure in clinical medicine (16–19). It reflects the World Health Organization's definition of health as "the state of complete physical, mental, and social well being and not merely the absence of disease or infirmity" (20). Increasingly, surgical intervention in children is directed at reducing morbidity rather than mortality. As such, measuring quality of life parameters has grown in importance.

Information about quality of life is most commonly collected in the form of a questionnaire completed by the parent or child (21). There are two types of health-related quality of life questionnaires: generic and specific. Generic instruments are comprehensive but have little depth. They are useful when comparing the burden of illness across different medical conditions. Specific instruments are more important for patients with a specific condition and are widely used in clinical trials and clinical practice. Specific pediatric health-related quality of life questionnaires exist for conditions such as asthma, cystic fibrosis, rhinitis, otitis media, and SDB (22–27).

The most common quality of life instrument used to study SDB is the OSA-18 (27). It is a disease-specific questionnaire that is practical, reliable, and validated. Children mostly present for the assessment of SDB because of parental anxiety related to sleep disturbance and its effect on daytime behavior. The OSA-18 instrument documents the child's sleep disturbance, physical symptoms, emotional distress, and daytime function as well as caregiver concerns.

This chapter will summarize our current knowledge of the association between SDB and quality of life in children. It will also discuss the impact of surgical therapy on the quality of life of children with sleep disorders. Lastly, the burden of less common sleep disorders in children and future direction of research will be highlighted.

The Association between SDB and Quality of life in Children

SDB appears to have a significant impact on health-related quality of life as measured by both global and disease-specific quality of life instruments (Table 16.1). Children with SDB have scores that are significantly worse than normal healthy children on a global quality of life measure. Stewart et al. (28) used the Child Health Questionnaire (CHQ) (29), a global health-related quality of life instrument, to study children with adenotonsillar disease. The CHQ has 12 subsets that evaluate family cohesion, family activities, parental impact, general health, mental health, self-esteem, behavior, bodily pain, and social limitations caused by physical and emotional problems. The results of this study showed that children with SDB did significantly worse than healthy normal children on the majority of the subscales of the CHQ. Surprisingly, their scores on several of the subscales were similar or worse than those of children with asthma or juvenile rheumatoid arthritis. Georgalas et al. (30) studied 43 inner-city children with SDB in London, UK, using the same questionnaire (29) and also showed that measures of quality of life were significantly depressed in these children compared with healthy children. Indeed, the global health subscale and the overall physical score were worse in children with SDB than in children with rheumatoid arthritis.

The relationship between the severity of SDB as measured by polysomnography and preoperative quality of life scores in children has not been studied extensively. It would be reasonable to expect that children with severe SDB will have worse quality of life scores than children with mild SDB. This correlation has been examined in a study (31) that showed a poor correlation between the severity of SDB as measured by polysomnography and preoperative quality of life scores.

TABLE 16.1. Quality of life in children with SDB.

Study	Age range	Target population	Diagnosis	Outcome measure	Conclusions
Stewart et al. (28) (n = 55)	2–16	Children with SDB and controls	Clinical	Quality of life (CHQ)	Children with SDB have lower mean quality of life scores on general health, physical functioning, and behavior than healthy children. Scores are similar to those of children with asthma or juvenile rheumatoid arthritis
Georgalas et al. (30) (n = 43)	2–14	Children with SDB and controls	Clinical	Quality of life (CHQ)	Children with SDB have depressed scores in 11 of 15 measures of quality of life compared to controls. Scores are the same or lower than for children with rheumatoid arthritis
Flanary et al. (39) (n = 57)	2–15	Children with SDB	Clinical	Quality of life (OSA-18)	Short and long-term improvements in quality of life after surgery
de Serres et al. (41) (n = 101)	2–12	Children with SDB	Clinical	Quality of life (OSD)	80% of children show improvement in quality of life across all domains after surgery
Avior et al. (48) (n = 19)	5–14	Children with SDB and controls	Clinical	Neurocognition, Behavior and Quality of life (CBCL, OSA-18)	63% of children had abnormal neurocognitive scores preoperatively and all but one improved postoperatively. Significant improvements in quality of life and behavior
Mitchell et al. (31) (n = 60)	3–12	Children with OSA	PSG	Quality of life (OSA-18)	Improvements in quality of life in every domain and item within 6 months of surgery. Significant reduction in caregiver concern after surgery
Mitchell et al. (40) (n = 34)	3–17	Children with OSA	PSG	Quality of life (OSA-18)	Improvements in quality of life seen 12–24 months after surgery. Improvements more pronounced in the short-term than in the long-term
Stewart et al. (42) (n = 31)	6–12	Children with OSA	PSG	Quality of life	Global quality of life significantly worse for OSA than healthy children
Tran et al. (44) (n = 83)	2–14	Children with OSA	PSG	Behavior and quality of life (CBCL, OSA-18)	Behavior and quality of life. Behavioral problems significantly more common in OSA than control children (n = 83). Non-OSA children (CBCL and OSA-18). Large improvement in quality of life in OSA compared to controls after surgery

Mitchell et al. (31) found that children with severe SDB did not necessarily have poorer quality of life than children with milder forms of the sleep disorder. They attributed this finding to the fact that polysomnography and quality of life instruments measure very different aspects of sleep disorders. However, several studies have shown that as the severity of SDB increases so do behavioral and emotional problems, factors that are known to impact quality of life in children. Kaemingk et al. (32) showed that children with an apnea–hypopnea index greater than 5 had more problems with learning and memory than children with an apnea–hypopnea index less than 5. An apnea–hypopnea index greater than 5 is commonly used as indicating significant SDB (32). Similarly, Archbold et al. (33) showed that children with even mild SDB displayed significantly impaired levels of cognitive executive functions.

There is increasing evidence that even mild airway obstruction evidenced by primary snoring is far from benign. Blunden et al. (34) showed that children with primary snoring had reduced neurocognitive performance compared to controls. This included deficits in attention, memory, and intelligence scores. Similarly, Kennedy et al. (35) and O'Brien et al. (36) showed that children with primary snoring had reduced verbal and global IQ scores and reduced attention and memory compared to controls. These studies did not examine the impact of snoring on quality of life. Clearly, there is a need for further studies of children with primary snoring and other forms of mild SDB since behavioral problems associated with low quality of life scores may be as prevalent in these children as in children with more severe SDB (37).

Improvements in Quality of life after Adenotonsillectomy in Children with SDB

Dramatic improvements in quality of life scores after adenotonsillectomy for SDB have been shown in a number of studies (1, 31, 38–40). The improvements seen after surgery were comprehensive and included all domains of quality of life. There is also evidence that these improvements in quality of life are maintained up to 18 months after surgery. The majority of studies used disease-specific rather than global quality of life instruments. Two recent studies (31–38) have reported short-term improvements in quality of life after surgery for SDB in children using the OSA-18 survey. Goldstein et al. (38) studied 64 children before and 3 months after adenotonsillectomy. The diagnosis of SDB was based on clinical parameters and did not include polysomnography in the majority of children. A highly significant change was seen postoperatively in the mean scores for all items and domains. Goldstein et al. (38) showed that caregiver reports

of improvements in their child's quality of life after adenotonsillectomy for SDB were much more dramatic and universal than improvements in the clinical scales of child behavior. Mitchell et al. (31) compared preoperative OSA-18 scores to postoperative scores obtained at a mean interval of 4 months after surgery in children with SDB diagnosed by polysomnography. Caregivers reported an improvement in sleep disturbance, physical suffering, emotional distress, and daytime problems in their children. The domain with the most significant improvement was sleep disturbance and the domain with the least improvement was emotional distress. Caregivers' concerns were also reduced after adenotonsillectomy for pediatric SDB. Change scores greater than 1.5, indicating a large change in quality of life, were found for all the domains after surgery. The results agree with the results of Goldstein et al. (38) and confirm that caregivers report a significant improvement in quality of life after their children undergo adenotonsillectomy for a sleep disturbance.

Similar results have been reported in studies that have used other validated disease-specific quality of life instruments to study the outcome of adenotonsillectomy for SDB in children (28, 41). Flanary et al. (39) studied changes in quality of life using the CHQ (29), a global instrument. They showed improvement in the physical summary score but not in psychosocial subscales. Stewart et al. (42) also used the CHQ and showed no significant improvement in the physical functioning or in the majority of the psychosocial subscales. This may reflect the short time between surgery and the postoperative assessment but may equally reflect the need to use disease-specific quality of life instruments to assess longitudinal change in children with SDB.

Mitchell et al. (40) showed that improvements in quality of life as reported using the OSA-18 are maintained up to 2 years after surgery. A comparison of the short-term results obtained at a mean interval of 4 months to the long-term results obtained at a mean interval of 16 months after surgery showed some important differences. The scores for the domains of sleep disturbance and physical suffering were lower in the short term than long term. These domains measure specific problems such as loud snoring, breath holding spells, mouth breathing, and nasal discharge. It is likely that with time, some of these symptoms recur but not to the extent that they were present prior to surgery. In contrast, the domains of emotional distress, daytime problems, and caregiver concerns were not significantly different in the short term than long term. These domains measure hyperactive behavior, attention and concentration spans, caregiver concerns about the child's general health and frustrations with the child. It is not clear why these domains do not show the changes seen in the domains of sleep disturbance and physical suffering. It may be that the recurrence of mild physical symptoms of sleep disturbance may not be sufficient to evoke changes in the child's behavior. Equally, the parents may feel that surgical intervention has produced a substantive improvement in the child's SDB and that occasional symptoms are normal and do not merit further concern. Despite the fact that caregivers note some recurrence of physical symptoms after adenotonsillectomy for OSA in children, they nevertheless perceive a long-term improvement in quality of life.

Mitchell et al. (43) studied 61 children with SDB confirmed by polysomnography, 43 children with severe SDB and 18 with mild SDB. They reported that preoperative values for the OSA-18 total score and for most domain scores were higher for children with severe than for children with mild SDB, but this difference was not significant. Improvements in quality of life measured by reductions in scores for the five domains of the OSA-18 postoperatively were dramatic regardless of the relative severity of SDB. They concluded that caregivers of children with SDB reported a significant improvement in quality of life after adenotonsillectomy regardless of the severity of the underlying disorder. Furthermore, Mitchell et al. (31) showed that when the severity of SDB in children was classified on the basis of the initial OSA-18 total score, there was a consistent relationship between the extent of improvement and the severity of the sleep disturbance as reported by the caregivers. When children were classified by the severity of the sleep disorder as measured by polysomnography, the most severely affected group showed the greatest degree of improvement as well. In contrast, the moderately affected group showed the least improvement.

The correlation between improvements in quality of life and behavior after adenotonsillectomy for SDB has not been studied extensively. Goldstein et al. (38) demonstrated a fair to good correlation between improvements in quality of life and in behavior after adenotonsillectomy for SDB. About 25% of the variation in one score could be explained by variation in the other. None of the other studies assessed the correlation between behavior and quality of life as outcome variables.

The relationship between polysomnography, quality of life, and behavior is complex and clearly non-linear. There are a number of reasons why objective assessment with polysomnography and subjective proxy reports might not generate identical results. For example, caregivers may not observe their child during REM sleep and might fail to note the peak incidence of apnea or hypopnea, which would be recorded during polysomnography. As none of the reported studies included postoperative polysomnography, there are clearly areas that require further study. Results from both pre- and postoperative polysomnography would be especially valuable to provide an objective measure of the outcome of surgical therapy for SBD that can then be correlated with quality of life and behavioral measures. Previous studies also did not use a control population of children with SDB that did not undergo surgical intervention. Because of ethical concerns, it is unlikely that randomized controlled studies of this kind will be performed. As a consequence, we cannot exclude the possibility that improvements in SDB after surgery are due in part to a tendency of the condition to improve with time.

To overcome some of the issues related to a control population, Stewart et al. (28) undertook a study of 29 children with polysomnography-proven SDB. Twenty-four children underwent adenotonsillectomy and were compared to five children in whom the parents refused surgery. Using the Tonsil and Adenoid Health Status Instrument (28), a validated disease-specific quality of life instrument, Stewart et al. demonstrated a significant improvement in airway, breathing, infections, swallowing, and behavioral subsets in the surgical versus non-surgical groups. The study population was, however, very small. Tran et al. (44) compared children undergoing adenotonsillectomy for SDB to children undergoing unrelated elective surgery. Using the OSA-18 instrument, they showed significant improvements in the survey scores between the SDB and elective surgery groups.

Thus, the evidence available to date indicates that adenotonsillectomy is helpful in the treatment of children with SDB. In addition to improvements in sleep, adenotonsillectomy is associated with improvements in quality of life and behavior and these improvements are maintained in the long-term.

SDB and Quality of life in High-Risk Children

The effects of SDB on quality of life are more complex in children that are considered high risk. These are children affected by obesity, neuromuscular or craniofacial disorders, Down syndrome, mucopolysaccharidoses as well as a number of other disorders including cerebral palsy, Prader–Willi syndrome, achondroplasia, Arnold–Chiari malformations and sickle-cell disease. Such children are more likely to have upper airway obstruction that is multifactorial in etiology, and surgical management in these cases requires a multidisciplinary approach involving general pediatrics, pediatric pulmonology, anesthesiology, and otolaryngology. The resolution of behavioral problems and changes in quality of life after surgery are also more difficult to evaluate in these children.

To date there have been few studies that have examined quality of life in high-risk children with SDB. Only one study in this group of children specifically reported quality-of life scores. Mitchell and Kelly (45) studied 30 obese children who underwent adenotonsillectomy for SDB. Children with neuromuscular, genetic, and craniofacial disorders were excluded. Polysomnography and the OSA-18 were used preoperatively to diagnose the severity of SDB in each child and postoperatively to evaluate the outcome of surgery. The study showed that obese children with SDB have a clear improvement in physiological parameters of sleep and in quality of life after adenotonsillectomy. Caregivers reported improvement in their children after surgery in all domains of the OSA-18 survey including sleep disturbance, physical suffering, emotional distress and daytime problems. The improvements in sleep disturbances occurred without any significant change in age- and gender-corrected body mass index (BMI) for the study population. They concluded that the dramatic improvement in quality of life seen after adenotonsillectomy for SDB in the general population of children also occurs in obese children.

There are a number of factors that limit research on quality of life in high-risk children with SDB. First, disease-specific quality of life instruments, such as the OSA-18, have been validated in mostly healthy children with SDB and their applicability to children in high-risk groups is unknown. Second, children in high-risk groups are a heterogeneous group based on the etiology of individual disorders and have a variety of co-morbidities. For example, children with Down syndrome have very different issues when compared to children with neuromuscular disease or mucopolysaccharidoses, and all these children may also be obese. Third, the study population in each group is usually small and difficult to study long-term. There is also a temptation to downplay the significance of sleep disturbances in these children given the other grave problems that affect them, and the problem is frequently underestimated. Nonetheless, the prevalence of SDB in these children is higher than in the general population of children.

Pediatric Sleep Disorders Other than SDB

Approximately 25% of children referred to a sleep laboratory have a sleep disorder other than SDB. Sleep problems have a negative impact on the child's physical, emotional, and social well-being and can affect family functioning. Furthermore, poor sleep in children may exacerbate medical, psychiatric or developmental problems (6). This diverse group of sleep disorders covers sleep conditions from infancy to adolescence. Most, if not all, of these conditions are likely to have a negative impact on the quality of life of the child and/or parent.

SIDS is the leading killer of infants between 1 month and 1 year of age in the USA. Equally, ALTEs or "near-miss SIDS" are unique to infants and rarely occur in children or adults. However, the most common sleep problem in infants and toddlers is "behavioral insomnia of childhood" defined as difficulty falling and staying asleep with an identified behavioral etiology. The disorder has a prevalence of 10–30%. The treatment is behavioral therapy that has been shown to be effective. (46) Difficulty falling asleep and awakening during the night are common in preschoolers and are usually a self-limiting problem. Children and teens can present with excessive daytime sleepiness, poor concentration and school performance and mood problems related to inadequate and insufficient sleep. Partial sleep deprivation is a common problem in teenagers with a prevalence of 20% (47). Narcolepsy and adolescent insomnia are also seen in teenagers and require early diagnosis and treatment.

Research on SDB in children is, as yet, in the early stages of discovering the fundamental causes of sleep disorders and the influence they may have on child development. However, it is

evident that the occurrence of sleep disturbances during critical phases of child development may have a profound impact on behavior and learning. Every effort should be made to mitigate the consequences of these disorders until future research provides methods to eliminate their underlying causes.

Issues that need to be addressed by future research:

- In future studies of quality of life and SDB in children there is a need to quantify the diagnosis of the sleep disorder on the basis of data from polysomnography so that selection criteria might be standardized, to include appropriate control groups in the study design, and to assess the impact of co-morbidities.
- It would be helpful to evaluate the outcome of adenotonsillectomy for SDB in children with a multifaceted approach that includes pre-and postoperative polysomnography as well as behavioral and quality of life reports from caregivers.
- The issue of co-morbidities such as obesity or craniofacial abnormalities should be given considerable attention. It is necessary to identify the forms of SDB that predominate in children with significant co-morbidities and to understand the quality of life consequences that SDB may have for these children in contrast to others.
- Standardizing studies on SDB in this way may help to resolve some of the difficult questions that have arisen in this research at the interface of quality of life and surgical outcomes.
- The high prevalence of sleep disorders in children and the importance of reporting outcomes using quality of life measures should make this a public health priority.

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17
Sleep and Quality of Life in Traumatic Brain Injury and Guillain–Barré Syndrome

Sheldon Kapen

Summary Sleep disorders in traumatic brain injury include insomnia, disruption of sleep architecture, excessive daytime sleepiness (EDS), and disorders of biological rhythms. Insomnia is common and is an important impediment to successful rehabilitation. Risk factors for insomnia in traumatic brain injury (TBI) include female gender, lesser degrees of injury, depression, and pain. EDS usually appears later in the course of illness than does insomnia. Circadian rhythm disturbances, particularly delayed sleep-phase syndrome, may present as insomnia. A number of reports have described behavioral aberrations in Guillain–Barré syndrome, a condition that targets mainly the peripheral nervous system. Hallucinations and oneiric experiences are among the behaviors seen in Guillain–Barré syndrome (GBS). These phenomena may be associated with reduced hypocretin-1 in the cerebrospinal fluid (csf) and with narcoleptic-like changes on polysomnography (PSG), suggesting the possibility of hypothalamic involvement in GBS.

Keywords Traumatic brain injury · Guillain–Barré syndrome · insomnia · sleepiness · hypocretins (orexins) · circadian rhythms · narcolepsy

Learning objectives:

- The prevalence of insomnia symptoms is up to 70% in TBI patients.
- The prevalence of an insomnia syndrome in TBI is about 30%.
- Disruption of sleep architecture can be useful for prognosis in TBI.
- Excessive daytime sleepiness may be present in the later stages of rehabilitation after TBI.
- Delayed sleep-phase syndrome may be seen occasionally after TBI.
- Behavioral aberrations and oneiric phenomena are sometimes present in Guillain–Barré syndrome.
- Some patients with Guillain–Barré syndrome have undetectable or low levels of hypocretin-1 in the csf.

Introduction

This chapter focuses on sleep and the quality of life in neurological diseases. An explosion of interest in this subject has occurred during the past 15 years, whereas the preceding years were marked by a relative neglect and lack of knowledge of the important role played by sleep in neurology. We now know that obstructive sleep apnea (OSA) is quite common in stroke patients and may be a major risk factor (1); that sleep disorders are associated with Parkinson's disease (2); that excessive daytime sleepiness (EDS) is ubiquitous in Parkinsonian patients (3) and may be related to some of the most widely used medications in this disease (4); and that fatigue and tiredness are considered the most debilitating symptoms in multiple sclerosis patients (5). Early work had already highlighted the importance of sleep in certain forms of epilepsy but more recent investigations have made great strides in enhancing our understanding of the role of sleep in epilepsy (6).

Further advances can be expected in the future but the clinician must incorporate sleep issues into the workups of neurological patients to take advantage of the latest research. A few key questions regarding sleep quality, snoring, sleepiness, and weight gain could suggest the likelihood of OSA and can lead to an appropriate diagnostic and therapeutic course. Correspondingly, the introduction of a new dopaminergic medication to a Parkinson's disease patient should be accompanied by cautionary comments regarding possible "sleep attacks" or excessive sleepiness. The following chapters in this section

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will expand on these and other topics in a number of neurological diseases and conditions.

Traumatic Brain Injury

Among the numerous serious consequences of head trauma, sleep disruption is strongly represented. Sleep problems are ubiquitous in head injury patients in both the acute and chronic stages. Only in the past 10 years has attention been paid in the literature to the sleep of head injury patients although a few earlier publications reviewed the role of sleep architecture in predicting recovery of patients in various stages of coma and vegetative state (7–11). Most of the recent work eminates from rehabilitation services following discharge from acute hospital care and has been generated by physiatrists, psychologists, and neuropsychologists. Consequently, the results have appeared in specialized head injury and rehabilitation journals that are not likely to attract the attention of sleep medicine practitioners. This chapter will cover the sleep problems of head-injured patients with an emphasis on insomnia, sleep disorders, and disruptions of circadian rhythms.

Insomnia: Prevalence and Clinical Features

The prevalence of insomnia symptoms in traumatic brain injury (TBI) patients ranges between 50 and 70% (12) while a diagnosis of insomnia, based on DSM-4 (13) or International Classification of Sleep Disorders (ICSD) (14), generally has a prevalence of 30% (15).

For a diagnosis of primary insomnia according to ICSD criteria, there must be a minimal frequency of symptoms and a minimal duration since onset and also daytime sequelae such as fatigue, cognitive disturbance, or mood changes (14). Insomnia as defined by the ICSD and associated with TBI would necessarily be considered secondary insomnia but would still require daytime consequences. Unfortunately, there is variability between published series as not all authors have used the clinical definition of insomnia to describe their patient populations. Ohayon et al. have emphasized this point when analyzing the results of surveys of insomnia in the general population (16).

The prevalence of insomnia in TBI patients is greater in women (12) as it is in most surveys of the general population. Women tend to complain more about their sleep in all age groups (17) even though polysomnographic evidence of gender differences in sleep architecture is lacking or even points toward worse sleep parameters in men (18–20). Another common denominator among different investigators is the finding that sleep problems are more prevalent in milder cases of TBI (Glasgow Coma Scale 13–15) (21) than in the more severe injuries (12, 22–26). The generally accepted explanation for this somewhat surprising result is that patients with milder forms of head injury are more likely to have the self-awareness and cognition necessary to recognize insomnia as a problem. A third risk factor for insomnia in TBI patients is the presence of depression (23, 24). The vast majority of patients with major depressive disorder have abnormal sleep (27) and it is to be expected that depression in TBI would be no exception. Age, education, and time since injury have not been shown to influence the degree of insomnia in TBI (12, 22–23, 28).

The association with depression raises the question whether sleep problems after TBI represent principally a reaction to a stressful situation (the trauma itself, hospitalization, pain, time away from work and family, etc.) or whether the sleep problems are a direct result of brain injury (perhaps related to specific damage to sleep-associated areas such as the preoptic region of the hypothalamus where a lesion in animals leads to total insomnia) (29). A definitive answer cannot be offered at this time but one case in the literature is suggestive for specific brain damage being the cause. Tobe et al. (30) published the case of a 35-year-old patient who developed profound and persistent insomnia immediately following a closed head injury. An extensive workup revealed only approximately 2 h sleep per night with a 4-h sleep latency. A positron emission tomography (PET) scan showed abnormally decreased metabolic activity in several areas of the basal ganglia, thalamus, and cortex and an increase in the cingulate-gyrus and the left prefrontal cortex.

Further supportive evidence for the direct brain injury hypothesis is contained in the study of Baumann et al. (31) who examined hypocretin-1 (orexin-A) in the cerebrospinal fluid (csf) of 44 TBI patients. Hypocretins (orexins) are synthesized solely by cells in the perifornical region of the posterolateral hypothalamus and play a major role in energy regulation, motor activity, and the sleep–wake cycle (32). Importantly, narcolepsy is now known to be caused by a marked depletion of the hypocretinergic cells and a reduction or absence of hypocretin-1 in the csf (33, 34). Baumann et al. (31) found low or absent (below sensitivity of the assay) hypocretin-1 levels in the csf of 37 out of 44 moderately or severely brain-injured patients, suggesting the possibility of hypothalamic damage in these patients. These findings are likely to be relevant to the issue of sleep after TBI (narcoleptics usually have disturbed nocturnal sleep) (35, 36) and in particular to the question of post-traumatic narcolepsy (see below).

With the exception of the paper by Kaufman et al. (28), all the insomnia studies in TBI were based on interviews and questionnaires. Kaufman et al. (28) performed one night of polysomnography (PSG) and five additional nights of actigraphy at home in 19 adolescent subjects who had suffered minor closed head injury (loss of consciousness which was 30 min or less in duration) 3 years prior to the study. The adolescents also answered questions about the quality and quantitative aspects of their sleep. These subjects continued to complain about sleep problems, thus reinforcing the finding that the time since injury was not a factor for insomnia in TBI.

The polysomnographic recordings were consistent with the subjective data; sleep efficiency (total sleep time divided by time in bed after lights out) was lower in the TBI group when compared with a control group (80 vs. 88%); wake time was higher; and the number of awakenings was non-significantly more numerous. In addition to emphasizing the long-term nature of sleep disturbance after TBI, this study confirmed that milder forms of head injury seem to result in greater degrees of insomnia than do more severe ones.

Treatment

There have been few published reports regarding the treatment of sleep problems in TBI patients. As with insomniacs in general, the three major types of intervention available are control of risk factors, pharmacological agents, and behavioral therapy (37). Among the risk factors that should be evaluated first are depression and pain (22–25). Effective management of these two entities might go a long way toward alleviation of the insomnia. Hypnotic medications can be beneficial either over the short term or as ancillary treatment (38–40). Although the administration of at least one short-acting non-benzodiazepine hypnotic (eszopiclone) retained effectiveness over a 6-month period in a controlled study (41), caution might be indicated in TBI patients due to brain damage and interaction with other medications. Morin and co-workers have advocated behavioral intervention—especially sleep restriction and stimulus control—in conjunction with hypnotics when appropriate and they have presented data suggesting favorable outcomes using this approach (42).

Sleep Architecture

The timing of sleep and the cyclicity and architecture of the stages of sleep are regulated by intricate and complicated mechanisms in the brain that involve the brainstem, thalamus, basal ganglia, hypothalamus, cerebral cortex, and numerous important pathways between these various regions (43). Numerous neurotransmitters and paracrine chemical substances participate in these mechanisms. Consequently, elements of the sleep–wake cycle can serve as markers of injury to and recovery from traumatic brain injury. The major correlates of a good prognosis for recovery have included the following:

1. The consolidation of sleep as opposed to a more disorganized pattern such as sleep disruption or alteration of the normal delineation of daytime wakefulness and nocturnal sleep (7, 8, 44–46).
2. The presence of a normal percentage and timing of the individual stages of non-REM (NREM) and REM sleep (46, 47).
3. Specific characteristics of sleep stages including sleep spindles and K-complexes in stage 2 and rapid eye movements and muscle atonia in REM sleep (46–48).

The presence of normal sleep patterns in comatose or recovering patients after TBI is an important predictive factor for the return of normal cognitive function. Several authors have found that sleep patterns are better than or at least as good as the Glasgow Coma Scale (21) in predicting successful recovery (9, 44, 48). Of the different sleep stages, a normal or improving percentage of REM sleep seems to correlate best with cognitive recovery as NREM sleep has been more resilient to brain injury than REM sleep (10,11,47). Intrasleep wakefulness is also sensitive to traumatic brain injury in that it decreases as the patient improves (46). Finally, Parsons et al. studied power spectral analysis of the sleep EEG and described changes in the amount of delta, theta, and slow alpha activity over the course of 12 weeks after minor head injury (49).

Excessive Daytime Sleepiness

Although not as frequent as insomnia, EDS does represent a not inconsiderable problem as a result of TBI. Data on the prevalence of EDS in TBI are sparse and are mainly based on small samples. Cohen et al. (50) used questionnaires to arrive at a figure of 72.5% complaining of excessive somnolence among a group of 77 patients who were 2–3 years following injury and had had coma lasting a mean of 12 days. They compared this cohort to 22 hospitalized patients who were 3.5 months following injury and had had coma lasting 6.5 days. Only 14% of the hospitalized patients had complaints of hypersomnolence while 72.7% had insomnia (51.9% of the discharged patients had insomnia) (50). These data suggest that EDS appears later after head injury than does insomnia and may perhaps be related to sleep problems causing insufficient sleep or multiple arousals. Masel et al. (51) studied 71 consecutive patients who were undergoing rehabilitation an average of 38 months after TBI and who underwent PSG and multiple sleep latency tests (MSLTs) and also completed the Epworth Sleepiness Scale (ESS) (52) and the Pittsburgh Sleep Quality Index (PSQI) (53). Forty-seven percent had MSLT mean latencies 10 min or less (the “hypersomnolent group”) while 18.3% had latencies of 5 min or less. A latency of 5 min is the cutoff for pathological sleepiness (narcoleptic range) in the MSLT (54).

Sleep Apnea

Among the hypersomnolent patients of Masel et al. (51) noted above, 4 had OSA and 12 had periodic leg movement disorder (PLMD). Guilleminault et al. (55) also reported on OSA in hypersomnolent TBI patients in an early report in which 20

patients were referred to a sleep disorders clinic because of EDS, of whom 8 had significant sleep-disordered breathing (SDB) [apnea–hypopnea index (AHI) 20 or more], most of whom did not seem to have had the condition prior to their injury based on their histories. In a later publication, Guilleminault et al. (56) described the features of 184 patients with EDS after TBI (they were referred because of EDS and did not form a random group) and found that 59 of them (32.1%) had SDB (50 had OSA with a mean AHI of 31 $\pm$ 11 and 9 had upper airway resistance syndrome). The presence of SDB was associated with a higher incidence of "whiplash" injury. For the whole group of 184 patients, a more severe injury was more likely to result in pathological sleepiness (ESS 16 or more and MSLT mean latency 5 or less). Several other smaller series also reported a significant number of post-TBI patients with a high percentage of SDB (57, 58). Thus, post-traumatic sleepiness seems to be prevalent after TBI and OSA and various forms of SDB are frequent accompaniments of EDS in these patients. However, the true prevalence of post-traumatic EDS awaits more extensive randomized, controlled studies.

Post-Traumatic Narcolepsy

An interesting aspect of post-traumatic hypersomnia is post-traumatic narcolepsy that has been reported as isolated cases over the years. A clinical diagnosis of narcolepsy requires the presence of hypersomnia and also cataplexy while narcolepsy without cataplexy requires the presence of hypersomnia; ancillary symptoms such as sleep paralysis and hypnogogic or hypnopompic hallucinations; two or more sleep onset REM periods during PSG and/or MSLT; and the occurrence of positive HLA typing in the form of HLA DQB1-0602 (14). One of the sleepy patients in the series of Guilleminault et al. (55) had cataplexy.

Several case reports have appeared in recent years that have highlighted the diagnosis of post-traumatic narcolepsy. The largest series is that of Lankford et al. (59) that was published prior to the availability of HLA genotyping, but serotyping was used. The series included nine patients; five of them had cataplexy but all nine underwent PSG and MSLT that revealed two or more sleep onset REM periods during the MSLT in eight patients but only one in the remaining patient. There was no indication whether the latter patient had cataplexy or not (indeed there was no definition of cataplexy in the paper). One of the nine patients had a SOREMP on his/her PSG, presumably characterized by a REM latency after sleep onset of 20 min or less. This patient also had three SOREMPs on the MSLT but again, there was no mention as to whether or not he/she had cataplexy. Three patients possessed DR2 on HLA typing and another one had DQw1 (over 90% of idiopathic narcoleptics with cataplexy possess DQB1-0602 which is a molecular genotype of DQ1) (60).

One abstract reported on three patients with post-traumatic narcolepsy and cataplexy with complete PSG and MSLT results and HLA typing (61). One patient who also had laboratory and HLA testing was published as a case report (62) and another was published with clinical information only (63). In 2004, Bruck and Broughton (64) reported a complicated case that required 8 years to make a definitive diagnosis. Finally, Francisco and Ivanhoe (65) described successful treatment of a patient with methylphenidate. The diagnosis was confirmed by the occurrence of cataplectic attacks and the presence of a pathological mean latency and four SOREMPs on the MSLT. The advent of the twenty-first century witnessed a major advance in our understanding of the mechanisms of narcolepsy with the discovery that dogs with narcolepsy lack the gene for the receptor of newly described chemical substances called hypocretins (orexins). The narcoleptic dogs lack the specific receptor for hypocretin-2 (66). Knockout mice without the gene for preprohypocretin, the precursor for both hypocretin-1 and hypocretin-2, showed features of cataplexy and abnormal REM sleep intrusions (67), similar to patients with narcolepsy. Finally, csf levels of hypocretin-1 are low or undetectable in the large majority of human narcoleptic patients compared with all controls (34), including neurological disease controls, except for cases of Guillain–Barré syndrome (68). Thus, it is remarkable to find that in a group of TBI patients with moderate to severe acute head injury, according to a widely used measure of severity, the Glasgow Coma Scale (21), 97% of severe and 88% of moderate TBI subjects had low or undetectable levels of hypocretin-1 in the csf (31). Three patients had visible damage to the posterolateral hypothalamus on CT imaging. These data raise the possibility that some cases of post-traumatic hypersomnolence are related to an irreversible destruction of hypocretin-secreting neurons even though they may not have the full narcoleptic syndrome, such as cataplexy or SOREMPs. It would be of great interest to study csf hypocretin levels in patients in the more chronic stages of post-traumatic hypersomnia.

Some of the patients in the Lankford et al. (59) series were not carriers of HLA DR-2 or DQ-1 as was the case for one of the three patients reported by Kapen et al. (61). As was stated in the latter abstract, it can be argued that in patients who are positive for HLA typing, the injury precipitated narcolepsy in a genetically susceptible individual. However, when the patient does not have the HLA marker, it is possible that the traumatic insult to the brain can induce narcoleptic-like findings in a genetically non-susceptible individual. The case report of a patient who had post-traumatic hypersomnolence with sleep laboratory findings consistent with the diagnosis of narcolepsy but without a narcoleptic HLA haplotype is replicated herein.

Case Report

A 71-year-old white male presented with a history of diabetes and EDS that began 2–3 months following a TBI due to a motor vehicle accident 28 years prior to his sleep medicine

evaluation. He had a history of automatic behavior but no other ancillary symptoms. After a very long sleep latency, his PSG revealed a SOREMP (1 min); stage 1, 28.2%; stage 2, 46.6%; no delta sleep; and 25.2% REM sleep. Mean sleep latency on the MSLT was 5.3 min with three SOREMPs. HLA studies were negative. He improved on pemoline.

Circadian Rhythm Disorders

Circadian (circa = about; dian = day) rhythms are robust and ubiquitous in man and animals and are expressed in essentially all bodily functions including physiological, cognitive, behavioral, and emotional (e.g., diurnal rhythms in depression)—down to the cellular level (69–71). Hierarchical control of these rhythms stems from the suprachiasmatic nucleus (SCN), a paired structure located in the anterior hypothalamus. The endogenous rhythm of the SCN is a bit greater than 24 h, so to keep the body synchronized with the light–dark cycle, the period of the clock (SCN) must be advanced on a daily basis. This is accomplished by light impulses being transmitted from the retina to the SCN in the form of chemical energy through the retinohypothalamic tract. In turn, the SCN transmits its influences to the rest of the brain and body using neurogenic and humoral mechanisms. One of the important connections of the SCN is to the pineal gland along a multisynaptic pathway to the intermediolateral region of the spinal cord at the C7-T1 level whence stimuli travel to the pineal through the superior cervical ganglion.

The pineal gland secretes melatonin, the "dark signal" hormone, so-called because it is synthesized and released only in the absence of light. It also feeds back on the SCN through melatonin receptors allowing it to influence SCN function in conjunction with environmental light stimuli. Melatonin has received wide attention because of its chronobiotic properties and its putative usefulness as a hypnotic. Light and melatonin (and other variables such as benzodiazepines) exert their effects on the SCN along a temporal spectrum represented by phase response curves (PRCs) that reveal the timing, direction, and intensity of specific stimuli on biological rhythms. Light advances the clock when exposure takes place in the early morning while it delays the clock in the evening and early nighttime hours. Melatonin possesses an almost mirror image to light in its effects on the clock – an advance in the late afternoon and evening and a weak delay in the early morning (69–71).

A number of cases of circadian rhythm disorders have been reported following TBI. All cases except one have been delayed sleep-phase syndrome (DSPS), a condition first described by Weitzman et al. (72) in which there is a discrepancy between the phase of the biological clock and the light–dark cycle such that the patient's sleep onset time is delayed by a number of hours beyond the desired time as dictated by social and environmental demands. Once the patient does fall asleep, however, he/she suffers no disruptions until wake-up time according to his/her physiological needs. Patients with DSPS usually present with sleep onset insomnia but some may also complain of EDS if they must shorten their sleep periods to report to work or school. Three cases have been described as case reports and another 16 were mentioned in a letter to the editor (73). Two of the three cases were juveniles (ages 13 and 15) (74, 75) (most of the spontaneous cases in the literature have been juveniles or young adults) and the other case was 48 years old (76). None of them had preictal rhythm disorders nor did they have sleep problems at all prior to the injury. Documentation in two of the cases was achieved with actigraphy (activity monitored with an accelerometer attached to a wrist); measurement of melatonin levels; and recording of body temperature (74, 76). Attempts to treat the condition were successful in one (melatonin) (74) and unsuccessful in another (chronotherapy) (76).

Another report described a 39 year old who developed a non-24-h sleep–wake syndrome following TBI (77). In this condition, there is a cycle duration significantly different from 24 h (usually a delay) so that left to their own devices, the patients will schedule their sleep periods at a later time each day, eventually going around the clock to their original sleep onset time and beginning the cycle all over again. In the TBI patient, psychiatric problems were mentioned after the injury, but it is unknown whether they triggered the rhythm disorder or vice versa. Surprisingly, the timing of melatonin secretion was normal and quite out of phase with the behavioral manifestations (the sleep–wake cycle).These cases suggest that head injuries may, in some instances, disrupt the SCN or its pathways. However, the incidence does not seem to be high based on the small number of cases reported. On the other hand, it may be that a lack of awareness has resulted in missed diagnoses in many cases of insomnia. Two studies examined the possibility of circadian rhythm disorders in 10 cases each. One study (78) used the timing of dim light melatonin onset (DLMO) (79) and the validated Morningness–Eveningness Scale (80) to look for phase shifts and the other (81) applied digital analysis of the body temperature curve. Neither study revealed any abnormalities in these measures but the *n* was quite small and there may be subgroups of TBI patients in whom the likelihood of subtle hypothalamic injury would be greater. The timing of the sleep–wake cycle should be part of the evaluation of TBI patients who have sleep problems.

Guillain–Barré Syndrome

Guillain–Barré syndrome (GBS) is an autoimmune acute inflammatory demyelinating polyradiculoneuropathy with a greater degree of motor than sensory involvement (82). The rapidity of onset varies, but it usually reaches its peak of dysfunction in 2–3 weeks resulting (in the worst cases) in tetraparesis, facial paresis, and respiratory suppression requiring ventilatory assistance. The majority of patients

survive, some of whom with significant disability, but there remains a relatively high percentage of patients who succumb to the disease despite the introduction of therapeutic modalities, such as plasmapheresis and IVIG, which have reduced morbidity and mortality (82).

Despite the fact that the disease targets the peripheral nervous system, there is evidence of central involvement in some cases. The syndrome of inappropriate antidiuretic hormone secretion (SIADH) has long been recognized (83) and has been considered possibly to occur secondary to lesions in hypothalamic pathways. More to the point are the more recent reports of hallucinations and other behavioral disturbances in GBS patients (84–86). Cochen et al. (87) studied 139 GBS patients in and out of the intensive care unit (ICU) and compared them with 55 ICU controls with other diagnoses. Thirty-one percent of the GBS and 16% of the controls had mental status manifestations that included primarily hallucinations but also frequent vivid dreams, illusions, and delusions. The patients with these mental aberrations were not confused and were not felt to be suffering from ICU psychosis. Furthermore, a small subset of GBS and controls underwent sleep studies that were remarkable for abnormal REM manifestations such as REM without atonia; short REM latencies and sleep onset REM periods; and unusual rapid eye movements during non-REM sleep. In 20 patients, hypocretin-1 levels were measured in the csf, and the levels were lower in those with mental changes than in those without mental changes although the hypocretin-1 levels were not pathologically low (below 200 pg/ml). However, other groups have reported undetectable hypocretin-1 in the csf of GBS (33) patients and some patients have been abnormally sleepy (88). When taken together, these findings suggest that narcolepsy-like phenomena may occur in some GBS patients secondary to damage to hypocretin-containing cells in the hypothalamus or to their pathways.

Issues that need to be addressed by future research:

- Objective measures are needed to confirm the prevalence and clinical significance of insomnia in TBI, including polysomnography and actigraphy.
- Polysomnography and MSLTs should be used to evaluate EDS in TBI patients.
- Prospective studies with sleep logs are needed for the study of circadian rhythms in TBI.
- Cooperative studies should be carried out to determine the incidence and course of hypocretin-1 deficiencies and to correlate the csf findings with clinical phenomena.

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18
Sleep and Quality of Life in Alzheimer's Disease and the Dementias

Doug Neef and David Larson

Summary Sleep changes are inherent to dementia but difficult to define or measure. As the sleep changes in dementia are probably related to neuronal changes in the brain, the location and severity of these changes, manifested as different clinical dementias, affects the presentation of sleep pathology. In the case of most dementias, including Alzheimer's dementia, the sleep problems affect both the patient and the caregiver. Treatment involves a multifaceted approach, including identification of treatable medical problems, correction of sleep hygiene, and identification and treatment of the particular form of dementia. Cholinesterase inhibitors seem to be emerging as the drug of choice for sleep problems in dementia.

Keywords Dementia · Alzheimer's disease · dementia with Lewy bodies · cholinesterase inhibitors · suprachiasmatic nucleus (SCN) · normal aging

Learning objectives:

- Sleep changes are frequently seen in dementia but are difficult to define and measure in this population.
- Sleep changes in dementia are probably related to specific neuronal changes in the brain. The location and severity of these changes, manifested as different clinical dementias, affect the presentation of sleep pathology.
- Treatment of sleep disturbance in dementia involves a multifaceted approach—identifying treatable medical problems and correction of sleep hygiene, as well as the identification and treatment of the specific form of dementia.

Introduction

Sleep problems are sometimes hard to define even in healthy patients, but when you add dementia and aging, these problems become even harder to define and harder to measure. For example,

1. How does one define a sleep problem in a demented patient?
2. How does the clinician measure a sleep problem in a demented patient?
3. Does the sleep problem bother the patient or the caregiver?
4. Is it a sleep problem if it bothers the caregiver but not the patient?
5. Who does the reporting, the patient or the caregiver?
6. Are caregiver reports adequate substitutes for patient reports in patients with dementia?
7. Can dementia patients accurately report a sleep problem?
8. What type of dementia is it?
9. How severe is the dementia?
10. What role do other factors (besides the dementia) play in the sleep problem?

Numerous other questions could be asked, and all would illustrate the problems associated with current research involved with sleep in dementia. Investigational studies must not only define the type of dementia, but also quantify it, as different dementias in different stages affect sleep differently. Similarly, methods must be developed to both identify and quantify sleep problems in the different forms of dementia. A useful first step is identifying the several causes of sleep disruption in the elderly and the demented which include: (i) physiological changes associated with "normal" aging; (ii) sleep problems associated with physical or mental health problems ("disease") and their treatment; (iii) primary sleep disorders; (iv) poor "sleep hygiene," that is, poor sleep-related practices and habits; and (v) some combination of the above (1). Sleep changes in dementia are likely related to the degenerative

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neuronal changes in the brain associated with the different clinical dementia syndromes. The location and severity of those changes, manifested as different clinical dementias, affects the presentation of both the disease and the sleep pathology. Treatment involves a multifaceted approach: identifying treatable medical problems, correcting sleep hygiene, as well as treating the particular form of dementia. In this chapter, we will concentrate on the sleep changes associated with Alzheimer's disease (AD) but also briefly look at sleep problems in other types of dementia such as dementia with Lewy bodies (DLB) and frontotemporal dementia (FTD), realizing that recognition of the sleep problem could even provide a helpful key in the differential diagnosis of dementia.

Sleep disturbances associated with early or mild dementia seem to be an exacerbation of the changes in "normal" aging. On EEG, aged normal subjects had less stage 3 and stage 4 sleep, less rapid eye movement (REM) sleep, and more wakefulness than normally found in young adults. Patients with AD had even less stage 3 sleep, no stage 4 sleep, very little REM sleep, and experienced fragmentation of their sleep, with frequent awakenings (2). This decrease in slow wave sleep (SWS) and REM sleep is manifested as the duration and frequency of awakenings and more daytime napping increases (1, 2), and although the sleep disturbance seems to worsen with increasing severity of the AD (a linear relationship), there is a possible inverted U-shaped profile in which patients with moderate dementia have more sleep impairment than persons in the early or advanced stages of disease (3). This highlights again the difficulty characterizing sleep problems in dementia, as problems can vary with both the type and severity of dementia.

The clinical changes in sleep associated with dementia are likely related to damage to the neuronal pathways that initiate and maintain sleep, starting with the SCN of the hypothalamus. As outlined by Vitiello and Borson, the SCN is believed to be the "internal" clock that generates circadian rhythms. It does this independently of environmental cues but uses light and physical activity, and perhaps social interaction and food, to synchronize these internal rhythms with our 24-h day (1). The SCN has input pathways that link it to the retina, limbic forebrain, other hypothalamic nuclei, the raphe nuclei, and reticular formation, and it also responds to various hormones. The output pathways through which the SCN controls circadian rhythms are not as well understood but seem to project to other areas of the brain controlling sleep, wakefulness, and arousal. The SCN also regulates the production of the "sleep hormone" melatonin, through connections to the sympathetic superior cervical ganglion and, in turn, to the pineal gland (1, 4). There are also subcortical pathways that regulate arousal and sleep–wake cycles, including cholinergic pathways (basal forebrain nuclei), serotonergic pathways (raphe nuclei), dopaminergic pathways (nigrostriatal and pallidostriatal), and noradrenergic pathways (locus coeruleus). Part of the pathophysiology of dementia is felt to be due to neurodegeneration of these different pathways, both at a pathologic and biochemical level, with different lesions manifesting as different forms of dementia. Thus, different aspects of sleep and wakefulness can be affected depending on the type and severity of dementia and the neurons and biochemical transmitters involved. However, there is also overlap between the structures and neurotransmitters affected. Ultimately, dementia pathology affects not only the cognitive functions of the cortex but also deeper portions of the brain that control such functions as memory and arousal. It is the damage to these deeper neuronal pathways that initiate and maintain sleep that is the probable cause of the acceleration of the normal age-related sleep changes found in dementia (1).

Thus, how and when sleep problems manifest themselves can depend on the type of dementia involved as well as the stage of the dementia although these differences in sleep pattern presentation show more variation during the initial stages of dementias than they do during the later stages of those same diseases. A helpful categorization of dementias is outlined by Boeve and Saper (5), who have divided the dementias into three groups based on the protein lesion involved. AD is primarily an amyloidopathy, with pathological changes caused by deposition of the β-amyloid protein. Pick disease, corticobasal degeneration, and progressive supranuclear palsy (PSP) are tauopathies, with changes to the tau protein. Finally, in Parkinson's disease (PD), PD with dementia (PDD), DLB, and multiple system atrophy (MSA), lesions are composed of intracellular α-synuclein and are thus termed synucleinopathies. Although there is often a mixture of more than one pathology (i.e., mixed dementia) and there can be an overlap of symptoms, especially later in the disease process, this distinction seems helpful in understanding the dementias in regards to their typical presentation. Although sleep problems differ somewhat with the different dementias, they tend to be similar within a pathologic class. Therefore, it is important to clarify both the type and degree of dementia as both can affect the sleep presentation. Research into the area of sleep and dementia is complex because it requires differentiation of the different dementia types as well as assessment of different sleep symptoms. Although most studies have been performed on AD patients, studies on patients with other dementias are starting to appear.

Sleep Disturbance in Alzheimer's Disease

Sleep disturbances in patients with dementia have been described for several decades in the medical literature (6, 7). The reported incidence of sleep disturbance in AD has been reported to range from 27 to 40% depending on the level of cognitive disturbance in the population being studied (8, 9). Sleep disturbance in patients with AD is often multifactorial in etiology. Individuals with AD may have disordered sleep due to co-morbid conditions such as obstructive sleep apnea, arthritis, heart failure, GERD, and nocturia. Additional factors including medication side effects, depression, anxiety, and

delirium can all contribute to sleep problems in AD (1). Those who care for individuals with AD may also suffer from disordered sleep. This may have a detrimental effect on quality of life measures for these individuals as well.

Description of Sleep Disturbance in AD

There is growing evidence that the neuropathologies of AD disrupt the circadian clock's output and result in sleep disturbance for many individuals affected by this disease. A recent study examining brain tissue from individuals with AD noted differential expression of the genes involved with rhythmic production of melatonin in the pineal glands of individuals with only histologic evidence of AD as well as those with clinical evidence of AD. It is believed that these changes are caused by uncoupling of the pineal gland from SCN control. Individuals with a more advanced stage of AD had more pronounced changes (4). These changes at the molecular level appear to manifest as characteristic alterations in the sleep behavior of affected patients. Individuals with AD are more likely than the non-demented elderly (NDE) to report sleep problems (8). When compared to the NDE, individuals with AD are noted to spend an increased amount of time in bed taking naps during the day, spend more overall time in bed at night, and have more fragmented nighttime sleep (10, 11). Sundowning or nocturnal delirium is another entity frequently referred to within this population in association with sleep disturbances. Although this concept has no consensus definition in the literature, it has been conventionally used to describe behavioral changes that occur in patients with dementia around the daily onset of darkness or that follow a diurnal pattern (12).

In 2003, a group of experts in the study of sleep changes and dementia proposed a set of criteria for diagnosing disturbances in the sleep–wake cycles of AD patients. A brief summary of their proposed criteria follows. First, a complaint regarding insomnia or increased daytime sleepiness is expressed by the patient or is observed by the caregiver. Second, polysomnography, actigraphy, or sleep log observations demonstrate two of the following four:

1. Episodes of wakefulness after sleep onset long enough or frequent enough to affect the daily functioning or well-being of either the patient or caregiver.
2. A decrease in total sleep time that is equal to one-fourth of the patient's total premorbid nighttime sleep or a pattern of sleeping less than 6 h between 9:00 p.m. and 6:00 a.m. if the premorbid sleep pattern is unknown.
3. Poor daytime wakefulness as evidenced by daytime napping increased in duration and/or frequency compared to the individual's premorbid state.
4. Disrupted sleep–wake rhythm evidenced by an altered ratio of day–night sleep.

The above changes are noted in association with a diagnosis of probable AD, are not present prior to the beginning of the dementia and evolve over the course of the disease. Finally, the sleep disturbance is not fully accounted for by comorbid general medical conditions, other sleep disorders, or parasomnias. These guidelines were put forth in an effort to facilitate the study of sleep disorders in the population affected by AD (13).

Implications of Sleep Disturbance for Patient and Family Members

Sleep disorders can diminish the patient's quality of life and become a specific challenge to caregivers. AD patients who engaged in nighttime behaviors such as eating, drinking, wandering, and waking up to talk were more likely to be institutionalized at 1 year when compared to AD patients who had no reported sleep disturbance at baseline. Sleep problems have been noted to correlate with increased aggression that is often a proximal cause for institutionalization in this patient population (9, 14). Caregivers report that being awakened at night is the sleep-related symptom they find most disturbing (15). Among individuals with AD, increased time spent in bed is associated with worsened mini-mental status exam (MMSE) scores. Disordered sleep appears to be a marker for more rapid progression of cognitive and functional deficits in individuals with AD. As the neuronal "hardware" responsible for cognition and daily function is damaged by the progression of AD, sleep seems to decay in parallel (8, 16–18).

Family caregivers of the disabled elderly have been noted to have an increased risk for psychiatric morbidity due to the strain associated with caregiving. In addition, caregivers experiencing emotional or mental strain in conjunction with their caregiving role have been reported to have an increased risk of mortality when compared with non-caregiving controls (19). Poor sleep among caregivers of AD patients is associated with increased serum levels of interleukin-6 and fibrin D-dimer, which have proinflammatory and procoagulant effects. It seems plausible that disturbed caregiver sleep may place the caregiver at an increased risk for cardiovascular morbidity (20).

Treatment Strategies

There are several approaches to the treatment of the sleep disturbances characteristic of AD. These strategies consist of therapy for any comorbid conditions that may be exacerbating sleep problems, non-pharmacologic therapy targeted at sleep pathology, and pharmacologic interventions. As an example of the importance of treating comorbid conditions that compromise sleep, recently published papers have demonstrated that treating obstructive sleep apnea (OSA) with continuous positive airway pressure (CPAP) is both feasible and beneficial for patients with dementia. The presence of dementia should not discourage clinicians from treating AD patients who suffer from OSA with CPAP (21, 22). Despite

these promising findings, there is a paucity of patient-oriented evidence regarding the value of many therapies currently used for sleep problems in the population affected by AD (1).

Non-Pharmacologic Strategies

Experts in the field of sleep disturbance and dementia have recommended multifaceted behavioral strategies for improving sleep in patients with dementia. Many of these strategies involve improvement of the sleep–wake cycle through modulators of the circadian rhythm (23). The so-called sleep hygiene practices to improve sleep include establishing consistent daily times for going to bed and arising from bed, establishing a bedtime routine, and limiting napping to a brief time in the morning or early afternoon. It may also be helpful to add daytime activities such as exercise or group interaction to the patient's routine in lieu of daytime naps. Efforts should be made to optimize the patient's exposure to natural outdoor light as well as bright light in the daytime living quarters. The use of alcohol and caffeine should be minimized. A light bedtime snack may decrease nocturnal awakenings related to hunger. Finally, the individual's sleeping area should be as quiet and dark as possible (24, 25).

Light therapy has also attracted interest as a potential treatment for sleep disturbance. The goal of light therapy is to expose the patient to increased amounts of natural or artificial light. This added light exposure may provide input to the SCN that will facilitate entrainment of the individual's circadian clock to the 24-h day. This may be especially important in institutionalized patients who receive suboptimal light exposure from their environment. Studies examining the efficacy of light therapy have had mixed results. An intervention that included caregiver education about sleep hygiene, daily walking, and light exposure from an artificial light source appeared to provide a benefit in terms of decreased number of nighttime awakenings, decreased total time awake at night, and decreased daytime sleepiness (26, 27). It seems that behavioral interventions pose a minimal risk of adverse side effects to patients and should be considered the first line of therapy for sleep disturbance in AD.

Pharmacologic Interventions

Data describing the safety and efficacy of medications for sleep problems in the population affected by dementia are scarce. Recent, small trials have examined the effects of cholinesterase inhibitors on sleep in patients with AD. These studies used actigraphy and polysomnography to measure patient response to treatment. In both studies, there appeared to be significant trends toward improvement in sleep-related parameters as measured by EEG and actigraphy (28, 29). It remains to be seen whether or not treatment with this class of medications will have a benefit for these patients as demonstrated by improvements in meaningful quality of life measures.

Typical and atypical neuroleptic agents are often prescribed for individuals with dementia to treat symptoms such as aggression, agitation and psychosis. The neuroleptics appear to be useful for the short-term treatment of these symptoms. Although it makes intuitive sense that the treatment of psychiatric symptoms would improve sleep, the usefulness of this class of medication for sleep in dementia is not known (1). The adverse effects of neuroleptics in the population of patients with AD have been well described. These adverse effects include extrapyramidal symptoms, drowsiness, and possibly excess mortality. Antipsychotic agents should be used judiciously, if at all, in this population (30–32).

Benzodiazepines and the non-benzodiazepine hypnotics such as zolpidem and zaleplon are frequently prescribed as short-term sleep aids in the general population. They have not been well-studied in individuals with dementia, and it is difficult to comment on their safety or efficacy in this population. Sleep aids with anticholinergic activity such as the tricyclic antidepressants and the sedating antihistamines may exacerbate the cholinergic abnormalities inherent to AD and should be avoided (1).

In light of the disturbance in melatonin production that has been described with AD, there has been considerable interest in melatonin and melatonin receptor agonists as a treatment for disordered sleep in AD. Studies of melatonin replacement have had mixed results (33, 34). Ramelteon, a melatonin receptor agonist, has recently been brought to market. Although this represents a promising possibility for the treatment of disturbed sleep in AD (35), further research is needed to determine the role this class of drugs will play in the treatment of sleep disturbances related to AD.

Other Dementias

Dementia with Lewy Bodies

Sleep disturbances in DLB, one of the synucleinopathies, are being increasingly studied and differ somewhat from AD. Core features of DLB include fluctuating cognition (delirium), recurrent visual hallucinations, and Parkinsonism. Suggestive features include REM sleep behavior disorder, severe neuroleptic sensitivity, and low dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET imaging (36). When compared with AD, sleep profiles in DLB are also different. Both groups suffer from sleep problems, but DLB patients seem to suffer from more overall sleep disturbance. DLB patients have a greater tendency to fall asleep at inappropriate times during the day and to also have more nighttime sleep disturbance (37). They are more likely to suffer from periodic limb movements, confusion on awakening, and bad dreams (38). A recent study suggested four differentiating characteristics between patients with DLB and AD: (i) daytime drowsiness and lethargy, (ii) daytime sleep of 2 or more hours, (iii) staring into space for long periods, and (iv) episodes of disorganized speech. Three or four of

these features were seen in 63% of DLB patients as compared with 12% of patients with AD (39). Patients with DLB also may respond to rivastigmine better than those with AD (38). Finally, patients with DLB can have a severe sensitivity to neuroleptics, and these medications should be strictly avoided in patients with DLB (36, 40). These findings illustrate the importance of distinguishing between the various dementias and how sleep patterns can aid in that distinction.

Frontotemporal Dementias

Research into the tauopathies, as represented by FTD (or Pick's disease), suggests that they differ from both AD and DLB. FTD and AD patients have been found to show different circadian abnormalities. The expression of an entrained circadian rhythm as an organized pattern of rest-activity is compromised in FTD, while a normal core-body temperature rhythm is maintained (41). Thus, in AD, both the central pacemaker (core body temperature rhythm) and behavioral expression are altered, whereas in FTD only the behavioral expression is altered. This suggests that chronobiological treatments such as light therapy may be ineffective in patients with FTD as their central circadian pacemaker "clock," as measured by core body temperature, seem to be functioning, and the behavioral problems are emerging "downstream" from the SCN (41).

Issues that need to be addressed by future research:

- Prospective investigations to more clearly elucidate the progression of sleep changes over the course of the various dementias.
- Establishment of validated criteria for the diagnosis of sleep disturbance in dementia.
- Studies to more clearly describe the efficacy of strategies for treating the sleep disturbances associated with the dementias.

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19
Sleep and Quality of Life in Headache and Migraine

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Summary Headache and sleep disorders are prevalent, comorbid conditions that challenge physical as well as psychosocial well-being. Headache is the most common pain-related complaint and the seventh leading ailment seen in medical practice, accounting for 18 million physician visits annually in the USA alone (1). Though historically headache often has been trivialized (perhaps because pain is not easily quantified and headache does not generally compromise life expectancy), headache is in a major quality of life (QOL) concern. In fact, migraine headache is among the 20 leading causes of "years lived with disability" according the World Health Report (2). The burden of headache is increasingly appreciated in psychological, family and interpersonal, vocational, and economic realms. Headache, particularly in its more chronic and severe forms, has been linked to sleep disorders. Interestingly, the sleep disorders associated with headache are varied in nature, including obstructive sleep apnea, periodic limb movement disorder, circadian rhythm disorder, insomnia, and hypersomnia. General symptom patterns, particularly morning headache and chronic daily headache, are suggestive of and aid in recognition of a sleep disorder. Management of the sleep disorder may improve or resolve the headache; sleep-disordered breathing is the most empirically supported example of this relationship. Although pure sleep-related headaches, such as hypoxemia-related headache, are less prevalent and more easily recognized, primary headaches as well are often impacted to some degree by sleep. Irrespective of sleep disorders, variation in the sleep/wake schedule is one of the most common acute headache precipitants while sleeping is one of the most common palliative responses to headache. Insomnia is the sleep disorder most often cited by clinical headache populations. Despite an emerging literature supporting the interdependence of sleep and headache, our understanding of the underlying mechanisms remains speculative. Few well-controlled studies are available, and it is difficult to generalize results across sleep and headache literatures due to inconsistencies in diagnostic nosologies, lack of standardized outcome measures, and varied populations. Future research with improved methods is needed to identify mediating factors between sleep and headache. This chapter reviews the co-morbidity of headache and sleep disorders, prevalence, diagnostic considerations, societal and individual burden of headache, clinical implications, and considerations for future directions.

Keywords Headache · Migraine · Tension-type headache · Cluster · Sleep · Snoring · Apnea · Insomnia · Circadian rhythm · Quality of life · Disability

Learning objectives:

- Migraine headache is among the 20 leading causes of "years lived with disability" according the World Health Report and thus a major quality of life concern.
- Migraine and other headaches may be precipitated or otherwise influenced by sleep.
- Specific headache patterns, irrespective of headache diagnosis, are suggestive of a potential sleep disorder (e.g., "awakening" or morning headache, chronic daily headache).
- Sleep disorders most implicated with headache include obstructive sleep apnea, primary insomnia, and circadian phase abnormalities.
- Sleep disorders tend to become prevalent among complex and severe headache disorders and regulation of sleep may favorably impact headache threshold and quality of life.
- Screening tools for sleep disorders and headache quality of life are readily available, practicable, and advantageous for application in the headache practice.

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Co-morbidity of Headache and Sleep Disorders

The relationship between headache and sleep has been documented at least anecdotally in medical literature for well over a century, with early observations describing the influence of sleep in both provoking and relieving headaches (3, 4) and with clinical texts alluding to the importance of sleep as a headache precipitant (5, 6). A small empirical literature has emerged, but the precise nature and magnitude of the headache/sleep association and underlying mechanisms remain poorly understood. The current nosologies for diagnosis of headache and sleep disorders offer limited guidance, but they are evolving to better represent the known associations.

Classification

The American Academy of Sleep Medicine's International Classification of Sleep Disorders-2nd Edition (ICSD-II) (7) categorizes "sleep-related headaches" among "sleep disorders associated with conditions classifiable elsewhere." This small list of specific medical conditions represents frequent reasons for referral to sleep specialists and may be encountered in the differential diagnosis of sleep disorders, but they are not considered primary sleep disorders. The criteria for sleep-related headaches state: "The patient complains of headache during sleep or upon awakening from sleep" and applies to a variety of primary headache diagnoses such as migraine, cluster, chronic paroxysmal hemicrania, and hypnic headache, as well as headache associated with other medical and sleep disorders. Within the ICSD-II, headache also is listed among associated symptoms for sleep-related bruxism and physical symptoms occurring in response to sleep loss with insomnia. "Morning headache" is listed among symptoms for sleep-related hypoventilation or hypoxemic syndromes and obstructive sleep apnea (pediatric).

The International Headache Society's International Classification of Headache Disorders-2nd Edition (ICHD-II) (8) nosology includes two specific diagnoses for sleep-related headaches: "Sleep apnea headache" and "Hypnic headache," and it lists sleep disturbance among symptoms of anxiety disorders that may be associated with headache. In the ICHD-II, "Hypnic headache" (ICHD-II code 4.5; Table 19.1) is coded under the category of "4. Other primary headaches." Although the new criteria have yet to be empirically validated, a series of case reports of hypnic headache meeting ICHD-II have been published to date (9).

"Sleep apnea headache" (ICHD-II code 10.1.3; Table 19.1) is coded as a subclassification of "10.1 Headache attributed to hypoxia or hypercapnia" under the major code heading "10. Headache attributed to disorders of homeostasis." Although the category "sleep apnea headache" was included in the original ICHD, the label was listed without diagnostic criteria. To our knowledge, these newly published diagnostic criteria have not been empirically validated, and there is some preliminary indication that a sizeable proportion of apneic patients with awakening headache would not fulfill the new criteria (10).

So while ICHD-II and ICSD-II have made preliminary attempts to provide criteria for diagnosis of sleep-related headaches, these criteria remain unvalidated and have seldom been employed in research. Instead, the nonspecific term "morning headache" (a.k.a., awakening headache and nocturnal headache) has been the most commonly used terminology used in sleep literature to refer to any headache temporally related to sleep. This terminology often is employed in sleep-specific journals but rarely is employed in headache-specific journals. Morning headache is not well defined with respect to headache features other than timing of the headache and represents a challenge in equating headache diagnoses across sleep and headache literatures.

Epidemiology

The available epidemiologic and clinical research is reviewed extensively elsewhere (11). The epidemiologic study by Ohayon (12) provided data on the broadest range of sleep disorders, reporting findings of a European study of 18,980 telephone interviews estimating the prevalence of "chronic morning headache" to be 7.6%. Prevalence rates were higher among women than men (8.4 vs. 6.7%). More individuals with morning headache than individuals without headache reported sleep complaints including insomnia (odds ratio or OR = 2.1), circadian rhythm disorder (OR = 1.97), loud snoring (OR = 1.42), sleep-related breathing disorder (OR = 1.51), nightmares (OR = 1.39), and other dyssomnia (OR = 2.30). The association between snoring or sleep apnea and morning headache has been observed in other epidemiologic (13–15) and clinical studies (16–19), and habitual snoring has been found more common among chronic daily than among episodic headache sufferers (20).

Headache has not commonly been described among sleep-disordered patients except specifically in relation to sleep-disordered breathing. Headache (not otherwise specified) in relation to obstructive sleep apnea has been examined in a number of studies with the occurrence of headache within this population varying widely from 15 to 60% (16–19). Morning headache, though common among sleep disorders, appears most strongly associated with sleep apnea. Headache of any diurnal pattern was reported by 49% of apneics and 48% of insomniacs in the sleep clinic patient population, whereas "morning headaches" were significantly more common among apneics (74%) than among insomnias (40%) (10). Morning headache apparently may present as migraine, tension, cluster, or nonspecific other (10) and often resolves or improves following treatment of sleep

TABLE 19.1. ICHD-II diagnostic criteria for sleep apnea headache (8).

10.1.3 Sleep Apnoea Headache
A. Recurrent headache with at least one of the following characteristics and fulfilling criteria C and D:
1. Occurs on >15 days per month
2. Bilateral, pressing quality and not accompanied by nausea, photophobia or phonophobia
3. Each headache resolves within 30 min
B. Sleep apnoea (Respiratory Disturbance Index ≥5) demonstrated by overnight polysomnography
C. Headache is present upon awakening
D. Headache ceases within 72 h and does not recur after effective treatment of sleep apnoea
4.5 Hypnic headache
Attacks of dull headache that always awaken the patient from asleep
A. Dull headache fulfilling criteria B-D
B. Develops only during sleep and awakens patient
C. At least two of the following characteristics:
1. Occurs >15 times per month
2. Lasts ≥15 min after waking
3. First occurs after age of 50 years
D. No autonomic symptoms and no more than one of nausea, photophobia, or phonophobia
E. Not attributed to another disorder

apnea with noninvasive positive pressure ventilation treatment or surgical modification of the upper airway to improve breathing (18, 19, 21–25). Interestingly, a recent study identified persistent morning headache as the best predictor of persistent apnea in a sample of patients compliant but insufficiently treated with continuous positive airway pressure (CPAP) (26).

Insomnia is the most common sleep complaint reported by clinical headache populations. Insomnia includes difficulty initiating or maintaining sleep or nonrestorative sleep. The largest clinical study published to date reported the prevalence of sleep complaints obtained from 1283 migraineurs presenting for headache treatment (27). Many patients reported difficulty initiating sleep (53%) and maintaining sleep (61%) at least occasionally. Similar rates of insomnia among headache patients are found in the headache literature including an epidemiologic study of headache in the general population (15, 28) and clinical studies of headache patients (29–31). Insomnia is greater among headache patients than normal controls (32) and with chronic headache greater than episodic headache (27, 30, 33).

Headache may be precipitated, or "triggered," by dysregulation of sleep patterns. Among patients with migraine and tension-type headache, changes in sleep patterns (e.g., sleep disturbance, sleep loss, and oversleeping) routinely are listed among the most commonly observed precipitants of headache (27–30, 34–38).

Headache Diagnoses

The following overview associates sleep with *specific* headache diagnoses (i.e., migraine, tension-type, cluster, chronic paroxysmal hemicrania, and hypnic headache), as well as *nonspecific* headache patterns (i.e., chronic daily headache, "awakening," or morning headache).

Migraine

Migraine has been examined in relation to circadian patterns, sleep stage, and sleep-related precipitants. A prospective longitudinal study examined migraine chronobiology over a 3-year period in 1698 migraineurs (3582 migraine attacks) (39). Nearly, half of all migraine attacks occurred between the hours of 4:00 and 9:00 a.m. Interestingly, this period of time typically would encompass the later stages of the sleep cycle [where the longest and most dense rapid eye movement (REM) sleep normally would dominate] and the early waking hours of the day. Early studies using polysomnography with small samples of patients also associated migraine (and cluster headache) with REM sleep (40, 41). Dexter (42) later examined polysomnography in five patients with migraine and observed an association between migraine and REM sleep as well as slow wave sleep (sleep stages 3 and 4, delta sleep). More recently, Drake et al. (43) observed minimal sleep disturbance among patients with episodic migraine evaluated by 4-channel electroencephalogram (EEG) recordings between attacks, with only modestly increased REM latencies and proportions. However, chronic headache patients with mixed features of migraine and tension-type headache exhibited significant sleep disturbance (i.e., reduced sleep time, increased awakenings, and diminished slow wave sleep), early REM latency, and reduced overall proportion of REM sleep for the night. The authors speculated that the chronic forms of headache may be worsened by chronically poor sleep.

Headache may be precipitated, or "triggered," by dysregulation of sleep patterns. Among migraineurs (and tension-type headache patients), changes in sleep patterns (e.g., sleep disturbance, sleep loss, and oversleeping) routinely are listed among the most commonly observed precipitants of headache (27–30, 34–38). In addition to acting as a potential precipitant to headache, sleep has been demonstrated to be a palliative treatment for migraine with attacks relieved by overnight sleep or a daytime nap (27, 32, 42, 44) particularly in children (45, 46).

Tension-Type

Relative to migraine, much less evidence exits concerning sleep in tension-type headache. The EEG study by Drake and colleagues (43) cited above examined the recordings of patients with episodic and chronic tension headache as well as migraine. Notably, subjects with tension-type headache did not exhibit the changes in REM sleep or latency that were noted in migraineurs but did exhibit reduced sleep time and sleep efficiency, decreased sleep latency, frequent awakenings, increased nocturnal movements, and marked reduction in slow wave sleep.

Similar to a pattern that is well established in migraine, sleep dysregulation may precipitate tension-type headache. Houle and colleagues (38) observed in a time-series fashion that both short (<6 h) and long sleep periods (>8.5 h) were associated with more occurrences of tension-type headache. Other studies similarly have related sleep disturbance to tension-type headache (28, 29, 34, 37).

Cluster Headache

Cluster headache has been associated with nocturnal circadian patterns, REM sleep, and sleep-disordered breathing. Interestingly, 75% of cluster headache episodes were found to occur between the hours of 9:00 p.m. and 10:00 a.m. (48). Cluster headache specifically has been associated with REM sleep and sleep-disordered breathing. A study of 37 cluster headache patients who underwent polysomnography identified an 8.4-fold increase in the incidence of obstructive sleep apnea relative to age- and gender-matched controls (58 vs. 14%, respectively), and this risk increased over 24-fold among patients with a body mass index >25 kg/m^2 (49). This marked increase in the incidence of sleep apnea among cluster headache patients had been noted in earlier research (24, 50, 51), and treatment of sleep apnea had been observed to improve cluster headache control (24, 25). Cluster headache attacks observed during polysomnography were linked to REM sleep (42) at least in cases of episodic cluster though perhaps not for patients having the chronic form of cluster headache (52).

Chronic Paroxysmal Hemicrania

Chronic paroxysmal hemicrania (8), like cluster, appears to have a predictable nocturnal patterns and has been associated with REM sleep (53–55); because of this pattern, it is sometimes referred to as a "REM-locked" headache disorder.

Hypnic Headache

By definition, hypnic headache is confined to sleep and is known to occur in the mid to latter portion of the night, and patients are abruptly awakened by pain (9, 56). Meta-analysis of data pooled from 71 cases of hypnic headache published in medical literature (9) revealed that the average duration of hypnic headache was 67 ± 44 min, and the frequency of attacks was 1.2 ± 0.9 per each 24 h. The majority (77%) reported the onset of headache between 120 and 480 min after sleep onset. A few cases have reported an association between hypnic headaches and specific sleep disorders such as restless legs, snoring, and sleep apnea. Polysomnography has not isolated hypnic headache to a specific sleep stage (9, 57).

Headache Not Otherwise Specified

Morning headache, though not a formal diagnosis, is the most common form of headache studied in relation to sleep. As noted above, between 15 and 60% of sleep apneics report morning headaches (10, 16, 18, 19, 21, 58–60). The pathogenic basis of morning headache was initially presumed to be a consequence of abnormal respiration (e.g., hypoxemia and hypercapnia). This hypothesis had been supported by polysomnographic research yielding a dose–response relationship between the severity of sleep apnea (e.g., number of apneic events and severity of nocturnal oxygen desaturation) and severity of morning headache (10, 19), resolution or improvement in headache following treatment of sleep apnea with noninvasive positive pressure ventilation treatment or surgical modification of the upper airway to improve breathing (18, 19, 21–25), and a higher incidence of morning headache in apneics than in similarly sleep-disturbed insomniacs (10).

Although evidence associating headache with sleep-disordered breathing through respiratory dysfunction appears compelling, contradicting studies dispute this hypothesis (61–63). In some cases, morning headache was observed to be more common among patients with nonrespiratory sleep disorders such as periodic limb movements (17, 64). Thus, while a relationship is established between sleep-disordered breathing and headache, it is not clear whether the pathogenic basis of this association is related to gas exchange abnormalities (e.g., hypoxemia and hypercapnia), some correlated but *nonspecific* consequence of the sleep breathing disorder (i.e., autonomic arousal, sleep dysregulation/deprivation, intracranial cerebrospinal fluid pressure changes, and cervical/cranial muscle tension), or a complex combination of these factors.

Pathogenesis

Reviewers of the literature examining pathogenesis of sleep-related headache are in agreement that sleep-related headaches are not well understood (11, 58, 65–73). Nevertheless, potential relationships between sleep and headache have been described and plausible mechanisms have been proposed.

Potential Relationship between Headache and Sleep

Hypothetical associations were proposed by Paiva et al. (58) to account for the interdependence of sleep and headache; Dodick et al. (73) succinctly summarized four potential relationships:

1. Headache is a symptom of a primary sleep disturbance.
2. Sleep disturbance is a symptom of a primary headache disorder.
3. Sleep disturbance and headache are symptoms of an unrelated medical disorder.
4. Sleep disturbance and headache are both manifestations of a similar underlying pathogenesis.

Likely, the sources of sleep-related headache are multifactorial, and cases supporting each association may be found.

Mechanisms

The convergence of sleep and headache disorders generally is believed to have its basis in neuroanatomical structures and neurophysiological mechanisms, involving especially the hypothalamus, serotonin, and melatonin (73). Wakefulness is principally a function of the reticular-activating system in the brainstem, maintained by influences of cortical neurotransmitters such as norepinephrine, dopamine, and acetylcholine. Non-REM sleep is primarily controlled by influences from the basal forebrain, with non-REM sleep functions maintained by gamma-amino-butyric acid (GABA) from basal forebrain neurons. REM sleep-generating processes have been localized within the dorsolateral pontine tegmentum. REM sleep is initiated by release of acetylcholine, which activates pontine neurons. Serotonin is abundant in the dorsal raphe nuclei and has a well established but incompletely delineated role in acute migraine. The trigeminal nucleus caudalis in the pons and midbrain has been considered to be a potential "migraine generator" by some researchers as there appears to be activation of vascular structures supplied by this nucleus during migraine attacks (74, 75). However, many of the migraine symptoms, especially those associated with prodrome and aura, are more likely to be the result of hypothalamic or cerebral cortical activity and include clinical features such as yawning, hunger, cravings, fatigue, mood changes, sensory, and visual distortions. The hypothalamus, which is the location of the suprachiasmatic nuclei, has extensive connections, some of which include connections to the limbic system, pineal gland (a source of neuronal melatonin), and brainstem nuclei involved in autonomic efferent control (nucleus tractus solitarius), sleep stage and motor control (locus ceruleus), and pain modulation (periaqueductal gray matter). The hypothalamus has exhibited specific activation during cluster headache attacks (76). Melatonin is well established as a factor in circadian rhythmicity and might have therapeutic efficacy in cluster headache (77, 78). Further studies of headache syndromes that exhibit chronobiological patterns, such as cluster headache as described below, have the most potential to provide a clearer understanding of the anatomical and physiological links between headache and sleep.

Quality of Life in Headache

The impact of headache can be described in individual, public health, or economic terms. Considerable attention has been paid to headache-related quality of life (QOL) in recent years and a number of standardized measures developed to quantify the impact of headache. QOL may be influenced by the frequency of attacks, severity of headache pain and associated symptoms, disability in vocational, social, and recreational performance, economic costs, and psychiatric co-morbidity.

Measurement

Measurement of QOL is becoming an important outcome in the field of headache. The well-developed general health-related QOL instruments [e.g., Medical Outcomes Study Short Form Health Survey (79)] permit demonstration of headache impairment compared to other chronic diseases and to the general population. A number of headache-specific and migraine-specific questionnaires also have been developed (Table 19.2), designed to measure the short- and long-term impact of migraine on QOL, and are responsive to changes in QOL secondary to headache treatment. Current guidelines for conducting clinical trials of headache interventions urge investigators to adopt standardized measures of disability, functional status, and/or "quality of life" for assessing outcomes and to employ well-validated headache-specific disability/QOL measures (80–82). The widespread use of these standardized instruments can increase awareness of the burden of headache and lead to improved patient care.

Prevalence of Headaches

Among headaches associated with sleep disorders, migraine has received the greatest attention with respect to QOL, no doubt due to its combined prevalence and severity. With a 1-year prevalence rate between 12 and 14% of the US population (83) and the substantial individual and economic impact described below, migraine is a formidable public health concern. Episodic tension-type is the most prevalent headache disorder impacting one-third of the general population per year but is generally less severe than migraine and seldom seen in the physician's office (84, 85), whereas its more severe form, chronic tension-type headache, impacts only 2–3% of the population. High-frequency headache (usually migrainous or tension-type in nature) commonly termed "chronic daily headache" occurs in approximately 4% of the adult population with disproportionately high medical utilization is also receiving attention (86). Several varieties of severe but rare

TABLE 19.2. Instruments for assessing headache-related quality of life.

Instrument	Description
MIDAS (113–115)	Measures pain and activity limitations due to headache, with emphasis on disability, including five disability questions in three activity domains and 2 headache frequency and severity questions
MSQ (116–118)	Measures general QoL among people with migraines. Subscales: Role Function-Restrictive, Role Function-Preventative, and Emotional Function.
HDI (119, 120)	Measures functional and emotional impact of headache on everyday life. Subscales: Functional Impairment & Emotional Impairment
HIT (121, 122)	Computerized dynamic tool designed to assess impact of headache on patient functional health and well-being.
HIT-6 (123)	Six items chosen from larger HIT item pool to assess six domains: pain, role functioning, social functioning, energy/fatigue, cognition, and emotional distress
RIIP-HA (124, 125)	Measures functional impairment associated with episodic or recurrent illness. Subscales: General Functional Impairment and Employment-Specific Functional Impairment
QLH-Y (126, 127)	Measures QoL for adolescents between ages 12 and 18 who experience chronic headaches or migraines. Subscales: Psychological Functioning, Functional Status, Physical Status, Social Functioning, and Satisfaction With Life in General
HANA (128)	Measures health status and migraine impact on daily activities. Subscales: Anxiety/Worry, Depression/Discouragement, Self-Control, Energy, Function/Work, Family/Social Activities, and Overall Impact

MIDAS, Migraine Disability Assessment, MSQ, Migraine-Specific Quality of Life Questionnaire; HDI, Headache Disability Inventory; HIT, Headache Impact Test; HIT-6, Headache Impact Test-6; RIIP-HA, Recurrent Illness Impairment Profile (Headache Version), QLH-Y, Quality of Life Headache in Youth; HANA: Headache Needs Assessment.

headaches associated with sleep disorders have been well-characterized but rarely been examined with respect to QOL. These disorders include cluster headache (prevalence <1% of the population) (87), hypnic headache (only 0.07–0.1% of patients in a specialty headache clinic setting—population prevalence unknown) (9, 56), and chronic paroxysmal hemicrania (prevalence is unknown but probably occurs more often than cluster) (54, 55). To our knowledge, QOL in "morning headache" per se has not been reported, but morning headache is known to encompass migraine, tension-type, cluster, and nonspecific other chronic headaches for which QOL has been characterized to some extent (10).

QOL in Migraine

Understanding of the impact of migraine was greatly advanced by the large population-based studies, American Migraine Studies I and II (88, 89). These epidemiologic studies have demonstrated that migraine headache sufferers are frequently disabled during their acute attacks. Function between attacks may also be below normal. Pain intensity is reported as "severe" by 80% of migraineurs. More than half experience nausea along with headache. Approximately 71% of females and 48% of males with migraine report attacks lasting more than 24 h. The median frequency of migraines was one to two headaches per month.

Ninety percent of migraineurs reported functional impairment with their headaches, 53% exhibited impairment severe enough to require bed rest, nearly a third had missed at least 1 day of work or school in the 3 months preceding the survey, and 51% reported that productivity was reduced by at least half due to headache (90). Household, family, and social activities were even more often disrupted than work. Migraineurs QOL appears affected not only during headache but also between attacks. Migraineurs exhibited greater emotional distress, decreased contentment, and lower vitality compared to age/gender matched controls (91). Migraine may even lead to unemployment—data from a health maintenance organization in the USA demonstrated an unemployment rate in severe migraine sufferers that was twofold to fourfold greater than that of the general population (92).

Although most individuals with headache in the general population do not have comorbid psychiatric disorders, many patients presenting to specialty clinics do. Epidemiological studies have identified a strong co-morbidity between migraine and psychiatric disorders and associate migraine with depression (OR = 2.2–4.0), generalized anxiety disorder (OR = 3.5–5.3), panic disorder (OR = 3.7), and bipolar disorder (OR = 2.9–7.3) (93). Moreover, migraine with comorbid depression often is further complicated by the presence of an anxiety disorder. The exact nature of the relationship between migraine and mood disorders remains unclear. Epidemiological studies suggest that the relationship is bi-directional making it unlikely that the co-morbidity occurs simply as a consequence of bearing the burden of a recurrent painful condition (93). It generally is believed that the co-morbidity arises from shared pathophysiology of migraine and mood disorders, but this pathophysiology has yet to be well articulated.

QOL in Chronic Daily Headache

Chronic daily headache generally is associated with poorer QOL and greater psychiatric symptoms than episodic headaches. Patients with chronic migraine showed an increased probability of missing days or reduced effectiveness in housework, work, school, family, social, and leisure activities compared with patients with episodic migraine (94). Depressive and anxiety disorders are frequent in patients with chronic daily headache. Juang et al. (95) evaluated

261 consecutive patients with daily headache, including 152 patients with chronic migraine and 92 chronic tension-type headache. Psychiatric disorders were prevalent among patients with daily headache including panic disorder (26%), generalized anxiety disorder (5%), major depression (55%), and dysthymia (11%). The frequency of any anxiety disorder was significantly higher in patients with chronic migraine than in chronic tension-type headache (43 vs. 25%).

QOL in Tension-Type Headache

Compared to migraine, much less is known about the psychosocial impact of tension-type headache. Population-based studies report that individuals with episodic tension-type headache experience headaches that are mild to moderate in severity and with an average frequency of three headaches per month, whereas individuals with chronic tension-type headache experience headaches that are moderate to severe in intensity that occur by definition with a frequency greater than 15 days per month (96, 97). In a recent epidemiologic study, 8.3% of episodic tension-type headache sufferers reported lost workdays (average 9 days per year) and 43.6% reported reduced effectiveness at work, home, and school due to headache (85). For those with chronic tension-type headache, 11.8% lost workdays (average 20 days per year) and 46.5% reported reduced productivity due to headache.

Although migraine generally is considered more disabling than is tension-type headache, a Danish study (98) suggested that tension-type headache was associated with greater absenteeism. Although 43% of migraineurs and 12% of tension-type headache patients (representing 2 and 9% of the study population, respectively) took absence from work, the average number of days absent from work was 270 per 1000 migraineurs and 820 per 1000 tension-type headache sufferers. Thus, frequent tension-type headache may impact QOL in a manner that rivals that of migraine.

Like migraine, tension-type headache also is associated with significant psychiatric co-morbidity. For example, among 245 chronic tension-type headache patients included in a recent clinical trial, almost half qualified for an anxiety or mood disorder diagnosis (anxiety = 35%; depression = 29%), whereas less than 10% of controls (who had fewer than 10 headache days per year) similarly qualified for a psychiatric diagnosis (47). Likewise, Puca et al. (99) found that among 217 tension-type headache patients, psychiatric disorders were observed more frequently among patients with chronic (n = 109) than with episodic (n = 108) headache (84 vs. 70%, respectively). The occurrence of depression was significantly higher among patients with chronic versus episodic headache (45 vs. 29%), but the occurrence of anxiety disorders did not differ significantly between the two groups (56 vs. 51%).

QOL in Cluster Headaches

Cluster headache is commonly cited as the most painful of the primary headache disorders—it was once even termed the "suicide headache" apparently because it was not uncommon for cluster headache sufferers to mention the possibility of suicide during an attack (100). As the name implies, cluster headache follows a temporal (usually nocturnal) pattern that recurs periodically or in clusters (48, 51). The most diagnostically significant clinical characteristics of cluster headache are strictly unilateral pain of exceptionally severe intensity, the presence of accompanying ipsilateral autonomic symptoms (e.g., eyelid edema, nasal congestion and/or rhinorrhea, forehead and facial sweating), and the restless behavior of patients during attacks. Although it is known anecdotally that patients are highly distressed and unable to perform in social or vocational realms during cluster attacks, QOL in cluster has seldom been examined. The available evidence indicates that patients with episodic cluster headache experience greater bodily pain and poorer social functioning than migraineurs while experiencing a cluster headache phase (101,102). However, after termination of the cluster phase, the QOL of patients was similar to that of headache-free controls (101).

Economic Impact

Attempts have been made to quantify the burden of migraine by calculating direct medical costs and indirect costs. An estimated, $1 billion is spent annually on direct medical costs for migraine in the USA (103). Direct medical expenditures form only a part of the financial equation, however. The $1 billion figure pales by comparison to indirect costs of migraine, which are estimated at approximately $13 billion annually in the USA. Indirect costs include the economic consequences of migraine on productivity at work, in the home, and in other roles. Female patients accounted for approximately 80% of total labor cost losses in both workdays lost and in reduced work productivity. Estimated average annual lost productivity costs were $690 for each man and $1127 for each woman. Notably, migraineurs have been observed to generate twice the medical and pharmacy claims as other comparable patients without migraine in a health maintenance organization (104).

Clinical Implications

Although there are no empirically-established algorithms to guide clinical practice, there are now at least a few empirically supported tenets that can be applied to clinical practice. As detailed above, sleep disorders are disproportionately observed among headache subgroups including migraine, tension-type, cluster, and chronic daily headache. The so-called morning headaches that occur during or after

sleep are particularly suggestive of sleep disorders and call for specific treatments. Likewise, primary headaches (i.e., migraine and tension-type headache) often are impacted by sleep, in that sleep deprivation and sleep/wake schedule changes are common headache triggers. Treatment of sleep disorders and regulation of sleep/wake cycle may impact headache threshold, and thereby facilitate headache management. QOL has yet to be examined specifically in relation to sleep-related headache but warrants consideration in future research and practice.

Headache Patterns Suggestive Sleep Disorders

Irrespective of diagnosis, the above review suggests that headaches temporally related to sleep (i.e., "awakening" or morning headache) and chronic daily headache may be consequent to or aggravated by a sleep disorder. Awakening headache occurs in 4–6% of the population but is present in at least 18% of insomniacs and in 15–74% of sleep apneics. Thus, it is beneficial for headache practitioners to conduct a thorough clinical interview examining the headache pattern and history in relation to the sleep/wake cycle. When headache is daily or is frequently present during sleep or upon awakening, it is particularly prudent to screen for presence of a sleep anomaly. The sleep/headache interview (70), standardized screening questionnaires (105), clinical prediction equations for sleep apnea (106), or headache/sleep diary (11, 107) (Figure 19.1) are cost-effective screening tools for sleep apnea, insomnia, or other relevant sleep disorder. In adults, asking four simple screening questions while taking a sleep history can identify patients "at risk" for sleep disorders. Inquiring about the restorative nature of the patient's sleep, excessive daytime sleepiness, tiredness or fatigue, the presence of habitual snoring, and whether the total sleep time is sufficient can be revealing. The mnemonic *REST* can help the clinician remember these four key questions in the screening history.

Treatment of Sleep-Disordered Breathing May Improve or Resolve Headache

The sleep disorders most implicated with headache include obstructive sleep apnea and insomnia, as described above. Treatment of sleep breathing disorders can improve and in some cases resolve headache. The symptoms (108) and risk factors (109, 110) for obstructive sleep apnea are widely recognized (Table 19.3). Generally, referral for polysomnographic evaluation is needed to confirm the diagnosis and initiate appropriate treatment for sleep-disordered breathing. Reevaluation of the headache syndrome following treatment is desirable and may allow for other options in headache management as the potential trigger from the sleep disorder is now gone.

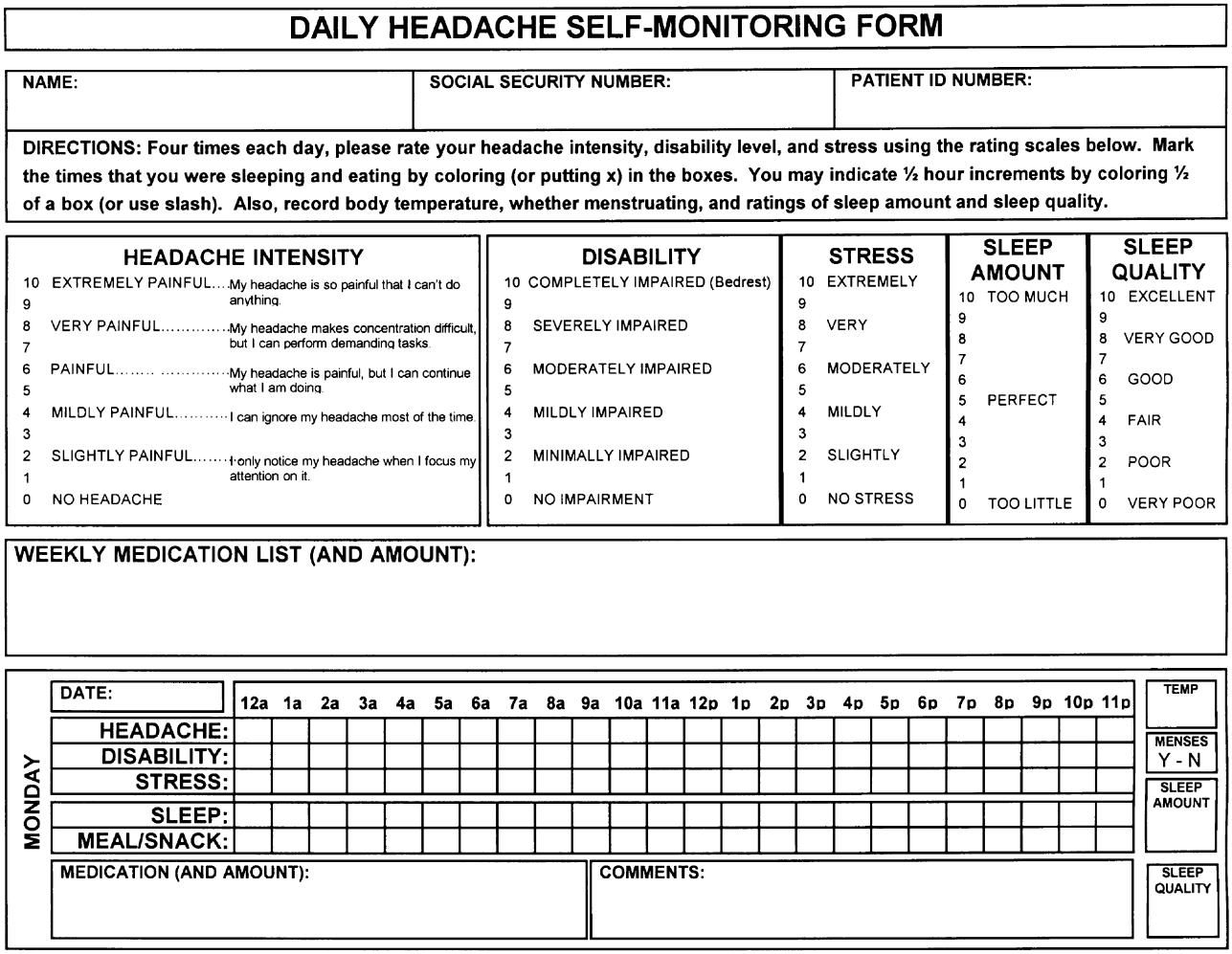
Primary treatments for obstructive sleep apnea include weight loss, treatment of nasal allergies, positional treatment for supine-related apnea, upper airway surgery, dental devices, and nasal CPAP (111). CPAP is the standard of care because of efficacy and the benign side effect profile, and its cost generally is covered by health insurance plans after documentation of the diagnosis (112). It is prudent to avoid sedation with hypnotics or opiates until the breathing is treated adequately.

Research Implications

Although anecdotal reports of sleep-related headache date back well over a century, it is only within the past three decades that an experimental literature has emerged with the large majority of studies published in the last decade. The phenomenon of sleep-related headache remains poorly understood in part due to the diagnostic and methodologic shortcomings of the literature. Historically, the nosologies to diagnose sleep-related headaches have provided little guidance. Though improved over earlier versions, even the revised editions of ICHD-II and ICSD-II are imprecise in their characterizations of sleep-related headache, they are inconsistent with one another, and neither has been empirically validated. Many published studies have reported no formal headache diagnosis that would facilitate comparison of symptoms and outcomes across studies. The popular terminology, morning headache, likely encompasses a variety of different forms of headache with varying pathophysiologies and introduces substantial variance into the research equation.

Research methods have varied widely across studies, and sampling methods and study populations often are not well described. Earlier studies, in particular, employed very small and selected diagnostic groups rather than larger unselected samples of headache patients or the general population. A small number of subjects might be unavoidable in some circumstances because of the rarity of certain disorders (e.g., hypnic headache and chronic paroxysmal hemicrania). However, it is a more common circumstance that a clinical study was designed to employ samples of convenience that are unlikely to adequately represent the population and phenomenon of interest. Many studies report single group outcomes and few have employed rigorous controls.

Many of the available studies have relied on nonstandardized questionnaires and subjective data. The studies that did use objective polysomnographic data to quantify measures of sleep have tended to include small numbers of subjects. In other studies that did include a larger number of subjects, the polysomnographic data often was collected for other clinical purposes and not specifically collected in a study that was prospectively designed to evaluate the associations of sleep and headache. No doubt this limitation is an unfortunate consequence of the substantial costs and labor involved in conducting polysomnography. Even low-cost tools, such



DAILY HEADACHE SELF-MONITORING FORM

NAME:	SOCIAL SECURITY NUMBER:	PATIENT ID NUMBER:

DIRECTIONS: Four times each day, please rate your headache intensity, disability level, and stress using the rating scales below. Mark the times that you were sleeping and eating by coloring (or putting x) in the boxes. You may indicate ½ hour increments by coloring ½ of a box (or use slash). Also, record body temperature, whether menstruating, and ratings of sleep amount and sleep quality.

HEADACHE INTENSITY

10	EXTREMELY PAINFUL	My headache is so painful that I can't do anything.
9		
8	VERY PAINFUL	My headache makes concentration difficult, but I can perform demanding tasks.
7		
6	PAINFUL	My headache is painful, but I can continue what I am doing.
5		
4	MILDLY PAINFUL	I can ignore my headache most of the time.
3		
2	SLIGHTLY PAINFUL	I only notice my headache when I focus my attention on it.
1		
0	NO HEADACHE	

DISABILITY

10	COMPLETELY IMPAIRED (Bedrest)
9	
8	SEVERELY IMPAIRED
7	
6	MODERATELY IMPAIRED
5	
4	MILDLY IMPAIRED
3	
2	MINIMALLY IMPAIRED
1	
0	NO IMPAIRMENT

STRESS

10	EXTREMELY
9	
8	VERY
7	
6	MODERATELY
5	
4	MILDLY
3	
2	SLIGHTLY
1	
0	NO STRESS

SLEEP AMOUNT

10	TOO MUCH
9	
8	
7	
6	
5	PERFECT
4	
3	
2	
1	
0	TOO LITTLE

SLEEP QUALITY

10	EXCELLENT
9	
8	VERY GOOD
7	
6	GOOD
5	
4	FAIR
3	
2	POOR
1	
0	VERY POOR

WEEKLY MEDICATION LIST (AND AMOUNT):

MONDAY	DATE:	12a	1a	2a	3a	4a	5a	6a	7a	8a	9a	10a	11a	12p	1p	2p	3p	4p	5p	6p	7p	8p	9p	10p	11p	TEMP
	HEADACHE:																									MENSES Y - N
	DISABILITY:																									
	STRESS:																									SLEEP AMOUNT
	SLEEP:																									
	MEAL/SNACK:																									

MEDICATION (AND AMOUNT):	COMMENTS:	SLEEP QUALITY

FIGURE 19.1. Sleep/headache diary. [Daily headache monitoring in relation to sleep, disability and precipitants.] Reproduced with permission of authors (11, 107).

TABLE 19.3. Obstructive sleep apnea: signs and symptoms (108–110).

Clinical symptoms	Risk Factors
• Habitual snoring	• Obesity (↑ BMI, neck, chest, waist, hips)
• Wake gasping	• Male gender (male preponderance less in elderly)
• Witnessed apnea	• Age (positive correlation)
• Morning headache	• Family history
• Hypersomnia or insomnia	• Craniofacial morphology and oral anatomy
• Night sweats	• Neuromuscular disorders
• Nocturia	• Substances (e.g., tobacco, alcohol, sedatives)

as standardized questionnaires and diaries, rarely have been utilized in this field of study. Finally, reporting of results, as in many areas of research, has been highly variable. A research base with commonly inconsistent diagnoses, low statistical power, skewed populations, multiple sources of variance, limited controls, and often lacking objective measurement and inconsistent reporting is likely to yield the sometimes contradictory outcomes and interpretations reported in this chapter.

Conclusions

Migraine and other headaches are increasingly recognized as a major public health concern due to their prevalence, pain frequency and severity, psychiatric co-morbidity, economic costs, and impact on QOL. Sleep has been shown both to provoke and to relieve headache. The collective literature as discussed in this chapter reveals specific headache patterns potentially indicative of sleep disorders that warrant treatment (i.e., chronic daily headache, "awakening," or morning headache); describes sleep complaints among specific headache diagnoses (e.g., migraine, tension-type, and cluster); and suggests common anatomic structures and neurochemical processes involved in sleep and headache. Although there are few well-controlled experimental studies

and an imperfect diagnostic classification system, the existing literature nevertheless reveals the value of sleep screening and management by headache practitioners. Future research will further illuminate underlying mechanisms and determine the ultimate outcome of sleep management in headache treatment and QOL.

Issues that need to be addressed by future research:

- Greater diagnostic precision and reporting in studies of sleep-related headache is necessary to facilitate comparison between sleep and headache literatures and foster cumulation of findings.
- Improved research methodology would increase the yield in future studies, particularly improved sampling methods that facilitate generalization of results, use of standardized questionnaires, objective measures for sleep, and uniform reporting of results.
- Headache-related quality of life including disability assessment should be employed as an outcome variable in evaluation and treatment of sleep-related headache.
- Future research may identify factors mediating the sleep and headache relationship.
- Prospective studies are needed to determine whether normalizing sleep times in the short sleeps would impact headache threshold.

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20
Sleep and Quality of Life in Parkinson's Disease

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Summary Sleep disturbances in Parkinson's disease (PD) are both widespread and wide-ranging. Emerging early in the disease process, sometimes prior to the onset of motor symptoms, sleep disruption results from the degeneration of the basal ganglia that is the hallmark of the disease, as well as changes in brain stem sleep centres. Accordingly, sleep problems consist of motor symptoms such as stiffness, difficulty turning and dystonia as well as disruption to the normal sleep–wake cycle, arousal and alertness. Sleep disruption has been associated with reduced quality of life (QOL) and increased depression and anxiety in PD patients and their caregivers alike, and may be severe enough to impair everyday functioning. It is also likely that presence of certain sleep symptoms such as REM behaviour disorder (RBD) and sleep-disordered breathing (SDB) are the harbingers of a poor prognosis. Although no studies have yet investigated the effect of sleep problems on institutionalization in PD, chronic disruption to the sleep of caregivers may well lead to a breakdown in the caregiving relationship and care arrangements. The following article reviews the prevalence, phenomenology, pathophysiology and impact of sleep disturbances on QOL for individuals with PD and their caregivers. Clinical management strategies are discussed.

Keywords Parkinson's disease · sleep · REM behaviour disorder · excessive daytime sleepiness (EDS) · periodic leg movements of sleep (PLMS) · restless legs · quality of life · sleep attacks

Learning objectives:

- Appreciate the range of sleep disturbances experienced by people with Parkinson's disease.
- Understand theories of brainstem pathophysiological change in PD and how these may be applied to disorders such as REM behaviour disorder and excessive daytime sleepiness.
- Appreciate the degree of impact sleep disturbance may have on the quality of life of both PD patient and caregiver.
- Appreciate the range of assessment methods for PD patients with sleep disturbance and the range of possible pharmacological treatments.

Introduction

Sleep disturbances are part of the non-motor symptom complex of Parkinson's disease (PD) that are increasingly recognized as an integral feature of the disease (1). Sleep symptoms characteristic of PD include sleep fragmentation at night, EDS and REM behaviour disorder (RBD) (2–4).

These disturbances tend to increase in severity as the disease progresses but may be exacerbated by or respond to changes in medication. It is important for the clinician to optimize drug therapy not only for motor function but also to minimize bothersome sleep symptoms that may impact on quality of life (QOL) for both patient and caregiver (1, 5).

Sleep problems are very common in the PD population with prevalence ranging from 25 to 98% depending on the criteria used. Perhaps the best-controlled study to date is that of Tandberg and colleagues (6) who used a community sample of 239 PD patients, finding a 60.3% prevalence of sleep problems in PD patients compared with 33% in healthy older adults and 45% in a sample of patients with chronic illness (diabetes mellitus). However, many studies use a single item question to ask about sleep problems, which does not reflect the multifactorial nature of these symptoms nor address which problems are most frequent and troublesome. The Parkinson's Disease Sleep Scale (PDSS) (7) and the Non-Motor Symptoms Questionnaire (NMSQuest) (1, 3, 8) both contain several items concerning common nighttime problems that can be used to give a profile of sleep disorders in PD. A recent study of 123

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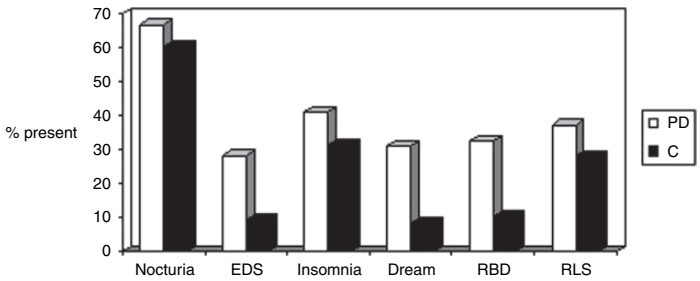

FIGURE 20.1. Sleep dysfunction in PD compared to age-matched controls (C). NMSQuest study (3). Dream, vivid dreaming; EDS, excessive daytime sleepiness; RBD, REM behaviour disorder; RLS, restless legs syndrome.

PD patients using the NMSQuest found a high prevalence of these sleep-related problems, with nocturia (66.7%) being the most frequent followed by insomnia (40.6%), restless legs (37.4%), acting out dreams (32.5%), intense vivid dreams (30.9%), and daytime sleepiness (28.4%) (3) (Figure 20.1). Given the high prevalence and frequency of these problems, it is not surprising that they impact on QOL in PD (see Table 20.1). Despite these figures, such disorders are frequently overlooked, even in specialist centres.

Sleep Symptoms in PD

Symptoms of sleep disorder experienced by individuals with PD are wide-ranging, and Tables 20.1 and 20.2 describe symptoms, give estimates of prevalence in PD and also identify clinical correlates of the symptoms. The problems experienced may be broadly classified as motor-related problems, which occur nocturnally, insomnias or changes to the normal sleep–wake cycle including sleep fragmentation and EDS, parasomnias, in particular RBD, sleep-disordered breathing (SDB) and neuropsychiatric problems such as nocturnal hallucinations.

Motor Problems of Sleep

One of the primary causes of disrupted sleep in PD is the occurrence of bothersome motor symptoms that lead to increased number of awakenings and discomfort during the night (9–11). Of these akinesia, restless legs and PLMS are primarily related to motor function, whereas dystonia, nighttime dyskinesias, pain and cramps are a complication of dopaminergic therapy often reflecting fluctuations in response to levodopa (5).

Nocturnal Akinesia

Rigidity, problems turning, and pain may interrupt sleep and tend to arise when levels of dopamine are fairly low, similar to daytime 'off' periods. Most PD patients take their last dose of dopaminergic medication well before bedtime, and so, controlled release levodopa preparations as well as long-acting dopaminergic medication such as cabergoline can alleviate these symptoms to some extent (12, 13). Conversely, a subgroup of patients report that their mobility is significantly improved on waking, the phenomenon known as 'sleep benefit'. It is possible that endogenous dopamine reserves are restored to some extent during sleep, or that dopaminergic function is subject to circadian influences, or that sleep benefit reflects an aspect of motor fluctuations (4, 14, 15).

Restless Legs Syndrome and Periodic Limb Movements of Sleep

Restless legs syndrome (RLS) occurs within an ageing population but individuals with PD have an approximately twofold greater risk, with prevalence estimated at 19.5% in one large study using the IRLSSG diagnostic criteria (16–18). RLS is a subjective symptom involving a 'creeping' sensation of discomfort in the limbs giving rise to a need to move the affected limbs, which temporarily relieves the sensation. Many RLS sufferers may also experience periodic limb movements of sleep (PLMS) usually involving rhythmic extension of the big toe and dorsiflexion of the ankle and occurring every 20–40 s, which can be detected and quantified using polysomnography and electromyography (17, 19). Unsurprisingly, RLS leads to increased sleep latency and interrupted sleep and PLMS are associated with arousals during polysomnography (17, 19).

Nocturia

Nocturia is a frequent problem in PD and is exacerbated by other risk factors such as old age and prostatism (3, 9, 11, 20). Nocturia may be related both to treatment, where nocturnal off period can lead to incontinence and bed-soiling, and to advancing disease when autonomic dysfunction can emerge (5). The reported incidence of voiding dysfunction in patients with PD ranges from 37–70% (21). Voiding dysfunction in patients with PD progressively worsens as disease advances, and the symptoms reported are urinary urgency, urinary frequency, nocturia, urinary retention and overt incontinence. The symptoms worsen in PD with significant akinesia and rigidity and symptom index and QOL index showed a gradual and steady increase with the severity of the disease (21).

TABLE 20.1. Prevalence and clinical correlates of sleep disturbance in Parkinson's disease.

Symptom	Prevalence in PD studies	Comparison with healthy older adults	Clinical correlates
Motor symptoms			
Akinesia, rigidty and pain	20–72% (self-reported) (9, 10, 14, 20)	>Severity of pain in PD (17)	Diurnal motor fluctuations
Sleep benefit	42.4–55.1% (self-reported) (14, 15)		Motor fluctuations (14) Disease duration (15) Levodopa dose (14)
RLS and PLMS	6.2–43% (self-reported) (10, 20, 27) 19.5% using clinical diagnostic criteria (17)	>Frequency in PD (16, 27)	Motor fluctuations (27) Poor sleep maintenance (27) Disease duration (46)
Nocturia	66.7–79% (3, 9) 59% urinate >3 times nightly(self-reported) (20)	>Severity in PD (7)	Autonomic dysfunction
Sleep–wake cycle disturbances			
Sleep fragmentation	40.6–77% (3, 20) % >2 awakenings nightly (self-reported) (20)	>Freq awakenings in PD (27) >Subjective severity in PD (7) >PLM associated arousals in PD	Levodopa dose (27) Age (27) Motor fluctuations (27) Restless legs (27)
Excessive daytime sleepiness	9.9–51% (self-reported) (14, 20, 36, 46) 15.5–28.6% (32–34, 36)ESS > 10 19% using MSLT criteria (30)	>Severity in PD (14, 33, 36)	Disease severity (14, 29, 30) Snoring (46) Hallucinations (31, 29, 49, 50) Cognitive decline (14, 29) Depression (14) Age (29)
Sudden onset of sleep	0–34.3% (self-reported) (36, 46)		
Parasomnias			
REM sleep behaviour disorder (RBD)	13–32.5% (self-reported) (3, 20, 42) 15–17.2% ICSD criteria (41, 42) 33% polysomnographic criteria (41)	>Frequency reported (3) >Frequency REM sleep muscle atonia during PSG in PD (41)	Hallucinations (42)
Sleep-disordered breathing			
	12% (self reported) (20) 43% patients referred to sleep lab using polysomnographic criteria (45)	Greater ratio of central and mixed to obstructive apneas in PD (45)	Disease duration Autonomic dysfunction

Sleep–Wake Cycle Disruption

PD patients show a characteristic combination of nocturnal sleep fragmentation and EDS (2, 4, 22). Although motor problems contribute to poor sleep at night and daytime sleepiness may result from poor nighttime sleep, there is evidence for more fundamental changes in the mechanisms controlling the sleep–wake cycle (23–25). Diederich et al. (24) describe a progressive 'destructuring' of sleep in PD, with changes in sleep architecture during overnight polysomnography.

Insomnia and Sleep Fragmentation

Sleep in PD is characteristically fragmented, with multiple awakenings during the night (17, 20, 26, 27). This differs from the patterns of sleep typical of depression, i.e. early morning waking and problems with sleep initiation. Although sleep tends to become more fragmented with age, PD patients report an increased number of awakenings and more frequently disrupted sleep than older adults without PD, even those with chronic illness (6, 11, 26). However, problems with initiating sleep do not appear to be more severe in PD than in healthy controls (11). Polysomnographic studies have revealed changes within the architecture of sleep including reduced REM sleep latency and reduction of percentage of both REM and slow wave sleep (24). These changes may reflect an inability to maintain a normal pattern of sleep, with a greater propensity to wake during lighter stages of sleep (28, 29).

Excessive Daytime Sleepiness

Daytime sleepiness in PD is common and is greater in frequency and severity than in healthy older adults. A large community study found that a subgroup of PD patients displayed EDS, 15.5% sleeping three or more times per day or for a total of 2 h or more compared with only 1% of healthy elderly (14). In PD, sleepiness is associated with more advanced disease, cognitive decline and hallucinations suggesting that EDS is a sign of poor prognosis (14, 28–30). Prevalence of EDS varies according to the means of assessment used, the characteristics of the sample and how 'excessive' daytime sleep is defined. Large epidemiological studies, which used a score of 10 or greater on the Epworth Sleepiness Scale (ESS), found prevalences between 15.5 and

TABLE 20.2. Causes of nighttime sleep disruption and daytime sleepiness in Parkinson's disease.

Disease related	
Insomnia	Fragmentation of sleep (sleep maintenance insomnia)
	Sleep-onset insomnia
Motor function-related	Akinesia (difficulty turning)
	Restless legs/Akathisia
	Periodic limb movements of sleep
	Sensory problems (pain, parasthease)
Urinary difficulties	Nocturia
	Nocturia with secondary postural hypotension
Neuropsychiatric/parasomnias	Depression-related insomnia
	Vivid dreams
	Nightmares
	Sleep talking
	Nocturnal vocalizations
	Somnambulism
	Hallucinations
	Panic attacks
	REM behaviour disorder
	Confusional awakenings
Treatment related	
Motor	Nocturnal off-period-related tremor
	Dystonia
	Dyskinesias
	Off-period-related pain/paresthesia/muscle cramps
Urinary	Off-period-related incontinence of urine
Neuropsychiatric	Hallucinations
	Vivid dreaming
	Off-period-related panic attacks
	REM behavior disorder
	Akathisia
Sleep-altering medications	Alerting effect, nocturnal agitation

Adapted from (5).

28.6% (31–33). A study using the Multiple Sleep Latency Test (MSLT) in a small PD sample found pathological scores (mean sleep latency of <5 min) in 19% of patients, or 37% using a less conservative criterion (30).

Sudden Onset of Sleep

'Sudden onset of sleep' (Soos) has also been described in PD, and in recent years, the literature has focused on the risk of falling asleep at the wheel as a side-effect of certain dopamine agonists (34). How exactly to differentiate a sleep 'attack' from EDS is controversial, with reported prevalence varying from 0 to 34.3%, according to how sleep attacks are defined (see Table 20.1). Parallels have been drawn with the narcoleptic phenotype, with sleep episodes occurring rapidly and without warning, interrupting any ongoing task such as driving. Up to 60% of PD patients may still be driving, and a large survey found that 11% of this population had been implicated as causing an accident in the previous 5 years (35). ESS scores may identify those at risk (34, 35), although one study found that three of four patients who had caused traffic accidents by falling asleep at the wheel were unaware of their sleep episodes during MSLT and would therefore have been likely to underreport on the ESS (36).

Circadian Rhythm Changes

Fragmentation of nighttime sleep and increased sleep in the day are together suggestive of a loss of stability and amplitude of the normal cycle of circadian rhythm (28). Central biomarkers of circadian rhythm in PD have been investigated by a small number of studies and with mixed results due to the confounding presence of dopaminergic medication and autonomic changes in PD. Melatonin appears to show a phase advance in PD patients compared with that in healthy older adults, although this is more apparent in those patients with levodopa-induced motor fluctuations, and it is unclear whether dopamine is affecting melatonin levels or whether melatonin affects dopamine receptor expression. Use of levodopa may also account for lower core body temperature in PD, although circadian rhythm of core temperature is unaffected (28). Abnormal circadian rhythm of heart rate variability is likely to be due to autonomic changes rather than circadian influences, and the presence of a flattened diurnal profile of cortisol may reflect changes in the sleep–wake cycle, but may also be accounted for by high levels of depression in PD. The measurement of rest–activity rhythms as an indirect marker of circadian rhythms is somewhat confounded by the presence of motor fluctuations, although Whitehead et al. (unpublished data) showed both reduced amplitude and relative amplitude of rest–activity rhythm in PD patients compared to controls as well as lower stability of circadian signal across days and greater variability within days. This disruption was greater in patients with a longer disease duration and those with hallucinations.

Parasomnias

RBD is characterized by limb or body movement during dreaming that may lead to harmful behaviour, dreams that appear to be 'acted out' or sleep behaviour that disrupts sleep. First described in humans by Schenck and colleagues in 1986 (37), RBD is associated with PD and other a-synucleinopathies such as Dementia with Lewy bodies (DLB) and Multiple System Atrophy (MSA) (38) and may emerge prior to the onset of movement disorder by several years (39). Clinically, muscle atonia, which is normally imposed during REM sleep, is lost in RBD, allowing complex motor patterns to emerge (40). Dreams associated with movement are often vivid, violent and frightening and tend to involve themes of being chased, fighting assailants or intruders in the house or (41, 42). Vocalizations may also form part of the 'acting out',

ranging from murmuring to speaking to shouting, screaming or crying (20, 42). Paradoxically, PD patients who experience very limited mobility and problems with voice projection during the day can display vigorous movement and shouting during sleep (43). Polysomnographic evidence of increased muscle tone and movement during REM sleep is required for the clinical diagnosis of RBD, and one study found a prevalence of 33% in a PD group using these methods (40). Interview assessment may actually be insensitive to RBD (40) with relatively few patients recalling unusual dreams and some caregivers being unaware of their partners nocturnal activity (41). When injuries are sustained during sleep to either patient or caregiver, however, RBD is a likely cause.

Sleep-Disordered Breathing

Relatively little information exists about the prevalence of SDB in PD populations relative to healthy older adults. One recent study found a prevalence of 43% in a small sample of PD patients referred for polysomnography (44). Both motor aspects (rigidity, dyskinesias of the diaphragm, abnormal movements in upper airway structures) and autonomic aspects of PD may be implicated in the development of obstructive and central apneas, respectively (4, 21), and prevalence in the PD population would therefore be expected to increase with disease severity. PD patients were found to show relatively equal amounts of obstructive, central and mixed sleep apneas, compared with greater prevalence of obstructive apneas found in non-PD patients referred for suspected SDB (44). In terms of outcomes of apnea, EDS has been described in non-PD populations with SDB, and one study found that the only significant predictor of EDS in a PD sample was snoring (OR = 3.64, CI = 1.00–11.9), which may be suggestive of SDB (45).

Neuropsychiatric Symptoms

Early studies of the side-effects of levodopa report changes in the nature and experience of dreaming, such as more vivid, emotionally charged or unpleasant dreams (46, 47). Prevalence of altered dream events ranges from 11 to 48% according to several surveys (Table 20.1), although this group may overlap with those with RBD. Many patients with hallucinations experience them nocturnally (9), and it is highly likely that the content of dreams often spills over into waking consciousness, leading to hallucinations, psychotic behaviour and episodes of confusion during the night (48). Some researchers have described a temporal relationship between daytime napping and hallucinations, again suggesting that dream narrative and episodes of REM activity drive waking hallucinations (49–55).

Pathophysiology

Useful Models

The pathophysiology of sleep disorder in PD is complex, reflecting the multifactorial nature of symptoms (4, 5, 55). Whilst the motor effects of PD certainly account for some aspects of disturbed sleep such as problems turning over, nocturia, dystonia, etc., more fundamental changes in the central mechanisms controlling the sleep and wake cycle are also involved. It is likely that the degeneration of dopaminergic pathways in the basal ganglia has a knock-on effect on sleep-regulating centres in the brain stem, but there is also evidence of degeneration of these centres themselves (55, 56).

Braak (56) has proposed a series of stages of degeneration of the brain in the α-synucleinopathies (PD, dementia with Lewy bodies, multisystem atrophy) (39, 51), in which loss of function in brainstem sleep centres such as the raphe nucleus, pedunculopontiine nucleus and locus coeruleus occurs. Importantly, Braak proposes that Lewy body formation in brain stem sleep centres begins in Stage 2, the 'preclinical' phase, *prior* to the emergence of motor symptoms in Stage 3 when the basal ganglia are affected by the disease process. This staging of the degenerative pattern may explain the onset of RBD prior to the diagnosis of PD (39) and the elevated prospective risk of PD in healthy men with EDS (57).

In summary, even in the early stages of PD, there is clear evidence of degeneration of brain stem nuclei, which may be crucial to the regulation of sleep and wake. Damage to these nuclei may result in loss of inhibitory tone to sleep-generating centres, destabilizing the mechanisms that maintain a steady state of wakefulness or sleep (28, 29). Evidence for loss of the regulatory influences of hypocretin, an alertness inducing peptide has recently been described (58, 59). Some PD patients experience sleepiness to a severity equivalent to narcoleptics (30, 60, 61), although they do not display the full narcoleptic phenotype i.e. cataplexy and sleep paralysis.

Impact of Sleep Disturbance on Quality of Life in PD

QOL in PD has been assessed using both non-specific measures of health-related QOL such as the Nottingham Health Profile and the SF-36 health survey, and also a QOL instrument specific to PD, the PD Questionnaire 39 (PDQ-39) (62, 63). These scales assess both emotional and physical functioning and are widely used to gauge the impact of specific disease on general well-being.

There is controversy related to the use of the term QOL in PD. Some would maintain that true QOL is an individual matter and concept and therefore cannot be measured by self-rating scales (64). A preferred terminology according to some is to refer to measures of scales such as PDQ-39 as 'self

reported health status' which is more accurate and reflects the measures of the scale.

Advantages of using QOL as an outcome to assess impact of poor sleep, compared with depression for example, is that QOL is less confounded by the somatic effects of PD than depression, which is highly prevalent in PD and may reflect the biochemical changes of PD rather than a reaction to illness and disability. Furthermore, sleep disruption is a key symptom of depression and a component of the relationship between the two may therefore be artifactual.

Despite the high prevalence of sleep disturbance in PD and the development of scales such as the PDSS to quantify the degree of disturbance, relatively few studies have sought to assess the effect of poor sleep on QOL in PD. A well-controlled study by Karlsen and colleagues (65), using a community-based sample of 245 PD patients, found that sleep disturbance was an independent predictor of lower QOL measured by the Nottingham Health Profile, as were low functional mobility, depression and higher doses of L-dopa. Other studies have found reduced QOL on the SF-36, NHP and PDQ-39 in those PD patients with self-reported 'insomnia' or 'sleep problems' and a weak but significant correlation between scores on the PDSS and the PDQ-39 (66, 67).

Little work has been done to characterize the effect of EDS on QOL in terms of everyday functioning, though it is likely that extreme sleepiness limits both physical and social functioning and may have a large impact on the caregiver. Accordingly, Weintraub and colleagues (68) found that daytime sleepiness measured by ESS was associated with greater impairment on an ADL scale, although not independently of disease stage. Also, one study found that it was 'reduced enthusiasm' rather than daytime sleepiness that was associated with higher scores on the Parkinson's Impact Scale (PIMS), which measures impact of the disease on general functioning (69). Studies using more objective measurement of EDS such as sleep diaries or the Osler vigilance task may reveal a stronger association with poorer QOL.

Other symptoms also may affect QOL and sleep in PD. Thermoregulatory disturbances in PD are well recognized and sweating disturbances are common and distressing symptoms of PD that are related mainly to autonomic dysfunction, off periods and dyskinesias. Often patients' sleep and in some cases partners' sleep is disturbed. Many feel uncomfortable and cold due to sweating, and as a consequence of sweating some feel embarrassed or depressed. In some patients, sweating restricts social functioning. In severe cases, additional help and even nursing home placement is required at least partly due to sweating disturbances (70).

Impact on Caregivers

Many spousal caregivers of people with PD experience frequent disruptions to their sleep as their partners rise frequently to urinate, may need help when turning over and getting out of bed, may kick, punch or shout in the night and may experience distressing dreams and hallucinations. Disruptive nocturnal behaviours in Alzheimer's disease such as calling for help, wandering and nocturnal confusion are cited by many caregivers as a key reason for institutionalization of the care-receiver (71, 72). Although fewer studies have assessed the effect of sleep problems in PD on risk of institutionalization, a small number have assessed their impact on the caregivers' own sleep and their general well-being. Between 25 and 40% of PD caregivers questioned reported sleep problems, a rate similar to PD patients themselves, with spouses providing daily care at a fourfold risk of sleep problems compared with those providing no care (73). Predictors of caregiver sleep quality include the caregiver's own anxiety, stress and depression, depression and sleep quality of the care-receiver, and also disease severity and duration of the care-receiver, which are particularly predictive of the level of nightly disruption experienced by the caregiver.

Though carer depression is the most consistent predictor of poor carer sleep, it is likely that frequent awakening to provide assistance to the care-receiver also accounts for a large component of sleep disruption though this has not been directly assessed in large PD sample using more objective methods. Frequent awakening of patients, usually associated with SDB also leads to the spousal arousal syndrome.

The impact of EDS on caregivers is unclear; according to anecdotal reports EDS can cause friction when the care-receiver is unresponsive to social interaction, although apathy plays a key role as well here. However, other carers welcome their partner's afternoon nap as a chance to get on with household chores without interruption or to catch up on some sleep themselves. Reducing the nighttime burden on caregivers may be approached firstly by improving the nocturnal mobility of the patient by optimizing drug therapy and installing physical aids, and secondly by providing greater support and overnight respite to allow caregivers to catch up on sleep periodically (74). Those caregivers who share a bed with patients with RBD are at risk of bruises, lacerations and even strangulation, and moving to separate beds in the same room may be necessary (75).

Assessment

Differential Diagnosis

It is important to distinguish between certain sleep symptoms in PD as the treatment for one problem may exacerbate another. RBD must be distinguished from sleep apnea, and it may be wise to administer an interview assessment for sleep apnea or proceed to polysomnographic verification, as apnea may be exacerbated by clonazepam. Furthermore, 46% of a sample of 58 patients with RBD and PD also had symptoms suggestive of sleep apnea, so it may be overrepresented in this

group (42). EDS may be an indicator of sleep apnea, especially if snoring is present too, and again, interview assessment for sleep apnea in cases of EDS may be valuable. Another possible contributing factor to EDS is post-prandial hypotension due to autonomic changes (76).

Sleep

Several well-validated scales exist for assessing sleep quality in the general population, i.e. the Pittsburgh Sleep Quality Inventory (PSQI) and the Karolinska Sleep Scale , although they do not address symptoms such as restless legs and RBD, which may underlie poor sleep quality in PD (5, 11, 77). The PDSS (7) and NMS questionnaire (3) both provide a measure of severity for the sleep problems characteristic of PD and a profile of *specific* sleep problems is valuable to the clinician as medication may be tailored to combat specific symptoms. The PDSS is a 15-item validated questionnaire, which can be completed quickly, and is currently available in five languages. SCOPA-SLEEP (78) is a brief validated scale assessing quality of nighttime sleep and levels of daytime sleepiness, developed for use primarily in PD research.

The ESS (79) is a widely used and validated self-report measure of daytime sleepiness, scores of greater than 10 indicating abnormal levels of sleepiness. However, it may be necessary to obtain an ESS rating from the caregiver as some PD patients were shown to be unaware of episodes of confirmed sleep during the MSLT and under-reported their own sleepiness on the ESS, suggesting that accurate recall of naps may be impaired in this group, especially where cognitive decline is present (36).

Quality of Life

The 39-Item Parkinson's Disease Questionnaire

39-Item Parkinson's Disease Questionnaire (PDQ-39) is a disease-specific questionnaire for PD, where the maximum score of 100 indicates the poorest health status (62). It comprises 39 questions each with five possible answering options: never, occasionally, sometimes, often or always. The PDQ-39 was first developed in 1995 being produced by interviews with patients suffering from idiopathic PD where they were asked to give areas of their lives that had been affected by their PD, including those negatively affected. The eight sub-dimension scores are mobility, activities of daily living, emotional well-being, stigma, social support, cognitions, communication and bodily discomfort as well as one summary index (marked out of a hundred). It is widely used and is regarded as a feasible, reliable, valid and responsive QOL questionnaire although criticisms include a disproportionate emphasis on physical aspects of the disease.

PDQ-8

The PDQ-8 is a short version of the PDQ-39, which was derived by selecting the items with the highest item-total correlation from each of the eight subscales in PDQ-39 (62, 63).

Scales for Outcomes in Parkinson's Disease-Psychosocial Questionnaire

QOL scales may fail to distinguish between the physical aspects and emotional and social aspects of PD. The Scales for Outcomes in Parkinson's Disease—Psychosocial Questionnaire (SCOPA-PS) allows these sections to be treated individually to enable separate evaluation, which could lead to additional beneficial treatment for the patient, for example help from a social worker or a counsellor (80). It is a short instrument consisting of eleven questions dealing with psychosocial issues that the patient may have experienced in the past month.

Parkinson's Disease Quality of Life Questionnaire

The Parkinson's Disease Quality of Life Questionnaire (PDQL) is a disease-specific questionnaire for PD, which was originally developed in Holland, from an integration of the current literature, disease-specific measures and patient interviews (81). It consists of 37 items contained within the following subscales: parkinsonian symptoms (14 items), systematic symptoms (7 items), social functioning (7 items) and emotional functioning (9 items). It has been validated and translated in many countries/languages. The PDQL has been criticized for missing items that have been deemed important to a PD sufferer: self-care, items on close relationships and role functioning (82).

The EuroQOL-5D Is a short generic questionnaire, which contains five sections; mobility, self care, usual activities, pain/discomfort and anxiety/depression each with three possible health ratings (83). A summary score, with a maximum of 1.0 (meaning the best possible health status), can be derived from the five scores. It is a reliable, widely used scale that has been shown to sensitive and consistent in wide range of PD patients.

Parkinson's Disease Quality of Life Scale

PDQUALIF is a disease-specific instrument that consists of seven sections; social/role function, self image/sexuality, sleep, outlook, physical function, independence and urinary function, which in total make 32 items (84). A total score out of a 100 can be calculated with a 100 being the highest health rating. It places much emphasis on the non-motor symptoms of PD, which include fatigue and autonomic dysfunction, which are very debilitating to sufferers of PD. These symptoms therefore are important to a PD patient. The PDQUALIF is the only instrument to have specific questions about fatigue and driving ability.

Management

Given that a large proportion of sleep disturbance stems from nocturnal motor problems, sleep disruption may be ameliorated to some extent by treating the motor symptoms of PD directly. A recent study from the UK reported for the first time that all domains of PDQ-39 scale worsen progressively if patients are left untreated at diagnosis while those who are treated appear to have a stable QOL (85). Levodopa remains the gold standard of treatment in PD, and one study reported that controlled release levodopa was superior to immediate release drug for emotional reaction and social isolation using Nottingham Health Profile (13). In a switch over study with COMT inhibitors, where immediate release levodopa /carbidopa was switched to controlled release, Martinez-Martin and O'Brien reported improved mobility, pain, activities of daily living and emotional well-being using the PDQ-39 (86). However, further studies have not shown any superiority of controlled release levodopa over immediate release preparations (87).

Levodopa is effective throughout all stages of the disease, but its use is limited by emergence of motor complications such as dyskinesias and the wearing off phenomenon, which interfere with patient's day-to-day activities and sleep. Motor fluctuations with levodopa become more common with disease progression.

Dopamine agonists are effective for symptom control as monotherapy or in combination with levodopa. In a multicentre double-blind, randomized controlled trial to compare initial treatment with pramipexole versus levodopa, patients on pramipexole had lower rates of dyskinesias and wearing off than the levodopa group (88). Those on levodopa had better symptom control on the UPDRS. However, both groups resulted in similar QOL (88). In a study to evaluate the effect of Rasagiline on the QOL in early PD using the PD QOL questionnaire (PDQUALIF), Biglan et al. reported an improvement in scores with Rasagiline compared with placebo and the benefit was as a result of improvement in symptoms (89). Rotigotine, a novel non-ergot transdermal dopamine agonist has been shown in preliminary studies to improve several aspects of sleep in PD and scores of the PDSS and thus have a secondary impact on QOL (90).

In PD, severe EDS needs treatment, and firstly, concurrent medications that may be sedating should be eliminated or reduced. Modafinil (100–400 mg/day), a non-addictive sleep–wake cycle activator is non-stimulating and the only drug that has shown efficacy in improving EDS in double-blind placebo-controlled trials (91).

Treatment options for bladder dysfunction are anticholinergic medications (oxybutynin, solifenacin and tolterodine). In general, these medications may be difficult to use in Parkinson's patients due to their side-effect profile, including sedation, dry mouth, and sometimes confusion and hallucinations. It may be beneficial to consider using an extended-release or transdermal patch in the idiopathic Parkinson's disease patients, as this has a more consistent blood level and may cause fewer side-effects (92).

Recently published studies on deep brain stimulation (DBS) of the subthalamic nucleus (STN) show that background neurostimulation of the subthalamic nucleus reduces levodopa-related motor complications in advanced Parkinson's disease and may help sleep problems in PD (93). In another study, comparison was made between DBS plus medication with medical management. Primary end points were the changes from baseline to 6months in the QOL, as assessed by the Parkinson's Disease Questionnaire (PDQ-39), and the severity of symptoms without medication, according to the Unified Parkinson's Disease Rating Scale, part III (UPDRS-III) (94). Neurostimulation resulted in improvements of 24–38% in the PDQ-39 subscales for mobility, activities of daily living, emotional well-being, stigma and bodily discomfort. Serious adverse events were more common with neurostimulation than with medication alone (13 vs. 4%, $p < 0.04$) and included a fatal intracerebral hemorrhage. The overall frequency of adverse events was higher in the medication group (64 vs. 50%, $p = 0.08$).

Conclusions

Sleep disturbances in PD are both prevalent and disruptive to the QOL for both the patient and the caregiver. Degeneration of brainstem sleep centres is implicated in the emergence of sleep problems, as well as the use of dopaminergic medication. New pharmacological and surgical treatments for PD patients that may benefit sleep regulation have emerged in the last 10 years, i.e. new formulations of dopamine agonists, non-dopaminergic treatments such as modafinil, apomorphine and DBS, and their efficacy needs to be explored more thoroughly. Lastly, although a substantial body of literature on the phenomenology, prevalence, correlates and to some extent the management and pathophysiology of sleep disorders in PD now exists, more studies must address the possible impact on QOL for patients and caregivers and the prognostic significance of various sleep disorders in terms of disease progression and institutionalization.

Issues that need to be addressed by future research:

- Studies assessing quality of life in PD patients and their caregivers in relation to objective measures of sleep are needed.
- The benefits of using MSLT or ESS versus MWT or Osler for unintended sleep episodes in PD needs to be tested for those patients who drive.
- The natural progression of sleep symptoms in PD should be examined longitudinally, starting with newly diagnosed and unmedicated patients.

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21
Sleep and Quality of Life in Chronic Pain

Dieuwke S. Veldhuijzen, Joel D. Greenspan, and Michael T. Smith

Summary Assessment of quality of life (QOL) is important in evaluating the well-being of patients suffering from chronically painful conditions. In addition to identifying the degree of psychosocial distress experienced by these patients, QOL assessments allow quantification of how pain specifically impacts daily functioning, and it serves as a treatment outcome in clinical research. The effect of pain on QOL depends on several characteristics of pain, such as the extent to which pain affects the anatomy, the duration of pain, the intensity of pain, the personal meaning of pain, and to some extent how pain may be a marker of, and directly impacts, an underlying disease state. However, pain is not a unique predictor of poor QOL. Sleep quality has been shown to be an important mediating factor in pain-related disability by influencing pain intensity and emotional distress. Chronic pain and sleep disturbances each independently and synergistically have profound detrimental effects on QOL, and psychosocial mediators have been identified.

Keywords Pain · sleep · insomnia · sleep disturbances · sleep deprivation · quality of life · disability

Learning objectives:

- Sleep disturbances are frequently found in chronic pain conditions.
- Recent evidence suggests that there is a bidirectional relationship between pain and sleep.
- Both sleep disturbances and pain can affect QOL severely.

Introduction

Pain is one of the most common reasons for patients to seek healthcare. The costs associated with medical treatment of pain are about 100 billion dollars per year in the USA alone (1). An estimated additional cost of 100 billion dollars yearly results from indirect costs of pain, such as work-related diminished productivity. Pain is an evolutionarily important response to a dangerous or potentially dangerous stimulus. The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential damage or described in terms of such damage" (2). Acute pain serves as a warning for illness or injury and encourages inactivity to promote healing from such injury (3). However, in some cases, the pain persists beyond the expected time frame for healing. When this occurs, pain transitions to a "chronic disorder," sometimes associated with multiple negative sequelae, such as mood disturbances, neuroplastic changes that maintain a state of hyperalgesia, and detrimental effects on health and quality of life (QOL). In practice, pain is classified, somewhat arbitrarily, as chronic if it persists for 6 months or more, either recurrently (with pain-free intervals) or continuously (2). Chronic pain is reported in all age brackets, with a peak in middle-age (4), and in both male and females, but differences between sexes have been reported for numerous pain syndromes with women generally showing an increased prevalence (5). Disability is frequently reported by individuals suffering from chronic pain conditions. Chronic pain often has negative effects on various functional areas, including concentration, overall activity levels, and fatigue (6). Moreover, chronic pain most frequently does not occur in isolation. The most common co-morbidities associated with chronic pain are depression, anxiety, and insomnia (7–9). These co-morbidities have significant clinical implications. They are associated with greater disability levels, poorer QOL, and poorer treatment outcomes (10, 11).

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Sleep in Chronic Pain

Individuals with chronic pain frequently report sleep disturbances (12). The Gallup Organization surveyed a random sample of adults in the USA for the National Sleep Foundation and reported that about 25% of US adults experienced disrupted sleep for at least 10 nights a month due to pain (13). In mixed clinical samples, larger portions of chronic pain patients have been found to report poor sleep, ranging from 42% to up to 88 % (14–17). Sleep problems that occur in the presence of another disease are often referred to as secondary insomnia (18) although more recently it has been argued that comorbid insomnia is a more appropriate term because insomnia occurring within the context of chronic medical disease is often multidetermined and not always entirely a direct result of the underlying disease(s). As insomnia becomes protracted, multiple psychosocial and behavioral factors often play an increasing role in the maintenance of sleep disturbances (19). These factors, such as sleep-related performance anxiety, classically conditioned hyperarousal, irregular sleep–wake schedules, and maladaptive beliefs and attitudes about sleep may require direct intervention to effectively treat insomnia beyond standard medical care for the underlying disease. Insomnia can be characterized as poor or unsatisfactory sleep and include different aspects such as quality, quantity, and timing of sleep (20). Symptoms of insomnia are difficulty falling asleep, difficulty staying asleep, and waking earlier than desired. Results from a sleep diary study show that pain patients mainly have disturbances in sleep quality, sleep onset, and total amount of sleep (21). Fragmented sleep, and impaired sleep maintenance are also associated with pain (12). Further, disrupted patterns in sleep architecture have been found in laboratory studies. Pain patients have lighter sleep, less deep slow wave sleep, more alpha intrusion in non-rapid eye movement (NREM) sleep, and frequent brief arousals (13, 22).

The relationship between pain and sleep is poorly understood and appears to be multifaceted. Sleep disturbances may precede, co-occur, or result from pain or its associated treatment. Recent studies indicate that there is a bidirectional relation between pain and sleep disturbances. Pain severity has been found to correlate with disturbed sleep when a diary method of assessment was used (23). In this study, patients with more severe pain reported greater sleep impairment than patients with low pain severity. Also, poor sleep may increase pain levels. Non-restorative sleep may increase pain sensitivity by influencing nociceptive thresholds (24, 25). Edinger et al. (26) found in fibromyalgia patients that improved sleep quality was associated with improved mood and reduced pain levels. Thus, greater sleep disturbances are associated with more severe pain, but pain can also lead to more severe sleep disturbances. This bidirectional relationship can lead to both worsening of sleep and pain symptoms in the long term, in that more pain is reported after poor sleep, and pain during the day may cause poor sleep again (27).

Relationship Between Pain and Sleep

From the above studies it is hard to determine a causal relationship between pain and sleep. Studies that permit drawing conclusions about directionality have recently emerged.

Prospective Study

One prospective study identified pre-morbid characteristics of individuals who developed chronic pain (28). The main focus of this study was to identify the contribution of measures of somatic symptoms, illness behavior, anxiety and depression, sleep problems, and traumatic life events in the development of widespread pain. Widespread pain was defined as pain in at least two contralateral quadrants of the body present for at least 3 months and is the main symptom of fibromyalgia. In a multivariate analysis adjusted for sex and age, three factors were found to make independent contributions to the risk of development of chronic widespread pain (CWP). These risk factors were illness behavior, somatic symptoms, and sleep problems (28). Further, it was found that these factors had an additive effect: individuals with high scores on all of these factors were at higher risk of the development of CWP. Similarly, Mikkelsson et al. (29) found that self-reported sleep disturbance and depression predicted the spreading of regional neck pain to widespread pain in children.

Sleep Deprivation

To further elucidate the effects of sleep on pain perception, sleep deprivation experiments in healthy subjects have been performed and have yielded valuable results. A literature review on the effects of sleep deprivation on experimental pain processing in healthy volunteers described that sleep deprivation increased sensitivity to painful stimuli in most studies. These results were particularly clear when pressure pain was used as the experimental pain method (30). The authors elaborated on this finding and proposed that pressure pain involves both superficial and deep tissue nociception and may be influenced stronger by a descending pain inhibitory control system that may be selectively affected by sleep. To date, it is still unclear whether interruption of total sleep or certain stages of sleep are critical for effects on pain to occur (30).

A recent study explored whether sleep deprivation alters descending inhibitory endogenous pain processing (31). Thirty-two women were randomized to a control condition, a forced awakening condition in which subjects underwent 8 hourly forced awakenings for three consecutive nights and a restricted sleep condition in which bedtime was delayed such that it matched the total sleep time of the subjects in the forced awakening condition. Sleep was recorded through polysomnography, and psychophysical assessments of pressure pain thresholds and pain inhibition were completed twice daily. Both sleep-deprived conditions showed a 50% reduction

in total sleep time and increased non-painful somatic symptoms. However, sleep deprivation did not have an effect on pain thresholds. Pain inhibition, as measured by the diffuse noxious inhibitory controls test (DNIC), was significantly reduced, and reports of spontaneous pain were significantly increased in the condition in which subjects were awakened frequently during the night but not in the matched sleep-deprived condition without frequent awakenings or in the control group. Both the forced awaking groups and restricted sleep groups reported similar increases in non-painful somatic symptoms. Surprisingly, no effects were found after a subsequent total sleep deprivation night following these three consecutive partial sleep deprivation nights, for any of the conditions (31).

Individual variations in sleep architecture may also modulate pain perception. Smith et al. (32) studied temporal summation elicited by repeated painful thermal stimuli in healthy female subjects when sleeping under normal conditions and correlated sleep stages as assessed by polysomnographic recordings with pain reports that were obtained in the day following the recorded night of sleep. Significant relationships were found between REM latency and percentage of REM sleep and suprathreshold pain ratings. Higher pain ratings and more painful aftersensations were reported when REM sleep was initiated sooner and/or when subjects had a greater percentage of REM sleep (32). Although preliminary, these findings may point to variations in REM sleep as a potential risk factor for the development of chronic pain conditions. Subsequent studies are needed to determine whether this is the case.

Most sleep deprivation studies utilized a short duration of sleep derivation of up to 3 days of either total sleep or selective sleep stages. Recently, a study reported on the effects of sustained sleep deprivation (33). Forty healthy volunteers were randomized to either 4 or 8 h of sleep per night for 12 consecutive days. Sleep deprivation appeared to contribute to both the onset and/or amplification of pain, mainly inducing significant increases in generalized pain and localized pain, specifically back pain and stomach pain (33). Non-significant trends were found for headache, joint pain, and muscular pain. These effects became apparent after the second sleep-restricted night and pain problems continued to increase up to five sleep-restricted nights after which it remained steady. Further, tiredness-fatigue was shown to have a role in sleep-loss-induced pain responses. The authors argue that pain and fatigue may have the same underlying mechanisms, involving inflammatory markers such as prostaglandins and interleukin-6 (IL-6) (33).

Neurobiological Mechanisms

A few studies explored the possibility that common neurobiological mechanisms underlie sleep and pain. Preliminary data is available on the effects of sleep loss on inflammatory mechanisms. Sleep loss may induce a complicated pattern of changes in inflammatory cytokines. Increased production of IL-6 and tumor necrosis factor-alpha (TNF-α) were found after partial sleep deprivation and also increases in transcription of messenger RNA of these two cytokines. TNF-α and IL-6 were found to be increased early after awakening after a night of partial sleep loss (34). Partial sleep deprivation was found to mediate the inflammatory response through classic hormone and growth factor pathways. Cytokines have also been found to enhance pain (35). Further, Ukponmwan et al. (36) showed that the analgesic action of endogenous and exogenous opioids depend on undisturbed sleep. Disturbed REM sleep seemed to prevent opioid analgesia. Furthermore, levels of the neurotransmitter serotonin may be decreased when REM sleep is deprived resulting in a disruption of the descending inhibitory modulation of pain (37). However, sleep deprivation has also shown to increase serotonin levels and may potentially underlie the well known but short-term antidepressant effects of sleep deprivation in clinically depressed individuals. Also, REM sleep is regulated by monoaminergic and cholinergic nuclei in the brainstem. The medial pontine reticular formation has been shown to play a role in cholinergic antinociception during sleep, especially during REM sleep in the cat (38). These cholinergic nuclei in the brainstem seem to be involved in both pain processing and sleep. Another brain area that has been suggested to play a role in modulating pain reactions during sleep and awake states is the raphe magnus (39). In the presence of chronic pain, increased activity of cells that are active during waking (ON cells) and cells that are most active during sleep (OFF cells) are found in the raphe magnus. The increased activity of the ON cells may contribute to increased vigilance to pain. In healthy individuals, painful stimuli presented during sleep will cause a change in the sleep pattern indicative of arousal but will not frequently cause awakening. However, increased activity of ON cells may potentially explain why chronic pain patients have difficulty inhibiting pain during sleep (39). Two studies have found that chronic pain patients have decreased sleep spindling activity, a thalamical-generated sensory gating process that blocks afferent input during sleep (40,41).

Psychosocial Factors

Although a direct relationship between pain intensity and sleep has been demonstrated, cognitive factors also seem to play a role in sleep disturbances in chronic pain patients. In fibromyalgia patients, sleep disturbances were found to predict pain on the following day which in its turn predicted next night sleep disturbances. This bi-directional relationship was, however, no longer significant when a measure of attention to pain was included. Attention to pain was found to mediate the association between sleep and pain; poor sleep predicted attention to pain the following day which again predicted sleep disturbances the next night (27). A recent model on the role of attention in pain processing proposes that

hypervigilance toward pain emerges unintentionally because of the threat value of pain, leaving chronic pain patients increasingly aware of pain and more easily distracted (42). Problems with disengagement of attention in chronic pain patients were not only found related to pain cues but also toward novel infrequent occurring stimuli (43). Pain catastrophizing has been shown to mediate difficulties in disengaging from experimental pain in healthy controls (44–46). Pain catastrophizing is a maladaptive coping mechanism that encompasses an exaggerated negative orientation toward pain stimuli and pain experience (47).

Cognitive-hyperarousal and rumination can also predict sleep quality in chronic pain patients. In a mixed chronic (non-cancer-related) pain population of 51 patients, cognitive arousal, somatic arousal, pain severity, and depressive severity were all associated with poorer sleep (17). Pre-sleep arousal was measured by retrospectively rating intensity of arousal symptoms, such as intrusive thoughts and worries, prior to sleep onset. In a regression model to sleep quality, only pre-sleep cognitive arousal was found to be a unique predictor (17). However, this only explained 11% of the variance in sleep quality, so other factors play a role as well. In a follow up study using an in vivo thought sampling procedure, pain patients who reported a greater proportion of pre-sleep thoughts pertaining to pain and environmental conditions (noises, temperature, etc) experienced prolonged diary measured sleep latency and middle of the night awakenings. The thought contents predicted sleep independently from the effects of nightly pain ratings (48).

Finally, the relationship between pain and sleep may be either directly or indirectly mediated by common features such as pain-related disability, physical functioning, and depression. A cross-sectional study investigated the relationship between sleep quality and pain in degenerative spinal disease and failed back surgery patients (49). These authors differentiated between ratings of everyday pain and highest pain experienced during the previous 2 weeks. Highest pain scores, but not everyday pain scores, were independent predictors of lower overall sleep quality and longer sleep latency. Further, longer duration of pain was associated with poorer sleep quality. However, pain was not found to correlate independently to daytime sleepiness or mental functioning. Physical functioning appears to be a strong predictor of sleep quality, more than daily pain and depression (49). Naughton et al. (50) demonstrated that mild depression scores and moderate pain severity scores were important mediators of the relationship between sleep quality and pain-related disability, with depression as a stronger mediator than pain severity. However, other studies found that poor sleep predicts physical activity, even when depression and pain severity are accounted for (12, 17). Nevertheless, these recent studies emphasize the potential importance of mediators such as depressive symptoms and pain severity in the role of sleep in pain-related suffering.

Quality of Life in Chronic Pain

QOL can be described as the individual's perception of well-being and functioning in all aspects of daily life (51). In a narrower sense, health-related QOL assesses impact of an illness on daily functioning. Chronic pain and sleep disturbances can each reduce QOL and substantially impact daily functioning. QOL is affected in many painful disorders, including low back pain (52), arthritis (53), chronic prostatitis/chronic pelvic pain syndrome (54), spinal cord injury (55), progressing neuromuscular disease (56), and irritable bowel disease (57). Chronic pain affects almost all aspects of QOL. Most strongly affected are dimensions of physical functioning, psychological well-being, and social and cognitive functioning (15, 51, 58). Specific facets of these domains that seem to be particularly affected in chronic pain patients are availability of health and social care, mobility, working capacity, daily activities, negative mood, sleep, physical safety, and dependence on medication (51, 58). Weaker or no associations between pain and QOL were found for personal relationships, perceptions of home environment, spirituality, personal beliefs, and religion (58). QOL measures did not change over time in patients with spinal cord injury over a 6-month time period (55).

Some patient characteristics are associated with severity of QOL; being unemployed, of older age, or of female sex all tend to increase the impact of pain on QOL (51). The effect of pain on QOL depends on the characteristics of pain, such as intensity, duration, and extent (widespread versus regional pain) of pain (51). Higher pain intensity and pain frequency are associated with greater impact of QOL in chronic pain patients (59). However, studies demonstrated that the relationship between pain intensity and functional impairment is nonlinear, and correlations between these concepts are modest at best (6, 60). It has been proposed that there may be a threshold above which pain intensity will severely disrupt daily living and that patients may function effectively with pain intensities below this threshold value (6). More studies are necessary to test this hypothesis. It can be argued that treatment of pain should focus on relieving the pain below this threshold value as to minimize functional disability. Besides intensity of pain, the duration of pain is also an important factor in QOL. In a large study, three groups of patients with different stages of pain were compared on QOL measures: patients with no pain, patients with pain for less than 6 months, and patients with pain for more than 6 months. It was found that the longer the pain was present, the lower QOL was (58). Some evidence suggests that the extent of pain also affects QOL, in that more widespread pain lowers QOL (51). However, pain characteristics are not unique predictors for poor QOL. Again, several psychosocial factors seem to mediate this effect. It has been shown that patients' beliefs about pain are important. Patients who accept their illness seem to be less distressed and disabled (61, 62). Further, the maladaptive coping strategy catastrophizing appeared to mediate the relation between pain

intensity and the psychological functioning subscale of the QOL questionnaire (59). Catastrophizing has been found to predict pain-related disability (63). In a large study of 1208 chronic pain patients, it was found that catastrophizing was strongly associated with all aspects of QOL, even stronger than pain intensity or demographic variables such as sex, age, education level, which all showed some association with QOL domains (64). Women were more disabled on the QOL measured but, remarkably, when other variables were taken into account, sex was no longer a significant predictor. Neuropathic pain patients with higher scores on catastrophizing had more spontaneous pain and were more disabled due to their pain. The helplessness subscale of catastrophizing was specifically found to predict pain. In contrast, catastrophizing did not predict evoked pain (63).

The effect of sleep on pain and QOL was demonstrated in a large telephone survey of 79,625 non-institutionalized adults (65). This study reports that sleep insufficiency is reported frequently (an estimated 26%) in the population. Moreover, those with frequent sleep insufficiency were more likely to report pain and poor general health. Also, physical distress, mental distress, activity limitations, depressive symptoms, and anxiety were reported more frequently in individuals with frequent sleep insufficiency. Sleep problems in chronic ill patients reduce QOL, especially in the mental health domain, diminish work productivity, and lead to increased use of the healthcare system (66).

Differentiating Between Pain Conditions

Chronic pain is not a uniform condition. There is some evidence that in some pain conditions, sleep problems and/or QOL are worse than in other conditions. Also, some disturbances may be specific to a certain condition. There are several reasons why variations between conditions can occur. Different pathophysiological mechanisms underlying pain conditions may elicit a different spectrum of symptoms and disabilities and may require different treatment management strategies. One important differentiation in this respect is between nociceptive and neuropathic pain. Nociceptive pain results from tissue damage and activation of specialized sensory neurons (nociceptors), whereas neuropathic pain results from a lesion or dysfunction of the nervous system. However, these conditions may co-exist in an individual suffering from pain. Some of the evidence for differential influence of chronic pain conditions on QOL and sleep are reviewed below.

Neuropathic pain is a common complication of many other conditions such as diabetes mellitus, herpes zoster, spinal injury, brain injury, and human immunodeficiency virus. Chronic painful neuropathy occurs in about 20% of patients with diabetes mellitus and in about 15% or higher of patients with herpes zoster depending on early antiviral therapy for herpes zoster (67). In both painful diabetic neuropathy and postherpetic neuralgia, incidence of pain increases with older age. Neuropathic pain contributes significantly to costs to society. Neuropathic pain is associated with an approximate threefold increase in the use of healthcare resources compared to patients without neuropathic pain (1). Neuropathic pain significantly interferes with several dimensions of QOL, including physical, psychological, social, and functional health (11,67). In one of the rare studies that controlled for effects of the disease, it was found that QOL was significantly worse in patients with diabetic neuropathy than in diabetic patients without neuropathy or healthy controls. Affected domains were energy, pain, physical mobility, and sleep (68). Also, sleep seems to be affected in neuropathic pain patients. In a study with patients with painful diabetic polyneuropathy, pain caused substantial interference with sleep, more than with other daily activities (69). A recent study showed that in chronic back pain patients, a neuropathic component, such as allodynia or hypoesthesia was commonly found (70). About 37% of an unselected cohort of chronic low back patients scored high on the pain *DETECT* questionnaire (PD-Q), which was developed to screen for the probability of a neuropathic component in patients with back pain. Moreover, it was found that patients with a neuropathic component had higher pain intensities, with more severe co-morbidities such as depression, panic/anxiety, and sleep disorders, which affected functionality and the use of healthcare resources, including more visits to healthcare providers and longer duration of pain treatment (70). This study demonstrated that it is important to determine whether there is a neuropathic component in pain conditions, as these patients generally had poorer QOL.

Irritable bowel syndrome (IBS) is one of the most common gastrointestinal disorders. IBS is a chronic episodic bowel disorder with symptoms of abdominal pain, bloating, and irregular bowel habits and affects predominantly women (71). IBS remains a poorly understood medical condition with individuals suffering from symptoms often for unexplained reasons. Health-related QOL assessments are important for describing the well-being of the IBS patient, especially because of lack of physiological indicators and potential psychosocial consequences of IBS symptoms. A variety of studies examined the detrimental effects of IBS on health-related QOL and these are reviewed in Luscombe et al. (57). General measures and condition-specific measures of QOL found lower physical and mental health scores. All aspects of life seem to be affected by IBS, and with more severe IBS symptoms, QOL becomes worse (72). Specifically, general health, vitality, social functioning, bodily pain, diet, sexual functioning, and sleep are negatively affected in IBS (57). The presence of abdominal pain was the strongest predictor of QOL with pain severity being more important than pain frequency (72). Moreover, reduced QOL was associated with lost time at work (57). QOL is also negatively affected in children suffering from IBS symptoms (73). Many (40–75%) of the individuals suffering from IBS symptoms do not seek

medical care (74). Best predictors for medical care seeking were frequency, duration, and severity of pain, and/or diarrhea (57). Those patients who are seeking medical care place an economic burden on society. Significant healthcare resources are being used and patients with IBS show decreased productivity at work (75). QOL in IBS patients who do seek healthcare is comparable to conditions with a high mortality rate, such as heart diseases and diabetes mellitus.

The specific type of gastrointestinal disorders does not seem to contribute separately to QOL. No differences were found between the subtypes Crohn's disease and ulcerative colitis of inflammatory bowel disease in QOL measures (76). However, more active disease, as determined based on patients report of symptoms over the past 6 months, was significantly associated with poorer QOL although QOL remained affected even in patients with inactive disease (76). Pain anxiety and pain-specific catastrophizing were not associated with disease activity in this study.

Musculoskeletal disorders, such as rheumatoid arthritis, osteoarthritis, and fibromyalgia, are highly prevalent and a leading cause for disability (53). These disorders are more common in females (77, 78) and are characterized by pain, stiffness and swellings in the musculoskeletal system. Musculoskeletal disorders are associated with poor physical and pain-related QOL (53). QOL in arthritis conditions has been found to be lower than gastrointestinal disorders, chronic respiratory or cardiovascular disorders, and close to that reported by cancer patients (53).

Fibromyalgia is characterized by symptoms including fatigue, tender points, muscle aches, and CWP. It has been proposed that fibromyalgia may be aggravated by sleep disturbances. Multiple sleep disturbances, including presleep cognitive arousal or stress, alpha intrusion in NREM sleep, fewer sleep spindles, and decreased frequency activity recorded by EEG in the stage 2 non-REM sleep, have been described in fibromyalgia (22, 41). Fibromyalgia patients report poorer sleep quality and more fatigue compared to controls (79). In fact, Nicassio et al. (80) report that non-restorative sleep accounts for most of the relationship between pain and fatigue. Of interest, the perception of inadequate sleep has been found to be out of proportion to the objective polysomnographic recordings in these patients and in certain subtypes of insomnia although recent work suggests that this phenomenon may be related to sleep microstructure abnormalities, that is, increased high frequency EEG activity in the beta range during sleep (81). Population-based prospective cohort studies showed that high levels of psychological distress, depression, sleep disturbances, threatening life events, and illness behavior were associated with increase risk of CWP onset (82, 83). In addition, subjects who already had some form of pain at the baseline measurement were more likely to report CWP at follow up. Further, it has been proposed that altered hypothalamic–pituitary–adrenal stress axis function, as measured by cortisol levels, is associated with the onset of CWP and, moreover, may partly moderate the psychosocial risk factors although high scores on threatening life events and illness behavior scales appeared to be independent predictors of symptom onset (83). Abnormal growth hormone secretion has also been associated with fibromyalgia (22). This finding is particularly relevant because slow wave sleep, which is frequently reduced in fibromyalgia, is known to regulate the somatotropic axis (84).

Cancer pain can be caused by numerous processes such as direct tumor infiltration, treatment procedures including surgery, or because of side effects of toxic treatments (85). Pain is a prominent contributor to insomnia as reported by cancer patients (86). In a longitudinal study among 93 women with metastatic breast cancer with assessments of baseline, 4, 8, and 12 months, pain was found to be a predictor of worsening of sleep disturbances (87). Higher levels of baseline pain predicted problems with sleep initiation, which implies that sleep disturbances can even get worse without a change of pain intensity over time. Further, a change in higher pain intensity predicted problems with sleep initiation and sleep maintenance but not with total hours of sleep, early morning awakenings, or daytime sleepiness in these patients (87). Studies point to fatigue as a common problem in cancer patients that may severely affect QOL. Higher fatigue levels were found to be positively correlated with insomnia (86, 88) and negatively correlated with QOL (88). Pain was found to be a strong predictor of fatigue in breast cancer survivors (88). When chronic cancer pain patients were compared to patients with daily headaches, these groups showed similar total sleep profiles, however, with some differences in specific sleep domains. Pain intensity scores were similar between groups, as were mood states, but chronic cancer pain patients had poorer daytime functioning. In contrast, headache patients reported more sleep disturbance, were more impaired in sleep efficacy, and used more sleep medication (89).

In sum, a great number of studies all show that QOL in chronic pain patients is low. When comparisons were made between chronic pain patients and other diseases, it was frequently found that QOL of chronic pain patients was among the lowest when compared to other conditions. This suggests that the presence of pain, independent of any other pathological condition, has a significant negative effect on QOL.

Treatment Considerations in Chronic Pain

The main goal of treatment should be patients' well-being. Treatment of pain has historically focused on reducing pain complaints in isolation, which in itself does not necessarily improve subjective well-being. However, patients' satisfaction and willingness to comply with a treatment depend on its impact on QOL. Therefore, QOL measures have been recently implemented as treatment outcomes in addition to pain relief measures. QOL can also be a relevant in choosing between treatments. If two agents have similar analgesic properties but varying impact on QOL, the agent with less negative impact on QOL should be considered first.

The crucial first step in treating chronic pain patients is to assess all symptoms in detail. Several easy to administer tools have been developed to assess sleep disturbances and psychiatric symptoms (Table 21.1). Sleep problems remain often unreported when patients are referred to a specialist for pain treatment (90). A detailed examination of the occurrence

TABLE 21.1. Most commonly used questionnaires for the assessment of pain, mood, sleep, and QOL in chronic pain patients.

Questionnaires	Items	Measurement	Components
Quality of life			
MOS 36-item Short Form Health Survey (SF-36; 98)	36	General health questionnaire	- Physical functioning - Role functioning-physical - Bodily pain - Social functioning - Mental health - Role functioning-emotional - Vitality - General health perceptions
World Health Organization Quality Of Life (WHOQOL; 99)	100	Cross-cultural multidimensional questionnaire	- Physical health - Psychological health - Level of independence - Social relationships - Environment - Spirituality/religion/personal beliefs
Sickness Impact Profile (SIP; 100)	136	Health-related quality of life	- Physical - Psychosocial
Sleep			
Pittsburg Sleep Quality Index (PSQI; 101)	19	Subjective sleep quality over 1-month time interval	- Sleep quality - Sleep latency - Sleep duration - Sleep efficacy - Sleep disturbance - Use of sleep medication - Daytime dysfunction - Global score
Epworth Sleepiness Scale (ESS; 102)	8	Level of daytime sleepiness	- Global score
Mood and anxiety			
Beck Depression Inventory (BDI; 103)	21	Existence and severity of symptoms of depression	- Global score
Center for Epidemiologic Studies-Depression (CES-D; 104)	20	Depressive symptomatology	- Global score
Profile of Mood States (POMS; 105)	65	Transient, fluctuating affective mood states	- Tension-anxiety - Depression-dejection - Anger-hostility - Vigor-activity - Fatigue-inertia - Confusion-bewilderment
State-Trait Anxiety Inventory (STAI; 106)	20 + 20	Anxiety symptomatology	- State anxiety - Trait anxiety
Pain*			
West Haven-Yale Multidimensional Pain Inventory (MPI; 107)	52	Multiple aspects of chronic pain experience	- Impact of pain in patients' life - The responses of others to the patients' communications of pain - The extent to which patients participate in common daily activities
Brief Pain Inventory (BPI; 108)	32	Intensity of pain and interference of pain in the patient's life	- Sensory (pain intensity) - Reactive (interference of pain in patient's life)
McGill Questionnaire (MPQ; 109)	20	Intensity and characteristics of pain experience using sensory, affective and evaluative word descriptors	- Pain rating index - Number of words chosen - Present pain intensity

Newer revised or shortened versions of these questionnaires may exist. This list is by no means exhaustive.

* Other pain scales frequently used: various Verbal Rating Scales, various Visual Analogue Scales — these are usually 100 mm lines with two words that anchor different ends of the spectrum, and various Numerical Rating Scales.

of sleep problems associated with pain is essential for the choice of treatment as analgesic drugs may affect the architecture of sleep. Some agents that are used to treat pain may promote sleep, such as sedative agents as tricyclic antidepressants which are commonly prescribed in the treatment of neuropathic pain. However, other agents can produce excitation or even mania and may worsen or even contribute to sleep problems, such as opioids (91) or NSAIDs (11, 13). Studies evaluating the effects of various pain medications on sleep, however, are sparse and much needed. A complicating factor in the management of pain is whether there is an interrelationship with pain and sleep disturbances or if they occur (partially) independent. In the latter case, treatment of pain alone may not be effective in relieving insomnia symptoms or may actually worsen these symptoms (92). Specific treatment of the sleep problem is then necessary. The challenge of prescribing drugs is to find a dose that optimizes pain relief with minimal side effects that may affect QOL. Combined measurement of pain intensity and functional disability may facilitate dosing of pharmaceutical treatment (6). Although studies are currently emerging, few data are available assessing the efficacy of newer benzodiazepine sedative hypnotics in chronic pain.

Besides disrupted sleep, also anxiety and depression often co-exist in a pain patient and may have superadditive effects upon functionality. Assessing these disorders should be a routine part of the evaluation of patients presenting with chronic pain. The same treatment considerations apply to these comorbid disorders.

Psychological Interventions

Several psychological and behavioral interventions are available for sleep disorders and pain conditions, with varying levels of evidence of success. These options include, amongst others, sleep hygiene, hypnosis, psychotherapy, relaxation therapy, exercise, biofeedback, and multicomponent cognitive behavioral therapy (93).

A recent overview of the literature demonstrated that cognitive behavior therapy is effective in treating insomnia occurring in the context of pain (19). Cognitive behavioral therapy is based on the biopsychosocial model of disease that acknowledges biological factors but also psychosocial factors in the development of chronic pain. It aims at reducing disability by modifying pain behavior and cognitive processes. The advantage of cognitive behavioral therapy lies in its low side-effect profile. This may be a particularly important consideration for older adults already taking multiple medications that may have negative interaction profiles with narcotic pain medications. Multicomponent cognitive behavioral treatment for chronic insomnia focuses on stimulus control and sleep restriction therapies that have demonstrated significant efficacy in a number of well-controlled clinical trials using both subjective and objective measures of sleep (94). Effect sizes for these treatments seem to be similar to the most potent sedative hypnotics in treating insomnia (19, 48) and have the advantage of long-term maintenance of treatment gains. Interventions to improve sleep may also reduce disability levels. Indeed, cognitive behavioral models targeting dysfunctional sleep habits and beliefs have found that improved sleep quality was associated with decreased depressive symptoms and reduced pain-related disability (95).

Cognitive behavioral therapy directly targeting pain is also effective in reducing pain intensity and pain-related disability. Therapy for pain focuses on coping-skills training, reducing psychological distress, and increasing activity levels (96). A recent meta-analysis examined 22 studies for the efficacy of psychological interventions in treating benign low back pain and demonstrated that psychological interventions have positive effects (97). Cognitive-behavioral and self-regulatory treatments in autonomic function, such as biofeedback and relaxation training, were found to be specifically effective for outcomes of pain intensity, pain-related interference, health-related QOL and depression. Multidisciplinary interventions with a psychological component were more effective in improving pain-related interference and work-related outcomes compared to other active treatments (97). Cognitive behavioral therapy for pain is likely to be only partially successful in reducing sleep disturbances (96). Hybrid treatments that combine elements of cognitive behavioral therapy for insomnia and pain are particularly promising and currently being developed and tested in several research laboratories.

Conclusions

Sleep disturbances are found in the majority of chronic pain patients. Recent evidence suggests that there is a bidirectional relationship between pain and sleep. These sleep disturbances have been shown to severely affect QOL in chronic pain patients. QOL in chronic pain patients appears to be very low compared to other patient groups, presumably because pain is a major aspect impairing daily functioning. However, pain characteristics are not unique predictors for poor QOL. This relationship is mediated by several pain characteristics and psychosocial factors. Future studies need to address depression, anxiety, and psychosocial factors in the complex interrelationship between pain, sleep, and QOL. In the treatment of pain, QOL outcome measures should be included besides pain severity measures. Further, the presence of comorbid disorders, including sleep disturbances, should be assessed by routine inquiries and standardized questionnaires. If sleep disturbances are found to be present for a substantial length of time or are associated with significant daytime impairment, in particular excessive daytime sleepiness (falling asleep at inappropriate places/times, fighting to stay awake), referral to a sleep specialist for evaluation and appropriate non-pharmacological and/or pharmacological management should be strongly considered. Treating pain with the aim of improving a chronic sleep problem is often insufficient.

Issues that need to be addressed by future research:

- Measures of sleep and QOL should be incorporated in pain research and pain treatment.
- More research is needed on the exact directionality of the relationship between pain and sleep and predictors need to be identified.
- Future studies need to address depression, anxiety, and psychosocial factors in the complex interrelationship between pain, sleep and QOL.

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22
Sleep and Quality of Life in Multiple Sclerosis

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Summary In multiple sclerosis (MS), an autoimmune inflammatory disease of the central nervous system (CNS), the myelin sheet insulating the axons is destroyed. This diminishes the electric conduction within the CNS. The exact pathologic mechanism responsible for the development of demyelinating plaques and axonal damage is still unclear. MS is probably a heterogeneous disease where different pathogenetic mechanisms are of importance (1, 2). We know from clinical evidence that demyelinization is mediated by autoreactive T-cells, and furthermore, certain hereditary and environmental factors seem to make certain individuals more susceptible to MS than others. In the MS population, sleep disturbances are three times more common as compared to the general population and MS patients are twice as likely to have reduced sleep quality (3, 4). MS-related sleep disorders can be subdivided into primary sleep disorders and secondary sleep disorders. The most common primary sleep disorders seen in patients with MS are insomnia, nocturnal movement disorders, sleep-disordered breathing, narcolepsy, and rapid eye movement behavior disorder (5–7). Secondary sleep disturbances can result from a clinical variety of symptoms seen in MS. Sleep disturbances, depression, and fatigue are often co-existing in MS and thereby influence and intensify each other. Identification of them is very important, because appropriate treatment will improve the symptoms itself, improve quality of sleep, and diminish fatigue. Altogether this reduces disability and will provide patients with a better quality of life (QOL). MS has a substantial negative effect on QOL, even when compared with other chronically ill patients (8). This is probably due to its unpredictable and most often progressive disease course. As a healthcare provider for MS patients, it is important to aid patients in maintaining social activity, employment, and regular exercise. All these factors are important for the improvement of patients' well-being. As attitudes toward MS and ways of coping with this unpredictable disease are vital to the experienced QOL, psychological support toward the acceptance of having MS is essential. Through maintaining a reasonable QOL institutionalization of those with MS may be delayed.

Keywords Multiple sclerosis · autoimmune inflammatory disease · heterogeneous disease · demyelinization · sleep disturbances · depression · fatigue · quality of life.

Learning objectives:

- Sleep disorders are common in MS, and a broad spectrum of different sleep disorders is prevalent in MS patients.
- Sleep disorders can be divided into primary and secondary sleep disorders; primary sleep disorders are caused by the disease process itself and secondary sleep disturbances result from neurological symptoms associated with MS.
- Sleep disturbances, disease severity, and depression all contributed to the existence of fatigue, with sleep disturbances being the largest contributor to fatigue.
- MS patients experience a reduced quality of life as compared to the overall population and as compared to other chronically ill or disabled patients.
- Unfavorable factors for a reduced quality of life are depression, progressive disease course, being unable to continue with their professional lives and social activities, and not being able to come to terms with having MS.
- Identification of sleep disturbance, depression, and fatigue is very important, because appropriate treatment of them reduces disability and will provide patients with a better quality of life.

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Introduction

Multiple sclerosis (MS) is an autoimmune inflammatory disease of the central nervous system (CNS). The immune system destroys the myelin sheet insulating the axons, thereby diminishing electric conduction within the CNS. There is clinical evidence that the inflammatory autoimmune process is mediated by autoreactive T-cells. However, the exact pathologic mechanism responsible for the development of demyelinating plaques and axonal damage is still unclear (1, 2). Furthermore, certain hereditary and environmental factors seem to make certain individuals more susceptible to MS than others. This makes MS a heterogeneous disease where different pathogenetic mechanisms are of importance.

MS mainly affects young adults between 20 and 40 years old. The median age of MS onset is 25.3 years, with a mean age of onset of 30 years. In women, MS usually develops 5 years earlier than in men. The incidence of MS is four to six per 100,000 persons per year. The worldwide predominance of MS varies geographically. In western countries, the prevalence ranges from 30 to 110 per 100,000, including Europe, Russia, southern Canada, northern USA, New Zealand, and southwestern Australia. The geographical variation can be partly explained by racial influences: White persons, especially those from northern Europe have a higher risk. Latitude seems to have an influence as well, with a higher risk for the northern latitudes as compared to the southern. This implies that exposure to sunlight may be protective, either through the effect of vitamin D or exposure to ultraviolet radiation.

Interesting is the finding that when somebody migrates between areas with different risk rates for MS before the age of 15, he/she will acquire the risk profile of the area where they moved too. However, individuals migrating after puberty will carry the risk of the area where they grew up with them for the rest of their lives (9).

Clinical Features and Entities of Multiple Sclerosis

The clinical course of MS has an episodic character in 60% of the MS population, with acute periods of neurological deficits, which often fully or partially go into remission after a few weeks. The synonyms for these acute periods are attacks, exacerbations, relapses, or schubs. There are four subtypes of disease courses in MS. The most common subtype (80%) is relapsing remitting MS (RR-MS) consisting of clearly defined disease relapses with full recovery or with sequelae and residual deficit upon recovery. In between the relapses, there is no disease progression (10). RR-MS starts typically with sensory disturbances, unilateral optic neuritis, diplopia, L'Hermitte sign, limb weakness, clumsiness, gait ataxia, or neurogenic bladder or bowel symptoms. In up to 60% of RR-MS patients, the disease course changes to a secondary progressive MS (SP-MS), which is characterized by a gradual worsening of neurological deficits, either with or without relapses, minor remissions, and plateaus.

RR-MS tends to have an earlier onset, averaging 25–29 years than primary progressive MS (PP-MS), which has a mean onset of 35–39 years. Ten to twenty percent of MS patients develop PP-MS, which has from the onset a progressive disease course without relapses and with occasional plateaus or even minor improvements. The last and rarest form is progressive relapsing MS (PR-MS), also characterized by progressive disease from the onset, with clear acute relapses, with or without complete recovery. The distinguishing feature is that the disease progresses in between the relapses (Figure 22.1).

The extent of axonal loss is thought to dictate the permanent neurological deficits. Disease progression of MS is overall slow, within 15 years after onset of symptoms, 50% will require use of an aid for walking and 10% will need a wheel chair. Patients with PP-MS often experience a more rapid detoriation than patients with RR-MS. Twenty-five years after disease onset, approximately 90% of MS patients have to deal with significant limitations and disability (11).

Diagnosis of Multiple Sclerosis

For many years, the diagnosis of MS was based on the history and the physical examination, which made it a purely clinical diagnosis. As magnetic resonance imaging (MRI) came into practice and specific laboratory tests, the diagnosis can be better objectivated and supported. This resulted in disease specific diagnostic criteria in the 1980s, which were revised in 2001 and 2005, known as the MacDonald criteria (12). The core diagnostic criterion is the presence of dissemination in time and space of neurological deficits in the CNS. MRI characteristics play a major role in these diagnostic criteria and can clearly determine the development of demyelinating plaques in the CNS. Furthermore, analysis of the cerebrospinal fluid (CFS) and visual evoked potentials (VEP) are supportive in the diagnosis of MS. In patients with clinical-definite MS, 86% has delayed nerve conduction velocities of the optical system (13). For diagnosing PP-MS, there must be progression from disease onset of at least 1 year in combination with oligoclonal bands and/or raised IgG index in the CSF. The differential diagnosis of MS includes autoimmune diseases [systemic lupus erythemathosus (SLE), Sjogren's disease, polyarteritis nodosa, Behcet's disease, and syphilis], infectious diseases (HIV/AIDS and Lyme disease), neoplastic diseases, metabolic disorders, and vasculopathies [e.g., cerebral autosomal dominant arteriopathy (CADASIL)].

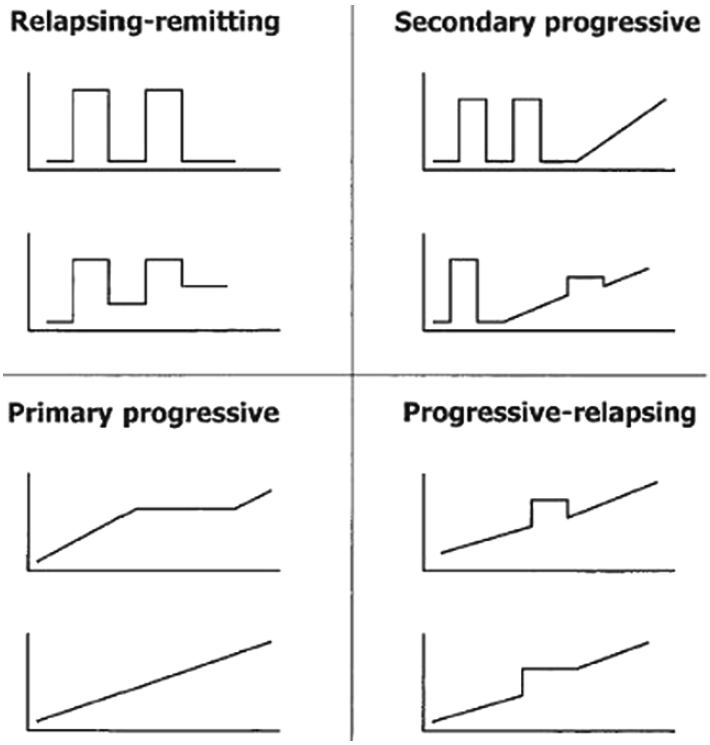

FIGURE 22.1. Graph representing the clinical course of the different subtypes of MS.

Treatment of Multiple Sclerosis

MS treatment can be divided into the following categories: (i) symptomatic therapy; (ii) treatment of relapses; and (iii) treatment for reducing disease progression of MS with disease-modifying therapy (DMT). The most common symptoms seen in MS patients are spasms, fatigue, sexual and bladder dysfunction, and cognitive dysfunction. Other frequently seen symptoms are bowel dysfunction, depression, and bipolar disorder and weakness. Symptomatic treatment is most effective when all present symptoms are treated at the same time, because certain symptoms induce or exacerbate other symptoms, and when left untreated individual symptoms may worsen and precipitate other symptoms. For example, fatigue and depression can lead to reduced physical activity, which leads to a decrease in condition and increase in spasms. A multidisciplinary approach, including education, physical and occupational therapy, and pharmacological intervention are important for an effective symptomatic management.

As there is evidence for an auto-immune pathogenesis in MS, most drugs used in MS are based on immune-suppression and immune-modulation. When patients experience a severe exacerbation, without the signs of fever or an infection causing an increase in pre-existent neurological impairment, methylprednisolon is given for 3 days. This reduces the severity and shortens the duration of attacks, but until now, it is not clear whether methylprednisolon treatment has an effect on the long-term disease outcome.

The DMT (interferon-β and glatiramer acetate) reduces the amount of exacerbations by about one-third, and MRI shows less new lesions as compared to placebo (14). In SP-MS, the effectiveness of interferon-β and glatiramer acetate has not been established. Higher interferon-β doses seem to have a slightly bigger positive effect, a disadvantage is the likeliness of inducing neutralizing antibodies, which may reduce the clinical benefit. Natalizumab is a promising drug for the treatment of MS. However, Natalizumab is only approved when used as monotherapy, because two patients using it in combination with interferon-β developed progressive multifocal leukoencephalopathy (15–17). Mitoxantrone, an immune suppressant, is generally reserved for patients with SP-MS, who have failed other treatments, because it is potentially toxic. Unfortunately, there are no pharmaco-therapeutic options for PP-MS, which have shown to slow-down the progression of neurological detoriation.

Sleep Disorders in Multiple Sclerosis

Beyond the focal neurological deficits and cognitive dysfunction seen resulting from the demyelinating MS plaques in the CNS, patients often suffer from secondary symptoms like sleep disturbances, fatigue, and depression. Formerly, the general idea used to be that these symptoms resulted from the psychosocial consequences of living with a chronic disease like MS either alone or in combination with the consequences of physical discomforts such as urgency and spasms. Remarkable is the high prevalence of these symptoms in MS patients as compared to other chronic diseases. This can be partially explained by the constant demand for adaptability

to the changing and often-progressive development of physical and cognitive limitations typical for the natural course of MS. However, with the development of MRI, there is growing evidence that sleep disorders and the other secondary symptoms, anyway, partially are a direct consequence of demyelinating plaques in the CNS, which makes them actual primary symptoms instead of secondary symptoms.

Sleep disturbances in MS patients have received less attention in research as compared to fatigue and depression. This can be partially explained because patients experiencing a reduced quality of sleep only notice its consequences, such as feelings of fatigue, lack of energy, and not feeling well rested. More than half of MS patients suffer from chronic sleep disturbances, leading to worsening of fatigue and depression (5). From the available clinical evidence, it is estimated that in the MS population, sleep disturbances are three times more common as compared to the general population, and MS patients are twice as likely to have reduced sleep quality (3, 4). MS-related sleep disorders can be subdivided into primary sleep disorders and secondary sleep disorders. The most common primary sleep disorders seen in patients with MS are insomnia, nocturnal movement disorders, sleep-disordered breathing, narcolepsy, and rapid eye movement behavior disorder (5–7). Secondary sleep disturbances can result from a clinical variety of symptoms. In clinical studies, it has been shown that bladder incontinence, muscle stiffness and spasms, and paralysis cause more nocturnal awakenings. When patients suffer from urinary urgency or incontinence, this has as a consequence that their nights are frequently disrupted, because they need to go the toilet. Spasms and pain are frequently experienced and disrupt sleep. By being paralyzed, patients are unable to lie down in a comfortable position and in the long term are prone to develop decubitus. To which extent patients suffer from these symptoms differs individually and is connected to which phase the disease is in. Therefore, each patient should be evaluated carefully to provide them with suitable forms of symptomatic treatment for these symptoms. Additionally, this will have a beneficial effect on the quality of sleep.

As mentioned before, there is growing evidence for a direct link between MS plaques and (primary) sleep disturbances. A hypothesis is that disruption of circadian rhythm could underlie primary sleep disturbances. Circadian rhythm abnormalities include several clinical conditions, such as an irregular sleep–wake pattern, delayed sleep-phase syndrome, advanced sleep-phase syndrome, non-24-h sleep–wake disorder, and circadian rhythm sleep disorder not otherwise specified.

Visual information of the 24-h-dark and light cycle reaches the suprachiasmatic nucleus (SCN) through the retinohypothalamic tract. Besides the visual input, the SCN receives hormonal input from the pineal gland (melatonin) and neuronal input from the raphe nucleus. A plausible theory is that demyelinating plaques near the SCN disrupt afferent and efferent nerve conduction important for the regulation of the sleep–wake cycle. This could result in primary sleep disorders. Because the circadian rhythm is influenced by the 24-h-dark and light cycle and the optical nerve is affected in about 90% of patients with definite MS, it could theoretically be that the reduced visual input to the SCN deregulates the circadian rhythm. In animal models where the SCN was destroyed, circadian rhythm of sleep–wakefulness disappeared (18). In Alzheimer patients, degeneration of the SCN resulted in changes in the circadian rhythm (19). In a study by Sorensen, MS patients had significantly lower levels of CSF somatostatin without a diurnal rhythm during a relapse, as compared to MS patients not experiencing a relapse and healthy controls. As human CSF somatostatin exhibits a diurnal rhythm correlating with the circadian rhythm, with a rise through the evening, peak levels around midnight, and lowest levels in the early morning, these findings are suggestive of reversible altered circadian rhythm during an exacerbation of MS (20).

Following clinical studies used different methods to objectivate whether there is a relationship between abnormalities in circadian rhythm and sleep disorders in MS patients. The results of these studies are not unequivocal. In the study by Ferini-Stambi et al. (1994), MS patients had significantly decreased sleep efficiency, increased awakenings, wake time after sleep onset (WASO), and periodic limb movements (PLM) (7). In a study by Attarian et al. (2004), three groups were compared: (i) 15 patients with RR-MS or SP-MS with fatigue, (ii) 15 patients with RR-MS or SP-MS without fatigue, and (iii) 15 healthy controls. They found a significant correlation in fatigued MS patients and the occurrence of disrupted sleep or abnormal sleep cycles ($p = 0.003$). In the 15 MS patients with fatigue, two had an abnormal circadian rhythm with a delay in sleep phase and 10 had disrupted sleep. Of the MS patients without fatigue, only one had an irregular sleep pattern (21). No abnormalities were found in the healthy control group. In a recent study by Kaynak, studying sleep disturbances in relation to fatigue, they examined the occurrence of spontaneous arousal. In this study the characteristics also objectivated that sleep characteristics were less efficient in MS patients. Furthermore, the number of spontaneous arousals was significantly higher in MS patients with fatigue. However, MS patients without fatigue did not experience more arousals than healthy controls, implicating that fatigue in MS patients could be partially explained by the fact that these patients experience an increased number of spontaneous arousals, resulting in a lack of refreshing sleep (4). The finding that disruption of sleep in MS patients is correlated with the presence or absence of fatigue is in contradiction with the findings of a study of Alarcia et al., who found that MS patients with sleep disorders and those without sleep disorders did not differ significantly in the extent in which they suffered from fatigue complaints (22). Two other studies, exclusively studying circadian rhythm in MS patients, found normal sleep–wake rhythm in MS patients with prominent sleep disturbances and fatigue (22).

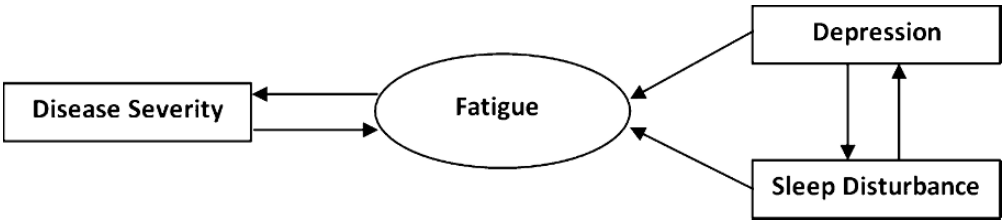

FIGURE 22.2. Model 3 reproduced from Strober (27).

With regard to nocturnal movement disorders, it was estimated that restless leg syndrome (RLS) is more common in MS, with 40.7% in patients with fatigue and 33% in patients without fatigue (22). Nightly arousals associated with movements during sleep associated with PMLS were significantly higher in MS patients with fatigue (4). Patients with nocturnal movement disorders have a greater MRI lesion load in areas of the brain subserving supplemental motor areas. For example, in a study by Ferini-Strambi et al., MS patients with PLM had a higher lesion load in the infratentorial regions of the brain, particularly in the cerebellum and brainstem (7). Another study showed that MS patients with sleep complaints had more demyelinating plaques in the right and left frontal supraventricular white matter and the deep white matter of the right insula, all areas in which motor pathways are present. Therefore, these findings are suggestive of a causative role for nocturnal movement disorders in the initiation of disrupted sleep in these patients (24). A recent case report described a MS patient with the onset of a REM sleep behavior disorder initiated by a severe attack of dorsal pontin demyelination. This patient experiencing nightly sleep-related groaning, screaming, and limb jerking and tonic and phasic muscle activity was registered on the EMG without epileptic activity on the EEG (25).

Sleep-related breathing abnormalities have been reported to occur in MS, especially in more advanced stages of the disease and particularly during relapses. In the study by Kayak and Attarian, no sleep-related breathing abnormalities were found. This could be explained by their younger study population and maybe because the area causing breathing abnormalities was rarely affected (4, 21).

Sleep Disturbances, Fatigue, and Depression

Other "secondary" symptoms besides sleep disorders frequently seen in MS patients are fatigue and depression. Fatigue is the most disabling symptom in MS and is seen in 78% of the MS population (26). MS-related fatigue typically occurs daily and worsens as the day goes on and is often aggravated by heat and humidity. Fatigue is often seen to precede or increase during an acute attack. The exact pathophysiologic mechanism of fatigue is poorly understood. Fatigue often appears to be associated with sleep disorders in MS patients. Depression has been shown to correlate with the extensiveness of demyelization and axonal damage leading to brain atrophy seen in MS patients (27). Fatigue and depression not always correlate with the disease severity in the means of the extent of focal neurological impairment. Consistent evidence to come to an understanding of the role and interactions of sleep disorders, fatigue, and depression is limited, because items of the different scales measuring fatigue, depression, and sleep are overlapping. A recent study estimated that sleep disturbances, disease severity, and depression all contributed to the existence of fatigue and accounted for 43% of the variance in fatigue. Sleep disturbances were the largest contributor to fatigue, followed by depression and lastly by disease severity. Sleep disturbances were related to depression but neither to disease severity. The model that represents these findings is shown in Figure 22.2 (28). These findings support that depression and fatigue as sleep disorders are also partially caused by the direct consequences MS has on the serotonergic neuronal networks and neuronal systems responsible for energy regulation and generation. Furthermore, they interact and amplify (with) each other.

In conclusion, sleep disorders are an underestimated problem in MS patients, and the extent of clinical evidence on a large scale is limited. In the available clinical evidence, there is evidence for primary- and secondary-related sleep disorders. The development of the MRI has made it possible that the pathological changes in MS can be better evaluated, and clinical evidence shows that sleep disorders are not only the result of physical discomfort but also significantly correlate with the extent of the demyelination and brain atrophy seen on MRI.

Besides sleeping disorders, fatigue and depression can be also primary related to MS, implicating that these symptoms are, at least partially, a direct consequence of the disease. Demyelinating plaques in specific areas and axonal loss in the CNS contributes to these "secondary MS-related symptoms" by disrupting specific neuronal systems important in the regulation of sleep, emotions, and energy. This is also supported by individual case reports showing a correlation between the onset of specific sleep disorders, such as REM and sleep apnea syndrome in relation to the demyelinating plaques in specific areas of the brain linked to this distinctive sleep disorder (25). The sleep-related breathing abnormalities seem to develop in a more advanced stage.

The secondary-related sleep disorders result from a variety of symptoms such as bladder incontinence, muscle stiffness and spasms, and paralysis. Either primary or secondary sleeping problems alone or a combination of both leads to the

increased arousal index seen in the MS population. Patients with a reduced quality of sleep do not wake up well rested in the morning and experience sleepiness and fatigue during the day.

Furthermore depression also contributes to the insomnia seen in MS patients and vice versa, that is, insomnia has an impact on depression as well. Because sleep disturbance, depression, and fatigue are often co-existing and thereby influence and intensify each other, identification of them is very important. Because of this, MS patients should be evaluated carefully to screen for these symptoms as there are appropriate treatment options. This will improve the symptoms itself, improve quality of sleep, and diminish fatigue. Altogether, this reduces disability and will provide patients with a better quality of life (QOL).

As the evidence on sleep disorders in MS is limited, additional larger scale studies are needed to examine sleep disturbances and specify the location of lesions seen on brain MRI to link them to the type of sleep disorder. Hopefully, this will increase the awareness among the medical community and make early detection and treatment of these sleep abnormalities possible in MS patients.

Quality of Life of Patients with Multiple Sclerosis

The psychosocial consequences and the extent to which hope and ambitions match the perception of life have only recently been the focus of clinical research in healthcare. As the QOL is most important for the chronically ill patients and their family as it is to every human being, it is important to understand which factors contribute to QOL. The impact which MS has on QOL is usually quite catastrophic. MS affects multiple body functions and can provoke various symptoms that can diminish patients' well-being during the disease course. It also affects the patients' family, professional, and social life. The models important for measuring QOL in MS patients include both general and disease-specific instruments. In the disease-specific models, such as the MSQOL-54 instrument, specific items important for MS patients are incorporated. To determine QOL in MS patients, it has been shown that using exclusively disease-specific models was not useful enough; therefore both models are necessary to determine QOL in the MS population (29). These models elicit patients' subjective evaluation of the effects of MS on QOL and are important to measure clinical outcome specific treatments for MS.

MS patients in general experience a reduced QOL as compared to the overall population. They are less satisfied with their health status, their physical functioning, and the ability to perform in professional life and major activities as compared to the general population (8). Some studies report even lower QOL among MS patients as compared to other chronically ill or disabled patients. In a study comparing QOL in patients with MS, irritable bowel disease, and rheumatic arthritis, MS has the worst outcome (30). This could be related to the unpredictable and often progressive disease course of MS. The related physical and cognitive limitations put an extreme burden on the person living with MS. Most studies show no direct correlation between duration of disease and QOL. Disease aspects that do correlate with QOL are severity and progression of MS, especially when a major increase in disability status in a short period is experienced; this has a huge impact on QOL (31, 32). Besides these disease characteristics we suppose that MS plaques in the CNS probably disrupt the serotonergic system, which can lead to depression. The level of depression is the strongest contributor to QOL in MS patients (33). Depression is more common in patients with progressive forms of MS as compared to RR-MS or benign MS ($p < 0.001$) (33). As patients with progressive forms of MS suffer from multiple unfavorable factors, they have a bigger change to experience a lower QOL. Besides depression, fatigue reduces QOL by interfering with physical function, which results in patients being unable to maintain full-time employment. When patients can continue with their professional life and can carry on with their social activities despite their illness, this is of substantial positive influence on QOL. Being highly educated has a positive impact on QOL. Probably, these patients have more perspective of carrying on with their jobs, because jobs with a higher educational level in general require less physical activities. Being unemployed and having a low income and educational level decreases satisfaction in life. When MS interferes with social life, patients have less positive life experiences and compromised feelings of personal control, which diminishes QOL. Interesting finding of Stuivenburg was that MS patients overall were more satisfied with their family and social life than the general population (32). Patti found that disease course did not have an impact on the family and social well-being of MS patients (33). Another aspect that influences QOL is the patient's attitude toward MS. Patients who have come to terms with MS and accept that they are chronically ill report a better QOL than patients who found it difficult to accept the fact that they have MS.

Quality of Life and Disease Modulatory Treatment

Immunomodulatory therapies have a beneficial effect on relapse rate, demyelinating process seen with neuroimagining and short-term disability. Contemporary studies are beginning to assess the effects of DMT through determination of the effect on QOL. Until recently, the primary clinical measure of disease activity in MS patients was the Expanded Disability Status Scale (EDSS). However, the EDSS is heavily influenced by physical limitations as limb dysfunction and gait dysfunction and has low sensitivity in detecting other important invalidating symptoms such as fatigue, depression, sexual, and cognitive dysfunction. By using QOL as an outcome, medical treatments can be selected which give an

improvement in QOL. Healthcare services and caregivers can provide patients with care, which matches the broad range of needs that matter for MS patients. The QOL instrument showed appropriateness, because they have shown to correlate with disease disability (34, 35).

In several studies, DMT is associated with a significant and sustained increase in QOL, even in some studies when the EDSS did not show an improvement. Patients with a poor QOL at the start of treatment showed the most benefit from it. Those who had their treatment stopped due to progression, side-effects, or lack of effect had significantly lower QOL scores on treatment, as well as patients with the most depressive symptoms at the start of treatment. There was no significant difference in treatment effects between relapsing-remitting and SP-MS patients. These results often concern the early period of treatment (36–40). In four recent clinical trials, the use of interferon-β has been evaluated exclusively in patients with SP-MS. The results were that interferon-β had the potential to significantly slow disease progression and improve QOL for patients with SP-MS (41).

In a British study, the cost effectiveness of treating patients with interferon-β was included in the endpoints of the study outcome. In comparing MS patients treated with interferon-β-1a with patients who did not receive DMT, it was estimated that significant cost savings would be realized after about 12 years of treatment. Due to slowing down disease progression, associated costs with increased disability are postponed (40).

The evidence suggesting a negative or no effect of interferon-β on QOL is less convincing. However, these studies all have a short follow up of 1 year. Two studies showed no significant worsening or improving over 1-year treatment with interferon-β (42, 43). In three other studies, patients receiving interferon-β therapy experienced a significant negative impact on their QOL compared to those not receiving this treatment (33, 44, 45). The impairment of QOL in MS was strongly associated with increasing fatigue and depression and was not associated with disease progression (44).

Conclusions

In the MS population, sleep disturbances are three times more common as compared to the general population and MS patients are twice as likely to have reduced sleep quality (3, 4). MS-related sleep disorders can be subdivided into primary sleep disorders and secondary sleep disorders. The most common primary sleep disorders seen in patients with MS are insomnia, nocturnal movement disorders, sleep-disordered breathing, narcolepsy, and rapid eye movement behavior disorder (5–7). Secondary sleep disturbances can result from a clinical variety of symptoms seen in MS. Sleep disturbances, depression, and fatigue are often co-existing in MS and thereby influence and intensify each other. Identification of them is very important, because appropriate treatment will improve the symptoms itself, improve quality of sleep, and diminish fatigue. Altogether this reduces disability and will provide patients with a better quality of life (QOL). MS has a substantial negative effect on QOL, even when compared with other chronically ill patients. This is probably due to the unpredictable and most often progressive disease course. The prevalence of depression is higher in MS patients and significantly worsens the experienced QOL. QOL measurement has a higher sensitivity detecting improvement of important invalidating symptoms such as fatigue, depression, and sexual and cognitive dysfunction. DMT has a beneficial effect on QOL and seems to be cost effective in the long run. As a healthcare provider for MS patients, it is important to aid patients in maintaining social activity, employment, and regular exercise. All these factors are important for the improvement of patients' well-being. As attitudes toward MS and ways of coping with this unpredictable disease are vital to the experienced QOL, psychological support toward the acceptance of having MS is essential. Through maintaining a reasonable QOL institutionalization of those with MS may be delayed.

Issues that need to be addressed by future research:

- In future research, it is important to identify the spectrum of sleep disorders and its pathofysiologic mechanism.
- Further research should estimate which localizations of demyelinating plaques is responsible for sleep disorders.
- For the patients, it is important to develop adequate treatment strategies for these sleep disorders.
- The long-term effects on quality of life of different disease modifying treatments should be evaluated in patients with MS.
- Besides pharmaco-therapeutic treatment, psychological treatment strategies should be examined to improve quality of life for patients with MS.

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23
Sleep and Quality of Life in Neuromuscular Disease

Amanda J. Piper

Summary Respiratory muscle weakness is a common feature of many neuromuscular disorders, contributing to the development of daytime respiratory failure. However, sleep-related breathing abnormalities and sleep disturbance can occur months or years before the emergence of daytime hypercapnia. Although obstructive events are commonly seen in the early stages of many disorders, with age and disease progression central events and nocturnal hypoventilation occur. Patients may complain of unrefreshing sleep, daytime sleepiness and impaired concentration although these symptoms can develop insidiously and be overlooked or mistaken as features of primary disease process. As management of neuromuscular disorders is primarily supportive not curative, therapeutic intervention must be directed towards managing symptoms and maintaining quality of life. Non-invasive ventilation (NIV) has been convincingly shown to improve physiologic parameters and extend survival in patients with a wide variety of neuromuscular disorders. Although an improvement in symptoms once therapy is commenced is frequently reported, the impact on sleep quality and health-related quality of life (HRQOL) has received far less attention. Assessing quality of life is essential to evaluate the financial and human costs and benefits of therapy. Health professionals frequently underestimate the quality of life in patients with neuromuscular disorders and significant disability, and this can affect the type of therapeutic options that are offered to patients. As sleep quality has been shown to be a major determinant of global quality of life in patients with chronic respiratory failure, evaluating sleepiness, specific sleep-related quality of life issues and neuropsychological function should be undertaken routinely before the institution of home ventilation and during follow up.

Keywords Neuromuscular disease · sleep quality · quality of life · non-invasive ventilation · respiratory failure · hypoventilation.

Learning objectives:

- Sleep disturbance and breathing abnormalities are common in patients with neuromuscular disorders.
- Sleep quality may also be impaired by other factors related to neuromuscular processes such as pain, secretion retention, cramps and periodic limp movements.
- Patients with neuromuscular disorders perceive themselves to have a good quality of life despite severe physical limitations.
- Nocturnal ventilation, usually applied non-invasively, can achieve significant improvements in clinical parameters as well as positively impacting on health related quality of life.

Introduction

Neuromuscular disorders encompass a wide range of diseases that cause abnormalities in muscle function due to lesions at the level of the muscle itself, the neuromuscular junction, the peripheral nerve or at the level of the spinal cord. A common feature of many of these disorders is weakness of the respiratory muscles, which will lead eventually to respiratory failure, a major factor contributing to morbidity and mortality in this population. Sleep-disordered breathing (SDB) is frequently seen (1) and precedes daytime respiratory failure by months or even years (2). However, a wide variation in the type and extent of sleep-breathing problems has been reported even amongst patients with the same disorder. In general, this reflects the fact that studies have been performed at various times after the clinical onset of the disorder, and longitudinal studies have rarely been performed. In addition, the degree

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to which the diaphragm is affected, and the ability of the accessory respiratory muscles to compensate for diaphragmatic dysfunction can also influence the pattern and severity of the sleep-breathing abnormalities seen. Likewise, the presence of upper airway muscle weakness will contribute to and worsen sleep quality and nocturnal respiration as will spinal and rib cage deformities, obesity and craniofacial abnormalities (3–5), all common associated features of neuromuscular disorders. Sleep quality may also be impaired by secondary factors such as an inability to change position, pain, secretion clearance problems, and depression (6). Whether nocturnal-breathing abnormalities or other factors are responsible for sleep disturbance, the consequences will be the same – the development of daytime symptoms that can affect cognitive function and impair quality of life.

Measuring Quality of Life in Neuromuscular Disease

Respiratory muscle weakness is a feature of many neuromuscular disorders and is associated with the development of terminal respiratory failure. However, with the introduction of home ventilation usually in the form of non-invasive ventilatory support, gas exchange and survival can be significantly improved despite progressive muscle weakness (7, 8). As life expectancy has improved, measuring health-related quality of life (HRQOL) has emerged as an important issue in ensuring patients derive benefit from therapy not just in terms of physiological changes but also with respect to psychological well-being and general satisfaction with life. It is also important that health professionals understand HRQOL in patients with severe and progressive disorders as this can influence therapeutic decision-making (9, 10). Despite this, there are few reports looking at HRQOL in this population, particularly studies examining the relationship between sleep quality and daytime impairments.

HRQOL in patients with neuromuscular disorders has been evaluated with a number of different instruments. Among the generic questionnaires, the Medical Outcomes Study Short-Form Health Survey (SF-36) has been the most commonly used instrument at baseline and following the introduction of non-invasive ventilation (NIV) in patients with neuromuscular disorders and sleep-breathing abnormalities (7, 8, 11–13). However, it was not designed to measure sleep disturbances or respiratory complaints. Disease-specific questionnaires have also been employed including the Chronic Respiratory Questionnaire (CRQ) (8, 12), the Epworth Sleepiness Scale (ESS) (12, 14), the Pittsburgh Sleep Quality Index (PSQI) (15) and the Sleep Apnea Quality of Life Index (SAQLI) (8, 12). Currently, there is no consensus as to which scales are most suitable for which neuromuscular disorders, and many do not specifically address issues of sleep quality. In addition, many patients have severe physical impairments so that a marked floor effect occurs when those instruments with a physical dimension are used (16). However, in patients with neuromuscular disease, physical status appears to be poorly correlated with quality of life, and psychological and coping factors are of greater importance in determining quality of life (17). Two disease-specific questionnaires have more recently been developed to evaluate HRQOL in patients with severe respiratory failure (18, 19). The Maugeri Foundation Respiratory Failure (MRF-28) item set (18) has been developed for use in patients with respiratory failure and measures domains of daily activities, cognitive function and invalidity. However, this instrument was developed primarily for use in patients with pulmonary and chest wall disorders, and its applicability to patients with neuromuscular disorders requires further validation. The Severe Respiratory Insufficiency (SRI) questionnaire has been validated for use in patients with SRI receiving home ventilation, including those with neuromuscular disease (19) and includes items relating to respiratory complaints and sleep. However, its use has not yet been widely reported.

Sleep and Breathing in Neuromuscular Disorders

The most obvious reason for patients with neuromuscular disorders to develop SDB is respiratory muscle weakness. Depending on the pattern of weakness, patients may present with upper airway obstruction, central apnea or hypoventilation although it is not uncommon for a combination of these abnormalities to be seen in the same patient in different sleep stages and over different time periods (20, 21).

Hypoventilation during rapid eye movement (REM) sleep is usually the earliest manifestation of SDB in many patients (2). Normally, during REM sleep, there is a marked generalized reduction in the tone of the skeletal muscles including those of the chest wall. Maintenance of ventilation and gas exchange becomes reliant on the functioning of the diaphragm. If the diaphragm is weakened, it will be unable to generate adequate inspiratory pressures and hypoventilation will ensue. Gas exchange deteriorates until arousal occurs. This will cause a shift, albeit briefly, to a lighter sleep stage, allowing return of muscle tone and restoration of ventilation and improvement in gas exchange. However, it will also cause sleep fragmentation (2). Conversely, if the diaphragm remains intact but the chest wall or upper airway muscles are weak, then obstructive apneas or hypopneas may be seen (22).

Irrespective of the primary neuromuscular disorder, sleep-breathing abnormalities can disrupt sleep architecture once respiratory or upper airway muscle weakness occurs. Sleep efficiency is reduced, with a high percent of total sleep time (TST) spent in stages 1 and 2 sleep, while slow wave sleep (SWS) and REM sleep are usually reduced (12, 23–25). However, this is not always the case, and a number of studies have reported relatively well-preserved sleep quality, especially in those with primarily nocturnal hypoventilation (26–29). However, even in these studies subtle changes in

sleep quality can be found including increases in SWS with hypoventilation (28), and increases in total arousals (30) or the frequency of sleep stage shifts (28).

Amyotrophic Lateral Sclerosis

In patients with amyotrophic lateral sclerosis (ALS), diaphragm weakness plays an important role in the respiratory and sleep impairments associated with this disorder. Respiratory muscle involvement commonly occurs in the latter stages of the disease, so that respiratory insufficiency usually manifests late although it may be the presenting symptom in approximately 5% of cases (31). Complaints of difficulty initiating and maintaining sleep are common (27), as are complaints of dyspnea and orthopnea (6). In addition to abnormal sleep breathing, sleep quality may be further impaired due to secretions and musculoskeletal factors such as cramps and fasciculations (6). Sleep studies have demonstrated reduced TST (6), reduced sleep efficiency (12) with more arousals (12) and sleep stage changes per hour of sleep as well as more SDB than age-matched controls (6). However, other studies have reported near normal sleep quality on polysomnography despite patient reports of difficulty sleeping or being sleepy during the day (27). When present, the respiratory abnormality is typically greatest in REM sleep and related to hypoventilation and oxygen desaturation. Although it was initially speculated that those patients with bulbar muscle involvement would show a high incidence of obstructive events (32), no significant association between bulbar dysfunction and severity of SDB or type of event has been found (6, 27, 32–34). However, if the diaphragm is weak, this may limit the ability of the subject to generate an inspiratory pressure above the closing pressure of the upper airway, resulting in less frank obstructive events and more hypopneas being recorded (6).

In patients with diaphragmatic dysfunction, recruitment of accessory respiratory muscles to aid inspiration commonly occurs during wakefulness as well as sleep (35), and it is thought that this recruitment is a major contributor to dyspnea in ALS (36). Arnulf et al. (34) studied 21 patients with ALS, of whom 13 had diaphragmatic dysfunction, to examine the impact of diaphragm weakness on sleep architecture. No differences in the incidence of dyspnea, awake oxygenation or daytime sleepiness between the two groups were found. Although TST tended to be shorter in those with diaphragmatic weakness, this was not significant, and the amount of stages 1–4 sleep was comparable in both groups and within normal values. The frequency of awakenings after sleep onset was significantly higher in those with diaphragm involvement but microarousals and awakenings were not different between the groups. In those with normal diaphragm function, REM sleep duration was normal at 18% of TST but reduced to 7% of TST in those with diaphragmatic dysfunction. However, within this latter group, two patterns of REM sleep quantity emerged. In six patients where REM was relatively well maintained, there was a preservation of phasic inspiratory sternomastoid and genioglossus activation during REM. In the other group, there was little or no REM sleep and also an absence of any accessory inspiratory muscle activity to assist the weakened diaphragm. The authors hypothesized that diaphragmatic dysfunction in ALS could be first compensated during REM by some degree of plasticity of the respiratory control system, with persistence of inspiratory activity of neck muscles during this sleep stage. In patients failing to establish this compensation, or losing it with progression of the disease, REM would be first reduced in duration due to hypoventilation and arousal and would eventually disappear as a protective mechanism against hypoventilation and oxygen desaturation (Figure 23.1). A decrease or suppression of REM sleep was associated with a threefold reduction in survival time. However, there have been no longitudinal studies to date to confirm these findings.

Duchenne Muscular Dystrophy

Most sleep studies in patients with Duchenne muscular dystrophy (DMD) have reported predominantly central events (3, 4), with hypoventilation and oxygen desaturation especially during REM sleep (3). However, obstructive events have also been reported (4, 20, 37). It has been suggested that in the presence of weak respiratory muscles, it may not be possible for the patient to move the chest wall against a closed pharynx, resulting in misclassification of obstructive events as central (3). Obstructive events may also be associated with macroglossia (4). It is also possible that there is an evolution of SDB with age (20). Obstructive events have more commonly been reported in younger patients (20, 37), with more frequent and severe central events (37) or hypoventilation (20) becoming apparent as the patient ages. A correlation between AHI and age has also been reported (3, 4, 37). Despite the presence of sleep-related breathing disturbances and oxygen desaturation, sleep architecture appears to be better preserved in DMD than in those patients with other neuromuscular disorders with a similar degree of respiratory impairment. Sleep efficiencies of 81–93% (3, 4, 20, 37) and percent REM sleep of 12–20% (3,4,37) have been reported in the various case series studied.

Myotonic Dystrophy

Myotonic dystrophy (MD) is a multi-system disease that affects skeletal and cardiac muscle, as well as the central nervous system and endocrine function. These patients usually present with generalized weakness and excessive daytime sleepiness. Respiratory abnormalities during sleep can occur secondary to a number of mechanisms including reduced central drive, upper airway obstruction, respiratory muscle weakness or reduced chest wall compliance (11, 38).

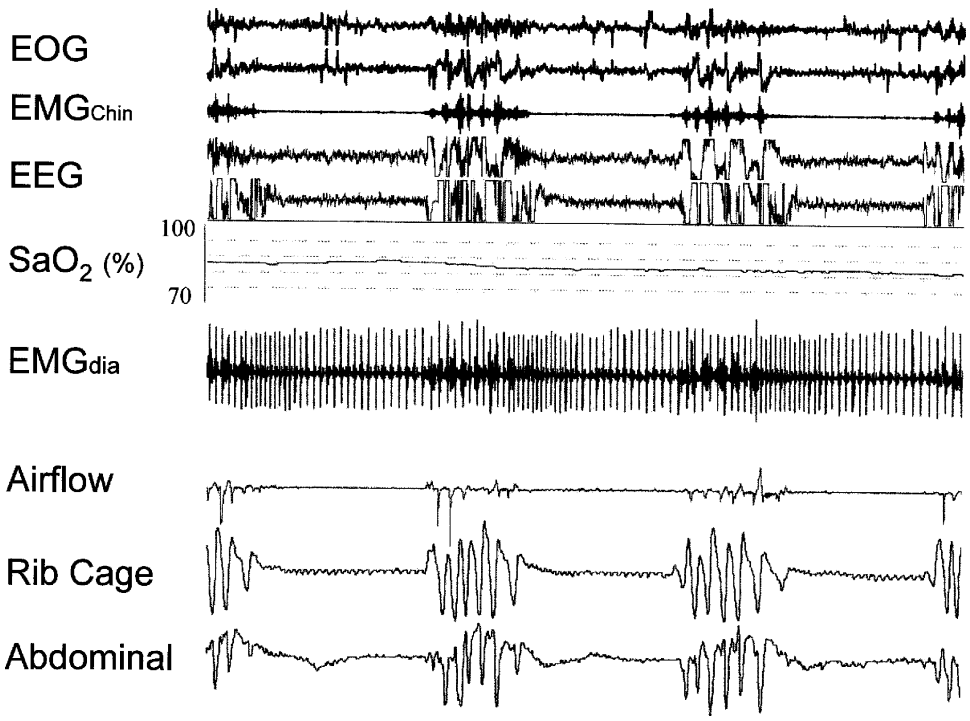

FIGURE 23.1. Two-minute recording of sleep from a patient with amyotrophic lateral sclerosis and diaphragmatic weakness. The patient was unable to maintain breathing during sleep resulting in severe sleep fragmentation and no sustained REM sleep stage. EOG, electro-oculogram; EMGchin, submental electromyogram; EEG, electroencephalogram; EMGdia, diaphragm electromyogram; SaO2, oxygen saturation.

Breathing pattern even during quiet wakefulness may be abnormal, unrelated to the degree of respiratory muscle weakness present (39). Excessive daytime sleepiness occurs in up to 80% of patients with MD and can be one of the earliest symptoms of the disease (40). These patients have greater daytime sleepiness compared to controls despite reporting more time in bed and sleeping longer (41). They also report being less alert on morning awakening, having more difficulty staying awake after meals, and feel their sleep is less restorative compared to normal controls (29,41). Both central and obstructive events have been demonstrated during sleep (29, 42, 43) as well as hypoventilation in more severe patients (44). Patients with MD appear to have significantly greater number of apneas and hypopneas and more severe desaturation during sleep than patients with comparable non-myotonic respiratory muscle weakness (29). Polysomnographic studies have shown long sleep latencies, high amounts of wakefulness after sleep onset, low sleep efficiencies (42, 43) and reduced stage 2 and REM sleep (42). However, this is not a universal finding and other studies have reported relatively well preserved sleep architecture (29), reflecting the variability of this disorder. In a study of 21 children with MD, sleep efficiency was normal at 88% although the mean arousal/microarousal index was high (30). A high prevalence of sleep-related abnormalities was found, consisting of periodic leg movements (PLMs) and abnormal respiratory events, most commonly central apneas. Although these respiratory events were not associated with oxygen desaturation, they did induce sleep fragmentation. The daytime hypersomnolence that is so characteristic of this disorder cannot be explained entirely by abnormal sleep-breathing or poor sleep architecture (30, 45) and is only weakly related to the extent of respiratory muscle impairment (41). This has led to the suggestion that there may be a brain stem abnormality associated with MD that would account for the hypersensitivity to anaesthetic agents and sedatives as well as the excessive somnolence that characterize this disorder (39,45). Neuropathological findings have shown severe neuronal loss and gliosis in the midbrain and reticular formation (45). Those patients with EDS have also been shown to have decreased cerebrospinal hypocretin-1 levels, suggesting dysfunction of the hypothalamic hypocretin system (46). Therefore, sleep and daytime function in this disorder are likely to be affected by more than just respiratory muscle weakness.

Post-Polio Syndrome

The post-polio syndrome (PPS) is characterized by the development of new muscle weakness and fatigue in skeletal or bulbar muscles, unrelated to any obvious cause and becomes apparent years after the initial attack. Apart from muscle symptoms, patients also complain of generalized fatigue and daytime somnolence – symptoms that may also be related to SDB. Respiratory function is often compromised in polio

survivors and a high incidence of apneic events and hypoventilation has been reported (21,47). Patients with previous respiratory polio have been shown to have altered daytime and nocturnal blood gases as well as less total time asleep and lower sleep efficiency, without significant differences in REM latency, movement time or movement arousals compared to age-matched controls (48). In 10 patients with PPS who had not required assisted ventilation associated with their initial acute polio attack, a broad range of sleep-related complaints was found (49). Although the mean sleep efficiency was 89%, this did not reflect the disrupted sleep architecture that was present, with awakenings both during REM and NREM sleep, as well as frequent arousals from SWS to stage 1 sleep. PLMs were also seen although most were non-arousing. No difference in sleep architecture between non-bulbar and bulbar patients was found, but those with bulbar symptomology were more likely to have SDB, predominantly central apnea in NREM sleep. It was proposed that this high incidence of central apnea reflected dysfunction of neural ventilatory control in the lateral medullary reticular formation (49). In another study of patients with PPS, poor nocturnal sleep was again reported along with complaints of daytime hypersomnolence (21). Obstructive events, hypoventilation and a combination of obstruction superimposed on hypoventilation were seen. However, those with obstructive events tended to be more obese, had normal pulmonary function and were not in hypercapnic respiratory failure when studied. In addition, these patients often had only limb involvement and rarely received mechanical ventilation during the acute event. In contrast, those with hypoventilation generally had diffuse neurologic deficits that involved the trunk muscles during the acute polio attack, frequently resulting in scoliosis. Irrespective of the type of SDB found, these patients reported a general decrease in their level of functioning as a result of new complaints that included fatigue, muscle weakness, musculoskeletal pain, respiratory difficulty, sleep disturbance and daytime sleepiness (21).

Spinal Cord Injury

Sleep complaints are common in spinal cord-injured (SCI) patients (50, 51) and include restless sleep, spasms, pain (51), difficulty initiating and maintaining sleep, snoring and daytime sleepiness (52). Anti-spasmolytic medication can further compromise sleep (53). They often sleep supine and have a tendency to develop obesity, both of which may contribute to the development or aggravation of SDB with sleep disruption (52). Obstructive sleep apnea appears to be common in this population with prevalence estimates ranging from 30 to 60% (50, 54–56). Although patients with tetraplegia have increased neck circumference and tend to spend more sleep time supine, these risk factors only account for around a third of the prevalence of SDB in this population (54). Serial sleep studies performed in 30 patients with tetraplegia during the first year following injury showed that SDB was not apparent until 2 weeks post-injury (56). Prevalence peaked at 83% after 3 months and then declined in the next 6-month period but still remained significantly elevated 1-year post-injury at around 60%. Most studies in SCI have focussed on nocturnal respiration, with less emphasis being placed on sleep quality. In patients with paraplegia, questionnaire data suggest that sleep quality is worse than that of control subjects with respect to insomnia, sleep latency, morning irritability, maintaining sleep and willingness to go to bed (57). More difficulties falling asleep, awakening more often at night, poorer general sleep quality, more snoring and more and longer naps have also been reported in patients with SCI compared to a general population (51). Spasms, paresthesia, pain and troubles voiding (51) contribute to the poor sleep quality. Polysomnographic recordings of sleep in tetraplegia have shown that sleep is disturbed with an increase in percentage stage 1 and decrease in percent stage 2 and REM sleep across all age groups compared with normative values (54, 58). In addition, TST is increased in patients with SCI compared to values seen in normal subjects (54). There is also some evidence to suggest that compromised sleep in patients with cervical SCI may in part be due to the absence of the nocturnal melatonin surge (59).

Spinal Muscular Atrophy

Spinal muscular atrophy (SMA) is a disorder characterized by degeneration of the anterior horn cells in the spinal cord and the motor nuclei of the lower brainstem. There is wide variability in muscle weakness ranging from severe generalized paralysis including bulbar dysfunction apparent from birth (type I) to a slower progressive loss of muscle function in individuals that can manifest in adulthood (types III and IV). In a study of infants with types I and II SMA, severe paradox was observed along with significantly higher apnea/hypopnea index compared to an age-matched control group (60). However, the impact this had on sleep quality was not measured. In a study of 12 children with types I and II SMA (mean age 7.8 years), full polysomnography was performed and demonstrated SDB in seven patients, with predominantly repetitive hypopneas with arousals from sleep (61). No patient showed obstructive events, and one patient had REM-related hypoventilation. As commonly reported in other groups of neuromuscular patients, sleep architecture was impaired compared to a reference group of healthy 6–12 year olds: sleep efficiency was reduced, with an increased proportion of stages 1 and 2 sleep, while REM and SWS were reduced.

TABLE 23.1. Summary of studies that have investigated changes in sleep architecture prior to and during nocturnal nasal ventilation in patients with neuromuscular disorders.

			Pre-NIV (%)					During NIV (%)				
Study	No. of patients	Type of disorder	SE	Stage 1/2 sleep	Stage 3/4 sleep	REM sleep	Arousals (events/h)	SE	Stage 1/2 sleep	Stage 3/4 sleep	REM sleep	Arousals (events/h)
Barbe (25)	8	Various, adults	59	81	8	12	NR	83	64	16	19	NR
Collard (63)	17	Various, adults	78	42	30	16	17	77	44	37	19	11
Annane (24)*	14	Various, adults	74	69	11	15	27[y]	87	62	20	17	3[y]
Schonhofer (23)	15	Various, adults	64	86	8	5	29	81	67	19	15	6
Mellies (26)	30	Various, children	NR	55	24	18	21	NR	44	34	20	10
Mellies (61)	7	SMA, children	83	55	28	18	23	89	43	36	22	9
Suresh (20)	9	DMD, children	78	NR	NR	NR	14[y]	88	NR	NR	NR	2[y]
Khan (28)	8	Various, children	91	15	65	20	5[z]	92	26	43	30	<1[z]

SE, sleep efficiency; NR, not reported.
*Study included five patients with idiopathic scoliosis.
[y]Respiratory disturbance index not arousal index.
[z]Wake shifts in deep sleep.

Impact of Nocturnal Ventilatory Support on Sleep Quality

In patients with neuromuscular disorders, therapy such as nocturnal ventilatory support (NIV) or CPAP is usually introduced with the aim of normalizing nocturnal ventilation and diurnal gas exchange, alleviating symptoms and improving survival. Therefore, a large proportion of the literature describing the use of NIV during sleep has not provided details of the sleep characteristics of patients before and after the introduction of this therapy. As a consequence, data concerning changes in sleep quality and its association with changes in daytime functioning are limited. However, the data that are available demonstrate the commencement of nocturnal ventilatory support can have a significant positive impact on daytime symptoms, irrespective of the disease process treated (8, 11, 20). On the other hand, nocturnal ventilatory support is not without side effects, including mouth leak that may cause arousal and sleep fragmentation in its own right (62). If this occurs not only will the efficacy of ventilation be affected but sleep quality may also be impaired.

In the small number of studies where sleep architecture has been reported pre- and post-nocturnal ventilatory support, most have found improved sleep quality, with less stages 1 and 2 sleep (23, 25), increased REM duration (23, 28) and better sleep efficiency (23, 25) (Table 23.1). Even when pre-ventilation sleep architecture is relatively well preserved, the introduction of NIV can reduce the number of shifts in sleep stage (28) and reduce arousals into the normal range (23, 24, 63). In addition, the increased amount of deep sleep that can sometimes occur in patients with severe sleep hypoxemia is also normalized with the use of NIV (28). Therefore, despite the possibility that nocturnal ventilatory support could in its own right cause sleep disturbance, the available evidence suggests that for most patients sleep quality and quantity are improved (Figure 23.2).

Impact of Sleep-Breathing Abnormalities on Quality of Life and Daytime Functioning

Irrespective of the type of the neuromuscular disorder, as respiratory muscle function deteriorates, increasing oxygen desaturation and sleep disruption results in altered sleep quality. As a consequence, daytime sleepiness, impaired concentration, fatigue, lethargy, orthopnea or morning headaches may occur. However, there is a poor correlation between daytime symptoms and sleep-breathing variables, and many patients with neuromuscular disorders will report minimum symptoms despite significant respiratory and gas exchange abnormality (1, 3, 37, 54). Even when symptoms are present, these may be mistaken as simply part of the evolution

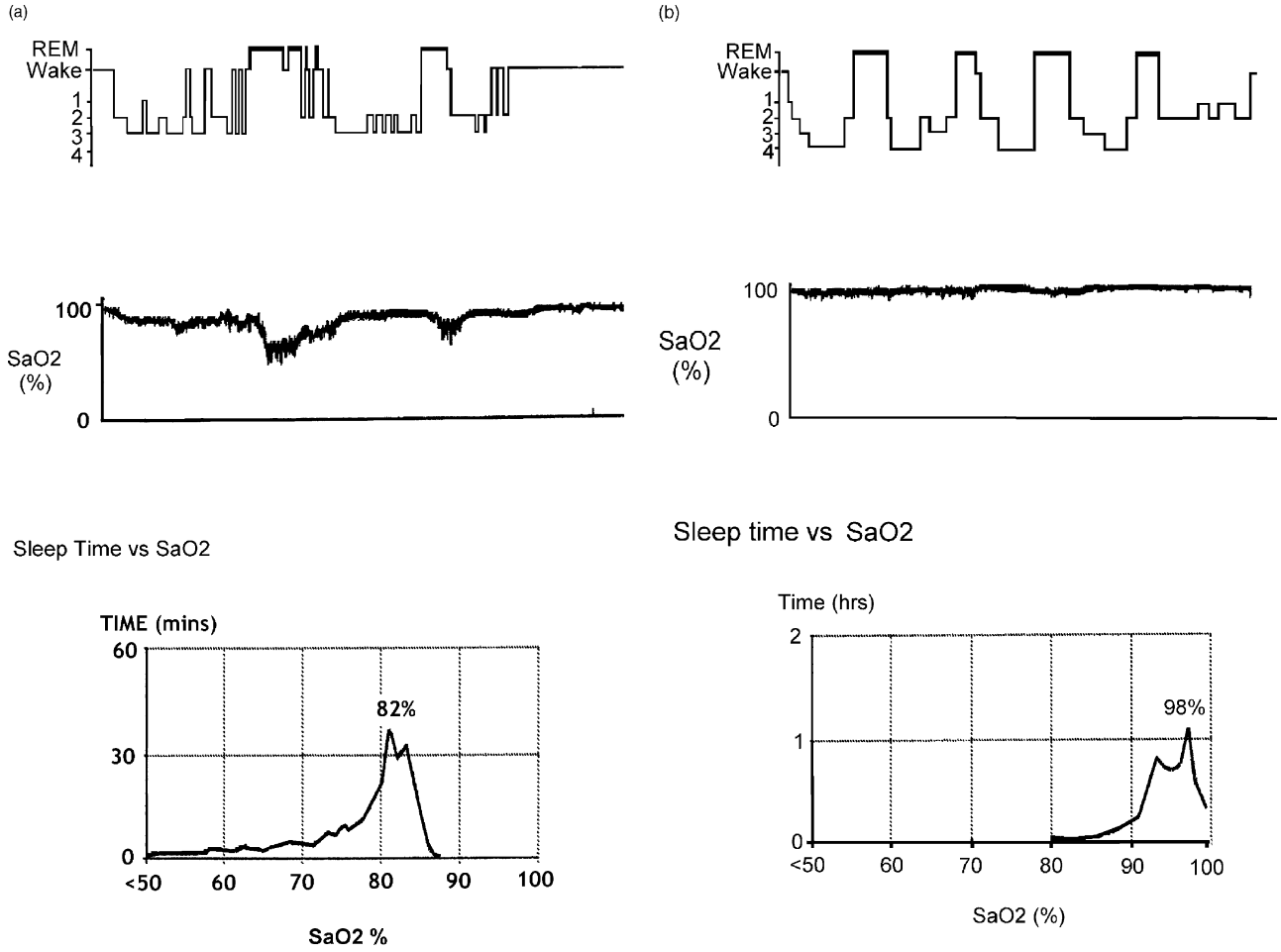

FIGURE 23.2. Panel A: Sleep hypnogram and oximetry from an overnight diagnostic study in a patient with Duchenne muscular dystrophy. Sleep efficiency is reduced and sleep architecture is abnormal with reduced REM stage and frequent sleep stage shifts. Large and sustained falls in oxygen saturation occur in REM sleep. Panel B: With the normalization of nocturnal ventilation using nocturnal ventilatory support, sleep architecture is significantly improved, with increased REM stage, more stage 4 sleep and fewer sleep stage shifts. Nocturnal oxygenation has also been normalized.

of the primary neuromuscular disorder and therefore overlooked as a treatable and reversible condition (4).

Generally, there is a lack of association between clinical findings such as lung function (64, 65) or polysomnographic variables (12) and HRQOL measurements in patients with neuromuscular disease. However, when chronic hypoventilation develops, HRQOL is severely impaired and appears to be related to age, underlying disease and severity of hypoventilation (65). These impairments are due primarily to limitations in physical health domains, with mental health similar to that reported in healthy populations (7). Self-reported sleep problems are common, as might be expected if sleep is disrupted due to respiratory or gas exchange abnormalities (65). Global quality of life is mainly determined by the mental state of the patient and their sleep quality (66). The introduction of nocturnal ventilatory support can significantly ameliorate daytime symptoms and improve patients' sense of well-being and quality of life.

Understanding factors related to quality of life, particularly those amenable to therapy, is particularly important in this population, in whom severe physical limitation is common and disease progression often inevitable. If intervention is to be offered, it must not simply prolong life but must also maintain or improve the quality of that life. Although it has been recommended that sleepiness, specific sleep-related quality of life questionnaires and neuropsychological function should be assessed before the institution of NIV and during follow up (67), to date such outcomes have not been systematically reported.

Amyotrophic Lateral Sclerosis

Respiratory muscle function has been shown to be a strong and independent predictor of quality of life and functional status in this disorder (12, 13). In those patients

with respiratory muscle weakness, the ESS and domains of energy, vitality, mental health and general health perception as measured by the SF-36 are impaired compared to ALS patients without respiratory muscle weakness (13). In addition, the degree of respiratory muscle weakness is related not only to symptoms of orthopnea and dyspnea but also to unrefreshing sleep and daytime somnolence (12). On the other hand, the degree of SDB as measured by AHI and polysomnographic indices do not predict QOL (12).

Patients with ALS who develop imminent or established respiratory failure have significantly more arousals from sleep and more respiratory events compared to those who have not yet developed daytime respiratory problems (68). Given the strong relationship between respiratory muscle strength and quality of life in ALS, a number of investigators have instituted supportive treatment with NIV, with the belief this could substantially improve quality of life (12, 69). Commencement of nocturnal ventilatory support reduces the frequency of arousals from sleep, proportion of TST spent hypoxic and the amount of stage 1 while increasing REM sleep (68). Improvements in sleep architecture are significantly greater in those treated with NIV than those requiring tracheal ventilation. However, in view of the rapidly progressive nature of ALS, it could also mean that any improvement in quality of life initially achieved by treating SDB and improving sleep architecture may be negated by the increased disability from prolonged survival.

Early investigations looking at the impact of nocturnal ventilation on quality of life found no improvement (70). However, more recent work suggests that meaningful gains can be achieved despite the continued decline in physical function (69). In prospective trials, initiation of NIV resulted in significant and sustained improvements in respiratory symptoms and quality of life (13, 15, 69, 71), especially in those domains reflecting sleep disruption: SAQLI Symptoms (71); CRQ Fatigue (71, 72), ESS (13), PSQI (15), SF-36 Vitality (69) and Mental Health – SF-36 Mental Health and Mental Component Summary (71). In a randomized trial of NIV in 41 patients with ALS, Bourke and colleagues (8) showed that those patients who received NIV had a modest improvement in survival with large improvements in the duration that quality of life remained above 75% of baseline. Those patients with normal to moderate bulbar impairment treated with NIV had large improvements in quality of life that were maintained for most of the survival period. In contrast, patients with severe bulbar impairment had no survival benefit from being treated with NIV although they did demonstrate some benefits in terms of quality of life. The greatest improvements occurred in domains assessing problems related to sleep (8).

Impaired cognitive function including executive function, memory and visual attention have been demonstrated in ALS (73) and could impact on the patient's perception of their quality of life. Sleep disruption secondary to respiratory muscle weakness and SDB are thought to contribute to this cognitive impairment. In a study comparing cognitive performance in ALS patients with and without sleep-breathing abnormalities, those with sleep disruption due to hypoventilation and arousal were found to have significant deficits in tests of memory and executive function compared to those without sleep symptoms (14). With the commencement of NIV, improved performance on neurocognitive testing has been demonstrated (13, 14). These findings suggest that impaired sleep quality from hypoventilation (14) or sleep fragmentation with daytime sleepiness (13) contributes to these deficits.

Duchenne Muscular Dystrophy

Only a few studies have addressed the HRQOL in patients with DMD, and the instruments used have not specifically looked at sleep quality. The SF-36 has commonly been employed in this population both as a baseline measure and to monitor changes in quality of life with therapy. Not surprisingly, in patients with advanced generalized muscle weakness, domains representing physical functioning were severely reduced (64). However, other aspects of well-being, such as general and mental health, emotions, social functioning and pain were not impaired according to the patient's judgement and close to values seen in the general population (64). In a group of 23 patients with DMD established on nocturnal ventilatory support (NIV), SF-36 quality of life showed that the social and mental health domains were not significantly different from age-matched male controls (7). Furthermore, health perception was superior to that of older patients with chronic lung disease using NIV and did not differ significantly from other patient groups using NIV with non-progressive disorders (7). Patients with DMD perceive that they have a high quality of life despite their chronic progressive illness and high level of dependency. This contradicts the assumption by many health professionals that quality of life in patients with DMD, and indeed in many other physically disabling neuromuscular disorders, is poor (9, 10) and that offering long-term ventilation would simply prolong suffering and death (10).

Myotonic Dystrophy

In patients with MD not only will symptoms related to muscle weakness arise but many will also develop intellectual impairment and emotional disorders secondary to cortical atrophy (74). These cognitive and emotional deficits including depression and anxiety are believed to negatively influence the quality of life in these patients. Overall, HRQOL as measured by the SF-36 is significantly lower in patients with MD than in age-, sex- and education-matched controls (75). However, the emotional changes such as depression in themselves may

directly affect the patient's judgement of their perceived HRQOL as measured with the SF-36 (75).

Young patients with childhood-onset MD frequently experience fatigue and daytime somnolence that could lead to learning difficulties (30). These symptoms are more common in children with SDB or PLMs than in those children without either disorder. Whether treating these abnormalities can improve learning difficulties has yet to be investigated. In adults, daytime sleepiness is also a common complaint. Significant correlations between somnolence and measures of disability and sleep quality have been reported (76). However, sleep quality was subjectively rated and a difference in subjective and objective sleep quality has previously been noted in this population (29).

In patients established on NIV, Nugent et al. (11) found the most marked difference in quality of life as measured by the SF-36 was a reduction in physical function while no significant differences in mental health or role limitation caused by emotional factors were found. Although depression was present in a small number of the patients, the proportion was probably not different to what would be seen in a general population (11). However, a major difficulty in interpreting this data is that the questionnaire was not administered prior to initiating NIV, so it is unclear what impact therapy had on alterations in quality of life. Other symptoms including shortness of breath, sleep disturbance and alertness were also reported to improve on therapy, but no specific data were provided.

Patients with MD score significantly worse on cognitive tests of concentration and vigilance than healthy controls or other neuromuscular patients with a similar degree of disability (76). Although both cognition and sleep worsen as the disease advances, no significant correlations between the degree of sleep fragmentation or sleep apnea at night have been found, suggesting that the deficits seen are not attributable to sleep problems but rather reflect a direct effect of a central nervous system abnormality (42).

Spinal Cord Injury

Patients with SCI show significant sleep disturbance and frequently complain of daytime sleepiness (54). However, there is a poor correlation between complaints of daytime sleepiness and degree of SDB present (50, 55, 56). Sleep quality may be affected by factors other than respiratory events such as spasms and pain, and studies have confirmed that the degree of self-reported daytime sleepiness is directly related to the frequency of sleep arousals of all types, not just respiratory arousals alone (54, 58). Nevertheless, treating significant SDB could be expected to alleviate daytime symptoms such as sleepiness, which could have considerable impact on quality of life and cognitive functioning in this population (54). However, there is surprisingly little information regarding the impact of treating sleep-breathing abnormalities on sleep quality or HRQOL in patients with SCI. Several case reports have documented the use of CPAP, with improvements in sleep architecture (77) and daytime sleepiness (78). However, it appears that a significant proportion of SCI patients either do not take up (55) or tolerate (50) CPAP. Burns et al. (79) conducted a mail survey of 40 SCI individuals previously diagnosed with sleep apnea. Thirty-two patients (80%) had tried CPAP, and 20 continued to use it. The other 12 patients were unable to tolerate CPAP, citing problems with mask comfort, claustrophobia and an inability to fall asleep with therapy. No difference in sleepiness as assessed by the ESS was seen in patients receiving treatment and those who were not. Likewise, sleepiness-related items from the SAQLI showed no significant difference between treated and untreated groups, with both groups reporting low energy, difficulty concentrating and excessive sleepiness (79).

In individuals with severe physical restrictions, significant neuropsychological deficits due to sleep apnoea that is untreated could have a major negative impact on quality of life (58). Although no relationship between the frequency of respiratory events and neuropsychological variables has been found in SCI, there is an association between cognitive impairment and sleep hypoxia (58). Attention, concentration, memory and learning appear to be affected. Prospective studies evaluating changes in cognitive function and HRQOL before and after treatment are required in this population.

Other Nuromuscular Disorders

There is little information about the impact of sleep on quality of life in patients with other neuromuscular disorders. Although patients with previous polio and SMA have been included in case series reports of the impact of nocturnal ventilatory support, patient numbers have been small, and specific details regarding outcomes particular to these disorders have not been provided. Untreated patients with chronic hypoventilation, including those with polio, have been shown to have significantly impaired quality of life, with a high incidence of sleep-related problems (65). In patients with SMA, a correlation between daytime symptoms and the respiratory disturbance index has also been reported (61). With the correction of SDB with NIV, improvements in objective and subjective sleep quality occurred. In addition, daytime symptoms improved to levels equal to those seen in SMA children without SDB (61). In a group of 39 patients receiving home ventilation, 21 of whom had neuromuscular disorders, sleep quality was reported as good, and there was a high satisfaction with ventilator therapy (66). Sleep quality had a major impact on the patients' global quality of life rating (66).

Conclusions

For many individuals with neuromuscular disease, physical disability is progressive and inevitable. Therefore, the primary emphasis should be placed on maintaining or improving the quality of daily living as high as possible on a long-term basis. Sleep disturbances are common, as are complaints of daytime sleepiness or fatigue. Although data are limited, available evidence suggests that sleep quality is an important determinant of HRQOL in this population. Irrespective of the underlying neuromuscular disorder, once breathing or gas exchange problems become apparent during sleep, intervention with positive pressure therapy can significantly improve sleep quality and daytime symptoms. For most individuals with neuromuscular disorders the resulting extension of life is positive and satisfying.

Issues that need to be addressed by future research:

- Additional investigation into characterizing sleep microstructure in patients with neuromuscular disorders.
- Development and evaluation of health-related quality of life instruments that are reliable, valid and sensitive in patients with severe disability and respiratory failure.
- Further work on the relationship between sleep quality and HRQOL in patients with neuromuscular disorders before and after the introduction of nocturnal ventilatory support.
- Detailed studies of the impact of positive pressure therapy on sleep architecture and quality of life in patients with tetraplegia.
- Assessment of neurocognitive function in patients with chronic respiratory failure prior to and following treatment with non-invasive ventilation.

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24
Sleep and Quality of Life in Autism

Beth A. Malow and Susan G. McGrew

Summary Disordered sleep affects daytime health and behavioral functioning in a variety of neurologic and psychiatric conditions. Sleep disorders lead to a multitude of secondary behavioral effects that affect both the individual and the family (1). Daytime sleepiness resulting from disrupted sleep often manifests itself in typically developing children as hyperactivity, inattention, and aggression (2). Those with autism, a spectrum of neurodevelopmental disorders characterized by difficulties in language and social communication with restricted and repetitive behaviors, may be at even higher risk for sleep disorders given the overlap of autism with sleep. In turn, behaviors inherent to autism, such as impairments in communication and stereotypies, may be exacerbated by sleepiness and interfere with the child's ability to function optimally, thereby affecting quality of life in autism. Aggression and hyperactivity, two problematic behaviors frequently associated with autism, may be further exacerbated by lack of sleep in the child with autism. This chapter will review our current understanding of the neurobiology of autism, especially in reference to sleep-related aspects of this disorder. Sleep disorders in autism, including prevalence, etiology, evaluation, and treatment, will then be characterized. The impact of sleep disorders on daytime behavior and on quality of life in individuals affected with autism and their families will then be discussed. Our chapter will conclude with future research directions for advancing our knowledge in this field.

Keywords Insomnia · polysomnography · actigraphy · melatonin · sleep apnea · sleep hygiene.

Learning objectives:

- To understand the neurobiological underpinnings common to both sleep and autism.
- To identify the major sleep concerns present in autism, as well as their causes and treatments.
- To recognize the impact of disordered sleep on quality of life in individuals with autism and their families.

The Neurobiology of Autism

Autism is a disorder of neurodevelopment characterized by core deficits in three major domains: social interaction, communication, and restricted interests with repetitive behaviors. Because of these shared features, the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) defines autism as a spectrum disorder, encompassing autistic disorder, pervasive developmental disorder not otherwise specified (PDD-NOS), Asperger's syndrome, childhood disintegrative disorder, and Rett syndrome (3). The prevalence of autism spectrum disorders (ASDs) has been estimated to be between 3 and 6 per 1000 children by the Centers for Disease Control and Prevention (4), with at least 300,000 US children aged 4–17 years diagnosed with the disorder as of 2003–2004. Individuals with autism vary in severity of symptoms, with some children completely non-verbal while others manifesting only subtle deficits in communication. Intelligence may be normal or above average although a proportion of children with autism manifest mental retardation.

The developmental neurobiology of autism, including the etiology of this disorder, is under intensive investigation, and the reader is referred to a recent comprehensive review (5). Autism is generally manifested in the first or second year of life although diagnosis may be delayed until later in childhood or even into adulthood, especially in milder cases (e.g., individuals with Asperger's syndrome) that do not involve language delay. Brain volume shows abnormal enlargement during early childhood, but differences diminish by later childhood or adolescence (6). Neuropathological studies have shown a discrepancy in brain volume among regions, with gray and white matter in the cerebrum and

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cerebellum increased, with reduction in size of the cerebellar vermis. In addition, misorientation of pyramidal neurons, cortical dysgenesis, and increased cell packing density have been noted suggesting alterations in primary developmental processes (5). Functional MRI studies have consistently shown hypoactivation in the fusiform face area, correlating with observed deficits in face perception in autism (7). The etiology of autism is primarily related to polygenetic factors, supported by the high risk of the disorder in monozygotic and dizygotic twins and siblings. However, complex gene–environment interactions are likely, and immunologic abnormalities including CNS autoantibodies, cytokine abnormalities, and altered T-cell function have been observed in the disorder (8, 9).

The Relation of Autism to Sleep

The complex regulation of the sleep–wake cycle involves coordinated neuronal activity in the hypothalamus, brainstem, thalamus, and cortex. Several neurotransmitter systems implicated in promoting sleep and establishing a regular sleep–wake cycle are also affected by autism, and their aberrations in autism may be responsible for a component of the prevalent sleep disturbances of autism. These neurotransmitter systems include gamma-aminobutyric acid (GABA), serotonin, and melatonin.

The preoptic area of the hypothalamus is a major sleep-promoting system that uses GABA as a neurotransmitter. Sleep-active neurons in the preoptic area project to brainstem regions that contain neurons involved in arousal from sleep, and inhibiting these regions in turn promotes sleep. These regions include the pedunculopontine and laterodorsal tegmental nuclei (PPT/LDT), the locus coeruleus, and the dorsal raphe (10). In autism, GABAergic inhibitory interneurons appear disrupted (11) and a genetic susceptibility region has been identified on chromosome 15q that contains GABA-related genes (12). The expression of these autism susceptibility genes may affect sleep by interfering with the normal inhibitory function of GABA through the preoptic area neurons.

Serotonin may promote sleep by dampening systems that normally stimulate cortical activation and arousal, such as the cholinergic system. Serotonin may also be responsible for stimulating the accumulation of other sleep factors in the anterior hypothalamus (13). Abnormalities in serotonin synthesis, metabolism, or transport, reported in autism, may influence the physiological effects of serotonin on sleep promotion (14).

Related but separate to the promotion of sleep is the regulation of sleep–wake cycles by the circadian system. Light received through the retinohypothalamic tract to the suprachiasmatic nucleus in the anterior hypothalamus times the sleep–wake cycles to the environment. Melatonin, a sleep-promoting substance synthesized from serotonin and released by the pineal gland, is inhibited by light (15). Decreased nocturnal excretion of 6-sulphatoxymelatonin, the major metabolite of melatonin, has been observed in children with ASDs compared to non-autistic children (16). The nocturnal secretion pattern of serum melatonin is also altered in autism, with decreased amplitude observed in young adults (17) and both decreased amplitude and a shift in phase (peak concentrations in the evening rather than the night) seen in adults (18).

The abnormalities in GABA, serotonin, and melatonin production in autism, along with accumulating evidence of clinical sleep and circadian disturbances (see Sleep Disorders in Autism: Prevalence, Characteristics, and Causes), provide evidence for involvement of the neurobiological networks regulating sleep in autism. Investigations linking these neurotransmitter abnormalities to the severity of sleep disturbances in ASDs have yet to be investigated. Whether subsets of individuals with ASD who have clinical abnormalities in their sleep–wake cycle are more likely to exhibit abnormalities in sleep-related neurotransmitters remains to be determined.

Sleep Disorders in Autism: Prevalence, Characteristics, and Causes

Although individuals with autism can have sleep disorders throughout life, most studies characterizing sleep in autism have been performed in children. This section will therefore emphasize sleep concerns in children with autism although will reference the available literature on adults.

Evidence from parental surveys and polysomnography (PSG) suggests that sleep disorders are more common in children with autism, with prevalence rates ranging from 44–83% (19) and varying in type. In contrast, the prevalence of parentally reported sleep problems in typically developing children is 11–37% (20, 21).

Symptoms of insomnia, defined as difficulty initiating or maintaining sleep, are the major sleep concerns reported by parents of children with autism. Questionnaires and/or sleep diaries completed by parents of children with autism and those of age-matched typical children are consistent in documenting that the children with autism are more likely to exhibit insomnia with prolonged time to fall asleep, decreased sleep duration and continuity with increased awakenings, and, in some reports, early morning wake time (19, 22–26). "Difficulty falling asleep" was reported in 53% of children with autism in one series (27). In another series of children with autism, 55% had "difficulty falling asleep" and 26% had "difficulty staying asleep" (28). Abnormalities in the sleep–wake cycle, with irregular bedtime and waking times (29) and a non-24-h sleep–wake ("freerunning") syndrome, in which any semblance of a consistent bedtime and waking time is present (30), have also been reported.

The causes of insomnia in autism are multifactorial (Figure 24.1) and include neurobiological factors, sleep habits, and sleep disorders. Insomnia may also result (or contribute to) coexisting psychiatric conditions such as

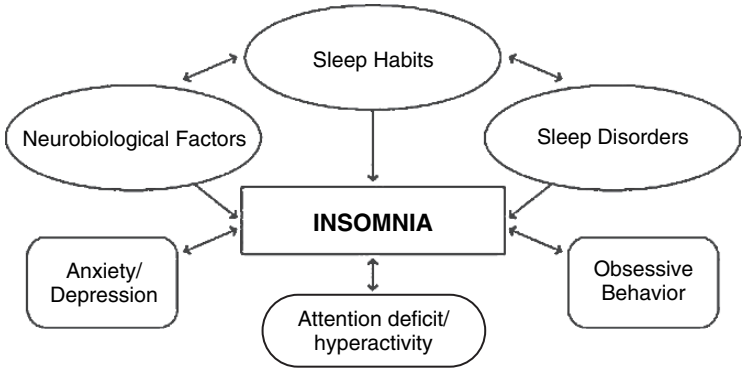

FIGURE 24.1. Causes and correlates of insomnia in children with autism spectrum disorders.

anxiety or depression, as well as from the psychotropic medications often used to treat these conditions. Symptoms associated with autism such as hyperactivity, obsessions, anxiety, or stereotypies may also contribute to difficulty falling asleep. Children may delay sleep onset for hours vocalizing or engaging in a repetitive behavior that interferes with sleep initiation. Whether these activities are the manifestations of anxiety, stereotypies, or poor sleep hygiene habits is uncertain although treatment with anxiolytics is often helpful. Depression may be manifested by early morning waking and bipolar disorder by decreased need for sleep. Although some psychotropic medications promote sleep through their treatment on anxiety or depression as well as through sedating effects, others like fluoxetine are highly stimulating and can interfere with sleep onset or maintenance (31). Coexisting epilepsy or its treatment may also disrupt sleep (32). Medications used to treat epilepsy are usually sleep-promoting, but some like lamotrigine and felbamate may be stimulating, prolong sleep latency, and promote night wakings. Other causes of insomnia in autism include primary sleep disorders such as obstructive sleep apnea or periodic limb movements of sleep.

Other sleep concerns reported in autism include symptoms of disordered breathing with loud snoring or noisy breathing and occasional pauses or apneas in breathing (33), leg movements, and bruxism (tooth grinding). Arousals from sleep may occur with confusion, wandering, or screaming, or daytime sleepiness may be present, reflecting the consequence of insufficient sleep, a specific sleep disorder, or in some cases overmedication. Rapid eye movement disorder, in which individuals engage in dream-enacting behavior, was documented in one series of children with autism although coexisting medications that can contribute to abnormal REM sleep were not specified (34). Rhythmic movement disorder is characterized by repetitive motion of the head (including head banging), trunk, or limbs, usually during the transition from wakefulness to sleep (35). It may also arise during sustained sleep. Although the condition most often affects infants and toddlers in a transient and self-limited fashion, it may persist in children with autism and other developmental disabilities. Epileptic seizures can mimic any of these nocturnal events and may require video-EEG PSG for appropriate diagnosis. Table 24.1 outlines the variety of sleep disturbances observed in autism.

Although the degree of mental retardation tends to predict sleep abnormalities across most developmental disabilities, the level of mental retardation does not appear to affect the prevalence or severity of disordered sleep in autism (19, 23). In one study, children with ASD and low IQs had more night wakings (27) although other sleep parameters were not affected. A recent study comparing parents' perceptions of the prevalence, severity, and pattern of sleep problems in children with normal intelligence with autism found a significantly higher prevalence and severity of sleep problems in those with autism as compared to children who were typically developing matched on age, gender, and postal code, with insomnia-related symptoms predominating (36).

TABLE 24.1. Causes of sleep disturbance in autism.

Insomnia
Anxiety
Depression
Psychotropic medications
Coexisting epilepsy
Obstructive sleep apnea
Periodic limb movements of sleep
Circadian rhythm abnormalities
Poor sleep habits
Hypersensitivity to environmental stimuli
Daytime Sleepiness
Insufficient sleep
Disrupted sleep from a primary sleep disorder
Depression
Epileptic Seizures
Medications
Narcolepsy
Nocturnal Events
Epileptic seizures
Non-REM arousal disorders
REM behavior disorder
Rhythmic movement disorder

Investigations using objective measures of sleep such as PSG (37) and actigraphy (38), in which an activity meter on the wrist that quantifies movement and rest serves as a surrogate of activity and sleep, have also documented prolonged sleep latency in high-functioning children with autism described by their parents as having symptoms of insomnia, supporting the validity of parental perception. Actigraphy studies have shown mixed results, however, with two studies showing that parental perceptions were not borne out by actigraphy, so further validation of this technology will be needed (25, 28).

Sleep problems in autism also tend to occur regardless of age. In one series, parents of younger children (less than 8 years) reported more severe sleep concerns (19). However, age differences were not noted in a larger series (28). This discrepancy may be due to differences in methodology as well as heterogeneity among participants. Insomnia is also a prominent sleep problem in adults with autism and commonly coexists with anxiety and mood disorders (39). As in children, PSG has confirmed prolonged sleep latency and other measures of disrupted sleep in these individuals (40).

Sleep Disorders in Autism: Evaluation and Treatment

Defining the cause of sleep disturbance is critical to appropriate intervention. For example, insomnia due to poor sleep hygiene may be responsive to behavioral interventions, insomnia due to impaired circadian control of sleep may be responsive to treatment with supplemental melatonin or other therapies that target the circadian cycle, daytime sleepiness due to obstructive sleep apnea should respond to treatment with adenotonsillectomy or other therapies, and nocturnal events due to epileptic seizures should respond to antiepileptic drugs. The first step in evaluation is the sleep history, which should include the bedtime, waking time, and any waking during the night, with estimated durations and associated behaviors. Daytime functioning should be assessed, including hyperactivity as well as sleepiness and daytime naps. Individuals with autism or their parents should be encouraged to keep a sleep diary to assess sleep latency, total sleep time, night wakings, and response to treatment. When a sleep disturbance emerges in conjunction with a change in or cycling of moods, neurovegetative symptoms, social withdrawal, or a loss of function, a psychiatric evaluation to assess for bipolar disorder, depression, or anxiety disorder should be obtained. Treatable conditions such as sleep-related breathing disorders should be sought by inquiring about the presence of snoring, apnea, snorting or gasping, sweating, screaming, or excessive leg movements or activity. Patients should be referred for PSG if there is a concern for sleep-related breathing disorder or sleep-related seizures.

In children diagnosed with obstructive sleep apnea, tonsillectomy and adenoidectomy are the first line of therapy. If symptoms persist or surgery is not an option, the child may be a candidate for continuous positive airway pressure (CPAP), which overcomes the upper airway obstruction with pressurized air delivered through a mask. In adults with obstructive sleep apnea, CPAP is the first-line option. In both children and adults, desensitization of patients to CPAP is often required and can be achieved, often in conjunction with a sleep technologist.

Sleep hygiene (habit) problems should be identified and individuals or their parents educated to pay attention to basic principles of sleep hygiene, including daytime exercise, a regular and consistent bedtime, a consistent bed which is not used for other activities (e.g., TV viewing or time out), a structured calming bedtime routine, and dim evening lights. Caffeine after noon and stimulating activities in the hour before bedtime should be avoided, as should falling asleep with the television on or with parents in physical contact. These sleep aids may promote sleep at bedtime but also contribute to night wakings—when the television or parent is not present, a brief arousal from sleep may become a prolonged night waking. It is critical to assist parents in learning how to teach their children to fall asleep on their own by helping the child settle into a relaxed state and by providing no stimulation or reinforcement for resisting sleep; visual supports showing what is expected of the child are a critical part of this approach in autism. For more information, the reader is referred to a comprehensive reference on behavioral techniques in promoting sleep in children with developmental disorders (41) and to two recent articles (42, 43).

When behavioral therapies are incompletely effective, pharmacologic treatment can be used to augment the behavioral therapy. With all medications, it is important to start with low doses and increase gradually, monitoring carefully for adverse effects as individuals with autism may be sensitive to certain classes of medications and unable to communicate side effects. Supplemental melatonin, available as a dietary supplement, has a gentle sleep-promoting effect and has been effective in open-label trials of sleep promotion in Asperger's syndrome, with a dose of 3 mg at bedtime decreasing sleep latency as measured by actigraphy (44). Although melatonin is a dietary supplement, is not approved by the Food and Drug Administration, and has not been rigorously tested for safety, efficacy, or purity of preparation, no serious long-term adverse effects have been seen in this widely used supplement. Clonidine is also useful for sleep initiation problems in individuals who are mildly anxious or overaroused at night. Diphenhydramine and the benzodiazepines are other options. Those with comorbid bipolar disorder, extreme mood irritability, aggression, or self-injurious behavior may benefit from treatment with the sedating atypical neuroleptics such as risperidone, olanzapine, or quetiapine. The dosages of these medications can be adjusted to give the higher dose at bedtime.

In the anxious or depressed individual with autism, specific antidepressants that promote sleep may be considered. These

include the highly sedating drugs mirtazapine, trazadone (should be avoided in males who cannot communicate reliably because of the risk of priapism), the mildly sedating selective serotonin reuptake inhibitor (SSRI) citralopram, and the tricyclic antidepressants (such as clomipramine, imipramine, and nortryptilline). The sedating SSRIs or tricyclic antidepressants may also be useful for those with obsessional thoughts that interfere with sleep onset. Bupropion, venlafaxine, fluoxetine, and sertraline are relatively stimulating and should be avoided in those with insomnia and reserved for those with daytime sleepiness without insomnia.

Impact on Treating Sleep Disorders on Quality of Life in Autism

Children with developmental disabilities, including autism, have a high prevalence of emotional, developmental, and behavioral problems that impact on quality of life. Problematic daytime behaviors may be associated with sleep disorders in children and adults with intellectual disabilities. A study of adults living in community homes showed higher scores for irritability, stereotypy, and hyperactivity as well as more aggression and self-injurious behavior in those with sleep problems (45). Another study found that children with severe intellectual disabilities and sleep disorders showed significantly more varieties and severities of challenging daytime behavior (46).

The emotional health of children with developmental problems has become a current focus of the World Health Organization and was the subject of a recent national survey of children's health (47). Children with developmental problems had lower self-esteem, more depression and anxiety, more problems with learning, missed more school, and were less involved in sports and other community activities. Their families experienced more difficulty in the areas of childcare, employment, parent–child relationships, and caregiver burden. The report emphasized that effectively addressing these issues had the potential to enhance the quality of life for a child as well as parents. An investigation comparing prevalence of psychiatric disorders in 36 teenagers with learning disabilities and autism who were matched by age, gender, and non-verbal IQ to those with learning disabilities alone showed higher rates of episodic psychiatric disorders in the autism group (17/36 vs. 6/36 in the control group). Depression was the most frequently identified disorder with half of the individuals having more than one episode of depression (48). Another investigation compared rates of emotional and behavioral problems on the Developmental Behaviour Checklist in 381 young people with autism compared to 581 children with intellectual disability (45). Children with autism were found to suffer from significantly higher levels of psychopathology including disruptive behavior, self-absorbed behavior, anxiety, attention deficit hyperactivity disorder (ADHD), and depression than young people with intellectual disabilities.

A separate investigation of health-related quality of life in parents of school-age children with high-functioning autism or Asperger syndrome reported impaired health-related quality of life in mothers, with lower scores on the 12-item Short Form Health Survey (SF-12) (49). The SF-12 measures physical and mental well-being. Maternal health was related to behavior problems such as hyperactivity and conduct problems in the child.

Quality of life has also been characterized in high-functioning adults with autism although study has been limited to variables such as disability characteristics and social and professional support rather than medical conditions such as sleep disorders. Taken together, these investigations support the importance of assessing quality of life in individuals with autism and their families. As described below, given the associations of disordered sleep with daytime behavior, consideration of sleep-related factors in future studies of quality of life in autism appear warranted.

Treatment of disordered sleep in those with autism has high potential to improve quality of life in these individuals and their families although research in this area has been limited and awaits further study. Associations between sleep disorders (particularly sleep apnea) and daytime neuropsychiatric symptoms, such as hyperactivity and aggression, are well documented in typically developing children (50, 51). Treatment of sleep apnea resulted in improvement in problem behaviors after adenotonsillectomy (52). In autism, short sleep duration has been associated with stereotypic behavior, as well as inflated overall autism scores and social skills deficits (53). There appears to be a relation between sleep problems and repetitive behaviors (stereotyped, self-injurious, compulsive, ritualistic, and restricted) and craving for sameness in children with autism (54) although this relation may have been moderated by their level of cognitive ability. Children with autism described by their parents as "poor sleepers" as opposed to "good sleepers" had higher scores related to affective problems on the Child Behavior Checklist and more problems with reciprocal social interaction on the Autism Diagnostic Observation Schedule, an objective diagnostic instrument for assessing ASDs (37). A case report of a girl with autism and obstructive sleep apnea documented improvement in a variety of domains, including social interaction and ability to focus, after treatment of sleep apnea with adenotonsillectomy (33).

In addition to a direct impact on the child, behavioral treatment of sleep problems in children with intellectual disabilities and challenging daytime behavior reduces parental stress, increases parents' satisfaction with their own sleep, their child's sleep, and heightens their sense of control and ability to cope with their child's sleep (28). Caring for a child with a developmental disability can be extraordinarily stressful, and ensuring that caregivers are sufficiently rested (rather than awakened due to the child's disordered sleep) is paramount to optimal treatment of the child. Furthermore, implementation of successful strategies for helping their child sleep through the night can empower and motivate parents of children with

developmental disabilities to achieve successes in daytime domains.

Sleep and Quality of Life in Autism: Future Research Directions

Although the above studies support an association between disordered sleep and daytime functioning, the impact of interventions to improve sleep on daytime functioning and other aspects of quality of life in autism require further study in large controlled trials. These trials have the potential to substantially impact quality of life in individuals with autism although scientific rigor in conducting these investigations will be essential. Careful characterization of participants, with emphasis on cognitive status, coexisting psychiatric and neurological conditions, medications, and other factors that may influence sleep, will be needed to properly interpret results. In addition, studies should also include measures that document improvement in the individual's behavior as well as the stress level in parents or caregivers. Improvements in sleep should also be objectively documented. Actigraphy, which is minimally intrusive and cost-effective, appears promising as an outcome measure in such studies, especially in studies of insomnia, in which measurement of sleep by traditional PSG may be confounded by placement of sensors in tactilely sensitive individuals.

Conclusions

Sleep concerns are common in children and adults with autism, with a variety of behavioral, pharmacological, and other options for therapy. The cornerstone of treatment is to establish the etiology of the sleep concern, which is often multifactorial. Identifying and treating sleep disorders may result not only in more consolidated sleep, more rapid time to fall asleep, and avoidance of night wakings but also impact favorably on quality of life. Future research in the area of sleep, quality of life, and autism appears warranted.

Issues that need to be addressed by future research:

- To design interventional studies to treat sleep disorders in individuals with autism.
- To develop minimally intrusive, cost-effective measures of sleep in this population, including actigraphy.
- To determine whether improving sleep in autism impacts favorably on quality of life in individuals with autism and their families.

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25
Sleep and Quality of Life in Chronic Fatigue Syndrome

Eva Libman

Summary The fatigue in chronic fatigue syndrome (CFS) appears to be more severe, more functionally impairing, and less likely to be alleviated by rest than fatigue commonly experienced by healthy individuals. The words used by individuals with CFS to describe their fatigue are characterized by terms that deal with functional limitations, frustration, loss of control, permanence, depression, and pervasiveness—language that clearly reflects their diminished quality of life (QOL). With respect to etiology, CFS has been conceptualized among a spectrum of stress-related, functional disorders characterized by profound fatigue and, frequently, pain. In terms of sleep characteristics, individuals with CFS display the characteristic signs of poor overall sleep efficiency that is typically seen in persons with insomnia. They frequently experience nonrestorative sleep, and their daytime functioning is also seriously compromised. QOL scores reflect findings which show that symptoms of CFS significantly undermine many facets of these individuals' lives and significantly impair physical and social functioning as well as participation in activities of daily living. Physicians have little to offer their patients who have CFS. Friends and family, also unable to help, often tell people who have CFS to "just get on with your life," "pull yourself together," and "stop moping around." By dismissing and invalidating the lived experience of individuals with CFS, they contribute to an already poor QOL. Despite recent progress in understanding the biological mechanisms of the illness, more work needs to be done to find effective clinical treatments. Healthcare professionals and disability insurance carriers need to be informed that CFS is a real and disabling physical illness.

Keywords CFS · sleep disorder · impaired quality of life.

Learning objectives:

- Acknowledgment that chronic fatigue syndrome is a medical illness that results in severely impaired quality of life.
- Appreciation of the fact that the severity of fatigue in chronic fatigue syndrome is greater and more functionally impairing than fatigue commonly experienced by healthy individuals.
- Awareness that sleep disorder (e.g., sleep apnea/hypopnea syndrome), insomnia, and nonrestorative sleep are common in CFS.
- Understanding that while psychological adjustment in chronic fatigue syndrome is poorer than in healthy individuals, it is generally not different from that seen in other chronic illnesses.

What is the Nature of Fatigue in Chronic Fatigue Syndrome?

In healthy individuals, fatigue is a universally experienced phenomenon that is typically short-lived, caused by identifiable events, and successfully treated with rest. In chronic fatigue syndrome (CFS), as in other chronic diseases, fatigue is a complex construct that is difficult to define and adequately assess. It appears to be more severe, more functionally impairing, and less likely to be alleviated by rest than fatigue commonly experienced by healthy individuals (1).

As in all human behaviors, there are objective (physiological/behavioral) and subjective (cognitive/affective) aspects in the fatigue experience. A part of that experience is reflected in the language individuals with CFS use to describe what they feel: "My fatigue is disruptive, disabling, irritating, annoying. It is overwhelming. I am powerless. It is constant and continuous. It is discouraging, demoralizing and it is immense,

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touching all aspects of my life" (author's files). These are some of the descriptors used by individuals with CFS when asked, "What words would you use to describe your fatigue?" Such language is in contrast to that of healthy individuals who in response to the same question reported, "My fatigue is transient, occasional, neutral, normal. I feel unmotivated and sleepy" (author's files).

These descriptors were derived from a recent study in our laboratory (2) where I examined whether there is an identifiable pattern of descriptors related to the fatigue experience of individuals with CFS and how their fatigue descriptors differ from those of healthy individuals. Fatigue-related words and phrases listed by participants with and without CFS were grouped into 18 mutually exclusive content categories. We found that the words and phrases generated by persons with CFS were significantly more numerous and were represented in more content categories than were those of their healthy counterparts.

Figure 25.1 shows that responses of individuals with CFS predominated in six categories with negative overtones: limitation of functioning, frustration/anger/irritability/ annoyance, permanent/persistent, out of one's control, depressed/ sad/discouraged, and pervasiveness/touches all aspects of one's life (3). The percentage of individuals with CFS who reported words in each of these categories ranged from 15 to 54% compared to 0–15% for healthy controls. On the other hand, healthy participants were significantly more likely to have responses in the following four categories: temporary/ transient/restoring/variable, comfortable, sleepy, and amotivational. The percentage of healthy individuals reporting words in these categories ranged from 22 to 33% compared with only 2–10% for individuals with CFS.

Notably, the majority of individuals in both groups (56–60%) used descriptors such as "exhausted," "insufficient energy," "tired," and "lacking in vitality," terms that fell into the most popular category: energy depletion/physical weakness. This suggests that while fatigue has a common core experienced by everyone, the affective quality in those with CFS differs dramatically from that typically experienced by healthy individuals.

To summarize, individuals with CFS used more categories to describe their fatigue and more descriptors overall. Their responses were characterized by terms that dealt with limitation of functioning, frustration, loss of control, permanence, depression, and pervasiveness, words that clearly reflect their diminished quality of life (QOL).

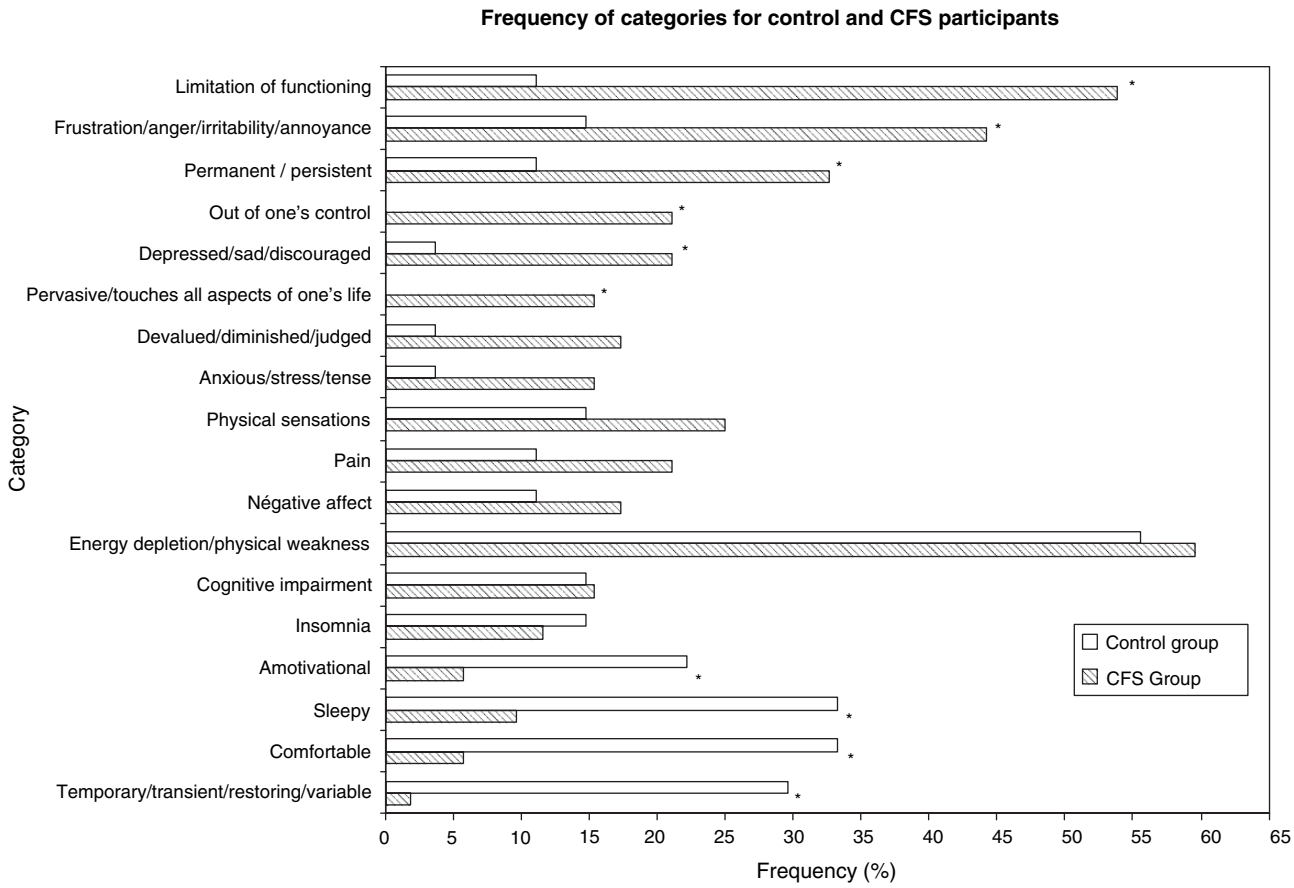

FIGURE 25.1. How language reflects fatigue in chronic fatigue syndrome?

Definition of CFS

CFS is a functional disorder characterized by debilitating daytime fatigue. Persons diagnosed with CFS are predominantly women between the ages of 30 and 40 (2, 4, 5). It has been estimated that among patients seeking primary medical care for any reason, CFS occurs in approximately 1 in 100 adults (6). The most widely used definition, internationally, specifies at least 6 months of persistent fatigue that substantially reduces the person's level of activity (7). In addition, four or more of the following symptoms must co-occur: impaired memory or concentration, sore throat, tender glands, aching or stiff muscles, multijoint pain, headache, nonrestorative sleep, and disproportionately intense and long-lasting fatigue after exertion. Many individuals with CFS also experience nausea, night sweats, dizziness, and intolerance to alcohol and have adverse reactions to pharmaceuticals that affect the central nervous system (8).

Recently, the International Chronic Fatigue Syndrome Study Group (9) identified ambiguities in the 1994 CFS case definition. They proposed that the core-defining features should be fatigue plus post-exertion malaise, sleep disturbance, and pain. In addition, it was recommended that at least two neurocognitive symptoms and at least one symptom from at least two of the autonomic, endocrine or immune dysfunction categories be included.

Should Primary Sleep Disorder be an Exclusionary Factor in the Diagnosis of CFS?

The traditionally accepted definition of CFS (4) as well as a more recent clarification (6) stipulates that the presence of a known primary sleep disorder, such as sleep apnea, precludes the diagnosis of CFS. Presumably, this is because it is believed that sleep disorder could account for the symptoms of CFS. Yet, abnormalities of sleep in patients with CFS have been widely reported (10–17). Excluding individuals with primary sleep disorders from samples with classic CFS symptomatology has been inconsistently applied. Also, individuals with CFS are not routinely sent for evalaution of sleep disorders, further confounding the CFS-sleep disorder diagnostic conundrum.

In a recent study evaluating the nature of CFS and the development of a treatment startegy for CFS patients, we documented the presence and nature of sleep disorders in individuals with this diagnosis. Here, in a comparative investigation of CFS, narcolepsy, and healthy control participants, we found that approximately 60% of the sample of individuals with CFS had a diagnosable primary sleep disorder such as sleep apnea/hypopnea syndrome and that almost everyone with CFS complained of nonrestorative sleep and/or insomnia characterized by difficulty initiating or maintaining sleep (18). Our interpretation of this finding, initially, was that sleep disorder constituted an important symptom cluster in CFS. In the hope that treating the sleep disorder might ameliorate the disabling fatigue in individuals who suffered from both, we selected for treatment those individuals in our sample who conformed to the diagnosis of CFS but who also had sleep apnea/hypopnea syndrome confirmed through overnight polysomnography.

First, we compared two groups of participants: those with CFS plus sleep apnea/hypopnea syndrome and those with CFS who had no diagnosable sleep apnea/hypopnea. Participants were evaluated on a broad range of sleep-related, daytime functioning, psychological adjustment, and QOL variables. We found no pre-treatment differences on any of these variables. Next, participants with CFS plus sleep apnea were offered a 3-month treatment program with continuous positive airway pressure (CPAP). At the end of this 3-month period, participants who had complied with CPAP treament were compared with those who did not comply. The two groups were found not to differ on fatigue-related variables. This suggests that CPAP treated the sleep apnea symptoms but did not improve the core fatigue aspect of CFS.

As (i) individuals with CFS who did and those who did not have sleep apnea failed to differ on fatigue-related variables and (ii) as those with apnea who were compliant with CPAP treatment did not differ from noncomplient participants, primary sleep disorder, such as sleep apnea, should be seen as a co-morbidity in CFS, not as a diagnostic exclusion criterion.

The Experience of CFS

CFS has a chronic course (19). Longitudinal studies of varying duration have shown that although 17–64% of patients improve, less than 10% fully recover, and another 10–20% deteriorate (8, 20, 21). There is no specific etiology or pathophysiology (22), no single diagnostic test (6, 23), and no consistently effective treatment (24). The current procedure for diagnosing CFS is one of elimination when no medical, psychiatric, or drug-related conditions could be found to explain the prolonged fatigue.

Patients often report excellent pre-illness physical fitness and energy (25) with an abrupt onset of fatigue. The impairment to their functioning is pervasive, adversely affecting both their social (26) and working (27) lives. Despite growing evidence that abnormal, objective biologic processes are present (28), many believe that CFS is primarily a psychiatric disorder because no physiological marker has been identified (29). Patients with CFS are often presented with the medical opinion that "it's all in your head," that their problem is "only depression" or perhaps a somatoform disorder (30, 31). Not only do they suffer from the symptoms of the illness, but they also often suffer from rejection and stigmatization by their family, friends, and physicians (32).

Etiology of CFS

CFS has been conceptualized on a spectrum of stress-related, functional disorders characterized by profound fatigue and, frequently, pain (33). The dominant physiological activation pattern associated with exposure to stressful circumstances largely involves the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system (SNS). The neuroendocrine components most often assessed include corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), cortisol, vasopressin, and the sympatho-adrenomedullary catecholamines (norepinephrine and epinephrine). When these stress hormones and others are turned on, metabolism is predominantly in the catabolic (breakdown or energy use) mode. This activation pattern is adaptive when it occurs in a periodic manner and dissipates within a short time. However, intense, frequent, or continuous activation can lead to chronic up-regulation of the stress emotional arousal and physiological activation mechanisms with negative health consequences (34, 35). Sleep patterns are normally synchronized with neuroendocrine function. For example, the early phase of nighttime sleep normatively coincides with suppressed HPA axis activity. This is characterized by nadirs in ACTH and cortisol hormones but peaks in growth hormone (GH). During late phase sleep, adrenocortical activity escalates to reach maximal cortisol output shortly after awakening (36).

It has been postulated that enduring sympathetic hyperactivity (i.e., at rest) might represent a neural functional correlate of fatigue (37). Excess stress arousal/activation, in addition to interfering with adequate sleep and disturbing the sleep and waking rhythms, also affects immune function. Stress neuroendocrine hormones, the SNS, sleep, and the immune system are highly interactive. Together, they make up a host defense system that is complex and represents multiple points of potential deregulation (38, 39).

Although explaining CFS etiology within this framework is intriguing, it does not explain why active energetic women between 30 and 40 are over represented in CFS samples. Nor does it have direct implications for treatment.

Measurement of Nighttime Sleep Quality and its Daytime Consequences

As with other aspects of human behavior, sleep can be evaluated according to three major dimensions: physiological, behavioral, and cognitive affective. The nature of sleep and its quality is evaluated in two main ways: by objective measurement (polysomnography and actigraphy) and by self-report. Each modality has strengths and weaknesses in providing an overall picture and objective findings, and reported experiences are often inconsistently related. For example, nonrestorative sleep is among the most commonly reported of the CFS-defining symptoms; this is characteristic of 88–95% of cases identified in population studies (4) and 70–89% of patients in published clinic-based research (7, 40). In addition, studies have consistently reported low sleep efficiency, insomnia, and variable amounts of previously undiagnosed primary sleep disorders (33). Nevertheless, none of these studies has identified characteristic changes in sleep architecture or specific polysomnographic abnormalities among individuals with CFS.

Even within a particular measurement modality, there may be ambiguities. For example, excessive daytime sleepiness and fatigue, highly prevalent in both community and patient CFS populations (41–45), have overlapping features that can lead to imprecise diagnostic formulations and subsequent sub-optimal intervention and management decisions. There is heterogeneity in the definitions of both sleepiness and fatigue (46) as well as in the assessment tools for these constructs (47). The problem is compounded by the counter-intuitive manner in which the constructs sometimes operate. For example, it has long been known that fatigue, rather than sleepiness, is correlated with the experience of insomnia (48). Even patients with obstructive sleep apnea complain of fatigue, tiredness, and lack of energy at least as often as they complain of the more expected sleepiness (49). In addition, scores on self-report measures of daytime sleepiness often correlate only minimally with either other self-report measures (50) or with direct, objective measurement of sleepiness (51).

In experimental studies, the constructs of fatigue and sleepiness are both separable and additive in their negative effects on performance (52). In medical practice, sleepiness and fatigue are often equated, leading to inadequate diagnosis and treatment (53). For example, the specific daytime sleepiness features of sleep apnea are often not recognized, leading to under-referral for further diagnostic evaluation, particularly in the case of women (54). Daytime fatigue (the hallmark CFS symptom), as distinct from sleepiness, is a concomitant of many physical (e.g., multiple sclerosis, systemic lupus erythematosus, and Parkinson's disease) and psychological (e.g., depression) disorders. A simple, reliable tool to distinguish sleepiness from fatigue made available to healthcare professionals would assist in the match between symptom identification and appropriate treatment (4).

Because available self-report measures of fatigue and sleepiness are confounded and because the distinction has important consequences for diagnosis, we set out to (i) operationalize the terms "sleepiness" and "fatigue" more precisely, (ii) enhance the distinction between them, and (iii) use items from existing measures to prepare empirically based sleepiness and fatigue scales to assess the constructs more accurately (55). Specifically, we devised and cross-validated "pure" scales of sleepiness and fatigue, where the items were empirically derived from existing sleepiness and fatigue measures. We also evaluated scores on these newly developed scales in relation to a range of psychological adjustment,

sleep, and perceived physical health instruments to develop distinctive sleepiness and fatigue profiles.

Both the sleepiness and fatigue constructs may be more complex than represented by these derived empirical scales, and the correlates of "pure" sleepiness and "pure" fatigue need further investigation. Nevertheless, we believe that the constructs measured by the Empirical Sleepiness and Fatigue Scales (55) represent those aspects that are most separable and refer to a situational tendency to doze during specific daytime activities and lack of energy.

Sleep and its Disorders in CFS

In the samples of individuals with CFS we have been studying (56), we found an approximately 60% incidence of primary sleep disorder, mainly sleep apnea/hypopnea syndrome. A small percentage had periodic limb movement disorder and/or restless leg syndrome. Considering the extent of the medically based sleep-related problems, it is notable that prior to participating in our studies, neither the CFS patients nor their physicians had been aware that they had these disorders.

More than 85% of the CFS sample self-reported insomnia relating primarily to difficulty initiating or maintaining sleep. In addition, almost 90% of individuals with CFS stated that they woke up feeling unrefreshed, resulting in only 0.5% of the CFS sample indicating no insomnia problem. The high rate of insomnia (i.e., disorder in initiating and maintaining sleep, including nonrestorative sleep—cf. (57,58)—is consistent with findings in the literature and attests to the debilitating nature of the sleep disruption experienced in this population (59,60).

Our CFS samples, on the whole, had a wide variety of sleep-related complaints. Besides waking up feeling unrefreshed and having significantly prolonged sleep onset latencies, individuals with CFS woke up frequently during the night and spent a large amount of time in bed at night not sleeping. They also rated their sleep quality as poor. In essence, the CFS sample displayed the characteristic signs of poor overall sleep efficiency seen in persons complaining of insomnia.

How does SLEEP in CFS Compare with Sleep in Other Clinical and Healthy Groups?

As part of a recently completed investigation, we compared quantitative and qualitative aspects of sleep in three groups: CFS, sleep apnea, and healthy controls (48). The pattern of scores in Table 25.1 illustrates the findings.

Clearly, healthy control participants had the highest sleep efficiency, the fewest reported insomnia episodes, and the best sleep quality compared with the two clinical groups. They also had the least psychological maladjustment. Nighttime sleep and daytime functioning were considerably impaired in individuals with CFS relative to their healthy counterparts. A similar pattern can be seen on psychological adjustment. What is striking is that in most cases, individuals with sleep apnea do not differ from individuals with CFS on most of these variables.

Interestingly, we found a similar pattern in a previous study where we compared a sample of individuals with CFS with a sample of participants with narcolepsy (56). Again, the incidence of sleep disorder in the CFS sample was substantially greater than that in the control sample. However, on many sleep-related aspects, individuals with CFS were not different from individuals with the physiologically based sleep disorder of narcolepsy. In fact, in some ways, it was the CFS sample that had a higher incidence of sleep disruption than the narcolepsy sample. It was not surprising to find that individuals with CFS were more fatigued during the day than the other two groups on most measures used in this study—this, after all, is the hallmark symptom in the diagnosis of CFS. Their scores on daytime sleepiness were also significantly elevated compared to the control group although, for the most part, the scores of the narcolepsy sample indicated somewhat greater sleepiness. Overall, the results show that daytime functioning in the CFS sample was seriously compromised.

Psychological adjustment in the CFS sample was significantly poorer than that in the control sample. There were no significant differences, however, between the two clinical groups, CFS, and narcolepsy, on any of the psychological adjustment variables evaluated. Both when compared to the control sample as well as when compared to normative data, scores of the two clinical samples showed slightly elevated anxiety and somatization as well as generally poorer psychological adjustment. Scores of the two clinical groups were also different from those of healthy controls on depression and neuroticism. However, despite their experience of debilitating fatigue, people with CFS did not score within the clinically maladjusted range on measures of depression. Of course, many medical patients tend to have poorer psychological adjustment scores than healthy controls (61). Despite such findings, individuals with narcolepsy, sleep apnea, and other medical illnesses are not typically told that their problem is "all in their head" or psychosomatic, as are people with CFS (62).

Quality of Life in CFS

The debilitating fatigue and other symptoms of CFS, as well as disrupted and poor quality sleep, can be assumed to undermine QOL and scores on standardized measures of this construct that support this assumption. The SF-36 Health Survey (SF-36) (63) is a measure used frequently in clinical studies. It was constructed to survey health status in clinical practice and research and assesses eight health domains:

TABLE 25.1. Sleep in CFS sleep apnea and healthy controls.

Controls	CFS	Apnea	Controls
Quantitative sleep variables			
Sleep efficiency (TST/TIB × 100)	0.76	0.74	0.88
Insomnia frequency (days/week)	3	3	0.3
Qualitative sleep variables			
Sleep quality (rated 1–10)	4	4	8
Refreshed in morning (rated 1–10)	3	5	8
Quantitative daytime sleep-related variables			
Empirical Fatigue Scale*	16	11	7
Empirical Sleepiness Scale*	7	7	5
Naps/week	4	2	
Average duration of activity periods (minutes: Actigraphy)	99	n/a	205
Qualitative daytime variables			
Feeling sleepy (rated 1–10)	6	5	3
Difficulty concentrating (rated 1–10)	7	5	3
Tired during the day (10 = very tired)	8	6	3
Psychological variables			
Anxiety[†]	44	41	36
Depression[‡]	5	3	2
SF-36			
Physical functioning	45	74	87
Role physical	3	55	85
Body pain	42	66	85
General health	38	60	78
Vitality	24	7	64
Social functioning	38	73	88
Role emotional	54	72	80
Mental health	61	69	72
Life Satisfaction Scale	17	n/a	29

TST, total sleep time; TIB, time in bed.
*Fatigue scores, 3–18; sleepiness scores, 0–18 (55).
[y] State-Trait Anxiety Inventory-Form Y2 (80).
[z] Beck Depression Inventory (BDI-II): Primary Care Subscale (PC) (81).

(i) limitations in physical activities because of health problems, (ii) limitations in social activities because of physical or emotional problems, (iii) limitations in usual role activities because of physical health problems, (iv) bodily pain, (v) general mental health (psychological distress and well-being), (vi) limitations in usual role activities because of emotional problems, (vii) vitality (energy and fatigue), and (viii) general health perceptions. Ware et al. (62) report reliability data from studies carried out on both patient and nonpatient samples. Results show that the SF-36 is reliable and has demonstrable validity in that the subscales were found to correlate with ability to work, utilization of health services, as well as with scores on other mental health, and QOL measures. Low scores on all subscales indicate disability due to illness while high scores indicate better functioning due to relatively good health.

The Satisfaction with Life Scale is another relatively commonly used measure of QOL. Developed by Diener et al. (64), this scale evaluates the cognitive, judgmental aspects of subjective well-being. It consists of five items that use a 7-point Likert scale. Higher scores indicate greater life satisfaction. Data reported by the scale's authors as well as in later investigations (65) indicate good psychometric properties: the measure has been shown to be internally consistent, and scores were found to be highly correlated with other measures of life satisfaction. What makes this measure different from many others is that it measures the presence of good adjustment rather than adequacy of functioning or the absence of difficulties.

Table 25.1 illustrates the comparative pattern of scores on QOL for the CFS, sleep apnea, and healthy control samples (higher scores indicate better functioning) in our study (66). Results show that SF-36 scores of the CFS sample were not only significantly poorer than those of the control group, these were also below the normative range on most subscales. It is of interest to note that both in our previous comparative study of individuals with CFS and with narcolepsy (16), and in our current study comparing CFS, sleep apnea, and control groups, all clinical groups had worse QOL scores than healthy controls. However, participants with CFS reported even poorer health functioning than those in the other clinical groups on most subscales. An important difference between the three clinical groups is that for people with narcolepsy or sleep apnea, their principal complaint, sleepiness, is treatable either with medication or CPAP, presumably mitigating the impact of their condition on their general functioning and perceived QOL. This is not the case for CFS.

What About Treatment for CFS?

The data show that symptoms of CFS significantly undermine many facets of these individuals' lives and impair life satisfaction as well as physical and social functioning and participation in daily activities. Clearly, effective treatments for CFS are urgently needed.

A comprehensive review that covers treatment procedures for CFS to date is available on the Internet (67). One area of extensive evaluation has been the role of physical exercise and conditioning/deconditioning in individuals with CFS. As an example, the consequences of excessive resting that occurs among people with CFS was reflected in a recent study by Kop et al. (68). This study involved a 5-day program of ambulatory monitoring of physical activity and symptoms. Results indicate that pain and fatigue were associated with reduced ambulatory activity subsequent to physical activity, but activity levels were not predictive of s1ubsequent symptoms. This suggests that physical activities may not necessarily lead to an increase in symptoms. Consistent with this finding, another study evaluated the effects of graded exercise (69). This study demonstrated that graded exercise was associated with improvement in a measure of physical work capacity as well as in a measure of depression and performance on a cognitive task (modified color-naming Stroop test).

As noted earlier, our team investigated the effects of CPAP treatment for individuals who had both CFS and sleep apnea/hypopnea on the core symptoms of CFS. A preliminary analysis of these data suggests that those who complied with CPAP treatment improved in terms of feeling more refreshed, less sleepy, and taking fewer naps during the daytime. However, their fatigue did not appear to be affected by this treatment. Our next step was to offer a 10-week cognitive behavioral (CBT) program targeting insomnia specifically, with some lifestyle components included (2), to all participants in our sample who had CFS, including those who were treated with CPAP. Preliminary analysis of these findings suggests that, not surprisingly, sleep efficiency improved, primarily because of the directives of the program, which includes restriction of time spent in bed. More interestingly, participants appeared to improve on an empirical measure of fatigue although not on perceived fatigue. There was some indication that anxiety level was somewhat diminished after CBT, but generally, there was no improvement on measures of perceived QOL.

What is the Current Status of CFS in the Eye of the Public?

Very recently (November 2006), The United States Centers for Disease Control and Prevention (CDC) identified CFS as a "disease that has been shrouded in. . . mystery and controversy," but one that is "a real illness (requiring) real medical care" (70). It is notable that the fatigue component in other physical illnesses may have equally mysterious aspects. For example, in systemic lupus erythematosus, it has been shown that there is either little relationship between disease activity and fatigue (71) or a variable association depending on dimension of fatigue examined and differential role of disease-related, psychosocial, and behavioral factors (72). Even more striking is the example of multiple sclerosis, a disease of the central nervous system, not involving other organ systems, as in the case of lupus. In this disorder, the patient may report a feeling of overwhelming exhaustion. This can occur in the absence of focal neurologic signs (73). It would appear that, once triggered, fatigue may follow its own independent course.

The CDC media advisory introduces a "CFS toolkit" for healthcare professionals. This contains information about the diagnostic process, treatment management, and physician–patient relationship. In addition, it publicizes a resource website for patients and physicians (http://www.cdc.gov/cfs/ and http://www.cdc.gov/about/news/2006_11/cfs.htm). It alludes to the over 4000 published studies that show underlying biological abnormalities in this illness (when this chapter was prepared—November 2006—a list of recent CDC research articles was available at www.futuremedicine.com/toc/pgs/7/3).

The CDC campaign is critically important in addressing the lack of credibility surrounding the CFS diagnosis, in pointing to evidence of its biological underpinnings, and in describing the associated level of disability as equal to that of individuals with late-stage AIDS, patients undergoing chemotherapy, and persons with multiple sclerosis. It points out that there is more work to be done in understanding the biological mechanisms of the illness, finding effective clinical treatments, and convincing disability insurance carriers that this is a real and disabling illness.

Implications for Future Research

Taken together with those of the CFS treatment literature, the pattern of our own findings suggests that there may be small, incremental improvement in symptoms as treatments target various specific symptom clusters. This implies that future studies need to link what we are learning about relieving symptoms and improving function in CFS with other behavioral and pharmacological strategies (14, 59) that have shown some efficacy. There is also a need to design multicomponent intervention packages that treat fatigue, disrupted sleep, and other associated symptoms. The outcomes of these interventions need to be evaluated long-term as well as short-term. An individual's perception of overall disability from an illness that she has had for years—and the associated poor quality of her life—may take longer to improve than the timeframe of the usual intervention outcome research study.

With respect to arriving at a clearer understanding of the pathophysiology of CFS, some of the most robust findings have been related to the HPA axis, with much evidence supporting mild HPA axis hypoactivity (74–76). The key question is whether this alteration is a cause or a consequence of longstanding CFS (35).

For example, an analog study showed that a subset of healthy regular exercisers, when deprived of exercise for 1 week, developed pain and fatigue. These individuals also had lower HPA axis function at baseline, suggesting that this type of HPA alteration may render individuals vulnerable to developing fatigue (77). On the other hand, the finding that HPA axis changes is more pronounced the longer CFS has been present supports the consequence hypothesis (75). Indeed, it may be that the slightly elevated anxiety and depression observed in our study may also be a consequence of having lived with a chronic disease for a long period of time. Two prospective studies of groups at high risk for developing CFS (post-infectious mononucleosis and post-surgery) found that when fatigue developed 6 months later, it was not associated with HPA axis changes (78, 79).

It is only recently that researchers have begun studying early-phase CFS and designing prospective studies. Clearly, more such research is necessary, both to explore the pathogenesis of CFS, to establish the role of disordered and disrupted sleep in the pathophysiology of CFS and to provide the basis for more effective treatments that may lead to an enhanced QOL.

Issues that need to be addressed by future research:

- Clarification of the pathophysiology of CFS requires study of the early phase of CFS.
- Prospective designs must be used to identify risk characteristics for CFS.
- Multi-component treatment plans for CFS need to be designed and evaluated.

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26
Sleep and Quality of Life in Anxiety Disorders

Matthew R. Ebben and Arthur J. Spielman

Summary This chapter will discuss the relationship between a select group of anxiety disorders [nocturnal panic/panic disorder (PD), posttraumatic stress disorder (PTSD), and generalized anxiety disorder (GAD)] and sleep disturbance. Of particular interest will be the outcome measure quality of life (QOL). QOL scales are well suited to investigate treatment outcome for some sleep disorders because often subjective measures of sleep are not sensitive enough to uncover disturbance. Therefore, global measures such as QOL may be more suitable. In both PTSD and GAD, studies that show the impact of sleep disorder treatment on improving anxiety symptoms will be discussed. Hyperarousal is a major underlying theme for various sleep and anxiety disorders; therefore, it will also be addressed.

Keywords Quality of life · nocturnal panic disorder · posttraumatic stress disorder · generalized anxiety disorder · insomnia · sleep disorders · anxiety disorders · hyperarousal.

Learning objectives:

- Anxiety disorders are frequently associated with sleep disruption.
- Quality of life is impaired in patients with anxiety and sleep disorders.
- Treatment of sleep disorders alone in patients with some anxiety disorders has been shown to improve both sleep and anxiety symptoms.

Introduction

It is a common occurrence, when seeing patients for sleep disorders clinically, to notice symptoms of anxiety, such as pressured speech or a jumpy disposition. Therefore, it is not surprising that the relationship between anxiety and sleep has been empirically investigated since the late 1960s. Some of the initial studies investigating the relationship between anxiety and sleep disturbance used questionnaires without accompanying objective measures. These questionnaire studies regularly demonstrated a relationship between anxiety and subjective reports of sleep disturbance (1, 2). However, when the relationship between anxiety and sleep disturbance was investigated using both subjective and objective measures (e.g., EEG), the results have been less consistent. Many of the first studies in this area sought to either induce anxiety or measure situational anxiety in subjects using various techniques (3–6). Overall, these studies showed a moderate relationship between anxiety and sleep disturbance.

However, other studies investigating chronic anxiety in poor sleepers did not find a consistent relationship between poor sleep and anxiety level (7–9). One of the early well-controlled studies in which subjects were selected on the basis of high scores on measures of chronic anxiety, as well as parceling out the confounding influence of depression, found a statistically significant relationship between anxiety and various sleep measures including total sleep time (TST), latency to rapid eye movement (REM) sleep, and amount of delta sleep (10). Moreover, when partial correlations were performed (controlling for depression), significant relationships were found between level of anxiety and number of awakenings (positive), sleep latency (positive), REM sleep percentage (negative), and percent of delta- or slow-wave sleep (negative).

More recently, Benca (11) performed a meta-analysis on a large number of studies (with a combined $N = 7151$) investigating the relationship between psychiatric illness and sleep disruption. In this study, it was found that anxiety level was associated with a reduction in TST, and sleep efficiency (the ratio of TST over time in bed), as well as an increase in sleep latency. When addressing the topic of insomnia, the question

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that invariably arises is whether insomnia is a symptom of another psychiatric illness, or whether, as a result of the development of insomnia, patients begin to display symptoms of psychiatric disorders. In one study, Ohayon and Roth (12) found that anxiety appeared before insomnia in 43% of cases and that insomnia co-occurred with anxiety in 39% of cases. In his 1997 meta-analysis investigating this issue, he came to the conclusion that insomnia is mostly an associated symptom of another psychiatric disorder (13). This conclusion has added significance given the relatively high estimated lifetime prevalence rate for anxiety disorders in the general population, which ranges from 15 to 25% (14). Moreover, 44% of insomniacs report a history of generalized anxiety (12), with an estimated prevalence of insomnia ranging from 6 to 33% of the US population depending on the precision of the definition being used (15). From these numbers, it appears that anxiety plays a major role in a number of patients with insomnia.

Anxiety is a term that includes a somewhat heterogeneous group of disorders with different epidemiology and symptomology. This chapter will discuss the relationship of various sleep disorders on a selection of disorders typically considered to be under the umbrella of anxiety disorders. In the introduction, an overview was given on the general body of research between anxiety level and sleep disturbance, and in the following sections, the relationship between specific anxiety disorders and their relationship with sleep will be explored. In addition, the outcome measure, quality of life (QOL), will be discussed in terms of its interaction with sleep and anxiety disorders, as well as the role for treatment of sleep disorders in persons with anxiety disorders and its impact on QOL.

Quality of Life

QOL is a concept with many meanings, and to measure it, a wide variety of QOL scales made up of vastly different components have been developed. More recently, a few valid and reliable instruments have been developed to measure QOL, and these scales have increased in popularity. These scales include (but are not limited to) the Medical Outcomes Study 36-item Short-Form Health Survey, Sheehan Disability Scale, Quality of Life Enjoyment and Satisfaction Questionnaire, and the Illness Intrusiveness Ratings Scale (16–19). In addition to specific QOL instruments, studies that investigate QOL based on large-scale investigations, such as the Epidemiological Catchment Area Study and the National Co-morbidity Survey, which used indicators such as physical and emotional well-being, financial reliance, and psychosocial functioning, will also be reviewed in this chapter. Used together, these indicators are thought to represent important measures of QOL.

Nocturnal Panic Disorder

A panic attack is a discrete period of intense emotion characterized by symptoms such as heart palpitations, air hunger, sweating, stomach discomfort, and derealization or depersonalization. Typically, these symptoms peak within 10 min and are accompanied by an intense fear of dying or going crazy. According to the DSM-IV (20), to be considered panic disorder (PD), these attacks must be followed by at least 1 month of worry or concern regarding another panic attack. Many patients who report daytime panic attacks also report nocturnal panic attacks, and survey studies have reported that anywhere from 44 to 71% of patients with daytime panic attacks have had at least one nighttime panic attack (21). The prevalence of nocturnal panic in the general population is estimated to be between 3 and 5% (22, 23). In general, patients with nocturnal panic attack report more daytime panic attacks than patients who suffer only from daytime panic attacks (24). This appears to suggest that nocturnal panic is a more severe form of PD. However, this does not seem to be the case. In a 2002 study, Craske et al. (25) investigated the disorder severity between patients suffering from only daytime panic attacks and those suffering from both nocturnal and daytime panic attacks in terms of the co-morbidity, interpersonal functioning, and sleep disturbance and found no significant difference between these two groups on these measures. In fact, they found that patients suffering from nocturnal panic attacks had less agoraphobia than patients with only daytime panic attacks. They speculated that patients with nocturnal panic attacks may be less likely to associate attacks with situational factors because many of the attacks occur out of sleep.

Nocturnal panic typically occurs within 3 h after sleep onset and is most often present in the transition from stage 2 to stage 3 sleep (21, 26, 27). This differentiates nocturnal panic from other panasomnias with similar behavioral manifestations, such as night terrors that typically occur out of stage 3–4 sleep (28) or nightmares that most often occur from REM sleep (29). Nocturnal panic can also be differentiated from night terrors because night terrors often involve blood-curdling screams accompanied by a look of intense fear; however, frequently once the event has subsided, the individual goes back to sleep and very often has no recollection of the episode upon awakening in the morning. On the other hand, nighttime panic attacks are rarely associated with screaming and frequently leave a lasting impression on the memory of the person suffering from the attack. Alternatively, nightmares characteristically occur in the last half of the night and are often associated with mentation that tends to have a strong visual component. Nighttime panic attacks typically occur without an obvious trigger, such as a dream (21, 26, 27). Interestingly, in Hauri's 1989 (26) investigation of sleep architecture in patients with spontaneous nocturnal panic attacks, he found that some of the patients he studied had eye movements in stage 2 sleep, short periods of chin atonia, numerous short muscle twitches, and increases in the

EEG frequency up to 21 s before awakening from panic attacks. This suggests that panic attacks occur during sleep and wake the patient, as opposed to a fright occurring after the patient is awake.

Individuals with PD also have a high rate of insomnia. In Ohayon and Roth's (12) recent review of the association between psychiatric disorders and insomnia, they found that approximately 61% of insomniacs had a history of PD: this prevalence rate was second only to major depressive disorder (MDD) (which was found in 65% of insomniacs) among past psychiatric diagnoses. It is likely that hyperarousal is an underlying factor affecting both panic attacks and difficulty sleeping. Hyperarousal will be discussed in more detail in the section on generalized anxiety disorder (GAD).

PD has also been associated with respiratory abnormalities. One of the most consistent respiratory irregularities in PD is hypersensitivity to carbon dioxide (30–34). Klein's suffocation false alarm theory (35), based on the finding that individuals with PD are hypersensitive to CO_2, hypothesizes that patients with PD have an abnormally low CO_2 set point; consequently, once the set point threshold has been reached, hyperventilation ensues. Increased sighing (36, 37) and shorter breath-holding ability (38) in PD patients are thought to bolster this theory. Breathing irregularities in PD have also been found to extend to the sleep period. Stein et al. (39) found an increased number of microapneas (apneas that fall short of the 10-s criteria) and increased irregularity in tidal volume in REM sleep during periods without panic attacks in patients with a history of PD when compared with healthy controls.

Quality of Life in Panic Disorder

The relationship between QOL and PD has been investigated more than that of other anxiety disorders. However, the relationship between nocturnal panic and QOL has not been specifically investigated. Therefore, this section will primarily describe what is known about PD in general and its effects upon QOL.

An important distinction that is often made in PD is between panic attacks with agoraphobia and without agoraphobia. This distinction may be particularly important because of the obvious impact fear of leaving the home has upon an individual's social and personal life, thus greatly affecting QOL. This may be why QOL in PD with agoraphobia was one of the first anxiety disorders to be investigated in terms of QOL. The first large-scale investigation was the Epidemiologic Catchment Area Study (40). This study found that PD sufferers had significantly lower ratings on measures of physical and emotional health and were more likely to be receiving welfare or disability payments than did individuals without a psychiatric disorder. When compared with other anxiety disorders such as obsessive-compulsive disorder and social anxiety, PD showed similar impairment (41).

Depression has long been used as a benchmark for comparison of other psychiatric disorders for QOL. This is likely due to the large-scale Medical Outcomes Study (42) which found that the effects of depression were similar to those of diabetes, arthritis, and gastrointestinal disorders on QOL measures. The comparison between PD and MDD has yielded inconsistent results. An early study by Markowitz (43) found that PD and MDD showed similar rates of impairment. However, Sherbourne (44) found that PD had little impact on general health. More recently, Candilis (45) found that not only did PD and MDD have similar rates of impairment, physical role function in patients with PD was worse than in patients with either hypertension or myocardial infarction. In this study, there was also evidence of lower social functioning in PD compared with hypertension, type II diabetes, congestive heart failure, and myocardial infarction.

In an impressive study, Hollifield (46) sought to identify variables that affect QOL in PD sufferers and found several variables that accounted for anywhere between 48 and 77% of the variance. These included psychiatric comorbidity, neuroticism, age, education level, and an interaction between PD diagnosis and age. Comorbid depression, chest pain, worry, and quality of social support have also been found to be predictors of QOL in PD (47). This group also found that patients with high rates of panic attacks had lower QOL than do patients with infrequent panic attacks. However, even individuals who do not meet the full criteria for PD, but suffer from panic attacks, have been found to have decreases in both physical and emotional health (40). Interestingly, it appears that even more important to QOL than the frequency of panic attacks is anticipatory anxiety and avoidance (48,49). Telch (49) found that phobic avoidance was the best predictor of QOL at baseline, and anxiety was the strongest predictor of QOL after treatment. This finding has been confirmed in a more recent study (48). It is possible that even infrequent panic attacks increase avoidance and anxiety because of their unpredictable nature. Essentially infrequent panic attacks reinforce anxiety and phobic avoidance on a variable ratio conditioning schedule, which is known to produce long-lasting conditioning effects.

QOL scales are frequently used to measure treatment response in PD. Various medications have been shown to improve scores on QOL measures in PD. These include alprazolam (50), clonazepam (51), fluoxetine (52), fluvoxamine (53,54), nefazodone (55), paroxetine (56), and sertraline (57). In addition, psychotherapy such as cognitive-behavioral treatment and cognitive-behavioral group therapy has also been shown to improve QOL in PD (48, 49). Exposure therapy has also been found to be effective in improving QOL in these patients (58). However, one study has questioned the effectiveness of talk therapy in improving QOL in PD (59). Nevertheless, in general it appears that talk therapies are effective in improving QOL in PD and may be indicated particularly in cases in which drug therapies prove ineffective (48).

Posttraumatic Stress Disorder

According to the DSM-IV (20), posttraumatic stress disorder (PTSD) is characterized by a traumatic event involving witnessed or threatened death or serious injury to one's self or others. This experience is accompanied by an emotional response involving fear, helplessness, or horror. Following the traumatic event, the individual re-experiences aspects of the event through either daytime or nighttime mentation. Often these flashbacks can seem so real that the person experiencing them feels that the traumatic event is actually reoccurring. Individuals with PTSD often avoid stimuli associated with the traumatic event and can have a numbing of responsiveness (such as a restricted range of affect or a feeling of detachment from others).

Sleep disturbance tends to be one of the most common symptoms after a traumatic event. In fact, after the Hanshin earthquake in Japan, more than half of the survivors reported sleep disturbances 3 weeks later, and almost half continued to have sleep disturbances 8 weeks after the earthquake (60). A very high percentage of prison camp as well as holocaust survivors reported difficulties with both sleep quality and disturbing nightmares after their internment (61, 62). In addition, a large study of Vietnam veterans found that even veterans who did not meet the full criteria for PTSD had elevated levels of sleep disturbance compared to civilians; however, veterans with PTSD had a higher proportion of sleep disturbance than either the non-PTSD veteran or civilian groups (63). The majority of individuals who experience traumatic events recover their sleep quality with time (64); however, a subset of trauma victims develop PTSD, which frequently involves persistent deficits in sleep quality. It is thought that persons with PTSD become hypervigilant to protect against external threats, and this hyperarousal prevents restful sleep (65).

Studies on the prevalence of sleep disturbance in PTSD have found that 70–87% of persons with PTSD also have sleep difficulties (66–69). There appears to be a relationship between severity of PTSD and sleep quality. In other words, sleep disturbance tends to increase in frequency as the severity of PTSD increases. In a 2004 study, Germain et al. (70) found a statistically significant relationship between moderate and severe PTSD and subjective sleep quality, sleep duration, and daytime dysfunction. Interestingly, this group found only a minimal relationship between age, gender, and psychiatric comorbidity on sleep quality and PTSD. This finding appears to be in contrast to other studies that have documented a relationship between these variables and PTSD (69, 71, 72). Sleep also seems to have prognostic value in PTSD. Koren et al. (73) found that sleep disturbance as early as 1 month after trauma predicted PTSD 1 year later.

In terms of objective measures of sleep architecture in PTSD, the results in many respects have been mixed. Some studies investigating sleep efficiency have found a decrease in sleep efficiency (74, 75); however, other studies have found no decrease (76–78). Studies investigating REM sleep variables have also largely been mixed. Some investigators have found more REM sleep in PTSD (77, 79), but other studies have not confirmed this finding (75, 80, 81). REM latency findings have also been contradictory, with some studies showing shorter REM latencies (82) and others showing longer latencies (83, 84). One consistent REM finding is an increase in REM density in PTSD (75, 79, 85); moreover, it appears that REM density is positively correlated with the severity of PTSD (74). Interestingly, Ohayon and Shapiro (69) found that individuals with PTSD had an elevated proportion of violent sleep behaviors, sleep paralyses, sleep talking, and hypnagogic and hypnopompic hallucinations. Another consistent finding in PTSD is an increased arousal threshold from delta sleep (86). It appears that individuals with PTSD are more difficult to awaken out of deep sleep than normal controls. Lavie et al. (86) has speculated that this increase in arousal threshold relates to either an active blocking mechanism that blocks out trauma-inducing external stimuli or that those patients with PSTD become so engrossed in dream-like mentation in delta sleep that it becomes more difficult to wake them.

Patients with PTSD appear to have a higher prevalence of both movement disorders in sleep and sleep-disordered breathing (SDB). A study by Lavie in the 1970s showed that war veterans with PTSD (or PTSD-like symptoms) have a higher rate of body movements during sleep (81). In addition, several studies have shown that patients with PTSD have an elevated amount of periodic limb movements during sleep as compared with normal controls (74, 76, 79, 87). In terms of SDB, Krakow et al. (65) recently performed a study on trauma victims (most of whom suffered from PTSD) and found that 90% of these individuals suffered from SDB (as measured by a clinical polysomnography). There is also growing evidence that treatment of SDB in patients with PTSD helps to reduce PTSD symptoms (88, 89).

Quality of Life in Posttraumatic Stress Disorder

Reduced QOL in individuals with PTSD has been documented in several studies as a result of various traumatic situations such as military combat, natural disasters, and life-threatening car accidents (90–95). In a study of Taiwanese earthquake survivors, Wu et al. (90) found that 3 years after the earthquake, survivors with PTSD or MDD had a similarly decreased QOL as measured by the Medical Outcome Study Short Form. This study found that poor QOL was predicted by age, female gender, economic problems, physical illness, negative memories, and a diagnosis of either PTSD or MDD. Schonfeld et al. (92) also showed that QOL was severely affected by PTSD and was only second (along with PD with agoraphobia) to MDD in terms of its level of impact. In a review article by Rapaport et al. (96), they found that patients with PTSD had more severe QOL deficits than

patients with other mood and anxiety disorders. Together, these studies show that PTSD has been consistently shown to have a significant impact on QOL and that it is either equal to or in some cases more severe than MDD in terms of its impact.

Krakow has investigated the effects of psychotherapy to improve sleep in PTSD in two recent studies. In one study, imagery rehearsal therapy was used to treat chronic nightmares associated with PTSD (97). This therapy reduced nightmares and improved both sleep quality and PTSD symptoms, and at 3- and 6-month follow-ups, the benefits remained. Even though the PTSD improved, subjects continued to suffer from clinically significant PTSD symptoms. In another study, Krakow (98) used various cognitive-behavioral therapies to attempt to improve insomnia in crime victims with PTSD. Like the previous study, these interventions improved both sleep quality and PTSD; however, it did not bring subjects symptoms on either measure into the normal range. Of note, no control group was used in either of these studies; therefore, it is possible that the benefits seen are due to a placebo effect. Nevertheless, these studies do suggest that treating sleep components can be helpful in patients with PTSD. Although these studies did not directly investigate QOL, it is likely that if both sleep quality and PTSD symptoms are improved, this would also improve QOL. However, this is an empirical question that needs to be investigated.

One of the more interesting psychological approaches to the treatment of PTSD is eye movement desensitization reprocessing (EMDR). This technique involves eye movements synchronized with either movements of the index or middle fingers or tapping of the hands on the knees. The theoretical underpinnings of this technique are unclear; however, it has been speculated that EMDR emulates REM sleep processes thereby simulating the same neural mechanisms (99). In a recent study by Raboni et al. (100), patients who were victims of either assault or kidnapping (and had a diagnosis of PTSD) were investigated on measures of QOL (SF-36) and sleep (polysomnography), as well as measures of depression and anxiety. EMDR was shown to produce significant improvement in sleep efficiency, wake after sleep onset, and QOL (as well as depression and anxiety). However, this study suffers from two methodological issues, which include not using a control group and not controlling for Type I error with multiple *t*-tests.

There have been several studies that have investigated pharmacological treatments for PTSD on QOL measures. In terms of antidepressant drug treatment, fluoxetine, sertraline, paroxetine, and nefazodone have all been shown to significantly improve QOL in PTSD sufferers (101–106). However, the only two FDA-approved drug therapies for PTSD are paroxetine and sertraline. Nevertheless, in a head-to-head study of nefazodone and sertraline, both medications were found to significantly alleviate not only PTSD symptoms but also sleep quality, QOL, and depression (104). There was no significant difference between these medications on any measure in this study; however, it was a relatively low-power study ($N = 37$). Prazosin, a medication used to treat hypertension, has also been shown in a few recent studies (107–110) to improve PTSD symptoms, nightmares, and sleep quality. Therefore, Prazosin may be an alternative non-antidepressant pharmacological treatment for PTSD sufferers. There have also been numerous small clinical studies and case studies of other medications that have been shown to improve insomnia and nightmares in PTSD (see van Liempt et al. (111) for a comprehensive review).

In summary, several techniques have been shown to improve QOL and/or sleep in PTSD. These treatments include several medications (mostly selective serotonin reuptake inhibitors otherwise known as SSRIs), which have been found to improve QOL in PTSD (fluoxetine, sertraline, paroxetine, and nefazodone) and improve sleep quality and QOL in PTSD (sertraline and nefazodone). Psychological treatments directed at the sleep deficits in PTSD (cognitive-behavioral therapy for insomnia) and treatments specifically designed to affect REM-related mechanisms (imagery rehearsal and EMDR) also show promising results; however, more well-controlled studies are needed in this area.

Generalized Anxiety Disorder

Individuals with GAD suffer from excessive worry, present most days, about multiple issues. According the DSM-IV (20), this excessive worry must be present for a duration of at least 6 months. The National Co-morbidity study and the Midlife Development Study (112) found GAD to have a 12-month prevalence in approximately 3% of the population. A common associated feature of GAD is insomnia. Approximately 44% of insomniacs have a history of GAD (12). Moreover, individuals with GAD are 5.4 times more likely to suffer from insomnia than persons without GAD (113). Along with MDD and PD, GAD is one of the most common psychiatric disorders associated with insomnia (12).

Psychophysiological insomnia is the term used to describe insomnia that results from excessive worry and conditioned associations that prevent sleep (114). Often an individual begins to have difficulty sleeping because of a traumatic event, such as a death in the family or work instability, or an environment factor such as nighttime noise, which causes awakenings from sleep. According to the Spielman 3P model (115), insomnia onset and maintenance are thought to be related to three factors: predisposition, precipitation, and perpetuation. Over time even when precipitating events are gone, other factors such as increased anxiety regarding sleep and conditioned wakefulness to the bedroom environment can cause the insomnia to be perpetuated. Patients with GAD may be at greater risk for developing insomnia after a precipitating event because of their tendency for excessive rumination (i.e., hyperarousal). In other words, in terms of the 3P model, GAD or hyperarousal can be a predisposing factor for

insomnia. This occurs when a triggering factor, such as stress, finds fertile soil in the pre-existing anxiety disorder.

Hyperarousal is essentially a combination of physiological, mental, and behavioral traits associated with arousal (116). Common behavioral and mental traits of hyperarousal include a strong startle reaction to loud noises, rumination, conscientiousness, and negative response to unexpected events. The physiologic measures of hyperarousal include responsiveness to the effects of caffeine and bright lights, cold or clammy extremities, trouble falling asleep on daytime naps, elevated blood hormone levels and metabolic rate, and cortical activation. One study (116) found that patients with primary insomnia suffered from increased daytime hyperarousal and also had higher evoked potential responses to auditory stimuli than normal controls. In addition, insomniacs have been found to have higher 24-h mean plasma cortisol levels (117) and also have a higher whole-body metabolic rate (118) when compared with controls. Interestingly, even though (by definition) insomniacs have difficulty sleeping at night, they have higher mean sleep latency scores during the day on the multiple sleep latency test (118–121). So even though insomniacs sleep less, they continue to be less sleepy during the day than individuals without insomnia; in other words, they are hyperaroused. When insomniacs with GAD have been investigated, they have been found to have decreased sleep efficiency and TST (11, 122). This finding is significant because even though insomniacs typically show decrements on subjective measures of sleep quality, often when objective measures such as PSG are used, these decrements are not confirmed. Therefore, sleep quality on the PSG may help differentiate hyperaroused insomniacs from individuals who suffer from sleep difficulties because of other factors such as environmental disturbances or circadian rhythm disorders.

On other measures of sleep architecture, many of the findings have been conflicting. Some studies have shown increases in stage 2 and decreases in delta sleep (123, 124), whereas another study showed the opposite (122). Data on REM sleep have also been conflicting with a couple of studies showing no change in REM sleep (122, 125) and an earlier study showing a decrease in REM sleep (126). In a study comparing the sleep of patients with either MDD or GAD, the GAD group showed a longer REM latency and less stage shifts than the MDD group (124). This led the authors of this study to conclude that REM latency can be used as a factor to discriminate between MDD and GAD.

Quality of Life in Generalized Anxiety Disorder

Measuring QOL in GAD has been complicated by its high co-morbidity with MDD. The National Co-morbidity Study and the Midlife Development Survey found that 58 and 70% (respectively) of patients diagnosed with GAD also met the criteria for MDD (112). When individual factors such as perceived mental health, work impairment, and social role impairment were compared between persons with GAD and MDD, significant differences were found (112). Stein and Heimberg (127) also investigated the relationship between MDD and GAD, and although they also found that MDD and GAD were highly comorbid, they found that GAD was associated with decreased well-being and life satisfaction independent of the association with MDD.

The Epidemiologic Catchment Area Study found that individuals with GAD received more lifetime disability benefits, had more impaired work performance, and were more likely to be single or divorced than individuals without GAD (128). GAD has also been found to result in lower life satisfaction and a decrease in social life (129). Patients with GAD have increased healthcare utilization and are 1.6 times more likely to be female (113). In terms of subjective measures of QOL, persons with GAD have more frequent physical and mental distress, poor general health, inadequate sleep, and increased pain symptoms (130). In the elderly population, GAD has been found to result in lower QOL than recent heart attack or type II diabetes and is similar to MDD in terms of its impact on QOL (131).

Relatively few studies have investigated treatment options for GAD compared with other anxiety and mood disorders. However, based on a review of treatments for GAD, Struzik et al. (132) concluded that the most effective treatment for GAD was a combination of either paroxetine or venlafaxine and cognitive-behavioral therapy. In a double-blind study comparing the effects of paroxetine and sertraline on GAD, both medications were found to significantly decrease anxiety symptoms and improve QOL (133). The improvement found in anxiety and QOL scores did not differ significantly between these medications. More recently, other SSRIs such as citalopram and escitalopram have also been shown to significantly improve GAD symptoms and QOL (134,135). Various benzodiazepines and tricyclic antidepressants have been found to be effective in treating GAD; however, these classes of medications have recently lost favor because of their side-effect profiles compared with those of SSRIs and serotonin–norepinephrine reuptake inhibitors (SNRIs) (136).

Gould et al. (137) performed a meta-analysis of cognitive therapy in the treatment of GAD and found that cognitive therapy was superior to controls for reducing anxiety symptoms. Moreover, he found that the effect size of treatment outcome was similar in cognitive therapy to benzodiazepine treatment. These treatment effects were maintained at the 6-month follow-up. In a recent study by Belanger et al. (138), cognitive-behavioral therapy was used to treat insomnia symptoms in patients with GAD. They found a significant improvement in GAD and insomnia symptoms after treatment, as compared with a wait list control group. Combined, these studies show that not only is cognitive-behavioral treatment effective in treating GAD, but even when therapy is

based only on improving insomnia associated with GAD, it continues to be effective.

Conclusions

The association between sleep disorders and anxiety disorders is becoming more and more apparent with each study investigating the issue. Numerous differences are seen in the sleep architecture of patients with anxiety disorders. In addition, disordered sleep is a diagnostic feature for many of the anxiety disorders listed in the DSM-IV (20). Besides the well-documented association between sleep-disrupting nightmares in PTSD (61, 62), an association between SDB and PTSD has recently been uncovered (89), and the association between insomnia and PD and GAD is clear (12). In general, anxiety disorders seem to have a natural association with insomnia because it appears that hyperarousal is a salient factor in both disorders. QOL is an ideal outcome measure to examine the treatment effects of both anxiety and sleep disorders. However, it may have added significance in investigating the benefits of insomnia treatment because often sleep complaints reported by insomniacs are not confirmed on objective measurement. Nevertheless, it should not be assumed that just because sleep decrements are not found with our current objective tests, they do not exist. In fact, on other measures such as plasma cortisol (117), core body temperature (139), and daytime sleepiness (118–121), insomniacs are shown to differ from individuals without insomnia. Therefore, global functioning scales such as QOL scales may be particularly useful in measuring treatment outcome in these cases. Moreover, in disorders like insomnia, QOL is arguably the most relevant issue, because it is typically not difficulty sleeping that makes insomniacs seek treatment, but it is the daytime consequences of that difficulty sleeping, and these daytime consequences are uncovered to some degree in most QOL scales.

Recently, studies have shown improvement in anxiety symptoms by treating sleep disorders. In PTSD, for example, treatment of SDB has been shown to improve symptoms in case studies (88, 89). Also, the treatment of insomnia in both PTSD and GAD has been shown to decrease symptoms related to both disorders (98,138). However, additional studies are needed to look specifically at the effects on QOL after the treatment of sleep disorders in anxious individuals. Nevertheless, treating sleep disorders in patients with anxiety is a valuable and QOL-enhancing option.

Issues that need to be addressed by future research:

- Quality of life as an outcome measure should be considered in future studies investigating improving sleep in patients with anxiety disorders.
- Large-scale studies need to be performed to look at the effects of sleep disorder treatment on anxiety disorders.
- A comprehensive model of the interaction between hyperarousal in sleep and anxiety disorders needs to be developed.

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27
Sleep and Quality of Life in Depression

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Summary Major depression is a common disorder; nearly 10% of the population suffers from a depressive illness in any given year. There is a strong association between sleep disturbances and depression. The most common sleep disturbance associated with major depressive disorder is insomnia. The relationship between insomnia and depression is bidirectional in that insomnia is one of the symptoms of depression and chronic insomnia can be a risk factor for depression. Depression causes changes in sleep patterns and sleep quality. Depressed patients showed prolonged sleep latency, increased wakefulness during sleep, early morning awakening, decreased sleep efficiency, decreased amounts of slow wave sleep and rapid eye movement (REM) sleep abnormalities. Depression is currently one of the leading causes of disability in the world. There is a direct association between the severity of depression and the level of disability. Depression has a big impact on quality of life of patients. Studies have showed that patients with major depressive disorder have poorer quality of life than persons from the general population. Effects of depression on quality of life are equal to or greater than those of patients with chronic medical conditions. Untreated depression usually does not go away by itself and often gets worse with time and increases a person's risk of suicide; it is a fact that up to 15% of those who are clinically depressed die through suicide. Clinical depression is treatable with counseling and medication. The majority of people with depressive disorders improve when they receive appropriate treatment. Improvement in depressive symptoms during the treatment is related to improvement in the quality of life. Antidepressants are shown to improve quality of life. There are some tools for evaluating quality of life in depressive patients, today. These tools help us to assess improvement in depressive patients beyond the extent to which depression rating scales do. In clinical settings, quality of life instruments can show us when patients begin to feel benefits of antidepressant therapy.

Keywords Major depressive disorder · Sleep quality · Quality of life · Antidepressant · Therapy · Sleep disturbance · Sleep deprivation.

Learning objectives:

- Depression is a serious and common medical condition that the prevalence of Major Depression for 12 months is 6.6% and the point prevalence for men is 2–3% and for women is 5–9%.
- Major depression is a leading cause of disability and suicide. Patients with major depressive disorder have poorer quality of life than persons from the general population.
- The majority of people with depressive disorders improve when they receive appropriate treatment. Improvement in depressive symptoms during the treatment is related to improvement in the quality of life.

Depression

Epidemiology and Types of Depression

Depression is a common psychiatric disorder. Studies have estimated that major depression occurs in 2–4% of persons in the community, in 5–10% of primary care patients, and 10–14% of medical inpatients (1). In psychiatric practice, clinical depression is also known as major depression, major depressive disorder, or unipolar depression. Major depressive disorder is classified under the mood disorders section of the *Diagnostic and Statistical Manual of Mental Disorders*; this section includes disorders that have a disturbance in mood as the predominant feature (2). The mood disorders are divided into the depressive disorders, bipolar disorders, mood disorders due to a general medical condition, and substance-induced mood disorders. While this chapter is going to

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explore "Sleep and Quality of Life in Depression," it is important to notice that depression can occur in mood disorders other than major depressive disorder. Bipolar I disorder is characterized by cycles between mania and depression; Bipolar II disorder is characterized by one or more depressive episodes accompanied by at least one hypomanic episode and dysthymic disorder is a long-term, mild depression that lasts for a minimum of 2 years.

There is no medical test for clinical diagnosis of depression today. Diagnostic systems; international classification of disorders (ICD-10), and diagnostic and statistical manual of mental disorders (DSM-IV) are used for diagnosis of mental disorders. According to the DSM-IV, major depressive disorder is characterized by depressed mood or a loss of interest or pleasure in daily activities consistently for at least a 2-week period. The patient with major depressive disorder must also experience at least four additional symptoms from the following list: changes in appetite or weight; insomnia or hypersomnia; psychomotor agitation or retardation; fatigue or loss of energy; feelings of worthlessness or excessive or inappropriate guilt; diminished ability to think or concentrate or indecisiveness and recurrent thoughts of death; recurrent suicidal ideation without a specific plan; or a suicide attempt or a specific plan for committing suicide. Bipolar disorder is diagnosed in patients who have experienced at least one manic or mixed episode. Generally, bipolar patients also have depressive episodes. Manic episodes are characterized by predominantly elevated, expansive mood, either euphoric or irritable, with a duration of at least 1 week. Accompanying behaviors may include increased activity, restlessness, talkativeness, flight of ideas, feeling of racing thoughts, grandiosity, decreased sleep time, short attention span, buying sprees, sexual indiscretion, and inappropriate laughing, joking, or punning. A hypomanic episode is a mild form of manic episode. During a hypomanic episode, the mood disturbance and some of the manic symptoms are present but are not as severe as in a full manic episode.

Etiology of Depression

The etiology of depression and other mood disorders are not fully understood. Complex interactions between biological and psychosocial factors are believed to be involved in the etiology of depression and other mood disorders. The biopsychosocial model is one of the best approaches to understanding the causation of depression. In this model, biological, sociological, and psychological factors interact to produce depression. There are many hypotheses developed to explain the pathogenesis of depression. Monoamine hypothesis explains depression by an absolute or relative deficiency of monoamine transmitters in the brain. Norepinefrin, serotonin, and dopamine are implicated in the etiopathology of mood disorders (3, 4). This hypothesized pathophysiology appears to be supported by the mechanism of action of antidepressants: agents that elevate the levels of these neurotransmitters in the brain have all been shown to be effective in the alleviation of depressive symptoms (5). Neuroendocrin regulation is important in mood disorders. Various neuroendocrine deregulations have been reported in patients with mood disorders. Adrenal axis changes especially hypersecretion of cortisol (6, 7), thyroid axis (8) changes, and thyroid disorders and growth hormone abnormalities (9, 10) are found related with depression. Genetic factors are involved in the development of mood disorders (11, 12). Genes are implicated more strongly in bipolar disorder than they are in major depression (13, 14). On the contrary, psychosocial factors are significantly implicated in the etiology of mood disorders. Stressful life events generally precede first episodes of mood disorders, and it is hypothesed that stress accompanying the first episode results in long-lasting changes in the brain's biology (15, 16). Predisposition to mood disorders is not related to personality traits or types, but a personality disorder or temperamental disturbance may mediate the relationship between stress and depression (17). Finally, psychodynamic, cognitive, and behavioralistic explanations of depression are also made (18, 19).

Depression and Sleep

Disturbances of sleep are characteristic of mood disorders. Insomnia or hypersomnia are the symptoms included in the diagnostic criteria of the major depressive disorder. The most common sleep disturbance associated with major depressive disorder is insomnia. Patients typically have middle or terminal insomnia. Middle insomnia refers to difficulty maintaining sleep. Decreased sleep efficiency is present, with fragmented unrestful sleep and frequent waking during the night. In terminal insomnia, also referred to as early morning wakening, patients consistently wake up earlier than needed. Initial insomnia may also occur that is characterized by difficulty falling asleep, with increased time between going to bed and falling asleep (sleep latency). The most frequently associated polysomnographic findings in depression include sleep continuity disturbances, reduced stages 3 and 4 sleep, decreased REM latency, increased phasic REM activity, and increased duration of REM sleep early in the night (2).

Another relationship between mood disorders and sleep regulation is that depressive symptoms are acutely alleviated by one night of sleep deprivation (20–22). In most cases, sleep deprivation effects last until the end of the sleep deprivation day. The mode of action of sleep deprivation is still not known, but there are many hypotheses about the way that sleep deprivation works. Similarly, phase advance of the sleep period has been proven to be an effective therapeutic strategy for patients with unipolar depression (23, 24).

Serotonergic mechanisms are believed to be involved in the etiology of depression and also in the sleep deprivation effect (25–27). Decreased serotonergic neurotransmission has been proposed to play a key role in the etiology of

depression. Most of the antidepressants induce an enhancement of serotonergic neurotransmission (28). There is some evidence that sleep deprivation induces an increase in serotonergic neurotransmission. Sleep deprivation may relieve symptoms of depression by reducing the autoinhibition by desensitizing the 5HT autoreceptors and increasing the serotonergic transmission (29). Insomnia induces mood improvement and enhancement of serotonergic neurotransmission that insomnia might represent is a compensatory mechanism for the depression (30). In conclusion, sleep deprivation therapy might show antidepressant effect by changing the serotonergic neurotransmission.

The relationship between insomnia and depression is bidirectional in that insomnia is one of the symptoms of depression, and chronic insomnia can be a risk factor for depression (31, 32). Individuals with insomnia are known to have significantly elevated rates of depression, and insomnia is a predictive factor for the future development of depression, both for new onset of a depressive disorder and for recurrence of depression (33).

On the contrary, it has been shown that sleep loss could trigger symptoms of mania or hypomania in some bipolar patients (34, 35). Wehr has suggested that sleep deprivation may represent a final common pathway in the genesis of mania and that sleep loss is both a precipitating and a reinforcing factor for the manic state (36). Insomnia related to the mania is generally with little sleep and patients may not sleep until physically exhausted. Treatment for mania tends to correct sleep architecture.

As mentioned above, mood disorders are related with sleep changes. Besides insomnia or sleep disturbances in mood disorders, timing of the sleep and circadian factors are also important. Subjective mood is shown to be influenced by a complex and nonadditive interaction of circadian phase and duration of prior wakefulness in healthy subjects (37). Depressive patients frequently represent chronobiological disturbances. One of the important indicators of chronobiological disturbance in depressed patients is diurnal mood variation. Patients are worse in the morning and feel better in the evening. The antidepressant effect of sleep deprivation is mainly observed in patients presenting a positive variation of mood. In light of these findings, a phase advance of circadian rhythms was proposed to be pathognomonic for major depression (38, 39).

Depression and Sleep Quality

Sleep quality is characterized by how restorative and undisturbed is the sleep that patients have. Sleep quality in depressive patients can be evaluated by the subjective and objective measures. A series of questionnaires is used for the subjective evaluation of sleep quality. Objective evaluation requires objective techniques such as polygraphic recordings, or from the recordings of wrist activity movements, and/or head movements and eyelid movements. The most commonly used objective measures of sleep quality are an index of sleep fragmentation and sleep efficiency. Subjective and objective measures of sleep quality are not necessarily concordant.

Quality of sleep can be evaluated by a standardized questionnaire. To provide a reliable, valid, and standardized measure of sleep quality, the Pittsburgh Sleep Quality Index was developed (40). There are also some instruments available for measuring quality of life in sleep disorders. Ferrans and Powers Quality of Life Index: Narcolepsy version, Sleep Apnoea Quality of Life Index, and Functional Outcomes of Sleep Questionnaire are used for the evaluating quality of life in some sleep disorders (41–43). However, the co-existence of insomnia with mood disorders makes it difficult to develop a quality of life measure for insomnia.

Most depressed people experience insomnia: difficulty falling asleep or, most often, staying asleep. Another small proportion of the depressed sleeps excessively. Insomnia and psychiatric disorders could share a common biochemical or neurophysiological mechanism predisposing to both conditions. Studies showed that about one-half of patients with chronic insomnia have a sleep problem that arises because of a psychiatric disorder. One of the most prominent psychiatric causes of insomnia is mood disorders (44). Specchio et al. reported that more than 60% of chronic insomniacs were suffering from a concomitant mental disorder of mood or anxiety type, and explained this co-morbidity by underlying that, on one side, insomnia is a part of diagnostic criteria of such psychiatric disorders but, on the other side, its well-defined that sleep disturbances precede the development of psychiatric disorders, especially depression, so stress could also be considered as a risk factor for them (45). Various epidemiological investigations agree in their findings that primary insomnia at baseline can predict the further development of depression. Thus, in people who suffered from insomnia, the probability for onset of depression increased four times during a 3-year follow-up (46–48). Insomniacs have poorer physical and mental health, and attempt suicide more often than controls. Studies consistently report that insomniacs are at greater risk for developing a depressive disorder. Longitudinal follow-up and family studies suggest that sleep disturbances in depression are trait-like. Sleep of depressed patients in remission is still disturbed (49).

The quality of sleep is linked to quality of life. Pilcher et al. have assessed whether measures of health, well-being, and sleepiness are more related to sleep quality or to sleep quantity. Results of the study suggested that sleep quality is more related to measures of health, well-being, and sleepiness than sleep quantity in a nonclinical population reporting an average of 7–8 h of sleep at night. However, a similar pattern was not shown between these measures and sleep quantity (50).

Sleep is important for optimal cognitive functioning and, when sleep is disrupted, individuals cease to function effectively. Sleep quality and quantity and related states such as energy levels are sensitive indicators of quality of life. Some quality of life domains are affected when patients experience

chronic sleep disturbance. The clinical consequences of diminution in deep, or delta, sleep are uncertain, but various disturbances of deep sleep are associated with daytime impairment. Reduced alertness, diminished reaction time, and reduced energy affect quality of life and frequently lead to impairments in social and occupational daytime functioning (51).

De Gennaro et al. studied the association between alexithymia and poor sleep quality, taking into consideration the contribution of depression. Results showed that alexithymia scores appeared to be correlated with many sleep complaints but any association between alexithymia and sleep complaints disappeared when the contribution of depression is partialled out (52).

Zeitlhofer et al. studied the associations between sleep disorders (or sleep quality) and quality of life in a representative healthy sample of the Austrian population. Their study showed a close correlation between self-assessed quality of sleep and self-assessed quality of life, and they concluded that complaints about a bad quality of sleep could be used as a screening method in the exploration of patients' quality of life (53).

Gender differences in sleep and depression are widely studied. The most common factors affecting sleep in women are associated with the life cycle of hormone levels, extending from menarche through and after menopause, including pregnancy (54). Depression and insomnia are both significantly more prevalent in women than in men, but the reason is unknown (55). On the contrary, neurobiological correlates of depression differ by gender and women with major depressive disorder may benefit more from behavioral management of sleep disturbances (56).

People with depression have up to a 15% risk for suicide, with the highest risk in patients who are hospitalized for depression (57, 58). Sleep disturbances may be of value in predicting suicide (59, 60). A prospective study conducted in the general population demonstrated that the frequency of reported nightmares was related to the risk of suicide (61, 62). Insomnia, hypersomnia, and subjective sleep quality are related to suicidal behavior. Agargun et al. examined the association between sleep quality and suicidality in major depressive disorder. Results showed that sleep in suicidal depressive patients was subjectively significantly more disturbed than in nonsuicidal patients. The authors came to conclusion that an association exists between poor subjective sleep quality and suicidal behavior in patients with a major depressive disorder (63).

Depression and Quality of Life

Major depressive disorder is a common disorder. The lifetime risk for major depressive disorder in community samples has varied from 10 to 25% for women and from 5 to 12 % for men (2). Most studies have found unipolar depression in general to be twice as common in women as in men (64). However, prevalence rates for major depressive disorders appear to be unrelated to ethnicity, education, or marital status. The incidence of major depressive disorder is 10% in primary care patients and 15% in medical inpatients (65).

Major depressive disorder is associated with disability. Disability refers to the temporary or long-term reduction of a person's capacity to function. A disability is defined by the World Health Organization as "any restriction or lack of ability to perform an activity in the manner or within the range considered normal for a human being." Depression affects daily functioning, and disability caused by depression is comparable to many chronic medical conditions (66, 67). Depression was the fourth largest contributor to the disease burden in 1990 and is expected to be the second largest by 2020 (68, 69).

The World Health Organization has introduced a new concept of measuring suffering of populations based on time lived with disability, which has been described as disability-adjusted life year (DALY). Depression accounted for nearly one-third of all neuropsychiatric DALYs. Depression was found the leading cause of years of life lived with disability for both males and females (70).

Severity of depression is classified in DSM-IV as mild, moderate, severe without psychotic features, and severe with psychotic features. It is expected that higher severity of depression could be related with more disability. A Dutch population study examined the associations of severity and type (a single or recurrent episode) of major depression with disability. Recurrent episode major depression was not found to be associated with more disability than single episode major depression. Higher severity classes, on the contrary (mild, moderate, severe, and severe major depression with psychotic features), were associated with increasing levels of disability, although not all classes differed significantly from each other (71).

Similar to the direct association between the severity of depression and the level of disability that improvement in mood is associated with a reduction in disability (72). Depression has an impact on physical functioning, pain, and general health perceptions. It is reported that self-reports from those with depression may be unrealistic; as such, individuals may magnify their level of disability in accord with their general negative bias; but self-perception is more important to the patient. It is suggested that when assessing the impact of depression on a patient that an evaluation of symptoms alone is insufficient, so that an assessment of disability becomes a valuable addition. Disability is an important determinant of quality of life in patients with depression. In addition to the broad disability definition of the World Health Organization, quality of life is defined as an individual's perception of his/her position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns. It is a broad-ranging concept affected in a complex way by the person's physical

health, psychological state, personal beliefs, social relationships, and their relationship to salient features of their environment.

Depression is characterized by feelings of helplessness, hopelessness, inadequacy, and sadness. In the clinical picture of depression, a loss of interest or pleasure in life, significant diet changes, psychomotor changes, decreased energy and tiredness, a sense of worthlessness and an impaired ability to concentrate and make decisions accompany each other. Disordered sleep in depression leads to fatigue, irritability, memory and concentration problems, loss of interest in social and other activities, and the inability to draw pleasure from them. Because of these depressive symptoms, the consequences for social or occupational functioning, biological or psychological effects of depression can change quality of life. Many studies have demonstrated that patients with major depressive disorder have poorer quality of life than persons from the general population (73–75).

A number of studies have compared major depressive patients with normal controls on quality of life changes. Barge–Schaapveld et al. investigated subjective well being and daily functioning in depressive patients (76). As expected, depressed subjects experienced lower levels of momentary quality of life than did the healthy control subjects. Negative mood and depression were significant predictors of global measures of quality of life in that study, and they conclude that quality of life has important situational determinants that can in part explain the impact of depression on daily functioning and well-being.

There are many scales developed to evaluate depression. The Beck Depression Inventory (77) and the Zung Self-Rating Depression Scale (78) are each used to measure characteristic attitudes and symptoms of depression. The Hamilton Depression Rating Scale (79) and the Montgomery-Asberg Depression Rating Scale (80) are administered by an interviewer to rate the severity of a patient's depression. There are also specific scales developed for clinical use like the Geriatric Depression Scale (81,82), the Edinburgh Postnatal Depression Scale (83), The Calgary Depression Scale for Schizophrenia (84), and The Hospital Anxiety and Depression Scale (85). On the contrary, evaluating the quality of life in depressive patients can require more specific scales. WHOQOL by World Health Organization (86, 87), the short-form health survey questionnaire; SF-36 (88, 89) and The Global Assessment of Functioning scale from DSM (2) are successfully used to detect quality of life changes in depression. The Quality of Life in Depression Scale was developed as a new instrument designed for use in monitoring individual patients and as an outcome measure for clinical trials (90). Because of the differences in goals of the depression-rating scales and quality of life scales in depression, comparison between these scales is difficult. However, quality of life scales in depression have been found to be correlated with specific depression questionnaires.

Many of the studies have investigated the early response to antidepressant therapy by using clinician rated scales like the Hamilton Rating Scale for Depression. Nevertheless, objective severity of depression may not be the most appropriate criterion of improvement, and quality of life is the most crucial factor in determining the onset of response to antidepressant therapy.

Bipolar disorder has a unique pattern of mood cycles, combining depression and manic episodes. Bipolar depression and unipolar depression share the same symptomatology. Bipolar depression is characterized by depressed mood or loss of, or markedly diminished, interest or pleasure in nearly all activities, significant weight loss when not dieting or weight gain, insomnia or hypersomnia nearly every day, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or excessive guilt, diminished ability to think or concentrate, as well as recurrent thoughts of death or suicidal ideation, or suicide attempt. There are many studies in the literature indicates that quality of life is markedly impaired in patients with bipolar disorder. Gazalle et al. studied the currently depressed, subsyndromal, and remitted patients with bipolar disorder and assessed whether the level of depression correlates with the scores of quality of life in bipolar disorder; they found that bipolar depression and residual symptoms of depression are negatively correlated with quality of life in bipolar disorder patients (91). Similarly, depressive symptoms are shown to be a strong predictor of quality of life (92). On the contrary, depressive symptoms predominate over hypomanic or manic symptoms in the courses of both bipolar I and bipolar II disorders (92, 93).

In a study that used qualitative interviews to assess how bipolar disorder impacts upon life quality, they found bipolar disorder had a profoundly negative effect upon their life quality, particularly in the areas of education, vocation, financial functioning, and social and intimate relationships (94).

Major depression is a most important risk factor for suicide. Over 60% of all people who commit suicide suffer from depression. People with depression have up to a 15% risk for suicide, with the highest risk in patients who are hospitalized for depression. The lethality of depression is measurable and is the result of completed suicide, which is the ninth leading reported cause of death in the USA (57, 58).

Quality of life in depression is related to suicidality in depression. O'Brien et al. reported in a study of 98 cases of deliberate self-harm that a high correlation was obtained between a diagnosis of major depressive disorder and scores on both the Hamilton Rating Scale for depression and the Suicide Intent Scale. There was also a high correlation between Hamilton Rating Scale and Suicide Intent Scale scores (95). Similarly, Goldney et al. examined the health-related quality of life of people with suicidal ideation in the general community; they concluded that suicidal ideation was associated with poor health-related quality of life (96).

Feelings of hopelessness are common in patients with major depressive disorder. Hopelessness is also one of the

most frustrating feelings that depressed individuals experience (97). People who are depressed struggle with feelings of hopelessness and helplessness more so than people who are not depressed. Research has also indicated that severe hopelessness may be a predictor of suicide, and hopelessness was found more important than depression for explaining suicidal ideation (97).

In this chapter, "depression" is used for major depression or unipolar major depression. Although minor depression is not considered an official clinical diagnosis, minor depression is common in the general population. Many people with minor depression have a chronic or recurrent condition, and some of them develop a more severe form of depression. There is also evidence regarding functional impairment in minor depression (98). Judd et al. evaluated the association between impairment in daily function and subsyndromal depressive symptoms as well as major depression to determine the economic and societal significance of these conditions; except for lower self-ratings of health status, no significant differences were found between subjects with subsyndromal symptoms and those with major depression (99). Minor depression has significant risk for suicide and future major depression. The high prevalence of minor depression, the significant psychosocial impairment associated with it, and the chronicity of its course make minor depression a matter for serious consideration by clinicians and researchers (100). These factors broaden the impact of minor depression on quality of life.

Hays et al. conducted a 2-year observational study of 1790 adult outpatients with depression, diabetes, hypertension, recent myocardial infarction, and/or congestive heart failure. Change in functional status and well-being was compared for depressed patients versus patients with chronic general medical illnesses, controlling statistically for medical comorbidity, sociodemographics, system, and specialty of care. Results demonstrated that depressed patients had substantial and long-lasting decrements in multiple domains of functioning and well-being that equal or exceed those of patients with chronic medical illnesses (101).

Quality of life is a broad construct, encompassing affective, cognitive, behavioral, and physical components. Depression is characterized by disturbances in many or all of these areas, which may explain why quality of life is even lower in depression than in serious somatic disorders such as diabetes or arthritis (102).

Bonicatto et al. investigated the quality of life in major depressive disordered patients in Argentina. Their results showed that patients with major depression show significantly poorer quality of life compared with healthy persons or individuals with chronic medical disease (74, 102).

We can compare the quality of life changes with depression and medical illness, as depressive symptoms occur commonly in medical illness. Those depressive disorders are more prevalent in patients with medical conditions compared with that in the general population. Depression in the physically ill has been shown to have a significant impact, with increased symptom burden, impaired functioning, and reduced quality of life. Several studies have shown that depression is more predictive of functional impairment over time than severity of physical illness. In the elderly, depression associated with physical illness has a particularly poor outlook. Factors associated with worse outcomes included more severe depression, more severe physical illness, and symptoms of depression before admission.

Similar to the medical conditions, other psychiatric disorders commonly occur with depression. High rates of outpatients with major depressive disorder met criteria for a co-morbid anxiety disorder. Social anxiety disorder panic disorder, generalized anxiety disorder, bulimia nervosa, obsessive-compulsive disorder, somatoform disorder, alcohol abuse/dependence, drug abuse/dependence, and posttraumatic stress disorder are reported to have high prevalence rates with major depressive disorders. Specific patterns of personality pathology were shown to be significantly related to anxious depression (74, 103).

Effect of co-morbid psychiatric disorders on the morbidity of major depressive disorder is important. Those with more concurrent psychiatric co-morbid cases reported to have earlier ages at first onset of major depressive disorder, longer histories of major depressive disorder, greater depressive symptom severity, more general medical co-morbidity, poorer physical and mental function, health perceptions, and life satisfaction, and were more likely to be seen in primary care settings (104). These results indicate that co-morbidity with depression and other psychiatric disorders would have great impact on quality of life. On the contrary, co-morbidity in depression is associated with reduced probability of successful diagnosis, greater impairment, more severe symptoms, and a less favorable treatment outcome (105).

The majority of people with depressive disorders improve when they receive appropriate treatment. It is reported that 80–90% of all people with depression, even those with the most severe cases, improve once they receive appropriate treatment. Treatment choice will depend on the patient's diagnosis, severity of symptoms, and preference. A variety of treatments, including medications and psychotherapies, have proven effective for depression. Electroconvulsive therapy (ECT) can also help. It is most often recommended when drug treatments cannot be tolerated or there is an unacceptable delay in when drugs would become effective.

Improvement in depressive symptoms during the treatment could be related to the improvement in quality of life. Antidepressants are shown to improve quality of life (106). Antidepressant treatment may lead to significant improvement in quality of life measures in the acute phase of depression, but the treatment in the maintenance and continuation phases show less-favorable improvement in psychosocial function over time for pharmacotherapy compared with studies focusing on the acute phase of treatment (107).

There are many studies in the literature showing the importance of ECT in restoring function and health-related quality of life for depressed patients (108). McCall et al. assessed for health-related quality of life at baseline, several days after ECT, and 24 weeks later in depressive patients. ECT is associated with improved health-related quality of life in the short and long term, with the enhancements largely explained by improvements in depressive symptoms (109).

Sleep deprivation has an impact on mood, cognitive, and motor tasks. Another relationship between mood disorders and sleep regulation is that depressive symptoms are acutely alleviated by one night of sleep deprivation (110, 111). Both total sleep deprivation and partial sleep deprivation therapies have beneficial effects on depression (112). Combination of medications and sleep deprivation therapy was found more effective than either alone (113–115). Sleep deprivation therapy can be used to improve depression during the period required for antidepressant medication to become fully effective. Furthermore, these combinations can induce more rapid improvement in the QOL items and facilitate the antidepressant therapy adaptation (116).

Despite great advances in treating clinical depression, a very small proportion of people with the disorder are actually diagnosed. Most people with a depressive illness do not seek treatment. There is also a gender issue, because men may be reluctant to discuss male depression with a health care professional, many men with depression may go undiagnosed, and consequently untreated. Depression often goes undiagnosed and untreated in the elderly because it can be masked by or confused with other existing factors such as other illnesses, medications, coping with personal losses, and cognitive deterioration associated with normal aging. Depression in young people can go undiagnosed and untreated because the symptoms are too often viewed as normal mood swings, typical of a particular developmental stage. Although nearly one-third of adult Americans experience symptoms related to mental health disorders, only 18% of them have been diagnosed by a doctor as having either generalized anxiety disorder or clinical depression. Almost three-quarters of doctor-diagnosed sufferers reported that their symptoms interfere with their routine activities compared with 44% of those undiagnosed (117). Treatment for depression is often lacking, especially in developing countries: The World Health Organization reports that less than one in every four people affected by depression worldwide have access to effective treatments. Untreated depression has many consequences for young people. It often results in poor academic performance, alcohol and drug abuse, problems with relationships, and greater risk for other health problems. In younger adults, associations of both major and minor depression with disability and well-being remained significant after controlling for chronic disease and functional limitations (118). All the consequences about the untreated depression are directly linked to the quality life changes and remain a public health issue.

Issues that need to be addressed by future research:

- Effects of sleep disturbances on quality of life need to be evaluated by excluding the other depressive changes in major depression.
- Correlation with sleep quality and quality of life changes in major depression needs to be evaluated.
- Antidepressant treatment modalities and combination therapy options should be compared in the light of quality of life changes.

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28
Sleep and Quality of Life in ADHD

Evelijne M. Bekker, J. J. Sandra Kooij, and Jan K. Buitelaar

Summary Attention-deficit hyperactivity disorder (ADHD) is a highly prevalent neuropsychiatric disorder characterized by symptoms of inattention, impulsivity, and hyperactivity. From early childhood to late adulthood, patients with ADHD (or their parents) complain about poor sleep quality and insufficient sleep quantity. As a result, ADHD patients experience excessive daytime sleepiness (EDS). Because EDS has been found to result in behavioral problems and cognitive impairments that mimic ADHD symptoms, sleep problems (e.g., due to a primary sleep disorder) may be misdiagnosed as ADHD. Alternatively, ADHD may actually cause sleep disturbances, e.g., due to dysfunctions in shared dopaminergic or noradrenergic neural systems. Here, we review studies on sleep and ADHD. Studies using subjective measures, such as questionnaires and diaries, have indicated a wide variety of sleep problems, a high prevalence of sleep disorders, and EDS. Studies using objective measures have only partly been able to confirm these findings. Studies using the Multiple Sleep Latency Test (MSLT) have clearly demonstrated EDS in ADHD. Actigraphic studies have inconsistently suggested an increase in nocturnal activity levels, whereas polysomnographic studies have mostly indicated deviations in REM activity and the presence of periodic limb movement disorder (PLMD). Intervention studies yielded mixed results. Sleep problems have been claimed to reduce, increase, and be unaffected by methylphenidate (MPH), the drug of choice for ADHD treatment. The large inconsistencies across studies are likely due to numerous confounding variables, such as small sample sizes, the heterogeneity of ADHD samples, the presence of comorbid conditions, differences in medication status and treatment regiments, differences in pubertal status, gender and the lack of methodological guidelines (e.g., the use of validated questionnaires and the inclusion of adaptation nights). Implications for future research are discussed.

Keywords Attention-deficit hyperactivity disorder · sleep · sleepiness · SBD · PLMD · subjective · objective · actigraphy · polysomnography.

Learning objectives:

- Attention-deficit hyperactivity disorder (ADHD) is a highly prevalent disorder that affects people of all ages.
- ADHD patients often complain about sleep disturbances and excessive daytime sleepiness (EDS).
- Daytime sleepiness may induce or intensify ADHD symptoms.
- Alternatively, ADHD and sleep abnormalities may share dysfunctions in neural systems.
- Studies using objective measures have not convincingly confirmed the occurrence of a wide range of sleep problems in ADHD.
- Evidence is strongest for EDS and comorbid periodic limb movement disorder (PLMD).
- However, numerous methodological issues and potential confounds preclude to draw any firm conclusions.

Attention-deficit hyperactivity disorder (ADHD) is a neuropsychiatric disorder that afflicts millions of people around the world. It is characterized by symptoms of inattention, impulsivity, and hyperactivity that profoundly impact the ability to function in social, academic, and occupational settings. In clinical practice, ADHD patients (or their parents) often complain about sleep problems. In line with these reports, the Diagnostic and Statistical Manual for mental disorders (DSM) once included restless and disturbed sleep as one of the defining characteristics of ADHD (1). However, due to a lack of empircal evidence, later versions excluded sleep

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abnormalities from the list of diagnostic criteria (2,3). Studies assessing the link between sleep and ADHD are hindered by numerous methodological issues. First, the relationship between sleep problems and ADHD is complex: disturbed sleep may result in behavior that mimics ADHD symptomatology, it may intensify existing ADHD symptoms, or it may actually be caused by ADHD. Furthermore, a specific portion of ADHD patients may suffer from a comorbid sleep disorder that is either completely unrelated to ADHD or caused by deficits in (partly) overlapping neural mechanisms. Second, the typical heterogeneity of ADHD samples, the presence of comorbid conditions, and the use of stimulant medication complicate the interpretation of study results. Despite these challenges, the number of studies on sleep disturbances in ADHD has grown rapidly over the past years. Here, we provide an up-to-date overview of these studies and discuss their limitations.

ADHD

Nomenclature

Over the past 100 years, different labels have been used to describe the developmental disorder that we now know as ADHD. These labels reflect changes in theoretical frameworks over time and have always been used to guide research. In 1902, Still (4) was the first to describe children with a "defect of moral control," who were hyperactive, unable to concentrate, and had learning difficulties and conduct problems. This moral deficit was thought to stem from an organic brain pathology. As a consequence, subsequent diagnostic labels all referred to an underlying brain deficit, for example, the brain-injured child, minimal brain damage, and minimal brain dysfunction. In the 1960s, researchers found that hyperactivity also occurs without evidence of neurological abnormalities and new labels, such as the hyperactive child syndrome and the hyperkinetic reaction of childhood disorder, were introduced accordingly. In 1972, Douglas (5) shifted focus by claiming that inattention rather than hyperactivity is the major cause of the behavioral problems reported in these children. This led to a new label in the DSM-III (1), namely attention-deficit disorder (ADD) with or without hyperactivity. As stated, sleep disturbances constituted one of its defining criteria. In the revised version (2), the label ADD was replaced with ADHD, and sleep problems were eliminated from the diagnosis. These changes were adopted in the current DSM-IV (3) and its text revised version DSM-IV-TR (6).

DSM-IV Criteria

The DSM-IV-TR (6) distinguishes three subtypes of ADHD: (1) the predominantly inattentive subtype; (2) the predominantly impulsive/hyperactive subtype; and (3) the combined subtype, associated with symptoms of inattention as well as impulsivity/hyperactivity. To be diagnosed, children and adolescents must meet 6 out of 9 criteria of inattention (e.g., problems organizing activities or completing tasks) and/or hyperactivity/impulsivity (e.g., problems awaiting turn or sitting still) that persist for a period of at least 6 months to a degree that is maladaptive and inconsistent with the developmental level. Furthermore, at least some of the symptoms should be present before the age of 7 years and cause a moderate to severe level of dysfunction in at least 2 different settings. In adults, the same criteria are used to retrospectively determine the presence of ADHD symptoms during childhood. Importantly, the continuity of symptoms from childhood onwards needs to be demonstrated. For diagnosis of current symptoms, the use of less stringent criteria has been recommended: the presence of 5 (or sometimes 4) out of these 9 criteria suffices (7–9).

Prevalence

ADHD is one of the most prevalent disorders in childhood, affecting between 3 and 10% of school-aged children (10,11). Longitudinal studies have shown that between 10 and 70% of affected individuals do not outgrow their problems with increasing age (8, 12). The wide variety in estimated rates of persistence mainly reflects the stringency of diagnostic criteria used. When all patients who currently do not meet full diagnostic criteria (6 of 9) are excluded, persistence rates are around 15%, but when patients who are in partial remission (who are struggling with a substantial though sub-threshold number of symptoms causing a high level of dysfunction) are included, persistence rates are around 65% (9). Generally, the prevalence of ADHD in adulthood is estimated to be around 2–5% (7, 13, 14).

Co-morbidity

Approximately 75% of ADHD patients are diagnosed with one or more comorbid conditions (15–17). In children, these typically consist of conduct disorder (CD), oppositional defiant disorder (ODD), bipolar disorder, depression, anxiety, Gilles de la Tourette, autism, pervasive developmental disorder (PDD), and learning disorders (LD). In adults, comorbidity additionally involves antisocial personality disorder (ASP) and substance abuse. The high incidence of comorbid disorders complicates data interpretation (results are not necessarily related to ADHD), comparison across different studies (that use different exclusion criteria), and generalization (strict exclusion of patients with comorbid conditions might not yield results that are representative for the entire population of ADHD patients).

Cognitive Deficits

Children with ADHD have been found to perform poorly on a wide variety of cognitive tasks measuring executive

functions, such as inhibition, attention, set shifting, working memory, planning, and fluency (18, 19). A comparable pattern of impairments has been reported for adults with ADHD (20, 21). Significant research effort has been expended to identify the core cognitive deficit in ADHD, which mediates a cascade of more secondary deficits. Most notably, inattention (5, 22) and deficient inhibitory control (23, 24) have been claimed to play a crucial role. The majority of studies support the notion that disinhibition, and more specifically, the inability to suppress ongoing motor responses, is central to ADHD (25).

Neural Substrates

Consistent with a core deficit in inhibitory control, functional imaging studies have mainly indicated deviant brain activity in (right) fronto-striatal regions (26, 27). Some studies have rather demonstrated recruitment of more diffuse networks during task performance, which may reflect differential deployment of task strategies (27). Structural neuroimaging studies have shown that the total brain volume of children with ADHD is up to 5% smaller than that of normal children (28). In particular, volume reductions have been reported for (right) prefrontal areas (29). Other regions include the basal ganglia, corpus callosum, and cerebellum; for review see (27, 30).

Etiology

Family, adoption, and twin studies have revealed that ADHD is a heritable disorder (31). Estimated concordance rates vary between 50 and 80% for monozygotic twins and between 0 and 30% for dizygotic twins (32, 33). Although ADHD most likely involves a polygenetic disorder, genes associated with dopaminergic functioning have typically been claimed to be involved in its etiology (34, 35). It should be noted that non-genetic factors, such as head trauma, prenatal exposure to alcohol or nicotine, and perinatal risk factors, have also been claimed to play a role in ADHD. Most likely, these factors contribute to the course and severity of ADHD (36, 37).

Treatment

Methylphenidate (MPH) is the most frequently prescribed medication for ADHD and has been found to be effective in the majority of children and adults (17, 38, 39). MPH is a stimulant drug that enhances the action of dopamine (DA) and noradrenaline (NE) in the brain. Administration of MPH not only brings about behavioral but also cognitive improvements (40, 41). Since up to 30% of ADHD patients does not respond to or does not tolerate stimulant medication, Atomoxetine, which selectively enhances the action of NE, has relatively recently been introduced as an effective alternative.

Sleep

Sleep Regulation

A detailed description of the physiology of sleep is beyond the scope of this chapter. Briefly, Borbely (42) developed a two process model of sleep regulation, which has served as an important guide for sleep research. According to this model, sleep and wakefulness are regulated by two sets of highly interrelated processes. First, the homeostatic process, or sleep drive, regulates the length and depth of sleep. It builds pressure from the moment one wakes up. The amount of sleep pressure depends on the quantity and quality of previous sleep periods and time awake. Second, the circadian system regulates sleep and wake cycles and is synchronized to a 24-h day by environmental cues, such as light. The homeostatic and circadian system are claimed to be mediated by different neural pathways. The mechanism underlying the homeostatic system is largely unknown but claimed to include cholinergic neurons of the basal forebrain. The neural mechanism of the circadian system involves the suprachiasmatic nucleus (SCN) of the hypothalamus. Sleep disturbances can be caused by deficits in either of these systems. Overlap in central nervous systems that regulate sleep and attention or arousal, especially those mediated by DA and NE, may underlie the high incidence of sleep problems and disorders in ADHD.

Causes of Sleepiness

Sleepiness is defined as an "awake condition that is associated with an increased tendency to fall asleep" (43), and has often been contrasted with alertness, or the "overall readiness to deal with incoming stimuli" (44). Although everyone feels sleepy once every now and then, some individuals regularly experience an excessive degree of daytime sleepiness that causes high levels of dysfunction. Owens (45) described a clinical framework distinguishing four basic mechanisms that may account for excessive daytime sleepiness (EDS): insufficient sleep (for example, because of delayed sleep onset or shortened sleep duration), fragmented or disrupted sleep (for example, because of a primary sleep disorder), disorders of daytime sleepiness (for example, narcolepsy), or disorders of circadian rhythms (for example, delayed sleep phase syndrome (DSPS)]. Poor sleep quality and insufficient sleep quantity may have external (excessive noise or use of drugs) or internal (motivation or hormonal changes) causes.

Some primary sleep disorders have been claimed to be associated with ADHD and therefore require further explanation. Sleep-disordered breathing (SDB) results in fragmented sleep and includes a variety of disorders that range from snoring to obstructive sleep apnea (OSA), which refers to a condition characterized by episodes of stopped breathing during sleep. Restless leg syndrome (RLS) and periodic limb movement disorder (PLMD) result in insufficient (delayed SOL) or fragmented sleep by inducing uncomfortable, tingly sensations

in the leg or other limb, especially when at rest. Narcolepsy results in daytime sleepiness and is characterized by irresistible sleep attacks. Although retrospective surveys have suggested onset in late childhood or adolescence, narcolepsy is rarely diagnosed in childhood (46). In childhood, these patients are often misdiagnosed with depression, CD, ODD, ADHD, or epilepsy. Finally, the DSPS is one example of circadian rhythm disorders. It results in insufficient sleep and is characterized by an increase in energy in the evening (difficulty falling asleep) and a lack of energy in the morning (difficulty waking up). DSPS is due to a circadian cycle that is slower than a 24-h day. As a consequence, the secretion of melatonin is not in synchrony with environmental cues reflecting day and night cycles.

Effects of Sleepiness

Overt behavioral manifestations of sleepiness are well-known and include increased yawning, rubbing eyes, resting the head, or falling asleep during tasks that require alertness. Studies in healthy subjects after sleep restriction or sleep deprivation have shown increases in risk-taking behavior, traffic accidents, oppositional behavior, aggressiveness, and negative mood (47, 48). Importantly, EDS has been associated with inattention, impulsivity, and hyperactivity, and thereby mimics ADHD symptomatology (49, 50). Regarding cognitive performance, both EDS and ADHD have been associated with impaired performance on cognitive tasks that measure (prefrontal) functions, such as cognitive flexibility, abstract reasoning, attention, vigilance, memory, and motor skills (51, 52). In line with these finding, PET studies have demonstrated decreased glucose metabolism in prefrontal cortex after sleep deprivation in healthy subjects (53).

Assessing Sleep Problems

A variety of techniques has been developed to assess sleep problems, sleep disorders, and associated EDS. These techniques can be categorized as subjective and objective. Subjective measures rely on questionnaires and diaries that provide insight into the individual's own experience of sleep problems. In the case of children, parents (or other caretakers) are often asked to report on the child's behavior. Although some questionnaires have been validated, e.g., the Pediatric Sleep Questionnaire (PSQ) (54) and the Epworth Sleepiness Scale (ESS) (55), many researchers use their own non-validated questionnaires. Results should be interpreted with caution, as normal sleep patterns may be misperceived as being problematic, especially in behaviorally disturbed children.

Objective measures can be further subdivided into behavioral and physiological measures. The Multiple Sleep Latency Test (MSLT) is typically used to assess EDS (56). Subjects are given a series of nap opportunities. If subjects fall asleep, they are awakened after a few minutes. If subjects do not fall asleep, the nap opportunity is terminated after 20 min. Both a decrease in sleep onset and an increase in the number of naps are indicative of EDS. Nocturnal activity levels are typically assessed with actigraphy, which involves monitoring movement during day and night with an ambulatory wrist or waist device. Because these devices are lightweight and non-invasive, subjects can take it home and wear it for an extended period of time. Finally, polysomnography (PSG) is used to measure physiological variables during sleep, such as heart rate and breathing parameters. Measurement of the encephalogram (EEG) enables insight into sleep architecture (stages). PSG procedures preferably include an adaptation night, in which subjects are given the opportunity to familiarize with the recording environment. Of note, result obtained with PSG and actigraphy have been found to correlate highly (>90%) (57, 58).

Dependent Measures

To assess sleep quality as well as sleep quantity, common outcome variables include sleep onset latency (SOL), total sleep duration, sleep efficiency (time asleep/time in bed $\times$ 100), number of nighttime awakenings, and the presence of sleep disorders. Subjective measures additionally provide insight into bedtime resistance, feeling refreshed in the morning, and external factors [such as excessive noise levels, use of drugs (e.g., caffeine), a lack of bedtime routines], whereas objective measures additionally assess nocturnal activity levels and sleep architecture, i.e., the percentage of stages 1,2,3 and 4, and REM sleep, the latency to the first REM onset, and the number of stage shifts.

Sleep Problems in ADHD

For this review on sleep abnormalities in ADHD, literature searches were conducted using PubMed databases. Keywords were "ADHD," "attention deficit," "hyperactivity," and "sleep." Case studies, abstracts, reviews, letters, and papers written in a language other than English were excluded. Furthermore, studies were limited to those actually including ADHD patients. This means that studies assessing the link between sleep problems and inattention or hyperactivity in the general population (59, 60) or studies assessing ADHD symptoms in patients with a primary sleep disorder were excluded (61). Selected papers were carefully examined to include relevant studies that had been missed. Below, papers are categorized according to methodology.

Subjective Measures

All the 18 studies using subjective measures have revealed sleep problems in ADHD (see Table 28.1a). These problems involve the full spectrum of complaints indicating poor sleep quality and quantity. In children and adolescents with

ADHD, longer SOL (because of difficulty falling asleep or bedtime resistance) (62–65), fragmented sleep (because of a higher rate of nighttime awakenings) (66), difficulty waking up in the morning (62), and abnormal sleep durations have been found. Regarding the latter, both increases, e.g., (66), and decreases, e.g., (64), in sleep duration have been reported. Because of these sleep problems, ADHD children and adolescents have been reported to be more sleepy during the day, e.g., (67,68). Finally, sleep disorders, especially SDB (67–69) and PLMD (63) have been shown to be more prevalent in children and adolescents with ADHD. Only two studies focused on adults with ADHD. Schredl et al. (70) showed that adults with ADHD rated their sleep quality and feelings of being refreshed in the morning significantly lower than healthy controls. Oosterloo et al. (71) found indications of EDS in 37.7% of adult ADHD patients with strongest correlations for inattention symptoms. Likewise, in ADHD children, Lebourgeois et al. (72) found inattention to be related to EDS, whereas hyperactivity was related to snoring (SDB).

Although subjective studies have clearly demonstrated a link between ADHD and sleep problems across the lifespan, some studies have stressed the potential contribution of confounding factors. First, it seems hard to differentiate sleep problems in ADHD from those in other psychiatric populations (73). Also, part of the sleep problems in ADHD may be mediated by the presence of comorbid conditions (74). More specifically, Corkum et al. (62) found that bedtime resistance, problems waking up, and SOL were mediated by the presence of ODD, whereas the increase in nocturnal activity levels found in combined subtype children was related to the presence of separation anxiety. Second, sleep problems in ADHD may be partly attributable to the use of (stimulant) medication (62, 74, 75). Stein (65) found an increase in SOL and insomnia when comparing medicated versus non-medicated children with ADHD. In contrast, Ball et al. (76) (children) and Schredl et al. (70) (adults) did not find a relation with medication intake. However, because these studies did not randomly assign subjects to treatment or placebo conditions, these results may merely reflect that medicated patients suffer from more severe forms of ADHD (77) [see however (78)] or are characterized by different or more severe comorbid conditions.

Actual intervention studies using subjective measures in ADHD children and adolescents have mainly yielded mixed results (see Table 28.1b). Out of 5 studies administering MPH, 2 found an increase in sleep problems (79, 80), whereas 2 others did not find any effect (81, 82). Kent et al. (83) showed that additional administration of MPH in the late afternoon (on top of drug intake in the morning and at noon) led to an increased feeling of being refreshed in the morning as reported by staff members of an inpatient psychiatric service. As for other interventions, dextro-amphetamine (D-amp) was associated with an increase in sleep problems (82), whereas Clonidine (84) and Melatonin (85) as well as the improvement of sleep hygiene procedures reduced the report of sleep problems in children and adolescents with ADHD.

MSLT

Two studies used MSLT to asses EDS in children and adolescents with ADHD (86, 87). Since the main focus of these studies was on PSG (discussed on page 269), the MSLT results are presented in Table 28.3a. ADHD patients were consistently found to be sleepier than healthy controls, as indicated by a decrease in SOL (86, 87) and an increase in the number of naps (87). Lecendreux et al. (86) found that children with the hyperactive/impulsive subtype fell asleep fast, whereas children with the inattentive subtype fell asleep more often. Palm et al. (88) assessed sleepiness in children diagnosed with deficits in attention, motor control and perception (DAMP), which is related to ADHD, and similarly found indications of increased EDS (also presented in Table 28.3a).

Actigraph

Findings from studies using actigraphic data are mixed. Out of 6 studies comparing ADHD children or adolescents to controls (see Table 28.2a), 2 reported higher nocturnal activity levels (89, 90), whereas 2 others did not find any differences (91, 92). Konofal et al. (93) replicated findings of increased activity using infrared video recordings (Table 28.3a). Strikingly, 2 studies performed by Gruber et al (94, 95) indicated increased night-to-night variability in sleep patterns (see also (96) et al., in Table 28.3a). This stresses the importance of collecting actigraphic data for an extended period of time. Other differences between ADHD patients and controls, such as decreased sleep efficiency and differences in sleep architecture, were less consistent (89). Van der Heijden et al. (97, 98) compared ADHD children with chronic sleep onset insomnia (SOI) to those without SOI. The first group was characterized by an increase in SOL and a delay in sleep phase. Only one study compared adults with ADHD to healthy controls (99). This study demonstrated an increase in nocturnal activity levels (see Table 28.2b).

After administration of MPH, 3 interventions studies showed shorter sleep duration in ADHD children or adolescents (100–102) (see Table 28.2b). Schwartz et al. (102) additionally found an increase in SOL and a reduction in sleep efficiency, which did not depend on the clinical effectiveness of MPH. Gruber et al. (103) divided a group of 29 ADHD children into 2 subtypes based on their polymorphism in the catechol-o-methyltransferase (COMT) gene, which codes for dopamine. Children who were Val allele carriers (Val-Val or Val-Met) were reported to have more sleep problems than children with the Met homozygous genotype. This was in line with actigraphic findings of fragmented sleep in this group, and did not improve after MPH intake. In adults with ADHD, Kooij et al. (99) demonstrated that MPH (or D-amp in one subject) reduced nocturnal activity levels and improved

TABLE 28.1a Studies comparing ADHD to control groups with main focus on subjective measures.

Author	Year	Method	Group	Age	Diagnosis	Subtype	Exclusion	Drug	Results
Ball et al. (76)	1997	P	MED(28;6) nonMED(74;18) CLIN(78;22)	9 (2.7) 8.7 (3.1) 8.9 (2.8)	DSM-III-R	–	–	I	More sleep problems in ADHD, not related to medication.
Carskadon et al. (67)	1993	P	AT(29;12) DS(70;32) DS-SIB(48;21) ADHD(21;1)	8.7(3) 11.6(4) 10.1(3.4) 9.1(2)	DSM-III	ADDwH	D1/M	–	SDB in 2 ADHD patients, EDS in 38%.
Chervin et al. (68)	1997	P	ADHD(27;1) CLIN(43;21) CNT(73;44)	9.5(3.7) 11.0(4.8) 7.7(4.6)	DSM-IV	I/C	D1/S	I	ADHD linked with snoring, and less with EDS and RLS.
Corkum et al. (62)	1999	P	nonMED(79;14) MED(22;3) CNT(36;8) CLIN(35;11)	9.2(1.5) 8.7(1.6) 9.4(1.4) 8.1(1.3)	DSM-IV	I/HI/C	D1/D2/M	I	Bedtime resistance, problems waking up, delayed onset related to ODD/medication, more movement to separation anxiety.
Day Abmayr (75)	1998	P	MED(20;4) CLIN(20;9) CNT(20;6)	7.9(1.8) 9.2(1.4) 7.0(1.3)	DSM-III-R	–(I/HI)	M	I	More sleep problems.
Gaultney et al. (63)	2005	P	GEN(283;142) subADHD(42)	9.8	–	–	–	MPH (n=37)	ADHD symptoms related to PLMD and bedtime resistance, but not to SDB.
Hoeppner et al. (127)	1996	P	ADD(48;9) CLIN(30;9)	9.3(3.4) 8.5(2.8)	DSM-III	(C)	D1/M	E	ADHD more sleep problems with onset 0-12 months and 1-3 years (retrospective).
Kaplan et al. (66)	1987	P	ADHD1(40;10) CNT1(40;10) ADHD2(116;0) CNT2(88;0) ADHD3(25;0) CNT3(27;0)	– – 4.5(0.9) 4.5(1.0) 4.5(1.0) 4.4(0.9)	DSM-III	ADDwH	–	E	Qp: more sleep problems, Dp: increased night awakenings only
LeBourgeois et al. (72)	2004	P	ADHD(45;7) CNT(29;11)	9.8(2.8) 9.2(2.5)	DSM-IV	I/HI/C	D1	I	More sleep problems. Hyperactivity related to snoring and inattention to EDS
Marcotte et al. (73)	1998	P	ADHD(43;12) LD(11;3) ADHD+LD(25;6) CNT(86;30) CLIN(79;21)	8.5(1.7) 9.2(0.9) 8.9(1.6) 8.9(1.7) 8.7(1.7)	DSM-III-R	–	D1/D2/D3/M	E	More sleep problems across all clinical group (except for duration on weeknights)

Mick et al. (74)	2000	P	ADHD(122) CNT(105)	14.6(3.1) 15.4(3.7)	DSM-III-R	–	D1/M	I	More sleep problems, mediated by co-morbidity and medication
Oosterloo et al. (71)	2006	S	ADHD(61;26) HSO(74;44)	35(10.3) 48.5(16.2)	DSM-IV	–	–	E/I	37.7% of ADHD reported EDS (strongest for inattention), and 18.9% of HSO reported ADHD
Owens et al. (64)	2000	S/P	ADHD(46;12) CNT(46;14)	7.5(1.6) 7.2(1.4)	DSM-IV	I/HI/C	D/1/D2/M/S	E	Qs: more problems, delayed onset. Qp: more problems, shorter duration
Pagel et al. (69)	2004	P	OSA AHI<5 (45;15) OSA AHI>5 (29;12)	9.7(–) 10.7(–)	DSM-IV	–	M	I	Patients with EDS underwent PSG. Mean AHI for 30 ADHD patients was 7.1, others 4.5
Ring et al. (78)	1998	P	ADHD(13;1) SIB(16;6)	8.4(2.7) 10.8(3.1)	–	–	D1/D2/D3/M	W	More sleep problems and disorders. No relation with severity
Schredl et al. (70)	2006	S	ADHD(120) Sub(61;34) CNT(444;376)	35.3(10.8) 23.5(5.7)	DSM-IV	I/HI/C	I	E	More sleep problems. Less refreshed in morning. No relation with medication
Stein et al. (77)	2002	S	nonMED(32;0) MED(35;0) CNT(77;0)	13.1(1.2) 13.3(2.0) 13.5(1.4)	DSM-IV	–	D1/D2/D3/M	I	Medicated group more sleep problems, also higher ADHD, depression and anxiety score
Stein (65)	1999	P	MED(40;6) Non-MED(61;11) CLIN(34;13) CNT(83;41)	10.1(2.8) 7.9(2.7) 9.3(3.7) 9.6(4.1)	DSM-IV	–	–	I	Sleep problems in 19.3% of ADHD, 13.3% of CLIN , 6.2%. Delayed onset or insomnia in 29% of medicated and 10% of non-medicated ADHD

Method (P = parental, S = self-report), Group (MED) =medicated, non-MED = non-medicated, CLIN = sample with DSM diagnosis other than ADHD, GEN = general population, CNT = control group, Sub = subgroup, AT = adenotonsillar enlargement, DS = Down Syndrome, SIB = sibling, LD = learning disorder, OSA = obstructive sleep apnea, AHI = apnea hypopnea index, HSO = hypersomnia (narcolepsy and idiopathic hypersomnia), Subtype (wH = with hyperactivity, I = inattentive, HI = hyperactivity/impulsivity, C = combined), Exclusion (D1 = at least one out of: mental retardation (IQ < 80), learning disorder, Tourette, PDD, autism, psychosis, D2: anxiety and/or depression, D3 = ODD and/or CD, D4 = disorders causing behavior and/or sleep problems, M = medical disorders, S = sleep disorders, I = included), Drug (I = included, E = excluded, W = washout), Results (Qp/Dp = parental questionnaire/diary, Qs/Ds = self-report questionnaire/diary). Parentheses [Group (n, female)], Age (mean, standard deviation).

TABLE 28.1b Intervention studies using subjective measures.

Author	Year	Method	Group	Age	Diagnosis	Subtype	Excl.	Drug	Intervention	Results
Ahman et al. (79)	1993	P	ADHD sub1(127;29) sub2(79;16)	5–15 5–9 10–15	DSM-III-R	–(C/HI)	D1	–	MPH 0.3/0.5 mg per kg/PLC7 days	MPH increased insomnia.
Barkley et al. (80)	1990	P	ADHD(83;12)	8.2(2.2)	DSM-III-R	C	D1/M	–	MPH 0.3/0.5 mg per kg/PLC7 days	MPH increased sleep problems. No effect of dose.
Efron et al. (82)	1997	P	ADHD(125;11)	8.7(2.3)	DSM-IV	–	D1/M	E	MPH/d-amp2 weeks	More sleep problems after d-amp vs baseline. No effect MPH.
Kent et al. (83)	1995	Stf	ADHD(12;1)	9.0(2.0)	DSM-III-R	ADDwH	D1/D2/M	MPH 7/12am	+MPH 10/15 mg at 4pm / PLC4 days	No effect on latency, but more refreshed in morning.
Pelham et al. (81)	2001	P	ADHD(68;8)	9.1(–)	DSM-IV	I/HI/C	M/D1	MPH	3 doses of fast/slow-release MPH/ PLC7 days	No drug effects on sleep quality.
Prince et al. (84)	1996	P	ADHD(62;11) Sub1(42) Sub2(20)	4–18 9.2(0.24) 15.4(0.33)	DSM-III-R	–	I	I	Clonidine∼3 yrs	Retrospective review: improvement of sleep problems in 85%.
Weiss et al. (85)	2006	P	ADHD(19;2)	10.3	DSM-IV	C/I	S	I	HygieneMEL/PLC10 days	Both reduced sleep problems, but this did not affect ADHD symptoms.

Abbreviations: Method (Stf = Staff), Intervention (PLC = placebo, MPH = methylphenidate, + = in addition to, MEL = melatonin, D-amp = dextro-amphetamine; duration of intervention is reported). For other abbreviations, see Table 28.1a.

TABLE 28.2a Studies comparing ADHD to control groups with main focus on actigraphy.

Author	Year	Method	Group	Age	Diagnosis	Subtype	Exclusion	Drug	Results
Corkum et al. (92)	2001	A(7av)/S	ADHD(25;5)	9.1(1.4)	DSM-IV	I/HI/C	D1/D2/M	E	Qp: disturbed sleep. Dp: longer duration. A: no effects
			CNT(25;5)	9.7(1.3)					
Dagan et al. (89)	1997	A(3av)/S	ADHD(12;0)	9.6(1.6)	DSM-IV	–	D4/M	I (n = 5)	Qp: no difference. A: more activity, lower efficiency, different architecture
			CNT(12;0)	7.9(1.2)					
Gruber et al. (94)	2000	A(5)/S	ADHD(38;0)	9.6(2.7)	DSM-IV	–	D4/M	E	Ds: no effect. A: increased variability
			CNT(64;0)	9.4(1.7)					
Gruber Sadeh (95)	2004	A(5)/C	ADHD(24;0)	8.9(1.25)	DSM-IV	I/HI/C	D1/D2/D3/M	E	C: relation with sleep in CNT only. A: increased variability
			CNT(25;0)	8.8(1.0)					
Porrino et al. (90)	1983	A(7av)	ADHD(12;0)	8.6(2.1)	DSM-III	ADDwH	D1/D2/M	–	More activity
			CNT(12;0)	8.6(1.9)					
Van der Heijden et al. (97)	2005	A(7)/DLMO	ADHD+SOI(87;21)	8.8(1.7)	DSM-IV	I/HI/C	D1/M	E	Delayed sleep phase and DLMO in ADHD+SOI
			ADHD(33;6)	8.2(2.0)					
Van der Heijden et al. (98)	2006	A(7av)/S	ADHD+SOI(74;18)	9.1(2.1)	DSM-IV	I/HI/C	D1/M	E	Qp: no difference. A: later onset in ADHD+SOI
			ADHD(23;3)	7.9(1.8)					
Wiggs et al. (91)	2005	A(5av)/S	ADHD(71;8)	8.8(2.6)	DSM-IV	I/HI/C	I	E	Qp/Dp: disturbed sleep. A: normal, no effect subtype
			CNT(23;7)	9.5(2.5)					

Method (A = actigraphy, number of days between parentheses, av = results are averaged over nights, S = subjective, C = cognitive performance, DLMO = dim light melatonin onset), Group (SOI = sleep onset insomnia). For other abbreviations, see Table 28.1.

subjective sleep quality. As for other interventions, Van der Heijden et al. (104) showed that the administration of Melatonin resulted in shorter SOL and longer sleep duration in a group of children with ADHD. However, this improvement did not affect behavior or cognitive measures.

PSG

Numerous studies used polysomnographic measures to assess sleep disturbances in ADHD (Table 28.3a). Hardly any of those convincingly indicated differences in sleep architecture between ADHD children or adolescents and controls. If anything, the data suggests abnormalities in the latency to the onset of the first REM period as well as the percentage of REM periods. However, the direction of REM findings varies widely: some studies have indicated increased REM latency (105–108), often in combination with decreased REM percentage (105, 107–111), whereas others found decreased REM latency (112, 113), often in combination with increased REM percentage (87, 113). Two studies of O'brien et al. (107, 108) additionally suggest that REM abnormalities may interact with the severity of ADHD. As for other sleep stages, increased slow-wave sleep (stage 3 and 4) (111), increased delta (114), and a higher number of stage shifts (111, 113) have been found. Lindberg et al (115) assessed sleep problems in adult patients diagnosed with ASP and Cloninger type 2 alcoholism, and found increases in sleep stage 4, delta and theta powers that correlated positively with the severity of childhood ADHD (assessed retrospectively). However, Philipsen et al. (116) could not replicate abnormalities in sleep architecture in a sample of ADHD adults.

PSG data has also been used to objectively assess the presence of comorbid sleep disorders. An increased prevalence of PLMD (87, 96, 107, 116, 117) has been reported in children as well as adults with ADHD. Crabtree et al. (110) even found that children who suffer from ADHD and comorbid PLMD have more sleep problems and display more PLMD arousals than children suffering from PLMD only. Other studies have indicated increased risk of SDB in ADHD patients across the lifespan (87, 96, 108, 118). Huang et al. (119) specifically studied the incidence of OSA in a group of children that were referred for behavioral problems and were diagnosed with ADHD. The apnea-hypopnea index (AHI) was found to be larger than 1 in 56.8%, and larger than 5 in 19.3% of ADHD patients. Of note, children that were diagnosed with ADHD and OSA were characterized by higher levels of hyperactivity.

TABLE 28.2b Intervention studies with main focus on actigraphy.

Author	Year	Method	Group	Age	Diagnosis	Subtype	Excl.	Drug	Intervention	Results
Gruber et al. (103)	2006	A(2*7av)/S	MET(8;1) VAL(21;4)	8.7(1.8) 9.3(1.9)	DSM-IV	I/HI/C	D1	I	MPH/PLC 7 days	Dp: no effect. Qp: VAL more sleep problems. A:VAL less continuity. I: no effect.
Kooij et al. (99)	2001	A(2*6av)/S	ADHD (8;3) CNT(8;4)	29.4(8.2) 33.1(7.2)	DSM-IV	I/C	I	W	MPH/d-amp PLC 3 weeks	D: lower quality. A: more activity. I: improved both.
Schwartz et al. (102)	2004	A(2*7av)	ADHD(44;7)	9.2(1.8)	DMS-IV	–(I/C)	D1	W	MPH/PLC 7 days	MPH: later onset, shorter duration, less efficient. No effect of clinical response.
Stein et al. (100)	1996	A(5*2)/S	ADHD(25;0)	8.0(1.8)	DSM-III-R	I/C	D1	W	MPH(2x,3x,t)/PLC 7 days	Dp/A: shorter duration with higher dose.
Tirosh et al. (101)	1993	A(3*4av)	ADHD+LD(10;3) CNT(20;6)	median 9.7;m	DSM-III-R	–	M	E	MPH/PLAC 8 days	I: shorter duration.
Van der Heijden et al. (104)	2007	A(2*7av)/S/DLMO	ADHD+SOI(105) MEL(53;18) PLAC(52;9)	9.1(2.3);9.3(1.8)	DSM-IV	I/HI/C	D1/M	E	MEL/PLC 4 weeks	MEL: shorter onset, longer duration. No effect on behavior or cognition.

Age (m=matched), Intervention (2x=twice per day, 3x=three times per day, t=titrated). For other abbreviations, see Tables 28.1 and 28.2a.

Despite these findings, SDB seems to occur less frequently in ADHD than PLMD does. Crabtree et al. (96) estimated prevalence rates to be around 7 and 36%, respectively.

As for other sleep parameters derived from PSG, increased nocturnal activity (106, 120), decreased SOL (114), fragmented sleep (114, 120), and reduced sleep duration (87, 111) as well as efficiency (87) have been demonstrated in children and adolescents with ADHD. Ramos Platon et al. (114) additionally found that children with hyperactivity symptoms displayed more fragmented and less efficient sleep than those diagnosed with other subtypes. In adults with ADHD, Surman et al. (118) showed higher sleep fragmentation, which corresponded with subjective reports of decreased quality. Taken together, results from PSG studies are mixed and suggest a wide variety in sleep problems. Recently, however, Sadeh et al. (121) performed a meta-analysis of PSG studies in ADHD children. Convincing evidence was only found for PLMD: children with ADHD are more likely to have comorbid PLMD or display a higher number of periodic limb movements (PLM) during sleep. Besides, a number of potential moderating factors was identified: age, gender, comorbidity and inclusion of an adaptation night all played a mediating role in the association between problems and ADHD.

Five PSG studies focused on the effect of interventions (Table 28.3b). Although Huang et al. (122) did not find any effect of MPH after 6 months of administration, Greenhill et al. (123) found an increase in SOL, sleep duration, REM periods and the number of stage shifts in children with ADHD. Sangal et al. (124) found that MPH increases SOL more than Atomoxetine does, and that subjective measures showed more improvement for the latter. As for other interventions, the administration of a late afternoon dose of D-amp was found to increase stage 1 and 2, decrease stage 3 and 4, delay REM onset, and decrease REM percentage (125). Walters et al. (126) found that dopaminergic treatment with L-dopa or Pergolide positively affected ADHD symptoms and improved symptoms of RLS and PLDM. Finally, Huang et al. (122) compared the effectiveness of adenotonsillectomy, MPH, and no treatment in ADHD children with mild OSA (AHI $> 1 < 5$). Children who underwent surgery showed the best improvements on subjective sleep quality (as reported by caretakers), sleep duration, REM percentage, slow wave percentage, OSA, snoring, cognitive tasks and ADHD symptoms.

Discussion

ADHD is a highly prevalent neuropsychiatric disorder characterized by symptoms of inattention, impulsivity and hyperactivity. Although ADHD was long considered to be restricted to childhood, longitudinal studies have shown persistence into adulthood in up to 70% of affected individuals. The majority of ADHD patients is additionally diagnosed with a comorbid condition, such as depression, drug abuse or CD. Across the lifespan, ADHD patients perform poorly on a wide variety of cognitive tasks, especially those measuring inhibitory control. This is in line with abnormalities in (right) fronto-striatal regions that are mediated by dopaminergic and noradrenergic pathways. MPH, which enhances the action of these neurotransmitters, is the drug of choice for ADHD. It has been found to improve behavioral problems as well as cognitive impairments. The exact mechanism of genetic transmission is not yet understood, but ADHD likely involves a polygenetic disorder that is exacerbated by adverse environmental factors, such as prenatal exposure to nicotine.

In clinical practice, ADHD patients (or their parents) often complain about a variety of sleep disturbances. Systematic studies on sleep abnormalities in ADHD have only partly confirmed these clinical observations. This may in part be attributable to the complex interaction between sleep and ADHD. Poor sleep quality and insufficient sleep quantity result in EDS, which induces behavioral problems and cognitive impairments that mimic ADHD symptoms. On the other hand, EDS may intensify existing ADHD. Furthermore, sleep abnormalities and ADHD may tend to co-occur, because they share dysfunctions in common dopaminergic and noradrenergic pathways. In this chapter, we reviewed studies assessing the occurrence of sleep disorders, sleep problems and EDS in ADHD across the lifespan.

Comorbid Sleep Disorders in ADHD

Studies on prevalence rates of sleep disorders in ADHD have demonstrated frequent occurrence of comorbid sleep related breathing disorders (SBD), RLS, and PLMD across the lifespan. Sadeh et al. (121) performed a meta-analysis of PSG studies in children with ADHD and concluded that evidence was convincing for PLMD only. Possibly, PLMD and ADHD share common dysfunctions in dopaminergic systems.

Subjective Measures

Studies using subjective measures, such as questionnaires and diaries, have largely confirmed the high prevalence of a wide range of sleep problems in ADHD, such as increased SOL (due to difficulty falling asleep or bedtime resistance), difficulty waking up in the morning (possibly reflecting delayed sleep phases), fragmented sleep (due to night awakenings, breathing problems, or periodic movement), decreased sleep efficiency, either decreased or increased sleep duration, and associated EDS. When comparing ADHD children to those diagnosed with other psychiatric disorders rather than healthy controls, results have been less convincing. This throws doubt on the specificity of sleep problems in ADHD. Also, subjective data have suggested that sleep problems in ADHD are mediated by the presence of comorbid conditions and the use of stimulant medication.

TABLE 28.3a Studies comparing ADHD to control groups with main focus on PSG.

Author	Year	Method	Group	Age	Diagnosis	Subtype	Exclusion	Drug	Results
Andreou et al. (120)	2003	P(1)	ADHD(18;4) CNT(18;4)	T10.6(2.1) M	DSM-IV	–	–	–	Apnea, awakening, limb activity and lower verbal IQ (WISC-III).
Busby et al. (106)	1981	P(3–5th)	ADHD(11;0) CNT(11;0)	10.6(1.7) 10.6(1.3)	DSM-III	ADDwH	D1/D2/M/S	E	Delayed REM onset, more movement.
Cooper et al. (128)	2004	P(1)	ADHD(18;3) CNT(20;9)	10.5(3.0) 10.0(3.9)	DSM-IV	–	–	W	No group effects.
Crabtree et al. (110)	2003	P(1)/S	ADHD+PLMD(40;8) PLMD(50;16) CNT(52;26)	7.8(1.9) 7.1(1.5) 6.7(0.5)	–	–	M	I	Qp/PSG: ADHD+PLMD more sleep problems and more PLM arousals than PLMD. Both showed less REM than CNT.
Crabtree et al. (96)	2003	A(14)/S/P(1)	ADHD(97;22)	8.3(3.0)	DSM-IV	–	I	I	Qp: disturbed sleep. A: variability in sleep schedules. PSG:36% PLMD, 7% SDB.
Golan et al. (87)	2004	P(1)/M/S	ADHD(34;8) CNT(32;11)	12.4(4.6) 12(3.6)	DSM-IV	–	–	W	PSG: increase in REM and higher prevalence of SDB and PLMS. Duration and efficiency worst in ADHD only. MSLT: shorter onset and more naps.
Huang et al. (119)	2004	P(1)/S/C	ADHD(88;11) CNT(27;6)	8.5(1.9) 9(2.0)	DSM-IV	I/HI/C	D1/D2/M	W	56.8% AHI>1, 19.3% AHI>5, 10.2% PLMS. ADHD+SD: worse TOVA and hyperactivity.
Khan (112)	1982	P(3th)	ADHD(16;0) CNT(12;0)	8.6(–) 8.1(–)	–	ADDwH	M	W	Shorter REM latency.
Kirov et al. (113)	2004	P(2nd)	ADHD(17;0) CNT(17;0)	11.2(2.0) 11.2(2.3)	DSM-IV/ICD10	C	D1/M	W	More cycles. Increase in REM and shorter latency.
Konofal et al. (93)	2001	P(4th)/V	ADHD(30;0) CNT+LD(19;0)	7.8(1.6) 8.4(1.4)	DSM-IV	–	D1/D2//M/S	E	PSG: no effect. V: more and longer movements.
Lecendreux et al. (86)	2000	P(4th)/M/C	ADHD(30;0) CNT(22;0)	7.8(1.6) 8.4(1.4)	DSM-IV	I/HI/C	D1/D2/M/S	E	MSLT: shorter onset. Longer RT. Differences across subtypes. HI fell asleep fast, I often. HI faster RT.
Lindberg et al. (115)	2004	P(2nd)	ASP+Alc(14;0) CNT(10;0)	30.6(2.7) 34.0(3.6)	DSM-IV	–	D1/D2/D3	W	ASP higher WURS, which correlated with amount of stage 4 and delta and theta powers.
Miano et al. (111)	2006	P(2nd)	ADHD(20;2) CNT(20;9)	9.3(–) 8.4(–)	DSM-IV	I/C	M	E	Decreased sleep duration and REM, increase in stage shifts and slow-waves.

O'Brien et al. (108)	2003	P(1)/S	ADHDcl(47;12) ADHDco(53;22) CNT(49;27)	8.0(1.6) 6.6(0.4) 6.7(0.4)	DSM-IV	–	D1/D2/D3	–	Qp: ADHD more disturbed. PSG: both ADHD delayed REM. ADHDcl decrease in REM and PLMS.
O'Brien et al. (108)	2003	P(1)/S/C	ADHDsi(44) ADHDmi(27) CNT(39)	5–7	DSM-IV	–	D1/D2/D3/M	–	Qp: more snoring. PSG: OSA in mild ADHD, REM delayed and decreased in significant ADHD.
O'Brien et al. (109)	2003	P(1)/S	MED(53;13) nonMED(34;16) CNT(53;30)	6.9(1.4) 6.5(1.5) 6.6(0.6)	DSM-IV	–	M	W/E/E	Qp: both ADHD more disturbed. PSG: both ADHD decreased REM.
Palm et al. (88)	1992	P(2)/M/C	DAMP(10;2) CNT(18;9)	9.3(1.8) 10.7(–)	NA	NA	D1/M	E	MSLT: shorter onset. Longer RT.
Philipsen et al. (116)	2005	P(2nd)/S	ADHD(20;9) CNT(20;9)	33.5(8.9) 33.3(8.8)	DSM-IV/ICD10	C	D2/S	W	Q: decreased time and quality. PSG: Increased PLM, larger first night effects.
Picchietti et al. (129)	1998	P(1)/S	ADHD+PLMD(18;6) SC(38;19)	8.7() 7.4(–)	DSM-III-R	–	D1/D2/M/S	W(hrs)	Prevalence PLMD: 18 out of 27 in ADHD had 2 out of 38 in SD.
Picchietti et al. (117)	1999	P(1)	ADHD(14;1) CNT(10;5)	8.2(–) 11.1(–)	DSM-IV	–	D1/M/S	E	64% of ADHD had PLMD, none of controls. This leads to insufficient and fragmented sleep.
Ramos Platon et al. (114)	1990	P(2nd)	ADD(13;4) wH(10) CNTp(43)	9.0(1.73) 6.8–12.1;6–12	DSM-III	I/C	D1/D2/D3/M	W	Faster onset, more awakenings, increase in delta. ADDwH more fragmented and less efficient.
Sangal et al. (105)	2005	P(1)	ADHD(40;8) CNTm(–)	10.5(2.0) –(–)	DSM-IV	I/HI/C	D1/D2/M/S	W	Delayed REM onset, decrease in REM.
Sangal and Sangal (130)	2004	P(1)/M/S	ADHD(18;3) SDB(38;9)	31.9(12.2) 48.7(15.5)	DSM-IV	–	–	–	Q: in snorers, but not in ADHD, EDS correlated with I and lowest saturation correlated with HI.
Surman et al. (118)	2006	P(1)/S	ADHD+SC(6;2)	45.5(5.09)	DSM-IV	C(4);I(2)	I	I	Q: decreased quality EDS(n=2) . PSG: SBD, fragmentation.

Abbreviations not explained in the text: Method (P = PSG, number of nights between parentheses, th/nd= night of actual recording), Group (ASP+Alc = antisocial personality disorder with Cloninger type 2 alcoholism, cl = clinical sample, co = community sample, si = significant, mi = mild, DAMP = deficits in attention, motor control, and perception, CNTp = extracted from previous published data, SC = sleep complaints), Diagnosis (NA = not applicable, ICD10 = International Statistical Classification of Diseases). For other abbreviations, see Tables 28.1 and 28.2.

TABLE 28.3b Intervention studies with main focus on PSG.

Author	Year	Method	Group	Age	Diagnosis	Subtype	Excl.	Drug	Intervention	Results
Chatoor et al. (125)	1983	P(2nd/3th)	ADD(7)	6–12	DSM-III	ADD	–	I/d-amp	D-amp/PLC afternoon and evening dose	Increase stage 1/2; decrease stage 3/4; decrease and delayed REM onset
Greenhill et al. (123)	1983	P(2av)/S	ADHD(7;0) CNT(11;7)	8.6(1.4) 9.3(1.1)	DSM-III	ADDwH	D1/D2/M	W	MPH 6 months	Baseline Q: restless sleep. MPH: increase in onset, duration, REM, stage shifts
Huang et al. (122)	2007	P(1)/S/C	AT(25;2) MED(27;3) Non-MED(14;2) CNT(22;4)	8.1(1.3) 8.2(1.7) 8.1(2.3) 8.9(2.1)	DSM-IV	I/HI/C	D1/D2/M/S	W	AT/MPH/none 6 months	All measures improved for AT: OSA-18, TOVA. PSG showed decrease in OSA and snoring, increase in duration.
Sangal et al. (124)	2006	P(3*2)/A(3*10)/S	ADHD(85;21)	10.1(2)	DSM-IV	I/HI/C	M/S	–	MPH/ Atomoxetine 7 weeks	MPH increased onset more than Atomoxetine. Dc/p: better quality, easy wake up, faster onset with Atomoxtine
Walters et al. (126)	2000	P(2*1)/S/C	ADHD+RLS PLMD(7;1)	4–18	DSM-IV	–	D1/D3/M	W	L-dopa/ Pergolide 6 months	Improved RLS/PLMD and ADHD symptoms

For abbreviations, see Tables 28.1, 28.2, and 28.3a.

Results from studies using subjective measures should be interpreted with caution. Subjects might be misperceiving their own sleep behavior. Parents, on the other hand, may be hindered by negative halo effects, i.e. the tendency to over-report problems in behaviorally disturbed children. Also, parental reports highly depend on what children tell them, and this may differ across different groups of subjects. Indeed, Owens et al. (2000) (64) demonstrated a higher correlation between parental and child reports in the ADHD group than in the control group.

Objective Measures

The MSLT has clearly confirmed subjective reports of increased EDS in children with ADHD. This seems a contra-intuitive finding, but has been claimed to reflect that ADHD is caused by hypo- rather than hyperarousal. Hyperactivity might be an adaptive behavior that counteracts sleepiness (45). This would also explain the seemingly paradoxical effectiveness of stimulant medication in reducing hyperactive behavior.

Studies using actigraphic and polysomnographic (PSG) measures have failed to convincingly demonstrate sleep abnormalities in such a wide range as was suggested by clinical observations and by studies using subjective measures. Actigraphic data has suggested an increase in nocturnal activity as well as a high variability in sleep patterns across nights, whereas PSG measures have mostly shown deviations in the latency and duration of rapid eye movement (REM) periods. The lack of correspondence between subjective and objective reports might indicate that subjects or their parents are not that good at judging sleep problems. On the other hand, reports and objective measures might simply provide completely different information. For example, objective measures are often collected during 1 or 2 nights. Parents hear their children's complaints every day, so inconsistencies may reflect instability of sleep patterns. This stresses the importance of collecting objective measures over an extended period of time, and analyzing data in a way that takes the night-to-night variability into account (many actigraphic studies collapse data over all recording nights). Also, it should be noted that laboratory settings do not reflect real-life situations. Often a fixed schedule is used, which may not correspond to what subjects are used to at home. Especially in behaviorally disturbed children and adults, it may be difficult to set a strict bedtime routine. Furthermore, in patients with circadian rhythm abnormalities, a fixed schedule may not correspond to the subject's sleep/wake cycle. Finally, the recording environment is new to subjects. This may differently affect sleep behavior in different groups of subjects. Indeed, Philipsen (2005) (116) found larger first-night effects in adults with ADHD than in controls, which stresses the importance of including adaptation nights.

Intervention

Sleep problems in ADHD have been claimed to reflect side effects of (stimulant) medication. In line with this notion, some studies have shown an increase in sleep problems in medicated as opposed to non-medicated children (62, 74, 75). However, these findings are likely confounded by group differences in other variables, such as ADHD severity or the presence of comorbid conditions, and could not be replicated by others (76,109). More systematic intervention studies have similarly yielded mixed results. Sleep problems have been found to reduce, increase and to be unaffected by the administration of MPH. These inconsistencies might partly be related to differences in dose and time of intake. MPH has a short half-life, which means that subjects might experience a rebound effect when the medication effect wears off at the end of the day, leading to restlessness at bedtime and difficulty falling asleep. Indeed, Kent et al. (83) showed that additional administration of MPH in the late afternoon made it easier to wake up the next morning. Pelham et al (81), however, did not find any differences between fast and slow-release (Concerta) MPH. As for other interventions, the administration of L-dopa, Pergolide, D-amp (see however (82), Clonidine, and Melatonin as well as the improvement of sleep hygiene procedures seem to reduce sleep problems.

Possible Confounds

Results of studies using subjective and objective measures are mixed, inconsistent and often contradictory. This could be due to a wide range of confounding variables that are usually not controlled for (both within and across studies). First, the criteria used to diagnose ADHD differ widely across studies. Some researchers use rigorous methods including a clinical interview performed by an experienced psychiatrist, whereas others simply administer one or two (parental) questionnaires to diagnose ADHD. The majority of studies provides evidence of ADHD in one setting only (e.g, only at home, not at school). Second, the presence of comorbid conditions is not always assessed, often not carefully reported and hardly ever controlled for (e.g., by means of covariate analysis). Some studies include children with sleep disorders (e.g., they are recruited through sleep clinics or diagnosed with the DSM-III) or breathing disorders. This may of course bias study results. Although most studies exclude patients with gross neurological or medical abnormalities and mental retardation (IQ $<$ 80), not all of them exclude comorbid psychiatric diagnoses. If so, most researchers exclude patients with Tourette, autism, PDD, and psychosis; some additionally exclude patients with depression and anxiety; and few also exclude patients with ODD, CD or learning disorders. Although obviously affecting sleep patterns, patients are hardly ever screened for drug abuse. Third, although some studies have suggested a link between inattention and EDS and between hyperactivity and SDB, most researchers fail

to report information on diagnostic subtype in their sample. Fourth, although teenagers are characterized by an increase in sleep problems and EDS (131), pubertal status is hardly ever reported. Also, the wide variety in subject's age complicates comparison across different studies. Fifth, most sleep studies in ADHD focus on male samples and fail to take possible interactions with gender into account. Sixth, medication status and treatment regimes (such as dose and time of intake) are not always reported and hardly ever controlled for. Finally, there is a wide range of other methodological issues that potentially confound study results, such as the use of small sample sizes, the administration of non-validated questionnaires and diaries, the lack of guidelines for actigraphy and PSG procedures (e.g., the inclusion of adaptation nights), non-random assignment to intervention conditions, and the absence of proper placebo conditions.

Conclusion

Accurate assessment of sleep problems in ADHD is crucial, since poor sleep quality and quantity result in EDS, which may in turn contribute to the behavioral problems and cognitive dysfunctions characterizing ADHD. This chapter reviews studies on sleep abnormalities in ADHD across the life span. Both within and across studies, results are mixed and inconsistent. Subjective measures reveal a high rate of sleep disturbances that may in part (but not exclusively) be attributable to the presence of comorbid conditions and the use of (stimulant) medication. The majority of subjective sleep complaints cannot be confirmed by more objective data. Overall, MSLT, actigraphic and PSG measures demonstrate an increase in EDS and a higher incidence of PLMD in ADHD. The use of small and heterogenous samples makes it difficult to draw any firm conclusions. The delayed onset of melatonin that has been shown in children with ADHD with sleep onset problems (97) may be a new direction for research in children as well as adults with ADHD (e.g., (132)), as it may offer an alternative explanation for the inconsistencies between subjective and objective findings.

Issues that need to be addressed by future research:

- ADHD needs to be rigorously assessed using DSM criteria and confirmed by multiple sources of information.
- Factors contributing to the heterogeneity of study samples (such as co-morbidity, subtype, medication use, treatment regiments, pubertal stage, gender) need to be assessed, carefully reported, and, if possible, controlled, for example, through covariate analysis.
- Larger sample sizes should be used.
- Selection bias should be avoided (e.g., avoid subject recruitment through sleep clinics).
- ADHD patients should not only be compared to controls but also to other clinical populations to assess the specificity of sleep problems in ADHD.
- The effect of medication intake as well as treatment regiments (dose and time of intake) should be systematically assessed by random assignment to intervention conditions and proper use of placebo conditions. The same holds for the effect of sleep hygiene training.
- Studies should focus on the direct comparison of different age groups (children, adolescents, and adults).
- Guidelines need to be developed for the assessment of sleep problems, sleep disorders, and EDS (e.g., validated questionnaires should be used and adaptation nights should be included).

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29
Sleep and Quality of Life in Eating Disorders

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Summary Anorexia nervosa (AN) and bulimia nervosa (BN) are well-recognized eating disorders clinically. Night eating syndrome (NES) and binge eating disorder (BED) are also of considerable importance and are increasingly recognized in the clinic, because of the distress they cause and their links with obesity. Each of these four eating disorders has the capacity to disturb sleep and in that respect additionally impair quality of life and the ability to function for sufferers supplementary to the characteristic eating disorder symptoms, per se. Sleep disturbance in the form of subjective impairments in sleep quality, initial- and mid-phase insomnia, changes in Rapid Eye Movement (REM) duration and density, and reduced sleep efficiency appear to be most marked in AN and NES. The NES produces the most clinically overt disturbance in sleep with frequent awakenings to ingest food and marked reductions in sleep efficiency being cardinal diagnostic features. It can be distinguished from the parasomnia, sleep-related eating disorder (SRED) by the presence of awareness during and the lack of amnesia for nocturnal eating episodes. Treatment of eating disorders is associated with improvements in quality of life measures. Sleep dysfunction is also ameliorated by successful treatment of the associated eating disorder. Although improvements in functioning and quality of life must no doubt to a large degree ensue from controlling of distressing eating disorder symptoms such as restricting, purging, and bingeing, it is also plausible that improvements in sleep quality and duration also contribute. Further research is needed to assess further links between sleep disturbance in eating disorders and quality of life.

Keywords Anorexia · bulimia · night eating syndrome · binge eating disorder · sleep-related eating disorder

Learning objectives:

- Eating Disorders have the capacity to disturb sleep, and in that respect impair quality of life.
- Subjective impairments in sleep quality, initial and mid-phase insomnia, changes in REM duration and density, and reduced sleep efficiency appear to be most marked in anorexia nervosa and night eating syndrome, compared with bulimia nervosa and binge eating disorder.
- Among obese patients with binge eating disorder, obesity, not the binge eating per se, is the factor most associated with poor sleep and consequent diminished quality of life.

Introduction

Sleep and eating are essential behaviors for human survival. Research on the relationship of sleep and eating has focused primarily on studies of (i) the effect of starvation and refeeding on sleep, (ii) the neurobiological connection among markers of sleep disturbance, eating disorders, and mood disorders, and (iii) more recently, the characterization of two conditions: the night eating syndrome (NES; 1) and sleep-related eating disorder (SRED; 2). Virtually no studies have directly examined the effect of sleep disturbance on quality of life among persons with eating disorders. The aim of this chapter is to review the clinical features of anorexia nervosa (AN), bulimia nervosa (BN), binge eating disorder (BED), and NES, and to discuss the literature on sleep, quality of life, and the impact of sleep function on quality of life in person with these disorders. The parasomnia, SRED, will be also reviewed briefly because of its overlap in certain respects with NES.

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Anorexia Nervosa

AN is characterized as refusal to maintain body weight, manifested by 1) a body weight that is less than 85% of what would be expected based on height and age, 2) an intense fear of gaining weight or becoming fat, 3) disturbance in the way in which one experiences body weight and shape, undue influence of body weight and shape on self worth, or denial of the seriousness of one's low body weight, and 4) for postmenarcheal females, the absence of at least three consecutive menstrual cycles (3). Two subtypes of AN have been identified: Restricting type and binge-eating/purging type. Dieting, fasting, and excessive exercise are indicative of the restricting subtype, whereas binge eating and/or purging behavior are necessary for the latter.

Sleep

EEG Findings of Anorectics Versus Comparison Groups

The findings from studies conducted in AN, BN, BED, and NES are summarized in Table 29.1.

Studies have compared the sleep continuity and sleep architecture of anorectics to comparison groups. In one early study, Nell and colleagues (4) compared patients with AN (n = 17, mean age = 23.1 years, range 14–37 years, six males) to healthy controls (n = 10; mean age 23.5 years, one male). In most AN subjects, EEG findings were judged to be normal (n = 10) but a subset (n = 7) had abnormal EEGs. Interestingly, the binge/purge subgroup of AN was more likely to have specific EEG findings. This group had significantly less percent time in stage 1 REM, less REM activity, less REM density compared with the "normal" EEG AN subgroup and the healthy control group. No differences were found between the groups for sleep latency, sleep efficiency, stage 1 sleep, or stage 2 sleep.

Because of the frequent co-morbidity of major depression in the setting of AN, possibly as a sequel to excessive weight loss, several studies have included a mood disorder comparison group. It is important to distinguish what may be specific findings because of the eating disorders versus those from the secondary major depressive episode.

Delvenne and colleagues (5) compared anorectics (n = 11; mean age = 18 years) to patients with depression (n = 11; mean age = 18 years) and controls (n = 11; mean age = 18 years). Results found that anorectics, compared with depressed patients, had significantly greater frequency and duration of awakenings (Table 29.1). Compared to controls, anorectics had significantly greater length of awakenings, reduced sleep efficiency, and less REM sleep. Thus, although insomnia is a cardinal clinical feature of major depression, it appears that patients with AN may in fact have an even greater degree of sleep disturbance that is independent of mood changes.

In support of this, the first quantified EEG study of AN, using spectral analysis, was conducted by Nobili and colleagues (6). Restricting subtype anorectics (n = 10; mean age = 14 years) were compared with 10 healthy controls (mean age = 14 years). Patients had increased number of awakenings, awakenings after sleep onset, and decreased slow wave sleep (% and minutes). The quantified slow wave activity analyses revealed significantly lower power density of the slow wave activity of the AN compared with that of the control groups through four sleep cycles, indicating that the sleep of anorectics is less deep and intense.

EEG Findings of Anorectics After Weight Restoration

The core clinical intervention in AN is weight restoration. Lacey and colleagues (7) studied 10 restricting subtype anorectics (mean age = 17.3 years, range 14–24 years; one male) before and after weight restoration in an inpatient treatment facility. As might be predicted, weight restoration had beneficial effects on sleep parameters. Total sleep time increased significantly after re-feeding, as did time spent in REM sleep. Total time awake after sleep onset was significantly decreased, but no significant changes were noted for stages 1–4. Similar results were reported by Lauer and colleagues (8) in a more recent study, which also included a heathy control group (Table 29.1).

Subjective Sleep Measures

One of the few studies to report subjective measures of sleep quality in addition to objective EEG findings was reported by Pieters and colleagues (9). Restricting type anorectics (n = 34; mean age = 19.4 years) were assessed before and after weight restoration. No significant differences were found between time 1 and time 2 for any EEG finding. Subjective measures of sleep quality, measured by the Pittsburgh Sleep Quality Index (PSQI; 10), however, did show significant improvements after weight restoration for subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, and consequently, the total PSQI score, indicating that EEG measures may be insensitive for detecting subtle but important impairments in quality of sleep (Table 29.1).

Predictors of Impaired Quality of Life among Anorectics

González-Pinto and colleagues (11) examined the predictors of physical and mental quality of life, as measured by the SF-36, among patients with AN (n = 47, mean age = 20.0 years, 74% restricting subtype). Predictors of poor physical quality

TABLE 29.1. Sleep studies of anorexia nervosa, bulimia nervosa, and binge eating disorder.

Study	Patient group (*n*)	Significant findings
Nell et al. (4)	Normal EEG AN (10); Abnormal EEG AN (7); Control (10)	Binge eating and purging: Abnormal EEG group > Normal EEG group % Delta: Normal EEG = 1.8, Abnormal EEG = 12.6, Control = 13.5 Stage 1 REM: Normal EEG = 22.4, Abnormal EEG = 13.2, Control = 20.3 REM Latency (minutes): Normal EEG = 62.1, Abnormal = 97.8, Control = 90.8 REM Activity (units): Normal = 94.8, Abnormal = 41.1, Control = 123.9 REM Activity/Total Sleep: Normal = 0.26, Abnormal = 0.12, Control = 0.33 REM Density: Normal = 1.11, Abnormal = 0.93, Control = 1.66
Delvenne et al. (5)	AN (11); MDD (11); Control (11)	Number of awakenings: AN = 40.5, Depressed = 21.1, Control = 36.1 Length of Awakenings (minutes): AN = 58.3, Depressed = 22.3, Control = 21.3 Sleep Efficiency: AN = 82.8, Depressed = 88.2, Control = 93.6 REM (minutes): AN = 73.5, Depressed = 76.1, Control = 117.8
Nobili et al. (6)	AN (10); Control (10)	Awakenings after sleep onset (minutes): AN = 57.1, Control = 1.3 Stage 1 (minutes): AN = 36.5, Control = 8.2 Stage 1 (%): AN = 9.5, Control = 1.8 Slow wave sleep (minutes): AN = 79.9, Control = 143.8 Slow wave sleep (%): AN = 19.5, Control = 30.6 Sleep Efficiency: AN = 87.8, Control = 99.6
Lacey et al. (7)	Anorexia, restricting subtype (10)	Pre-TST(minutes) = 386.90, Post TST (minutes) = 427.2 Pre time awake after sleep onset = 26.72 minutes, Post time awake after sleep onset = 6.76 minutes Pre-REM = 100.85 minutes, Post REM = 141.08 minutes
Lauer et al. (8)	AN (10); Control (10)	Intermittent time awake (minutes): AN Pre = 21.2, AN Post = 2.0, Control = 7.8 Slow wave sleep (%): AN Pre = 26.7, AN Post = 26.2, Control = 19.6 Stage 3 (%): AN Pre = 53.9, AN Post = 36.0, Control = 47.9 Stage 4 (5%): AN Pre = 54.1, AN Post = 65.9, Control = 33.1 Duration of first REM period (minutes): AN Pre = 9.3, AN Post = 17.8, Control = 14.6
Pieters et al. (9)	AN Restricting Subtype (34)	Pittsburgh Sleep Quality Index (lower scores indicate less disturbance): Subjective Sleep Quality: Pre = 1.43, Post = 0.83 Sleep Latency: Pre = 1.56, Post = 1.04 Sleep Duration: Pre = 0.91, Post = 0.35 Sleep Efficiency: Pre = 0.96, Post = 0.22 Sleep Disturbances: Pre = 1.48, Post = 0.96 Total Score: Pre = 8.35, Post = 4.26
Walsh et al. (13)	AN (8); BN (14); Control (14)	TST (minutes): AN = 349.0, BN = 403.3, Control = 437.5 Stage 1 (%): AN = 16.5, BN = 11.7, Control = 11.2
Lauer et al. (14)	AN (20); BN (10); Control (10)	Sleep Efficiency (%): AN = 90.2, BN = 87.9, Control = 93.3 Intermittent Awake (minutes): AN = 15.9, BN = 21.1, Control = 7.8
Lauer et al. (15)	AN (20); BN (10); Major Depressive Disorder (10); Control (10)	First REM Density (%): Depressed AN and BN (n = 14) = 19.3, Non-Depressed AN and BN (n=16) = 20.4, Major Depressive Disorder = 31.1, Control = 22.4 Mean REM Density (%):Depressed AN and BN (n = 14) = 29.1, Non-Depressed AN and BN (n=16) = 24.2, Major Depressive Disorder = 41.2, Control = 32.2
Hudson et al. (16)	BN (11); MDD (44); Control (20)	Sleep latency (minutes): BN = 16.8, MDD = 28.1, Control = 15.4 Sleep maintenance (%): BN = 97.5, MDD = 94.0, Control = 97.1 Stage 1 (%): BN = 5.3, MDD = 5.5, Control = 7.9 REM density: BN = 1.02, MDD = 1.28, Control = 0.97
Waller et al. (17)	BN (12); MDD (61); Control (20)	Sleep latency (minutes): BN = 15.2, MDD = 23.4, Control = 10.4 Sleep efficiency: BN = 93.0, MDD = 87.5, Control = 93.1 Number of arousals: BN = 2.0, MDD = 8.3, Control = 2.6 REM latency (minutes): BN = 64.1, MDD = 56.3, Control = 81.5 Mean REM density: BN = 1.1, MDD = 1.9, Control = 1.3
Latzer et al. (21)	BN (25); Control (21)	Actigraphy and sleep log Sleep onset: BN = 00:58, Control = 23:45 Sleep offset: BN = 08:11, Control = 07:15 Mini-Sleep Questionnaire total score: BN = 29.7, Control = 22.1 The Standard Technion Clinical Sleep Questionnaire Difficulty falling asleep: BN = 3.8, Control = 2.5 Wake up too early: BN = 3.5, Control = 2.4 Headaches upon wakening: BN = 2.2, Control = 1.5 Excessive daytime sleepiness: BN = 4.5, Control = 2.4

TABLE 29.1. Continued

Study	Patient group (n)	Significant findings
Tzischinsky et al., (22)	Obese BED (18); Obese Control (13); Non-obese Control (16)	Actigraphy Total Sleep Time (minutes): BED = 349, Obese Control = 316, Non-obese Control = 407 Sleep Efficiency (%): BED = 85, Obese Control = 79, Non-obese Control = 94 Longest episode of continuous sleep (minutes): BED = 146, Obese Control = 145, Non-obese Control = 212 Minutes of wake during sleep: BED = 63, Obese Control = 86, Non-obese Control = 23 Self Report Mini-Sleep Questionnaire Total Score: BED = 34.2, Obese Control = 28.9, Non-obese Control = 22.7 Snoring (1 = low, 7 = high): BED = 3.7, Obese Control = 3.6, Non-obese Control = 2.1 Midsleep Awakenings (1 = low, 7 = high): BED = 4.6, Obese Control = 4.4, Non-obese Control = 3.0 Excessive Daytime Sleepiness (1 = low, 7 = high): BED = 4.2, Obese Control = 3.2, Non-obese Control = 2.1 Restless Sleep (1 = low, 7 = high): BED = 4.1, Obese Control = 2.4, Non-obese Control = 2.2
Vardar et al. (23)	Obese BED (8); Obese Control (28); Non-obese Control (37)	Pittsburgh Sleep Quality Index total score: BED = 7.88, Obese Control = 5.07, Non-obese Control = 5.54 Pittsburgh Sleep Quality Index sleep latency (minutes): BED = 25.6, Obese Control = 16.6, Non-obese Control = 15.5

Note. TST = Total Sleep Time; AN = Anorexia Nervosa, BN = Bulimia Nervosa; MD D = Major Depressive Disorder

of life included history of poor treatment outcome during the previous year and psychiatric co-morbidity. Predictors of poor mental quality of life included psychiatric co-morbidity and the presence of purging behaviors. In contrast, successful treatment of AN is associated with improvements in quality of life measures. Padierna and colleagues (12), in a prospective study of 131 patients (mean age = 22.3 years) seeking treatment for AN-restricting subtype (33%), AN-binge/purge subtype (36%), and BN (31%), found significant improvements in several subscales of the SF-36 2 years after treatment: physical functioning, role limitation because of physical health, bodily pain, general health, vitality, social functioning, and mental health. It is not known if some of these improvements were mediated through improvements in sleep.

Impact of Sleep on Quality of Life in AN

Much of the research on sleep and AN has focused on objective EEG sleep measures, rather than on subjective measures of sleep quality and its impact on daily functioning. As such, the impact of sleep on quality of life among anorectics can only be addressed speculatively. As reviewed above, Pieters (9) showed that although weight restoration did not significantly change objective measures of sleep, subjective aspects of sleep did improve. Specifically, patients fell asleep faster, slept longer, reported better quality and efficiency of sleep, and reported fewer sleep disturbances. These subjective reports suggest that weight restoration is associated with improved sleep quality, and presumably quality of life. Future studies in AN should assess whether quantifiable improvements in sleep quality correlate with positive changes in measures of quality of life.

Bulimia Nervosa

The core features of BN are binge eating and inappropriate compensatory mechanisms to avoid weight gain. The diagnosis of BN is established when a person 1) engages in binge eating, defined as eating a large amount of food during which time the person feels a subjective sense of loss of control over the eating behavior, 2) engages in recurrent compensatory behavior, such as vomiting, laxative use, or excessive exercise, to prevent weight gain, and 3) bases self-evaluation unduly on body shape and weight (3). Similar to AN, BN has two clinical subtypes: purging and non-purging. The purging subtype is characterized by self-induced vomiting and misuse of laxatives, diuretics, or enemas; the non-purging subtype is characterized by fasting and/or excessive exercise (3).

Sleep Findings of Bulimics Versus Comparison Groups

Similar to the literature on sleep and AN, studies have also compared the sleep continuity and architecture of patients with BN with that of comparison groups. In an early study, Walsh and colleagues (13) included 16 normal weight bulimics (mean age = 26.1 years) in a sleep study comparing 8 patients with AN (mean age = 26.9 years; five met criteria for binge/purge subtype) to 14 healthy, normal weight controls (mean age = 26.6 years). This was a negative study, failing to find differences between the BN and the control groups on any sleep parameter.

Lauer and colleagues (14) compared the EEGs of 20 anorectics (mean age = 21.0 years), 10 bulimics (mean age = 23.2 years), and 10 age-matched controls. Similar to Walsh's (13) sample, nearly 50% of the patient groups were depressed. Sleep architecture and REM measures did

not differ between groups. The BN group, however, had slightly reduced sleep efficiency (87.9%) and more intermittent wakefulness than the AN or control group (in fact, threefold greater than the control group, whereas the AN group was intermediate). In a subsequent study, Lauer and colleagues (15) again compared the EEG sleep pattern of 20 patients with AN (age range = 16–27 years; 9 met concurrent criteria for major depressive disorder), 10 patients with BN (age range = 18–27 years; 5 met concurrent criteria for major depressive disorder), 10 patients with depression (age range = 18–26 years, none met criteria for an eating disorder), and 10 healthy controls (age rage = 18–27 years; none met criteria for an eating or mood disorder). Sleep continuity, architecture, and REM latency did not differ between groups. The only notable finding was that eating-disordered patients with concurrent depression had higher REM densities than eating-disordered patients depression-free or the control group (Table 29.1).

Hudson and colleagues (16) compared the EEGs of 11 women with BN (mean age = 25.2 years; 5 met concurrent criteria for major depressive disorder; 5 met lifetime criteria for AN), 44 women with major depression (mean age = 31.5 years), and 20 healthy female controls (mean age = 28.4 years). Consistent with the above studies, only modest differences were found in the BN group as compared with that in the controls. The BN group exhibited less stage 1 sleep (%; Table 29.1). Patients with BN could be distinguished from patients with major depression on several variables including sleep latency, sleep efficiency, sleep maintenance, and REM density, but in each case, the BN group score was much similar to that of the controls'. Thus, this study implies that major depression has a bigger impact on sleep architecture than BN, which is in contrast to the findings described earlier with AN.

Waller and colleagues (17) compared 12 non-depressed patients with BN (mean age = 25.6 years) to 61 patients with MDD (mean age = 30.8 years) and 20 healthy controls (mean age = 29.3 years). This group found that REM latency, when adjusted for age, was significantly less for the BN compared to the control group (Table 29.1). Similar to Hudson (16), the depressed group differed significantly from both the BN and the controls on several additional sleep variables (Table 29.1).

In summary, the sleep findings in BN are less consistent and appear more modest in nature than those detected in AN when these patient groups are compared with healthy controls. Sample sizes are small in all of these studies, so the power to detect differences may be limited.

Quality of Life

Hay (18) examined the quality of life, as assessed by the SF-36 (19), of 3010 community individuals with varying degrees of eating disorder pathology (mean age = 46.9 years, 60% female). Those who reported regular binge eating ($n = 78$) had significantly lower scores than participants without regular binge-eating behavior on all SF-36 subscale scores: physical functioning, role limitation because of physical health, bodily pain, general health, vitality, social functioning, and role limitations because of emotional and mental health.

de la Rie and colleagues (20) examined the quality of life of patients with AN ($n = 44$, mean age = 26.3 years), BN ($n = 43$, mean age = 29.0 years), EDNOS ($n = 69$, mean age = 29.4 years), and former patients with eating disorders ($n = 148$, mean age = 28.7 years), and a healthy control reference group. Patients with current eating disorders, compared with patients with former eating disorders, scored significantly lower on several of the SF-36 subscales: physical role functioning, emotional role functioning, general health perception, social functioning, and mental health. No differences were noted among the current eating disorder subtypes. This suggests, similar to AN, that successful treatment of BN also results in significant improvements in quality of life.

Impact of Sleep on Quality of Life

Similar to studies of sleep and AN, few studies of BN patients have examined both subjective and objective measures of sleep or the relationship of sleep quality to quality of life among this population.. One study provides preliminary evidence of this relationship. Latzer and colleagues (21) compared the subjective and objective sleep parameters of 25 patients with BN (mean age =22.3 years) with that of 21 healthy controls (mean age = 24.0 years), all in their natural home environments. Actigraphy, sleep log, and self-report questionnaires measured difficulty with sleep and its consequences. Results of the actigraphy and sleep log showed significantly later sleep onset times and later sleep offset times for the BN, compared with the control group. The BN group reported significantly more subjective sleep disturbance and negative consequences associated with sleep disturbance (Table 29.1). Specifically, BN patients reported more difficulty falling asleep, waking too early, having headaches upon wakening, and excessive daytime sleepiness.

These limited findings imply that disturbed sleep among patients with BN likely negatively impacts quality of life. Consistent with the AN literature, additional research is necessary to fully understand the relationship between BN, sleep, and quality of life.

Binge Eating Disorder

The primary feature of BED is "eating, in a discrete period of time … an amount that is definitely larger than most individuals would eat under similar circumstances," (3) accompanied by a perceived loss of control over one's eating. Binge eating causes a sense of shame and disgust with oneself, as well as significant distress. BED differs from BN in the absence of compensatory behaviors such as vomiting, laxative abuse, or compulsive exercising (3).

Sleep

Few studies to date have examined the sleep of patients with BED. Tzischinsky and colleagues (22) compared 18 obese binge eaters (mean age = 45.1 years) with two comparison groups: 13 obese controls (mean age = 41.9 years) and 16 non-obese (mean age = 39.7 years) controls on actigraphy, sleep diary, and self-reported sleep assessments. There were no differences in actigraphy findings between the BED and obese non-BED control group. An effect of weight on actigraphy was evidenced by significant differences between the normal weight controls and the obese patient and control groups. Similarly, self report data suggested that differences were due to weight status, not binge-eating status (Table 29.2).

Similarly, Vardar and colleagues (23) compared the subjective sleep quality of treatment-seeking, obese patients with BED (n = 8, mean age = 31.1 years) with treatment-seeking, obese non-bingers (n = 28, mean age = 30.2 years), and with controls (n = 37, mean age = 28.6 years). In this instance, in contrast to the study above, the obese BED group, compared with both reference groups reported significantly more subjective sleep disturbance on the PSQI measure of sleep latency and the total score (Table 29.2); sleep duration and habitual sleep efficiency did not differ among groups.

Quality of Life

The quality of life of 94 treatment-seeking binge eaters (mean age = 44.9 years, 71 obese, 23 non-obese) was compared with national norms on health-related quality of life (24). Binge eaters reported significantly decreased quality of life compared with the national norms (Table 29.2); obese, compared with non-obese binge eaters, had significantly lower physical component quality of life scores. Similar findings have been reported by Mond and colleagues (25) in a large study comparing patients with eating disorders with controls.

Impact of Sleep on Quality of Life

The literature on sleep and quality of life among persons with BED is confounded by the obesity that is so often associated with BED. Among obese patients with BED, it appears that the obesity, not the binge-eating behavior per se, is the factor most associated with poor sleep and consequent diminished quality of life.

Night Eating Syndrome

Of the disorders discussed thus far, NES is the most directly relevant to a discussion of the impact of sleep on quality of life, as core clinical features include insomnia and nocturnal awakenings. NES was first described in 1955 as a stress-related eating disorder consisting of morning anorexia, evening hyperphagia, and insomnia (1). NES has also been associated with a depressed mood, which lowers in the evening and nighttime (26). The current conceptualization of NES as a disorder characterized by a circadian delay in eating requires the presence of evening hyperphagia (i.e., consumption of $\geq$25% of total daily food intake after the evening meal) and/or three or more nocturnal awakenings with ingestions of food (27). Associated features include morning anorexia, insomnia (initial- and mid-phase), and depressed mood.

Sleep

There have been three reports of polysomnographic characteristics of NES in clinical case series (28–30; Table 29.3), and two controlled studies of sleep in NES, one outpatient with actigraphy (27; Table 29.3), and one inpatient with Polysomnography (PSG) (31; Table 29.3). Sample characteristics of the three non-controlled studies are 1) Spaggiari et al. (28) studied 10 persons with recurrent nocturnal eating, 23–62 years old; 2) Manni et al. (29) studied a series of 120 insomnia referrals and found 7 persons (5.8%) who had nocturnal eating (18–86 years); and 3) Vetrugno et al. (30) studied 35 consecutive patients presenting with nocturnal eating (24–77 years). In the latter study (30), the patients were labeled as having SRED, but, in fact, they had full recollection of all of their eating episodes and seemed similar to the classification NES patients in the previous two studies (28, 29), so they are included in this discussion of NES. The controlled polysomnographic study included 15 overweight females (mean age 41 years) with NES and 14 similar control participants (mean age 39 years; 31). None of these studies included persons with daytime eating disorders, who were in fact specifically excluded in the interest of sample homogeneity.

Sleep latency for night eaters varied across the studies from 9 to 31 min, and REM latency ranged from 72 to 157 min. Uniformly, sleep efficiency was low, ranging from means of 72–76%. Awakenings to eat were brief, and resumption of sleep was swift. Patients from all studies reported full awareness of their eating episodes, and the majority of awakenings were from NREM sleep.

The drive to eat was described similarly across studies as "an urgent abnormal need to swallow food, with an absence of real hunger" (28, p. 341). Medical and neurological findings were unremarkable, but psychiatric co-morbidity was high. Weight gain resulting from NES was reported in about half of the patients. Two studies also reported the occurrence of chewing and swallowing throughout sleep (28, 30).

Comparison of sleep architecture between NES and control participants found less total and percent of stage 2 sleep, less stage 3 sleep, reduced sleep efficiency, and reduced total sleep time in NES participants, with trends for more awakenings and increased percentage of REM sleep (31). A logistic discriminant analysis determined a model that identified NES containing: 1) number of awakenings, 2) increased percentage of REM sleep, and 3) total minutes of stage 3 sleep.

TABLE 29.2. Quality of life studies of anorexia nervosa, bulimia nervosa, and binge eating disorder.

Study	Patient Group (n)	Significant findings
Gonzalez-Pinto et al. (11)	Anorexia (47)	Predictors of poor physical quality of life: history of poor treatment outcome & psychiatric co-morbidity Predictors of poor mental quality of life: psychiatric co-morbidity and purgative behaviors
Padierna et al. (12)	Eating Disorder (131)	*SF-36* Physical functioning: Time 1 = 88.7, Time 2 = 91.1 Physical role: Time 1 = 55.4, Time 2 = 67.0 Bodily pain: Time 1 = 64.6, Time 2 = 70.7 General health: Time 1 = 48.5, Time 2 = 56.5 Vitality: Time 1 = 46.8, Time 2 = 53.4 Social functioning: Time 1 = 54.0, Time 2 = 65.9 Mental health: Time 1 = 43.8, Time 2 = 50.0 Improvement in SF-36: No anxiety or depression > Co-morbid anxiety or depression
Hay (18)	Binge Eating (78); Control (2932)	SF-36 Subscale scores: Binge Eating Group < Control Group
de la Rie et al (20)	Anorexia (44); Bulimia (43); Eating Disorder NOS (69); Former Eating Disorder Patients (148); Reference Group (767)	*SF-36* Physical role: ED patients = 45.2, Former ED = 65.1, Reference group = 73.8 Bodily pain: ED patients = 65.8, Reference group = 71.9 General health: ED patients = 51.4, Former ED = 61.7, Reference group = 69.9 Vitality: ED patients = 39.4, Former ED = 53.1, Reference group 64.3 Social functioning: ED patients = 47.9, Former ED = 65.5, Reference group = 82.0 Emotional role: ED patients = 26.8, Former ED = 49.9, Reference group = 78.5 Mental health: ED patients = 41.8, Former ED = 59.7, Reference group = 73.7
Masheb et al. (24)	Binge Eating Disorder (94); Obese Binge Eaters (71); Non-obese Binge Eaters (23); Depressed Binge Eaters (47); Non-depressed Binge Eaters (47)	*SF-36* Physical functioning: BED = 75.2, US norms = 84.5 Physical role: BED = 67.3, US norms = 81.1 Bodily pain: BED = 60.7, US norms = 75.4, Obese treatment seekers = 52.8 General health: BED = 65.4, US norms = 72.2 Vitality: BED = 39.9, US norms = 61.0, Obese treatment seekers = 47.4 Social functioning: BED = 66.7, US norms = 83.5, Obese treatment seekers = 77.1 Emotional role: BED = 52.5, US norms = 81.2, Obese treatment seekers = 75.4 Mental health: BED = 59.2, US norms = 74.8, Obese treatment seekers = 69.7 Physical summary component: Obese BED = 45.3, Non-obese BED = 53.6
Mond, et al. (25)	ED (84); Control (495)	SF-12 Mental summary component: ED = 30.1, Control = 47.4

Note: ED = Eating Disorder; AN = Anorexia Nervosa, BN = Bulimia Nervosa; BED = Binge Eating Disorder.

TABLE 29.3. Mean polysomnographic features of persons with nocturnal/night eating syndrome.

Study	Latency to sleep onset (min)	Latency to REM onset (min)	Number of nocturnal ingestions	Eating latency from awakening	Sleep latency after eating (min)	Sleep efficiency (%)	Awakenings stages of sleep
Spaggiari et al. (28)	19	157	3.6	30 s	3	74	80% stages 1–2; 20% stages 3–4
Manni et al. (29)	31	78	4.0	2 min	3	75	NREM
Vetrugno et al. (30)	9	109	1.3	7 min	14	76	NREM
Rogers et al. (31)	26	72	1.2	Mean total time awake: 23 min		72	79% non-REM; 21% REM

Comparison of PSG findings of persons with NES to controls revealed that sleep onset and morning sleep offset did not differ (31). This finding was corroborated by the same research group in an outpatient study using actigraphy with 46 persons with NES and 43 similar controls (27). Therefore, the authors concluded that the timing of the sleep cycle is preserved in the presence of a phase delay in eating.

Quality of Life

Quality of life has been reported in persons with NES as compared with controls and in two treatment studies, measured by the quality of life, enjoyment, and satisfaction scale (QLES-Q; 32). Both studies used sertraline to treat NES; one was a randomized controlled trial ($n = 17$ sertraline, $n = 17$

placebo; 33) and one was a long-distance open-label trial in which persons with NES were diagnosed by the research team and treated by their own physicians in the community ($n = 50$; 34). Rating scales were completed during treatment, and exit interviews were conducted by the researchers. Sertraline treatment significantly reduced percent of calories consumed after the evening meal, number of awakenings, number of nocturnal ingestions, and weight. In both studies, scores on the QLES-Q increased significantly with the decrease in NES symptoms, from 47 to 56 (33) and 47 to 55 (34), over 8 weeks of active treatment.

Impact of Sleep on Quality of Life

Rogers et al. (31) administered subjective sleep questionnaires in their controlled inpatient study of NES. On the PSQI (10), NES patients also endorsed more initial insomnia, more awakenings, more trouble with breathing and coughing, being too cold, more bad dreams, and increased leg twitching than control participants. Surprisingly, excessive daytime sleepiness was not identified on the Epworth Sleepiness Scale (35), but it was endorsed on the MAP Index (36). There were no additional differences on the MAP between groups for sleep-disordered breathing, difficulty sleeping, and frequency of narcolepsy-like symptoms. Taking together these significantly poor subjective reports of sleep quality with reports of improvement in quality of life when awakenings and nocturnal ingestions are decreased with treatment, it seems appropriate to conclude that poor sleep quality impacts the quality of life of NES sufferers.

Sleep-Related Eating Disorder

The literature is not as large for the rare parasomnia, SRED. Until recently, the main differentiation between SRED and NES is the lack of awareness in SRED for nocturnal eating episodes. During these eating episodes, odd foods or non-food items are often ingested with no recollection. Physical injury also tends to occur due to food preparation and cooking accidents during parasomnic events.

SRED has more commonly been associated with daytime eating disorders and other sleep disorders, such as RLS, OSA, night terrors, and somnambulism (2, 37). This may differ from the relationship between NES and other sleep disorders, although there have been mixed reports of the frequency of co-morbid sleep disorders in persons with awareness of their nocturnal eating (31, 38). No controlled PSG studies of SRED have been published. Two PSG studies in clinical case series have found sleep efficiency at 86 and 88%, sleep latency at 13 and 9 min and REM latency at 76 and 115 min (37, 39). Sleep architecture and continuity data were largely intact.

Criteria for SRED have recently been revised in the ICSD, 2nd edition, and they no longer require amnesia for nocturnal eating events. Criteria include 1) recurrent episodes of involuntary eating and drinking that occur during the main sleep period and 2) just one of the following associated features: insomnia, eating peculiar foods, sleep-related injury, dangerous behavior in the pursuit of food, morning anorexia, and adverse health consequences from eating high caloric food. With these revised criteria, it is unclear what separates NES from SRED diagnostically. More research is needed to explore whether these are two entirely distinct disorders or whether they occur along a nocturnal eating spectrum (40).

General Conclusion on the Impact of Sleep on Quality of Life among Patients with Eating Disorders

Eating disorders have a significant negative impact on the quality of sleep. This appears to be particularly the case with AN and NES and is less established with BN and BED. Not one sleep finding is common or specific to all four eating disorders but common themes include poor subjective sleep quality, repeated episodes of wakefulness, variable REM changes, and reductions in sleep continuity measures. Sleep efficiency appears most markedly reduced in NES. Quality of life indices are also clearly negatively affected by eating disorders, and these measures appear to return toward normal with successful treatment of the relevant eating disorder. It is unclear however how much on this improvement in quality of life following treatment is mediated through improved sleep. It will be important in future studies examining the morbidity of eating disorders to look more specifically for links between daytime impairments in functioning and impairments in sleep. Future treatment studies in eating disorders could also, with benefit, test whether changes in subjective sleep measures correlate with overall improvement in quality of life.

Issues that need to be addressed by future research:

- Future studies of eating disorder should assess whether quantifiable improvements in sleep quality correlate with positive changes in quality of life.
- Because studies of sleep, quality of life, and Binge Eating Disorder are often confounded by obesity, future studies should examine these variables while controlling for weight status.
- Future research is needed on the relationship between Night Eating Syndrome and the parasomnia, Sleep-Related Eating Disorder

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Sleep and Quality of Life in Obsessive-Compulsive Disorder

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Summary Patients suffering from obsessive-compulsive disorder (OCD) scarcely complain primarily of insomnia. However, sleep disturbance is very common in this population as shown by epidemiological and polysomnographic studies. Clinical psychiatrists have to check for sleep disruptions through a careful medical history of the patient. Special attention will be paid to patients with checking of washing rituals who can delay their sleep during endless compulsive activities. To what extent these sleep problems are related to the pathophysiology of OCD or simply a consequence of the obsessive-compulsive symptoms remains to be addressed in future studies. In OCD, despite initial confusing findings, there is no specific alteration of the sleep structure. However, impaired sleep continuity, intrusion of wake during sleep, and reduction of sleep duration are constantly observed. Endocrine functions are also strongly modified during sleep of OCD sufferers. Adrenocorticotrophic hormone (ACTH) and cortisol are significantly elevated whereas sleep onset-related GH secretion is blunted in patients compared with healthy controls. Clinical experience suggests that the improvement of OCD is strongly linked to the decrease of sleep alterations but the specific impact of insomnia on the course of the illness and the quality of life (QOL) of patients has not been investigated precisely. Neurobiology shows that sleep regulation and OCD pathophysiology share common serotoninergic mechanisms, suggesting that their relationship is not fortuitous. Prescription of serotonin-acting antidepressant for OCD has to be reassessed to prevent further alteration of sleep structure. Actually, antidepressants active on OCD stimulate vigilance and could disrupt sleep continuity. From a therapeutic point of view, we need to determine the reciprocal effects of specific treatments (ODC or sleep focused) on the evolution of the other variables. It is likely that sleep care should facilitate OCD treatment and reciprocally.

Keywords Sleep · obsessive-compulsive disorder · polysomnography · serotonin · quality of life · cognitive behavioural therapy.

Learning objectives:

- OCD sufferers have little complaints about sleep.
- Sleep quality is systematically altered in OCD patients.
- Effect of OCD treatment on sleep must be monitored.

Introduction

A brief exploration of the biomedical literature through *PubMed* shows that the key words "sleep" and "obsessive-compulsive disorder" bring only 172 references since 1951. Barely one-third of these papers are directly involved in studies concerning the specificities of sleep in patients suffering from this pathology. In the field of the interactions between sleep and psychiatric disorders, it is probably one of the least treated topics. What is the reason for such a lack of interest from the scientific community?

Firstly, patients with obsessive-compulsive disorder (OCD) do not easily volunteers for scientific research. Insel et al. (1) emphasized that patients presenting cleaning rituals are particularly stressed by research procedures, like attaching leads, and have marked difficulty in sleeping in the laboratory.

The second reason is due to the frequent co-morbidity of OCD with depression (2). Sleep in depressive patients has been extensively studied and shows some specific features. It is often when depressive symptoms are prominent that patients seek treatment. Consequently, several studies have been questioned about the specificity of the sleep findings in this population.

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Nevertheless, there is a growing body of studies in this area and recent publications have better defined the sleep problems in OCD and their consequences on quality of life (QOL) of patients.

Obsessive-Compulsive Disorder

Epidemiology

OCD is not a rare disease its lifetime prevalence is about 2–3%, with a sex ratio of 1:1 (3). The age of onset is generally adolescence or early adulthood, and the disorder intensity fluctuates throughout the life of the patients. Compared to the lifetime prevalence of 8% for anxiety disorders in the general population, it can be assumed that OCD is one of the most frequent pathologies in the field of anxiety. The Epidemiologic Catchment Area (ECA) survey outlined that OCD is the fourth most frequent psychiatric disorder (4).

Symptomatology

As mentioned in its denomination, OCD is characterized by two specific symptoms: obsession and compulsion.

Obsessions correspond to thoughts or ideas recognized as being irrational or absurd by the patient. Despite the superficial belief that these thoughts or images are useless and illogical, the patient cannot get rid of the obsessions. Sometimes, obsessions can take the form of impulses. These specific features are described as the most disturbing of frightening type of obsession (impulse to kill or hurt somebody, to precipitate himself through a window).

Compulsions are repetitive and deliberate behaviours performed by the patient in order to respond to a particular obsession. These manifestations are achieved in predictable sequences according to specific rules. The repetitive actions of the patients aim to neutralize or diminish the stress induced by obsessions. Most of the time, compulsions are not adapted to prevent efficiently the patient from the stressful event (catching an infectious disease) or are an exaggeration of normal behaviour (washing one's hands twenty-three times in a specific sequence of movements). There is a powerful inner drive to perform the action, although the patient tries desperately to resist the compulsion. Like obsessions, the majority of OCD patients recognize the illogical nature of their compulsions and actively resist the urge to act. The most classic compulsions are checking (door, windows, mail), hand washing, and rumination.

Pathophysiology

Neurobiological mechanisms are the fundamental basis of the pathophysiology of OCD. A large body of evidence points in the direction of a disturbance in the functioning of fronto–striato–thalamocortical circuits as the principal abnormality (5). This point of view is largely supported by neuropsychological findings (6, 7).

Concerning neurotransmission, serotonin seems to play major part. This assertion is based on the efficacy of serotonin (5-HT) reuptake inhibitors (SRI) in the treatment of OCD (8). Moreover, some studies show an exacerbation of obsessive-compulsive symptoms after administration of metachlorophenylpiperazine (m-CPP), a 5-HT agonist, in patients suffering from OCD (9). In the same way, metergolin (a 5-HT antagonist) antagonizes the positive effect of clomipramine in OCD patients (10). Reinforcing this point of view, a recent study demonstrates that treatment with SRI normalizes glucose metabolic rates in basal ganglia in correlation with the improvement of specific neuropsychologic functions, known to be altered in OCD (11). Finally, a German group, using single photon emission tomography (SPECT), shows that the availability of serotonin transporter is reduced in these patients (12).

Conversely, there are some arguments against the implication of 5-HT in the mechanisms of OCD. The metabolite of 5-HT, 5-hydroxy-indol-acetic acid (5-HIAA), is not lowered in the cerebrospinal fluid in patients suffering from OCD (13). Furthermore, tryptophan depletion, a way to reduce 5-HT transmission in the CNS, did not induce an exacerbation of obsessive-compulsive symptoms (14, 15).

Co-morbidity

It is very common for patients with OCD to be diagnosed with other psychiatric disorders. LaSalle et al. (16) showed that 92% of their population received one or more additional Axis I DSM-IV diagnosis. Furthermore, certain disorders are more represented in the relative of OCD patients, providing supplementary evidences for an etiologic relationship (17). Familial studies reveal that generalized anxiety disorder, tic disorders, panic disorder, agoraphobia, and recurrent major depression are often find in the same patients, suggesting an etiologic connection between these pathologies and OCD. However bipolar disorders, social and specific phobia, alcohol and substance dependence are not associated with OCD (18).

The relations between affective disorder and OCD are complex. Moritz et al. (19) suggest that core depressive symptoms are specifically associated with aggression-related obsessions. Another study revealed a strong correlation between obsessive-compulsive symptoms in OCD and bipolar spectrum disorders, whereas unipolar depression was not associated with this OCD dimension (20). These discrepancies are probably explained by the relative heterogeneity of affective disorder as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). Indeed, Fineberg et al. (21) shows that depressive symptoms profile of OCD patients differs from those of severity-matched major depressive disorder patients. For example, OCD patients were less symptomatic than depressive subjects on items that measure vegetative response to depression, especially sleep

and appetite, but are particularly high on items such as inner tension and pessimism.

Treatments

Recommended pharmacological treatment for OCD consists of clomipramine or selective SRI (SSRI) during the acute period. For patients who respond positively, this treatment must be continued for up to 12 months (22, 23).

Cognitive behavioural therapy (CBT) has proved its efficiency with techniques such as exposure with prevented response and cognitive therapy (24).

Sleep in OCD

Sleep Complaints

Sleep complaints are not particularly important in OCD patients (25). For years the scientific community was satisfied with the assertion: laboratory sleep studies confirm sleep disruptions in patients presenting subjective complaints (1) and subnormal sleep in those who do not complain (26). So, very few studies have been carried out on sleep disturbance in OCD. More recent works show that the reality is somewhat more complex.

Sleep onset insomnia is a very frequent symptom. Usually, the patient considers that he or she sleeps well, even when delayed sleep onset and premature morning awakening occur every night. There is an *agrypagnosia*, i.e., the patient does not know that he or she does not sleep. Insomnia occurs when the trigger stimuli for anxiety are associated with sleep, or when the disease is so severe that it affects the whole life of the patient. Rumination, checking rituals, repetitive washings, and obsessive thoughts may considerably delay bedtime and sleep onset.

Sleep Disturbances

Few well-conducted polysomnographic studies have been performed in OCD patients without psychotropic treatment.

In one of the first attempts to explore sleep of OCD sufferers, Insel et al. recorded fourteen adult OCD patients. Nine of the patients complained about difficult in obtaining normal sleep before they entered the study. The analysis of the night records showed significantly decreased total sleep time (TST) with an augmented number of awakenings. Slow wave sleep (SWS) was altered, with a decrease of stage 4 sleep. As far as rapid eyes movement (REM) sleep was concerned, there was a decrease in its efficiency and a reduced REM latency compared with the control group. The authors underlined the similarity of such abnormalities with those observed in the sleep of depressed patients. Their conclusion was in favour of a relationship between OCD and affective illness revealed by common sleep alterations, especially a decrease of REM latency. However, there was no significant difference between patients presenting depressive symptoms and those without depressive symptoms in the group of OCD patients (1). Uhde (25) relates that NIMH team compared secondarily the 14 patients who participated in the Insel et al. study with 14 age-matched depressed patients. There were few differences between the two groups. The only significant difference was that OCD patients had greater amounts of stage 1 and stage 3 sleep than depressed patients.

These results were coherent with those of a limited study performed with nine adolescent OCD patients (27). But, in adolescent OCD, there was a significant increase of the percent of SWS compared with healthy controls.

However, in 22 adult inpatients with OCD, Hohagen et al. did not replicate the results concerning the reduction of the REM latency. In fact, the authors found no differences between patient and normal volunteers on any sleep parameters except for lower sleep efficiency and an increase in the number of awakenings in the OCD group (28).

Given that numerous patients involved in the preceding studies present depressive symptoms, Robinson et al. selected 13 OCD outpatients, free of depressive diagnosis and medication free for 2 weeks before polysomnographic procedures (26). The results are comparable to those of Hohagen et al., except for an increased number of awakenings; there is no clear pattern of polysomnographic findings in OCD. The authors suggest that many patients with OCD have REM latencies similar to those of normal control subjects.

The most recent study has just been issued online and reveals that OCD patients do not show characteristic abnormalities of sleep structure such as reduced REM latency or diminished SWS that have been classically described in depressive disorder (15). The only remaining similarity is an increased first REM episode of REM in the found in both pathologies. This study is the largest to date, with 62 OCD patients and an equivalent number of healthy controls. The results confirm once again the alteration of sleep continuity in these patients with reduced TST, impaired sleep efficiency, and increase of wake after sleep onset.

In this study, the authors performed a tryptophan depletion challenge to test the serotonin hypothesis of OCD. After this challenge test, worsening of sleep continuity was observed without changes in REM or SWS. Sleep duration was reduced, so was sleep efficiency whereas wake and stage 2 sleep percent were augmented. This effect was stronger in OCD patients than in healthy subjects. Symptoms of OCD were not modified after the procedure.

Sleep Disturbances and OCD Treatment

Another issue that needs to be addressed is the effect of OCD treatment on the subsequent quality of sleep.

There is no report of specific effect of CBT specifically oriented to insomnia in OCD patients. Similarly, the utility of

CBT of OCD symptoms for the improvement of sleep quality has not been specifically studied (29).

Pharmacological treatment of OCD is based on antidepressant, especially clomipramine and SSRI. These products present a well-known stimulating effect, potentially responsible for sleep onset insomnia, sleep fragmentation, and low sleep efficiency (30, 31). It is recommended to prescribe this treatment well before sleep onset to reduce this side effect. Usually, this does not induce pharmacological problems because the half-life of these antidepressants allowed only one administration per day.

Alterations During Sleep

During sleep, numerous physiological phenomena occur. First of all, let us talk about the most mysterious: dreaming. To our knowledge, there is only one study dealing with dreams in OCD patients. This French team made the following hypothesis: if dreams play a role in the processing of information and mental storage of events during the day, the dream report of OCD patients should present some representation of diurnal obsessive or ritual themes. In the end, no differences were found between OCD and healthy groups concerning dream recall and mental activity concerning anxiety, failure, sadness, and obsessive-compulsive themes (32). These results are somewhat surprising because dreams in depression and panic disorder show content related to the pathology (33, 34). Perhaps the technique of delayed dream collection in the morning could have modified the reported content of dream in this study.

More somatic, but not less important, endocrine functions could be modified during sleep in OCD. A recent study (35) performed in nine inpatients suffering from OCD without comorbid depression show an increased level of ACTH and cortisol during nocturnal sleep. Consequently, the activity of the hypothalamic–pituitary–adrenal (HPA) axis is increased in patients with OCD compared with that in healthy controls. This activation seems to occur without major changes in the sleep structure but we cannot check sleep data, which will be published soon. Usually, cortisol increase is associated with arousal and disruption of sleep. As sleep is modified in this way in OCD, elevated cortisol during sleep may be a potential explanation.

Growth hormone (GH) is predominantly released during the first half of night, closely related to SWS. This sleep onset-related GH release appears to be controlled by GH-releasing hormone (GHRH), occurring during a period of reduced somatostatin activity. Compared to healthy subjects, the GH response after stimulation with the dopamine agonist apomorphin was found to be decreased, suggesting a dysregulation of central dopamine systems (36). Stimulation with the acetylcholinesterase inhibitor pyridostigmine caused an increased GH response, pointing to a cholinergic supersensitivity (37). Serotoninergic stimulation with clomipramine (38) or 5-HT precursor tryptophan (39) resulted in an increased GH response, being consistent with a role of 5-HT_{1D} receptors in OCD. A recent study showed that sleep onset GH secretion is significantly blunted in OCD patients. These findings confirm the presence of an altered functioning of the somatotropic axis in this pathology (40). Moreover, GH secretion was more fragmented in patients with OCD than in controls. In most of the patients participating in this study GH release was not synchronized with SWS. Sometimes the secretion peak occurs before sleep onset or in the second half of the night, when SWS was absent. OCD patients, in this work, show a reduced amount of Stage 4 sleep that could explain the blunted sleep-related GH secretion. Actually, reduction of stage 4 sleep production seems to be related with decreased GHRH activity (41).

QOL in OCD

Impact of OCD on the QOL

OCD has been found to be the 10th leading cause of disability of all the medical conditions in the industrialized world (42). But, until the last 10 years, few studies have addressed the impact of this disease on QOL and psychological functioning of the patients. Several investigations have explored the impairment of QOL in OCD sufferers using self-report questionnaires sent to patients' national associations involved in ODC (43). Only two have assessed the impact of severity of OCD symptoms on QOL (44, 45). All these studies reported an important impairment in QOL of the patients.

A recent study involved 197 American OCD, using the Quality of life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) among other methods of QOL evaluation (46). The authors show a substantial impairment in QOL and psychosocial function in OCD versus healthy controls. In the OCD population, 34% were unable to work because of the disease. Marked impairment was observed in all specific domains of QOL measured during the study: ability to work and perform household duties, subjective sense of wellbeing, social relationships and ability to enjoy leisure activities. Severity of OCD was significantly associated with the magnitude of impairment in all domains of QOL. A regression analysis revealed that marital status and symptom severity of both obsession and depression contribute to the severity of alteration in QOL. Age, education, insight, and duration of the illness did not have an impact on QOL.

An important finding of this study is that obsessions but not compulsion were associated with impairment of QOL as assessed by the Q-LES-Q. The severity of obsessions was highly correlated with overall rating of QOL and with almost all specific domains, whereas severity of compulsion was not. Only one domain, work functioning, was more correlated with compulsion severity. These observations are coherent with the classical complaint of the patients, who find their obsessions more distressing than their compulsions in term of ability to

enjoy leisure activities and emotional well-being. Compulsions are usually an attempt to reduce anxiety generated by obsessions, when they are successful, patients associate these activities with relief and complain less about them. Paradoxically, CBT of OCD is frequently focused on behavioural intervention on compulsion rather than cognitive techniques dealing with obsessions.

Fortunately, the QOL improve when OCD symptoms are treated (47). Moritz et al. show that QOL improvement is larger in treatment responders than in non-responders. This suggests that symptom reduction alleviates the patients' daily life burden. However, correlations show that the number of OCD symptoms and the severity of depression were stronger predictors of QOL than OCD severity. Whereas QOL seems to be a predictor for health seeking, it could not predict treatment outcome. The only variable that was able to reveal modest predictive power for outcome was the number of obsessions.

Another interesting point outlined by a German team is the impact of OCD on QOL of relatives of OCD patients (48). Impairment of relatives' QOL is seen mainly in psychological well-being and social relationship. These results are of importance as they suggest the need to involve families of OCD patients in the therapeutic procedures.

Impact of Sleep Disturbances on QOL in OCD

In this field, no study was found assessing precisely the impact of sleep problems on OCD symptoms and QOL.

A significant body of evidence demonstrates that sleep problems, especially insomnia, have a drastic impact of QOL in general population (49–52). Ohayon and Lemoine (53) show that after a bad night's sleep subjects are seven times more likely to feel anxious. In a large community-based sample (772 subjects), Taylor et al. noted that insomnia sufferers were 17,35 times more likely to present clinically significant anxiety. Moreover, the severity of insomnia was directly correlated to the intensity of anxiety measured by State-Trait Anxiety Inventory (STAI) score. Unfortunately, the cross-sectional design of the study does not permit analysis of the relation of causality between the two entities (54). In panic disorders, especially in response to nocturnal panic attacks, many patients develop a conditioned fear and avoidance of sleep. The resultant sleep deprivation causes increased of anxiety (55). Two studies conclude that insomnia precedes anxiety in a large number of patients, suggesting that insomnia is at least a risk factor for anxiety (56,57). The direction of the link has not been confirmed in a population of adolescents in a recent work (58).

From a neurobiological point of view, has already been mentioned the implication of the serotonin both in sleep regulation and in OCD pathophysiology. In animals, Roman et al. (59) showed recently that chronic sleep deprivation, without stress, gradually induces a desensitization of the 5-HT1 receptors. If the serotonin hypothesis of OCD is correct, chronic sleep deprivation, as observed in OCD patients, can lead to an increase of obsessive-compulsive symptoms. Reinforcing this serotonin link between sleep and OCD, in animal models of OCD, inactivation and blockade of 5-HT_7 receptor reduced stereotypic behaviour. It is worth underlining that manipulation of this receptor is particularly efficient in modifying sleep parameters, especially REM sleep (60).

The constant and important alteration of sleep in these patients suggests that, as in other anxiety disorders, sleep disturbance could have a deep impact on the obsessive-compulsive symptoms and the QOL of OCD patients. Future research should address this question and its potential preventive and therapeutic consequences.

Conclusions

Links between insomnia and OCD are strong. Epidemiology shows their close association in most of the patients, although it is not their principal complaint. In fact, patients seeking help from a psychiatrist for their OCD are severely ill and suffer from pervasive obsessions and endless rituals. Such a situation prevents patient from complaining of their sleep, unless the physician asks specifically about sleep problems. Polysomnography reveals non-specific but constant alteration of sleep organization with an impairment of sleep duration and continuity. These manifestations result in chronic sleep deprivation, which could be a risk factor for OCD maintenance, and depression. Neurobiology underlines the common serotoninergic mechanisms involved in genesis of sleep and pathophysiology of OCD. It is likely that the future therapies of OCD will follow this route.

Despite this network of evidence, we lack studies to transform this knowledge into useful therapy for our patients. We do not know the magnitude of the impact of insomnia on symptoms of OCD and patients' QOL. Consequently, we cannot be certain that specific treatment of insomnia would result in improvement of OCD symptoms. Research in this field is necessary, because we have efficient of insomnia (i.e., CBT) that could be of great help; even in ad on, for patients non-responsive to classical CBT of OCD.

As in depression, the modern way to treat OCD patients would be to take into account all dimensions of the problem and give a documented answer to each. Treatment of insomnia is known to reduce anxiety in the following day. If OCD is still an anxiety disorder, it seems obvious that we need to combat anxiety on all fronts.

Issues that need to be addressed by future research:

- Evaluate longitudinally the chronic sleep debt of OCD patients.
- Interaction between sleep problems and OCD symptoms need to be addressed.

- Whether sleep-oriented therapy could ameliorate QOL of OCD patients?

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31
Sleep and Quality of Life in Schizophrenia

John R. Hofstetter and Aimee Mayeda

Summary Patients with schizophrenia have severe and persistent sleep disturbance. Multiple mechanisms contribute to poor sleep in patients with schizophrenia, including high brain dopamine levels, high anxiety, and medication side effects. Persons with psychoses generally rate their QOL worse than both the general population and physically ill patients. Although patients with schizophrenia can self-rate their QOL, the most complete picture of QOL includes assessment by family members and professionals. Negative symptoms, depressed mood, anxiety, medication side effects, and stigma correlate with low QOL in patients with schizophrenia. Positive mood, high self esteem, good social support, a sense of personal control and empowerment, and an extroverted, agreeable personality promote QOL. Sleep deprivation may foster poor functioning and high levels of thought disorder, hostility, and excitement. Improving sleep in patients with schizophrenia is likely to improve their psychiatric symptoms.

Keywords Validity · psychosis · dysfunctional beliefs · insomnia.

Learning objectives:

- Patients with schizophrenia have severe and persistent sleep problems even with optimal treatment for psychosis.
- Patients with schizophrenia can reliably complete self-reports of QOL.
- Poor sleep contributes to poor QOL in patients with schizophrenia.

Introduction

Psychosis is a disturbance of perception and thought that commonly includes hallucinations, delusions, paranoid beliefs, and agitation. The prevalence of psychotic disorders other than schizophrenia is vanishingly low. In a large clinical study concerning quality of life (QOL) assessment in psychosis, 83% of the subjects in the 173-member cohort had schizophrenia or schizoaffective disorder as a primary diagnosis (1).

The first part of this chapter will briefly describe schizophrenia. The next parts will summarize recent important studies of sleep in schizophrenia and address the challenges of assessing QOL in patients with schizophrenia. Following that will be a brief discussion of the effects of insomnia on QOL in the general population, and the final part is a discussion of sleep and QOL in patients with schizophrenia.

Schizophrenia

Schizophrenia is a chronic and potentially devastating disease. It presents symptoms characterized as positive (hallucinations, delusions, and disorganized speech and behavior) and negative (apathy, lack of volition, poverty of speech). Depression, loss of interest in activities, anxiety, and irritability are also common. It affects about 1% of the population. It has extended chronicity punctuated with acute psychotic exacerbations that usually require hospitalization and lead to significant social and occupational dysfunction. The cornerstone of clinical management is the use of antipsychotic medications (2).

Schizophrenia is not homogeneous. It has variable etiological, prognostic, and treatment response patterns that continue to confound the search for causes of the disease. Although genetic factors play a major role in the etiology of schizophrenia (in a population-based twin study of schizophrenia, heritability was estimated at 83%, 3), when the

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broad diagnostic category called schizophrenia is treated as one trait, the inconsistencies of genetic linkage studies suggest that it is not an entity (4).

This chapter contains many references to the Positive and Negative Syndrome Scale (PANSS, 5). Clinicians use the scale to measure symptoms in patients with schizophrenia and psychosis. It comprises 30 symptom items: seven positive, seven negative, and sixteen general. Each item is scored on a 7-point severity scale. Patients with many symptoms have high PANSS scores.

Sleep in Schizophrenia

Sleep Disturbances

In schizophrenia, sleep disturbance affects most patients during acute psychotic agitation and may last for days (6, 7). Sleep problems plague over half of patients in the chronic, non-acute phase (8). Unfortunately, sleep disturbance and its sequelae persist under optimal antipsychotic therapy (9–11). Over twice as many patients with schizophrenia on antipsychotic medications report poor sleep quality (Pittsburgh Sleep Quality Index, PQSI, 12) as compared with age- and sex-matched controls (8).

A list of some sleep abnormalities that accompany schizophrenia is in Table 31.1 Patients experience severe sleep problems; for example, mean sleep latency (time to fall asleep) in 30 medication-free patients with schizophrenia was 51 min; the mean for thirty age- and sex-matched control subjects was 11 min. In addition, mean sleep efficiency, the ratio of time in bed to time asleep, was 78% for patients and 94% for controls (13).

The most robust polysomnographic (PSG) measures that discriminate patients with schizophrenia from normal controls are reduced deep or slow-wave sleep (SWS) and short rapid eye movement (REM) latency (time from falling asleep to first episode of REM sleep) (6, 11, 13–16). Ten of the twenty unmedicated persons with schizophrenia in one study (17) have no scorable stage 4 sleep and seven have sleep-onset REM. Furthermore, REM latency correlates inversely with negative symptom severity (16).

TABLE 31.1. Sleep abnormalities in schizophrenia—Adapted from Benca, 1996 (14).

Subjective complaints	Sleep and EEG
Insomnia	↓sleep continuity, ↓total sleep, ↓sleep efficiency
Reversal of sleep-wake cycle	Normal or ↓slow-wave sleep, Normal or ↓REM latency
Nightmares	

Mechanism of Sleep Disturbance

It is likely that multiple mechanisms account for the pervasiveness of sleep disturbance in schizophrenia. In their excellent review, Benson and Zarcone (6) propose clarifying the state versus trait dichotomy underlying the sleep disturbances in patients with schizophrenia. Difficulties in resolving this issue include the heterogeneity alluded to earlier, the ethics of keeping patients medication-free to avoid the artifacts of medication side effects, and difficulties in assessing acutely psychotic patients accurately. Nevertheless, trait versus state mechanisms can be conceptualized under the following: dysfunctional sleep may be an intrinsic property of the disease process in schizophrenia; or, disrupted sleep, primarily manifesting as insomnia, may be a separate, comorbid entity arising from behavioral adaptations to schizophrenia and its associated problems with social interaction. Additional adverse impacts on sleep may arise from the antipsychotic medications used to treat schizophrenia. Finally, both the above mechanisms may be present, but the primary manifestation (i.e., phenotype) occurs in select, at-risk subgroups of patients with schizophrenia.

A group of disparate clues point to a connection between sleep problems and disease in schizophrenia. The persistence of sleep abnormalities irrespective of clinical status is evidence for the trait model. Sleep deprivation as well as both positive and negative symptoms of schizophrenia seem to share behavioral traits. Apathy, indecision, and behavioral disorganization are common to both extremely sleep-deprived normal subjects and patients with fatal familial insomnia, a prion protein disease causing lesions in the thalamus. Both groups also hallucinate (18–23). Schizophrenia is often considered a disorder of high brain dopamine levels, and dopamine agonists cause sleeplessness in control subjects. Finally, in childhood onset schizophrenia, although usually surrounded by a safe and nurturing environment, young patients commonly complain of poor sleep. There are also suggestive links between short REM sleep latency and the hallucinations in narcolepsy, psychotic depression, and delirium tremens as well as schizophrenia (24).

There are many theories linking neurophysiologic or neurochemical dysfunctions of schizophrenia with sleep but no single, coherent theory. Examples suggestive of links are that sleep efficiency diminishes upon administration of both dopamine agonists and cholinesterase inhibitors, consistent with the increased dopaminergic and cholinergic activity hypothesized to occur in schizophrenia (10). Levels of hypocretin, a peptide involved in sleep control, correlate with sleep latency in patients with schizophrenia (25). Melatonin, a hormone linked to signaling in the circadian system, is low in cerebral spinal fluid of patients with schizophrenia (26).

An adverse impact on sleep may arise from the secondary effects of medications. A side effect of traditional antipsychotic medications is akathesia, an unpleasant bodily sensation relieved only by moving frequently. Akathesia is detrimental to sleep. However, whether akathesia arises

from an intrinsic dopaminergic abnormality or from long exposure to antipsychotics is unknown. In addition, difficulties that patients with schizophrenia have in finding appropriate housing and in dealing with the pervasive social stigma both can adversely affect restful sleep.

Intrinsic and extrinsic mechanisms may operate together. Difficulties sleeping parallel the acuity of illness. Acutely psychotic patients may not sleep for days, and sleep often improves as acute symptoms subside (6, 7). According to patients and their clinicians, severe insomnia is often one of the best signs of an impending acute psychotic relapse (6).

Antithetical to good sleep, anxiety, agitation, and fear are commonplace in schizophrenia (27). Patients may adopt a reversed day–night sleep pattern to reduce the anxiety and responsibility associated with interacting with others (6). Suggesting that psychotic symptoms may interfere with falling asleep, Zarcone et al. (17) find that the delay in falling asleep correlates with the "Thinking Disturbance" scale of the Brief Psychiatric Rating Scale (BPRS). Furthermore, there is a higher incidence of periodic limb movements in patients with schizophrenia than in non-psychiatric controls (6).

QOL in Psychosis

Importance

Increasingly, over the last decade, QOL measurement became important to those evaluating the course and treatment of both somatic and psychiatric chronic diseases (28). QOL is an inclusive, convenient concept capable of capturing all the impairments and consequences that often compound chronic illnesses such as schizophrenia.

Health-related QOL is an internationally recognized concept. It is defined as the patient's perceived position in life in the context of his or her culture and value system in light of goals, expectations, standards, and concerns. It is a multidimensional concept incorporating health and ability to function physically, mentally, and socially (1). There is increasing emphasis on a patient's self-report; it can capture the many dimensions of complex illnesses and underscore their impact on someone's life.

General Outcomes

Irrespective of the setting and the assessment instruments, persons with psychoses generally rate their QOL worse than the general population and worse even than that of physically ill patients (29). Young patients with first episode schizophrenia have lower QOL in all eight scales of the Medical Outcome Study (MOS) 36-Item Short-Form Health Survey (SF-36, 30) compared with controls matched for age, sex, marital status, and educational level (31). Stabilized outpatients with schizophrenia have lower QOL overall and on four of six subscales of the World Health Organization Quality of Life Assessment (WHOQOL, 32) than controls matched for age, sex, and employment status (33).

QOL Research in Psychiatry

Early studies of QOL in schizophrenia began in the 1980s when patients moved from institutions into the community. These studies focus on QOL of severely mentally ill (SMI) patients in the community. The development of atypical antipsychotic medications prompted renewed interest in QOL in the 1990s. Now, QOL is accepted as an important outcome in studies of antipsychotic medications (34).

Studies of QOL in patients with schizophrenia use both generic health-related QOL instruments and schizophrenia-specific instruments (see Table 31.2). The selection of a QOL instrument depends on the study's purpose (34).

Multiple QOL Definitions and QOL Models

Difficulties with early studies of QOL in schizophrenia include not only lack of agreement on definitions of QOL, appropriate integrative conceptual models, standardized QOL measures for schizophrenia but also concerns about reliability of patients' self-reports (35). Recent studies address the underlying theoretical concepts.

According to Ritsner (2004), mental health-related QOL involves factors influencing QOL in three models. One is a "clinical model,' involving symptoms, side effects, and psychosocial performance. Another is the ''mediation model,' linking self-constructs and QOL (36). A third is the distress/protection model positing interactions between distress/clinical factors and stress-protective factors. QOL should decrease if distress/clinical factors outweigh the protective factors (37).

Are Patients Able to Self Rate QOL?

Psychotic disorders present special problems to the assessment of QOL. Psychosis can affect perception, cognitive ability, insight, and judgment. Many question whether patients can adequately evaluate their QOL (38,39). Certainly patients are unreliable historians during episodes of severe psychopathology, but can they evaluate their QOL appropriately when symptoms are less severe? Several kinds of evidence support the validity and reliability of self-report from patients with schizophrenia: limited impact of neurocognitive deficits on self rating, comparisons of self-rated and observer-rated QOL, and the large number of QOL instruments validated for schizophrenia.

Impact of Neurocognitive Deficits on Self-Rating

Neurocognitive deficits (problems with attention, concentration, memory, and executive function) in schizophrenia can be

TABLE 31.2. Validated quality of life (QOL) instruments for schizophrenia.

	Method	Validation in schizophrenia
Generic Health-related QOL Instruments		
World Health Organization Quality of Life Assessment (WHOQOL, 32)	Self-report questionnaire	33
Medical Outcome Study (MOS) 36-Item Short-Form Health Survey (SF-36, 30)	Self-report questionnaire	52, 53
EuroQoL-5 Dimensions (EQ-5D, 54)	Self-report questionnaire	55
Sickness Impact Profile (SIP) Multi-dimensional QOL(56)	Self-report questionnaire	57
PCASEE*(58)	Self-report questionnaire	59
Munich QOL Dimensions List (MLDL, 60)	Structured self-report interview	61
Everyday Life Questionnaire (EDLQ, 62)	Self-report questionnaire	28
QOL Instruments for Mental Illness		
Quality of Life Enjoyment and Satisfaction Questionnaire (Q-Les-Q, 63)	Self-report questionnaire	64
Oregon Quality of Life Questionnaire (QLQ, 65)	1.structured self-report 2. semi-structured interviewer rated	66
QOL Instruments for Severe Mental Illness		
Lehman Quality of Life Interview (QoLI, 67)	Structured self-report interview	68
Lancashire Quality of Life Profile (LQoLP, 41)	Structured self-report interview	69—pts with psychosis
Modular System for Quality of life (MSQoL, 70)	Self-report questionnaire	70, 71
Quality of Life Index for Mental Health (QLI-MH, 72)	Self-report, primary clinician and family input	72, 73
Psychiatric Status You Currently Have (PSYCH, 74)	Structured interview, include family data, medical records	75
QOL Instruments for Schizophrenia		
Quality of Life Scale (QLS, 76)	Semi-structured self-report interview. Clinician judgment involved	76
Quality of Life Questionnaire in Schizophrenia (S-QoL, 77)	Self-report questionnaire	77
Schizophrenia Quality of Life Scale (SQLS, 78)	Self-report questionnaire	78
Satisfaction With Life (79)	Self-report questionnaire	79
Personal Evaluation of Transitions in Treatment (PETIT, 80)	Self-report questionnaire	80
Subjective Wellbeing under Neuroleptics (SWN, 81)	Self-report questionnaire	82, 83

profound, but they usually do not impact patients' abilities to complete QOL assessments. There is no correlation between QOL and performance on the Wisconsin Card Sort Test, a test of executive function, problem solving, and abstract thinking (40). Nearly 90% of patients with schizophrenia can understand and fully complete a self-report SF-36. Only 3% have an unreliable SF-36. Nearly 90% can understand the questions and give consistent and valid answers to the interview questions of the Lancashire Quality of Life Profile (LQOLP; 41, 42). Wong et al. (43) use the Capacity to report subjective Quality of Life Inventory (CapQOL) to assess the abilities of patients to appraise their subjective QOL. The CapQOL is a brief, simple screen for people with a wide range of mental disabilities who may be unable to complete an extensive QOL assessment because of cognitive impairment, communication disorders, or distress. When Wong et al. (2005) administer the CapQOL to 442 patients with early psychosis, almost 90% can successfully complete a subjective QOL measure.

Patient-Rated QOL Versus Observer-Rated QOL

Another way to examine patients' abilities to self-rate is to compare self-reports with those of proxies or care providers. Patients' subjective judgments of QOL are very similar to reports of family members in a study by Khatri et al. (2001). In a study of the veracity of self-report, the investigators compare patients with schizophrenia versus proxy scores on the Lehman Quality of Life Interview (QoLI, 44) with patient versus proxy ratings in cancer (45). Concordance between patient and proxy responses is similar in both groups. Khatri et al. (2001) conclude that self-report of most patients with schizophrenia can be taken at face value.

However, there is much lower agreement between patients' subjective judgments of QOL and reports of proxies who are not family members (46). Patient-reported QOL and observer-reported QOL seem to have different determinants (47, 48); patients and observers differ in what they think is important (49). Both patients and psychiatrists recognize the importance of work, social relationships, family, and independence to QOL. However, patients understand QOL more in terms of standard of living and lifestyle. Psychiatrists focus on minimizing the effects of illness on functioning and on the importance of professional and self-help (50).

There are also differences between how patients and non-family observers judge the same domain. Observers generally (46, 49) but not universally (39, 51) underestimate patients' physical and psychological QOL. Herrman et al. (1) use case-managers as proxies to evaluate the ability of patients with psychosis to give accurate self-reports. The case-managers consistently rate their clients' QOL lower than the patients rate their own QOL. Although there is bias in the reports of caseworkers, there is little in those of patients. The authors conclude that the patients' self-reports are valid.

Observers judge that clinical symptoms, especially negative ones, are the primary contributor to poor QOL. Among patients, depression is the symptom most often correlating with poor QOL. Both Fitzgerald et al. (47) and Sainfort et al. (49) compare responses of schizophrenia patients with those of their primary clinicians. There is moderate agreement on symptoms and function, less agreement on physical health, and little to no agreement on social relations and occupational aspects of QOL. Patients rate their physical health worse and social relations and occupation better than did their clinicians.

QOL measures in studies of patients with schizophrenia are not exchangeable (42). The validity of a QOL assessment tool depends on the study's purpose. Patients are not incompetent to assess their own QOL, but the most complete picture of QOL includes not only the patients' assessment of QOL but also that of family members and professionals (1, 38).

QOL Instruments Validated in Patients with Schizophrenia

Lehman (1983) was the first to look at QOL in schizophrenia. From a structured self-report interview he elicits patients' subjective QOL. In a sample of 268 mentally disabled patients, two-thirds diagnosed with schizophrenia; the patients provide statistically reliable responses and make reasonable judgments about their QOL (44).

There are many validated instruments for assessing QOL in patients with schizophrenia. These are in Table 31.2 Different QOL instruments come from the need to answer different questions; nevertheless, they fall into the categories of generic instruments (not specific to a particular disorder), instruments for general mental illness, and instruments for severe mental illness and schizophrenia.

Validity of QOL assessment in patients with schizophrenia with the best-known generic instruments is good. The WHOQOL is a self-rated generic QOL instrument with 100 questions. Orsel et al. (33) find WHOQOL to be reliable in patients with schizophrenia. They find good internal consistency with a Cronbach's alpha of 0.94 for the entire scale. The physical, psychological, independence, and social domains discriminate between patients with schizophrenia and healthy controls. Patients with schizophrenia have lower QOL than healthy controls.

The SF-36 is a widely used self-rated generic QOL instrument. Russo et al. (52) find that the SF-36 has good internal consistency, stability, and concurrent validity in a group of 36 outpatients with schizophrenia. Tunis et al. (53) find evidence for the instrument's reliability and validity in patients with schizophrenia (n = 1155). The patient population has marked deficits in the following subscales: General health, Vitality, Mental health, Social functioning, and in Role limitations resulting from both physical and emotional problems.

Voruganti et al. (1998) assess QOL with the SIP at weekly intervals for 4 weeks in 63 patients with schizophrenia. They find high consistency and reliability (39).

Distressing Factors Influencing QOL

Given that patients with schizophrenia have lower QOL than their healthy counterparts in the community, we might expect that psychopathology and severity of psychotic symptoms would have a large impact on QOL. In fact, although negative symptoms predict poor QOL, depression is the most consistent predictor of poor QOL. Anxiety, psychosocial factors, insight, and medication side-effects also contribute to QOL (48).

Psychopathology and Symptom Severity

General Psychopathology and QOL

The psychopathology of schizophrenia falls into three broad categories: positive symptoms, negative symptoms, and neurocognitive decline. Studies of associations between measures of general psychopathology and QOL in schizophrenia produce contradictory results. Many investigators find that the severity of psychopathology is inversely associated with QOL for both chronic patients and first-episode patients (55). Both Heslegrave et al. (1997) and Voruganti et al. (1998) find that QOL (SIP) decreases as general psychopathology on the PANSS increases (39, 84). Similarly, QOL scores (QoLI) go down as general psychopathology on the BPRS increases (85). Auquier et al. (77) find negative correlations between the S-QoL and total PANSS, GAF, and CGI.

However, several investigators find no association between general psychopathology and QOL (31, 67). A longitudinal study by Awad and Voruganti (2000) finds no interaction over time between symptom severity, side effects, neurocognitive deficits, or antipsychotic drug dosages and the SIP (86). In another longitudinal study 1 year after stabilization patients improve on most dimensions of the WQLI, but the improvement is largely independent of symptom changes (87).

Positive and Negative Symptoms and QOL

Some studies find no association between positive or negative symptoms and QOL (70). However, many find correlations between negative symptoms and QOL.

Because positive symptoms (hallucinations, delusions, and disorganized speech and behavior) are so disturbing to patients, it is surprising that studies of positive symptoms and subjective QOL are few and controversial (37). Many investigations fail to find a relationship between QOL and positive symptoms (33, 70, 71). However, in a longitudinal study, changes in self-esteem/self-efficacy and distress intensity account for about 12% each of the QOL index score change with time. Positive symptoms account for less than 3% (88). When Rudnick (73) assesses the relationships between positive and negative symptoms on the PANSS and various domains of QOL (WQLI) in adult outpatients, positive symptoms relate to distress-assessing domains. Finally, positive

symptoms on the BPRS correlate with diminished global life satisfaction (QoLI) (85).

Negative symptoms almost universally predict poor QOL (37, 85). Rudnick (73) finds that negative symptoms on the PANSS predict low scores on the activities of daily living domains (WQLI). Aksaray et al. (59) also find that negative symptoms (SANS) and low QOL go together on the PCASEE scale. The anhedonia scales of the BPRS predict low QOL in the psychological, social, and spirituality domains of the WHO-QOL (33). Furthermore, high scores on the PANSS negative subscales correlate with low scores on two of seven dimensions of the MSQoL (71).

Neurocognitive decline

As noted; the neurocognitive deficits (problems with attention, concentration, memory, and executive function) of schizophrenia, even when profound, appear to have little impact on a patient's perceived QOL (84).

Depression and Anxiety

Patients with schizophrenia often have depression and anxiety. As in psychoses-free patients, both depressive and anxiety symptoms predict poor QOL (see Chapters 35 and 38) (28, 31, 37, 47, 48, 89). The anxiety/depression scales of the BPRS predict low QOL in the physical, psychological, independence, and environmental domains of the WHO-QOL-100 (33). High scores on the PANSS depression and anxiety subscales predict low scores on six of seven dimensions of the MSQoL (71). In addition, low QOL (SQLS) correlates with both depression and anxiety subscales of the Hospital Anxiety and Depression Scale (78).

Anxiety is the predominant factor in QOL in patients with schizophrenia or schizoaffective disorder. In a longitudinal study, Huppert and Smith (68) find that changes in anxiety (BPRS) correlate with general life satisfaction and satisfaction with five of seven domains of the QOLI.

Psychosocial Factors

Patients with psychosis are disadvantaged in all areas of life circumstances compared with either healthy control subjects or patients with non-psychotic mental illness. These include employment, mean hours worked, owning a home, being accused of a crime, being victims of crime as well as family and friend contacts, i.e., living with family, having a friend, seeing friend in the last week (69). However, patients with psychosis are not necessarily restricted in life opportunities, particularly in countries where there was a strong social safety net. Some hypothesize that this is because caseworkers assist patients with severe mental illness to secure entitlements (69).

Economic class, age, and ethnicity do not correlate with QOL in patients with schizophrenia. A few studies find that low verbal intelligence (90), low educational level, and female sex correlate with high QOL (38), but sex is not a factor in other studies (70). Perceived stigma is also related to low QOL (38).

Insight

Insight involves awareness of being mentally ill, attribution of pathological symptoms to mental illness, and awareness of the need for treatment (48). Lack of insight is a symptom of schizophrenia and accompanies poor treatment compliance. Thus, improving insight is a major goal in treatment because improving insight may lead to improvements in both treatment engagement and prognosis (28). However, studies of the impact of insight on QOL in schizophrenia are contradictory.

Early studies that use observer-rated QOL find either no association (91) or high QOL in patients with insight (92). However, more recent studies find that insight into having a psychosis and low QOL go together (93, 94). Karow and Pajonk (2006) link these results to studies of insight and psychosis that find associations between insight and depression, measures of distress, and suicidality (95). They conclude that an individual's ability to appraise the implications of psychosis on his/her perceived social identity and future prospects leads to poor perceived QOL (94).

Medication Side Effects

Antipsychotic medications can have unwanted side effects including drowsiness, restlessness, tremor, dry mouth, or blurred vision. Most cross-sectional studies of the effects of antipsychotic medications on QOL find that side effects decrease QOL (2, 37, 59, 91). Ritsner et al. (96) find that the patients' subjective response to side effects is a better predictor of QOL than the number of side effects.

Protective Factors Influencing QOL

Personality traits, coping styles, self-esteem, self-efficacy, and social support are potential protective factors that may improve QOL (37).

Self-Esteem and Social Support

QOL in patients with schizophrenia correlates with self-esteem (97), sense of personal control, and empowerment (38). Community tenure (98), and the size of the patient's social network also tend to improve QOL (90). Furthermore, the social skills and social adjustment they had before they became ill predict QOL (99).

Personality and Coping Style

Personality and coping style have a large impact on QOL in patients with schizophrenia. Extroversion and agreeableness on the Neuroticism, Extroversion, Openness Personality Inventory (NEO-PI) correlate with high QOL in patients

with schizophrenia; neuroticism correlates with low QOL (100). Low levels of harm avoidance and high levels of self-directedness on the Tridimensional Personality Questionnaire (TPQ) correlate with high subjective QOL (101).

Temperament (TPQ) explains some (6–16%) of variance in QOL scores among patients with schizophrenia. However, different temperament factors influence different domains of QOL. High levels of novelty-seeking predict high general QOL, physical health, and positive feelings. Furthermore, high reward-dependence and satisfaction with social relationships seem to go together. High harm-avoidance correlates with low satisfaction with both general activities and medication (48).

Coping style accounts for as much as a quarter of the variance in self-reported QOL (n = 161 patients with schizophrenia). Task-oriented and avoidance-oriented (distraction) coping styles correlate with high QOL. In contrast, emotion-oriented coping correlates with low scores (102).

Subjective Versus Objective Subscales of Self-Reported QOL

There are both objective and subjective aspects of QOL irrespective of how information is obtained. Objective measures are easily quantified, measured, and observed, i.e., income and employment status. Subjective measures are, for example, how much is one satisfied with one's job or roommate (45). In countries with well-functioning social services where patients with significant disability are provided with housing and income, patients frequently report good objective QOL but unsatisfactory "inner experiences" (29, 103).

In a large number of studies, patients with schizophrenia consistently report better QOL than their objective living conditions predict (49, 104, 105). Several studies find the discrepancy between subjective and objective QOL ratings greater among patients with schizophrenia than among patients with other illnesses (45, 103, 105). Patients with schizophrenia have not only significantly higher subjective QOL scores but also more adverse life events on objective QOL assessments than severely depressed patients (39, 106, 107).

Khatri (2001) reports a high correlation between subjective and objective indexes from the QoLI in patients with cancer but not for patients with schizophrenia. Patients with schizophrenia rate subjective QOL higher than objective QOL. As previously noted, the ratings of family members of the patients with schizophrenia show the same discrepancy as the patients, suggesting that the difference between objective and subjective QOL may be valid (45).

This outcome is puzzling and merits further investigation. Patients with psychosis report lower QOL than healthy controls and patients with non-psychotic mental illness in all areas except leisure on the LQOLP (69). This suggests that greater satisfaction with leisure can improve subjective QOL in patients with psychosis irrespective of having low socioeconomic resources.

Several researchers suggest that after time, patients with schizophrenia become satisfied with substandard socioeconomic resources. This adaptation elevates the subjective QOL (38, 45). One theory says that QOL improves as the gap between expectations and achievements narrows. One can narrow the gap by either arriving at one's aims or by lowering one's expectations. When ability to achieve is limited by an illness like schizophrenia, patients adjust their aspirations downward to narrow the gap (38).

Conclusions

There are a large number of valid generic and disease-specific instruments to assess QOL in patients with schizophrenia. Irrespective of the setting and the assessment instruments, persons with psychoses generally rate their QOL worse than the general population and of physically ill patients (29).

Patients with schizophrenia can self-rate their QOL, but the most complete picture of QOL includes the patients' assessment of QOL as well as that of family members and professionals. Patients report better subjective QOL than their objective living conditions predict.

Negative symptoms, depressed mood, anxiety, medication side-effects, and stigma correlate with low QOL in patients with schizophrenia. Positive mood, high self esteem, good social support, a sense of personal control and empowerment, and an extroverted, agreeable personality correlate with high QOL.

Sleep and QOL

Many studies in persons with primary insomnia without psychosis support the link between good sleep and good QOL. In normal subjects, chronically impaired sleep is detrimental to psychological well-being, ability to cope with stressors, and QOL (27, 108); See Chapters 5 and 9.

Insomnia is almost always associated with fatigue and mood disturbances, such as irritability and dysphoria (109). Sleep-deprived individuals experience difficulties in coping with novel situations and tend to fall back on simpler but riskier strategies (110, 111). Impaired cognition, increased accidents, depression, aggression, fatigue, and confusion and sleep deprivation or disruption go together (21).

Zammit et al. (1999) find that subjects with insomnia report greater reductions in QOL than subjects without insomnia when assessed with the SF-36. Subjects with insomnia have lower mean scores on all subscales of the SF-36 and lower scores on the cognitive scale than subjects in the control group have (112). There are associations between insomnia and reduced health-related QOL and increased healthcare resource use (113).

Untreated sleep disturbance may contribute to the severe social and occupational dysfunction common in schizophrenia. Some of the disorganized behavior of patients with schizophrenia may be sequelae of sleep deprivation compounded with impaired functioning. Because sleep plays an important role in memory consolidation, the sleep deficits may be an important source of the memory deficits that underlying cognitive difficulties seen in schizophrenia (114).

Persons with primary insomnia often have dysfunctional beliefs about sleep that play a significant role in maintaining their inability to sleep (115). Examples of typical dysfunctional beliefs and attitudes held by persons with primary insomnia are exaggerated beliefs about the negative consequences of insomnia, hopelessness about the fear that their sleep is uncontrollable, and helplessness about the unpredictability of sleep (116). Patients treated with cognitive behavioral therapy (CBT) that focuses on improving both sleep behaviors and beliefs about sleep show simultaneous improvement in sleep, QOL on the SIP, and dysfunctional beliefs about sleep on the Dysfunctional Beliefs and Attitudes about Sleep Scale (DBAS) (109, 117).

Sleep and QOL in Schizophrenia

Can Patients Self-Rate Sleep?

As with self-reports of QOL, some question whether persons suffering from schizophrenia can validly self-report on their own sleep (38). However, at least one study in patients with schizophrenia compares PSG sleep measures and subjective estimation of sleep and finds them highly correlated (118).

Sleep and Symptoms

Does anomalous sleep structure affect symptoms and psychopathology? (109) Sleep disturbances in patients with schizophrenia apparently predict heightened levels of thought disorder (17) and symptoms of hostility and excitement (119). It is possible that disorganized or disrupted sleep may negatively affect symptoms and complicate function in ways that lead to a declining clinical path. For example, REM latency has a strong inverse correlation with negative symptoms, scores on the BPRS (16), and scores on the Scale for the Assessment of Negative symptoms (SANS) (10).

In two small clinical trials, as patients with schizophrenia reported improved sleep on a non-benzodiazepine hypnotic they also experienced a reduction in psychiatric symptoms measured by the BPRS (120, 121).

Further evidence that sleep deprivation in schizophrenia may influence overall function comes from a clinical trial of modafinil, a long-acting stimulant. Overall functioning as rated by a blinded clinician improves in patients with schizophrenia on modafinil compared with that on placebo. Performance on memory task in a subset of patients also improves (122). The improvements, however, may be either from a direct effect of modafinil on cognition or to the drug overriding the effects of sleep deprivation (123).

Dysfunctional Beliefs, Sleep Quality, and QOL in Schizophrenia

Ritsner et al. (2004) are first to report that persons with schizophrenia who judged themselves as poor sleepers (PSQI below 5) also report poor QOL (124). They point out that poor sleep quality is an important part of poor QOL for the general population and for patients with chronic cardiac and pulmonary disease, cancer, cirrhosis, Parkinson disease, and others. Their hypothesis is that low QOL and low sleep quality go together in patients with schizophrenia as well. They assess QOL with the Q-LES-Q (63). The Q-LES-Q is a self-report questionnaire validated in schizophrenia that is mental health related but not schizophrenia-specific (64). In their patient population as in normal subjects, low sleep quality correlates with high levels of depression, overall distress, adverse medication side effects, and discomfort, both mental and somatic.

Indeed, they find, in a cohort of 145 patients with schizophrenia, about equally divided between good and poor sleepers, that low QOL and poor sleep go together. Furthermore, the relationship holds even after accounting for the potentially confounding effects of depression, distress, and treatment medication. As in other studies, symptoms of depression correlate with low QOL but PANSS scores do not. Finally, the component of daytime dysfunction on the PSQI seems to be the most robust predictor of QOL in patients with schizophrenia. This implies that, at least for some, the daytime consequences of sleep loss predict poor QOL (124).

We tested the hypotheses that poor sleep would predict low QOL and use of avoidant coping mechanisms. We compared QOL (QLS) in a group of 29 subjects diagnosed with schizophrenia or schizoaffective disorder in a post acute phase of illness with the PSQI, the PANSS, and the Ways of Coping Questionnaire (WCQ). The QLS is a semi-structured self-report interview for QOL. It is schizophrenia-specific and has been extensively validated in schizophrenia. The WCQ is a self-report instrument. Subjects score how frequently they use any of 66 unique ways to cope with a recent stressor. Persons with schizophrenia complete this form reliably but differ from community controls in ways one would expect (125). We use relative scores for two of the subscales: “escape avoidance” and “positive reappraisal.” Escape avoidance is wishful thinking and behavioral efforts to escape or avoid the problem; Positive reappraisal tries to create positive meaning.

Not only was QOL low in patients with the poor sleep, but subjects in this population seemed to prefer an avoidant coping strategy and eschew a strategy of positive reappraisal (126). The results are consistent with the idea that inefficient sleep may play a unique role in sustaining poor QOL and impaired coping in patients with schizophrenia. Actigraphic

records in a subset of patients support their perception of having disrupted and inefficient sleep.

Studies of QOL and Sleep in Schizophrenia

We also developed a semi-structured interview that probed the nature, course, and daytime sequelae of sleep problems. The interviewer asks about the regularity of a patient's sleep routine; the details of the routine; the nature of their sleep problems; about a patient's napping patterns; and how sleep changes as schizophrenia becomes acute. Our interviewees consistently reported that they could not manage their sleep. They believed that their behavior did not impact sleep, and perhaps as a consequence of this belief, most failed to follow basic sleep hygiene practices. Less than half had a regular bedtime or wake-up time. Many smoked cigarettes and drank caffeinated coffee or cola when they woke up in the middle of the night.

From the interviews, we formulated and tested several hypotheses: persons with schizophrenia have high levels of dysfunctional beliefs about sleep that correlate with poor sleep. High levels of dysfunctional beliefs about sleep correlate with psychotic symptoms and anxiety. In a cross-sectional survey of patients with schizophrenia, 31 male participants completed the following instruments: PSQI; PANSS; DBAS, and the State-Trait Anxiety Inventory (STAI, 127). Anxiety, agitation and fear are common symptoms of schizophrenia and are antithetical to good sleep (27). We examined correlations between the measures. We also compared our data from the DBAS with studies in patients with primary insomnia (128, 129).

Patients with schizophrenia had high levels of dysfunctional beliefs about sleep similar to otherwise healthy subjects with primary insomnia. Furthermore, high dysfunctional beliefs about sleep correlated with poor global sleep quality among this population. High dysfunctional beliefs were not related to positive or negative symptoms but correlated instead with measures of depression, emotional distress, and trait anxiety. Poor sleep quality was also related to high trait anxiety. Poor sleepers endorsed a pattern of responses on the DBAS suggesting that they have poorer sleep practices than good sleepers (130). High levels of dysfunctional beliefs about sleep correlated with poor QOL in a subset of patients.

To look for characteristics that differentiated patients with good sleep from those with poor sleep, we compared eight good sleepers (PSQI < 5.5) to 23 poor sleepers (PSQI ≥ 5.5) for differences in demographic measures, DBAS, PANSS, and STAI scores. Poor sleepers took more antipsychotic medication than good sleepers and had almost three times as many lifetime psychiatric hospitalizations as good sleepers. Good and poor sleepers did not differ in age, education, or symptom level on the PANSS total or Positive or Negative subscale. Good and poor sleepers did not differ on the STAI, although there was a tendency for poor sleepers to have higher trait anxiety than good sleepers (130).

Although we cannot infer causality from these correlative analyses, our results support the idea that most patients in our population perceive their sleep as poor. Actigraphic records support their perception of having disrupted and inefficient sleep. Sleep deprivation of this sort has a powerful impact on subjective QOL and the ability to appraise stressors in a positive light, independent of age and symptoms. Chronic sleep deprivation may fuel anergy that impairs performance of daily tasks, further eroding self-confidence and self-sufficiency. Our results are consistent with PSG studies where sleep deficits are independent of illness acuity (11, 13, 15–17).

These findings suggest important clinical implications. If efficient sleep is critical to QOL in schizophrenia, clinicians will want to focus on and aggressively treat sleep problems. Improving sleep may improve cognition in patients with schizophrenia, increase their ability to cope with stress, and decrease the need for antipsychotic medications and hospitalizations. All changes would improve QOL. Further research is needed to determine whether therapies to decrease dysfunctional beliefs about sleep can improve sleep and QOL in patients with schizophrenia.

Summary

Patients with schizophrenia have severe and persistent sleep disturbance, marked by difficulty initiating and maintaining sleep, diminished SWS and short REM latency. Multiple mechanisms contribute to poor sleep in patients with schizophrenia, including high brain dopamine levels, high anxiety, and medication side effects.

Persons with psychoses generally rate their QOL worse than the general population and physically ill patients (29). Patients with schizophrenia can self-rate their QOL, but the most complete picture of QOL includes the patients' assessment of QOL as well as that of family members and professionals. Negative symptoms, depressed mood, anxiety, medication side effects, and stigma correlate with low QOL in patients with schizophrenia. Positive mood, high self esteem, good social support, a sense of personal control and empowerment, and an extroverted, agreeable personality correlate with high QOL.

Sleep deprivation may contribute to poor functioning in patients with schizophrenia. Poor sleep correlates with high levels of thought disorder, hostility, and excitement. Medication that improves sleep in patients with schizophrenia also improves psychiatric symptoms.

Poor sleep predicts poor QOL in patients with schizophrenia. The daytime consequences of sleep loss have a large effect on QOL. Subjects with poor sleep were more likely to be depressed and use avoidant coping mechanisms than good sleepers.

Patients with schizophrenia had high levels of dysfunctional beliefs about sleep similar to otherwise healthy subjects

with primary insomnia. High dysfunctional beliefs correlated with poor global sleep quality, measures of depression, emotional distress, and trait anxiety. Poor sleepers took more antipsychotic medication than good sleepers and had almost three times as many lifetime psychiatric hospitalizations. High levels of dysfunctional beliefs about sleep correlated with poor QOL in a subset of patients.

Aggressive treatment of sleep problems in patients with schizophrenia may improve QOL. Further research is needed to determine whether therapies to decrease dysfunctional beliefs about sleep can improve sleep and QOL in patients with schizophrenia.

Issues that need to be addressed by future research:

- Can sleep be improved in schizophrenia?
- If sleep can be improved in schizophrenia, does QOL improve; do symptoms improve?
- Are the dysfunctional beliefs about sleep held by patients with schizophrenia the same as those with insomnia or unique to psychosis?

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32
Sleep, Psychological Trauma, and Quality of Life

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Summary This chapter explores the interface among sleep patterns, psychological trauma, and quality of life. This chapter is written with the conceptual model, health-related quality of life (HRQL), as the backdrop for understanding the relationships between sleep, psychological trauma, and HRQL. It incorporates an understanding of the interrelationship of health, biological, social, and psychological markers as it relates to a person's HRQL. Under this framework, sleep acts as a biological variable that intersects with psychological trauma causing alterations in HRQL. In this chapter, we 1) review the current literature on the characteristics and uniqueness of sleep disturbances that are associated with a psychological trauma, 2) examine the relationship among: sleep, psychological trauma, and quality of life among select groups, and 3) focus on empirical gaps present in our knowledge related to trauma, sleep, and quality of life.

Keywords Psychological trauma · sleep disturbance · quality of life · psychiatric co-morbidity · survivorship.

Learning objectives:

- Health-related quality of life (HRQL) is impaired in patients with psychological trauma and impaired sleep.
- Patients who experience psychological trauma and sleep problems have decreased functional capacity, compromised physical health, increased pain, physical limitations, fatigue, higher levels of depression, substance use, and increased health services utilization.
- Cognitive-behavioral therapy is associated with improvement in sleep and psychological trauma and HRQL, but few research studies have incorporated HRQL as an outcome.

Introduction

Sleep is defined as a reversible physiological behavioral state of perceptual disengagement from the environment susceptible to changes occurring within the individual and from the environment (1). An environmental event, such as a psychological trauma (unexpected death of a loved one, rape, torture, natural disaster), can easily influence and change short-term sleep patterns, which, in turn, can precipitate greater long-term psychological disruption, such as posttraumatic stress disorder (PTSD), anxiety, or depressed mood (2). Individuals who meet full criteria for PTSD must be experiencing significant sleep disturbance related to the presence of hyperarousal and re-experiencing the traumatic event.

Health-related quality of life (HRQL) refers to a synthesis of an individual's perceptions, experiences, feelings, and values in combination with the biological and physiological factors, symptoms, functioning, and general health perceptions (3). Rogerson (4) also supports a conceptual framework on HRQL that emphasizes symptom characteristics, individual perception of health, and over all life satisfaction and well-being.

This chapter is written with the conceptual model, HRQL (3), as the backdrop for understanding the relationships between sleep, psychological trauma, and HRQL. It incorporates an understanding of the interrelationship of health, biological, social, and psychological markers as it relates to a person's HRQL. Under this framework, sleep acts as a biological variable that intersects with psychological trauma causing alterations in HRQL. In this chapter, we 1) review the current literature on the characteristics and uniqueness of sleep disturbances that are associated with a psychological trauma, 2) examine the relationship among sleep, psychological trauma, and quality of life within select groups, and 3) focus on

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empirical gaps present in our knowledge related to trauma, sleep, and quality of life.

Sleep and Psychological Trauma

Sleep is an essential behavioral and physiological state that has a significant impact on overall functioning. The internal biological and regulating clock, located in the suprachiasmatic nuclei of the hypothalamus, is responsible for periodic changes in alertness, arousal level, and performance level (5). Traumatic events also contribute to poor daytime function. If the stressful event is of significant magnitude, an acute stress disorder is diagnosed. If the psychological stressor or psychological trauma is not resolved within 30 days and seriously impairs daily functioning, the individual is diagnosed with PTSD (6). The trauma response depends on the extent, intensity, and duration of the psychological trauma.

Alterations in sleep occur when an individual experiences symptoms of psychological trauma. The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) (6) in Table 32.1 outlines six criteria for a full diagnosis of PTSD. Sleep disruption, hyperarousal (having trouble falling or staying asleep), and reexperiencing (bad dreams and nightmares) are embedded in the scoring. The cluster of symptoms comprising PTSD influences psychological functioning through alterations in brain chemistry, but also contributes to poor quality of life, including function in daily activities, problems with interpersonal relationships, conflictual interactions, co-occurring psychiatric illnesses, such as alcohol and substances abuse, and mood and anxiety disorders (7–10).

One of the primary PTSD criteria is functional impairment in domains of living. Utilization of health care services is increased in individuals who have PTSD (11–13). Sleep alterations are part of the trauma response but also contribute to other comorbid psychiatric disturbances (e.g., anxiety and depression) (14, 15) and quality of life.

Risk Factors Associated with PTSD

Risk factors for PTSD may include demographic, cultural, and economic factors, as well as the nature of the traumatic event. Women are twice as likely as men to experience PTSD (10 vs 5%) (10). Disadvantaged immigrant populations, in particular, Hispanics, are at increased risk for a range of mental illnesses after exposure to a traumatic event (16–19). In a study of the aftermath of World Trade Center Disaster, researchers found that at 1 year, PTSD was related to being female and younger, experiencing more WTC exposure, more negative life events, less social support, and self-esteem. At 2 years post WTC attack, PTSD was associated with being Latino, more negative life stress, and poor self-esteem (20).

Manifestations of trauma are multifactoral and have been highlighted in our previous article (21). Psychiatric co-morbidity is associated with sleep quality in PTSD, such as substance use disorders, mood disorders, and anxiety disorders (22). However, the severity of sleep disturbance in individuals with PTSD did not differ according to gender, age groups, types of trauma, or psychiatric co-morbidity (23).

Sleep and Qualify of Life

Disturbed sleep is responsible for an array of physiological and emotional problems and decrements in quality of life. Sleep disorders are associated with functional impairment (24, 25), depression and alcohol dependence (26–29), lower levels of physical functioning, energy/vitality and social functioning (30), impaired coping (31), functional performance and mental health (32), fair to poor general health, physical and mental distress, pain, and obesity (33, 34). Psychological trauma appears to be as strongly associated with decrements in quality of life (35). Particular impairment in cognitive, motivational, and emotional function was associated with major depression, dysthymia, and PTSD.

Physiological Changes Associated with Psychological Trauma that Influence Sleep

Physiologic alterations in people with psychological trauma, including increased activation of the HPA axis, elevated levels of sleep-disordered breathing (SDB), autonomic and immune dysfunction, may contribute to medical co-morbidity, sleep disturbance, and poor quality of life. Individuals with PTSD have enhanced activation of the HPA axis and increased adrenal response to stress and glucocorticoid receptor sensitivity (36–39). Release of corticotrophin-releasing factor (CRF) is associated with decreases in delta sleep activity in men and women with chronic PTSD (40, 41). Autonomic alterations associated with increased heart rate in PTSD victims, who had nightmares (42) as well as SDB (43, 44), may increase the likelihood of cardiovascular morbidity (45), and immune dysfunction secondary to PTSD (46). These changes may contribute to comorbid health problems, such as psoriasis, glomerulonephritis, and rheumatoid arthritis (46).

In summary, there are several pathophysiogical pathways through which trauma may negatively contribute to sleep and quality of life. Excess medical co-morbidity may negatively contribute to excess burden on quality of life. The hormonal response may contribute to a person's perception of experiencing routine daily stress as being more distressful (47). Sleep disturbance secondary to psychological trauma may also contribute to decrements in quality of life.

TABLE 32.1. Posttraumatic stress disorder (APA, 2000).

Diagnostic Criteria for 309.81 Posttraumatic Stress Disorder
A. The person has been exposed to a traumatic event in which both of the following were present:
(1) the person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others.
(2) The person's response involved intense fear, helplessness, or horror. Note: In children, this may be expressed instead by disorganized or agitated behavior.
B. The traumatic event is persistently reexperienced in one or more of the following ways:
(1) recurrent and intrusive distressing recollections of the event, including images, thoughts, or perceptions. Note: young children, repetitive play may occur with specific themes.
(2) Recurrent distressing dreams of the event
(3) Acting or feeling as if the traumatic event were reoccurring (includes a sense of reliving the experience, illusions, hallucinations, and dissociative flashbacks)
(4) Intense psychological distress at exposure to internal or external cure that symbolize or resemble an aspect of the traumatic event
(5) Physiological reactivity on exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event
C. Persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness (not present before the trauma), as indicated by three or more of the following:
(1) efforts to avoid thoughts, feelings , or conversations associated with the trauma
(2) efforts to avoid activities, places, or people that arouse recollections of the trauma
(3) inability to recall an important aspect of the trauma
(4) markedly diminished interest or participation in significant activities
(5) feeling detachment or estrangement from others
(6) restricted range of affect (unable to have loving feelings)
(7) sense of foreshortened future (does not expect or have a career, marriage, children, or a normal life span)
D. Persistent symptoms of increased arousal (not present before the trauma) as indicated by two (or more) of the following:
(1) difficulty falling or staying asleep
(2) irritability or outburst of anger
(3) difficulty concentrating
(4) hyperviligence
(5) exaggerated startled response
E. Duration of the disturbance (symptoms I Criteria B, C, and D) is more than 1 month
F. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning

Attributes of Sleep in Individuals with Psychological Trauma

Sleep disturbance is a core clinical feature of PTSD (23). As reviewed in our previous article (21), there are several ways that PTSD may be related to sleep: 1) sleep is a symptom of PTSD, 2) poor sleep quality can contribute to the development of PTSD, 3) PTSD can cause sleep disturbances, and 4) common symptoms of sleep disturbance and PTSD are the foundation for hyperarousal leading to changes in HPA.

Sleep, Psychological Trauma, and Quality of Life in Current Military and War Veterans

The following sections will explore sleep and trauma, trauma and quality of life, and the interrelationship among these phenomona. A summary highlights deficiencies in the science and identifies foci for future research.

Sleep and Psychological Trauma

Veterans with PTSD reported sleep quality considerably poorer than objective measures (44,48). Their sleep was characterized by more awakenings and restlessness (49). Sleep state misperception may be associated with REM dysregulation as found in PTSD (50), but perceptions about sleep may also be influenced by enhanced HPA axis activity that contributes to perceptual changes.

Veterans with PTSD report difficulty falling asleep, staying asleep, and frequent nightmares (51). Hyperarousal is a significant part of the experience of PTSD and may explain a significant part of the frequent nocturnal awakenings (52). Nightmares may be associated with greater acuity and recency of the trauma, as well as higher levels of hyperarousal and more accessible nightmare content (52). Dreams and nightmares were more intense in individuals with PTSD than in controls (53). Nightmares appear to develop from disrupted REM sleep (54) and are associated with increased wake-after-sleep onset and more nocturnal activity (54). Veterans with nightmares may also deliberately wake themselves up to avoid re-experiencing the traumatic event (52).

Although nightmares are a common feature of PTSD, they do not occur in all groups with this diagnosis, and there is little consistency in reports of other characteristics of sleep disturbance. Some investigators have noted reduced total sleep time (TST) and sleep efficiency. However, data on the patterns of REM sleep were conflicting with REM latency as prolonged or normal, percentage of REM as reduced or

normal (15, 55–57). One study found no sleep disruption among people with PTSD when measured with polysomnography (PSG) (48).

SDB appears to be higher in prevalence among veterans with PTSD, mood disorders, and anxiety disorders (43, 44). Although the reason for this is not completely known, SDB may be more likely to occur in people who have more transitional sleep stages, a characteristic that may be associated with PTSD-related hyperarousal.

Although female veterans and currently serving military women may have higher rates of PTSD than the civilian population as a result of military sexual trauma (MST), few researchers have focused on this group of veterans (58, 59). Such research is necessary, especially due to the increased risk of PTSD in women.

In summary, sleep patterns in veterans with PTSD are characterized by (a) reduced in duration and efficiency, (b) nightmares and increased limb movement, (c) increased arousal with elevated REM, (d) discrepancies in REM responses, and (e) co-occurring affective disorders that may further influence sleep. Although more studies are needed, PTSD victims also appear to be at increased risk for SDB. Further research is needed on the factors that may contribute to sleep disturbance in veterans with PTSD, and related factors are likely to include age, gender, war theatre exposure, pre-war psychiatric illness, treatment patterns, and medication management.

Psychological Trauma and Quality of Life

PTSD significantly impacts quality of life (60, 61) in many dimensions. Among veterans, these include negative affectivity (62), reductions in functional capacity, compromised physical health, physical limitations, greater involvement in violent activities, and lack of employment (59). PTSD also appears to be associated with shorter lifespan, secondary to increased risk-taking behaviors (63).

Influences on decrements in quality of life among veterans with PTSD appear to be multi-factorial. Rural veterans experienced greater clinical impairment, higher levels of PTSD, depression, and other psychiatric illnesses (64). This was attributed to restricted access to mental health services, social supports, recreational resources, and transportations systems. Exposure to combat was associated with increased somatic complaints, a component of quality of life (65), and to poorer quality of life in general (66). Veterans who had comorbid depression experienced poorer quality of life and increased medical symptoms and health utilization (11).

Depressed deployed Gulf veterans had significantly more cognitive dysfunction related to anxiety, phobias, substance abuse, and PTSD (67). Cognitive functioning, chronic pervasive pain, body mass index, hypochondriacal symptoms, and symptoms of PTSD were also associated with lower HRQL (67).

Women veterans who experienced physical and sexual assault sustained the greatest impairment in their quality of life, particularly at work, with daily activities due to physical and mental health problems, including chronic pain, fatigue, depression, and anxiety (65).

There may be several explanations for the relationships between PTSD and quality of life. First, stigma of mental illness drives individuals to seek medical care rather than psychiatric services. Second, PTSD symptoms may be misinterpreted as originating from a physiological illness. Third, individuals with PTSD, in fact, may have more physical problems and require medical care (11).

Serious attention to improvement in the diagnosis and treatment of co-occurring psychiatric illness may improve HRQL. A treatment study targeting veterans with PTSD using behavioral activation therapy was associated with significant reduction in depressive and PTSD symptoms and improved quality of life (68). Therefore, treatment may hold promise for improvements in quality of life for veterans with PTSD.

Sleep, Trauma, and Quality of Life

There has been only one study that addressed sleep, trauma and quality of life, and a second study indirectly referenced sleep quality. In a study of Gulf war veterans, self-reported physical health was significantly related to PTSD, accompanied by reduced overall health functioning and quality of life and associated with vascular reactivity, hyperarousal, disrupted sleep patterns and serious psychiatric comorbidity (69). PTSD was found to be significantly related to self-reported physical and mental health problems, in particular, obesity and poor HRQL (70). Over time, participants in the study reported improvements in their overall quality of life, except employment and physical health, but the veterans continued to report little change in standardized measures (63).

Future studies should focus on several areas. First, objective and subjective sleep measures will provide necessary data to evaluate sleep patterns and the relationship with PTSD and quality of life. Second, since most of the studies of veterans were conducted in men, gender differences should be evaluated because women are at higher risk for PTSD and sleep disturbances that are common among women of childbearing age (71, 72). Third, more comprehensive contextual variables about family, education, living circumstances, social supports, physical health, pre-war psychiatric history, and quality of health services access should be considered in any models relating to sleep, PTSD, and quality of life. Particular attention will increase the understanding of quality of life and how treatment interventions should be focused.

Sleep, Psychological Trauma, and Quality of Life in the General Population

Recent community-based studies have estimated that 90% of adults have been exposed to a traumatic event (73,74), and the rate of development of PTSD is approximately 15% of those exposed (75,76). Traumatic events may include assaults (e.g., rape, muggings, beatings, sexual assaults), accidents, terror attacks, and natural disasters, such as earthquakes.

Similar to the rates of disturbed sleep among veterans, sleep disturbance appears to be common among non-veterans. Objective measures of sleep disturbance include reductions in delta sleep (41), decreases in REM sleep, and prolonged REM latency (77). However, PTSD patients exhibited a greater number of REM sleep periods (more fragmentation), shorter average duration of continuous REM sleep than those without PTSD during the month after a physical injury. This finding provided some further evidence of a disruption of REM sleep in PTSD, possibly linking this disruption to the negative impact on memory consolidation (78).

Other objective characteristics of sleep disturbance include reduced total sleep time (TST), sleep efficiency, nightmares, awakenings, and increased periodic limb movement (79). SDB, sleep movement disorders are more common than expected and related to daytime functioning. Lower arousal threshold is a link to sleep disruption in individuals with PTSD (57,80).

SDB, associated with apneas, hypopneas, nocturnal arousals, and hypoxia, appears to be common among sexual assault victims (81), crime victims (82), and victims of fire. Individuals with psychological trauma had greater sleep onset and maintenance insomnia, poor sleep quality, nightmares, and shorter TST. Both groups had high levels of fatigue and daytime sleepiness when controlling for obesity (83).

Difficulty initiating and maintaining sleep and nightmares are common in several groups of people who had PTSD, including American Airline flight attendants after September 11, 2001, Oklahoma City bombing survivors, substance abusers, and mental health staff (84–87). Crime victims with PTSD experienced both objective and subjective disturbances, but discrepancies have been found. No differences were found among the groups of accident victims on any PSG measure including the awakening thresholds during REM sleep (88). Crime victims with PTSD did not have any deficits in daytime alertness but did have reduced REM sleep compared with a non-PTSD group. This implicates sleep state misperception in PTSD crime victims that is similar in veterans with PTSD.

Consequences of disturbed sleep, particularly SDB, include exacerbation of PTSD symptoms and psychiatric distress (89). Among earthquake survivors, PTSD, in combination with major depressive episode, was significantly related to poorer quality of life, in particular, insomnia (90). Co-occurring problems, such as poor sleep quality, sleepiness, and fatigue, contributed to PTSD sequalae and other psychiatric illness such as anxiety and mood disorders (2, 89). Resilience did not protect trauma survivors from sleep or dream disturbances (91).

Objective and subjective sleep disturbances are prevalent among victims of various physical and psychological traumas and include 1) sleep onset and maintenance insomnia, nightmares, daytime fatigue, and hyperarousal; 2) sleep apneas, upper airway resistance syndrome (UARS), periodic leg movements, changes or reductions in REM and Delta, reduced sleep efficiency, hyperarousal and increased sleep fragmentation, and sleep misperception syndrome. Although many groups have been studied, there has been little research focusing on PTSD and quality of life among immigrants arriving from war zones who have symptoms of trauma, poor sleep quality, and poor quality of life (92–95).

PTSD and Quality of Life and Sleep and Quality of Life in Life-Threatening Illness

Life threatening and physical illnesses, such as cancer, myocardial infarction, cardiac surgery, miscarriage, abortion, severe acute respiratory syndrome, renal failure, and HIV, can result in symptoms of psychological trauma or PTSD (96, 97). PTSD in young adult cancer survivors was negatively associated with social functioning, and current and future relationships (98), developmental tasks (99), and psychological functioning (100). Between 2 and 9% of breast cancer survivors met criteria for PTSD. The two most frequently endorsed arousal symptoms were sleep disturbance and difficulty concentrating (101).

Sleep, Trauma, and Women and their Quality of Life

PTSD is more prevalent in women than in men (10), and sleep problems are part of the criteria in determining a PTSD diagnosis. Sleep disturbances are common among women (71,72) especially insomnia, a disorder of initiating and maintaining sleep. Insomnia has been reported in 57% of women who experience one or more symptoms of insomnia during a 7-day period (24,102,103).

Quality of life is impacted with individual who experience both sleepiness and insomnia, a combination that can constitute sleep disordered breathing (SDB). SDB is associated with impairment in cognitive functioning and PTSD such as attention, concentration, and memory (104, 105). In a study of sexual assault survivors, psychiatric symptoms and quality of life, significant impairment in PTSD, quality of life (physical functioning, body pains, energy, social functioning, etc.), and SDB were found. These women had an average of 20 years of treatment without referrals to a sleep facility.

Subjective sleep problems, such as insomnia, SDB, and sleep movement disorder, occur in sexual assault survivors (106). SDB and sleep movement disorders were

associated with elevated intrusion, arousal, and avoidance items, as well as elevated body mass index, a well-known risk factor for SDB.

Few objective sleep studies have been conducted to examine the influence of the psychological symptoms of trauma on sleep patterns. Battered women living in temporary housing experienced longer sleep onset latencies based on objective and subjective sleep measures and higher percentage of awake after sleep onset based on objective measures. The researchers believe that the poor sleep quality was related to less TST, difficulty initiating sleep, and increased nighttime awakenings (107).

Krakow (81) was the only researcher to utilize PSG and found that over 90% of the sample had evidence of SDB with complaints of sleepiness, insomnia, distress, and impairment. In this study, UARS (presence of repetitive transient arousals interrupting the inspiratory effort causing sleep fragmentation and daytime hypersomnia) was diagnosed in eleven participants who had sleep complaints for an average of 25.4 years despite ongoing psychological treatment and medication. Again, the woman's quality of life was not investigated.

Summary

In summary, sleep is not a well-developed area of research in women with psychological trauma. Subjective symptoms found in PTSD survivors of violence were insomnia, daytime sleepiness, poor daytime functioning, and nightmares. Objective sleep problems noted in women with PTSD are longer sleep onset latencies and sleep disorders (UARS, obstructive sleep apnea, sleep movement disorder). Sleep problems are associated with daytime functional abilities and coping skills, which over time may be related to ongoing stress (108). However, no clear relationship between developments of the sleep-related breathing disorders and trauma in this group are unknown.

Sleep, Psychological Trauma, and Quality of Life in Children and Adolescents

Sleep is a critical developmental process responsible for maturation of physiological and psychological processes. Alterations in the environment, such as war, terror or disasters, and stressors related to the family system can impact sleep patterns. Genetic makeup, health status, and temperament can also influence sleep–wake regulation (109).

With the increase in global unrest and wars, there is a significant increase in asylum seekers and refugees who are children. There are 10 million refugee children (110). Variables that need to be considered are preflight stressors, such as witnessing violence, murder, and not having basic food, clothing, and shelter (111). Children have been drawn into war time action by being given the responsibility to fight and enlisted as soldiers. PTSD is rampant in many of the refugee camps with rates ranging from 38 to 93% (112,113). Children from Kosovo war zones complained of nightmares and sleep problems, such as night terrors, nocturnal bedwetting, and sleepwalking (125). Physical health quality is also compromised by gunshot wounds and residual deformities (95, 114, 115). There is no research in the area related to this type of psychological and physical trauma, sleep disturbances, and a child's or caretaker's quality of life.

International disasters are also a significant source of sleep disturbance in children. High levels of PTSD (87%) were present in children before the tsunami because of ongoing war and terrorism and violence in the affected countries. An additional 13.9–38.8% of the children were diagnosed after the event (116). PTSD symptoms of intrusion and hyperarousal, both of which influence disturbed sleep, were noted. Forty-four percent of Rwandan orphans met full criteria for PTSD, 10 years after the genocide. Female gender and subjective threat appraisal involving witnessing either their mother or their father murdered contributed to the symptoms (117).

Caretakers of sleep-disturbed children are also affected. They reported greater problems with their quality of life (118) due to the behavioral and emotional problems in their children. Sleep disturbances in children can be responsible for awake time irritability, hyperactivity, difficulties in concentration, attention and problem solving, problems with academic learning, family and peer relationships and behavioral problems, such as depressed mood, anxiety, and difficulty regulating their anger (119). Psychological symptoms of a traumatic in children are normally similar to those experienced by adults, but may also include disorganized or agitated behavior, recurrent or distressing thoughts, repetitive play, nightmares, sleep disturbances, and difficulty concentrating, according to the DSM-IV-TR (6). Children and adolescents experiencing serious psychological or physical trauma can display out-of-control anger, aggression, suicidal ideation, substance dependence, and academic and legal problems (120).

Two objective sleep studies have examined sleep patterns using wrist actigraphy in children with psychological trauma and depressed mood (121, 122). Abused children with PTSD who were not depressed had more sleep difficulty, as demonstrated by more nocturnal activity, longer intervals to sleep onset, and reduced sleep efficiency, as compared with PTSD subjects who had depression. Physical abuse appeared to impact sleep efficiency more so than sexual abuse (121). These findings are similar to the study where physically abused children had lower sleep efficiency than sexually abused patients (122). No discussion of quality of life was noted.

Subjective sleep studies in the adult and child research seldom screen for psychological trauma or quality of life. Children who witness intimate partner violence reported emotional and behavioral problems including sleep disturbances, temper tantrums and depression (123). Abused and depressed children reported flashbacks and significant sleep problems (124). Adolescent rape victims reported frequent

waking during the night, sleeping poorly, and nightmares along with feeling tired most of the day, in addition to depressive symptoms, tobacco consumption, running away behaviors, stealing, and school absenteeism (126).

Child and adolescent who experience physical traumas, such as life-threatening illness, are at risk for developing PTSD and concomitant sleep problems. In a study of children undergoing cardiac surgery, five (12%) of the children met diagnostic criteria for PTSD and another five (12%) children had psychological trauma symptoms. The only predictor of postoperative PTSD was 48 hours or more in the pediatric ICU. Stressful procedures during the length of stay and sleep disruptions were causal factors (127). No discussion on quality of life of parents or guardian was noted.

In summary, no studies examining sleep, psychological trauma, and quality of life were noted in the literature related to children and adolescents. Given the restorative nature of sleep to healthy development in children, more extensive research is needed to explain the impact of trauma on sleep and its impact on quality of life for the family and the child. Specific gaps in the research are as follows: (a) a lack of integrating sleep, PTSD, and quality of life for family and/or child, (b) lack of objective data on sleep patterns in psychological trauma in children exposed to war, terror, disasters, etc., (c) development of quality of life instruments for specific types of traumatic events, (d) cultural and developmental levels of children experiencing psychological trauma, sleep problems and quality of life, and (e) studies targeting sleep as an intervention in childhood psychological trauma treatment, possibly with quality of life as a treatment outcome.

Implications for Research and Clinical Practice

The incorporation of quality of life construct as a critical variable in the examination of sleep patterns and psychological trauma is warranted. The development of conceptual models to refine research studies is crucial, especially as it relates to intervention studies. Conceptual frameworks will address the role of mediating variables, such as psychiatric illness, family dynamics, access to services, etc., and provide a clearer understanding of how they influence these relationships (128). Construction of the conceptual models will be necessary based on specific targeted groups, such as children, women, or refugees.

Attention to the selection of instruments measuring the quality of life variable should be examined. Instruments with subscales appear better equipped to provide greater understanding of the construct and direction for treatment interventions (129). Sleep studies have demonstrated that sleep state misperception is operating in veteran groups and crime victims with PTSD, and therefore, both objective and subjective sleep measurements are necessary. Particular attention should be placed on highlighting and controlling for confounding variables, such as family dynamics, access to services, educational and employment status, pre-trauma history, and physical health. Longitudinal studies would provide greater clarity as to the timing and development of symptoms with particular attention on targeting interventions (130). Recent studies have examined PTSD in with varying lengths of follow-up where findings varied based on type of trauma, population, and onset of follow-up (131–132). Pathways can be elucidated and treatment interventions formulated based on more comprehensive data.

Addressing the limitations of research completed in non-Western countries on individuals experiencing psychological trauma and torture is important because of the incongruence between cultural and religious differences and current instruments to measure sleep, psychological trauma, and quality of life (133). Furthermore, in the examination of the burden of mental illness and quality of life by the ESEMed/MHEDEA 2000, psychological trauma, in particular, PTSD, contributed to greater loss of work than physical illness. These researchers also indicate that emotion, motivation, and cognition may have a greater contribution to role functioning and quality of life (134). Future studies will need to focus on globally accepted instruments, such as those generated by the World Health Organization on Quality of Life (135), to provide greater standardization of measurement.

Issues that need to be addressed by future research:

- Objective and subjective sleep assessment and their relationship with psychological trauma and HRQL are necessary.
- Gender sensitive studies, especially on women in the military, should be a focus with attention to HRQL and psychological trauma and objective and subjective sleep assessment.
- Contextual dimensions, such as family functioning, living circumstances, social supports, physical health should be explored in relationship to the military, psychological trauma, objective and subjective sleep assessment and HRQL.
- HRQL, as part of larger conceptual models, should be incorporated into ongoing research and treatment intervention studies as it relates to psychological trauma and objective and subjective sleep assessment.

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Caffeine, Sleep, and Quality of Life

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Summary Caffeine is regarded as a mild stimulant acting on the central nervous system that is responsible for a significant portion of the behavioural and physiological effects of coffee and tea. Motives why people take caffeine are reflected in consumption patterns. Early in the morning caffeine might help to wake up, whereas during the day it is an aid to stay awake or counteract fatigue. The intake of caffeine shortly before sleep might affect sleep characteristics, especially if high doses of caffeine are used. Moreover, these disturbances of sleep might result in tiredness in the morning. Caffeine is frequently used as a countermeasure for fatigue and sleepiness. During sub-optimal circumstances such as working night shifts and sleep deprivation it maintains performance and wakefulness at satisfying levels. These effects of caffeine depend largely on its antagonistic actions on the A_{2A} adenosine receptor. Simple task performance seems in particular sensitive to caffeine. Part of the caffeine effects might be due to withdrawal reversal, although caffeine is stimulating in non-withdrawn subjects, as well. In addition, in habitual users, there is no complete tolerance to the effects of caffeine.

Keywords Caffeine · wakefulness · sleepiness · night shift · sleep deprivation · withdrawal · fatigue

Learning objectives:

- Caffeine increases physiological arousal by antagonizing the effect of adenosine.
- Caffeine is effective in maintaining performance and wakefulness at satisfying levels during sub-optimal circumstances, occurring during the normal sleep–wake cycle, and in sub-optimal periods, occurring after disturbances of the normal sleep–wake rhythm (e.g., working night shifts and sleep deprivation).
- Simple task performance is more sensitive to caffeine than complex task performance, involving higher level cognitive control processes.
- A modest disturbance of sleep quality is found with caffeine taken shortly before sleep.
- Stimulating caffeine effects have been found in both non-withdrawal and caffeine-withdrawn subjects.
- Part of the caffeine effects might be ascribed to relief of withdrawal.
- Habitual caffeine consumers do not develop complete tolerance to the effects of caffeine.

Introduction

Caffeine is a widely used alkaloid mainly derived from coffee or tea. The popularity of caffeine may be related to its stimulating effect on the central nervous system. There is indeed a substantial amount of evidence illustrating that caffeine increases subjective energy and alertness (1–6). Moreover, caffeine is legally available and consumption is socially accepted. It is, therefore, no surprise that caffeine is frequently used as a countermeasure for fatigue and sleepiness related to working night shifts and sleep deprivation.

The relation between caffeine, sleep, and performance was and still is the topic of many studies (7–10). Do the results of these studies justify the use of caffeine to postpone sleep and improve wakefulness? Also, sleep is important for cognitive performance. Therefore, if caffeine keeps people awake, what about its effects on sleep?

Caffeine is responsible for a significant proportion of the behavioural and physiological effects of coffee, tea, cocoa and chocolate. After oral ingestion, caffeine is rapidly and almost completely (99%) absorbed from the gastrointestinal tract into the bloodstream (11, 12). It is widely distributed throughout the body tissues, and passes through all biological membranes, including the blood–brain barrier and the

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placental barrier. Peak plasma concentrations are reached in about 30–60 min after ingestion. The half-life of caffeine is approximately 3–5 h, although individual clearance rates vary tremendously. For example, the clearance rate is speeded up with 30–50% by nicotine, and doubled in woman taking oral contraceptives. Caffeine has hardly any side-effects, and it has a low profile as a drug of abuse (13).

Caffeine effects, at doses comparable with those of normal human intake, are primarily related to its blocking of the A_1 and A_{2A} subtypes of the adenosine receptors (12, 14, 15). Adenosine is an inhibitory neuromodulator involved in sleep–wake regulation (16, 17). Extra-cellular concentrations of adenosine in the basal forebrain cholinergic region were, for example, found to increase during spontaneous wakefulness and during sustained, prolonged wakefulness, whereas a slow decline in concentration was observed during recovery sleep (17). Caffeine-induced wakefulness depends in particular on its antagonistic actions at the A_{2A} receptor subtype (18).

Normal Sleep–Wake Cycle

During the day, natural fluctuations of arousal and sleepiness exist. The desire to increase arousal at certain times of day may be a factor influencing the amount of caffeine intake. In a review by Bättig (19), this hypothesis was actually supported; Bättig reported that 27% of 20- to 40-year old women drank coffee at wake-up, 73% at breakfast, 60% at the morning break, 23% late in the morning, 52% with the lunch, 48% at the afternoon break, 32% in the late afternoon, 18% at dinner, and 43% after dinner. To assess diurnal patterns in caffeine consumption, Brice and Smith (20) used a caffeine diary, a retrospective questionnaire, and a detailed personality and psychosocial profile. They found that consumption levels peaked between 8 a.m. and 12 noon and decreased thereafter. Corresponding consumption patterns were also found in 691 undergraduate students (409 women) (21). While average caffeine consumption decreased from the morning through the evening, the consumption of decaffeinated coffee increased throughout the day from hardly 1% at breakfast to 13% after dinner (19). These patterns might reflect the shift over the day in motives why people take coffee. Early in the morning caffeine is taken mainly to wake up. After a night of caffeine abstinence with a low level of arousal, caffeine can help to increase the activity of the sympathetic adrenal-medullar system. The acceleration by coffee may help to reach sooner the habitual level of functioning (22). During the day, caffeine might be of help to counteract fatigue. Fatigue is a natural consequence of many daily-life activities, which may underlie sub-optimal functioning or even human error such as found in traffic situations and professional activities. No surprise that people look for ways to compensate fatigue and sleepiness when necessary. A specific increase in sleepiness and performance decline has been found in the mid-afternoon, the so-called ‘post-lunch dip of attention’, which has been related to increased accident rates (23, 24). Smith (25) found in a double-blind, placebo-controlled study that a dose of 1.5 mg/kg caffeine was indeed an effective countermeasure against this post-lunch dip. Hayashi, Masuda and Hori (26) compared the effects of 200 mg caffeine, bright light (2000 l×) and face washing in combination with a short daytime nap on sleepiness. They found that the combination of caffeine and napping was the most effective in alleviating mid-afternoon sleepiness and related performance deteriorations.

Although caffeine might compensate sleepiness during daytime, it might also cause sleep disturbances, especially when taken shortly before sleep (27). Drapeau et al. (28), for example, evaluated the effects of caffeine on sleep variables in moderate caffeine users (1–3 cups a day), while they maintained their habitual caffeine consumption. Subjects received 100 mg caffeine 3 h before bedtime and another 100 mg 1 h before bedtime. Caffeine increased sleep latency, reduced sleep efficiency, the duration and amount of stage 2, and also spectral power in the delta frequencies, indicating that moderate caffeine consumers remain sensitive to the effects of caffeine despite their habitual daily intake. Alford and co-workers (29) used a 4 and an 8 mg/kg dose of caffeine to evaluate the effect on sleep quality. They found in six young healthy volunteers (aged between 21 and 25 years), who abstained from caffeine for 2 weeks, that a 4-mg/kg dose given 20 min before bedtime doubled sleep onset latency. Effects on sleep efficiency (17% decrease), the number of awakenings (7% increase), slow wave sleep (4% decrease) and non-REM sleep (8% decrease) were restricted to the higher dose of 8 mg/kg.

In general, a relative high dose of 4 mg/kg caffeine, which is comparable to normal use in everyday life, may cause only a slight postponement of falling asleep, while the effects on sleep structure remains fairly small. Åkerstedt and Ficca (30) argued that, even for doses up 6 to 7 cups a day, sleep disturbance due to caffeine ingestion in everyday situations seems small.

Orbeta and colleagues (31) examined the relation between caffeine consumption, sleep quality, and the frequency of feeling tired in the morning in a large group of students in grades 6 through 10. High caffeine intake was related to an increase in sleeping difficulties and morning tiredness. Disrupted sleep, causing morning tiredness and sleepiness during daytime were ascribed to a disrupted sleep–wake cycle due to the consumption of caffeine containing beverages till late at night. Twenty to twenty-five percent of children and adolescents report sleep disturbances, part of which might be related to caffeine intake. In 13–17 years old US children caffeine intake comes mainly from soft drinks (62%), among them energy drinks. Only one-third comes from coffee and 3% from tea (32), whereas in adults these figures are 75 and 15%, respectively (33).

‘Energy’ drinks not only contain different levels of caffeine but some also contain high sugar levels. Anderson and Horne

(34) examined the effects of an energy drink with low caffeine content (30 mg) and high sugar content (42 g) on afternoon sleepiness induced by restricted sleep (5 h) the night before. The performance on a vigilance task was worse after the intake of this energy drink. They concluded that it is the caffeine content of energy drinks that is effective in counteracting sleepiness.

In summary, the intake of caffeine, especially high doses, shortly before sleep might disturb sleep, causing tiredness in the morning. Moreover, habitual caffeine consumers remain sensitive to these effects of caffeine.

Irregular Sleep–Wake Cycle

Shift Work

In our 24-h economy, flex- and irregular work schedules are common. Adaptation of the circadian rhythm to night work, however, occurs only partially over time, because adjustment is severely opposed by compelling Zeitgebers such as the natural light–dark cycle, family and social activities during the day, and the forced reversal of wakefulness during daytime and sleep at night on non-working days. As expected, persons who work night shifts frequently report that sleep at daytime is disrupted and non-refreshing. In both permanent night workers and in rotating shift workers, total sleep time is reduced to about 5–6 h per day. Moreover, about 10% of shift workers suffer from 'shift-work sleep disorder' defined as a primary complaint of insomnia or excessive sleepiness when temporally coupled with a work period that occurs during the habitual sleep phase, and which is associated with increased risks for several diseases (35).

Torsvall and colleagues (36) found that 20% of shift workers fell spontaneously asleep during night shift. Such naps did not occur during afternoon or evening shifts. Especially between 3 and 6.30 a.m., people are least alert and most likely to fall asleep. Parallel to the circadian arousal rhythm, human performance shows a trough for most cognitive skills during the early morning hours. The magnitude of these performance deteriorations during night versus daytime in the laboratory ranges from 10 to 35% of the 24-h mean level of performance (37). Additionally, accidents and injuries are 1.3 times more likely to occur on a night shift than on a day shift (38). Connor and colleagues (39) showed that the risk of serious and fatal traffic accidents may even increase 5.6 times between 2 and 5 a.m., particularly when travelling between the workplace and home (40). Prevention of sleepiness related to night work is therefore of direct relevance for road safety.

Two main sources of reduced alertness and performance during nightly work hours are the disturbed circadian rhythm of sleepiness and alertness, and increasing homeostatic sleep pressure related to the period of wakefulness preceding work time. There are indications that caffeine affects the circadian rhythm of humans (41–43). Shilo and colleagues (44) examined the effects of caffeine in six volunteers who regularly consumed coffee during the afternoon and evening hours. Although subjects were unable to determine whether they had consumed regular or decaffeinated coffee during the study periods and did not report significant differences in sleep quality estimations or bedtime, caffeine increased sleep latency and affected all other sleep variables. In addition, caffeine consumption decreased secretion of melatonin. In a simulated shift work situation, the influence of 200 mg caffeine was studied in none to moderate caffeine users ($\leq$2 cups a day; aged between 19 and 36 years) (45). Work started at 5:30 p.m. and went on until 10 a.m. the next morning. During the 1-h rest period from 1:30 to 2:30 a.m., the participants performed performance tests lasting 90–95 min. Caffeine was found to be beneficial for performance during the night, which was ascribed to its lowering effect on melatonin, an endogenous regulator of the sleep–wake cycle secreted nocturnally by the pineal gland (46).

In addition to the effect of caffeine on the circadian rhythm, it has been argued that caffeine primarily promotes wakefulness by its effect on adenosine. In other words, consumption of caffeine might be responsible for the altered expression of sleep homeostatic pressure (47–49). Wyatt and colleagues (50) used a 29-day forced desynchrony protocol in which the sleep–wake cycle was scheduled to be 42.85 h, that is, far removed from the circadian range. The aim was to examine the contributions of sleep-homeostatic and circadian-timing systems in caffeine-related performance modulations. Sixteen men (aged between 18 and 30 years) consumed caffeine (0.3 mg/kg) or placebo hourly during 28.6-h wake episodes. This high-frequency low-dose caffeine was effective in countering the detrimental performance effects of extended wakefulness, which was ascribed to attenuation of the homeostatic sleep drive.

Workers nap frequently between 1.5 and 2.5 h per nap before night-shift work (51). The aim of Bonnet and Arand (52) was to compare the effect of either napping for 4 periods of 1 h each or for one 1 nap period of 4 h in combination with or without a dose of 200 mg slow-release caffeine (SRC) on alertness and performance. Caffeine in the form of SRC is valuable, because it may result in long and good-quality wakefulness not only in laboratory situations but especially in those real-life situations in which opportunities to consume caffeine may be limited. Addition and logical reasoning improved during the night after the combination of SRC and a 4-h nap before the shift. It should be noted that the use of SRC is not advisable in situations in which unexpected sleep opportunities might arise, because of its long-lasting efficacy.

Philip and colleagues (53) examined the effects of a 30-min nap taken before a drive in addition to coffee containing 200 mg caffeine or decaffeinated coffee in a real-life environment. Twelve young men (aged between 20 and 25 years) ingested caffeine 30 min before a 200-km (125 miles) driving session between 2 and 3:30 a.m. In the caffeine condition, for 75% of the participants, nighttime driving performance was

similar to daytime performance as compared with 66% after the nap and only 13% in the placebo condition. Schweitzer and colleagues (54) combined caffeine (4 mg/kg) with a 2.5-h nap in both a laboratory and a field setting. They confirmed that caffeine and napping improved alertness and vigilance; however, the combination of caffeine and napping was superior to coffee or napping alone both in the laboratory and in the real-life environment.

In sum, simulated and real-life studies of shift work indicate that caffeine reduces sleepiness and is useful as countermeasure for performance deteriorations during nighttime work. In combination with a nap, caffeine might be even more effective in contributing to a safer environment by maintaining performance and wakefulness at satisfying levels.

Sleep Deprivation

Sleep Characteristics

The ability to remain awake over a long period of time is of vital importance under specific conditions, such as military operations in times of crisis, medical care, and driving. Caffeine is used to stay awake during these periods. However, any intervention that significantly increases sleep loss affects sleep quality and sleep structure of subsequent sleep periods. The question is whether caffeine influences the relation between sleep deprivation and the quality and quantity of successive sleep.

Wesensten and colleagues (55) showed that a dose of 600 mg caffeine increased sleep onset latency after a sleep deprivation period of 64 h. However, no effects were found during a 12-h recovery sleep period commenced 20 h after caffeine administration which fits to the half-life of caffeine which is on average 3–5 h. Philip et al. (53) examined sleep latencies during recovery sleep 2–3 h after the consumption of 200 mg caffeine and after overnight sleep deprivation. They found that sleep latency was only delayed marginally (<1 min) compared with the placebo condition. Sleep efficiency was not influenced by caffeine in their study.

The effects of 200 mg caffeine on sleep latency following one night of sleep deprivation, in six volunteers without a history of regular coffee consumption were examined by Salín-Pascual and colleagues (56). They found no effects of caffeine on daytime sleepiness; similar sleep latencies were found in both the caffeine and the placebo conditions. Thus, even in subjects not accustomed to coffee, effects of caffeine were small or absent.

Another phenomenon challenging the circadian timing system is jet lag, the transient period of impairment following rapid travel to a different time zone. On arrival in the new time zone, the sleep–wake cycle is not timed appropriately relative to the time of day in the new situation. Jet lag is characterized by sleep disturbances, daytime sleepiness, and impaired performance (57). Beaumont and colleagues (58) studied the effects of caffeine on sleep and sleepiness after a seven-time zone eastward transmeridian travel. This double-blind, randomized, placebo-controlled study was performed on 27 healthy volunteers (aged between 19 and 47 years). In the caffeine condition, reduced levels of daytime sleepiness were observed. However, a dose of 300 mg SRC a day affected sleep quality on six subsequent recovery days (sleep latency increased, with less rebound of slow-wave sleep).

In conclusion, caffeine in simulated and real-life work situations is effective in counteracting fatigue and sleepiness, thereby improving performance, while the effects on sleep quality are modest.

Performance

A shortage of 1.3–1.5 h sleep for 1 night might result in a one-third reduction of daytime alertness. The hypothesis is that caffeine may help to maintain alertness at satisfying levels in situations where the sleep–wake cycle is disturbed, because the stimulating effects of caffeine have found to be especially salient under sub-optimal conditions, such as mental fatigue (59, 60).

Frontal brain regions are in particular sensitive to the effects of sleep loss. Metabolic activity, for example, reduced significantly in these regions during sleep deprivation (61). Cognitive processes mediated by the frontal cortex might therefore be particularly vulnerable to the detrimental effects of sleep loss. Especially, the prefrontal cortex is crucial in dynamically controlling and co-ordinating the activities of other, often widely separated, brain regions supporting more basic functions. Bonnet and Arand (52) showed that individuals who took a prophylactic nap and used caffeine during work shifts significantly increased performance on complex tasks such as logical reasoning and additions. A follow-up study (62), comparing the effects of repeated versus single-dose administration of caffeine and naps of 0, 2, 4, and 8 h taken before sleep loss confirmed the finding that alertness and performance during sleep loss improved by a combination of short naps and small repetitive doses of caffeine (150 mg caffeine) administered every 6 h starting at 1:30 a.m. on the first night of sleep loss. A repeated dose of 150 mg caffeine improved alertness and performance better than larger doses (300 and 400 mg) of caffeine. However, neither naps nor caffeine alone or combined could preserve functioning at baseline levels beyond 24 h after which alertness and functioning approached placebo levels.

Differential effects of moderate doses of caffeine (100, 200, or 300 mg) or placebo given after 72 h sleep deprivation formed the subject of Lieberman's study (63). Sixty-eight US Navy Sea–Air-Level trainees were tested after sleep deprivation on cognition and mood. Sleep deprivation and stress elicited in the simulated combat situation adversely affected performance and mood. However, 300 mg caffeine, but especially the 200-mg dose, improved visual vigilance, reaction time, and alertness. More complex performance, requiring fine motor control, was not affected by caffeine.

Gottselig and colleagues (64) studied the effects of 200 mg caffeine on cognitive control functions in healthy young men. In two periods, occurring 1 week apart, participants received either caffeine or placebo, after either 11 or 23 h of the 40-h sleep-deprivation period, according to a randomized, double-blind crossover design. A random number generation task was completed at 3-h intervals during the experimental session. It appeared that caffeine preserved simple aspects of cognitive performance during sleep deprivation, but did not so on more complex cognitive functions. Kohler and co-workers (65), on the other hand, did report an effect of 200 mg caffeine administered at midnight before an overnight sleep-deprivation period, on higher-level cognitive performance. The 14 young adults (aged between 18 and 36 years) showed faster reactions in a grammatical reasoning task after caffeine as compared with placebo.

Effects of 600 mg caffeine on alertness and psychomotor performance in 48 healthy men (aged between 19 and 38 years; ±6–8 cups of coffee) were evaluated by Wesensten and colleagues (55). Caffeine given after 64 h sleep deprivation improved alertness and psychomotor performance. Caffeine enhanced some aspects of higher order cognitive functions (complex judgement and conceptual efficiency), as well. A 600-mg dose was also used by Killgore et al. (66) in 29 men and 24 women on the ability to appreciate humour in visual (cartoons) or verbal (headlines) stimuli. Appreciating humour is generally regarded as one of the most complex forms of high-level cognition in humans. As expected, sleep loss for 49.5 h adversely affected the capacity to appreciate humour. However, there was no effect of caffeine on the appreciation of visual or verbal humour, although caffeine did improve simple psychomotor response speed and ratings of subjective sleepiness.

The effect of 200 mg caffeine on driving performance after partial sleep deprivation was examined in 16 students (mean age 23 years) (67). They either slept 5 h or were sleep deprived for the whole night until they had a 2-h drive (6–8 a.m.) on a dull, monotonous road. Caffeine clearly improved driving performance with fewer incidents and less subjective sleepiness. In a flight simulation task, the effects of 200 mg caffeine were examined during sustained wakefulness in 24 male students (aged between 25 and 31 years) (68). The observed positive effects of caffeine were in agreement with the effect on cognitive performance reported by Reyner and Horne (67).

Wesensten et al. (69, 70) studied the efficacy of 600 mg caffeine in maintaining performance and alertness during the early morning hours, when the combined effects of prolonged sleep loss and the circadian morning trough of alertness are most manifest. Ten healthy young adults were totally sleep deprived for 54.5 h. After they were awake for 41.5 h, they received double-blind 600-mg caffeine. Again, performance and alertness were significantly improved by using caffeine.

The former studies show that caffeine compensates for performance deteriorations induced by sleep deprivation. Simple task performance benefits most from caffeine.

Comments

Typically, caffeine studies use acute caffeine challenges following a period of abstinence (usually overnight). Some regular caffeine consumers experience a "withdrawal syndrome," starting on average after 12–24 h of abstinence with a peak between 20 and 48 h, which manifests itself in headaches, irritability, and occasionally nausea (71). This withdrawal syndrome may already start after a relatively short-term exposure from 6 to 15 days with doses above 600 mg caffeine a day. An important issue is whether the effects of caffeine, and individual differences in these effects in particular, can be explained by the relief of withdrawal effects (e.g., 72, 73), by the stimulating effects of caffeine itself or by both.

Rogers and colleagues (74) compared the effects of caffeine (1.2 mg/kg) in sleep-restricted (5 h) participants, who were either caffeine-withdrawn for 3 weeks to avoid acute withdrawal symptoms or received regular coffee or tea followed by overnight caffeine-withdrawal. The results supported the withdrawal reversal hypothesis: cognitive performance was affected negatively by overnight, acute caffeine withdrawal. Even after partial sleep deprivation and without withdrawal effects, cognitive performance was not improved by caffeine. James and Gregg (75) examined the effects of caffeine in healthy habitual coffee drinkers (aged between 17 and 52 years). The 1.75-mg/kg caffeine dose showed no significant mood-enhancing effects when participants were well rested and also did not produce restorative effects when mood was worsened by lack of sleep. All participants in this study were habitual caffeine consumers, although with strongly varying intake (180–680 mg per day). Interpretation of these results should be done with care because Attwood et al. (76) showed that high consumers (>200 mg/day) were more likely to report positive effects of caffeine than low consumers who in general did not report an effect of caffeine. High consumers may be more sensitive to the effects of caffeine, which may in turn drive their regular self-administration of caffeine. Expectancies on effects of caffeine could be involved, as well (77). Johnson and co-workers found that nocturnal sleep was associated with objectively measured daytime sleepiness but not with subjective sleepiness. Apparently, the subject's expectancy on the efficacy of caffeine determines his perception of wakefulness and alertness and may explain discrepancies in findings. It illustrates that baseline differences between high and low caffeine consumers might hinder explaining experimental results.

Hewlett and Smith (78) compared the effects of caffeine (1 mg/kg) on mood and performance in overnight withdrawn consumers and non-consumers (who by definition are not withdrawn). It should be noted that overnight caffeine

withdrawal is part of most people's daily life. There was no evidence of negative effects of caffeine withdrawal on performance and mood. On the contrary, caffeine significantly improved performance, although there were differences between regular consumers and non-consumers. Caffeine tended to reduce reaction time in regular consumers whereas the opposite was true for non-consumers. Habitual users and non-users of caffeine were also studied by Haskell and colleagues (79), using a placebo-controlled, double-blind, balanced crossover design. They found in both groups, following overnight caffeine withdrawal, significant improvements in performance after 75 and 150 mg of caffeine. Concerning mood, caffeine tended to have greater benefits for mood of habitual users than for the non-consumers. The authors argued, in line with Attwood et al. (76), that basic differences between habitual consumers and non-consumers might explain why some individuals become caffeine consumers and others do not and why some people may profit more from caffeine than others.

Issues that need to be addressed by future research:

- Assess the influence of situational factors related to caffeine intake in the effects of caffeine.
- Retain detailed information total habitual caffeine intake from all sources.
- Measure the effects of caffeine as used everyday practice in non-withdrawn subjects.
- Determine the metabolic rate of caffeine while taking into account level and pattern of caffeine consumption, and co-current use of other recreational substances as nicotine and alcohol.
- Study over the day the changes in expectancy and motives why caffeine is taken.
- Look for strategies people use in their caffeine consumption to maintain wakefulness and alertness in suboptimal conditions like in shift work and/or during sleep deprivation.
- Unravel inter-individual differences in caffeine effects.
- Examine dose-dependent effects of caffeine on performance and well-being both in optimal and suboptimal states.
- Examine the different sensitivity to caffeine of different underlying brain structures.

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34
Sleep, Alcohol, and Quality of Life

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Summary Alcohol disrupts sleep even in healthy individuals, and when consumed in excessive amounts for long periods, the sleep disturbance remains even after prolonged abstinence. Disturbed sleep is an important factor contributing to poor quality of life (QoL) in clinical samples of alcohol-dependent subjects as well as in population-based samples. Relapse to alcoholism, which clearly lessens QoL, is associated with disturbed sleep in both prospective treatment and population-based studies. However, these alcohol, sleep, and QoL associations found in treatment and population studies are confounded by other risky health behaviors and co-morbid medical and psychiatric diseases. Controlled laboratory studies have documented the sleep-disruptive effects of alcohol and its impairing effects on functioning the following day. The exacerbating effects of alcohol on sleep-related breathing disorders and an increased association of periodic leg movements with alcoholism have also been well documented. And each of these primary sleep disorders are known for their own impairing effects on daytime function. Finally, and most importantly from a public health perspective, studies have demonstrated that reduced sleep and increased daytime sleepiness, not due to alcohol consumption, will enhance the impairing effects of alcohol.

Keywords Alcohol · alcoholism · quality of life · daytime sleepiness · sleep disturbance

Learning objectives:

- Disturbed sleep is an important factor contributing to poor quality of life in clinical samples of alcohol dependent individuals.
- Controlled laboratory studies have documented the sleep-disruptive effects of alcohol and its impairing effects on function the following day.
- Alcohol exacerbates primary sleep disorders and their own impairing effects on daytime function.
- Reduced sleep and increased daytime sleepiness will enhance the impairing effects of alcohol.

Introduction

The inter-relation of sleep, alcohol, and quality of life (QoL) is complex. Acute alcohol ingestion disrupts sleep and when consumed in excessive amounts for long periods of time (i.e., alcoholism), the sleep disturbance remains, even after abstinence of a year and more. Alcohol also exacerbates primary sleep disorders which of themselves reduce QoL. Owing to the extensive effects of alcohol on various organ systems, as discussed in the pharmacology section below, alcoholism is associated with a number of medical diseases which can be disruptive of sleep and reduce QoL. Alcoholism also is associated with psychiatric diseases, which are also associated with sleep disturbances and reduced QoL. Finally, the alcohol-related sleep disturbance can further worsen the coexisting medical or psychiatric disease.

Assessment of QoL in alcohol and alcoholism using any of the various standardized QoL scales has been very limited. Only recently have investigators applied QoL assessments (1). Attention to QoL arose in response to a need to assess alcoholism treatment outcomes beyond the usual outcome measure, days of abstinence or days of heavy drinking, particularly in comparing the effectiveness of different treatment modalities. Similarly, QoL has rarely been assessed in normative variations in sleep as well as sleep disorders medicine. However, extensive laboratory assessment of impairment in cognitive-behavioral domains associated with alcohol and alcoholism has been conducted and the same is true for sleep and sleep disorders. This chapter after reviewing the pharmacology of alcohol, which is important to understanding its effects on sleep and daytime function, will discuss the newer research that has assessed QoL in

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alcohol and alcoholism. As noted, QoL has not frequently been assessed in sleep and sleep disorders medicine, but the most predictable and well-documented consequence of sleep disruption is daytime sleepiness and associated impairment in ability to sustain attention (2). Based on the variety and nature of complaints among patients with daytime sleepiness, their QoL is extensively impaired. The relation of daytime sleepiness to impairment in various cognitive-behavioral domains is well established. This extensive laboratory literature on the sleep-disruptive effects of alcohol and the daytime functional consequences of such sleep disruptions also will be reviewed.

Pharmacology of Alcohol

Alcohol Pharmacokinetics

Alcohol is a small, water soluble molecule that is distributed throughout the body and consequently, its effects are ubiquitous, disrupting many organ systems and most neurobiological mechanisms. Alcohol is rapidly absorbed reaching peak plasma or breath concentrations within 30–45 min after consuming doses of 0.3–0.9 g/kg. Table 34.1 provides an approximate breath alcohol concentration (BrEC) to dose (g/kg) conversion, with the proviso that BrEC for a given dose can vary widely as a function of type of beverage, concentration of alcohol, speed of consumption, contents of the gastrointestinal tract, and the drinker's total body water which varies with sex, age, and height. Because alcohol is water soluble, after it is absorbed and peak concentration is achieved, there is no distribution phase in alcohol's plasma concentration, as it is distributed evenly throughout the body. Its metabolism is linear with between 10–20 mg/dl (0.01–0.02% BrEC) metabolized per hour depending on drinking history. Metabolic tolerance develops to alcohol and the heavy drinker and alcoholic will show the higher hourly metabolic rates. Thus, a plasma concentration of 50 mg/dl (or BrEC of 0.05%) at bedtime is completely metabolized in 2.5–5 h. Sleep does not appreciably alter the alcohol metabolism rate.

Alcohol Pharmacodynamics

The primary mechanisms for the CNS effects of low alcohol doses are hypothesized to be GABA facilitation and glutamate inhibition; these transmitter systems are critically involved in sleep-wake state control. With high doses and excessive intake (i.e., alcoholism) other various transmitter systems are then involved. GABA is the major CNS inhibitory neurotransmitter and evidence indicates that alcohol enhances GABA-activated chloride flux (3). The ventrolateral preoptic nucleus (VLPO) is the primary sleep-promoting region of the brain. VLPO axons terminate on the various wake-promoting areas of the posterior hypothalamus; labeling and electrophysiological studies have confirmed that these projections are GABAergic and inhibitory in function (4). Thus, facilitation of GABA-mediated inhibition may explain alcohol's sedative and slow wave sleep promoting effects as described below. The major excitatory neurotransmitter in the CNS is glutamate and among the glutamatergic receptor subtypes is the NMDA receptor. Alcohol has been shown to inhibit NMDA receptor function in many biochemical and electrophysiological studies (5). Glutamate is present in the reticular activating system (RAS) and these glutamatergic neurons project to the forebrain where they have excitatory effects. Alcohol inhibition of NMDA receptor function may be another important mechanism by which alcohol has its sleepiness enhancing effects. A recently identified putative mechanism for alcohol-sleep effects is facilitation of the inhibitory effects of adenosine (6). The hypothesized mechanisms for the adenosine facilitation have included enhancement of synthesis, reuptake inhibition, and the enhancement of receptor function. Adenosine is hypothesized to function as the sleep homeostat promoting sleep, as well as slow wake activity in sleep. Adenosine levels increase over accumulating hours of wakefulness and during the sleep period those levels decline with the rate of decline related to the amount of slow wave EEG activity (7). If the adenosine hypothesis is correct, alcohol enhancement of slow wave sleep could occur through it's adenosine facilitation.

TABLE 34.1. Ethanol dose and peak breath ethanol concentration (BrEC).

Dose	Br EC (%)	# 12 oz. US beers
0.2 g/kg*	0.02	1–2
0.4 g/kg†	0.03 (0.011)	2–3
0.6 g/kg†	0.05 (0.008)	3–4
0.8 g/kg†	0.07 (0.015)	4–5
1.0 g/kg‡	0.09 (0.005)	5–6
	Mean (SD)	

*from (38)
† from (39)
‡ from (40)

Alcohol's Impact on QoL

Treatment Populations

Disturbed sleep is an important factor associated with poor QoL in samples of alcohol-dependent subjects. In a study that used the Nottingham Health Profile to assess QoL in 60 alcohol dependent subjects, the severity of alcohol dependence was positively associated with all six of the Nottingham subscales including the scale for sleep (8). Important co morbidity in populations treated for alcoholism is psychiatric disease. QoL was assessed in 41 men and 41 women alcoholics three months after treatment (9). When equated for level of dependency, the women had poorer QoL on all the scales compared to men. Disturbed sleep associated with depression was a unique feature of the reduced QoL in the female alcoholics. In an attempt to relate sleep disturbance to level of alcohol dependence, mildly to severely alcohol-dependent outpatients (n = 31) completed the Pittsburgh

Sleep Quality Index (PSQI), the Alcohol Problems Questionnaire, Severity of Alcohol Dependence Questionnaire, and the Beck Depression Inventory (10). Compared to age-matched controls ($n = 49$) the alcoholics had higher total PSQI scores reflecting more sleep problems. Among the alcoholics, the sleep problems subscale of the PSQI was positively related to severity of dependence, alcohol problems, and Beck depression scores and the total PSQI score was positively related to severity of alcohol problems and Beck scores.

Disturbed sleep is also an important predictor of relapse in treatment studies. The above cited paper included a sample of 60 inpatient alcoholics who completed the Nottingham Health Profile to assess QoL, the Alcohol Problems Questionnaire, and the Beck Depression Inventory and then were followed for 12 weeks (10). The most significant predictor of relapse (67% of the 60 patients relapsed) as determined by a logistic regression was the sleep subscale of the Nottingham. Among individual items "sleeping badly at night" and "taking long to fall asleep" differentiated those who relapsed from those who did not relapse.

Large, Non-treatment Populations

Surveys of large populations have found an association between alcohol, sleep, and QoL. The Behavioral Risk Factor Surveillance System is an ongoing, state-based, random-digit-dialed telephone survey of health related QoL and various health risk behaviors (11). A 2004 assessment of 82,918 individuals in the surveillance system was conducted with 22% reporting current smoking, 24% past smoking, and 54% never smoking. Current smokers had poorer QoL than non-smokers and were more likely to report heavy drinking and more anxiety and depression symptoms. They also reported more frequent sleep problems. A population-based study of 1968 men and 1737 women in northwest Russia evaluated QoL by the Cantril Ladder method in which one imagines the best QoL vs the poorest QoL on a 10-point scale and rates their current QoL (12). Depression, anxiety, and sleep problems were assessed by questionnaire and alcohol dependence by the Alcohol Use Disorders Identification Test. Depression and sleeping problems were associated with heavy drinking and alcohol dependence and these were associated with poorer QoL. Additional associated factors were circulatory diseases and gastrointestinal diseases. A survey of twin men (n = 8870) who served in the military in Vietnam between 1964–1975 found heavy alcohol consumption was associated with a higher risk of sleep problems which were also associated with less physical activity and social involvement, which the authors interpreted as a lessened QoL (13). As with the previous studies, contributory factors were identified, including cardiovascular disease, chronic pulmonary disease, and diabetes. Finally, risk factors for accidental injuries among Canadian senior citizens, 10,059 individuals older than 65 yrs, were assessed (14). While QoL was not directly assessed, injury to older individuals negatively impacts QoL. The identified risk factors for injury were alcohol consumption, smoking, and the rest and sleep patterns of these senior citizens.

Finally, relapse to alcoholism, which clearly reduces QoL, was associated with sleep disturbance in a prospective population-based study (15). This confirmation of the relapse-sleep disturbance association from the general population is important since the relapse-sleep disturbance association found in treatment populations could merely be due to selection bias. Many alcoholics do not seek treatment and the nature of the relapse-sleep association could be quite different in a non-treatment seeking population. The study followed-up with the 248 individuals identified with alcohol dependence in the 1981 Epidemiologic Catchment Area program. After 13 years 73% of the original sample was re-interviewed and those with continued alcohol dependence had greater odds of reporting insomnia than those whose alcohol dependence remitted.

Alcohol and sleep problems are associated with poor QoL and relapse in these various treatment and population-based studies. However, the associations found in these studies are potentially confounded by other risky health behaviors (i.e., smoking), other co-morbid psychiatric disorders (i.e., depression), and medical diseases (i.e., diabetes, pulmonary or cardiovascular disease). Thus, it is unclear as to how great an impact the alcohol-sleep disturbance itself has on QoL. The laboratory studies to be reviewed in the next section, while not directly assessing QoL, for the most have controlled for these confounding variables and more directly show alcohol-sleep related impairment in various cognitive and behavioral domains that one would predict should produce a lowered QoL.

Laboratory Assessment of Alcohol Effects on Sleep and Waking Function

Alcohol Effects on Nightime Sleep and Primary Sleep Disorders

Sleep Effects in Healthy Normals

The effects of alcohol on the sleep of healthy volunteers have been extensively studied and have been recently reviewed (16, 17). Ethanol, in doses from 0.16 to 1.0 g/kg and administered 60–30 min before sleep, typically reduced sleep latency and at the lowest dose studied (0.16 g/kg) increased total sleep time. Analyses of the sleep period by halves of the night have revealed increased wake and stage 1 NREM sleep in the second half of the night. This second-half of the night sleep disturbance has been interpreted as a rebound effect following completed alcohol metabolism (17). The majority of studies in healthy volunteers administered doses of 0.5 g/kg and greater and produced BrECs of 0.06–0.10% at bedtime. With an average 0.15% BrEC metabolized per hour, alcohol

would be completely metabolized within 4–5 h of bedtime. Thus, the second half of the night results reflect rebound (i.e., a worsening of sleep relative to a no alcohol condition).

Sleep stage effects of alcohol are also reported. Some studies report increased stages 3 and 4 NREM sleep (17), a result likely associated with higher alcohol doses and/or lower basal levels of stages 3 and 4 in the study population. For example, a study of alcohol's effects on the sleep of insomniacs and age-matched normal controls found a 0.5 g/kg dose of alcohol which raised BrEC to 0.042% at bedtime increased stages 3 and 4 sleep in the insomniacs, but not the controls (18). On placebo the insomniacs had lessened amounts of stages 3 and 4 sleep and the alcohol normalized their stages 3 and 4 sleep relative to their age-matched controls. Also, the direct effect on stages 3 and 4 is not surprising given alcohol's effect on GABA. GABA agonists (e.g., gaboxodol and gabapentin) as well as GABA reuptake inhibitors (e.g., tiagabine) have been shown to significantly increase stages 3 and 4 sleep. Turning to REM, the majority of studies report a suppression of REM sleep in the first half of the night (17). The REM suppression is reflected in either an increased latency to REM sleep or a reduction in min of REM sleep. As with the second-half of the night rebound in wake time , the reemergence of REM sleep or even enhancement in the second-half of the night is likely a rebound effect.

Several studies have assessed alcohol effects in healthy normals over repeated nights of administration (19, 20). Clear tolerance development within 3–5 days to both the stages 3 and 4 NREM enhancing and the REM suppressing effects of alcohol has been found. In insomniacs tolerance to the total sleep time and stages 3 and 4 enhancement occurred over 6 nights of repeated administration of 0.6 g/kg alcohol (21). Some studies have reported a rebound in REM sleep duration after tolerance development and discontinuation of nightly alcohol, while other studies have failed to show this (17). Failure to observe rebound during discontinuation probably relates to methodological issues, including dose and duration of nightly use, and to the degree of tolerance.

Sleep of Alcoholics

The sleep of alcoholics during periods of heavy drinking is typically characterized by a rapid sleep onset, but a shortened duration that consists primarily of NREM sleep (16, 17). Under conditions of an 8 h enforced bedtime the sleep of the second 4 h is fragmented with frequent awakenings and disruptions of REM sleep. Alcoholics describe an inability to fall asleep without drinking, as well as shortened sleep durations. In an interesting inpatient study of the sleep and drinking behavior of alcoholics given free access to alcohol, bouts of short sleep alternated with drinking bouts, both of which continued alternating across the whole 24-h day (22).

During acute discontinuation from alcohol consumption a decreased percentage of slow wave sleep relative to age-matched controls is found (16, 17). The NREM-REM sleep cycles are shortened and REM sleep is fragmented with frequent awakenings. The hallucinations characteristic of alcohol withdrawal have been hypothesized to be intrusions of REM sleep fragments into wakefulness. These REM intrusions are the expression of a "REM rebound" due to REM suppression during active drinking.

During prolonged abstinence the laboratory studies, consistent with the self-report QoL studies reviewed above, uniformly show disturbed sleep. Sleep time is shortened and sleep latency is prolonged (17). The shortened sleep is composed of fragmented sleep as evidenced by increased stage 1 and reduced stages 3 and 4 NREM, while REM sleep is frequently interrupted. These disturbed sleep patterns are reported to endure for up to two years of abstinence. Recent laboratory studies of abstinent alcoholics have found that REM sleep measures suggestive of "REM pressure", shortened REM latency, high REM percentage, or high REM density are predictive of relapse (17). In addition, relapse in some other studies was predicted by low percentage of stages 3 and 4 NREM sleep (23).

Alcohol Effects on Primary Sleep Disorders

During wake alcohol is a mild respiratory depressant, while during sleep it can worsen obstructive sleep apnea and precipitate sleep-related breathing disturbance in persons at risk (i.e., persons who snore or are obese). In patients with moderate sleep-related breathing disturbance (i.e., respiratory disturbance index (RDI) = 22) 300 ml of bourbon two hours before sleep increased their RDI to 28 (24). In asymptomatic snorers with no apneas pre-sleep alcohol induced apnea during sleep (25). On the other hand, several studies of asymptomatic persons without risk factors have shown that pre-sleep alcohol does not produce apnea de novo (17). The likely mechanism for alcohol's effects on breathing during sleep is a depressant effect on upper airway muscles relative to respiratory effort muscles. Consequently, in obese people or people who snore and whose airway tone and anatomy is already compromised, the addition of alcohol with its depressant effects on airway tone is sufficient to induce complete airway occlusion. Given these acute effects of alcohol on upper airway tone, it is not surprising that abstinent alcoholics show higher rates of sleep-related breathing disturbance than age and weight matched controls (26). Several different mechanisms can be hypothesized. Chronic alcohol exposure may have altered central ventilatory control mechanisms or upper airway muscle control. Additionally, the disturbed and fragmented sleep of the abstinent alcoholic described above may increase daytime sleepiness. Enhanced daytime sleepiness has been shown to reduce upper airway muscle tone. Finally, state instability (i.e., fragmented sleep) is known to produce upper airway instability.

Another primary sleep disorder, periodic limb movements during sleep (PLMS), may also be associated with increased alcohol use and alcoholism. In a study of consecutive patients

at a Sleep Disorders Center, the likelihood of having clinically significant PLMS was increased two-fold in men and three-fold in women drinking two or more alcohol drinks per day (27). In a sample of 40 alcoholics from an alcohol treatment program the average PLMS index was greater in the alcoholics compared to age-matched controls (28). Fifteen of the 40 alcoholics had indices of greater than 15 and the average index was significantly higher in the 23 patients that relapsed over the next 6 months than those that did not relapse.

Effects of Alcohol-Disrupted Sleep on Next-Day Function

The critical question is whether these alcohol-related sleep effects impact daytime function, both the day after as well as chronically. Unfortunately these effects have not been extensively investigated. Several large studies have linked self-reported excessive daytime sleepiness, alcohol and sleep disturbance. A study of a population-based sample of adults aged 18–65 years in Metropolitan Detroit ($n = 1325$) assessed the risks of use of various substances as sleep aids (29). Ten percent of the sample reported exclusive use of alcohol as an aid for sleep and unlike those using OTC or prescribed medications, as well as controls, those using alcohol reported more symptoms of daytime sleepiness. Similarly, a large sample of adults ($n = 335$) in the Netherlands who reported having previously experienced alcohol hangovers prospectively reported on their sleep after a normal night of sleep and after an evening of heavy drinking (30). Compared to their normal night of sleep, on nights after excessive alcohol intake, respondents reported poorer sleep quality and increased daytime sleepiness the following day. Unlike the previous two reports of alcohol related impaired sleep and next-day function, a study of elderly (65–98 years) people recruited from retirement communities found the opposite (31). A sample of elderly reporting excessive daytime sleepiness (n = 149) was compared to a case-controlled sample (n = 144) without sleepiness. In this study drinking more than 7 drinks per week actually reduced the risk of sleepiness. However, two times as many respondents in the control, non-sleepy, sample (32%) reported drinking more than 7 drinks per week, which may explain this discrepant result.

Several laboratory studies have assessed the next-day consequences of nighttime alcohol use. The first such study was conducted in airplane pilots (32). Pilots consumed 1.0 g/kg alcohol from 6 to 9 p.m. producing BrEC of 0.101–0.121% before sleep and were tested the next day 14 h after consuming the alcohol in a flight simulator. With BrEC at zero before testing, their simulated flight performance was impaired. Since nocturnal sleep was not assessed in this study, a follow-up study administered 0.8 g/kg alcohol producing BrECs of 0.06% at sleep and assessed both sleep and next-day impairment (33). The alcohol produced disrupted sleep in the second half of the night and was further associated with increased daytime sleepiness and impaired divided attention performance the following day. Thus, the impaired performance in the pilots who had 0 BrEC at the time of testing, probably was mediated by the sleep disruptive effects of alcohol.

Nightime Sleep Loss and Effects of Next-Day Alcohol Consumption

A final body of research addressing sleep, alcohol and QoL has evaluated the impairing effects of a sleep-alcohol interaction, as opposed to a alcohol-sleep interaction. To this point the previous literature that has been discussed assessed the impact of alcohol on sleep and in turn on QoL or other measures of daytime function. There is a literature showing that alterations in sleep, not necessarily due to alcohol consumption, interact with the subsequent next-day impairing effects of alcohol which will of course ultimately alter QoL.

While classified as a CNS depressant drug, alcohol has both sedative and stimulatory effects. These differential effects, described as biphasic, are dependent on dose and the phase of the alcohol concentration curve (34). Stimulatory effects are evident primarily at low to moderate doses and as alcohol concentrations ascend to a peak plasma concentration. Sedative effects follow on the descending phase of the plasma concentration curve and occur with higher doses. Thus, those nighttime studies that showed reduced sleep latencies in healthy normals typically raised alcohol concentration above 0.05% BrEC (16, 17) and administered alcohol 30–60 min before sleep, thus allowing for alcohol concentrations to peak before bedtime. A daytime study used a modified Multiple Sleep Latency Test (MSLT). The MSLT is a reliable and well validated electrophysiological methodology in which the subject is given an opportunity to fall asleep at 2-h intervals across the day. Short latencies to fall asleep suggest enhanced sleepiness and longer latencies enhanced alertness. This MSLT study found increased sleep latencies at peak breath concentrations relative to placebo, consistent with alcohol's stimulatory effects. Thereafter, on the descending phase of the plasma concentration curve, sleep latencies were reduced relative to placebo (35). In other studies, all done on the descending phase, alcohol reduced sleep latency, as measured by a standard MSLT, and impaired attention and reaction time performance all in a dose-related fashion (36). These impairing effects remained for at least 2 h after the alcohol has been completely metabolized, as evident by BrECs of zero (36).

A series of studies has been conducted exploring the modulation of these daytime sedative and performance-disruptive effects of alcohol by the basal level of sleepiness, which is determined by the time of alcohol consumption in the circadian phase and the duration of the previous nights' sleep (36). In these studies nocturnal sleep time is either shortened or extended and then the following day alcohol is administered. Thereafter, level of sleepiness/alertness and psychomotor performance are assessed for approximately 8 h.

These studies have found level of sleepiness/alertness at the time of alcohol administration alters the subsequent sedating and performance-disruptive effects of alcohol. For example, one study compared the sedating effects and impairing effects on simulated automobile driving of alcohol after 8 versus 4 h of sleep the previous night (37). With BrEC at half of legal intoxication in most states of the US and many European countries, minimal impairment of driving was found after 8 h, but after 4 h of sleep alcohol significantly impaired driving, leading to simulated crashes. These interactive effects of sleep were demonstrated in sleepy compared to alert healthy subjects (i.e., individuals who have basally high vs low MSLT scores). They also were shown within subjects before and after both sleep restriction and sleep extension. Finally, the interactive effects were shown within subjects at times of the day when the levels of sleepiness are known to differ according to the typical circadian rhythm of sleepiness-alertness (36). To summarize, increased alertness diminishes alcohol's effects and increased sleepiness compounds alcohol's effects. This raises the interesting possibility that the decreased QOL resulting from alcohol consumption interacts with the impaired QOL seen in alcoholics even when sober. In conclusion alcohol consumption as well as alcoholism impairs QOL. However, more research is needed to define the specific nature and etiologies of this impairment as well as the reversibility of this impairment with prolonged sobriety.

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Issues that need to be addressed by future research:

- Understanding the pathophysiology that underlies the sleep disturbance in abstinent alcoholics is a critical step in preventing relapse and reduced quality of life
- Understanding how the sleep disturbance in abstinent alcoholics leads to relapse is another important step in preventing relapse and reduced quality of life
- Understanding the mechanisms by which sleepiness interacts with the impairing effects of alcohol will emphasize the risks of low dose alcohol consumption

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Drugs of Abuse, Sleep, and Quality of Life

Brian Johnson

Summary Attempting to treat patients who are actively using addictive drugs is unlikely to be helpful and is potentially harmful. Actively using patients should be referred for detoxification before treatment for insomnia is implemented. All drugs of abuse cause insomnia. Although insomnia is most severe during withdrawal, it may be a long-lasting complication of addiction. Cocaine has been shown to provoke "occult" insomnia: degraded sleep accompanied by deteriorated cognitive functioning without the sensation of lack of sleep. This is thought to be caused by a decreased drive for sleep. Insomnia during methadone maintenance is the rule. Because of methadone-provoked central sleep apnea and because of the common lethality of benzodiazepines added to methadone, benzodiazepines are contraindicated during methadone maintenance. Physicians should be sure to include non-medication approaches for insomnia such as sleep hygiene, and if available, acupuncture. If medications are indicated for insomnia, trazodone, low-dose mirtazapine, quetiapine, clonidine, and valproic acid are good choices. Drug dreams are probably provoked by the same mechanism as drug craving: up-regulation of the ventral tegmental dopaminergic seeking system. Attention to drug-seeking during dreams may facilitate recovery.

Keywords Addiction · insomnia · occult insomnia · methadone-provoked apnea · drug dreams

Learning objectives:

- All drugs of abuse commonly provoke insomnia.
- Cocaine causes "occult" insomnia, deteriorating sleep with deteriorating cognitive functioning accompanied by a sense of improved sleep.
- Treatment of methadone-maintained patients with benzodiazepines is potentially lethal.
- Sleep hygiene, acupuncture, trazodone, mirtazapine, quetiapine, clonidine, and valproic acid can be helpful.
- Discussing drug dreams is useful for maintaining abstinence.

Introduction

Addiction is a morbid and mortal disease that makes sleep and life miserable. The universal goal of the addicted person while they are actively using drugs is to keep their addiction, and at the same time have all the attributes of a pleasant life. The reality is that as long as one is using addictive drugs, nothing can be treated effectively, including insomnia. Physicians responding to actively addicted patients' complaints of poor sleep must always refuse medications and refer the patient to detoxification as a bridge to recovery. Trying to ameliorate insomnia during active addiction is potentially lethal, as seen in the following example.

A sober woman who had been treated for depression returned with the following story. The neighbors broke down her daughter's door one morning because the baby would not stop crying and no one would respond to their knocking. Her daughter had been dead long enough for rigor mortis to have set in. Her mother-in-law was stuporous, each having taken half a month's prescription of clonazepam and oxycodone the night before. I called the mother-in-law's internist to inform him that he had issued lethal medications. He said, "I had sent her to detox twice, and she still wanted the drugs, what was I supposed to do?" My patient's grief and rage overwhelmed her. She returned to active heroin use that finally remitted only after two hospitalizations and many hours of outpatient psychotherapy combined with participation in Alcoholics Anonymous.

Once patients begin detoxification, insomnia will be part of the withdrawal syndrome. The general principle is that intoxication is always the opposite of withdrawal. Abused drugs that cause somnolence such as opiates, benzodiazepines, and

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barbiturates have withdrawal syndromes that feature persistent dysphoric hyperalertness. Abused drugs, such as methamphetamine and cocaine, that cause hyperalertness result in a "crash" on cessation where patients cannot seem to fully wake up for several days. However, following a cocaine crash, apparently sleep degrades over time (1).

It might be said therefore that poor sleep is a consequence of all drug addiction, and that physicians who treat patients in recovery are required to become specialists in insomnia. Conversely, in any primary care practice, patients complaining of insomnia will have a high incidence of addiction (2). Careful evaluation of psychiatrically hospitalized patients requesting as needed (prn) hypnotics revealed that 70% were actively addicted (3). As another factor, childhood insomnia may predispose to addiction (4).

Common drugs of abuse will be discussed individually, although the reader is cautioned that use of multiple addictive drugs is more common than addiction to a single drug. The next section will discuss treatment of insomnia. Addictive drugs also cause drug dreams, a significant aspect of sleep, and a helpful aspect of recovery. The final section will discuss this phenomenon and its use in treatment.

Effects of Specific Drugs on Sleep

Cocaine

Morgan et al. (1) have done the most careful evaluation of sleep during drug withdrawal in the addiction literature. Twelve chronic cocaine users completed a 23-day study on an inpatient research ward. Six subjects received intravenous cocaine on demand for days 4–6 and the other six received cocaine for days 18–20. The surprising findings were that total sleep time and sleep latency were at their worst when the observations were last made, days 14–17. These insomnia findings were "occult" in the sense that the subjects reported their sleep most refreshing when it was measured as worst; decreased sleep efficiency (time asleep divided by time in bed), decreased total sleep time, increased sleep latency, latest bed times, accompanied by cognitive deterioration; decreased vigilance and decreased sleep-dependent learning. The authors hypothesized that the cocaine had impaired the homeostatic sleep drive: the equivalent of losing weight and eating less despite feeling satisfied because of decreased hunger signals.

This might be the equivalent of Volkow's finding that other natural rewards are less sought following cocaine exposure (5). All drugs of abuse have a common action in the ventral tegmental dopaminergic seeking system (6–8). As such, they are impinging on a system that is shared between sleep, dreaming, and desire (9). More drug exposure causes more desire for drugs by an up-regulation of the seeking system (6) but a degradation of its functioning for survival-based behaviors (5), including sleep.

Methamphetamine

Research on insomnia in methamphetamine withdrawal has been limited to the demonstration of a 9-day crash, followed by normal sleep duration but increased sleep latency and increased awakenings, persisting to the end of the 3-week study (10). Given that the duration of action is longer than cocaine, although the mechanism of action is similar, it may be that both cocaine and methamphetamine disrupt sleep for long periods because of their dysregulation of monoamine-driven sleep systems. This is certainly consistent with the clinical experience that users of both these drugs complain of chronic insomnia with great frequency, 70% in one study of cocaine (11).

Opiate Withdrawal

All aspects of sleep are disrupted by opiate withdrawal (12). Tramadol, a commonly prescribed medication that does not have an opiate structure but occupies the opiate receptor has an identical withdrawal syndrome, including insomnia (13). Methadone withdrawal features the most severe and long-lasting insomnia (14). Treatment of insomnia during and after opiate withdrawal is an important feature of retention in treatment (14). Withdrawal insomnia continuing for more than a month is not unusual, and because opiates are commonly taken with other abused drugs, persistent insomnia may reflect multiple kinds of withdrawal (14).

Methadone Maintenance

About 75–84% of methadone maintenance patients complain of poor sleep (15, 16). A comparison of opiate-dependent patients maintained on methadone against a group treated at the same center with the pure opiate-blocker naltrexone showed that the methadone-maintained patients showed increased sleep latency, decreased total sleep time, less time in slow wave sleep, REM suppression, and more time awake at night. The authors believed that the methadone-induced insomnia resulted in irritability, loss of appetite, fatigue, and depression. They suggested that treatment of insomnia in methadone-maintained patients was essential to lessen insomnia and stress-related use of potentially lethal drugs such as heroin and cocaine during methadone maintenance treatment (17).

Methadone maintenance patients commonly use multiple other addictive drugs (18). This problem is compounded by the presence of a central sleep apnea caused by the methadone (19, 20) in about 30% of examined subjects. Srivastava and Kahan (21) discussed methadone-related deaths; 92% of New South Wales, Australia, deaths during the first week of induction on methadone were related to use of other drugs with methadone; benzodiazepines were a co-intoxicant in a majority of methadone-related deaths in a county in Alabama, and benzodiazepines have caused a fivefold increase in fatal

overdoses. For these reasons, benzodiazepines are contraindicated in this population.

Marijuana

Marijuana withdrawal features craving, anxiety, anger, loss of appetite, depression, restlessness, increased dreaming, and insomnia (22, 23). Insomnia is self-limiting, although it takes a month for the withdrawal syndrome to end (22).

Methlenedioxymethamphetamine

Ecstasy causes short-term insomnia (24, 25), although the fact that over 90% of Methlenedioxymethamphetamine (MDMA) users also use marijuana makes marijuana-induced withdrawal insomnia the dominant feature of early sobriety (26). Users who had negative urine screens, i.e., no use in the immediate past showed increased sleep latency and decreased slow wave sleep (27).

Other Abused Drugs

Crushing prescription stimulants such as methylphenidate so that they can be injected or snorted (28) is commonly seen on addiction services. Prescribed stimulants disrupt sleep in a similar manner to methamphetamine. Gamma-hydroxybutyrate has been reported to cause a withdrawal syndrome that includes insomnia for up to 2 weeks (29). 1-Benzylpiperazine sold as "herbal party pills" causes insomnia (30). Drugs of abuse not mentioned here are likely to disrupt sleep as well as other homeostatic functions because of their perturbation of monoamine systems. Insomnia is a constant in addiction.

Treatment of Insomnia Provoked by Substance Abuse

The patient who presents with complaints of insomnia caused by attempts at self-medication is likely to expect the physician to cure their distress by the use of drugs despite the reality that their experience is one of continual failure using the drug approach. The treating physician needs to stay conscious of the subtle interactions that may include threats of abandonment, hostile clinging, and invitations to join the group that believes in magical cures through drug use (31). The physician stance should not be attempting to ameliorate a symptom, but rather of working with the patient to prevent a recurrence of the active disease, a stance Pies has named "Hippocratic psychopharmacology" (32).

A drug-using lifestyle, possibly complicated by increasing sleep latency, often results in patients who need basic instruction in techniques of sleep hygiene. These techniques include always getting up early, not drinking coffee (often furnished at evening meetings of Alcoholics Anonymous), arriving home well before bedtime to allow time to relax, avoiding the use of the bed for eating, watching television, etc. (33). Acupuncture treatment in early abstinence can be helpful for insomnia (34).

If medications are part of the treatment, of insomnia, trazodone is a popular choice, especially given its efficacy for comorbid depression, anxiety (35) and pain (36). Therapeutic doses for depression, anxiety, and pain should be in the 200–600 mg/day range. Quetiapine in the 25–600 mg/day range has been shown to help with the insomnia of opiate withdrawal, as well as with pain, anxiety, and craving for opiates (37). Use of quetiapine has been shown to help with insomnia during a 28-day rehabilitation for alcohol, cocaine, and methamphetamine (38). Sleep has also been shown to improve with the use of divalproex in cocaine-dependent bipolar patients at about 1000 mg/day (39). Clonidine is another agent with efficacy for insomnia during opiate withdrawal because it specifically opposes the hyperadrenergic withdrawal state. Gabapentin at doses of at least 600 mg has a latency of onset of 2–3 h and is often helpful. Use of benzodiazepines or zolpidem is contraindicated because of their abuse potential (40, 41) and because of their possible lethality, especially if combined with other drugs of addiction (as in the opening vignette of this chapter). Tricyclic antidepressants such as amitriptyline and doxepin, formerly popular (33), have fallen out of favor because of the risk of fatal overdose. Mirtazapine, especially in low doses, lacks this liability, and has become increasingly popular (42) (Table 35.1).

Drug Dreams

The two specimens that follow are taken from the report of Johnson (43). The "hours" refer to hours of 4 days per week psychoanalysis, and represent points at about 1 and 4 years sober. In the second dream, the analyst is being internalized as a helpful and protective figure.

Hour 30: "I was doing drugs with Joey, shooting coke. I was having a hard time getting high. I couldn't get a vein, or it would blow. Then he was my cousin Larry. I said, 'You got percs, right?' I'm thinking, if I use percs, is it a relapse?—While I'm shooting coke! I took the percs."

Hour 658: "My mother looked sad. I walked away from her. I felt so sad. I said, 'Dope is the only thing that will take

TABLE 35.1. Approach to insomnia for addicted patients.

- Sleep hygiene
- Acupuncture
- Trazodone 200–600 mg
- Quetiapine 25–600 mg
- Valproic acid or divalproex 1000 mg
- Clonidine 0.1–0.2 mg
- Gabapentin 600 mg
- Mirtazapine 7.5–15 mg

away this feeling. I know who has dope, I'll call. Then there was a guy standing there. I had to call without him knowing. Someone interrupted the call. I heard his voice. 'I know what you are doing. You are *not* buying dope.' I thought, 'Shit, how did he hook into my phone line?' I figured I'd try again, find a way around him. I had to have it. But I didn't get the dope."

There are many reports suggesting that dreaming about alcohol and drugs is an important aspect of both addiction and recovery. The presence of dreams about specific drugs of addiction has been repeatedly documented; alcohol (43–48), nicotine (43, 49, 50), cocaine (43, 51–54), opiates (43, 55–58), benzodiazepines (41, 43), and marijuana (59). Reports of multiple drugs appearing in multiple dreams come from Christo and Franey (60) and Johnson (43). These drug dreams have frequently been reported to correlate with or be helpful for maintaining abstinence (41, 43, 45, 47, 49, 50, 53, 60). Colace (58) suggested, "...drug dreams as biological-drive-related dreams may contribute to reducing the intensity of frustrated drives in the post-dream period. Patients who have drug dreams show a better ability to deal with drug-craving stimulation than those who do not have drug dreams." However, there has been no systematic study of how common such dreams are in the addicted population, when in the course of addiction and/or treatment they are first reported, whether they persist over a lifetime, and how they are related to age, gender, cognitive functioning, or specific drug exposure.

Drug dreams do not appear to be present while addicted persons are actively using their drug (45,49,50,57,58). Rather, they appear as withdrawal and drug craving begin. Colace (58) showed that subjects who used heroin constantly did not have drug dreams, whereas subjects who became abstinent began to have frequent dreams of seeking or using heroin, apparently correlated with physical withdrawal. Araujo et al. (61) found that the 27% of their subjects who dreamed of alcohol had significantly higher scores on a craving scale. This increase of alcohol and drug dreams is greatest in the period immediately following cessation of use; Reid and Simeon (53) found that 89% of cocaine-dependent subjects had drug dreams within the first month of abstinence, whereas only 57% reported them at 6 months. Furthermore, 6-month treatment outcomes were better for the 57% of subjects reporting drug dreams 6 months after intake (53). Johnson reported the use of alcohol and drug dreams as a tool in helping patients to become aware of their unconscious urges to use (41, 43, 48).

As to why alcohol and drug dreams appear during abstinence rather than while using, the only "explanation" is a variant of Freud's "dreams are the guardian of sleep;" that dreaming of alcohol and drugs allows the addicted individual to postpone motor activity until they complete needed restorative sleep by giving an illusion of wish-fulfillment (43). A second "explanation" might be that the user is now trying to develop new strategies and schemas for maintaining abstinence by rehearsing activities during the motor paralysis of sleep.

All drugs of addiction up-regulate the dopaminergic system, which runs from the ventral tegmentum through the lateral hypothalamus to basal forebrain, amygdala, hippocampus, ventral striatum, anterior cingulate, and frontal areas (6, 7). This is the identical pathway that is hypothesized to be the initiator of the dream-on system (9, 62), although this position is controversial [as discussed, for example, by Hobson (63–65), Hobson and Pace-Schott (66), Hobson et al. (67), Reiser (68), Hartmann (69), Greenberg (70), Johnson (71, 72)]. Although "tolerance" is common in some brain areas, the ventral tegmental dopaminergic seeking system shows "reverse tolerance," that is increased activity with repeated drug exposure (6). It is possible that the origin of alcohol and drug dreams is that this system is up-regulated by recurrent exposure to addictive chemicals and is subsequently active in producing dreams that remind the person of their wish for these drugs (41, 43, 58, 73).

Although addicted patients frequently complain of insomnia, and leave their interaction with physicians at that, the physician would be well advised to ask what might be going on during sleep. Apparently, addicted patients are doing some of their best thinking while asleep. Recovery from addiction and improving quality of life are best facilitated by actively discussing issues with the patient in a comprehensive manner that includes lifestyle, sleep hygiene, and drug dreams rather than simply prescribing medications for the isolated symptom of insomnia.

Issues that need to be addressed by future research:

- Mechanisms of degradation of sleep by drugs of abuse
- Treatments for insomnia that target the specific drug-induced mechanism of insomnia in addicted/recovering persons
- Age of onset, amount of exposure required for onset, prevalence of drug dreams in the addicted population, prognostic value

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Sleep, Sleep Disorders, and Quality of Life in People Who Have Cardiovascular Disease

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Summary Hypertension and coronary heart disease are leading global causes of death, disability, and decrements in health-related quality of life. Sleep disorders are also intimately associated with health-related quality of life, appear to be factors influencing the progression of cardiovascular disease, and are more common among people with these disorders than the general population of middle-aged and older adults. Factors that contribute to sleep quality and sleep disorders appear to be multifactorial in this setting and may include demographic, clinical, and treatment-related characteristics. The purposes of this chapter are to evaluate the nature of sleep and sleep disorders and quality of life in adults with cardiovascular disease, as well as those who may be at-risk for cardiovascular disease; to critically review research findings addressing the relationships between sleep, sleep disorders and quality of life; and to propose directions for future research.

Keywords Sleep · sleep disorders · quality of life · hypertension · coronary heart disease

Learning objectives:

- To evaluate the importance of sleep disorders, including insomnia and sleep disordered breathing to the development of cardiovascular disease.
- To understand the associations between sleep disorders and quality of life for people with cardiovascular disease.
- To appreciate the potential quality of life consequences of treatment and adherence to treatment for sleep disorders by people with cardiovascular disease.
- To describe the multivariate factors that contribute to sleep disturbance in people with cardiovascular disease.
- To appreciate the potential interrelationships between depression and sleep disturbance in cardiovascular disease.

Introduction

Cardiovascular disease is a worldwide and highly prevalent cause of premature death, disability, and decrements in quality of life. Hypertension and coronary heart disease (CHD) are the two most common disorders in middle-aged and older adults. Sleep disorders, especially insomnia and sleep-disordered breathing, are common in middle-aged and older adults and people with, or at risk for, cardiovascular disease. Recent scientific advances have emphasized the potential significance of sleep and sleep disorders to cardiovascular morbidity and mortality (1), but there is also evidence that sleep and sleep disorders are intimately associated with quality of life in people with chronic illness and cardiovascular disease in particular (2–6). The purposes of this chapter are to evaluate the nature of sleep and sleep disorders and quality of life in adults with cardiovascular disease, as well as those who may be at-risk for cardiovascular disease; to critically review research findings addressing the relationships between sleep, sleep disorders, and quality of life; and to propose directions for future research. Because detailed chapters on sleep and quality of life in cardiac surgery and heart failure are included separately in this book (see Chapter 37, 38), the chapter emphasizes sleep and quality of life relative to patients' experiences with hypertension and medical or non-surgical treatment of CHD.

Associations Between Sleep Disorders and the Development of Cardiovascular Disease

Obstructive sleep apnea/hypopnea syndrome (OSA), a condition associated with repetitive partial or complete obstruction of the upper airway during sleep, frequent nocturnal arousals,

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hypoxia and excessive daytime sleepiness; and insomnia, characterized by difficulty initiating or maintaining sleep and/or the perception of non-restorative sleep, are the two most common sleep disorders among middle-aged and older adults. For more than 30 years, since the identification of OSA and observations that it might be associated with hypertension and other adverse cardiovascular outcomes, there has been increased interest in the relationships between these two primary sleep disorders and hypertension and CHD and growing evidence that OSA is a risk factor for cardiovascular disease. Less is known, however, about the quality of life implications of managing this risk.

Linkages Between OSA and the Development of Cardiovascular Disease

OSA seems to be highly prevalent, yet under-diagnosed, and appears to be an important part of the pathway to the development of cardiovascular disease, including heart failure, stroke, hypertension, atrial fibrillation, and CHD (7). (The relationships between heart failure and stroke and sleep disorders are discussed in other chapters in this volume.) A well-designed and widely cited epidemiological study conducted in the Midwestern USA (8) found that the prevalence of OSA was 4% in men and 2% in women when the criterion of daytime somnolence was included with the apnea–hypopnea index (AHI). Using somewhat less-restrictive criteria, the prevalence was 9% of women and 24% of men. More recently, the Sleep in America Poll determined that as many as 26% of American adults (31% of men and 21% of women) might be at risk for sleep apnea (2). The prevalence is estimated to be similar in other Caucasian groups throughout Europe and Australia, as well as India and Hong Kong, and there is a need for further study in various ethnic and racial groups (9). However, there is widespread agreement that OSA presents a major public health problem.

There appears to be a reciprocal relationship between hypertension and OSA, and most epidemiological and physiological research suggests that obstructive apnea contributes to the development of hypertension (10).

Approximately 50–60% of OSA patients have hypertension (11), whereas more than 30% of hypertensive individuals have OSA (12). Several large studies have demonstrated "dose–response" relationships between OSA and hypertension (13–16). Investigators for the Wisconsin Sleep Cohort Study (17) found a linear association with blood pressure and the AHI (total number of apneas and hypopneas/hour) in 1060 employed men and women between the ages of 30 and 60 years. Sleep disordered breathing at baseline-predicted hypertension 4 years later (18). Investigators for the Sleep Heart Health Study (SHHS) (19) found that mean systolic and diastolic blood pressure and prevalence of hypertension increased significantly at higher levels of the AHI. The odds ratio for hypertension, comparing the highest AHI level (AHI $>$ 30/h), to the lowest (AHI $<$ 1.5/h) was 1.37 (CI:1.03–1.83, $p < 0.005$) (14).

Obstructive apnea may also contribute to the development of CHD. Investigators for the SHHS found an odds ratio of 1.27 (CI: 0.99–1.62) for the relationship between CHD and sleep-disordered breathing, although the odds ratio was higher for heart failure and stroke. Similarly, the Nurses Health Study found that self-reported snoring, a significant sign of OSA, was an independent risk factor for CHD (20), and severe sleep-disordered breathing also appears to be associated with a higher incidence of nocturnal arrhythmias (21).

Apneas and hypopneas that occur with OSA cause hypoxemia and sympathetic activation during daytime and nighttime hours. Sympathetic activation, in turn, results in elevated heart rate, increased cardiac output, decreased heart rate variability, peripheral vascular resistance, and tubular sodium reabsorption (22)—pathophysiological changes that contribute to hypertension. Sleep-disordered breathing may be linked with CHD through the pathway of chronic hypertension, the development of insulin resistance and obesity, or through inflammatory responses and endothelial injury secondary to hypoxia (1). Several of the risk factors for OSA are shared with CHD, such as obesity and hypertension. Therefore, these factors must be addressed in studies of these relationships (23, 24).

Quality of Life Implications Relative to OSA as a Risk Factor for Cardiovascular Disease

Findings from the SHHS, a project that included several large cohorts of subjects who were followed for risk of heart disease, mild to moderate sleep-disordered breathing was related to decreased vitality, and severe sleep-disordered breathing was associated with decrements on most of the SF-36 subscales (25), as well as decrements on aspects of neurocognitive function, including motor speed and processing speed (26). Therefore, OSA is a particular quality of life concern for people who may be at-risk for heart disease.

Although there is considerable literature on the contributions of sleep-disordered breathing to quality of life, there has been little emphasis on the quality of life issues specific to people with hypertension. Yet, given the higher prevalence of OSA in people with hypertension (12), and the documented quality of life concerns of people with hypertension (27–31), the presence of sleep-disordered breathing may magnify these problems through its symptoms and the quality of life burden of treatment.

Three primary strategies, weight loss, nasal continuous positive airway pressure (CPAP), and dental appliances, are recommended for treating OSA. CPAP is the most widely used, and there is evidence of its efficacy in treating apneas

and hypopneas, as well as reducing blood pressure (32–35). There is also some evidence that use of CPAP reduces cardiac events in people with CHD and OSA (36). Although there are improvements in somnolence and vigilance (37), improvements in quality of life for patients who use CPAP may be primarily in those who are pathologically sleepy, in addition to having pathological levels of apneas and hypopneas (38). Therefore, improvements in quality of life are not a universal consequence of this treatment. Moreover, adherence to use of CPAP is a widely acknowledged problem and appears to be positively related to perceived beneficial outcomes and negatively associated with side-effects that occur in as many as 2 of 3 patients. These include dry mouth, nasal stuffiness, insomnia, and claustrophobia among others (39).

It seems logical that long-term prevention of hypertension and CHD would improve quality of life over the long term, especially because hypertension (27–31), CHD (40–42), and atrial fibrillation (43) have negative quality of life consequences themselves. Reducing the burden of sleep-disordered breathing by addressing pathological sleepiness, cognitive dysfunction, and other negative sequelae of sleep apnea may also improve overall health-related quality of life for patients with cardiovascular disease. However, the quality of life issues associated with the treatment itself, and the inconsistent improvement in quality of life associated with treatment must be balanced against its potential to prevent long-term negative cardiovascular consequences. Further research is needed into patient and provider perceptions and decision-making regarding these questions.

Contributions of Insomnia to CVD and Quality of Life

Although research efforts have primarily focused on sleep-disordered breathing in relation to cardiovascular disease, insomnia may also contribute to the development of hypertension and CHD. Insomnia, a disorder of initiating and maintaining sleep, may be primary or idiopathic or secondary to other factors, such as psychiatric or medical disorders, psychological stress, medications, or environmental conditions and is very common. As many as 54% of surveyed adults report having had one or more symptoms of insomnia at least a few nights a week in the past year and 33% say they have insomnia every night or almost every night (44).

Insomnia appears to be associated with non-fatal myocardial infarction (45–47) and death from CHD (45), independently of sleep-disordered breathing (48). The odds ratios of increased risk of hypertension in Japanese male workers were 1.96 (CI: 1.42–2.70) for difficulty initiating sleep and 1.88 (CI: 1.45–2.45) for maintaining sleep (49). Although the underlying mechanisms for the relationships between insomnia and cardiovascular morbidity and death are not clearly understood, insomnia may be a marker for underlying stress and autonomic dysfunction (48), and/or disturbed mood. A potential limitation of past studies is the absence of polysomnographic sleep measurement, and it is possible that reported insomnia was secondary to OSA. However, in at least one study (47), participants did not report snoring, Therefore, it is not likely that OSA was the cause of difficulty maintaining sleep. Moreover, difficulty initiating sleep, a significant risk for hypertension (49), is not usually associated with sleep apnea.

Insomnia is closely linked with decrements in quality of life in the general population, as well as in people with chronic illness. For example, daytime sleepiness is related to general health and functional status, especially energy and fatigue in the elderly (4). A meta-analysis of 19 studies demonstrated that sleep deprivation impairs human functioning (5). Schmitt and colleagues (50) reported that self-reports of sleep symptoms were associated with self-reported health in a community-based sample of older adults. In a community-based population without severe chronic medical or psychiatric illness, daytime sleepiness explained 8% of the variance in general health perceptions, 17% of the variance in energy/fatigue, and 6% of the variance in wellbeing. Better sleep quality was associated with fewer psychological and physical complaints, more positive affect, better life satisfaction, increased vigor, and decreased fatigue and confusion in adults from the ages of 40–70 years; sleep quantity, reported in a sleep log, was related only to physical health, fatigue, and confusion (51).

In the Medical Outcomes Study, a cross-sectional project that included 3484 people with chronic illness including myocardial infarction and hypertension among others, there was an association between sleep problems in decrements in HRQOL. Mental health was the primary and most consistent dimension of the SF-36 affected. In people with recent MI, however, the physical function component was the scale most affected (3). There were also significant relationships between sleep problems, work productivity, and health care utilization (3). More recently, investigators for the SHHS (25) reported that persons with disorders of initiating and maintaining sleep (DIMS) were significantly more likely to fall within the lowest quartile of all SF-36 dimensions (physical function, role physical, bodily pain, general health, vitality, social functioning, and mental health) (OR: 1.36–2.11, $p < 0.001$) than persons without DIMS. These findings were independent of the associations found between sleep-disordered breathing and the quality of life indicators.

Insomnia is also closely linked with poor mental health, an important component of quality of life. Although the relationships are not completely defined, insomnia may be a precursor to the development of mental health problems, such as depression; a symptom or marker of depression and other mood disorders, or a consequence (52, 53). Given recent interest in the extent to which depression may contribute to the development of CHD (54), understanding the relationships among depression and insomnia may have important implications for prevention of CHD or its exacerbation. Further research is

needed on the true prevalence of insomnia in people with CHD, as well as the threshold at which insomnia contributes to quality of life including mental health. Clarity is needed on the conceptual questions related to consistent definitions of insomnia, as well as the components of the construct of quality of life, as many studies have used available instruments, such as the Nottingham Health Profile, Sickness Impact Profile, or the Medical Outcomes Study SF-36 to define this construct.

Sleep Disorders in Adults with Hypertension and CHD

Disturbed sleep appears to be common among people with CHD, a condition that is also associated with other symptoms, such as chest pain and fatigue, and for some individuals, depressed mood. Although the proportion of study participants reporting sleep disturbance varies widely, depending on the population and method of sleep evaluation, disturbed sleep is common among male and female patients with stable angina who are awaiting coronary artery bypass graft surgery (55–57), patients hospitalized for myocardial infarction and unstable angina (58), coronary artery bypass graft patients (59), and patients who have undergone percutaneous transluminal angioplasty (PTCA) (60, 61).

A limitation of many previous studies is the absence of comparative data on the sleep of people who do not have CHD. However, Sumanen and colleagues (41) reported that CHD patients reported more depressive mood, daytime sleepiness, and disturbed sleep than a comparison group of health participants. Twenty-five percent of working angina pectoris patients versus 10% of the comparison group and 32% of the myocardial infarction patients, compared with 13% of the comparison group reported usually poor sleep. The comparison group was randomly selected from a larger pool of participants. Another group of investigators reported that self-reported sleep quality was poorer among patients awaiting CABG for chronic angina than the general population (57). Therefore, it appears that disturbed sleep is more prevalent among CHD patients than other groups.

Although studies seem to support the idea that CHD patients suffer from sleep disturbance, few investigators have explored in-depth the specific attributes of sleep disturbance using objective measures or the multivariate factors that might contribute to disturbed sleep. This focus is an essential first step in focusing sleep-promoting interventions that may include pharmacological or behavioral strategies to reduce insomnia or treatments for sleep-disordered breathing.

Little attention has been focused on understanding the factors that may contribute to sleep disorders among CHD patients. These problems may simply reflect pre-existing OSA or insomnia, disorders common among the general population, or may be influenced by demographic and illness-related factors, such as aging and gender. For example, women report more sleep disturbance during hospitalization after myocardial infarction (62) and while awaiting revascularization for stable angina (63) than men, but they almost universally also report poorer quality of life. Aging and the severity of CHD may also play a role. For example, Redeker and colleagues found that pre-hospitalization sleep disturbance, aging, gender, and New York Heart Association functional classification explained 29% of the variance in wrist actigraph-recorded sleep efficiency in a group of male and female patients hospitalized for treatment of unstable angina and myocardial infarction (58). Disorders that are often comorbid with cardiovascular disease, such as diabetes, chronic respiratory disease, and arthritis, may also contribute to the presence of sleep disturbance among CVD patients, but the contributions of these problems to sleep in patients with CHD has undergone little study. There is a pressing need for multivariate study of factors contributing to sleep disorders and their quality of life consequences among people with cardiovascular disease.

Disturbed mood, especially depression, is thought to be common among patients with CHD (41, 64). It is a significant determinant of disability (65), symptoms, and functional status decrements (66, 67), and a factor contributing to quality of life that may be more important than CHD treatment method (68). Mood disturbance may be a cause or consequence of sleep disturbance among patients with CHD, or sleep disturbance may be a marker for undiagnosed mood disturbance, as disturbed sleep is an important somatic component of depression. Two studies reported that involuntary and intrusive thoughts, behaviors that may be associated with anxiety or depression, were associated with self-reported sleep disturbance among cardiovascular patients (55, 60). Poor sleep was attributed to increased psychosocial symptoms at 1 year after PTCA, and these problems appeared to be more severe in women (60). There has been little consistency in the methods used to measure depression or its conceptualizations (e.g., depressive symptoms vs. clinical depression) among people with CHD, and little is known about the threshold of depression necessary to cause decrements in other components of quality of life. Systematic study to evaluate the relative contributions of depression and sleep disturbance; the threshold at which depression and sleep disturbance contribute to health-related quality of life, and their interactions is necessary to a more complete understanding of these phenomena and their contributions to quality of life.

The contributions of the long term effects of revascularization on improvements in sleep must be evaluated relative to the discomforts associated with early treatment and recovery (69) after procedures such as CABG and PTCA. Patients with CABG and PTCA showed significant improvements on the sleep dimension of the Nottingham health Profile over 6 and 12 months, compared with baseline, but there was no improvement in this dimension among patients treated with medications only (70). Others found that chronic stable angina

patients treated with CABG surgery had better sleep quality at 21 months, compared with those who underwent PTCA (71). At eight-year follow-up, the PTCA patients deteriorated somewhat on the sleep dimension. There was no statistically significant change in the CABG group or the medication-treated group (72). A significant limitation of all of these studies is deficient information on the baseline clinical characteristics of the study participants used to determine the specific treatment group. Therefore, the results might be biased due to factors associated with patient selection for specific treatments.

The foregoing studies considered sleep disturbance as a component of quality of life. A few investigators have considered sleep as a phenomenon separate from health related quality of life and the relationships between these 2 phenomena. Self-reported sleep quality was related to physical function, physical role function, and vitality in a small group of PTCA patients (73). Self-reported sleep disturbance has also been associated with number of disability days, daily activity levels (74), and symptoms of cardiac illness (75, 76). In the only study reporting objective sleep measurement among, male Swedish patients awaiting CABG, reduced deep sleep, measured with polysomnography, was associated with poorer overall health (55). This is not surprising, given the restorative effects of deep sleep. Reduced sleep efficiency and daytime naps were associated with emotional distress. Among myocardial infarction patients, use of hypnotics (a marker for sleep disturbance) was associated with quality of life at 4 years post-event (42). Although these studies generally implicate the contributions of sleep quality to health related quality of life, causality cannot be inferred in most of this work. It is equally plausible that quality of life or positive affectivity (77) contribute to self-reports of positive sleep quality. Furthermore, there is little consistency or standardization of the sleep dimensions that were evaluated or in the quality of life dimensions. Further research is needed to address these issues.

Summary

Over the past few years, there has been great interest in the associations between sleep, sleep disorders, and the development and exacerbation of cardiovascular disease. Health-related quality of life is also of interest relative to people at risk for CVD and for those who are living with these chronic disorders. Although the quality of life consequences of sleep disorders have also been a focus of recent research interest, the science on sleep and quality of life in people with cardiovascular disease is not fully developed. Further research is needed to maximize the development of strategies to promote sleep and quality of life or to promote quality of life by improving sleep among people with cardiovascular disease.

Issues that need to be addressed by future research:

- Evaluate the demographic, clinical, and treatment-related factors that predict sleep disturbance and sleep disorders among well-defined groups of patients with cardiovascular disease.
- Evaluate the relative impact of CVD treatment on sleep and sleep disorders.
- Explore the quality of life-related decision-making processes that people at-risk for CVD use relative to adherence behavior concerning the use of CPAP.
- Evaluate the interactions of depressive mood and sleep disorders relative to the development of CVD, and its consequences relative to morbidity, mortality, and quality of life.
- Characterize the nature of sleep disturbance over the trajectory of chronic cardiovascular disease in large, well-defined patient groups.
- Examine the efficacy of sleep promotion interventions targeted to specific dimensions of sleep disturbance among patients with CVD.

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Sleep and Quality of Life in Heart Failure and Stroke

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Summary Congestive heart failure (CHF) because of left ventricular systolic dysfunction is a prevalent syndrome and associated with morbidity, mortality, and huge economic cost. Hallmarks of CHF are exercise intolerance, poor prognosis, and poor quality of life (QoL). According to reports from several laboratories, a large number of patients with heart failure also have sleep apnea (SA). SAs cause arousals and sleep disruption, alter blood gases, and increase sympathetic activity. SA has a major impact on QoL, and disturbed sleep itself significantly contributes to depressive syndromes in patients with stable CHF. The correlation of the apnea/hypopnea index (AHI) with most of the QoL measures and depressive syndromes indicates that patients with AHI indices estimated their impaired physical and emotional health status lower as opposed to patients without sleep-related breathing disorder. Fatigue leads to reduced QoL after stroke. Sleep-disordered breathing precedes stroke and may contribute to the development of stroke. It is an independent prognostic factor related to mortality in stroke and associated with fatigue and impaired QoL. Obstructive events seem to be a condition before the neurological disease whereas central events and Cheyne–Stokes respiration (CSR) could be its consequence. In this article, the impact of sleep-disordered breathing on patients with heart failure and stroke and its influence on QoL are discussed.

Keywords Sleep apnea · congestive heart failure · stroke · quality of life · depression

Learning objectives:

- Sleep apnea in congestive heart failure is associated with reduced quality of life, elevated mortality rates, and associated with depression. Treatment of sleep apnea in CHF improves quality of life, EF, and possible effect on mortality.
- Sleep-disordered breathing precedes stroke and may contribute to the development of stroke, which is an independent prognostic factor related to mortality. Obstructive events seem to be a condition before the onset of the neurological disease whereas central events and Cheyne–Stokes respiration could be its consequence.

Introduction

Congestive heart failure (CHF) is common, especially in older patients, and its incidence is predicted to even further increase (1). It is among the congestive diseases that most reduce quality of life (QoL), exercise tolerance, and survival. Depending on the severity of symptoms, heart dysfunction, age, and other factors, CHF is associated with an annual mortality of 20–30% at 1 year and 50% at 5 years, and it is one of the most common causes of hospitalization. Prognostic factors in CHF include haemodynamic, neurohumoral, electrophysiological, and treatment variables. There is increasing evidence that sleep-disordered breathing (SRBD) is also a prognostic factor (2).

Two types of sleep apnea (SA) in heart failure are common. The obstructive SA episode is defined as a loss of inspiratory airflow coupled with rib-cage excursions and/or abdominal excursions. Obstructive SA syndrome (obstructive SA, OSAS) might also be a cause of heart failure. In a study by Dursunoglu et al. (3), the left ventricular mass and myocardial performance indexes in obstructive SA patients were assessed. Severe and moderate OSAS patients had higher left ventricular mass and left ventricular mass index, and left ventricular global dysfunction.

The simultaneous absence of inspiratory airflow and respiratory movement indicates the presence of central SA episodes. Cheyne–Stokes respiration (CSR) is a form of periodic breathing in which apneas and hypopneas with

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ventilatory periods having a crescendo–decrescendo pattern of tidal volume (John Cheyne 1777–1836, William Stokes 1804–1878). Although obstructive SA is common in patients with and without heart failure, most individuals with CSR and central SA have heart failure. Increased left ventricular filling pressures can lead to pulmonary congestion and activation of pulmonary vagal irritant receptors, provoking hyperventilation and hypocapnia. CSR occurs when arterial carbon dioxide partial pressures fall below the apneic threshold. The cycle length of alternating periods of hypocapnia induced apnea and reflex hyperventilation, i.e., CSR (2) is inversely proportional to cardiac output (4) and thus directly related to the severity of heart failure. A reduced left ventricular function delays the circulation time between the lungs and the chemoreceptors (5), and increases the sensitivity of chemoreceptors, especially to carbon dioxide (6). The degree of carbon dioxide hypersensitivity is a major determinant of CSR (7).

Prevalence of SA in CHF

Javaheri and colleagues determined the prevalence and effects of SA in 42 ambulatory patients with stable CHF (8). In this population, the severity of left ventricular dysfunction was an independent risk factor for sleep-disordered breathing [SRBD which was commonly occult and severe (45% had AHI > 26)]. A higher prevalence of ventricular arrhythmia was also found in patients with CHF and SA, mainly of the central type. More recently, the same group prospectively evaluated a larger sample of CHF patients, and found a prevalence of SA of 51% (with an average AHI of 44/h) (9). These patients had a higher prevalence of atrial fibrillation (four times higher) and ventricular arrhythmias and had significantly lower ejection fraction (EF) (22 vs. 27%). Central type was more common (40 vs. 11%), but there were no significant differences between these two groups, namely in relation to the severity of ventricular dysfunction. The authors suggested that the interaction between SA and left ventricular dysfunction could result in a vicious cycle, further increasing morbidity and mortality in patients with CHF. Non-diagnosis of SA in this population might be related to the predominance of CSR, which is more frequently asymptomatic. Oldenburg et al. (10) screened 700 patients with CHF (NYHA class $\geq$ II, LV-EF $\leq$ 40%) for the prevalence and nature of SRBD in patients with CHF receiving therapy according to current guidelines. Medication included ACE-inhibitors and/or AT1-receptor blockers in at least 94%, diuretics in 87%, beta-blockers in 85%, digitalis in 61%, and spironolactone in 62% of patients. SRBD was present in 76% of patients [40% central (CSR), 36% obstructive sleep apnoea (OSA)]. Vazir et al. (11) determined the prevalence and characteristics of SRBD in male patients with NYHA class II symptoms of CHF. Thirty-eight percent were diagnosed for central sleep apnoea (CSR) and 15% had OSA. SRBD patients had steeper VE/VCO (2) slope (31.1 vs. 28.1), enhanced chemoreflexes to carbon dioxide during wakefulness, and significantly higher levels of brain natriuretic peptide and endothelin-1 compared with patients without SRBD. No differences in left ventricular EF, percent predicted peak oxygen uptake, or symptoms of SRBD were observed. Even in mild symptomatic CHF, a high prevalence of SRBD was found, so patients with SRBD could not be differentiated by symptoms or by routine cardiac assessment making clinical diagnosis of SRBD in CHF difficult.

Pathophysiological implications of SA in heart failure

Despite improvement in survival over recent years, CHF mortality remains high (20–30% at 1 year and 50% at 5 years), and it is one of the most common causes of hospitalization. Prognostic factors in CHF include haemodynamic, neurohumoral, electrophysiological, and treatment variables. There is increasing evidence that SRBD is also a prognostic factor.

SRBD is associated with systemic and pulmonary hypertension (PH), sleep fragmentation, cardiac arrhythmias, nocturnal angina, and impaired QoL. Patients with SRDB had higher activation of a neurohumoral marker and more severe CHF (12). Patients with SRBD had significantly higher levels of BNP and noradrenalin than those without SRBD. The presence of CSR in patients with CHF is associated with a significantly increased risk for death and cardiac transplantation. Lanfranchi et al. (13) studied 62 patients with CHF and CSR for 28 months and found a higher value of AHI in the nonsurvivors ($p < 0.03$). In other study, patients with CHF and CSR had shorter survival than those with just CHF or SRBD or neither disorder (14–17). More recently, OSA has been also recognized in CHF and thought to have impact on outcome (18).

Patients with SRBD have activation of neurohumoral and inflammatory systems that are also activated in CHF (12) and increased the severity of CHF. In SRBD, several factors (hypoxia, hypercapnia, arousals) activate the sympathetic nervous system (SNS), especially in CHF patients. This sympathetic activation leads to hypertension, decreased heart rate variability, vasoconstriction. Intermittent hypoxia may directly impair cardiac contractility, further activate the SNS, leading to myocardial ischemia and arrhythmias and might increase the production of reactive oxygen species with subsequent ischemia–reperfusion lesions. Increased levels of atrial natriuretic peptide have been observed in SRBD patients, suggesting an increase in atrial tension. There are conflicting results about changes in levels of B-type natriuretic peptide (BNP) and whether it has a precise role or just reflects blood pressure variations. In this group of patients, inflammatory markers, C-reactive protein (CRP), interleukin-6 (IL-6), and tumour necrosis factor-a (TNF-a) are also increased. Moreover, increased levels of intracellular cell adhesion molecule-1 (ICAM-1) and vascular cell adhesive molecule (VCAM-1)

and decreased nitric oxide have been reported, suggesting endothelial injury and a state of increase oxidative stress. There is also evidence that SRBD leads to a prothrombotic state with increased levels of fibrinogen, plasminogen activator inhibitor, and enhanced platelet activity and aggregation. Left ventricle (LV) wall thickness has been shown to be increased in normotensive patients with OSAS compared with that in normotensive control subjects, suggesting that OSAS by itself can lead to left ventricular hypertrophy independently of the effect on blood pressure. Repeated negative intrathoracic pressure swings during obstructive apnoeas lead to increased wall tension and subsequent increase in LV afterload. Overdistention of the right ventricle leads to a decrease in preload caused by a leftward shift of the intraventricular septum. The net effect is a reduction in stroke volume and cardiac output, which is more pronounced in patients with CHF. In a canine model, OSA was associated with sustained decrease in LV systolic performance in previously healthy animals. These results suggest that OSA may be involved in the initiation of the CHF process. SRBD can cause PH leading to cor pulmonale and right ventricular dysfunction (19, 20). The potential mechanisms involved are increased pulmonary vascular tone secondary to hypoxic pulmonary vasoconstriction, hypoxia-induced endothelial dysfunction, and pulmonary vascular remodeling. PH is found in 27–39% of patients with OSA, tends to be mild, and its presence is associated with a lower daytime PaO_2 and oxygen desaturation during sleep. In animal models, intermittent hypoxic episodes like those mimicking SRBD, lead to pulmonary artery remodeling and PH. This suggests that SRBD should be considered in CHF patients with severe PH.

There are pathophysiological links between CHF and SRBD, suggesting CHF can induce SRBD. Breathing is normally controlled by a negative-feedback system in which an increase in CO_2 stimulates breathing and a decrease inhibits it. A prolonged circulation time proportionally related to dysfunction severity and recumbent position can lead to pulmonary congestion, increased sensitivity of chemoreceptors, hyperventilation, hypocapnia, suppression of the respiratory drive, and subsequent CSR. Patients with CHF may have increased sensitivity to CO_2, which elicits a large ventilatory response when its partial pressure rises. The consequent hyperventilation, by driving CO_2 below the apnoeic threshold, results in CSR. As a result, CO_2 rises again, which leads to an increase in ventilation. In this way, cycles of central apnoea and hyperventilation recur during sleep—CSR.

CSR patients were symptomatic and had a lower LV-EF than OSAS patients had. Oxygen uptake (VO2) was lowest in CSR patients as were 6-min walking distances (10).

QoL in CHF

Approximately 5 million Americans are currently living with CHF, and 550,000 new cases are diagnosed yearly. Because of dyspnea and fatigue, patients with CHF are often restricted in the performance of everyday activities, which gradually may lead to hypoactivity. Because of the lack of a cure for patients with CHF, there has been a progressive interest in the use of health-related QoL as complementary end-point to mortality and morbidity. CHF symptoms and activity status influence QoL negatively (21). Patients with CHF demonstrate a poor QoL compared with patients who have other congestive diseases, scoring poorly on measures of physical function, emotional wellbeing, and overall social function. QoL is significantly decreased with NYHA functional class (22). In a study by Juenger and Gott, NYHA class III reduced the scores of five of the eight QoL domains to around one third of those in the general population. The pattern of reduction was different in patients with congestive hepatitis C and major depression, and similar in patients on congestive haemodialysis (23). Compared with other congestive diseases, such as arthritis and congestive obstructive pulmonary disease, QoL has been demonstrated to deteriorate much more seriously in patients with CHF (24). Impairment is related to intolerance to exercise and symptom distress, impaired role functioning in marital and family relationships, diminished job functioning, and reduced social support (25–27). Poor QoL may have a negative affect on compliance to medical treatment and behavioural regimens (28) and thus result in further impairment of exercise tolerance, prognosis and QoL (21).

Depression is prominent, and high rates are found with dimensional instruments in hospitalized heart failure patients. Studies have shown that patients with CHF have high rates of depression compared with the general population; in addition, depression may confer a negative prognostic impact when present in CHF patients, with an increased risk of both rehospitalization and mortality. Reported prevalence rates have ranged from 11 to 25% for outpatients and 35 to 70% for inpatients. In contrast, 5–10% of the general population meets the criteria for depression (29). What remains largely conjecture, however, is why CHF patients display such a markedly elevated prevalence of depression. Some researchers believe that the connection may lie in shared pathophysiology. Neurohormonal activation, rhythm disturbances, inflammation, and hypercoagulability may all play a role in the development, progression and outcomes of CHF. Interestingly, each of these pathologic states is also seen in depressed patients. This suggests that physiologic states brought on by depression might hasten the development of CHF and worsen prognosis for established CHF or that a single underlying factor might affect both depression and CHF (30).

Psychosocial factors may also contribute. Depression is associated with medical non-compliance, a higher prevalence of smoking and lower levels of social support, each of which have been correlated with worse outcomes in CHF, which are also affected by SRBD (31). Patients with CHF and depressive disorder have a 2–3 times higher mortality. Readmission rates are also 3 times higher (32), and over a third of CHF patient's depression does not remit within 1 year after

discharge. Comorbid depression and CHF raise medical costs by 25–40% as well as hospitalization rates, medical costs and impairment of the NYHA status and daily activities (33, 34).

In CHF patients, non-compliance is a very important concern in response to complex medication, restrictive diet regimens and other lifestyle changes (35). Non-compliance with drug regimens leads to rehospitalization in 20–60% of CHF patients and up to a 2.6 times higher mortality (36–39).

Effect of SA on QoL and depression in chronic heart failure

Patients with sleep-disordered breathing in CHF have increased time in bed and poorer sleep quality. Patients with SRBD when compared with patients without SRBD are significantly sleepier. Despite the lack of subjective symptoms of daytime sleepiness, CHF patients with sleep-disordered breathing were objectively sleepier during the day and had reduced daytime activity with longer periods in bed and poorer sleep quality when compared with those without sleep-disordered breathing (40). SRBD has a potential role in the pathogenesis of CHF. High rates of CSR are found in patients with severe CHF, and equal proportions of OSAS and CSR are found in CHF patients referred to sleep clinics (41). Subjective sleepiness indexes of impaired cardiac function including Minnesota Living With Heart Failure Questionnaire scores, shuttle walk distance, and NT-BNP levels are higher in patients with SRBD than without SRBD. CSR patients had lower left ventricular function (EF), atrial fibrillation and severe left ventricular impairment increased the likelihood of SRBD (particularly CSR).

Depression and breathing disorders usually affect each other. In sleep apnea, depression was identified in more than 20% of patients. On the other hand, CHF favours the occurrence of even moderate SRBD, which correlates with the degree of depressive syndromes. Sleep disorders, a common clinical sign in depression, are also common in CHF, with fragmentation of sleep, excessive daytime sleepiness, and increased mortality. Cerebral hypoxia might be a neurobiological basis for depression, as more severe CHF patients often show central SA with CSR or obstructive SA (9, 12, 20, 42). The extent to SRDB and excessive daytime sleepiness are associated with impairment of QoL using the SF-36 as enrolled in the nation-wide population-based Sleep Heart Health Study (SHHS) (43). Men (11.6%) were significantly more likely to have SRBD compared with women (5.6%), whereas women (42.4%) were significantly more likely to report difficulty initiating and maintaining sleep than men (32.5%) were. Individuals with severe SRBD indicated significantly poorer QoL on several SF-36 scales. Daytime sleepiness was strongly associated with reduced QoL. Findings suggest (i) mild to moderate SRBD is associated with reduced vitality, whereas severe SRBD is more broadly associated with poorer QoL, (ii) subjective sleep symptoms are comprehensively associated with poorer QoL, and (iii) SF-36 mean score profiles for SRBD and sleep symptoms are equivalent to other congestive diseases in the US general population.

In our own study (44) on 69 consecutive ambulatory patients with stable HF (NYHA II–III, EF 25%), patients underwent two night polygraphies. Spiroergometry was performed, and patients were examined for sleep quality (PSQI), depressed mood (BDI) and health-related QoL (SF-36). The data were compared with 10 age-matched healthy controls and 11 patients with OSAS (AHI 14–29/h) not suffering from HF. Fifty-two percent were positively diagnosed for SRBD (AHI 16–30/h: 12 patients CSR, 5 patients OSAS, 9 patients mixed); 25 patients (48%) showed no relevant SRBD). Patients with CHF and SRBD had a significantly lower QoL in 6 of 8 subjective measures compared with patients with CHF without SBRD. There were no differences between patients with CHF and CSR, CHF with OSAS or CHF with mixed apnea. In particular, bodily pain, physical functioning and emotional functioning showed the largest impairment in the study group with CHF with SRBD as compared with CHF without SRBD. In patients with CHF and SRBD, there were significant correlations between the AHI and following scores of the SF-36: physical wellbeing ($r = –0.7$, $p = 0.0001$), physical role functioning ($r = –0.53$, $p = 0.006$), pain ($r = –0.53$, $p = 0.006$), general health ($r = –0.45$, $p = 0.02$), social functioning ($r = –0.6$, $p = 0.001$), but not for emotional functioning, emotional wellbeing or vitality. Furthermore, elevated depression rates in correlation to the AHI were only observed in patients with SRBD similar to patients with OSAS without HF. Patients without SRBD median BD score was 4.63 ± 2 points (range 0–8). In patients with CHF and SRBD, the median score was 11.6 ± 5 (range 8–17, $p = 0.0001$). There were no differences between patients with CHF and CSR, OSAS or mixed apnea. Thiry-one percent (8 patients: 5 men, 3 women) met the criteria for some syndromal depression on the basis of a score > 10 (0 patients > 20 points) similar to patients with OSAS not suffering from CHF reaching a score of 9.7 ± 5. There was a significant correlation in patients with CHF and SRBD between the AHI and the severity of depression ($r = 0.88$, $p = 0.0001$). There were no correlations between BDI and age, body mass index (BMI), EF or oxygen uptake. Our findings suggest that SRBD has a major impact on QoL, and disturbed sleep itself significantly contributes to depressive syndromes in patients with stable CHF. There were no differences between patients with CHF and OSAS, CHF with CRS or CHF with mixed apnea in our study group, showing that the appearance of SRBD leads towards reduction of life quality. The correlation of the AHI with most of the QoL measures and depressive syndromes indicates that patients with AHI indices (in our group all below 30/h) estimated their impaired physical and emotional health status lower as opposed to patients without SRBD. The data correspond to patients with OSAS without any heart condition showing the psycho-physiological impact

of even an AHI < 30/h in patients with CHF suffering from minor SRBD.

Despite patient education, lifestyle modification, and improved pharmacological therapy available for CHF, many patients have persistent severe symptoms. Commonly, these patients have intra- and interventricular conduction delays that are associated with cardiac mechanical dyssynchrony. This compromises ventricular function and is frequently associated with severe symptoms and poor prognosis (45, 46). The presence of CSR in patients with severe CHF (24 ± 6%) and conduction disturbance affects sleep quality (42) and reduces QoL compared with that in patients without CSR in severe CHF (47). Measurement of exercise capacity by spiroergometry and EF showed no difference between patients with and without SRBD.

SA and stroke

Stroke is the second leading cause of death worldwide and the leading cause of long-term disability. Strategies for stroke prevention, including the control of hypertension, treatment of atrial fibrillation, and smoking cessation, have reduced the disease burden, but stroke still remains an important public health challenge. The prevalence of sleep-disordered breathing with clinical signs and symptoms of SRBD were high in patients with acute ischemic stroke. Patients with nighttime stroke had more obstructive sleep-disordered breathing and a higher clinical probability of obstructive apnea events before stroke. These findings support the hypothesis that obstructive SA is a risk factor for ischemic stroke, particularly for strokes presenting at night (48, 49).

Prevalence of sleep-disordered breathing (SRDB) (AHI > 5) in acute stroke patients ranges between 44 and 95%, compared with the community prevalence, 9–35% for women and 8–57% for men (age range 30–60 years) (50, 51). The reduction in hypercapnic cerebral vascular reactivity that occurs in the morning after sleep is associated with an increased risk of cerebral ischemia and stroke (52).

A diminished vasodilator reserve in OSAS patients, particularly evident in the morning, could be linked to hyposensitivity of cerebrovascular chemoreceptors after the continuous stress caused by nocturnal hypercapnia (53). The effect of cerebral stroke on sleep and breathing has not been well defined. The diffuse cerebral symptoms such as cognitive deficits, depression or fatigue after hemispheric stroke mimic those present in patients with SA. Patients with stroke had abnormal sleep architecture with significantly lower slow wave sleep and rapid eye movement (REM) sleep when compared with controls. Sleep was fragmented because of the presence of increased respiratory disturbances. Stroke patients had a respiratory disturbance index (RDI) of 52 ± 10 events per hour when compared with 3 ± 1 in controls. Majorities of respiratory events were obstructive apneas and were associated with arterial oxygen desaturations and arousals. The pathogenic mechanism of sleep-disordered breathing in patients with hemispheric stroke seems to be related to the physiological effect of sleep on already compromised upper airway muscle control (54). There is significant improvement in the number of obstructive apneic events occurring in the stable phase of a first-ever ischemic stroke in patients with transient pharyngeal muscle alterations secondary to the neurologic lesion (55). Patients with dysphagia showed the largest number of obstructive apneic episodes in the acute phase, with a significant reduction in this type of apnea during the stable phase of stroke, coinciding with the recovery of pharyngeal muscle function. In contrast, nondysphagic patients showed no significant changes in nocturnal disordered breathing from the acute to the stable phase of stroke.

Patients with stroke have an increased incidence of obstructive SA compared with normal sex- and age-matched control subjects. Hypoxia and haemodynamic responses to obstructive SA may have predisposed these patients to stroke (56). In patients with acute ischemic stroke and SRBD (AHI > 30), age, male gender, BMI, diabetes, hypertension, coronary heart disease, Epworth Sleepiness score, and macroangiopathic aetiology of stroke were significantly higher/more common than in patients with AHI < 10 and associated with an increased post-stroke mortality. Multivariate analysis selected four independent variables associated with mortality: (i) age; (ii) AHI, with an implied 5% increase in mortality risk for each additional unit of AHI; (iii) involvement of the middle cerebral artery; and (iv) the presence of coronary disease (57).

Furthermore, SRBD with an AHI > 20 is associated with an increased risk of suffering a first-ever stroke over the next 4 years (58). The presence of SRBD has been linked with poorer long-term outcome and increased long-term stroke mortality. About 20–40% of stroke patients have sleep–wake disorders, mostly in form of insomnia, excessive daytime sleepiness/fatigue, or hypersomnia (increased sleep needs). Depression, anxiety, SRBD, and stroke complications, and medications may contribute to sleep–wake disorders, and should be addressed first therapeutically (59).

Jonsson et al. (60) examined longitudinal changes of QoL covering physical and mental factors in an unselected group of stroke patients. Depressive symptoms are common in determining QoL of stroke patients. Fatigue is a common complaint after stroke (61) and associated with impaired QoL. It occurs in 39–72% of stroke survivors. Some studies show a severe functional impact of this symptom as well as a high mortality rate. Available evidence concerning associated factors is limited, but fatigue is clearly multifactorial. Some studies show that limited exercise capacity, increased gait energy cost, sleep-disordered breathing and sleep disorders can be related to physical fatigue. Other studies show a link between fatigue and depression (62), which are well documented in medically ill patients. Fatigue is also a hallmark depressive symptom and associated with obstructive SA (63, 64). It is important to be aware of the occurrence of fatigue after stroke, because these symptoms are common,

they impair QoL and they are potentially treatable. Post-stroke depression may coexist with pain and fatigue. In univariate analysis, fatigue was also associated with sleep disturbances (65).

Treatment of sleep-related breathing disorders in CHF and stroke and Effect on QoL

Management of heart failure starts with an accurate diagnosis and requires a rational combination drug therapy (66, 67) and non-pharmacological management (education, fluid control, weight monitoring, and training). An integrated and comprehensive heart failure intervention program that includes provision of adequate pharmacologic treatment, exercise training, patient information, and counselling, as well as emotional support, is recommended (68) and can be improved by pharmacologic intervention (69), exercise training (70), and heart failure management programs in highly selected patients (71).

In end-stage heart failure, heart transplantation should be considered if possible, as heart transplantation declines SRBD because of recovery of left ventricular function. We reported on a 55-year-old male patient with dilative cardiomyopathy (NYHA IV) and CSR (RDI: 40/h, lowest desaturation 76%) and body position-dependent snoring. Three weeks after heart transplantation, sleep analysis was repeated and demonstrated a lack of evidence for periodic breathing. Daytime sleepiness improved significantly (Epworth Sleepiness Scale: 6 points). Three weeks after normalizing left ventricular function, a complete recovery from severe CSR was observed (72). Adequate therapy of CHF sufficiently abolishes any CSR and should be optimized before additional treatment of sleep-related breathing disorders is initiated.

Treatment of OSAS in heart failure

Basic treatment for OSAS in CHF included a lateral sleeping position, avoidance of alcohol and sedatives, and weight loss (73) possibly through a decrement in upper airway collapsibility (74). At present, there is no effective drug therapy for OSAS in heart failure. Oral appliances or surgery are not as effective as CPAP, which requires a flow generator and mask (75, 76).

CPAP is the treatment of choice, which eliminates upper airway obstruction, apneas, hypoxia, sympathetic activation, and arousals from sleep, while lowering blood pressure and heart rate (77, 78). In patients with heart failure and coexisting obstructive SA, CPAP also increases left ventricular EF (79). CPAP improves functional capacity (NYHA class, 6 min walk-test), QoL and cardiac function. CPAP reduced overnight urinary norepinephrine levels and improved general and disease-specific QoL (fatigue, disease mastery, and emotional wellbeing as measured by the chronic heart failure questionnaire). Improvement in dyspnoea scores or exercise capacity was not observed (80). It provides non-invasive mechanical assistance to the failing heart by several mechanisms: increasing intrathoracic pressure, reducing LV transmural pressure, which reduces LV afterload, augmenting preload, stroke volume and cardiac output; reducing mitral regurgitation and ANP levels, possibly through reverse remodelling; decreasing sympathetic tone and improving nocturnal baroreflex sensitivity; assisting inspiratory muscles and increasing end expiratory lung volume (81, 82). In patients with OSAS, compliance with CPAP treatment is between 50 and 80% and the average duration of use ranges from 3.4 to 4.5 h per night (83).

These studies, evaluating patients on optimal therapy for CHF, suggest that CPAP can improve cardiac function in CHF patients with systolic dysfunction. However, there are some limitations as the studies only included a small number of patients and long-tem effects and mortality were not evaluated. Larger randomized trials are warranted to evaluate the long-term outcome after CPAP in patients with CHF and SRBD. Oral appliances such as mandibular and tongue advancements can be useful, but they are less effective than CPAP. They should be considered for patients who refuse or fail to tolerate CPAP and for the mildest cases.

Treatment of central SA (CSR) in heart failure

The best way of treatment for CSR remains controversial. Optimization of CHF therapy can be effective and should be the first approach in these patients. However, evidence suggests CSR can also have adverse cardiovascular consequences and specific treatment can be beneficial. Treatments can be divided into those which stimulate ventilation and override the periodic breathing pattern and those directed towards improving underlying cardiac function. Inhaled carbon dioxide, inhaled oxygen and theophyline reduce the severity of CSR showed improvements of LV function and QoL in a small study population over a short period, but a long-term effect has not been demonstrated (84). Agents that improve cardiac function have had greater success in the management of CSR. Captopril reduced the severity of CSR by 50% over a 4-week period in an observational study of eight patients (85).

In short-term, single centre, randomized trials lasting 1–3 months, CPAP attenuated central SA in chronic heart failure and reduced daytime levels of atrial natriuretic peptide, increased left ventricular EF and improved patient's QoL (86, 87). The Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure (CANPAP) study evaluated the effect of CPAP on survival rate without heart transplantation in severe heart failure. CPAP attenuated central SA and improved nocturnal oxygenation, left ventricular function, sympathetic nervous activity and exercise performance, but it did not demonstrate a beneficial

effect of CPAP on morbidity or mortality (88). After 6 months, the study was terminated because of an early divergence of the transplantation-free survival and rate of death-curves favoring the control group. On the basis of this finding, the Consensus conference recommendation on heart failure 2006 pointed out that CPAP should not be used for the treatment of central SA in heart failure patients because of lack of evidence (class III, level B) (67).

Otherwise, small studies have shown that the AHI of patients and QoL with heart failure with CSR can be improved by adaptive servoventilation (89, 90), but these effects have only been demonstrated in small, brief trials. Thus, the search for alternate therapies continues.

Cardiac pacing has also been proposed as a potential effective therapy. Garrigue et al. (91, 92) subjected 15 patients with an AHI of greater than 15/h, and with a relatively equal distribution of CSR and obstructive SA, to this nocturnal pacing protocol. Obstructive apneas fell from 6 to 3/h, central apneas from 13 to 6/h, and the overall AHI from 28 to 11/h. They proposed that surges in parasympathetic tone caused marked nocturnal heart rate variability, and suggested, without providing evidence, that atrial pacing might stabilize respiration by preventing this nocturnal vagotonia. However, as the authors admitted, it would be difficult to explain the observed reduction in obstructive events on this basis. Another possibility is that an improvement in cardiac output with atrial overdrive pacing led to reductions in lung to chemoreceptor circulation time and left ventricular filling pressure, and thereby stabilized breathing by reducing loop gain and preventing the hyperventilation that initiates CSR (93).

If so, then one would expect a greater effect on CSR than obstructive SA where respiratory control system instability plays less of a pathophysiologic role. Could this be a novel therapy for SA, and a new indication for cardiac pacing? In other studies (94,95) neither AHI-reduction, oxygen desaturation, sleep architecture, urinary norepinephrine excretion, nor brain natriuretic peptide were affected by overdrive pacing at either rate. There was no specific effect on the frequency of obstructive or central events compared with CPAP. However, where might cardiac pacing fit in the therapy of SA? Neither study addresses patients with SA and heart failure. In such subjects, the potential role of respiratory control system instability related to circulatory delay and hyperventilation is greater than in the subjects included by these two groups.

Randomized controlled trials generally suggest that cardiac resynchronization improves outcomes in patients with heart failure because of left ventricular systolic dysfunction and cardiac dyssynchrony. Cardiac resynchronization therapy (CRT) uses biventricular pacing to attempt to synchronize the activation of the septum and left ventricular free wall, and to improve the overall left ventricular function. The left ventricular free wall can be paced percutaneously through the coronary sinus in the majority of patients (96, 97). CRT reduces mortality and hospitalization for worsening heart failure (98). Oxygen uptake, maximum exercise capacity and EF increased on CRT. This was associated with an improvement in QoL as evaluated with the Minnesota-Living with heart-failure questionnaire and Karolinska Quality of life Questionnaire (98). Therefore, patients with symptomatic heart failure (NYHA III–IV) despite optimal medical therapy who are in normal sinus rhythm with conduction disturbance (QRS duration of 120 ms or longer) and an EF of 35% or less, should be considered for CRT as class I, level A-recommendation (67).

Biventricular resynchronization pacing holds more promise on SA than atrial overdrive pacing because of its more pronounced haemodynamic benefits. In our small, nonrandomized study of 24 patients (7 females, 62 ± 11 years) with heart failure (mean left ventricular EF of $24 \pm 6\%$) with left bundle branch block (QRS duration 173 ± 22ms) and CSR, the effect of CRT on the severity of CSR was studied. It was hypothesized that CRT, through its known beneficial effects on cardiac function, would stabilize the control of breathing and reduce CSR. CRT lowered the AHI from 19.2 to 4.6/h, and simultaneously, sleep quality improved as measured by the Pittsburgh Sleep Quality index (PSQI, 10.4 ± 1.6 to 3.9 ± 2.4, $p < 0.001$) (99). Our study was the first to show that CRT improves cardiac function and reduces the severity of central SA with CSR in heart failure patients with ventricular conduction delay. A significant decrease of the AHI and a significant increase in SaO_2min was observed during CRT without the application of any non-invasive ventilatory support.

Gabor et al. (100) were able to report similar results in patients who were eligible for CRT and already received optimized medical treatment for CHF.

These beneficial effects could be explained by the CRT-related improvement in cardiac function. It has been shown that CRT leads to a more efficient left ventricular contraction accompanied by a reduction in functional mitral regurgitation. This may in turn result in reduced pulmonary congestion as a triggering factor of the reflex mechanisms responsible for CSR.

In an additional study, we also investigated the effect of CRT on QoL and depression in patients with heart failure and CSR (101). Both depressive mood and congestive CHF affect clinical status in important ways. The most important finding of this study was that CRT had an impact on depressive syndromes and qualities of life by effect on sleep quality and AHI in patients with sleep-related breathing disorders, mostly CSR. Patients with HF and CSR showed more reduced QoL in 7 of 8 subjective measures with largest impairment in bodily pain, physical role and social functioning compared with patients without SRBD. In both groups, QoL was improved with CRT, but patients with CSR had more benefit in most measures compared with patients without SRB. Patients with obstructive SA did not benefit from CRT with regard to AHI association and depressed mood (101). Additionally, we found a significant decrease in ventilatory response to exercise measured by the VE/VCO2 slope in CSR patients (47, 99). This is possibly based on a reduction in circulation time between lungs and peripheral chemo receptors, and a decrease

in chemo reflex sensitivity to carbon dioxide. Therefore, our findings suggest that impaired left ventricular function may be the primary cause of the reflex cascade leading to CSR. CRT showed effect on CSR and sleep quality by reduction of end diastolic LV-volume with improvement of cardiac output. Improvement of AHI also results in improvement of depressed mood and possible reduction of sympathetic activation. As elevated VE/VCO2 slopes and CSR (13, 58) are associated with increased mortality in heart failure patients, the interruption of this vicious circle of CSR may have a positive effect on prognosis.

In conclusion, cardiac resynchronisation therapy is associated with a reduction in CSR, which may contribute to improved clinical outcome in patients treated with cardiac resynchronisation therapy, as Bradley and colleagues (88) reported: treatment with CPAP in patients with CHF and CSR did not affect morbidity and mortality, although several functional parameters significantly improved.

Both ICDs and CRT pacemakers may significantly reduce overall mortality in selected CHF patients, as ventricular arrhythmia is common in patients with heart failure and CSR (101). Furthermore, it has recently been demonstrated that CRT alone is able to not only improve sleep quality, QoL and symptomatic depression, but that it may also reduce the AHI (99), while avoiding any potential detrimental effects of CPAP on cardiac function. Therefore, in order to reduce morbidity and mortality, it might be more promising to target sudden death and left ventricular failure more directly before initiating CPAP therapy in these patients (101).

Whether SA could become an independent indication for some form of cardiac pacing remains an open question.

Treatment of SA after stroke

CPAP therapy showed significant improvements in certain objective and subjective sleepiness, measures of QoL and cognitive function in the treatment of OSA in adults. In the *Cochrane Database Syst Rev* 2006, the effects of CPAP in the treatment of OSA in adults were assessed (102); twelve trials involving 475 people were included. Most studies had methodological shortcomings and were of crossover design. Compared with placebo, CPAP showed significant improvements in objective and subjective sleepiness and several QoL and depression measures. In a study in mild to moderate Alzheimer's disease and SRBD, CPAP reduced subjective daytime sleepiness and improved QoL (103).

Hsu et al. (104) randomized patients with stroke with AHI > 30 with predominant OSA or hypopnoea to either CPAP treatment or conservative treatment for 8 weeks. Outcomes were measured blind to treatment allocation at 8 weeks and 6 months after the stroke. The primary outcome was physical function on the Nottingham Extended Activities of Daily Living Scale. Despite intensive efforts, objective use of CPAP was poor, averaging 1.4 h a night. CPAP treatment resulted in no significant improvements in the primary outcome or in neurological function or sleepiness, and in poorer health status on some measures, which is possibly based on poor acceptance of CPAP treatment.

Hui et al. showed corresponding results in Chinese patients with ischemic stroke and obstructive SRBD (105) with poor CPAP acceptance, and partial spontaneous improvement at 1 month, which, in many cases, is different from classic obstructive SA syndrome, and this is reflected by the lack of significant sleepiness. Bassetti et al. (106) prospectively studied 152 patients (mean age 56 ± 13 years) with acute ischemic stroke. Continuous positive airway pressure (CPAP) treatment was started acutely in patients with SRBD. Initial AHI decreased in the subacute phase. CPAP was started in 51% and continued chronically only in 15% of SRBD pts. Therefore, SA after stroke is treatable, but there is only a small acceptance of CPAP.

Palombini et al. (107) prospectively evaluated the acceptance of nasal CPAP by recent stroke patients with OSA. The majority of OSA stroke patients rejected CPAP treatment. Subject dropout was related to difficulties with CPAP usage as perceived by patient and family members, facial weakness, motor impairment and increased difficulties and discomfort with usage of full-face mask (108). Demographic data, vascular risk factors, clinical manifestations associated to SA-hypopnea syndrome and neurological parameters were recorded in a group of patients presenting with acute ischemic stroke at least 2 months previously. Two groups were defined: patients who could tolerate CPAP (group 1) and patients who could not tolerate CPAP after 1 month of initial adaptation (group 2). The incidence of new vascular events was evaluated throughout follow-up (18 months) in all patients, with an analysis of the role of CPAP in protecting the patients against such events. Ninety-five patients were studied. Only 29% tolerated CPAP. As the incidence of new vascular events was greater in group 2 (6.7%) versus group 1, intolerance of CPAP increased the probability of a new vascular event fivefold. As it has been shown that CPAP treatment during 18 months in patients with an AHI ≥ 20 afforded significant protection against new vascular events after ischemic stroke CPAP treatment should be advocated for patients with stroke only if they have symptoms of SRDB, because acceptance of CPAP in these trials was poor. Fatigue is common after stroke and related to impaired QoL and possibly associated with SA, therefore further trials are needed to evaluate CPAP treatment, fatigue and improvement of acceptance.

Issues that need to be addressed by future research:

- The presence of sleep apnea affects quality of life, depression, and mortality and presents another treatment opportunity in CHF and stroke. There is now a burgeoning field of evidence that respiratory support in CHF or stroke or cardiac pacing in CHF for

these patients has considerable physiological benefits. Larger longer term studies are required to determine whether these benefits have an impact on mortality and QoL. Increased awareness of the prevalence and pathophysiological implications of SRBD is required: by health come professional in CHF and stroke are essential to promote and encourage the further development of this facet of treatment.

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Sleep and Quality of Life in Cardiac Surgery

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Summary Cardiac surgical procedures, especially coronary artery bypass surgery used to treat coronary artery disease (CAD), is most frequently utilized in the USA, but utilization of this procedure is increasing in countries that have not in the past used such high-technology health care interventions. Most people experience improvements in multiple dimensions of quality of life, especially those associated with mobility and physical activity. Sleep disturbance is common pre-operatively and extends through the recovery period, but appears to improve over the long term and may contribute to various dimensions of quality of life. The purposes of this chapter are to review the literature on dimensions of quality of life and sleep and the relationships between sleep and quality of life among cardiac surgical patients and to propose implications for future research.

Keywords Sleep · sleep disorders · quality of life · coronary artery bypass surgery · actigraphy · hospitalization

Learning objectives:

- To recognize the prevalence of sleep disturbance in people who have undergone cardiac surgery.
- To evaluate changes in sleep and their association with recovery of function over the course of cardiac surgery.
- To evaluate age-related changes in sleep after cardiac surgery.
- To evaluate factors that predict sleep quality after cardiac surgery.

Introduction

Cardiac surgical procedures, especially coronary artery bypass (CABS), is common in the USA and increasingly utilized throughout the world (1). CABS is the most commonly performed cardiac surgical procedure and continues to be the standard of care for coronary disease of the left-main and patients with 3-vessel disease (2), despite newer less-invasive procedures, such as percutaneous coronary intervention. CABS is touted as the means to improve quality of life among patients with ischemic heart disease. Disturbed sleep also appears to be common in these patients, and there is significant evidence that sleep and sleep disorders are associated with many dimensions of quality of life in the general population, as well as people with cardiovascular disorders (3–6). Therefore, the purposes of this chapter are to review the literature on dimensions of quality of life and sleep and the relationships between sleep and quality of life among adult cardiac surgical patients and to propose implications for future research. This review will focus on research conducted on adults who undergo CABS. Studies of heart transplantation are not included because of the smaller number of these procedures and the differences associated with their post-operative management.

Nature of Sleep in Cardiac Surgical Patients

As summarized in two recent publications (7, 8), cardiac surgical patients report poor nocturnal sleep quality, short duration, high degrees of fragmentation, and large amounts of daytime sleep, especially during the first few post-operative days (9–12). Mean sleep efficiency for groups of cardiac surgery patients during the early post-operative period has been reported in the range of 52–58% (9, 13)—well below the sleep efficiency levels associated with restorative sleep. Polysomnographic sleep studies (9, 14–16) documented high

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degrees of sleep fragmentation and little REM or slow wave sleep in small groups of patients. Awakenings occurred frequently and were not always associated with external stimuli. During the early post-operative period, as much as half of daily sleep occurs during the day (9–11, 17). Although the extent to which daytime sleep (napping) has a deleterious impact on post-surgical outcomes is not known, efforts to measure the total quantity of sleep must take this circadian pattern into account. Taken together, these findings indicate that the circadian patterning and continuity of sleep appear to be severely disrupted during the early post-operative time period.

Sleep appears to be dynamic in the weeks and months after cardiac surgery. Redeker and colleagues (11) reported that sleep became less fragmented and more consolidated during the nocturnal period (reflecting less daytime napping) toward the end of the first post-operative week, but there was no difference in total sleep occurring over the 24-h day. In a subsequent study that included 26 men and women, people over the age of 65 years had poorer sleep efficiency and more prolonged nocturnal awakenings, as well as poorer self-reported sleep than middle-aged participants over the first 5 post-operative days (18). However, the sleep continuity of both groups of patients improved over time. These findings extended the findings of an earlier study of self-reported sleep in cardiac surgery patients in which the investigators found improvements in sleep effectiveness and sleep supplementation (less napping), but no improvements in sleep effectiveness between the third and the sixth post-operative mornings (17).

Changes in sleep continue after the first post-operative week and appear to parallel improvements in functional status associated with recovery. Edell-Gustaffson and colleagues (9) found that the proportion of sleep occurring during the daytime continued to decrease through the first post-operative month in 38 male patients. Sleep efficiency was higher, and there was less stage 1, more delta and REM sleep, and fewer arousals at 1 month compared with the second post-operative night. Among women cardiac surgery patients, improvements in sleep consolidation and reductions in daytime sleep, as measured with wrist actigraphy, continued through the sixth month after hospital discharge (11). These changes were consistent with self-reported sleep quality (11) in women and men (9). Among a group of 72 men and women, sleep fragmentation, measured with wrist actigraphy, and self-reported sleep quality improved from the first through the eighth post-operative weeks (13). The absence of a difference in self-reported sleep quality at 8 weeks compared to the pre-operative assessment suggests that perceptions of sleep had returned to the pre-operative level by this time period. However, the duration of the nocturnal sleep period, efficiency, and nocturnal movement remained poorer at 8 weeks than during the week before surgery. Therefore, objectively recorded sleep disturbance, but not perceptions of poor sleep, appears to persist in some patients beyond the eighth post-operative week. These differences may reflect greater sensitivity of the wrist actigraph compared with self-report as measured by the Pittsburgh Sleep Quality Index, but may also underscore the importance of considering objective and subjective attributes of sleep.

There has also been some interest in examining sleep patterns at time frames more distant from the early post-operative period. Unlike sleep patterns during the early post-operative period that likely reflect the profound physiologic changes and discomforts associated with early recovery, these assessments are more likely to reflect improvements in cardiovascular status associated with revascularization as a result of the surgical procedure. Investigators for three studies noted improvements in post-operative self-reported sleep at the sixth post-operative month (9, 19). Nevertheless, as many as 68% of patients continue to report disturbed sleep at this time period (20).

Data on the nature of sleep at 12 months are somewhat contradictory. Researchers (10, 21) found improvements at 12 months compared with the pre-operative period. However, Lukkarinen and colleagues (19) found that self-reported sleep quality decreased at 12 months, compared with 6 months, and others found that approximately 40% reported sleeping "poorly" at least some of the time at 12 months (22). In the study with the longest post-operative follow-up, Caine and colleagues (23) found that self-reported sleep, measured with the Nottingham Health Profile, deteriorated slightly at 5 years compared with the first year, but remained improved over the pre-operative assessment. The time frames of these studies—well beyond the period of post-operative recovery—suggest that some, but not all, cardiac surgical patients may experience beneficial effects on sleep because of the surgical procedure. Given the absence of comparison groups who did not undergo cardiac surgery, it is not clear how much of the deterioration in sleep may have resulted from factors, such as new health problems or advanced age, rather than the CABS. It is also likely that these findings are biased toward the experience of patients who recovered successfully and did not have severe complications, significant disturbance in cognitive function, or prolonged hospital stay.

Factors associated with Sleep after Cardiac Surgery

The dynamic nature of sleep across the period of early recovery is likely to reflect the physical and psychological trauma of the surgery itself and associated pain and other discomforts. As described in our earlier work and depicted in our published organizing framework (8), influences on sleep appear to be multifactorial over the course of recovery. Demographic and developmental characteristics of the individual (age, gender), comorbid health problems, and cardiovascular disease are likely to contribute. Factors associated with illness and treatment, such as symptoms (e.g., pain), emotional

response, medications, and the hospital environment have been proposed as influences. For example, Simpson and colleagues (24) found that self-reports of inability to perform usual routines, inability to get comfortable, pain, noises, and procedural care were associated with self-reported sleep quality during hospitalization after CABS surgery. However, the evidence to support the relationships between these factors and sleep patterns among cardiac surgical patients and other groups of hospitalized patients is based primarily on clinical observation and small bivariate correlational studies (8, 25). There have been few reports of studies that employed objective measurement of sleep or environmental conditions, such as light or noise levels, and there has been little experimental or prospective longitudinal work in this area.

An important, but understudied, question is the extent to which sleep during the recovery period reflects underlying primary sleep disorders, such as insomnia, sleep disordered breathing (Cheyne–Stokes breathing and obstructive sleep apnea/hypopnea syndrome), restless leg syndrome, or periodic limb movements during sleep. These conditions are quite common in middle-aged adults, despite growing evidence of a higher prevalence in patients with hypertension and coronary artery disease (CAD). Therefore, it seems logical that these primary sleep disorders are also likely to be prevalent among patients presenting for surgical cardiac procedures because of shared risk factors (e.g., obesity, diabetes, and post-menopausal status), and unlikely to be corrected by the cardiac surgical treatment. However, there has been little systematic study of the impact of these conditions on post-operative sleep, recovery, or quality of life in cardiac surgical patients.

A few investigators have compared post-operative sleep with pre-operative/baseline levels of sleep. Patients who retrospectively reported sleep disturbance at home were no more likely than other patients to report sleep disturbance in the early post-operative period. However, pre-operative sleep duration was associated with sleep duration during hospitalization (26). In a prospective study, we (13) found that pre-operative self-reported sleep quality and actigraph-recorded sleep efficiency and daytime sleep duration explained 12–18% of the variance in post-operative sleep, 11–28% of the variance at the fourth week, and 20–44% of the variance in sleep at the eighth week, after statistically controlling for the effects of age and gender. The increasing proportion of variance explained at the eighth week suggests a partial return to habitual sleep patterns by the eighth week and the withdrawal of the effects of early post-operative discomforts. However, the large proportion of unexplained variance suggests that there are other unmeasured potential influences.

Research on the sleep of cardiac surgical patients has spanned a period of almost 40 years, beginning with early studies that focused on the intensive care environment [e.g., Woods (27)]. Since that time, there have been many changes in the nature of the surgical procedure itself, use of cardiopulmonary bypass, anesthesia, and pain management, as well as changes in the hospital environment and indications for the various surgical procedures. These factors, separately and in combination, are likely to have an impact on post-operative sleep. Differences in treatment practices suggest the difficulty in generalizing the findings of earlier studies to the experience of today's patients, but also suggest the need to consider changes in these characteristics of the surgical experience on sleep. For example, Hedges examined the sleep of patients who had undergone CABS surgery performed without cardiopulmonary bypass (OPCAB) and found that nocturnal sleep was short and fragmented during the early post-operative period (28). However, sleep was less fragmented in the OPCAB patients compared with patients who had undergone sleep using traditional cardiopulmonary bypass (29) during the first post-operative week. Given the absence of longer term follow-up, there is a need for longitudinal studies and clinical trials to evaluate the persistence of these differences over time, as well as other variations in surgical technique and patient care management. Unstudied are the effects of global and regional and global differences in patients who undergo CABS (high risk vs. lower risk patients) or differences in post-operative care and rehabilitation practices.

Strategies to Improve the Sleep of Cardiac Surgical Patients

Despite acknowledgment of the problem of disturbed sleep in cardiac surgery patients for many years, there have been few investigations of sleep-promoting interventions for this group of patients. Only two studies have been reported in the literature, and these have focused on the early post-operative period. Cardiac surgery patients who participated in two daily sessions of a music video with soft instrumental music for two post-operative days after cardiac surgery reported better sleep quality on the third post-operative morning than the control group who had only a rest period. There was a non-significant trend for the third group, exposed to audio-recorded music, to have improved sleep compared with the control group (30). Among cardiac surgical patients, exposure to recorded ocean sounds, used as white noise to mask noxious sounds improved self-reported sleep depth, awakenings, and return to sleep in the experimental group compared with a control group (31). However, objective measures were not obtained, the control group did not receive a comparable level of attention, and the study was not blinded (32). Both these studies considered reduction of sleep disruption because of external stimuli, but did not address characteristics of the patient (e.g., aging, gender), co-morbidity, or primary sleep disorders that might also contribute to sleep during the early post-operative period. Future studies are needed of the effects of pharmacological and behavioral sleep-promoting interventions across the trajectory of recovery after hospital discharge, given evidence that sleep disturbance persists for

weeks and months after the surgical procedure. These interventions should be targeted at the factors that contribute to disturbed sleep, but also based on a sound understanding of the specific nature of the characteristics of sleep and sleep disorders in these patients.

Given the need for cooperation of study participants with any sleep research protocol, especially one with a longitudinal design, it is likely that previous studies are biased toward study participants who had good post-operative results. Those with significant post-operative complications may be less likely to enroll in studies of sleep over recovery, and less likely to be willing and able to adhere to the study protocols, especially those that employ repeated measures or objective measurement, such as wrist actigraphy or polysomnography. Therefore, a major limitation of past research has been the inability to generalize the findings to cardiac surgical patients with more complicated recovery. There is a need to specifically address the needs of these individuals, as they may be at highest risk for both poor sleep quality and poor quality of life.

Health-Related Quality of Life after Cardiac Surgery

Health-related quality of life (HRQOL) is a construct that has been defined in many ways, but the dimensions of physical functioning, social functioning, role functioning, mental health, and general health perceptions, as well as vitality, pain, and cognitive functioning have often been described as components (33), and many studies of cardiac surgery have used various conceptualizations of these dimensions—whether or not they use the label "quality of life." Elliott and colleagues reported that several aspects of quality of life deteriorated in a group of Australian cardiac surgery patients at the time of hospital discharge, compared with the pre-surgery period, but improved significantly at 6 months post-discharge (34). However, mental health and social functioning deteriorated. For most people who have undergone cardiac surgical procedures, many aspects of HRQOL, especially physical function, appear to improve during the year following surgery (19, 22, 35–37), with some deterioration in physical mobility and energy at 5 years because of revascularization, but continued reports of better function compared with pre-operative baseline levels (23).

A limitation of the majority of the recent studies of quality of life in cardiac surgery patients has been the absence of comparative data obtained from people who did not have cardiac surgery. To address this, Lukkarinen (19) compared CABS patients with angioplasty and medically treated CAD patients. and found that the quality of life of CABS patients and angioplasty patients improved on the dimensions of energy, pain, and mobility at 6 and 12 months compared with the pre-operative period, unlike patients who received medication management only and experienced deterioration in energy and mobility. Follow-up of this cohort of patients at 1 and 8 years after intervention revealed that energy, pain and mobility continued to be improved at 8 years, compared with baseline (38). The investigators attributed the differences in these quality of life responses to improvements associated with the beneficial effects of revascularization. However, beneficial effects are not achieved for all patients. Hunt and colleagues reported that 92% of patients reported that they benefited from CABS, although 22% of the total sample reported poor or very poor quality of life at 1 year (22). Continued research is needed to assist in identifying those patients who might be at highest risk for poor outcomes.

Gender appears to be one factor that influences recovery and successful revascularization, with women having somewhat slower recovery and more symptoms, such as shortness of breath, fatigue, depression, sleep disturbance, swelling, and anxiety, and lower physical activity than men (39–41). Women reported greater improvement in functional status than men at the third post-operative month than men, despite greater pre-operative functional limitations (42). However, pre-operative quality of life as well as comorbid conditions such as diabetes (43) also appear to contribute to post-operative decrements in quality of life, and women's pre-operative quality of life (44) was poorer pre-operatively.

Relationships between sleep and quality of life

Sleep appears to be closely associated with quality of life in patients who have undergone cardiac surgery. In some cases, sleep has been conceptualized as a component of quality of life. For example, several studies used the Nottingham Health Profile (9, 19, 38, 45) and the Sickness Impact Profile (46) as primary measures of quality of life—both of which include sleep–rest as a dimension. Others have considered the extent to which sleep patterns or sleep disturbance are correlated with or predict various dimensions of health-related quality of life (9, 14, 47). These discrepancies highlight the need for a clear conceptualization of the construct of quality of life in order to understand its associations with sleep but underscore the potentially close connections between sleep and quality of life.

Circadian patterns of activity-rest (of which sleep patterns are a component), measured with wrist actigraphy, were associated with quality of life and length of hospital stay at the end of the first post-operative week in a group of 25 female CABS patients (47). Follow-up of 13 of these women up to the sixth post-operative month revealed that circadian rhythms of activity rest corresponded with improvements in the Sickness Impact scale (11). However, the sample was too small for parametric correlational analyses. Therefore, the size of the correlation between activity-rest and quality of life could not be evaluated.

In an effort to explore the specific aspects of sleep that might contribute to health-related quality of life, we

conducted a study of 72 cardiac surgical patients, beginning during the pre-operative period and extending to the eighth post-operative week. Self-reported sleep disturbance (Pittsburgh Sleep Quality Index) and actigraph-measured sleep efficiency were moderately correlated with the physical function component of the SF-36 at 4 and 8 weeks after surgery. Sleep efficiency and self-reported sleep quality were related to physical function at 4, but not at 8 weeks. Self-reported sleep quality was correlated with the mental health component of the Medical outcomes Study Short-form 36 (48). Regression analysis revealed that sleep quality (self-report) and sleep efficiency (actigraph) explained 16% of the variance in physical function at 4 weeks and sleep quality explained 8% of the variance in self-reported physical function at 8 weeks, after controlling for the influence of aging, gender, and pre-operative physical function. These findings, obtained in the first prospective study to employ objective measurement of sleep, suggest that sleep may be most relevant to self-reported physical function during the first post-operative month, and also highlight differences between sleep assessment using self-report versus objective measurement, as the highest correlations were found between self-reported sleep and self-reported physical function. Future studies are needed to evaluate the extent to which primary sleep disorders and polysomnographic attributes of sleep contribute to quality of life after cardiac surgery.

Sleep may contribute to long-term quality of life after cardiac surgery. In a cross-sectional study of quality of life at 12 months after cardiac surgery, 17.6% of participants reported poor or very poor sleep quality and these ratings were associated with a 4.8-fold likelihood of poor to very poor global quality of life, as measured by the SF-36. Patients who had both pain and poor sleep quality were seven times more likely to have poor global quality of life (22). However, the causal direction of these findings could not be evaluated and the measurement of sleep quality with a single item quality scale and the global quality of life scale obscured ability to detect specific attributes of sleep.

Mental health is also an important component of quality of life, and mood disorders, particularly anxiety and depression, appear to be common after cardiac surgery (49–51) and most salient in women and younger patients (52). Doering and colleagues (53) found that clinical depression decreased from 31% of women during the pre-operative period to 16% at 1 month and 13% at 6 months, a trend that continued up to 1 year, as reported by others (54). The importance of mental health to quality of life is illustrated in a recent study of 90 cardiac surgical patients in which pre-operative depressive symptoms predicted 6-month physical function and post-operative increases in depression predicted psychosocial functioning at 6 months (55). One group of investigators examined the association of stress experienced in the intensive care unit during early recovery with post-traumatic stress disorder (PTSD). PTSD predicted both physical and mental health components of health-related quality of life at 6 months after surgery (56). These findings suggest the potentially enduring effects of experiences during early recovery on long-term outcomes.

Insomnia is common in persons with mood disorders and may be both a precursor and a consequence. Therefore, the potential interactive or overlapping effects of mood disorders and sleep problems should be considered. Redeker and colleagues (48) found that self-reported sleep disturbance explained a small percentage of the variance in mental health at 4 and 8 weeks after cardiac surgery. However, objective measures of sleep were not associated with mental health. In a study of patients with stable heart failure, some of whom had undergone cardiac surgery in the past, elevated levels of depressed mood in the heart failure patients compared with a group who did not have heart failure were explained by symptoms, such as insomnia, fatigue, and dyspnea (57); therefore, it may be useful to consider the interactive effects of these symptoms, when evaluating mental health of recovery cardiac patients.

Sleep patterns and quality of life are dynamic phenomena over the course of recovery and rehabilitation after cardiac surgery and appear to be closely related. Despite more than 30 years of interest in sleep and quality of life after cardiac surgery, significant questions remain unaddressed but essential to improving clinical intervention for both sleep and quality of life.

Issues that need to be addressed by future research:

- Is there a causal relationship between poor sleep and quality of life among patients who undergo cardiac surgery?
- What are the effects of behavioral and pharmacological sleep-promoting interventions on sleep and quality of life among recovering cardiac surgical patients?
- What is the effect of cardiac rehabilitation and exercise on sleep after cardiac surgery?
- Do gender and age moderate the relationship between sleep and quality of life after cardiac surgery?
- What is the relationship between sleep-disordered breathing and quality of life after cardiac surgery?
- What are the sleep patterns of patients who have post-operative complications, and do they have an influence on recovery?
- What is the effect of off-pump cardiac surgery compared with traditional on-pump cardiac surgery on sleep and quality of life among cardiac surgery patients?

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Quality of Life and Sleep Disturbances in Gastroesophageal Reflux Disease

William C. Orr and Chien-Lin Chen

Summary Nighttime heartburn is a symptom that clearly mitigates quality of life and work performance, but it remains a symptom that is commonly ignored. Patients with nighttime heartburn consistently report that these nighttime symptoms disturb them more than their daytime heartburn, and the resultant disturbance in sleep and the impaired daytime performance takes its toll in terms of the quality of daily life in these patients. It is also evident that although there are many causes of sleepiness, nighttime heartburn is indeed associated with disturbed sleep, and in a majority of such patients, sleep disturbances and quality of life can be markedly improved by eliminating the symptoms of nighttime heartburn.

Keywords sleep · GERD · nighttime heartburn

Learning objectives:

- Nighttime heartburn is a common occurrence in patients with GERD.
- Nighttime heartburn results in daytime consequences of sleepiness and reduced quality of life.
- Subjects with nighttime heartburn report that this is more bothersome than daytime heartburn.

Introduction

Not uncommonly, clinicians observe that patients who are effectively treated for severe heartburn will spontaneously report that they are sleeping better in addition to achieving a resolution of their substernal burning. Such reports from patients have focused attention on the relationship between gastroesophageal reflux (GER) during sleep and the extent to which this phenomenon will result in disturbances of sleep and its attendant complications. With the evolution of sleep laboratories from purely research facilities documenting physiologic and psychological changes associated with sleep, to clinical laboratories, which document important physiologic changes in individuals complaining of a variety of sleep-related problems, an awareness of the relationship between sleep and various gastrointestinal phenomena has rapidly emerged. Perhaps the most notable of the more recent focus on gastrointestinal complaints is that of the relationship between sleep-related GER and the development of esophageal and extraesophageal complications. As the result of some recent epidemiological studies, which have focused on nighttime heartburn, there has been a particular focus on the issue of nighttime heartburn as related to the consequences of sleep disturbance and reduction in the quality of life.

GER disease (GERD) is a highly prevalent disorder that affects a substantial proportion of the population in the USA and western countries. Fifteen percent of US adults experience symptoms of GERD, the most common of which are heartburn and regurgitation, at least once a week (1). The fact that symptoms of heartburn are readily treated with either antacids, histamine-2 receptor antagonists (H_2 blockers), and more recently proton-pump inhibitors, have obscured the frequency and importance of the symptom of nighttime heartburn. Thus, until recently, clinicians would rarely, if ever, inquire about the frequency, characteristics, and consequences of nighttime heartburn.

Nighttime Heartburn and Sleep Disturbances

Several studies have recently focused attention on both quality of life and the sleep disturbance consequences of nighttime heartburn. In understanding how to interpret these data, it is important to understand how "nighttime heartburn" is

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defined. In general, such studies define nighttime as the time when the patient lays down to attempt to go to sleep until waking in the morning occurs. Among the first observations regarding the relationship between nighttime heartburn and sleep disturbance, was a report by Janson and colleagues (2) describing the results of a survey of the general population in several Scandinavian countries. In this study, the authors found a significant relationship between the occurrence of nighttime heartburn at least once a week, and daytime sleepiness, daytime tiredness, and snoring. Symptoms of GER were associated with daytime sleepiness (odds ratio 2.6), daytime tiredness (odds ratio 4.5), and disrupted breathing (odds ratio 3.8). The relationship between snoring and GER at least one night per week showed an odds ratio of 2.75. Another epidemiologic study was conducted by Farup and colleagues (1) that described the impact of nighttime heartburn on health-related quality of life. In this study, nighttime heartburn was reported to be a common symptom in patients with frequent daytime heartburn. The authors reported that 74% of those individuals with frequent heartburn had symptoms of nighttime heartburn. It was also noted that subjects who reported nighttime heartburn were significantly more impaired with regard to quality of life than subjects who reported daytime symptoms only. Subjects with nighttime heartburn reported significantly more pain than patients with diabetes and similar pain compared with those with angina and congestive heart failure.

This surprising prevalence of nighttime heartburn has been described in a more recent study by Shaker and colleagues (3). This study, which involved a nationwide telephone survey of 1000 adults experiencing heartburn at least once a week, was conducted on behalf of the American Gastroenterological Association. The results revealed that 79% of respondents reported experiencing nighttime heartburn. Among these individuals, 75% reported that symptoms altered their sleep, and 63% believed that nighttime heartburn negatively affected their ability to sleep well. Forty percent of patients with nighttime heartburn believed that these nocturnal symptoms impaired their ability to function the following day. Of particular interest was the fact that the prevalence of sleep disturbances among the respondents increased with increasing frequency of nighttime heartburn episodes over the course of a week. That is, individuals who had nighttime heartburn three times a week had complaints of being kept awake (67%) and of waking up during the night (70%). A surprising percentage (16%) of these individuals reported trying sleep medications to treat their presumed GER-related sleep disturbance. Patients with nighttime heartburn had tried a variety of treatment mechanisms in addition to sleeping pills, but with surprisingly poor success. For example, 41% of this patient population indicated that they used prescription medications, but less than half reported that they were satisfied with this treatment approach. A similar percentage of individuals had also tried elevation of the head of the bed, but only 23% reported satisfaction with this treatment approach.

Consequences of Resolving Nighttime Heartburn

An epidemiologic study of general symptomatic GERD patients (n = 6215) revealed similar results in terms of there being diminished quality of life in this patient cohort (4). Kulig and colleagues found that the generic quality of life of these patients was diminished and that quality of life was significantly improved in patients with both erosive and nonerosive GERD, as well as Barrett's esophagus, after 2 weeks of treatment with esomeprazole. Baseline quality of life in this cohort of GERD patients was comparable with that of patients with coronary artery disease. Treatment resulted in a similar improvement in quality of life in all three subpopulations of GERD patients, indicating that endoscopic results and severity appeared to be unrelated to quality of life measures. This study indicates that quality of life measures can be substantially and significantly improved quickly with appropriate resolution of symptoms. This study did not address the issue of nighttime GERD.

Other studies have more formally documented the presence of sleep disturbances in patients with nighttime GERD, as well as response to treatment. Chand and colleagues (5) studied 18 patients with erosive esophagitis using subjective GERD rating scales, the Pittsburgh Sleep Quality Index (PSQI), and ambulatory wrist actigraphy (a watch worn on the wrist that monitors motion). Patients were assessed at 4 and 8 weeks subsequent to treatment with esomeprazole 40 mg/day. In this cohort of patients, the baseline sleep efficiency determined through wrist actigraphy was 87%, which is indicative of a significant sleep disturbance. The PSQI and GERD symptom questionnaire scores were significantly improved after both 4 and 8 weeks of treatment.

Results from a randomized clinical trial involving patients with both nighttime heartburn and sleep disturbance were recently published by Johnson and colleagues (6). This multicenter, randomized, double-blind, placebo-controlled trial included adults with GERD-associated sleep disturbances and moderate to severe nighttime heartburn, as noted by a subjective patient diary. Patients received either esomeprazole 40 mg, 20 mg, or placebo once daily for 4 weeks. Outcome variables were the relief of nighttime heartburn, the change in the PSQI global score, and changes in work productivity as assessed by the Work Productivity and Activity Impairment questionnaire. A significantly higher percentage of patients reported relief (no heartburn on 6 of 7 nights), and complete resolution (no heartburn on 7 nights) of symptoms with treatment compared with placebo. There was no significant difference between the 40 and 20 mg doses of esomeprazole; approximately 50% of treated patients had relief of nighttime heartburn symptoms compared with approximately

13% on placebo. Approximately 82% of patients in the treatment arms reported relief of GERD-associated sleep disturbance compared with 55% on placebo. The PSQI data, which measures general sleep quality, showed significant improvement to nearly normal levels in both treatment groups. It was documented that approximately 16 work hours were lost due to GERD-related sleep disturbances at baseline; this was improved to approximately 12 h subsequent to treatment. Using an average total employee compensation cost of $24.59, the cost of hours saved per patient per week was approximately $290.00 in the two treatment groups. Indeed, results of a recent Internet survey showed that GERD-related symptom severity was strongly associated with work impairment and that nighttime GERD was associated with substantially greater work impairment, as was symptom severity (7). In a smaller study using polysomnography to define sleep parameters, rabeprazole 20 mg once daily was shown to improve subjective sleep measures without any change in the objective sleep measures (8). Additionally, another study done by Dimarino et al., using polysomnography during oesophageal pH monitoring, have shown that omeprazole 20 mg twice daily improves the objective sleep measures (reflux related arousals and awakenings) in a group of patients with sleep complaints and GER (9). Pantoprazole is the only PPI with an indication for nighttime heartburn, but there are no outcome studies on treated patients with nighttime heartburn and sleep disorders.

Obstructive Sleep Apnea and GER

GER is a symptom commonly observed in patients with obstructive sleep apnea (OSA), and patients with both GER and OSA have been shown to have significantly poorer quality of life compared with patients with OSA alone (10). It is clinically well established that OSA is associated with a profound degree of daytime sleepiness, depression, and irritability—all of which are factors that weigh heavily in diminishing the quality of life. GER exacerbates to an even greater degree the quality of life in this patient population (i.e., those with sleep disorders). In contrast to the intuitive assumption that upper airway obstruction would predispose to GER, less than 4% of OSA episodes are observed to occur with reflux (9). The treatment of OSA with positive airway pressure is an effective therapy in subjects with both disorders (11, 12).

Issues that need to be addressed by future research:

- Are symptoms such as daytime sleepiness or sleep disturbance noted in some patients without daytime or nighttime heartburn but who have sleep-related GER?
- What are the effects of taking a hypnotic drug on nighttime heartburn and GER?
- Is depression and independent predictor of sleep disturbance in patients with nighttime heartburn?

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Sleep and Quality of Life in Allergic Rhinitis

Helene J. Krouse and John H. Krouse

Summary Allergic rhinitis (AR) is a common inflammatory illness that affects over 10% of the world's population. Among patients with AR, difficulties with falling asleep and maintaining sleep often result in decreased daytime energy, easy fatigability, decreased cognitive and psychomotor function, and reduced quality of life. Two models have been proposed to explain sleep-related symptoms associated with AR. One model focuses on the role of nasal congestion and ventilation during sleep, resulting in obstructive arousals and awakening. An alternate model involves the direct role of systemic inflammatory mediators on the regulation of sleep and nocturnal events, resulting in daytime symptoms and decreased quality of life. The present chapter explores the interaction of nasal obstruction and systemic inflammatory mediators using these two models to evaluate their role on sleep quality and resultant symptomatic and functional effects. It also examines pharmacologic and nonpharmacologic therapies that are commonly used to treat AR, and how these agents can have both beneficial and adverse effects.

Keywords Allergic rhinitis · nasal obstruction · congestion · sleep · cytokines

Learning objectives:

- Allergic rhinitis is associated with daytime sleepiness, decreased energy, impairment in cognitive and psychomotor function, and reduced quality of life.
- Two models have been proposed to explain sleep-related symptoms in allergic rhinitis: (i) Mechanical obstruction interferes with nasal ventilation during sleep and (ii) systemic inflammatory mediators interfere with sleep regulation at a central level.
- Medical therapies designed to treat allergic rhinitis can have both beneficial and adverse effects on sleep and daytime function.
- Reduction in nasal congestion with decongestant medications and intranasal corticosteroids can improve sleep quality among individuals with allergic rhinitis.

Introduction

Allergic rhinitis (AR) is a common condition that affects children and adults around the world. Individuals with AR often experience disturbances in sleep quality and worsening of nasal symptoms upon awakening. Common daytime complaints include easy fatigability, poor concentration, reduced energy level, and feeling tired during the day. Difficulties in falling asleep and staying asleep throughout the night may leave individuals feeling unrefreshed upon awakening, resulting in fatigue and somnolence during the day (1).

Both local and systemic factors that are present in patients with AR can affect sleep quality and daytime function. In addition, treatments that are commonly prescribed for the treatment of AR, such as antihistamines, can further disrupt sleep patterns and contribute to daytime somnolence and cognitive-motor dysfunction. The relative importance of these various factors in contributing to sleep disturbances in patients with AR is not precisely understood.

It is the purpose of this chapter to review the association of sleep disturbance and AR, and to discuss the various models that have been described to explain this association. This chapter will review the definition, epidemiology, and pathophysiology of AR, and will discuss research that examines the direct relationship of sleep and AR. It will finally discuss treatment strategies that may be of benefit in managing sleep issues in children and adults with AR.

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Allergic Rhinitis

AR is a very common disease both in the USA and around the world. Prevalence studies internationally suggest that the prevalence of AR varies somewhat by country, but generally affects between 10 and 20% of both the adult and the pediatric population (2). Current reports estimated that 58 million Americans annually experience symptoms of AR (1). The direct and indirect costs of AR are estimated to exceed $5–10 billion annually in the USA alone and are certainly much greater worldwide (3).

Definition of AR

The term AR refers to an inflammatory disorder of the nasal epithelium and activation of the immune system with targeted effects on the nasal and sinus mucosa. AR is generally divided into two overlapping categories based on the temporal and seasonal course of its development and the persistence of the symptoms. These two forms of AR include (i) seasonal AR (SAR), which refers to an immune-mediated nasal disorder triggered by seasonal increases in common inhalant antigens, including tree, grass, and weed pollens and outdoor molds; and (ii) perennial AR (PAR), which refers to an immune-mediated nasal disorder occurring perennially throughout the year, and generally triggered by indoor antigens such as cat and dog dander, dust mites, cockroach, and indoor molds (4).

Symptoms of AR

AR is generally classified by expression of a cluster of four common nasal symptoms: sneezing, nasal itching, rhinorrhea, and nasal congestion (5). In addition to these nasal symptoms, patients also complain of local, non-nasal symptoms, including tearing, itching of the eyes and palate, and conjunctival injection and erythema. Although these nasal and non-nasal symptoms are directly attributable to inflammation in the upper respiratory tract, individuals often also experience generalized symptoms that include fatigue, difficulty concentrating, and disturbed sleep.

In addition, nocturnal sleep impairment is an important component of the overall symptom complex experienced by patients with AR. Sleep disruption is associated with the nocturnal symptoms of AR, which include difficulty falling asleep and difficulty staying asleep. In addition, impaired sleep can be responsible for a variety of daytime symptoms, including somnolence, decreased alertness, and decrements in cognitive and psychomotor function (6). In patients with obstructive sleep apnea, the presence of nasal obstruction is associated with an increase in the number and duration of apneic events (7), as well as with increased microarousals (8) and increased snoring (9).

Pathophysiology of AR

The primary mechanism underlying the pathogenesis and development of symptoms in AR involves a type-I hypersensitivity reaction that involves the coordinated expression of various cellular and humoral agents. This response is primarily mediated by immunoglobulin E (IgE) and is expressed and regulated through the influence of many humoral and cellular mediators. The presentation of symptoms in patients with AR is regulated by T-helper 2 cells and involves a complex interaction of various inflammatory mechanisms. The allergic response is biphasic, involving both an immediate, histamine-triggered response and a more delayed reaction, mediated by other inflammatory agents and cellular influx.

The allergic response in the nose is initiated when the nasal mucosa of individuals previously sensitized to one or more inhalant antigens is again exposed to these specific antigens. Sensitization can occur any time in life, although it is most commonly begun in childhood. IgE molecules are synthesized during the sensitization process in response to these antigens, and are bound to the surface of mast cells in the nose, conjunctiva, and other mucosal surfaces. They remain present on the surface of mast cells throughout life. When a patient again encounters those specific antigens through environmental exposure, antigen particles bind to adjacent IgE molecules on the mast cell surface, and a sequence of biochemical events occurs, resulting in the degranulation of mast cells and the release of preformed inflammatory mediators into the nasal tissues. The most important of these agents is histamine, a vasoactive amine that possesses the ability to cause significant local inflammatory changes. This process of mast cell degranulation with subsequent histamine release is the primary process involved in the initiation of the immediate allergic response (10).

Upon release, histamine binds to specific histamine-1 (H1) receptors on the surface of target cells in the nose and sinuses, resulting in local effects in the nasal mucosa. These effects include transudation of plasma from capillaries, edema of the nasal mucosa, increased engorgement of vascular channels in the nose, stimulation of mucous glands with increased mucous secretion, and other direct inflammatory events (11). In addition to these effects, histamine, as well as other mediators and neuropeptides released during the initial allergic response, stimulate sensory nerves in the nasal mucosa, which results in irritative effects such as sneezing and itching (2). These events occur in the nasal and sinus mucosa rapidly after antigen exposure and lead to the development of rhinitis symptoms within 10 min. Patient symptoms of AR, such as sneezing, itching, rhinorrhea, and nasal congestion, develop in response to antigen exposure. This rapid release of inflammatory mediators and development of rhinitis symptoms characterize the *early-phase allergic response*.

Although allergy symptoms develop rapidly with exposure, the acute reaction is self-limited and begins to wane within 30 min after exposure. Many patients, however, experience a

prolonged period of symptoms, or may have the recurrence of rhinitis symptoms hours after a discrete exposure. This delayed expression of symptoms is referred to as the *late-phase allergic response*, and usually results in expression of rhinitis symptoms 2–4 h after a single exposure. This late-phase response can be persistent, resulting in symptoms for 24 h or more. Although the immediate, early-phase response occurs primarily because of the effects of histamine, the late-phase response is mediated by other inflammatory agents such as cysteinyl leukotrienes (CysLTs), and by inflammatory cells such as eosinophils and basophils (11). The presence of this biphasic response can account for many of the symptoms expressed by patients with AR. Figure 40.1 illustrates the sequence of events that occurs in the expression of the allergic response.

Models of Sleep Disturbance in AR

Two models have been proposed to attempt to explain the apparent increase in sleep-related symptoms among patients with AR. The first model involves the role of nasal obstruction in interfering with nasal ventilation during sleep, leading to arousals and awakenings. This model suggests a direct mechanical effect with increased nasal resistance playing a central role in the pathogenesis of symptoms. An alternate model involves the direct role that systemic inflammatory mediators may play in the regulation of sleep at a central level. In this model, proinflammatory cytokines and other agents may interfere with normal patterns of sleep and wakefulness, leading to both nocturnal events and daytime symptoms such as fatigue and somnolence.

The model of mechanical obstruction has been best developed by Craig and colleagues (12). These authors believe that mechanical obstruction of the nasal airway leads to an increase in nasal airway resistance, and results in sleep dysfunction in a similar manner to that seen with obstructive sleep apnea. Disruption in nasal breathing overnight leads to increased numbers of arousals, resulting in a disrupted sleep cycle. Intervention strategies have been designed to decrease nasal congestion and improve nasal airflow, and have demonstrated benefit in improving both nocturnal and daytime symptoms.

The model of inflammation-induced sleep disruption has been offered by Krouse and colleagues (13), and suggests that inflammatory mediators adversely impact sleep systemically among patients with AR. In this model, proinflammatory cytokines such as interleukin (IL)-1β and IL-4 can contribute directly to disruptions in sleep, leading to adverse effects on sleep architecture and sleep quality. Daytime symptoms such as fatigue and somnolence are secondary to these inflammatory effects on sleep. It would be reasonable to consider systemic therapies such as allergen-specific immunotherapy for the modulation of these immune mediators and to assess their ability to improve sleep among patients with AR. Although changes in IL levels with immunotherapy can be demonstrated (14), and although improvement in sleep-related symptoms can be noted with immunotherapy (15), it is difficult to separate out the effects of immunotherapy on nasal congestion from those on systemic immunomodulation.

It is likely that some interaction of these two mechanisms may be active in disrupting sleep among patients with AR. Craig has suggested that these two models do not operate in isolation from each other, and may in fact be interdependent. Further study is indicated to assess the role of each of these two mechanisms in sleep-related symptoms in AR. These two models will be discussed in greater detail in the next section.

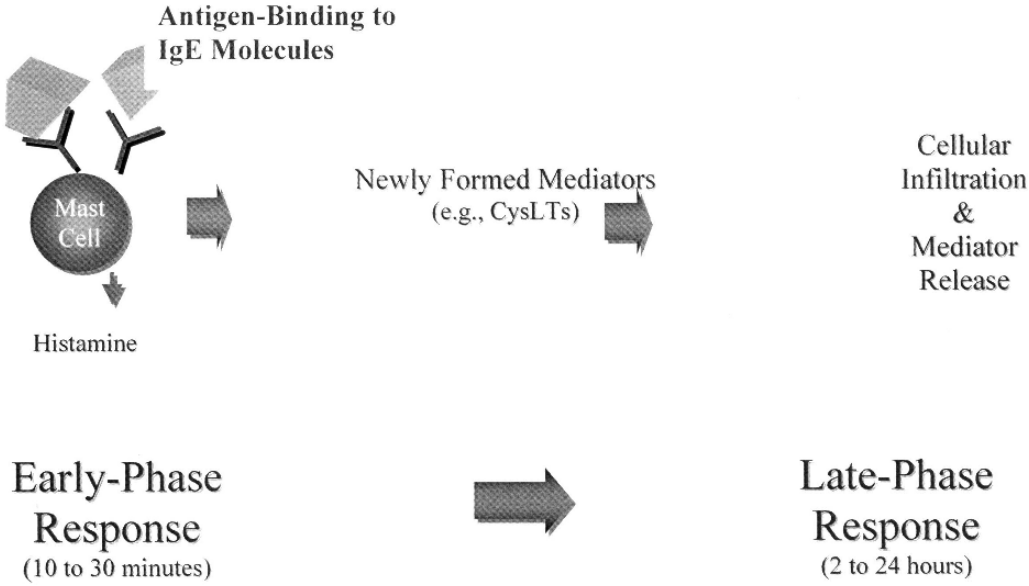

FIGURE 40.1. Early and late phase allergic response.

Sleep and Nasal Obstruction

Nasal Congestion

It is clear that sleep can be affected by a variety of factors, leading to disruption in normal sleep patterns and associated daytime somnolence and fatigue. One model that has been offered to explain this observation is that of increased nasal obstruction leading to sleep interference. This model has been suggested for at least 25 years and proposes that nasal congestion interferes with normal nasal airflow through increased resistance, resulting in a pattern of airway obstruction similar to that seen with obstructive sleep apnea (16). Support for this model has been noted in research suggesting that treatments that are efficacious for the reduction of nasal congestion are also associated with improvements in self-reported sleep, daytime alertness, and quality of life (12). Despite improvement in the clinical symptoms of sleep and alertness, accompanying objective changes in polysomnographic indicators have been inconsistent.

In one large survey assessing the association between the symptoms of AR and several indicators of effective sleep, nearly 5000 individuals were sampled by questionnaire and nearly 1000 of those 5000 subjects were then evaluated using polysomnographic recordings in a sleep laboratory (17). The authors noted that among those patients reporting frequent symptoms of AR, including rhinorrhea and nasal congestion ($\geq$5 nights/month), there was a significantly higher prevalence of sleep-related symptoms such as snoring, nonrestorative sleep, and daytime fatigue. In addition, those subjects with frequent nasal congestion were nearly twice as likely to have moderate to severe sleep-disordered breathing when compared with subjects without nasal congestion.

In another study, 25 subjects with SAR documented by skin testing and 25 matched nonallergic subjects completed both symptom scales and two consecutive nights of polysomnographic monitoring both before and during their pollen seasons (18). With the onset of the pollen allergy season, allergic patients had both an increase in the symptoms of their AR and an increase in daytime sleepiness. These findings were accompanied by a statistically significant increase in the apnea–hypopnea index (AHI) among allergic subjects when compared with their nonallergic counterparts, as well as an increase in snoring among these allergic subjects. Changes in sleep stages, however, were inconsistent. The authors concluded that the symptoms of AR contributed directly to daytime fatigue and somnolence, with the intervening effects of sleep disruption playing only a secondary role.

Evidence supporting the role of nasal congestion in sleep disruption and daytime somnolence has been found in a series of treatment outcome studies (19–21), conducted by Craig and colleagues. These studies demonstrated that reduced nasal congestion through the use of topical intranasal corticosteroid medications (INS) improved self-reported sleep and daytime functioning. Craig (12) concluded, based on these data, that the predominant mechanism involved in sleep disruption among patients with AR is mechanical obstruction in the nose. He acknowledged, however, that inflammatory mediators could play a role in affecting sleep parameters as well.

Nasal Reactivity

It is known that sympathetic tone of the nasal mucosa declines at night, which produces a relative excess in parasympathetic function. Parasympathetic input is responsible for an increase in nasal congestion and rhinorrhea. The inferior nasal turbinates are innervated by both sympathetic and parasympathetic fibers, and the relative parasympathetic excess noted at night in these turbinates is associated with increased nasal congestion (22, 23). Although the role of parasympathetic excess in AR has not been studied, it is logical to infer that nocturnal autonomic dysregulation may play a role in increased nasal congestion and sleep disruption.

Sleep and Inflammatory Mediators

A number of inflammatory mediators that are present in AR also are involved in the regulation of sleep. These mediators can interfere with the onset and maintenance of sleep, and can also stimulate somnolence and daytime fatigue.

Histamine

As was noted earlier, histamine is the major mediator responsible for the acute onset of the allergic response. Histamine has local effects on the nasal mucosa, which causes swelling, increased secretions, and tissue edema. In addition, histamine can exert effects of sleep centrally. There is some evidence that histamine is involved in regulation of the sleep–wake cycle, as well as in cognitive functions such as memory (24). Medications that block the effects of histamine can reduce these bothersome symptoms, but if central H_1 receptors are affected, as with first-generation antihistamines, adverse effects of these agents can interfere with central nervous system cognitive and psychomotor functions.

Cysteinyl Leukotrienes

CysLTs are potent inflammatory mediators that induce significant local changes in the nasal mucosa, resulting in congestion and rhinorrhea (25). They are important agents in the pathogenesis of the allergic response and are responsible for late-phase inflammation and increased eosinophil presence and function. CysLTs are synthesized as metabolites of the arachidonic acid cascade, catalyzed through the 5-OH-lipoxygenase pathway. It is known that medications that antagonize the binding of CysLTs to leukotriene receptors will improve nocturnal symptoms and sleep among patients

with AR (26). Although CysLTs have not been extensively studied in their direct systemic role on sleep, one study that infused leukotriene D4 into rats suggested that this mediator stimulated a 17% increase in slow-wave sleep (27). The clinical significance of this observation is unknown, and similar studies have not been conducted in humans.

Prostaglandins

Although prostaglandin D2 (PDG_2) has been demonstrated to have significant effects in promoting sleep (28), it is not generally considered to be a major mediator in AR. One study using a novel PDG_2 antagonist in a guinea pig model suggested that AR symptoms such as sneezing, rhinorrhea, and congestion could be decreased through use of this medication (29). These findings suggest that PDG_2 may play a role in AR, although in humans this association has not been confirmed.

Cytokines

Cytokines are peptide mediators of inflammation that are involved in a wide range of immune functions, including the regulation of the allergic response. IL-4 and IL-5 are major Th2 cytokines that regulate and modulate the immune response among patients with AR (30). In addition, IL-1β can be involved in upregulation of the late-phase response among these patients (31). In addition to their effects on the pathogenesis of AR, certain cytokines, including IL-1β and tumor necrosis factor-α (TNF-α) are closely involved with regulation of sleep and the sleep–wake cycle (32). The infusion of IL-1β into animals produces increased amounts of nonrapid eye movement (NREM) sleep, suggesting that IL-1β plays a major role in sleep regulation and induction of somnolence.

In one study, Krouse and colleagues (13) assessed nocturnal serum cytokine levels in adults with and without AR and obtained polysomnographic recordings from these individuals over two nights in the sleep laboratory. In this study, allergic individuals demonstrated increases in serum levels of the cytokines IL-1β, IL-4, and IL-10 when compared with their nonallergic counterparts. The presence of elevations in these cytokines was associated with changes in sleep architecture, including a decreased latency to sleep onset and a decreased duration of REM sleep. These findings suggest that increased proinflammatory cytokines levels present in patients with AR may exert a modulatory effect on sleep, resulting in decreased sleep quality and the presence of daytime somnolence.

Diurnal Variability

Allergic inflammation demonstrates a circadian pattern, with increased levels of inflammatory cells and mediators overnight (33). These changes occur in both the upper and the lower respiratory tracts. The diurnal variability in these mediators is likely responsible for many of the observations of increased nasal and pulmonary allergic symptoms overnight. Nocturnal awakenings and increased symptoms of cough and congestion at night can, in part, be related to peaks in inflammation overnight (34).

A variety of mediators are known to have diurnal variability, with resultant increase in symptoms nocturnally. Histamine and eosinophilic cationic protein (ECP) are shown to increase overnight, peaking at about 6 a.m. in one study (34). Cortisol levels decline overnight, and the affinity of the glucocorticoid receptor decreases until early morning, when it again begins to rise (35). CysLTs also are elevated overnight and correlate with decreases in pulmonary function in the early morning (36). In addition, sympathetic tone decreases overnight, with a resultant parasympathetic excess. Increased parasympathetic tone is associated with increased nasal and bronchial symptoms, and may contribute to increased nasal inflammation and congestion overnight (23).

Summary

It is clear that immune mediators play a significant role in the pathogenesis of AR. These immune mediators cause local mucosa effects, leading to increased nasal resistance and obstruction. In addition, they exert central effects with direct disruptions in sleep architecture and the normal sleep–wake cycle. It is likely that a combination of local inflammatory effects and systemic immune-mediated effects is responsible for sleep-related nocturnal and daytime symptoms in patients with AR. Table 40.1 presents a summary of the effects of various immune mediators on sleep.

Management of AR with Attention to Sleep

A variety of therapies, both pharmacologic and nonpharmacologic, are available to treat both symptoms and inflammatory processes associated with AR. These therapies will be examined in relation to managing AR and its impact on sleep.

Decongestants

Decongestants are α-adrenergic agonists that reduce blood flow to the nasal mucosa resulting in decreased cross-sectional area of the nose and improved airflow. Decongestants can be administered orally or intranasally. Intranasal or topical administration of decongestants acts directly on the nasal mucosa to reduce nasal congestion and airway obstruction associated with AR. This improvement in nocturnal airflow can result in decreased nasal obstruction and improved sleep (6). Topical decongestants, however, can only be used for short-term therapy as prolonged overuse (beyond 3–5 days) may negatively affect the nose and cause increased rebound mucosal swelling leading to a worsening of nasal congestion.

TABLE 40.1. Mediators Associated with Allergic Rhinitis and Their Impact on Sleep.

Mediator	Effect on sleep	Effect on nasal congestion
Histamine	Affects H_1 receptors in the CNS, resulting in effects on wakefulness and slow-wave activity	Mild ↑
CysLTs	Increases slow-wave sleep	↑
IL-1β	Promotes sleep. Increases NREM sleep. Decreases latency to sleep onset. Increases latency to REM sleep with decreased REM duration	Unknown
IL-4	Decreases latency to sleep onset. Increases latency to REM sleep with decreased REM duration	Probable ↑ due to pro-allergic effects
IL-10	Decreases latency to sleep onset. Increases latency to REM sleep with decreased REM duration	Unknown
PGD_2	Promotes sleep. Increases both REM and NREM sleep	↑

NREM, nonrapid eye movement

Oral decongestants are effective agents in decreasing the blood flow to the nose, thereby decreasing nasal congestion and improving nasal airflow. These medications are absorbed systemically, which can result in a number of adverse sympathetic effects, especially among sensitive individuals. These effects include increased heart rate and blood pressure, irritability, restlessness, headaches, and urinary retention. One of the major difficulties in using oral decongestants in AR is that they may cause insomnia, especially when taken late in the day or in the evening.

Antihistamines

Antihistamines are commonly used medications that are effective in reducing symptoms in the early phase of the allergic response. These medications antagonize the effects of histamine by competing for and binding to H_1 receptor sites on target organs. They are effective in reducing symptoms associated with histamine, such as itching, sneezing, tearing, and rhinorrhea, but are relatively ineffective in reducing nasal congestion. The effects of early or "first-generation" antihistamines in antagonizing central histamine receptors are well known and are associated with significant sedation and somnolence when these agents are used systemically. First-generation antihistamines are lipophilic and freely cross the blood–brain barrier, thus exerting direct effects on the central nervous system, including sedation and anticholinergic responses (37). Although these first-generation antihistamines are very effective in reducing symptoms of AR, they are highly sedating and can impair motor and cognitive functioning (38). Even when administered at bedtime, individuals using these earlier antihistamines often complain of feeling lethargic and groggy upon awakening from sleep.

Newer antihistamines, often referred to as second (and sometimes third) generation antihistamines, do not readily cross the blood–brain barrier and do not have significant effects on central H_1 receptors. These newer agents are effective in reducing AR symptoms associated with histamine; however, they also have little or no effect on nasal congestion and have not been shown to improve sleep. Examples of first- and second-generation antihistamines are presented in Table 40.2.

Combination medications containing both antihistamines and decongestants are available and can relieve symptoms of AR, including congestion. As previously discussed, however, decongestants can interfere with sleep and cause insomnia, even when used concurrently with sedating antihistamines.

Corticosteroids

Corticosteroids are anti-inflammatory medications that can be administered either systemically or topically to reduce inflammation. In AR, corticosteroids are administered intranasally and are associated with minimal systemic absorption (37). Intranasal corticosteroids (INS) are effective in reducing inflammation and swelling in the nose by decreasing levels of cytokines and chemokines in the nasal mucosa. These drugs effectively treat nasal congestion and obstruction caused by chronic inflammation of the nasal mucosa and turbinates.

The use of INS medications to reduce nasal congestion from AR has been linked to improvements in subjective reports of sleep quality and daytime functioning. In three studies, Craig and his colleagues treated patients with PAR with one of three INS medications (budesonide, flunisolide, and fluticasone propionate) and assessed both daily symptom diaries for severity of rhinitis and daily sleep diaries (19–21). In each of these three trials, the active medication was efficacious in both reducing the symptoms of rhinitis and in improving daytime fatigue and somnolence.

TABLE 40.2. Examples of First and Second Generation Antihistamines.

First generation	Second generation
Diphenhydramine	Loratadine
Chlorpheniramine	Cetirizine
Azatadine	Fexofenadine
Hydroxyzine	Ebastine
Acrivastine	Levocetirizine
Cyprohexadine	Desloratadine

In the one study that examined objective measures of sleep using polysomnographic recordings, individuals treated with an INS, fluticasone propionate, demonstrated no significant changes in arousals, awakenings, hypopneas, and apneas compared with the placebo group. Although no significant changes were found using polysomnography, patients who received the INS reported significant reduction in daytime fatigue and improved self-reported sleep quality and daytime function (20). In each of these studies, there was a strong correlation between the degree of reduction in nasal congestion and the improvement in daytime sleepiness, somnolence, and function. When INS are used to reduce nasal congestion and obstruction, they are effective in improving daytime sleepiness and fatigue experienced by patients with AR.

Leukotriene Receptor Antagonists

Leukotriene receptor antagonists (LTRAs) block specific CysLT receptor sites on target organs such as the nasal mucosa (37). CysLTs cause local inflammation in the nasal mucosa resulting in rhinorrhea, nasal congestion, and nasal obstruction. In a study using a nasal allergen challenge, individuals who received a medication that reduced CysLT synthesis demonstrated a significant decrease in symptoms of nasal congestion compared with a placebo group (39). Several other studies have demonstrated similar reductions in nasal congestion scores as well as decreased symptoms of rhinorrhea and sneezing using direct CysLT receptor antagonists (40–42).

The effects on sleep of one LTRA, montelukast, has been examined in a series of studies involving nighttime symptoms and self-reported sleep quality (40–42). Patients who received montelukast reported significant improvements in nocturnal symptoms, difficulty falling asleep, and nighttime awakenings. They also experienced significantly less nasal congestion during the night and upon awakening. On the basis of these initial studies related to subjective sleep indices, LTRAs may be beneficial in reducing symptoms and improving sleep in patients with AR.

Immunotherapy

Immunotherapy is a treatment for AR that employs therapeutic systematic desensitization to specific inhalant allergens. The mechanism of immunotherapy involves the modulation of elements of the immune system, primarily T lymphocytes, and immunoglobulin production. Successful immunotherapy affects the proportion of T helper cell subclasses, shifting the T_h1/T_h2 balance from an orientation that promotes allergic inflammation (T_h2 orientation) to one that inhibits allergic inflammatory processes (T_h1 orientation). In several studies that examined specific cytokine levels over time, T_h2 cytokines IL-4 and IL-5 were found to decrease during the course of immunotherapy while levels of T_h1 cytokines IL-2 and IL-12 increased. It is important to note that changes in these immune mediators occurred gradually and were usually not noticeable until therapy had continued for periods of up to 1 year (43, 44).

Krouse and Krouse studied the effects of an accelerated approach to immunotherapy on specific immune mediators over a 12-week treatment period (14). After 12 weeks of immunotherapy, there was a significant decline in the levels of two T_h2 cytokines, IL-1β and IL-5. IL-1RA was the only T_h1 cytokine studied to significantly increase after 12 weeks of therapy. In addition to immunologic changes, patients also reported improved symptoms and functional scores. Although only a limited number of studies have examined immune changes and immunotherapy, initial results demonstrate that immunotherapy can shift the ratio of T helper cells by decreasing levels of T_h2 cytokines that stimulate allergic and inflammatory responses and increasing T_h1 cytokines that inhibit this response. The implications of these results pose some intriguing issues for the study and treatment of AR, sleep, and inflammation.

Conclusions

AR is a common disease that clinicians around the world will encounter on a daily basis. While the local nasal symptoms of AR are well recognized, the adverse effects of AR on sleep are often not appreciated. Although many treatments exist that can improve the symptoms of AR, not all of these treatments have been shown to be efficacious in the treatment of sleep disturbances related to AR; in fact, some of these treatments may actually worsen sleep and daytime quality of life. Whereas effective management of nasal congestion and airway obstruction is essential in improving nocturnal symptoms and sleep quality, direct treatment of the underlying systemic immune dysregulation may also play a role in enhancing sleep quality and improving daytime function and quality of life. Additional research is necessary to explore this important area.

Issues that need to be addressed by future research:

- Clarifying and elaborating upon the role of cytokines and other immune mediators in AR as they impact on sleep quality and daily function.
- Evaluating the interactive effects of local mechanical factors in the airway and inflammatory mediators in their impact on sleep.
- Assess the effects of immunotherapy on immune mediators involved in AR and sleep, and their impact on sleep quality and daytime function.

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Sleep and Quality of Life in Renal Disease

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Summary Chronic kidney disease (CKD) leading to renal insufficiency and failure is a growing health care problem. It is well established that patients with end-stage renal disease (ESRD) have a diminished quality of life (QOL), as well as increased sleep complaints. Much less is known about individuals with early-stage CKD who do not require dialysis. Sleep disturbance appears to be part of the uremic syndrome, and manifests as excessive daytime sleepiness, changes in sleep architecture, sleep-disordered breathing/sleep apnea, and periodic limb movements (PLMs)/restless legs syndrome. Numerous studies in patients with ESRD have associated sleep disturbances with poor QOL, but very limited data exist on pre-dialysis CKD patients. There is increasing evidence that correction of uremia by intensification of dialysis or renal transplantation can improve sleep disturbances, as well as perceived QOL. These and other treatments for sleep disorders used in the general population require further research to demonstrate efficacy and the impact on QOL in patients with all stages of CKD.

Keywords Quality of life · chronic kidney disease · sleep disorders · renal failure · dialysis · sleep apnea · restless legs syndrome · insomnia

Learning objectives:

- Patients with kidney failure treated with dialysis have a lower quality of life than the general population.
- Several sleep disorders are highly prevalent in patients with kidney failure treated with dialysis and may be improved with non-traditional dialysis techniques.
- Sleep disorders are associated with poorer quality of life in patients with chronic kidney disease, but the effect of interventions to improve sleep on quality of life in this group are largely unknown.

Introduction

Renal insufficiency and failure are becoming more common, especially in Western and industrialized countries. This can largely be attributed to longer life spans, aging populations, and an increase in the prevalence of diabetes mellitus. In an analysis of the US adult population using NHANES III data, approximately 400,000 individuals had advanced renal insufficiency, as defined by a predicted glomerular filtration rate (GFR) of 15–29 mL/min/1.73 m^2 of body surface area. Perhaps even more alarming, the prevalence of moderate renal insufficiency (GFR, 30–59 mL/min/1.73 m^2), was estimated to be 7.6 million individuals in the USA. The major predictors of renal insufficiency in this study were hypertension, diabetes, and age (1).

The population with advanced renal failure, or end-stage renal disease (ESRD), has grown rapidly in the USA over the past 30 years, with a prevalent population of 335,963 patients treated with dialysis, and an additional 136,136 patients with a functioning kidney transplant, by the end of 2004 (2). ESRD and renal replacement therapy (RRT) have tremendous medical, as well as social and financial, consequences to the individual patient with renal failure, and to the USA as a whole. The annual cost of the US Medicare ESRD program has grown tremendously since its inception in 1974 to over $22 billion (combined Medicare and non-Medicare spending) by 2004 (2).

Patients with ESRD suffer from a greatly increased risk of death, with a 5-year survival for patients on hemodialysis (HD) and peritoneal dialysis at 34.2 and 33.5% between 1995 and 1999, respectively (2). Recipients of a kidney transplant fare better, with a 5-year survival of 74.2% between 1995 and 1999 (2). This increased mortality is primarily attributed to

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cardiovascular and infectious causes (2–6). The known risk factors for mortality in HD patients are age, diabetes and, to lesser extent, the presence of comorbid cardiovascular or cerebrovascular disease, cancer, collagen vascular, and chronic obstructive lung disease (2, 3). Potentially modifiable risk factors, such as anemia and amount, or "dose," of dialysis have also been associated with mortality in HD patients (3, 7–9). Elevated serum phosphate concentration and increased serum calcium-phosphate product have been identified as independent mortality risk factors in HD patients (10).

Interventions aimed at modifying known mortality risk factors are expected to have a considerable impact in this patient population in survival and, hopefully, quality of life (QOL). Amelioration of level of anemia with recombinant human erythropoietin, administering a minimum dose of dialysis and modification of known vascular risk factors such as blood pressure, hyperlipidemia, and tobacco use is common clinical practice in patients with renal disease. Although correction of anemia does improve QOL parameters, complete correction of anemia is avoided because of concerns of increased cardiovascular risk in chronic kidney disease (CKD) patients pre-dialysis and for those on dialysis (11–13). It is also known that further increases in the dose of dialysis above the current minimum suggested requirements do not significantly improve clinical outcomes as shown in large randomized controlled trials (RCT) (14). Longer dialysis treatments in the form of nocturnal and daily dialysis treatments show promise in improving the health of patients with renal failure and are the subject of ongoing NIH-funded trials.

QOL in Patients with ESRD

Although further improvements in the technical aspects of dialysis are certain, the process has been gradual over the past 20 years. Focusing on the QOL of these patients is now of increasing importance. HD has enabled physicians to prolong the life of patients with renal failure by reversing many of the metabolic derangements associated with the uremic state; however, the QOL perceived by patients with ESRD remains poorer than the general population (15). This may at last be in part due to the process of dialysis itself, as well as the financial and social costs of continuing a life support therapy. In addition, not all of the uremic symptoms are eradicated with dialysis. Renal transplant recipients have a better QOL than HD patients, and it is more comparable with the general population (15–18). Renal transplantation is the preferred treatment modality for ESRD, for both the improved QOL and the improved survival it bestows on recipients (15, 19).

There is evidence that QOL may potentially impact mortality in a variety of conditions (15, 20–24). McClellan and colleagues (25) showed that functional status and QOL predict early mortality among patients entering treatment for ESRD. We showed that ESRD patients' assessments of burden of illness predicted mortality (26).

Psychosocial variables, such as extent of depression and social support, and patients' perception of their well being, may also be related to clinical outcomes in HD patients (27). Depression or depressive symptoms are common in patients with chronic illness, including those on dialysis, and may represent another mortality risk factor (28–30). Furthermore, we have shown that patients' perception of social support predicts survival in ESRD HD patients (26), as seen in other populations with chronic illnesses (31–33). Despite the appreciation that psychosocial factors are associated with morbidity and mortality in many illnesses, well-designed intervention studies are lacking (34).

Sleep Complaints in Patients with ESRD

Sleep complaints have been reported as being quite prevalent in patients with ESRD being treated with dialysis (35–37) and in patients with chronic renal insufficiency (38, 39). These complaints include delayed sleep onset, frequent awakenings at night or during sleep, restlessness, and daytime sleepiness. In an early study in the 1980s, Millman and coworkers reported a prevalence of sleep complaints of 41% in a male ESRD HD population (40). The patients surveyed had complaints of insomnia, restless sleep, snoring, and daytime somnolence. Holley et al. and Walker et al. reported that the prevalence of subjective sleep complaints was as high as 50–80% in the patients studied (35, 36). Holley and coworkers (35) studied the prevalence of sleep complaints in 48 HD patients, 22 peritoneal dialysis (PD) patients, and 41 control subjects using a sleep questionnaire. In the study, about half the HD and PD patients reported problems sleeping, compared with only 12% of the control subjects. Walker et al. not only found a higher prevalence (83%) of sleep complaints among HD patients, but also reported that male gender, age greater than 60 years, caffeine intake, and symptoms of the restless legs syndrome (RLS) were associated with a greater number of sleep complaints (36). International studies have revealed a similar prevalence of sleep complaints, in the range of up to 70%, in ESRD patients treated with HD (41,42). Similar findings have been identified in ESRD patients treated with PD (43–45).

Numerous demographic, clinical, and laboratory correlates of sleep complaints in the dialysis population have been identified. Several studies have reported that sleep complaints are more common in elderly patients on dialysis than in younger patients (36, 46). Male patients are more likely to have sleep complaints than female patients, even though women report using more sleep medications than men (36,46). White patients may have a higher prevalence of restless sleep than blacks (46). Positive relationships between subjective sleep complaints and caffeine intake, pruritus, bone pain, cigarette use, and premature discontinuation of dialysis have also been reported (35, 36). Number of health conditions and perceived health status were significant predictors of restless sleep in one

study (46). Similar to the general population, increased stress, anxiety, depression, and worry are also associated with poor subjective sleep quality in dialysis patients (35, 46). Although no consistent relationships between subjective sleepiness complaints and blood urea nitrogen (BUN) or creatinine levels, or Kt/V (a measure of dialysis adequacy) have been typically detected (35, 36, 40, 47), anemia has been associated with complaints of poor sleep with improvements noted after treatment with recombinant erythropoietin (48, 49). Mild hypercalcemia has also been associated with frequency of subjective insomnia episodes (50).

Changes in Sleep Architecture

There is substantial evidence that dialysis patients have overall reduced quantity and quality of sleep. The few studies (40, 44, 51) that have assessed polysomnographic parameters in patients on dialysis report decreased total sleep time (between 260 and 360 min), irregular sleep cycles, and long periods of interspersed waking. Dialysis patients have low sleep efficiencies (between 66 and 85%) and numerous arousals (25–30/h of sleep). In general, ESRD patients were found to have increased amounts of Stage 1 and 2 sleep, and decreased amounts of slow-wave sleep (SWS) and rapid eye movement (REM) sleep (52, 53). These variabilities could be related to differences in age and presence or absence of other factors known to affect sleep, such as medications, co-morbidities, and other sleep disorders. These variables were not controlled in these studies. Metabolic changes and treatment-related factors may also affect sleep. A recent study by Parker et al. (54) also reported on polysomnographic findings in patients with CKD who were not on HD. The CKD patients reported significantly poorer functional and psychological QOL. Both groups had reduced total sleep time and sleep efficiency in comparison with normative data. Patients on HD had lower amounts of REM sleep and a higher brief arousal index. HD patients also had less total sleep time, increased wake after sleep onset, lower sleep efficiency, higher PLM index scores, and longer latencies to sleep onset and REM sleep.

Sleep-Disordered Breathing

The term "sleep-disordered breathing" describes a spectrum of abnormal respiration during sleep, ranging from simple snoring to obstructive sleep apnea (OSA) and the obesity-hypoventilation syndrome. OSA is a condition characterized by repetitive obstruction of the upper airway, often resulting in oxygen desaturation and arousals from sleep. Apnea is defined as the complete cessation of airflow for 10 s or more (55–57). If there is evidence of continuing respiratory effort during the episode, it is termed obstructive apnea. The term central apnea is used if there is no evidence of accompanying inspiratory effort. Hypopnea is defined as a decrease in airflow or chest wall movement by 30% or more from the baseline movement, accompanied by oxygen desaturation of 4% or more. Both apneas and hypopneas are recognized as having similar underlying pathophysiologic mechanisms and consequences (58). The sum total of these different sleep-related respiratory events divided by the total amount of sleep (in hours) is used to calculate the respiratory disturbance index (RDI) or the apnea–hypopnea index (AHI). An AHI greater than 5 per hour of sleep is considered to be abnormal. An abnormal AHI accompanied by excessive daytime sleepiness (EDS) is termed OSA-hypopnea syndrome (OSAHS). The prevalence of OSAHS is estimated to be approximately 4% in men and 2% in women between the ages of 30 and 60 years in the general population (59).

The prevalence of sleep-disordered breathing in patients with CKD on HD has been estimated to be between 30 and 80% (40, 45, 51, 52, 60), a rate significantly greater than that reported for the general population (59). The apneas seen in the dialysis population are mostly obstructive in nature, as in the general population, although many patients also have central and/or mixed events (40, 44, 51, 52, 60–62). Apneas occur in both REM and non-REM (NREM) sleep (60). The type and severity of the apnea does not appear to depend on treatment modality (HD, PD, or CAPD) (45, 52) or vary between nights "on" or "off" treatment (44, 51, 62). Kimmel et al. (60) also reported that both female patients on HD, and patients with chronic renal insufficiency (not treated with HD), were equally likely to have sleep-disordered breathing. No consistent relationships between apnea indices and biochemical measures such as BUN, creatinine, hematocrit, waking arterial blood gases, or dialysis adequacy have been described (44, 52). Unlike in the general population, where there is a strong correlation between obesity and prevalence of OSAHS, no consistent relationship between apnea prevalence or severity and weight/BMI has been described in dialysis patients (40, 53, 60, 61, 63, 64). In fact, the BMIs of dialysis patients are often below the obesity level, secondary to anorexia and disturbed protein metabolism. Some studies also showed that dialysis patients with sleep-disordered breathing were less likely to snore compared with typical OSA patients (53, 64).

The factors responsible for the higher prevalence of sleep-disordered breathing in ESRD patients are not well understood (60, 62). Upper airway edema as a component of generalized volume overload, along with decreased muscle tone from uremic myopathy and neuropathy, may predispose this patient population to develop OSA (60). The chronic metabolic acidosis of renal failure may induce a decrease in the partial pressure of carbon dioxide (pCO_2) or hypocapnia, thus reducing an important stimulus for respiration. This, in combination with the altered sensitivity to carbon dioxide in uremia, may contribute to the pathogenesis of abnormal respiration (60, 65, 66). However, Kimmel et al. (60) failed to show a correlation between the number of disordered breathing events and hydrogen ion or carbon dioxide concentration. The study by Hanley and Pierratos (66), comparing conventional

HD and nocturnal HD, revealed relative hypocapnia during conventional HD that improved significantly after initiation of nocturnal HD. It is possible that sleep-disordered breathing in this population is secondary to a combination of upper airway occlusion and dysregulation of central ventilatory control. Patients with ESRD have been shown to have periodic breathing. Periodic breathing can promote a decrease in drive to the upper airway muscles during apnea, with a disproportionate increase in the drive to the inspiratory muscles, promoting upper airway occlusion (65, 66). The mechanical effects of peritoneal fluid on diaphragmatic action may also contribute to ventilatory control instability (67).

Testosterone was used for treating ESRD-associated anemia, before the advent of recombinant erythropoietin, to help stimulate erythropoiesis. Testosterone has been implicated in the pathogenesis of OSAHS for clinical and epidemiologic reasons (68). The relationship between therapy with testosterone andsleep-disordered breathing was assessed by Millman et al. (40). They performed polysomnography in patients with ESRD before and after treatment with testosterone. No difference in subjective symptoms of sleep disorders or in sleep parameters was noted, suggesting that testosterone does not play a major role in the pathogenesis of OSA in HD patients. Similarly, in the general population, the prevalence of apnea increases in post-menopausal women and becomes comparable to that seen in men (59). Disease-associated hormonal changes often render women on dialysis anovulatory and amenorrheic (69). This effect may not only increase the prevalence of sleep-disordered breathing seen in the dialysis population, but also lead to the lack of significant gender differences with regard to OSA prevalence (53,61,64).

Other metabolic factors may play critical roles in the pathogenesis of sleep-disordered breathing in patients with kidney disease. A small study (70) investigated the effects of infusion of branched chain amino acids in HD patients, demonstrating their stimulatory effect on respiration during REM sleep. The case reports of resolution of OSA after renal transplantation suggest that OSA may be a direct consequence of renal failure and the uremic state (66).

Treatment of sleep-disordered breathing and OSAHS in ESRD patients is similar to that in the general population. Both surgical and non-surgical methods may be used. One of the primary treatment modalities for patients with OSA is the use of continuous positive airway pressure (CPAP) (56, 57). The positive pressure helps keep the upper airway patent by functioning as a pneumatic splint. Studies by Sullivan et al. (71) and others have shown significant benefit of using nasal CPAP in OSA patients. The effectiveness of CPAP was studied by Pressman and colleagues in a group of 8 patients with ESRD and significant sleep apnea that was predominantly of the central or mixed type. Sleep-disordered breathing was normalized in 6 of the 8 patients. Five of the six patients reported improvement in their symptoms. Two of the eight patients, however, were unable to tolerate the therapy (72). Poor compliance with CPAP, however, is common and can be a major limitation in the effectiveness of this therapy (73). The causes of non-compliance vary from physical discomfort to lack of perceived benefit. Several surgical techniques, such as uvulopalatopharyngoplasty (UPPP), have been used to alleviate upper airway obstruction in selected patients (56, 57). The long-term impact of treatment of sleep-disordered breathing in ESRD patients has not been assessed, and improvements in cognition and other aspects of functional status in dialysis patients remain to be described.

RLS and PLM Disorder

RLS is a sensorimotor disorder characterized by a distressing urge to move the legs (and sometimes also other parts of the body), usually accompanied by a marked sense of discomfort or pain in the leg or other affected body part. The feeling is often described as "creepy crawly," and the urge to move the limbs has been characterized as "irresistible." RLS is triggered by rest or inactivity, and its symptoms are relieved or suppressed by movement. It follows a circadian pattern, with symptoms more intense in the evening and nighttime hours. The disorder can be relatively mild or may have profoundly disruptive effects on a patient's sleep and daily life. RLS is frequently associated with semirhythmic leg movements during sleep that are referred to as PLMs of sleep (74–77). Approximately 80% of patients with RLS also have periodic limb movement disorder (PLMD), characterized by the presence of PLMs. These episodic limb movements are associated with nocturnal awakenings and disrupted sleep. The leg movements are typically 0.5–5 s in duration and occur approximately every 20–40 s. The severity of the condition is described in terms of leg movements per hour of sleep (periodic limb movement index, PLMI). A PLMI $\geq$ 5 is considered abnormal.

RLS may be idiopathic (primary RLS, which often has a familial component) or secondary, occurring in conjunction with other medical conditions, particularly iron-deficiency anemia, pregnancy, or ESRD (78). The prevalence of RLS is estimated to be between 5 and 15% in the general population. PLMD can also occur as a distinct nosological entity, independent of RLS (79). PLMD is more common with advancing age and is present in up to 34% of patients over the age of 60 years.

The prevalence of RLS symptoms in ESRD patients has been estimated to be between 20 and 60% (36,80). Winkelman et al. (78) studied 204 dialysis patients and reported that RLS symptom severity score correlated strongly with self-perceived sleep problems, nocturnal awakenings, delayed sleep-onset latency, decreased total sleep time, increased use of medications to assist sleep, and self-reported nocturnal leg movements. Polysomnographic studies of dialysis patients with RLS and/or PLMD confirm these subjective reports, as evidenced by increases in sleep-onset latency, increases in Stages 1 and 2 sleep, and decreased total sleep time and sleep efficiency (81, 82). Some studies have suggested that

symptoms of RLS experienced by renal failure patients may be more severe compared with the idiopathic form (78, 83). Similar to idiopathic RLS, a circadian pattern of symptom expression has been described in uremic patients, with symptoms worsening during periods of immobility, especially during dialysis treatments. The prevalence of PLMD in dialysis patients, both in association with RLS and as an independent condition, is also high, and may approach 70% (80).

Most prevalence studies have relied on self-administered questionnaires. Questionnaire approaches to the diagnosis of RLS may, however, be inadequate in ESRD patients (84, 85). Kimmel et al. (60) showed, in an unexpected finding, that asymptomatic patients with renal failure had a higher mean number of PLMs during a night compared with patients with renal disease who had classic symptoms of sleep disturbances.

There are no consistent data regarding clinical and laboratory correlates of RLS and PLMD in dialysis patients. One study of a large group of Italian patients (86) reported that patients with RLS were more likely to have had a longer duration of time because the initiation of RRT. In another study (78), however, RLS severity was unrelated to age, gender, body weight, number of years on dialysis, or median, ulnar, or sural nerve amplitudes. Similarly, in one study (36), higher predialysis urea and creatinine levels were associated with increased RLS complaints, whereas two other studies could detect no relationship between these variables (78, 87). These last two studies also found no specific relationship between RLS symptoms and anemia, but the SLEEPO study found that normalization of hematocrit with therapy with recombinant erythropoietin resulted in a significant reduction in PLMs in a sample of dialysis patients (81).

The pathophysiology of RLS is not known exactly. It has been suggested that RLS is caused by blockade of the D2 receptor in the diencephalon (88). Exacerbations with dopamine antagonists and remission with dopamine agonists and gamma-aminobutyric acid (GABA) analogues suggest primary roles of dopamine and GABA (89, 90). Iron deficiency has been associated with RLS (91, 92). The mechanism is probably central because iron is a key catalyst in brain dopamine metabolism, and serum iron levels correlate poorly with central nervous system concentrations (93). Anemia secondary to decreased production of endogenous erythropoietin and reduced iron stores from dietary restrictions and blood loss during HD may be important risk factors predisposing ESRD patients to RLS and PLMD. Nutritional abnormalities may be important for the expression of RLS/PLMD in ESRD patients. Peripheral neuropathy associated with uremia and/or diabetes and skeletomuscular abnormalities related to secondary hyperparathyroidism may also predispose dialysis patients to RLS/PLMD. Alterations of dopamine and opioid synthesis/metabolism may also be responsible for the higher prevalence of RLS/PLMD in dialysis patients. Low plasma levels of tyrosine (amino acid precursor of dopamine) have been reported in uremic humans (94) as have abnormalities in the endogenous opioid system (95).

Treatment and management of RLS includes avoiding factors known to exacerbate RLS symptoms, such as caffeine, alcohol, nicotine, and exposure to temperature extremes. It is helpful to eliminate medications that may precipitate the condition, such as lithium, tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), and dopamine antagonists. Pharmacological interventions that have been tried for RLS include dopamine agonists, dopamine precursors, benzodiazipines, and opiates (96). However, data regarding effective therapy of RLS and PLMD in dialysis patients are limited. High-dose iron dextran injection in ESRD patients has been shown to be associated with significant but transient improvement in RLS (97). Substantial improvement in RLS after renal transplantation has also been demonstrated in an observational study of 11 patients (98). L-dopa has been studied in prospective clinical trials, and shown to reduce RLS symptoms, improve nocturnal sleep, decrease number of nocturnal limb movements, and improve subjective QOL in patients with ESRD and RLS (99).

Excessive Daytime Sleepiness

EDS is an important complaint by patients undergoing HD (36, 44, 51, 53). Daytime sleepiness and "day/night reversal" have been anecdotally described in dialysis patients for decades (100). More recently, Stepanski et al. (61) studied the sleep complaints, habits, and medical history of 81 patients treated with chronic ambulatory PD (CAPD). They found that 77% of the patients reported taking daytime naps and 51% reported falling asleep unintentionally. Eighteen patients underwent overnight polysomnographies followed by the Multiple Sleep Latency Test (MSLT), an objective measurement of daytime sleepiness, the next day. An MSLT score of ¡8 suggests abnormal sleepiness. The mean sleep latency for the overall group was 6.3 ± 3.7 min, suggesting that the group was indeed objectively sleepy during the day. Eleven patients had significant OSA, and three patients had PLMD. Their mean sleep latencies were 5.5 and 6.9 min, respectively. Even the subjects without sleep apnea or PLMD had MSLT scores consistent with moderate sleepiness (7.7–8.2 min). Similarly, Parker et al. (101) studied EDS in HD patients and found nearly one-third (15) of their 46 subjects had MSLT scores consistent with abnormal sleepiness (mean sleep latency ≤ 8 min). A higher RDI was significantly associated with lower MSLT scores; however, RDI explained only approximately 10% of the variance in MSLT scores. This suggests that additional factors play a role in the expression of daytime sleepiness in this patient population.

The higher prevalence of OSAHS and RLS/PLMD in the dialysis population is certainly one of the likely reasons for EDS in these patients. However, data from the above studies and others (102, 103) suggest that other factors, possibly related to renal disease and its treatment, may contribute to EDS. The subclinical uremic encephalopathy commonly present in dialysis patients may play a role

in making CKD patients more susceptible to sleepiness. Mild elevations in BUN and creatinine in patients with CKD have been associated with increased slow-wave activity in the wake EEG and abnormalities in cognitive function (104). CKD patients also have increased visual and auditory evoked potential latencies, suggesting a dampened response to external stimuli (105, 106). Elevated parathyroid hormone levels seen in this patient population may also have neurotoxic effects (107). In uremic animals (108) and stable dialysis patients (109), elevated parathyroid hormone levels have been associated with increased waking EEG slow-wave activity. Uremic patients have also been reported to have lower serum levels of tyrosine, an important precursor of norepinephrine and dopamine, two of the neurotransmitters important in neurologic arousal (94, 110, 111).

Impact of Sleep Disorders on QOL in the ESRD Population

Similar to the general population, dialysis patients' perception of poor sleep is associated with lower health-related QOL (HRQOL). In a study of 89 HD patients, sleep quality was measured using the Pittsburgh Sleep Questionnaire Index (PSQI), and correlated with HRQOL, measured using the Medical Outcomes Study 36-item Short Form (SF-36) (112). This study demonstrated that 71% of the patients were poor sleepers, as determined by a Global PSQI score > 5. Subjects with PSQI greater than 5 had lower HRQOL in all SF-36 domains. Of note, the Global PSQI score was a significant independent predictor of the mental and physical component summary scores of the SF-36. The Choices for Healthy Outcomes in Caring for End-Stage Renal Disease (CHOICE) Study examined 894 patients with ESRD and also used the SF-36 as part of a QOL assessment (113). The investigators found an association between symptoms of RLS and lower QOL.

The perception of disturbed sleep also correlates significantly with a number of psychosocial variables that are related to standard QOL measures. In an early study, Devins et al. (114) found an association between illness intrusiveness, an important HRQOL indicator, as well as depressive symptoms and self-reported sleep disturbances in patients with ESRD. Sleep disturbances were associated with depressive symptoms in a multivariate analysis of HD patients conducted by Williams et al. (37). In a cross-sectional study of 78 patients on maintenance HD, Mucsi et al. (115) found that patients with a self-reported sleep disorder had higher illness intrusiveness and worse self-perceived health than those that did not.

Objective measures of sleep disorders and their relation to QOL has undergone study recently. Parker et al. (101) evaluated forty-six HD patients using subjective as well as objective measures of nocturnal and daytime sleepiness. These evaluations included a nighttime polysomnogram, followed the next morning by assessment using the MSLT. Selected measures of both nocturnal sleep and increased daytime sleepiness were correlated with decreased QOL measured by the Quality of Life Index, dialysis version. Sanner et al. (116) also linked sleep-disordered breathing with impaired QOL in 33 HD patients. Patients with a clinically significant sleep-related breathing disorder determined by polysomnography showed diminished vitality, social functioning, and mental health as assessed by the SF-36. In addition, lower apnoea/hypopnoea index scores were associated with lower physical functioning, social functioning, role limitation due to physical and emotional problems, general health and vitality scores. Pain, sleep, social isolation, and emotional reactions were also significantly diminished in the group with sleep-disordered breathing, as measured by the Nottingham Health Profile Part 1.

Preliminary data from our center in 128 HD patients using the PSQI have shown perception of global sleep quality, subjective sleep quality as well as other sleep parameters such as sleep efficiency, perception of sleep disturbance, and daytime sleep dysfunction all correlate with various QOL indicators. QOL was assessed using a variety of questionnaires that aimed to assess depression, satisfaction with life, burden of illness, and perception of social support (117).

Very little is known about disturbed sleep and QOL in patients with renal insufficiency but not ESRD. A cross-sectional study of 120 prevalent patients attending a CKD clinic was undertaken by Iliescu et al. (38). Quality of sleep was measured using the PSQI. The only significant independent predictor of "poor sleep" (PSQI > 5) in a multiple logistic regression analysis was the presence of depression. No relation between degree of renal insufficiency and sleep quality was found. This study did find a high prevalence of poor sleep (PSQI > 5) of 53%, similar to that reported in the ESRD population. However, there was no control population in this study.

We evaluated 93 pre-dialysis outpatients with CKD, and 61 general medical outpatients using the Beck Depression Inventory, Illness Effects Questionnaire, Multidimensional Scale of Perceived Social Support, Satisfaction with Life Scale, Karnofsky, Quality of Life and Pittsburgh Sleep Questionnaire scores, and a modified McGill Pain questionnaire (118) (55.2% had disordered sleep). Disordered sleep correlated with depression, illness burden, social support, and pain frequency. There was no difference in the proportion of patients with sleep disturbance according to CKD stage. There were no differences in perception of pain or sleep disturbance between CKD and control patients. Of note, the mean age in both groups was over 60 years, and approximately 40% had diabetes.

Interestingly, Kurella et al. (119) found a high prevalence of sleep disturbances in patients with renal insufficiency and ESRD patients using the sleep scale within the Kidney Disease Quality of Life (KDQOL) questionnaire. The authors were able to demonstrate a direct association between

estimated glomerular filtration rate (eGFR) and scores on the KDQOL sleep scale. In summary, published studies consistently demonstrate an association between subjective as well as objective sleep disturbances and QOL in patients with ESRD. However, information on patients with early stage CKD is limited, and the associations appear to be less robust. Potential reasons for the disparities in results of all of the above studies would include the use of different instruments, size of studies, sample population, and study design used.

Renal Replacement Modality and Sleep Disorders

Sleep disorders have been noted to be highly prevalent in ESRD patients being treated using conventional HD as well as PD (45, 51). Although there are some data to support better sleep quality with HD versus PD in the CHOICE study (113), sleep apnea syndrome has been noted to occur with similar incidence in patients treated with either modality (45). Despite clearance of uremic toxins, neither conventional HD nor PD have been shown to reduce the prevalence or severity of sleep apnea (35, 45, 60). It should be noted that treatment with dialysis may also predispose patients to excessive daytime sleepiness. Both HD and PD induce abnormal production of tumor necrosis factor-a and interleukin-1, substances with somnogenic properties (60, 120, 121). Rapid changes in serum electrolytes, acid-base balance, and serum osmolarity may decrease arousal and alertness (122). Disruption of circadian rhythms and circadian patterns of sleepiness may be seen in dialysis patients, secondary to inappropriately timed elevations of serum melatonin in response to the hemoconcentration (123) or from changes in the rhythm of body temperature (124). Medications, including antihypertensives and antidepressants, may also contribute to EDS.

Changes in conventional HD and the impact on sleep disorders in patients with ESRD were studied in the large HEMO trial (125). About 1846 patients were randomized to high dose dialysis, a high flux dialysis membrane, both, or neither in this 2×2 factorial design study. About 1813 participants (98%) completed the HRQOL questionnaire at baseline. The questionnaire included the KDQOL-LF and was administered every year for the 3-year follow-up period. Two questions regarding subjective sleep quality were analyzed. The mean sleep scores were not significantly different in the two groups at baseline and through the study period after adjustment. Of note, outside of small changes in the SF-36 physical component summary score and the pain scale, none of the other QOL parameters were improved by the interventions. Although this study did not demonstrate improvement in sleep quality with greater urea or middle molecule clearance, it should be noted that treatment was confined to the limits of conventional in-center HD.

Newer modalities of HD have shown some promise in improving disordered breathing during sleep and ESRD patients' perceptions regarding sleep. In nocturnal HD, patients receive dialysis every night of the week at home while sleeping (126). Hanly and Pierratos reported on 14 patients in whom the conversion from conventional to nocturnal HD was associated with a reduction in frequency of apneic and hypopneic episodes per hour of sleep. The authors reported that in a majority of their patients, sleep apnea became apparent after chronic renal failure occurred, persisted after starting conventional HD, and resolved shortly after conversion to nocturnal HD (66). These studies however were not randomized and involved highly selected patients.

The mechanisms by which nocturnal HD might improve sleep apnea remain to be well understood. Better clearance of uremic toxins has often been postulated as the underlying mechanism. Hanly and co-workers also suggested the possibility of an increase in the transcutaneous partial pressure of carbon dioxide that may reflect stabilization of ventilatory control. In addition, they speculated about the role of improved extracellular volume control in HD patients, particularly on the upper airway in nocturnal treatments (66, 126). Another study evaluated the impact of conversion to nocturnal HD on daytime sleepiness by measuring mean sleep latency using the MSLT. About 54% of patients were pathologically sleepy during conventional HD and were noted to have higher mean BUN and PLM index levels. After conversion to nocturnal HD, there was a trend in the somnolent group to become less sleepy, associated with a modest reduction in the frequency of PLMs (127).

Future Directions in Research

Sleep apnea and sleep disturbances are extremely common in patients with CKD, although generally unappreciated by nephrologists and sleep physicians as well as general internists. Polysomnography is underutilized as a diagnostic tool in symptomatic patients with CKD. In addition, almost nothing is known about sleep complaints and sleep pathophysiology in patients at an earlier stage of CKD than ESRD. The effects of interventions for OSA and RLS, as well as the impact of more intensive dialysis and renal transplantation on QOL in patients with CKD is essentially unknown. Future directions for research include understanding the neurologic and neurohumoral correlates of sleep disturbances in patients with renal disease, as well as the effects of renal disease and its treatment on relevant anatomic structures and their function. Effects of medications in patients subjected to polypharmacy must be carefully determined in future studies. The association of extent of disordered sleep and subsequent psychosocial consequences has not been well studied, but links between poor QOL and subjective sleep complaints have been consistent in the great majority of studies in which they were assessed.

Patients at an earlier stage of CKD than ESRD represent an attractive group for further intensive study. Case reports regarding remarkable improvements in patients who received

renal transplantation or quotidian and nocturnal dialysis will need to be validated by the results of well-designed prospective studies. Well-designed studies, including appropriate interventions, addressing QOL as well as objective parameters urgently need to be performed. The field of sleep disorders in CKD, however, represents an open area for research, to provide better care for the symptoms our patients find so vexing, in order to increase quality and quantity of life.

Issues that need to be addressed by future research:

- Sleep complaints and sleep pathophysiology in patients at earlier stages of chronic kidney disease than end-stage renal disease.
- The neurologic and neurohumoral correlates of sleep disturbances in patients with chronic kidney disease.
- Well-designed studies on the impact of more intensive dialysis on sleep disorders and quality of life in patients with chronic kidney disease.
- Well-designed studies on the effects of standard interventions for obstructive sleep apnea and restless legs syndrome, and quality of life in patients with chronic kidney disease.

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Sleep Disorders and Quality of Life in Patients After Kidney Transplantation

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Summary There has been an increasing interest in sleep problems of patients after organ transplantation. Despite the high prevalence of sleep disorders and the potential impact on both health-related quality of life and on morbidity and mortality, there is still a paucity of published data in the transplanted population. We aim to review here the few studies that address these issues in the kidney-transplanted population.

Keywords Sleep disorders · restless legs syndrome · sleep apnea · insomnia · transplantation · dialysis · quality of life · survival

Learning objectives:

- Although sleep complaints and sleep disorders are frequent in patients after kidney transplantation, there are only a few studies addressing this issue.
- Patients with sleep disorders have impaired quality of life and the presence of sleep disorders might even effect survival.
- Screening, diagnosis and treatment of sleep disorders should be included in the routine clinical care of patients after renal transplantation.

Introduction

Kidney transplantation (Tx) is the treatment of choice for patients with end-stage renal diseases (ESRD), or, according to the new classification and terminology, stage 5 chronic kidney disease (CKD). Those patients are dependent on renal replacement therapies, and Tx has been reported to provide better patient survival (1), and health-related quality of life (HRQoL) (2, 3) than dialysis therapy. Life after kidney transplantation, however, is not exempt of emotional and somatic-physical problems for the patients: fear of graft rejection, worries about the graft function, psychological integration of the newly acquired kidney, rejection episodes, deteriorating graft function, side effects of medications are all new challenges (4). A number of factors have been reported to influence quality of life in those patients such as anemia and erythropoietin therapy (5), side effects of immunosuppressive medications (6), and depression (7). A small number of studies with limited number of participants analyzed HRQoL of hemodialysis (HD) patients on waiting list suggesting that successful transplantation improves the HRQoL of these subjects (8, 9). Fujisawa et al. (10) in their cross-sectional study compared HRQoL outcomes of 49 HD patients on waiting list, 65 HD patients not awaiting for Tx, and 117 Tx patients using the SF-36 generic HRQoL questionnaire (11). Transplanted patients had significantly better results in "Role-physical function," "Bodily pain," and "Social function" than HD patients not on the waiting list. Interestingly, there was no significant difference between Tx and wait-listed patients regarding the scores of any HRQoL domain, except for "General health." On the contrary, using the same generic tool Rebollo et al. (12) found that the HRQoL of Tx patients was significantly better than that of HD patients presuming that the source of bias is due to non-selected HD patients.

Which aspects of quality of life do change after kidney transplantation? What are the factors that potentially have an impact on QoL of kidney-transplanted patients? What role sleep disorders play in shaping QoL of this patient population? Unfortunately, there is a substantial shortage of information in these areas.

In response to the lack of information on this field, we have launched a large prospective cohort study (TransQoL-HU Study) in 2002, to assess HRQoL, sleep disorders and depression in a large group of kidney-transplanted patients and in wait-listed dialysis patients (13, 14). Socio-demographic data, history of renal disease, medication,

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co-morbidity, and laboratory parameters were collected at enrolment. Patients completed a battery of self-administered questionnaires including the Berlin Sleep Apnea Questionnaire, Restless Legs Syndrome Questionnaire, Athens Insomnia Scale (AIS), Epworth Sleepiness Scale, and Kidney Disease Quality of Life Questionnaire-SF^{TM} (KDQOL-SF^{TM}) to assess sleep disorders and quality of life. The KDQOL-SF^{TM} includes the Medical Outcomes Study Short Form-36 generic core (SF-36) and several multi-item scales targeted at quality of life concerns with special relevance for patients with CKD (15). The generic dimensions consist of eight multi-item measures of physical and mental health status: "Physical functioning"; "Limitation in role function for physical reasons"; "Bodily pain"; "General health perceptions"; "Energy/fatigue"; "Social function"; "Limitation in role function for emotional reasons"; and "Emotional well-being." The disease-targeted domains, which are used in this analysis, focus on particular health-related concerns of individuals with kidney disease: "Symptoms/problems"; "Effects of kidney disease on daily life"; "Burden of kidney disease"; and "Sleep." Scores for each item are computed in order to gain a potential range from 0 to 100 within each dimension/domain, with higher scores indicating better HRQoL (16). We have recently provided evidence that most of the sub-scales of the Hungarian KDQOL-SF^{TM} are psychometrically sound and reliable both in dialyzed or transplanted populations (17).

In addition to reviewing the literature, we will summarize our results from the TransQoL-HU Study for this chapter. Some of the findings described below have already been published, but a significant proportion of the results presented here are currently under review or in preparation. However, given the importance of the questions and the scarcity of published data, we felt it important to include all those data in this review.

Sleep Disorders in Organ Transplantation

There is an increasing interest in the prevalence and significance of sleep disorders in patients who are awaiting organ transplantation or following the procedure (18–21). This interest has been especially reinforced by the increasing amount of evidence suggesting an association between sleep apnea and cardiovascular diseases (22). In a recent study, Javaheri found that 37% of patients with heart failure had central sleep apnea and 12% had obstructive sleep apnea (OSA) (23). More and more data support the idea that patients should be screened for sleep apnea before surgery. Unfortunately, OSA is still not generally acknowledged as a perioperative risk factor, although increased risk for postoperative complications is suggested in patients with OSA undergoing cardiac surgery (24, 25). On the contrary, both anesthesia and surgery itself affect the architecture of sleep. Recently, the American Society of Anesthesiologists published guidelines for the perioperative management of patients with OSA (26). Aside from the postoperative effects of anesthesia and surgery, sleep deprivation and fragmentation have been shown to produce apneas and desaturations even in patients without overt sleep apnea (25). There are a few studies that addressed this topic specifically and used polysomnographic assessment for the diagnosis of sleep apnea and sleep-related movement disorders (23, 27).

Earlier studies suggested that sleep complaints especially insomnia are not only prevalent in patients both before and after the transplant surgery, but these problems also contribute to impaired quality of life of transplanted patients (23, 28, 29). Insomnia is also often a side effect of immunosuppressive medications (30).

In a recent study, symptoms of insomnia have been successfully treated by mindfulness-based stress reduction training (31). Treatment of sleep apnea with continuous positive airway pressure (CPAP) have been shown beneficial in a small study of heart transplant patients, but high rate of non-compliance had been found in this study (19).

These studies suggest that there should be an increased awareness of diagnosing and treating sleep disorders in the organ transplant population.

Sleep Disorders in Kidney-Transplanted Patients

Recently, it has become increasingly appreciated that disorders of sleep and wakefulness are prevalent and have a significant impact on different aspects of health in patients receiving maintenance dialysis and also in CKD patients in the predialysis stage (32–37).

Although several studies describe the high prevalence of sleep disorders in patients on maintenance dialysis, there is only very limited data available regarding this problem in the kidney-transplanted population.

Sleep complaints and sleep disorders in the kidney-transplanted population can be of multifactorial origin, reflecting the bio-psycho-social aspects of this problem (Box 1).

Potential causes of sleep disorders in kidney transplanted patients

Pre-existing sleep disorders (insomnia, RLS, sleep apnea)
Transplant surgery, hospitalization
Anxiety and uncertainty—fear from rejection
Immunosuppressive medications
Deteriorating kidney function and co-morbid medical conditions psychological, psychosocial problems (intimacy, sexual problems, role changes, rehabilitation, etc.).
Psychiatric and neuropsychiatric disturbances, delirium, depression
Lifestyle, dietary, and environmental factors
Aging

In our data from the TransQoL-HU 2002 study, we found a high prevalence for sleep disorders in this population, and the presence of each sleep disorders was associated with impaired quality of life (see next chapters).

Despite the very limited published data on this topic, the available results suggest that sleep disorders represent an important clinical entity, and treatment of these problems may improve quality of life in kidney-transplanted patients.

Insomnia, Poor Sleep, and Quality of Life in Patients After Kidney Transplantation

Insomnia is characterized by difficulty falling asleep (sleep onset insomnia), difficulty staying asleep (sleep maintenance insomnia), or poor sleep quality (non-restorative sleep) (38, 39). These sleep problems may lead to impaired daytime functioning, tiredness, fatigue, and sleepiness. The presence of insomnia has repeatedly been shown to be associated with impaired quality of life (32, 37, 40, 41), increased morbidity and mortality (42, 43), and increased use of health care resources (40, 44).

Recently, questionnaires that are based on diagnostic criteria outlined either by Diagnostic and Statistical Manual of Mental Disorders-IV (SLEEP-EVAL) (45–48) or by the International Classification of Diseases-10 (AIS) (49,50) have been developed and validated. Data obtained with these instruments in large epidemiologic studies suggested a comparable, 6–9% prevalence in the general adult populations in different countries. The prevalence of sleep problems in patients on maintenance dialysis is reported—using various, sometimes non-standard instruments—to be close to 50% (32, 36, 37). Recently, Iliescu et al. (33) using the Pittsburgh Sleep Quality Index (PSQI), reported "poor sleep" in 53% of CKD patients in the predialysis stage.

In one of the three studies enrolling kidney-transplanted patients, Sabbatini et al. compared data obtained from 301 kidney-transplanted patients with data from normal controls and from patients on maintenance dialysis using the PSQI (51). The PSQI score of the Tx patients was significantly lower, indicating better overall sleep quality, than in patients on maintenance dialysis. The sleep score of the Tx patients, however, was still higher than that of the control subjects, reflecting impaired sleep. When the patients were divided into "good" (PSQI < 5) or "poor" (PSQI > 5) sleepers, the proportion of "poor sleepers" in the transplanted group was remarkably high, 52.5%. "Poor sleep" was associated with a significant risk of psychological problems (OR: 2.3; $p < 0.02$), with no further associations detected (51).

In another study, Eryilmaz et al. the used the PSQI for measuring quality of sleep, WHOQOL-BREF for quality of life, and Beck Depression Inventory (BDI) for depression in 100 renal transplant patients. One-third of the subjects were classified as "poor sleepers" (global PSQI > 5). "Poor sleepers" were younger, less educated, and more depressed. There were significant inverse correlations between global PSQI and physical health and psychological state with a significant correlation with BDI scores (52). These authors reported an association between "poor sleeper" status and impaired quality of life (52).

In our TransQoL-HU study, the prevalence of insomnia was 15% in wait-listed hemodialyzed patients ($n = 183$), whereas it was only 8% in transplant recipients ($n = 884$), which, in turn, was not different from the prevalence of this sleep problem measured in a matched sample from a representative population sample (8%) (13). The prevalence of insomnia in the transplant group was associated with deteriorating renal function. However, estimated glomerular filtration rate was no longer associated significantly with insomnia in the transplant population after statistical adjustment for several covariates. In a multivariate model treatment modality (transplantation versus wait listing), the presence of depression, restless legs syndrome (RLS), and high risk for OSA syndrome and increased co-morbidity was significantly and independently associated with insomnia (13).

In this study, insomnia was associated with significantly worse HRQoL along all the dimensions of the KDQOL-SF^{TM}. This difference was quite substantial, reaching 15–20 points on most of the sub-scales. Importantly, scores on the AIS remained strongly significantly associated with quality of life scores even after extensive correction for socio-demographic and clinical co-variables (age, gender, renal function, co-morbidity, serum albumin and hemoglobin and the score on the Centre for Epidemiologic Studies-Depression (CES-D) scale) (M. Novak et al., unpublished data). These results point to the importance of diagnosing insomnia in transplanted patients, as treating this disorder may significantly improve their quality of life.

Sleep Apnea and Quality of Life in Kidney-Transplanted Patients

OSA hypopnea syndrome (OSAHS) is characterized by disordered breathing during sleep resulting in symptoms such as snoring, morning headaches, restless sleep, frequent arousals, mood changes, and daytime sleepiness (53).

The prevalence of OSAHS is 2–4% (54) in the general population. The prevalence of sleep-disordered breathing is significantly higher in men than in women (54), and the disorder is associated with impaired quality of life (55). Studies that used sleep questionnaires or polysomnography reported found high prevalence (20–54%) in dialysis patients. We found a similar prevalence in our patient group (56–62). The prevalence of the disorder in CKD patients not yet requiring renal replacement was 54% and the apnea–hypopnea index (AHI) was correlated with renal function (63). In a recent study, Chen et al. screened more than 700 dialyzed patients using the Berlin Sleep Apnea Questionnaire. In that survey, 20% of the patients were at high risk for OSAHS (58). Nocturnal HD that provides superb blood

purification significantly reduced the prevalence of OSAHS compared with conventional dialysis, suggesting that uremia-related factors may play a role in the pathogenesis of CKD-associated OSAHS (64).

Despite the potential clinical impact, there is a lack of information about OSAHS in kidney-transplanted patients. The first case study was published in 1993 presenting two patients with sleep apnea (one patient with obstructive and one with central apnea) in whom the syndrome disappeared after kidney transplantation (65). Auckley et al. (66) reported a similar case in 1999.

Correlates of OSA in Kidney-Transplanted Patients

In the TransQoL-HU Study, we surveyed 841 kidney-transplanted patients in 2002 (unpublished data, manuscript in preparation). Patients were asked to complete the Berlin Sleep Apnea Questionnaire and the Epworth Sleepiness Scale to assess risk status of OSAHS and daytime sleepiness, respectively. The prevalence of high risk for OSAHS was unexpectedly high, 27%, in the transplanted group. Male gender, older age, use of hypnotic drugs, the presence of three or more comorbid conditions, and lower educational status were independent and significant predictors for high risk of OSAHS. Worse residual renal function was also an independent risk factor for the syndrome supporting the hypothesis that, in addition to the known risk factors, uremia-related factors may have a role in the pathogenesis of OSAHS in kidney-transplanted patients.

Sleep Apnea and Quality of Life in Kidney-Transplanted Patients

No study was published analyzing the association between quality of life and sleep apnea in kidney-transplanted patients. Some data suggested sleep apnea might be associated with impaired quality of life after solid organ transplantation. Recently, Javaheri et al. (23) found that 36% of heart transplant recipients had moderate to severe OSA that resulted in disrupted sleep, desaturation, and impaired quality of life. In the TransQoL-HU study, we used the KDQOL-SF™ questionnaire to assess HRQoL. We found that quality of life of patients with high risk for OSAHS was significantly worse along all the quality of life domains assessed by the questionnaire compared with patients with low risk for OSAHS. Patients with high risk had significantly worse self-perceived physical function, vitality, emotional well being, burden of kidney disease, and sleep. Finally, high risk for OSAHS remained a significant, independent predictor of worse quality of life after adjusting for socio-demographic and clinical co-variables in multivariate models (67).

Apnea and Graft Failure in Kidney-Transplanted Patients

Sleep apnea is a known risk factor of cardiovascular disease in the general population (68). It is also known that nocturnal hypoxemia predicts cardiovascular events in dialyzed patients (69). There is substantial evidence suggesting an association between the presence of OSAHS and stroke (70), hypertension (71), diabetes mellitus (72), congestive heart failure (73), arrhythmias (74), and the metabolic syndrome (75). Similarly to patients on chronic dialysis, cardiovascular disease is the leading cause of death in the kidney-transplanted population (76, 77). It is therefore conceivable that the presence of OSAHS is an important cardiovascular risk factor in kidney-transplanted patients. Furthermore, through contributing to cardiovascular morbidity, OSAHS may also contribute to chronic allograft nephropathy, as well. To address this question, we analyzed prospectively collected outcome data from the TransQoL-Hu study. More than 800 kidney-transplanted patients completed the Berlin Sleep Apnea Questionnaire at the study baseline. After 4-year follow-up, we found that high risk for OSA was a significant, independent predictor of chronic allograft nephropathy that is returning to dialysis. This association remained significant after adjusting for socio-demographic and clinical co-variables (unpublished data).

Sleep-Related Movement Disorders (RLS and Periodic Limb Movements in Sleep) and Quality of Life in Kidney-Transplanted Patients

RLS is characterized by an urge to move the legs that is often hard to resist and is usually but not always associated with disagreeable leg sensations. The symptoms occur during inactivity and may interfere with sleep. Clinical diagnostic criteria for RLS have been established by the International RLS Study Group (IRLSSG) (78) and have recently been modified (79).

The pathogenesis of the disorder is still unclear, but it is widely accepted that it involves disruption of the dopaminergic function in the central nervous system (80), mainly in the subcortical brain areas. Finally, there are supportive results for a proposed relationship between brain iron metabolism and RLS (81). RLS may occur in an idiopathic form or secondary to other conditions such as end-stage renal failure, iron deficiency, pregnancy, and rheumatoid arthritis.

The prevalence of RLS is estimated between 0.1 and 15% in the general population (82–86). In most of the studies, the prevalence of RLS increased with age and women were more frequently affected than men (83, 86, 87). Phillips et al. (86) found that RLS was significantly associated with lower social status, worse somatic and mental health, and diabetes. Other

potential correlates of both idiopathic and uremic RLS are anemia and iron deficiency (83, 86, 88–90).

Previous studies have shown an RLS prevalence of 12–62% in dialysis patients (37, 59, 91–93). This large variation could be attributed in part to the heterogeneity of the study populations and also to the differences in the definition and instruments used to diagnose RLS. More recent studies, using the IRLSSG criteria, reported a 6.6–21.5% prevalence in dialysis patients (37, 92, 94, 95).

Prevalence and Correlates of RLS in Kidney-Transplanted Patients

Two studies have been published on RLS in kidney-transplanted patients (96,97). Winkelmann et al. (97) followed 11 patients with uremic RLS who had undergone successful kidney transplantation. The symptoms of RLS disappeared after transplantation in all patients within a month but reappeared in some of them after several years and in most patients in whom the transplanted kidney was failing. Only one previous publication dealt with the epidemiology of RLS in transplanted patients (96). In that cross-sectional study, enrolling 992 patients (816 transplanted and 176 wait-listed hemodialyzed), the presence of RLS was assessed using the Restless Legs Syndrome Questionnaire. The prevalence of RLS in transplanted patients was 4.8% (96), which is close to the reported prevalence of the disorder in the general population. The prevalence of RLS increased strongly with declining renal function. There was also a significant association between RLS and lower serum hemoglobin, higher number of self-reported co-morbid conditions, and higher prevalence of iron deficiency. RLS was significantly less frequent in patients taking steroids than in patients not taking this medication (4 vs. 9%, $p < 0.05$). In multivariate analysis, not taking steroids, eGFR, self-reported co-morbidity, and iron deficiency were significant and independent predictors of RLS. Dialysis treatment was associated with increased odds for RLS (odds ratio 2.2; 95% confidence interval 1.11–4.35) even after adjusting for serum hemoglobin and co-morbidity (96).

RLS and Quality of Life in Kidney-Transplanted Patients

Unruh et al. (94) reported that symptoms of restless legs were associated with impaired quality of life and higher mortality rate among dialyzed patients in the Choices for Healthy Outcomes in Caring for End-Stage Renal Disease Study. In that study, symptoms of restless legs were associated with lower Physical and Mental Component Scores, vitality, bodily pain, and sleep quality using the CHOICE Health Experience Questionnaire assessing quality of life.

No published study so far has analyzed the potential association between RLS and quality of life in kidney-transplanted patients. In the TransQoL-HU study, we studied 785 kidney-transplanted patients from one transplantation centre (submitted manuscript under review). The RLS Questionnaire (RLSQ) and the AIS were used to assess the prevalence of RLS and insomnia, respectively. Quality of life was measured with the Kidney Disease Quality of Life-SF^{TM} Questionnaire.

RLS patients were three times more likely to have insomnia than patients without RLS (29 vs. 19%, $p = 0.001$), and the presence of RLS was a significant and independent predictor of insomnia in multivariate analysis (submitted manuscript under review). Quality of life in all assessed dimensions was worse in patients with RLS than in patients who did not have the syndrome. The difference observed was highly statistically significant for both the general domains assessing physical health status (e.g., "Physical functioning"; "Bodily pain") and also for the mental aspects of QoL as assessed by the SF-36 generic instrument. Similar differences were found in the kidney disease-specific quality of life domains ("Symptoms/problems list"; "Effects of kidney disease"; and "Burden of kidney disease") between patients with and without RLS. The kidney disease-targeted domains of the KDQOL-SF^{TM} questionnaire include a subscale related to sleep. Similarly to the other QoL dimensions, RLS patients had significantly worse score on this sub-scale than patients without RLS.

RLS was independently associated with impaired HRQoL along several quality of life domains after statistical adjustment for clinical and socio-demographic co-variables. Importantly, this association remained significant for some of the quality of life domains even after adjusting for insomnia (submitted manuscript under review).

Data from TransQoL-HU study also showed that the presence of RLS was a significant and independent predictor of depression after adjusting several co-variables (including insomnia) (manuscript in preparation).

RLS and mortality in kidney-transplanted patients

The ESRD population has a high incidence of sleep disorders, including sleep apnea, RLS and periodic limb movements in sleep (PLMS). Sleep disorders result in sleep deprivation, which might have a negative effect on immune function (98–100) and cardiovascular-related outcomes (101–103), common causes of death in patients with end-stage renal failure. Previous studies indicated that RLS was correlated with an increased risk of cardiovascular diseases (104, 105). Ulfberg (105) found an elevated prevalence of heart disease in men with RLS and Winkelman showed an increased risk of cardiovascular disease in those with daily RLS symptoms (104). The underlying mechanisms for these associations are not clear, although cardiovascular risk may be related to the sleep loss (106) commonly found in RLS patients.

Two studies examined predictors of mortality in patients on maintenance dialysis with sleep problems (94, 107). Benz et al. enrolled 29 consecutive patients with end-stage renal failure reporting disrupted sleep or daytime sleepiness. These

patients underwent all-night polysomnography (107). All patients were followed up until death, transplantation, or study termination. Median survival of patients with a PLMS Index greater than 80 was only 6 months. PLMS Index, Arousal PLMS Index, and total arousals per hour of sleep were strongly associated with mortality (107). Unruh and his colleagues examined and followed 894 patients on maintenance dialysis in the Choices for Healthy Outcomes in Caring for End-Stage Renal Disease Study (94). In that survey, severe symptoms of RLS were significantly associated with an increased mortality hazard ratio after adjustment for several clinical co-variables (94).

In our prospective cohort study (TransQoL-HU), more than 800 kidney-transplanted patients were followed at a single transplant clinic for about 46 months and data on outcome were collected prospectively. Our results revealed that the presence of RLS is independently and significantly associated with mortality in kidney-transplanted patients. Mortality at 4 years was significantly higher in patients who had RLS at baseline (for presence of RLS versus absence of RLS in patients: mortality 26 vs. 11%; $p < 0.05$, respectively). In multivariate Cox proportional hazard model, the presence of RLS significantly predicted mortality (HR = 2.017; 95% CI: 1.030–3.949) after adjustment for several co-variables.

Summary

Recently, there has been an increasing interest in sleep problems of patients after organ transplantation. Despite the high prevalence of sleep disorders and the potential impact on both HRQoL and on morbidity and mortality, there is still a paucity of published data in the transplanted population. These data suggest that sleep complaints and sleep disorders, including insomnia, poor sleep quality, and sleep apnea are frequent in this population and contribute to impaired quality of life, and may even have an impact on patient and/or graft survival.

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Issues that need to be addressed by future research:

- Polysomnographic studies as gold standards are needed to establish the prevalence and correlates of sleep disorders in patients after renal transplantation.
- Further studies are needed to explore the pathomechanism, correlates, and course of sleep disorders in patients after kidney transplantation.
- Randomized controlled trials are needed to identify effective treatment methods of sleep disorders in this patient population.

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43
Sleep and Quality of Life in Nocturia and Nocturnal Polyuria

Ragnar Asplund

Summary Nocturia, waking up at night to void, is a highly prevalent disorder in the elderly, with a profound impact on life expectancy, health, and quality of life (QoL). Elderly persons with nocturia are troubled by sleep impairment because of involuntary awakenings, increased nightmares, and a general feeling of insufficient and non-restorative sleep. Consequently, their daytime performance is impaired and they are more inclined to daytime sleepiness and napping than the elderly in general. Particularly, waking up three or more times a night to void is related to a steep increase in sleep disturbances. Giddiness both at night and during the daytime is another common consequence, since in three cases of four nocturia is due to nocturnal urine overproduction, causing a negative fluid balance. Nocturia may be attributable to nocturnal polyuria (nocturnal urine overproduction), a diminished nocturnal bladder capacity, or a combination of the two. In some elderly people, a disorder of the vasopressin system, with very low or undetectable levels of vasopressin at night and in some cases throughout the entire 24-h period may cause an increase in nocturnal urine output, which in most extreme cases will account for 85% of the 24-h diuresis. The increased urine output can be treated with desmopressin orally at bedtime, in generally low doses. Nocturia is also more prevalent in association with reduced bladder capacity. Antimuscarinic drugs may be administered to depress involuntary bladder contractions. This chapter emphasizes the importance of correctly diagnosing and treating nocturia in order to improve the patients' sleep and, in turn, to reduce the risk of fall injuries and their detrimental consequences and to improve health and QoL.

Keywords Depression · desmopressin · fall injury · health · nocturia · nocturnal polyuria · quality of life · sleep · sleepiness · vasopressin

Learning objectives:

- Nocturia is associated with pronounced sleep impairment, negative health perception, and impaired quality of life.
- Nocturia can be caused by increased nocturnal urine output, a reduced bladder capacity, or both.
- Sleep and quality of life can both be improved by medication, aiming to normalize the bladder capacity and nocturnal urine output.

Introduction

Nocturia, waking up at night to void, is a highly prevalent disorder, with a profound impact on life expectancy, health, and quality of life (QoL). Its prevalence is fairly equal in men and women and shows an age-related increase in both sexes (1).

In elderly people with a need to get out of bed twice or more at night, the reported impairment of health-related QoL is similar to that in type II diabetes (2). Many elderly people regard nocturia as an inevitable part of growing old and thus underestimate the extent of the problem, and some doctors share their misconception (3, 4).

In this connection, it must be pointed out that the occurrence of nocturia and nocturnal polyuria are deeply interrelated. An increase in nocturnal urine output is involved in the origin of nocturia in three of four cases. Some symptoms, such as thirst, nocturnal giddiness, and dryness of the mucous membranes in the eyes, mouth, and throat may be symptoms of a negative fluid balance as consequences of nocturnal polyuria (5–7). Other symptoms, first and foremost sleep-related ones, can be attributed to an increased number of nocturnal awakenings for passing urine (8). In many cases, both the increased number of nocturnal micturition episodes

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and the increase in nocturnal urine output are involved in the pathogenesis of a particular symptom, or their influence cannot be separated. Thus, to differentiate between the influence of nocturia and that of nocturnal polyuria on over-all health, QoL, and sleep is not a simple matter.

The prevalence of nocturia increases throughout the whole adult lifespan: Two or more episodes of micturition per night occur in 3.4% of men and 3.1% of women of ages up to 30 years, 5.7% of men and 7.2% of women of ages 30–59 years, and 32.4% of men and 26.7% of women 60 years old or older (9). In a recent Finnish study on nocturia, it was found that the occurrence of two or more voids per night was somewhat more prevalent in 18- to 49-year-old women than in men of these ages. The prevalence of nocturia increased at a constant rate with age (1). In the age group 80 years and above 4 of 10 men and women have two or more episodes of nocturnal micturition (6).

Elderly persons with nocturia report impairment of health and QoL more frequently than do the elderly in general. They are troubled by frequent awakenings, difficulty in falling asleep after nocturnal awakenings, and increased nightmares, and consequently by the feeling of having slept too little. Lying awake in bed more than half of the night is twice as common in elderly men (74 ± 6 years) with three or more nocturnal micturition episodes than in those with no nocturnal voids (7.8 vs. 3.7%) and correspondingly seven times increased in elderly women (14.3 vs. 2.4%). Total night's sleep decreases in both sexes in parallel with increasing nocturnal voiding (10).

Elderly people of both sexes are also increasingly prone to suffer from different somatic symptoms such as muscle cramps in the calves, leg tinglings, and nocturnal sweating in parallel with increasing nocturnal voiding (8). As nocturia is often caused by nocturnal polyuria, they may also be troubled by consequences of a negative fluid balance at night in the form of giddiness when standing up, and as a result, they are at increased risk of sustaining fall injuries (7).

Waking up in the morning without feeling fresh and well-rested is a common complaint in elderly nocturia sufferers. The total extent of their sleep disturbances creates increased daytime sleepiness and a need for napping (8). Thus, their QoL is impaired and their possibilities of participating in social activities are restricted.

Definitions of Nocturia and Nocturnal Polyuria

The International Continence Society (ICS) has defined nocturia as "the complaint that the individual has to wake at night one or more times to void." Also included in the definition is that "each void is preceded and followed by sleep" (11). "Night" is most often interpreted as the period of time from going to bed with the intention to sleep to getting up in the morning with the intention of staying out of bed.

However, voiding once a night is regarded as being within the normal limits. In most studies undertaken before this definition was adopted, nocturia was often considered to occur if the number of voiding episodes during the night was two or more (12–14). As most studies dealing with nocturia were carried out before 2002, and as only persons with at least two nocturnal micturition episodes are considered to suffer from clinically significant sleep disturbances or other detrimental consequences of nocturnal micturition, the term "nocturia" in the present review is used to refer to "two or more nocturnal micturition episodes."

Nocturia may be attributable to nocturnal polyuria (nocturnal urine overproduction), a diminished nocturnal bladder capacity, or both (15). The nocturnal fraction (11 p.m.–7 a.m.) of the 24-h urine output increases with age (10, 16, 17). Among healthy men and women of ages 21–35 years, this nocturnal fraction has been found to be 14% (95% confidence interval, CI, 10–19%), and the corresponding fraction in elderly men and women 34% (95% CI 30–36%) (17). Nocturnal polyuria is defined as a nocturnal fraction exceeding 20% of the 24-h urine output in young adults and exceeding 33% in elderly persons and in middle-aged men and women the figure lies between these extremes (17).

On the basis of analyses of information collected from frequency-volume charts, the pathophysiological conditions underlying nocturia have been categorized as (i) nocturnal polyuria or nocturnal urine overproduction, (ii) a low nocturnal bladder capacity, and (iii) mixed (a combination of the two) (15). The increased production of urine at night that occurs in nocturnal polyuria is often balanced by a reduced daytime urine production, resulting in a normal or only slightly increased 24-h urine volume (5, 10).

Nocturia and Health

Nocturia is associated with an increased number of nocturnal voiding episodes, resulting in gradual overall health impairment as a consequence of profound sleep disturbances (2, 8, 18). In the elderly, these nocturnal disturbances are detrimental not only to the patient but also to his or her partner (19). The sleep disruptions are often associated with excessive daytime fatigue both in the patient and in the partner (8, 18, 19). Among elderly people in nursing homes, a number of diseases and symptoms may be expected, but nocturia appears to be the most common cause of sleep disturbance (71%), followed by disturbing lights or noise (38%), pain (33%), and muscle cramps in the calves (6%) (20).

Partly as a consequence of its propensity to cause sleep impairment, nocturia interferes with daily activities, especially in people who still have an active professional and social life. In one study, it was demonstrated that healthy people with nocturia showed significantly reduced productivity at work and a lower level of vitality, energy, and

activity compared with non-nocturic persons (21). In a sample of middle-aged women, the number of sick days per year was found to increase linearly with increasing numbers of nocturnal voids (18). Frequent nocturnal micturitions resulted in impaired daytime performance and general well-being (18).

In a questionnaire survey among more than 6000 elderly men and women of ages 74 ± 6 years in northern Sweden, poor health was reported by 14.7% of the men with ≤2 nocturnal voids and by 29.6% of the men with ≥3 nocturnal voids ($p < 0.001$). The corresponding frequencies in women were 17.4 and 39.9%, respectively ($p < 0.001$) (8). Correspondingly, the number of visits to a doctor, the amount of medication used, and the occurrence of respiratory tract infections were all increased in a step-wise manner in parallel with increasing numbers of nocturnal voiding episodes (10).

In another study among randomly selected men and women of ages 20–64 years, it was found that unfavorable reports on somatic health and pain increased in frequency occurred in parallel with increasing numbers of nocturnal micturition episodes in both men and women after adjustment for age (22). Sickness absence increased accordingly. Sick-listing for 7 days or more during the past year was reported by 13.4% of the men with no nocturnal voids and by 19.9, 20.4, and 55.6% of the men with one, two, and three or more nocturnal voids, respectively ($p < 0.0001$). Among the women, the corresponding frequencies were 24.7%, 25.4, 44.6, and 50.0%, respectively ($p < 0.0001$). The occurrence of sick-listing for 60 days or more during the past year was also increased sevenfold in men and fivefold in women with three or more nocturnal voids compared with men and women, respectively, with no voids (22).

Life satisfaction is decreased in parallel with increased nocturia. Total agreement with the statement "I am on the whole satisfied with my life" was increasingly less prevalent in parallel with increasing nocturnal voiding in both sexes (Figure 43.1). In a group of women of ages 40–64 years, the subjectively evaluated state of health, feeling of happiness, and feeling of confidence in the future were worsened in association with an increasing number of nocturnal voiding episodes (18).

Mental Diseases and Symptoms

Sleep

There are many diseases and symptoms that have a detrimental effect on sleep. In young and middle-aged adults, stress and different mental conditions play an important role in the occurrence of sleep complaints, but in the elderly, both sleep complaints and sleep medication show a stronger relation to somatic health than to mental health and age (23).

The influence of nocturia on sleep is more pronounced, the larger the number of nocturnal awakenings for voiding (8). There are studies indicating that nocturia is the most bothersome symptom from the urinary tract (24). A potentially important practical consequence of this fact is that recent studies have shown that poor sleep is associated with an increased risk of overweight, one of the most threatening disorders in western countries, one of the symptoms included in the metabolic syndrome, with vascular diseases, hypertension, and diabetes as its other constituents. In a questionnaire survey comprising more than 1.1 million men and women of ages 30–102 years, an association was found between elevated BMI and habitual amounts of sleep below 7–8 h, and this relationship was stronger in men than in women (25). Furthermore, a prospective, longitudinal study covering a period of 13 years showed an association between sleep curtailment and future weight gain, indicating that poor sleep is a cause rather than a consequence of overweight (26).

Nocturnal urgency results in waking from sleep and often in being wide awake. The uninterrupted time in bed from one void to the next is in many cases shorter than 2 h. For this reason, it is common that elderly people with numerous nocturnal voiding episodes do not fall asleep after a void before they have to get up to void again. Among elderly men with three or more nocturnal voids, lying in bed awake for more than half the night has been found to be twice as common as in an unselected group of men of the same ages and among corresponding women, four times as common (10).

In a questionnaire survey of more than 3600 women aged 40–64 years, it was found that sleep was more strongly correlated to the number of nocturnal voiding episodes than to age and the menopause. This was true for the ability to sleep without waking up in the night and to get to sleep again after waking. A four times higher proportion of women with three or more voiding episodes per night reported that they slept too little, compared with women with no nocturnal voiding. Correspondingly, the frequency of nightmare increased fivefold and that of daytime sleepiness threefold (18).

Depression

An increased prevalence of depression is one of the most apparent effects of nocturia on mental health and QoL. In a recent study, it was found that the occurrence of two or more nocturnal micturition episodes was associated with a sixfold increase in major depression in men and a threefold increase in such episodes in women after taking into account age and health (27). A minor increase in nocturia can also be attributed to the use of certain antidepressants, particularly selective serotonin reuptake inhibitors (SSRI) (28).

Numerous explanations of this increase in the prevalence of depression can be suggested. There is a close relationship between nocturia and sleep impairment, and sleep impairment is always present in major depression as it is one of the diagnostic criteria of such depression (29). The pattern of antidiuretic hormone (ADH) release is thought to be important in the pathophysiology of affective disorders (30). In depressed patients, both the synthesis and the release of

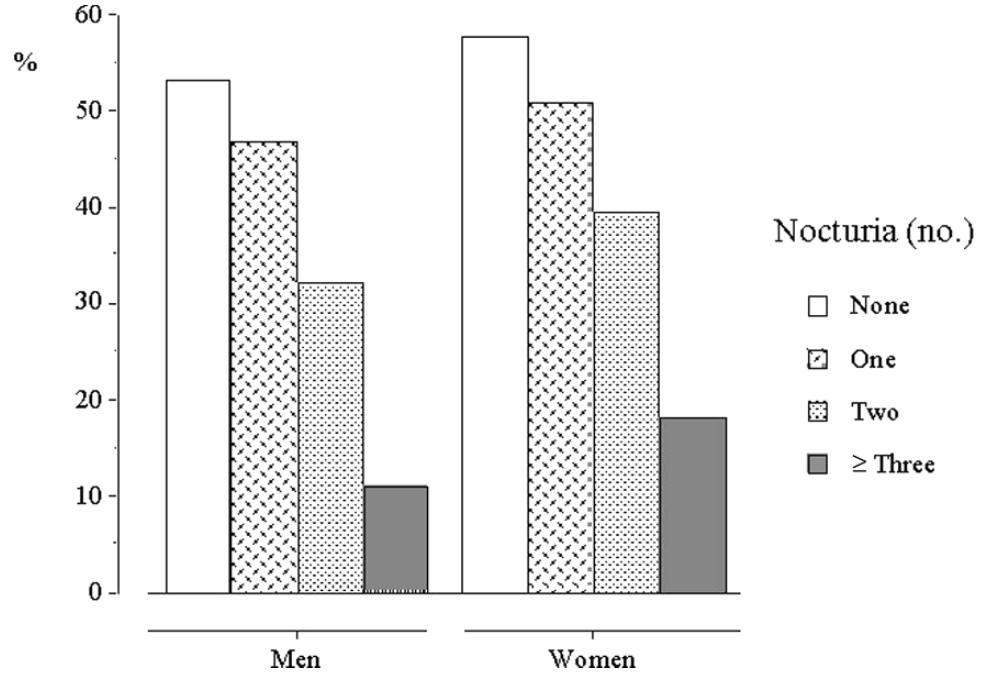

FIGURE 43.1. Affirmative answers (I totally agree) to the statement "I am on the whole satisfied with my life" in men and women with no, one, two, and three or more nocturnal micturition episode ($p < 0.0001$ in both sexes) (22).

ADH in the suprachiasmatic nucleus in the hypothalamus are reduced (31). This nucleus is responsible for initiating and maintaining the circadian rhythm (32). A disturbance in the 24-h rhythm of ADH with absence of nocturnal rise in the plasma ADH level is a common mechanism underlying nocturia caused by nocturnal polyuria in adult and elderly people (10, 33, 34). Most of the ADH secretion takes place in neurones in the supraoptic and paraventricular nuclei in the hypothalamus (35). In patients with major depression, the circulating ADH level is elevated, both in the daytime and at night, compared with healthy controls, but there is no nocturnal rise in this level (36). A circadian rhythm of circulating ADH is necessary to maintain the circadian rhythm of diuresis, with high urine output in the daytime and low urine output at night (35, 36).

Memory and Cognitive Functioning

As nocturia interferes with the quality of sleep, it may be expected to have a significant negative impact on how the person feels the next day. Concentration, mood, and overall QoL may all be affected by poor sleep or non-restorative sleep (37). As consequences of sleep impairment, learning and memory difficulties can be anticipated. In students, it has been shown that sleep quality and quantity are closely related to learning capacity and academic performance. Sleep loss is frequently associated with poor learning, and studies in which sleep was actively restricted or optimized showed worsening and improvement, respectively, in neurocognitive and academic performance (38). Sleep is important for the memory function, and different disturbances of the sleep pattern may result in different kinds of memory disorders. Rapid eye movement (REM) sleep promotes procedural learning processes and seems to be particularly important for the processing of emotional memories, whereas non-REM sleep facilitates declarative learning processes (39–42). Activation of the amygdala during REM sleep plays a decisive role in the processing of emotional stimuli. Sleep in the late part of the night improves memory retention, compared with the effects of wake intervals (42).

Somatic Diseases and Symptoms

Nocturia and Thirst

QoL in cases of nocturnal polyuria may be impaired by a negative fluid balance, particularly at night, as a result of thirst with a need for nocturnal drinking. Many people with increased nocturnal urine output, and in this category elderly people in particular, drink too little, especially in the afternoon, as they believe that by doing this they can reduce their nocturia. At night, however, they cannot resist the desire to drink, so they get up to drink or they drink in connection with toilet visits (8, 10). The nocturnal diuresis is not decreased by fluid restriction, as their hormonal system for fluid regulation, the vasopressin system, is not functioning appropriately. Fluid restrictions should not therefore be recommended to elderly people with nocturia without a careful and immediate evaluation of the effect (8, 10). Thirst, particularly at night, and a nocturnal need for drinking are both uncommon in elderly

persons without nocturia (10). In one of the studies mentioned above (8), thirst at night was reported by 13.7% of the men and 24.1% of the women ($p < 0.0001$), and 14.0% of the men and 24.1% of the women ($p < 0.0001$) stated that they needed to get up at night to drink. Both the occurrence of thirst at night and that of a need to get up to drink at night were increased with increased nocturnal micturition, and this relationship was more pronounced in women than in men (8). The occurrence of thirst in the daytime increased in parallel with the numbers of nocturnal micturition episodes in both men and women (Figure 43.2).

Dryness of Mucous Membranes

The assumption that there is a link between dry mucous membranes and a negative fluid balance, mediated by nocturia, is supported by the fact that thirst, the sensation of dryness in the mouth and throat, increases in parallel with increasing nocturia (6, 43). In a study in hospitalized elderly men and women, dryness of the mouth was reported by more than half of the study group (44). A dry mouth causes significant suffering in some elderly persons, having a serious impact on the eating ability, chewing ability, swallowing, and oral function in general, and consequently on the QoL (45,46).

Dryness of the mucous membranes may have many causes. The prevalence of dry eyes and mouth increases in elderly persons with inflammatory diseases, especially in Sjögren's syndrome, and in those treated with certain drugs, particularly anticholinergics, analgesics, and diuretics (6, 47). Nocturia also plays a role in the origin of mucous membrane dryness, probably as a consequence of the simultaneous occurrence of nocturnal polyuria and a subsequent negative fluid balance (6, 43). In a study of a large group of elderly men and women, a multiple logistic regression analyses revealed that dryness of the eyes and the mouth increased with increasing nocturnal micturition independently of the influence of age, sex, analgesics, and the use of diuretics (6). After adjustments for these factors, dryness of the eyes increased from 6.5% in men without nocturnal micturition to 15.8% ($p < 0.05$) in those with $\geq$3 nocturnal voids, and correspondingly from 9.9 to 33.1% ($p < 0.0001$) in women (Figure 43.3). Dryness of the mouth increased similarly from 15.7 to 37.3% ($p < 0.001$) in the men and from 17.0 to 56.7% ($p < 0.0001$) in the women (Figure 43.4).

Burning Mouth

The burning mouth syndrome (BMS), a condition of the oral mucous membranes, has a profound impact on sleep and QoL (48). This syndrome, which is characterized by a burning pain in the tongue or other oral mucous membranes, usually in the absence of clinical and laboratory abnormalities, is a fairly common complaint with an age-related increase in prevalence (49, 50).

Oral dryness, the use of different kinds of medication, depression, and anxiety are often noted in association with BMS (50). Consequently, extensive health care consumption has been observed in this group of patients (51).

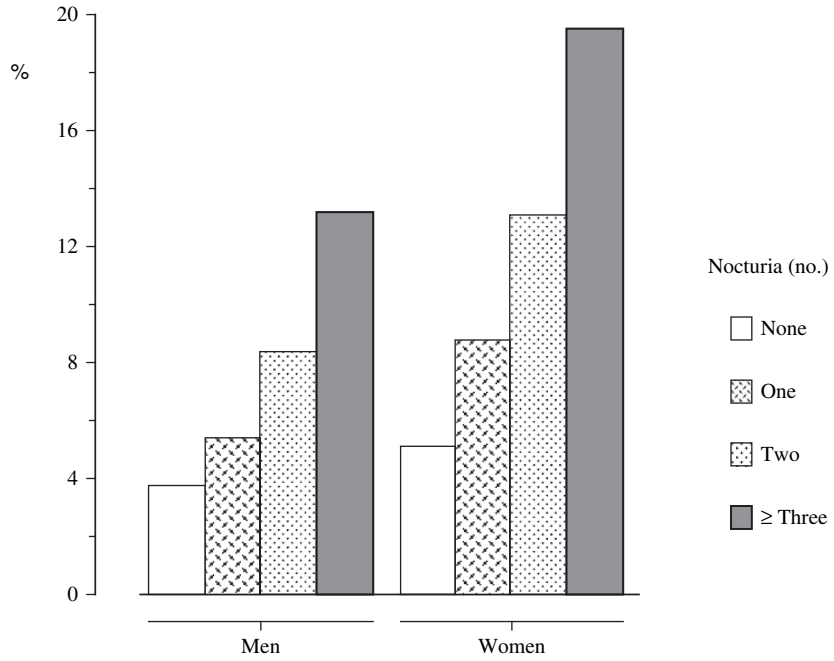

FIGURE 43.2. The occurrence of thirst in the daytime (%) in men and women with different numbers of nocturnal voiding episodes (men: $p < 0.05$; women: $p < 0.001$) (6).

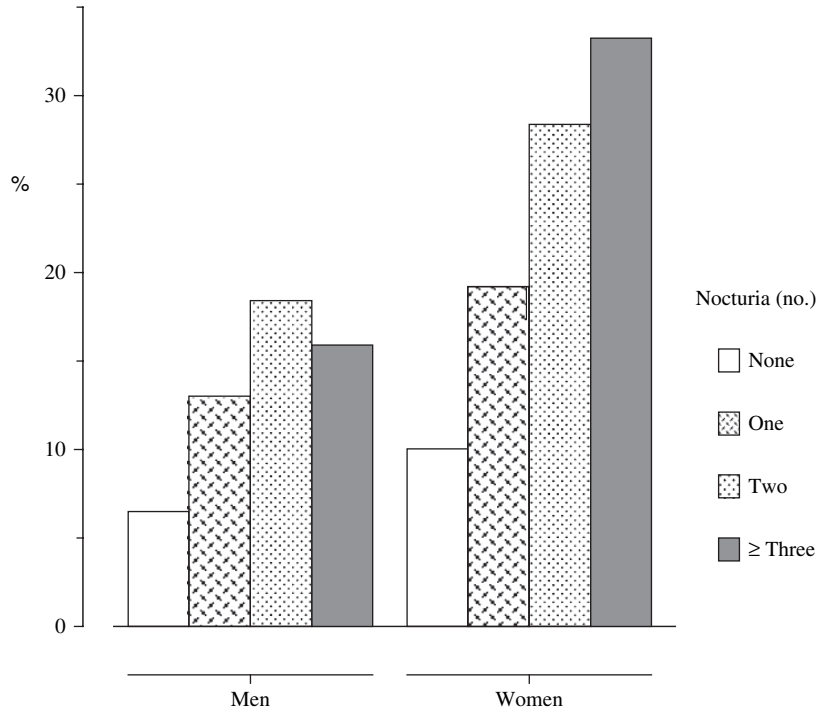

FIGURE 43.3. The occurrence of dry eyes (%) in men and women with different numbers of nocturnal voiding episodes (men: $p < 0.05$; women: $p < 0.0001$) (6).

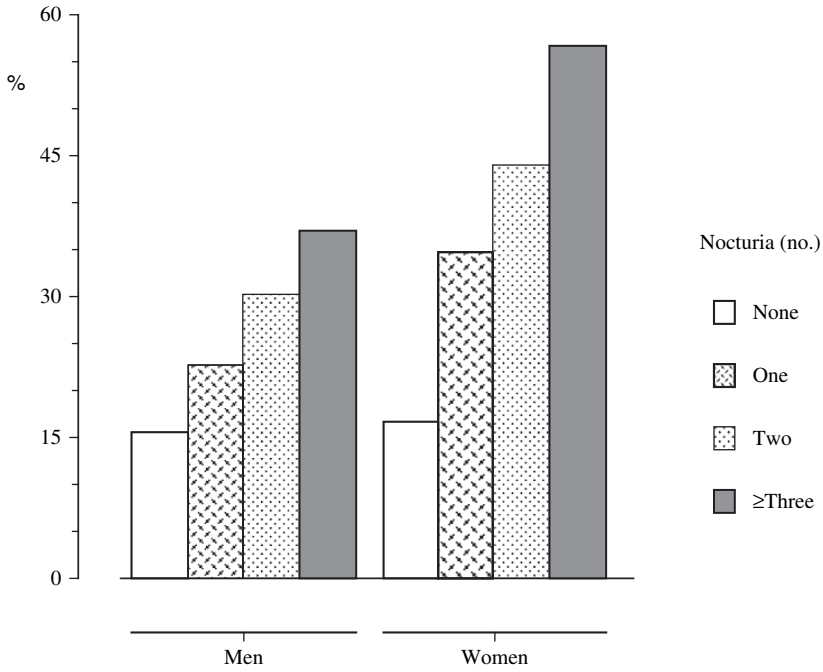

FIGURE 43.4. The occurrence of dry mouth (%) in men and women with different numbers of nocturnal voiding episodes (men: $p < 0.001$; women: $p < 0.0001$) (6).

BMS and nocturia not only are interrelated but also have many associated symptoms in common (52). Both have a highly disturbing effect on sleep (6, 52). In both conditions, oral dryness and thirst, particularly at night, and a need to drink during the night, are increased, in contrast to the findings in elderly people in general, in whom thirst and drinking at night are fairly infrequent (6, 10, 53).

The frequency of poor sleep is three times higher in elderly persons with BMS than in people of the same ages who are not troubled with BMS (53). Nightmares in particular are increased in BMS, threefold in men and fivefold in women, and waking up with a feeling of anxiety is increased fivefold in women (53).

Nocturnal Giddiness

In a study among elderly men and women, the occurrence of nocturnal giddiness was 60% more common in those with three or more nocturnal voiding episodes than in those with no more than two such episodes after adjustment for marital status, age, eyesight, hearing, pain in the cervical spine, spasmodic chest pain, diabetes, analgesics, and diuretics. Gender, irregular heart beats, and sleep medication did not contribute to any change in the occurrence of giddiness (7) (Figure 43.5).

The two most common causes of nocturnal polyuria are sleep apnoea (described in Chapter 9 of this book), resulting from an increase in circulating atrial natriuretic peptide, and the nocturnal polyuria syndrome, caused by a disturbance of the circadian rhythm of vasopressin secretion both of which are characterized by disturbances in the fluid and electrolyte balance, which may partly explain the relationship between nocturia and nocturnal giddiness (33, 34, 54).

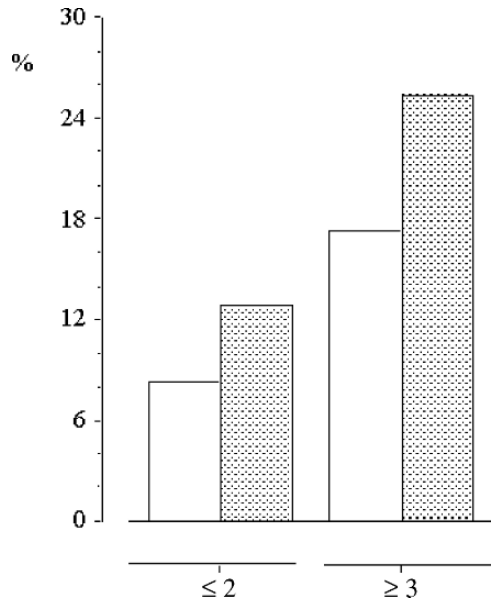

FIGURE 43.5. The occurrence of nocturnal giddiness (%) in men (white bars) ($p < 0.01$) and women (dotted bars) ($p < 0.0001$) in relation to the number of nocturnal micturition episodes (7).

Sleep disturbances are often treated symptomatically with hypnotics, and many elderly patients run a risk of being treated this way rather than being diagnosed correctly and treated accordingly. Nocturia and nocturnal polyuria are often overlooked sources of sleep disturbances. The use of sleep medication is often considered in association with nighttime falls, but there are good reasons to believe that sleep medication serves as a proxy for risk of fall injury.

Sleep medication in the elderly is closely related to poor somatic health and different somatic diseases (55, 56). After evaluation of many health-related mechanisms involved in the risk of falling in the elderly, it has been concluded that although the use of hypnotics causes an increase of the risk of falling, chronic diseases and multiple pathology are more important predictors of falling (57). Furthermore, in a large, prospective study on 34,163 nursing home residents (76% women, mean age ± standard deviation, 84 ± 8 years), living in 437 nursing homes in Michigan, USA, hypnotic use did not predict falls. In contrast, untreated insomnia was associated with a 55% increase in the risk of falling during a 6-month period after the start of the study, and women with hypnotic-treated, unresponsive insomnia showed a 32% increase in this risk, whereas treatment with hypnotics and no persistent sleep impairment was not associated any increased risk at all. After adjustment for potentially confounding variables, insomnia and use of hypnotics were not associated with subsequent hip fracture (58).

Falls and Fractures

Falls and fractures during visits to the toilet and back are the most serious consequences of nocturia, especially in older, frail people with decreased cognitive and motoric functioning. People over 65 years with at least two nocturnal voids are significantly more likely to fall during their nocturnal visits to the toilet than non-nocturics, and this risk is further increased by increasing age and female gender (59–62).

One reasonable interpretation of this fact is that the risk is related to the number of times that a person has to get out of bed at night, often, probably, in a state of tiredness and sometimes orthostatic hypotension. In a recent study, however, it was found that both increased nocturnal urine output and the number of nocturnal micturition episodes increased the 5-year risk of having a hip fracture. This risk was increased twofold by the occurrence of three or more such episodes as compared with two or fewer, and threefold by the occurrence of large nocturnal urine volumes, very often versus very seldom or never (59) (Figures 43.6 and 43.7). This indicates that the increased nocturnal urine output increases the risk of fall injuries by increasing the propensity to orthostatic reactions when getting out of bed and walking to and from the toilet (7, 25, 59).

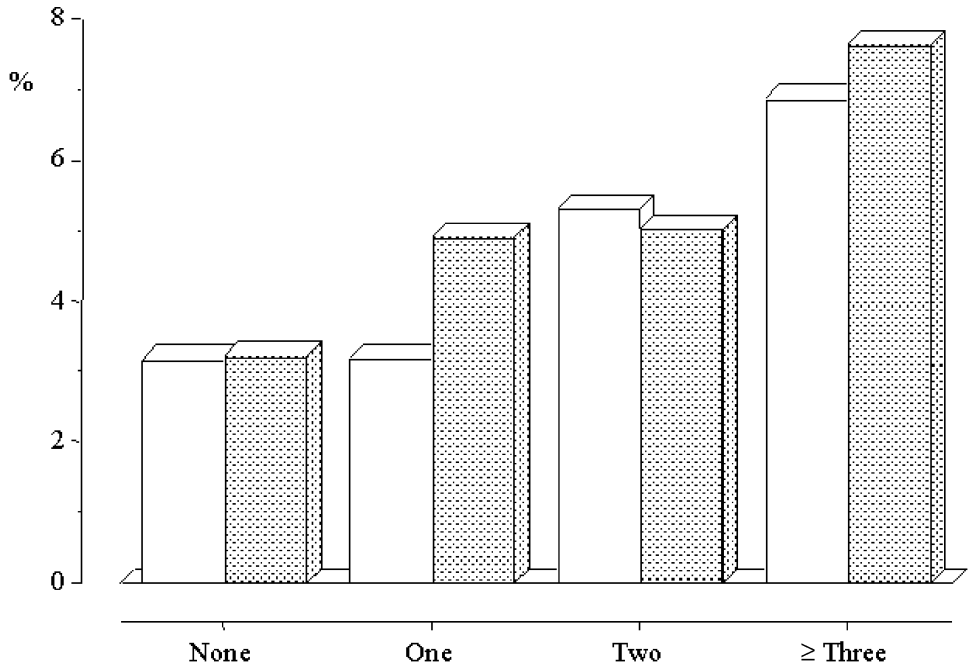

FIGURE 43.6. The 5-year prevalence (%) of hip fractures in relation to the number of nocturnal micturition episodes in men (white bars) and women (dotted bars) (59).

A condition of particular interest in this connection is reduced vision. Visual impairment has been found to be associated with poor sleep, and simultaneous occurrence of these two conditions contributed independently to increased nocturnal micturition (63, 64). Among elderly men and women with both visual impairment and poor sleep, visual impairment was associated with an 80% increase in the occurrence of three or more such episodes in men and a 60% increase in women after adjustment for age and sleep. Reports on three or more nocturnal micturition episodes were three and four times more frequent among men and women, respective with visual impairment and poor sleep than among those with good vision and good sleep (Figure 43.8) (64).

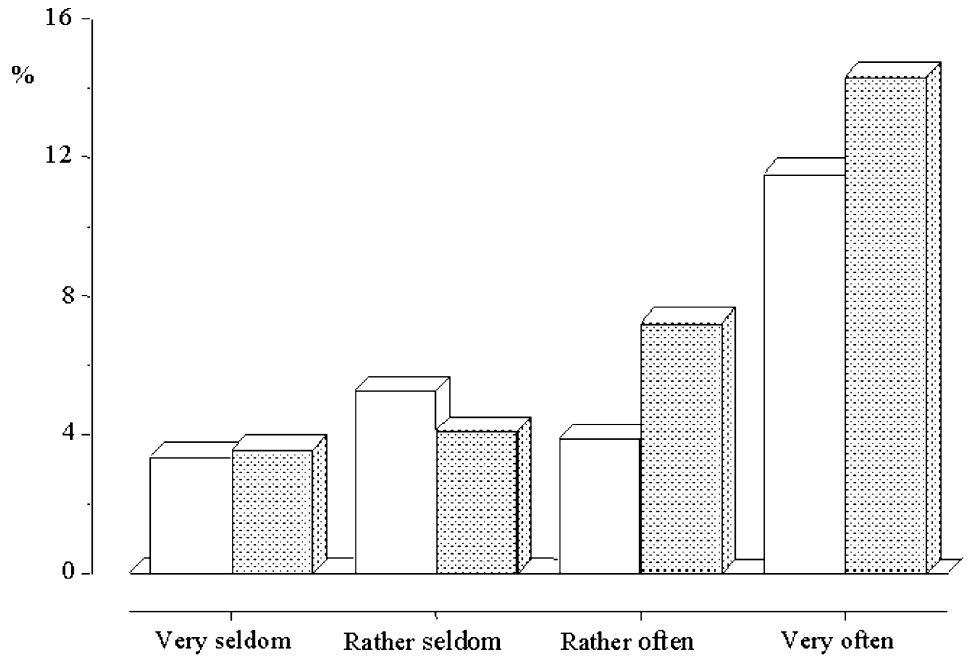

FIGURE 43.7. The 5-year prevalence (%) of hip fractures in relation to the occurrence of subjectively very high nocturnal urine output in men (white bars) and women (dotted bars) (59).

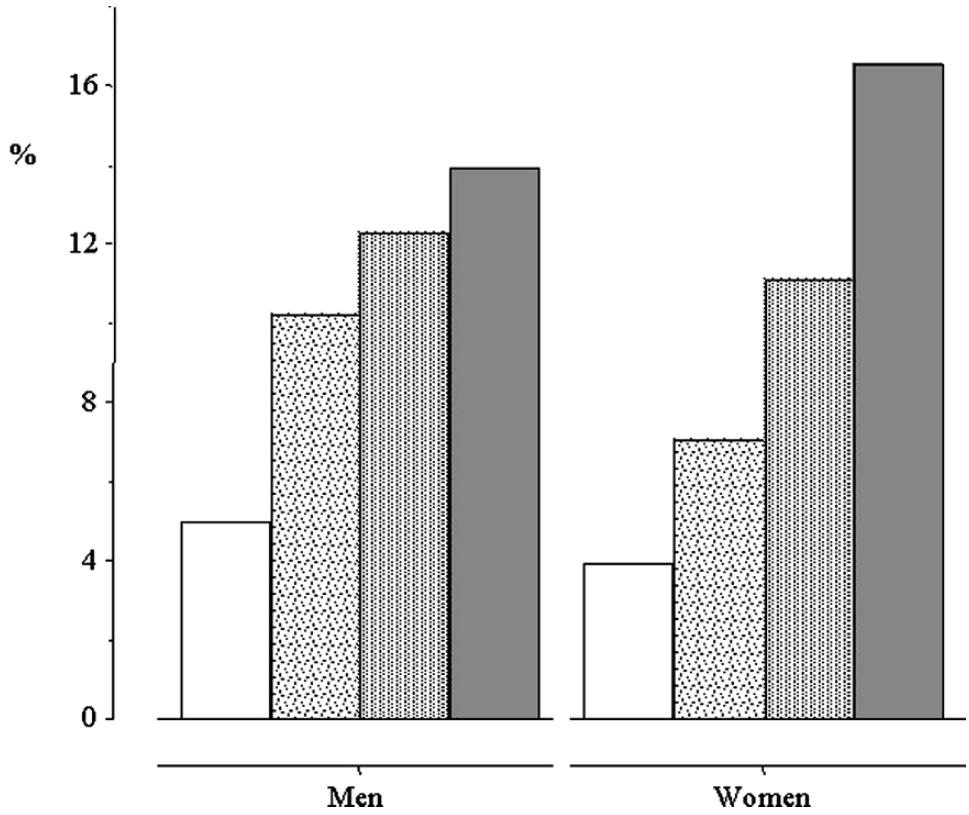

FIGURE 43.8. The percentage occurrence of three or more nocturnal micturition episodes in men and women with good vision and good sleep (white bars), poor vision and good sleep (dotted bars), good vision and poor sleep (grey bars), and poor vision and poor sleep (dark grey bars) ($p < 0.0001$ for both sexes) (64).

A reasonable explanation of this may be that in persons with visual impairment, the nocturnal rise in the plasma melatonin levels is greatly reduced or lacking, resulting in absence of a normal vasopressin rhythm (65). The absence of a nocturnal rise in the plasma vasopressin level is associated with incomplete or a lack of inhibition of the nocturnal diuresis, resulting in nocturia as a consequence of nocturnal polyuria (5, 33, 34).

Treatment of Nocturia and Nocturnal Polyuria

Reduction of nocturia and nocturnal polyuria should be considered in attempts to reduce the risk of falls in elderly persons, in whom multiple falls might occur as a result of an increased need to get up at night to void or drink. Both distressing urinary urgency and nocturnal polyuria can be alleviated by pharmacological treatment (66–69).

The view that there is a cause-and-effect relationship between nocturia and sleep impairment is supported by the fact that sleep is improved by treatment that reduces nocturia. Thus, it is possible to diminish the nocturnal disturbances from voiding in certain groups of patients. In all long-term studies on the effect of treatment with the alpha-1-antagonistic drug alfuzosin 10 mg orally in a slow release formulation in men with nocturia and benign prostate hyperplasia (at baseline 43.9% $\geq$3 episodes per night), it was found that the occurrence of three or more nocturnal voiding episodes was reduced by two-thirds after 3 months, and these results persisted after 2 years (67).

There was a consequent improvement in QoL in the group of men with improved nocturia. The proportion of men with a bother score of 4 or more [mostly dissatisfied (4), unhappy (5), or terrible (6), as expressed level of bother in the International Prostate Symptom Score] improved correspondingly (67).

In cases of nocturnal polyuria, sleep improvement can also be achieved by reducing the nocturnal urine output. This was shown in a double-blind study of the effect of desmopressin on nocturia caused by nocturnal polyuria, carried out in a group of 12 men and 5 women of ages 67.7 ± 4.6 years. The participants were examined before the start of the study, and the inclusion criteria were healthy except for nocturia and nocturnal polyuria; two or more nocturnal micturition episodes; and a nocturnal urine output of $\geq$0.9 ml/min (70). They were treated with desmopressin in the best dose found in a previous dose-titration procedure (71). They were given desmopressin and placebo for 2 weeks each in a cross-over design with 1 week of wash-out between the treatment periods. During the desmopressin treatment, the number of

voids per night decreased from 1.8 to 1.0. The longest period of uninterrupted sleep was 1.4 h longer during desmopressin treatment than during the placebo period (5.4 vs. 4.0) (70,71). In another double-blind placebo-controlled study in adult men and women with nocturia and nocturnal polyuria, desmopressin in a previously established optimal dose or placebo was given for 3 weeks. The duration of the first sleep period improved from 161 to 269 min (59%) in the men and from 142 to 272 min (78%) in the women (72). And, in a long-term study, the mean duration of the first sleep period from baseline to 12 months gradually increased in men (157–288 min) and women (142–310 min) (73).

Issues that need to be addressed by future research:

- The influence of nocturia and nocturnal polyuria on life expectancy, health, and quality of life needs to be further clarified.
- Better screening programs should be developed for elderly persons at risk of disease and accidents in association with nocturia and nocturnal polyuria.
- Further development of pharmacotherapy should include better drugs both for normalizing the nocturnal urine output and for improving bladder capacity.

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Sleep and Quality of Life in Cystic Fibrosis

Amanda J. Piper and Catherine J. Dobbin

Summary Cystic fibrosis (CF) is a progressive disorder. Patients face rigorous daily treatments and fears of an uncertain future, both of which can impact on the physical, social and psychological aspects of their lives. In addition, with ongoing lung damage and airway obstruction, hypoxemia and hypercapnia during sleep can develop, contributing to daytime physiological and neurocognitive deficits. Health-related quality of life (HRQoL) in CF has become increasingly important as patient survival has increased. As a result, CF-specific measures of HRQoL have been developed. Quality of life research suggests that, despite chronic symptoms of dyspnoea and cough, reduced functional capacity, and the burden of repeated respiratory infections and hospitalization, people with CF generally report a good HRQoL in the psychosocial domain. However, scores for most physical domains are lower than those seen in matched healthy controls. Many patients with CF perceive their quality of sleep to be poor, with those individuals with more severely impaired lung function and worse gas exchange more likely to report poorer subjective sleep quality. Sleep disturbance appears to be a major factor in the poor overall sleep quality that patients with CF report. Although hypoxia and hypercapnia might contribute to sleep disruption and impaired daytime function in the presence of severe lung damage, other mechanisms likely to contribute include cough, airway inflammation, sinusitis and gastrointestinal disturbances. Pulmonary exacerbations also adversely affect sleep quality, quality of life and cognitive function, but no cause-and-effect relationship between exacerbation-related sleep disturbance and quality of life and cognitive changes has been demonstrated. Although treatments such as oxygen and NIV can improve nocturnal gas exchange, little evidence of a long-term benefit on either quantity or quality of life in CF has yet been demonstrated. As survival increases, there will be increasing focus on issues such as sleep quality, its effects on daytime function and management of respiratory failure. Improving the impact of the illness and its treatments on quality of life will become an increasingly important goal for interventions in this patient group.

Keywords Cystic fibrosis · sleep quality · quality of life · hypoventilation

Learning objectives:

- Patients with cystic fibrosis report poor sleep quality.
- There appears to be a relationship between the severity of lung disease and sleep disturbance.
- Significant changes in ventilation and gas exchange during sleep occur in those with severe lung disease.
- Patients with cystic fibrosis generally report a good health-related quality of life in the psychosocial domain despite reduced functional capacity.
- Pulmonary exacerbations are common and associated with poorer sleep, quality of life and cognitive function.

Introduction

Cystic fibrosis (CF) is a genetic disorder that affects the respiratory, reproductive and digestive systems. For most individuals, the respiratory system is most severely affected, with progressive bronchiectasis and airway narrowing leading to severe respiratory impairment. Defects in the ion transport system affect airway epithelium, depleting surface liquid. This in turn promotes mucus retention, chronic colonization with bacterial pathogens such as *Pseudomonas aeroginosa* and airway inflammation. The clinical course is punctuated by recurrent infective exacerbations and remissions. Over time, chronic infection and inflammation lead to a progressive loss of lung function and eventually cor pulmonale and respiratory failure.

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CF was once considered a paediatric disorder, with most individuals dying in childhood or early adolescence. However, with advances in medical care over the past 20 years, the majority of patients can now expect to survive to adulthood. As life expectancy increases, CF patients are increasingly facing the same developmental hurdles as their healthy peers, as they strive for independence and control of their situation and focus on career, education, finances and relationships. Because of the progressive nature of the disorder, patients face daily time-consuming treatment and fears of an uncertain future, both of which have the potential to impact on the physical, social and psychological aspects of their lives (1). In addition, with ongoing lung damage and airway obstruction, hypoxemia and hypercapnia during sleep can develop (2), contributing to daytime physiological and neurocognitive deficits (3). As survival increases, there will be greater focus on issues such as sleep quality, its effects on daytime function and management of respiratory failure. Improving the impact of the illness and its treatments on quality of life will become an increasingly important goal for interventions in this patient group.

Measuring Quality of Life in CF

Traditionally, pulmonary function, exercise tolerance and anthropometric measurements have been used to monitor progress of patients and their response to treatment. Although important as objective physical outcome measures, these measures provide no indication of the global impact this chronic illness or its treatments has on the social functioning, emotional wellbeing or the coping ability of the patient. More recently, the value of routinely measuring health-related quality of life (HRQoL) in CF has been recognized (4). Most studies of HRQoL in patients with CF have used generic instruments such as the Quality of Well-being Scale, the Short Form-36 Health Questionnaire (SF-36), the Pittsburgh Sleep Quality Index (PSQI) and the Profile of Mood States (POMS) (3, 5–8). It is only within the last decade that the added value of CF-specific measures of HRQoL has been recognized. This has led to the development and validation of a number of CF-specific HRQoL measures.

The Cystic Fibrosis Questionnaire (CFQ) was designed to reflect areas of specific concern for patients with CF better than generic HRQoL measures (9, 10). The CFQ is a 48-item self-completed questionnaire that includes subscales related to body image, treatment burden and respiratory and digestive symptoms and has been validated in adults and adolescents with CF. It can be used to monitor a patient's progress and responses to treatment (3). The CFQ consists of three modules including quality of life, perception of health state and symptoms. Within each module are questions addressing various dimensions of daily life. Dimensions in the module on quality of life include physical, role, vitality, emotional state, social marginalization, body image, eating disturbances and treatment burden. Dimensions in the symptoms module include weight, respiratory and digestion. In each dimension, higher scores indicate better quality of life (9).

The authors of the Cystic Fibrosis Quality of Life (CFQoL) questionnaire set out to develop an instrument that measured areas of function meaningful to adults with CF, was brief enough to apply in a clinical setting and was simple to administer and score (4). The CFQoL is patient derived. Validation studies suggest it is sensitive enough to detect transient changes in health status; allow for cross-sectional comparisons of groups of patients with different levels of disease severity; and describe longitudinal changes that take place in adults with CF as a function of progression and deterioration in disease status (4).

In other cases, existing generic measures have been modified to include a CF-specific module. The Questions on Life Satisfaction instrument for adolescents and adults with CF, for example, was developed by adapting the existing Questions on Life Satisfaction instrument (11).

Quality of Life in CF

Both generic and disease-specific questionnaires have been used to establish what we know so far about quality of life in patients with CF. Research suggests that, despite their reduced functional capacity, symptoms such as dyspnea and cough, and the burden of repeated respiratory infections and hospitalization, people with CF generally report a good HRQoL in the psychosocial domain (8, 12). However, scores for most physical domains are lower than those seen in matched healthy controls (6, 12). Indices of psychological functioning suggest that even patients awaiting transplantation adapt well to their disease process (13). Although reporting impaired physical function in recreational activities, household activities, sleep and ambulation, these patients report low levels of depression and anxiety, while describing high levels of functional coping and social support (13). Similarly, in a study of adolescent subjects with CF, the majority perceived themselves as having a good quality of life and a positive future (14). The generally good quality of life reported by CF patients despite significant physical restrictions may be because most have been symptomatic from a young age and have had time to adjust to the limitations of their disease.

However, good psychological adaptation is not a universal finding. Some studies have found that adults with severe disease have higher levels of psychological distress and are less likely to be employed or attending school (15). Lower depression scores have been reported in CF patients who are able to continue working despite significant lung impairment, adding support to the suggestion of a relationship between work and quality of life (16).

Reported quality of life also appears to be influenced by gender. In a study by Congleton and colleagues, women with

CF scored significantly worse than the norm in the dimensions of pain, emotion and sleep, whereas for men, lower scores than the norm were seen in the dimensions of energy, pain and social isolation (8). Compared with a healthy population of the same age, there was an age-related trend for men with CF to worsen in several dimensions, including sleep. This trend was not apparent in women (8). In a cohort of adolescents with CF, significant gender differences in HRQoL were found using a generic instrument, the Child Health Questionnaire (17). Even when controlling for age and severity of lung disease, females had significantly lower scores in mental health, global health and perceptions of general health. A study using the CF-specific CFQoL measure also found that females reported poorer HRQoL for chest symptoms, emotional functioning, concerns for the future and career issues, whereas males experienced poorer body image (18).

Sleep Quality in CF

With chronic inflammation and infection, patients with CF develop airflow obstruction, air-trapping and eventually hypoxemia. These abnormalities in lung mechanics, gas exchange and cardiac function eventually lead to sleep abnormalities. In addition, other factors such as chronic sinusitis, cough, reflux, medications and chronic anxiety have the potential to disrupt sleep, impair daytime functioning and affect HRQoL.

Many patients with CF perceive their quality of sleep to be poor, with those individuals with more severely impaired lung function and worse gas exchange more likely to report poorer subjective sleep quality (7). Using the PSQI, several investigators have found that a significant number of patients with CF rate themselves as poor sleepers, with poor habitual sleep efficiency and sleep disturbances being the subcomponents that contribute most to the perception of poor sleep (7, 19).

However, there are few studies that use polysomnographic measures to compare sleep quality and architecture in patients with CF and healthy controls. In a study by Bradley et al. comparing the sleep quality of 14 adult CF patients with moderate lung disease with eight healthy controls, no significant differences in sleep efficiency, arousal frequency or sleep architecture between the two groups were detected, despite the CF group experiencing significantly more sleep hypoxemia (20). Milross et al. also reported normal sleep architecture in a group of stable CF patients with moderate to severe lung disease (7).

In contrast, another group has reported significantly reduced total sleep time (TST) and sleep efficiency in patients with CF and severe lung disease when compared with control subjects (21). This was mainly attributable to prolonged wakefulness after sleep onset. In this study, CF patients also tended to have longer sleep latencies, a higher proportion of Stage I sleep and more movement arousals, although these differences did not reach statistical significance (21). Spier and colleagues also noted reduced sleep efficiency in patients with CF compared with controls, along with less time spent in rapid eye movement (REM) sleep, more awakenings longer than 5 min and more changes in sleep state (22). Patients in this study, like those in the previous study, had severe lung disease, with a mean FEV_1 of 22% predicted.

Several investigators have commented on coughing bouts as a cause of arousal from sleep during overnight studies and have noted the potential for coughing to impact significantly on sleep quality and microstructure in patients with CF (22–24). However, large-scale studies examining this are lacking. With the limited data currently available it appears that sleep architecture and efficiency are probably preserved in CF patients with mild to moderate lung disease. However, as lung function declines, sleep quality, as determined by reduced sleep efficiency, more frequent arousals and more sleep state changes, deteriorates.

One of the limitations of polysomnography (PSG) is that it measures sleep at a single point in time in an artificial environment. It may not, therefore, accurately reflect the patient's habitual sleep pattern. To overcome some of the shortcomings of using a single night of study, recent studies have used wrist actigraphy to document sleep/wake behaviour in this population. Jankelowitz et al. (19) studied 20 young adult CF patients over a 2-week period in their own home and used actigraphy to determine whether sleep quality in CF patients was diminished compared with age-matched controls. The control and CF patients had similar TST, sleep latency and sleep efficiency measures as well as total and mean activity scores. However, CF patients had more restlessness and less immobile time than control subjects. In addition, CF patients displayed greater night-to-night variability in both restlessness and immobile time, a finding consistent with greater sleep disruption. There was also a small but significant association between FEV_1 and both restlessness and immobile time, suggesting a relationship between severity of disease and sleep disturbance.

Wrist actigraphy and questionnaire data have also been used in children with CF to determine the contribution of nocturnal pulmonary and gastrointestinal symptoms to sleep disturbance (25). Compared with age-matched controls, children with clinically stable, mild to moderate lung disease had significantly lower sleep efficiency and more frequent awakenings from sleep compared with control subjects. From the questionnaire data, children with CF reported more frequent awakenings with cough, more frequent awakenings for bathroom use and more frequent difficulty initiating sleep compared with controls. Parents of children with CF also reported that their children had more frequent awakenings with cough, more frequent awakenings for bathroom use and morning sleepiness and more frequent difficulty initiating sleep compared with reports from parents of control children. In this study, lung function was positively correlated with sleep duration and sleep efficiency, and negatively correlated with the duration and number of awakenings after sleep onset. The reported frequency of awakenings because of cough was

independently associated with FEV_1, adding further support to an association between declining lung function and more disturbed sleep.

Causes of Sleep Disturbance in CF

Patients with CF frequently perceive themselves as poor sleepers, and, when measured, their sleep does appear more fractured than that of healthy controls. Although cough no doubt plays an important role in the sleep fragmentation of CF patients, it is unlikely to be the sole contributor to sleep disturbance.

In those with moderate to severe lung disease, sleep-related hypoxemia and alterations in ventilation have been proposed as major contributors to sleep disruption and impaired daytime function. Although relatively few studies have examined the impact of deteriorating lung function on sleep architecture, far more studies have examined the changes in sleep oxygenation that occur in CF. Early studies clearly documented the development of hypoxia and hypercapnia during sleep, most notably during episodes of REM, and primarily in patients with severe lung disease (23,24,26,27) (Figure 44.1). Although further ventilation–perfusion mismatching in those already on the steeper portion of the oxyhemoglobin dissociation curve would be expected to impair oxygenation, changes in neuromuscular output and pattern of ventilation have been shown to be major contributors to the falls in oxygen saturation and rises in carbon dioxide, especially in REM sleep. Ballard et al. were able to demonstrate falls in tidal volume from wakefulness to NREM sleep, resulting in a decrement in minute ventilation. These falls in ventilation were accompanied by a reduction in oesophageal pressure, suggesting a reduction in respiratory drive. Unfortunately, no patient studied was able to achieve REM sleep so it was not possible to determine mechanisms for the more profound falls in SaO_2 that typically accompany this sleep state. However, other investigators have reported reduced chest wall movement (22, 23, 27) or decreased electromyographic activity of the diaphragm (26) during phasic REM, coinciding with reductions in minute ventilation and falls in oxygenation. Milross et al. showed that minute ventilation was significantly lower in REM sleep compared with either NREM or wakefulness and that this resulted in not only poorer oxygenation during REM but also a concurrent rise in carbon dioxide levels (2).

Alterations in ventilation and gas exchange could affect sleep quality and daytime function in several ways. Falls in oxygenation or rises in carbon dioxide might stimulate arousal from sleep or a change in sleep state in order to restore ventilation and blood gases. Hence arousal from sleep might act as a defence mechanism to minimize the consequences of abnormal breathing, although at the expense of causing sleep

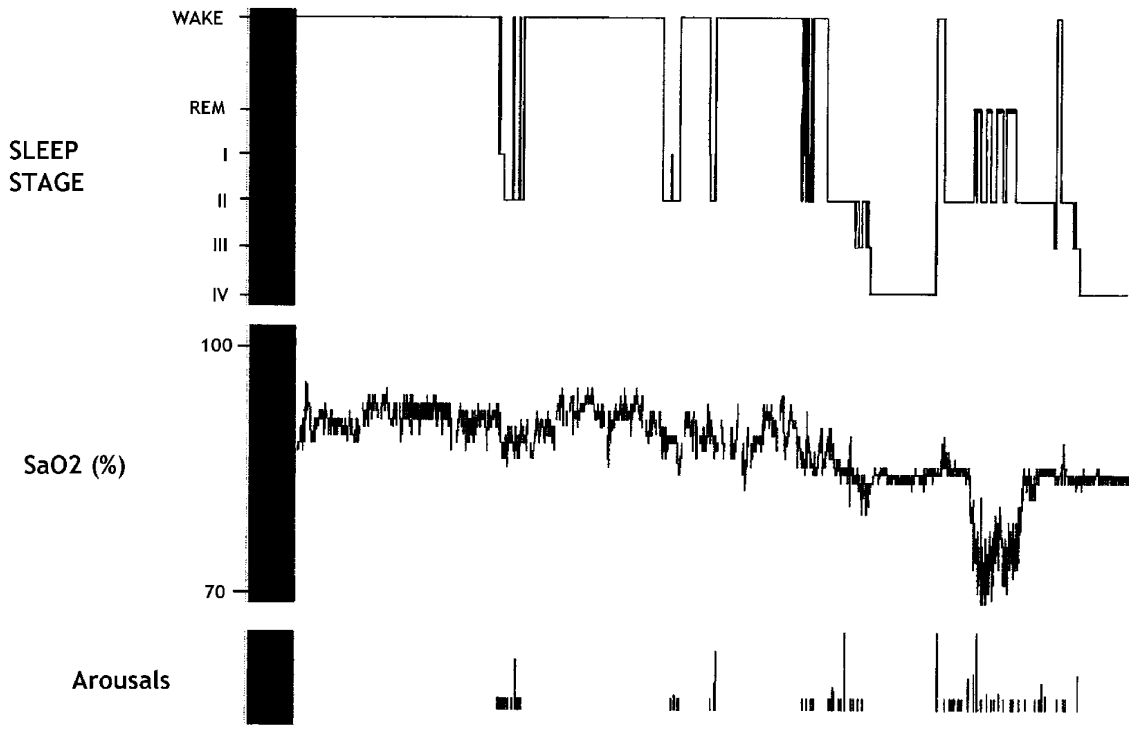

FIGURE 44.1. A sleep hypnogram and overnight oximetry taken from a patient with severe cystic fibrosis lung disease. Sleep architecture is abnormal with poor sleep efficiency. Only one period of rapid eye movement sleep occurred, which was fragmented and associated with significant and sustained falls in oxygen saturation. The sleep and gas exchange abnormalities occurred despite the use of supplemental oxygen.

disruption. However, at odds with this proposal is the finding, in several studies, of an inconsistency in the arousal response following falls in SaO_2 in REM sleep. Both Francis et al. and Spier et al. found that falls in SaO_2 often did not result in arousal (22, 24). Although this might act to preserve sleep architecture, it would expose the patient to prolonged periods of hypoxemia. This could have implications for the progression of respiratory failure and the development of pulmonary hypertension, as well as affecting the quality of sleep itself.

Dancey et al. (21) found a significant correlation between mean nocturnal oxygen saturation during sleep and sleep efficiency, and speculated that sleep hypoxemia might contribute to sleep loss in this population. Similarly, Milross et al. found that the lower the minimum sleep saturation the worse the patient's reported overall sleep quality (7). However, use of oxygen therapy during sleep has not been shown to modify sleep architecture, nor to improve sleep efficiency in patients with CF (2, 22).

Sleep disturbance appears to be a major factor in the poor overall sleep quality that patients with CF report (7). While hypoxia and hypercapnia might contribute to this in the presence of severe lung damage, other mechanisms also need to be considered. As discussed earlier, accumulation of secretions resulting in cough and sleep disturbance has been reported both in polysomnographic studies (22, 23) and in studies using actigraphy (19, 25). Airway inflammation alone might also promote cough in this population (28). Those with more severe lung disease may also experience a high work of breathing. As FEV_1 falls, there is an increase in the elastic load and work of breathing (29), which may worsen during sleep (20). The resulting increased inspiratory effort could be responsible for the increased incidence of awakenings from sleep even in the absence of significant changes in gas exchange (30, 31). Bronchodilators are commonly prescribed for these patients to reduce bronchial obstruction and improve lung function (32). While this may improve overnight oxygenation (33), it may alter sleep quality (21). Gastrointestinal symptoms may be another potential source of sleep disruption. In a survey of CF children and their asymptomatic siblings, Scott et al. found that symptoms of gastroesophageal reflux, heartburn and regurgitation were more frequent in the children with CF than in their siblings and that gastroesophageal reflux was significantly more common in the CF group than in the controls (34). However, there are no data linking symptoms of reflux with sleep quality in this population. Other CF-related gastrointestinal disorders such as nocturnal use of bathroom for defecation might also contribute to disturbed sleep (25).

Relationship Between Sleep Disturbance and Daytime Function

Although patients with CF have more disrupted sleep and rate their sleep as being worse than controls on the PSQI (7, 19) they do not report greater daytime sleepiness as measured by the Epworth Sleepiness Scale (19, 21). However, despite limited data, sleep quality does appear to have an impact on daytime functioning. Using a Mood Scale based on the POMS and the Stanford Sleepiness Scale, Dancey et al. found that CF patients reported significantly lower levels of activation, happiness and greater levels of fatigue compared with control subjects (21). In the CF group, activation was correlated with sleep efficiency and both activation and happiness correlated with wakefulness after sleep onset. In this study, CF patients also showed significant deficits in three of five neurocognitive performances tests, performing at a level of around 60% that of controls. Importantly, performance of these tasks did not improve over the day as it did in control subjects. Neither daytime nor nocturnal oxygenation explained the impaired neurocognitive function and there was no clear relationship between polysomnographic changes in sleep and the daytime performance tests. The authors proposed that the neurocognitive deficits seen in their CF study population may have been related to the long-term impact of chronic sleep deprivation rather than to nocturnal hypoxemia.

Sleep, Lung Function, and Quality of Life

A number of studies have looked at the association between lung function and HRQoL in patients with CF. Most studies have found that patients' psychological function is not essentially different to that of age-matched controls, suggesting that most patients cope well with their disease (12, 35). Rather, quality of life, at least in adults, appears to be affected more by limitations in physical functioning. Dyspnea, reduced exercise capacity and impaired pulmonary function have all been implicated in reduced physical functioning and quality of life (12,36). Gee et al. found that quality of life in adolescents and adults with CF progressively deteriorated as disease severity increased (18). Congleton et al. also found a strong relationship between perceived quality of life and other measures of disease severity such as FEV_1, breathlessness and time spent on home treatment (8). Although Wahl et al. (35) found a generally high level of global quality of life in adults with CF, the lowest global quality of life was reported by those with the most severe lung disease (FEV_1 <30% predicted).

There is limited information about the effect of disease severity on sleep quality or about the impact of sleep quality on perceived global quality of life. In the few studies that have examined sleep and breathing, attention has focused on ventilation and gas exchange (2, 37). Although resting awake saturation, exercise tolerance and lung function have been found to be of limited value in predicting nocturnal desaturation, it can be said that nocturnal desaturation is less likely to occur when FEV_1 percent predicted is greater than 65 and stable awake resting SaO_2 is greater than or equal to 93% (38). However, a clear relationship between abnormalities of nocturnal gas exchange and sleep quality has not been established. One study has demonstrated a relationship between nocturnal hypoxemia and reduced sleep efficiency

on PSG (21), whereas another study has demonstrated a relationship between worse overall sleep quality and lower minimum sleep SaO_2 (7). However, these findings may also have been related to the severity of lung impairment in the patients studied. Amin et al. (25) found that sleep efficiency decreased with increasing severity of lung disease. Significant proportions of CF patients rate their sleep quality as poor and attribute this perception most frequently to reduced sleep efficiency and sleep disturbance (7). Actigraphy monitoring has also shown that restlessness is correlated with FEV_1 percent predicted (19). However, no significant correlations between sleep disruption and daytime function or quality of life have been established (19).

Impact of Acute Exacerbations on Sleep and Daytime Function

CF is characterized by frequent pulmonary exacerbations, during which time lung function worsens while sputum production and work of breathing increases. Sleep hypoxemia and fragmentation could conceivably worsen during these episodes. Increased cough leading up to and during the initial stages of the exacerbation could also add to poor sleep quality (28). With greater sleep disturbance, daytime function and quality of life are also more likely to be adversely affected. However, despite the high incidence of exacerbations, particularly in those with severe disease, investigations in this area have been limited.

Acute pulmonary exacerbations have been shown to cause a deterioration in HRQoL, which improves following treatment (39, 40). It appears that physical aspects of HRQoL are affected more than the psychosocial aspects (40), with improvement in pulmonary function correlating with improvement in HRQoL (39). In a cross-sectional analysis, recent pulmonary exacerbations were found to be the most important factor determining physical and psychosocial HRQoL in patients with CF (6). It was suggested that HRQoL in CF patients had more to do with the disruptive effects of the exacerbations than with the severity of the underlying lung disease (6). However, any relationship between acute pulmonary exacerbations and sleep disturbance was not addressed in this study.

Dobbin et al. (3) studied 22 patients with acute exacerbations at the beginning of their hospital admission. These patients with exacerbations experienced reduced sleep efficiency, more time awake after sleep onset, reduced amounts of REM sleep and more sleep hypoxemia when compared with stable CF controls. Those individuals with worse lung function experienced more severe sleep hypoxemia during exacerbations. By the end of the 10- to 14-day treatment period, sleep architecture had improved to levels similar to those seen in the stable CF group. Gas exchange during sleep also improved significantly. When admitted with an exacerbation, patients reported more respiratory symptoms, a worse perception of their health state, and reduced physical functioning and vitality than control subjects. After inpatient treatment, they reported a reduced treatment burden compared with controls and demonstrated significant improvements in 8 of 12 dimensions of the CFQ. No dimension of the CFQ changed significantly in control subjects between study visits. Significant improvements in subjective sleepiness and neurobehavioural performance, as assessed by a psychomotor vigilance task and a driving simulator task, also occurred with treatment (Figure 44.2). However, correlations between neurobehavioural function and objective measures of sleep fragmentation or hypoxia were not performed. Although not proven, the results of this study suggested that the effects of exacerbations on cognitive function and quality of life could be related to the physiological consequences of exacerbations on sleep and gas exchange. Given that a number of patients can now be treated at home during exacerbations, it would be interesting to compare the effects of home-based versus inpatient treatment on cognitive function and quality of life (3,40).

Treatment

A significant proportion of patients with CF develop cor pulmonale. Patients with pulmonary hypertension have increased mortality compared with patients of similar disease severity without pulmonary hypertension (41). Pulmonary hypertension is correlated strongly with hypoxemia (41). Oxygen therapy is widely used in this patient population to minimize or eliminate hypoxemia, including that seen during sleep. However, whether treatment with oxygen slows disease progression or improves daytime function remains uncertain because of a lack of large-scale, properly controlled trials examining relevant outcomes. Spier et al. studied eight CF patients on consecutive nights using either low-flow oxygen or room air (22). Although supplemental oxygen improved nocturnal saturation, it produced no change in sleep architecture or sleep efficiency. It did, however, significantly reduce the number of sleep stage changes per hour from 10.1 to 8.1. Milross et al. (2) also found no change in sleep architecture or arousal when using low-flow oxygen to maintain oxygen saturation above 90% throughout the night. Gozal (42) reported an increase in the amount of REM sleep with oxygen use, but no other sleep measure, including NREM duration, sleep latency or arousal index, changed. These studies were all single night interventions, and there are no data looking at either objective sleep disturbance or subjective sleep quality with longer term nocturnal oxygen use.

In the only long-term study comparing nocturnal oxygen to room air in patients with CF, no change in survival, frequency of hospitalizations, right-sided heart function, or disease progression were found between the two groups (43). Furthermore, oxygen therapy did not improve mood, self-esteem or cognitive function, although more participants in the oxygen arm of the study reported regular attendance at school or work after six and 12 months of therapy.

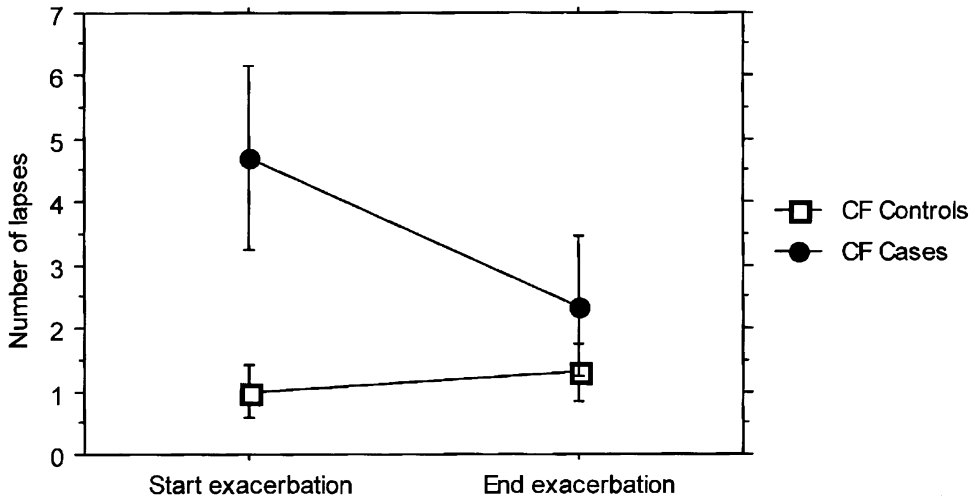

FIGURE 44.2. Cystic fibrosis (CF) patients studied at the beginning of a pulmonary exacerbation have significantly more lapses (i.e. response time >500 ms) ($p < 0.05$) on a psychomotor vigilance task than stable CF controls. At the end of treatment for the exacerbation, there is no significant difference in the performance of cases and controls.

Patients with advanced lung disease hypoventilate during sleep and especially during REM sleep. Non-invasive ventilatory (NIV) support has been advocated as a therapeutic option to maintain alveolar ventilation and minimize the retention of carbon dioxide (2, 42). However, few studies have evaluated the effectiveness of nocturnal NIV. Two studies have compared NIV with supplemental oxygen and both were single night interventions (2, 42). Both oxygen therapy and NIV were superior to room air in maintaining oxygenation during sleep. However, compared with oxygen therapy alone, NIV was able to maintain higher minute ventilation in both NREM and REM sleep, resulting in less carbon dioxide retention. Sleep architecture was similar during the night spent on oxygen and the night spent on NIV. Recent preliminary data from a six-week, randomized crossover trial comparing NIV to oxygen and air has provided some evidence that NIV can improve quality of life, nocturnal hypoventilation and exercise capacity in hypercapnic CF patients. However, no changes in lung function, sleep architecture or daytime hypercapnia were observed (44). Further studies, conducted over longer periods, are required to confirm these findings to assist clinicians and patients in determining the benefits and costs of these therapies.

Conclusions

In a chronic illness such as CF the dual goals of care are to improve quantity and quality of life. When instituting therapy in these patients, it is important that we not only monitor physiological changes, in pulmonary function and exercise capacity, for example, but that we also take into account the impact these therapies have on HRQoL. For over 20 years, abnormalities in nocturnal gas exchange and sleep disruption have been recognized as part of the clinical picture of disease progression in CF, with patients themselves frequently reporting poor quality sleep due to sleep disturbance. However, scant attention has been paid to how sleep abnormalities may impact on patients' daytime functioning and quality of life. Although reduced sleep quality and quantity appear to be related to severity of lung disease, and poorer lung function is associated with reduced HRQoL in the physical domain, a definite link between the two is yet to be established. Oxygen therapy, and to an increasing extent NIV, is now used routinely to improve gas exchange during sleep. However, there is no evidence that these interventions have any long-term positive impact on a patient's daytime function or quality of life. Understanding the interaction between sleep disturbance and CF lung disease could have important therapeutic implications, but substantially more work needs to be done to determine whether optimizing sleep quality in CF is able to modify the clinical course of the disease and improve quality of life.

Issues that need to be addressed by future research:

- Further study into the neurocognitive deficits that develop in patients with cystic fibrosis and severe lung disease and the impact, if any, of therapy to correct hypoxia.
- Longitudinal studies looking at the relationship of sleep quality and health-related quality of life.
- Further investigation into the impact of acute pulmonary exacerbations on sleep disturbance and cognitive function.

- Comparison of home-based versus inpatient treatment of acute exacerbations on cognitive function and quality of life.
- Large randomized trials evaluating nocturnal oxygen and NIV therapy on sleep quality, HRQoL and survival.

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Sleep and Systemic Lupus Erythematosus

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Summary It has become increasingly evident that sleep problems are common in patients with systemic lupus erythematosus (SLE). Approximately 56–60% of patients with SLE report poor sleep quality, characterized mainly by difficulties initiating and/or maintaining sleep. Emerging data also indicate that sleep respiratory and movement disorders are prevalent in patients with SLE. Despite their prevalence and potential to negatively impact health and quality of life, sleep problems remain underrecognized, undertreated and understudied in this patient population. Only a handful of studies have been conducted to investigate determinants of sleep problems in SLE. The findings to date suggest that disease expression (activity, pain), behavioural and psychosocial factors including physical inactivity and depressed mood contribute to sleep problems in SLE. More studies, integrating a biopsychosocial approach, are needed to clarify the specific factors and underlying mechanisms that trigger and maintain sleep problems in SLE. The course of sleep problems in SLE remains unknown as studies have been cross-sectional. Directions for future research are discussed herein. Routine assessment and management of sleep problems in SLE should be part of the comprehensive care of patients with SLE. While effective pharmacological and nonpharmacological treatments are available to manage sleep problems, there are currently no studies which have specifically evaluated these strategies for patients with SLE. Given the complex interplay of factors contributing to sleep problems in SLE, a multimodal treatment approach combining several nonpharmacological strategies and possibly medication for more chronic and difficult cases, should be utilized for the management of sleep difficulties in SLE.

Keywords Systemic lupus erythematosus · sleep problems · biopsychosocial · depression · multimodal management

Learning objectives:

- Sleep disturbance are highly prevalent among patients with SLE.
- Sleep problems remain underrecognized, undertreated and understudied in SLE.
- Disease expression, behavioural and psychosocial factors including physical inactivity, depressed mood and stress contribute to sleep problems in SLE.
- A multimodal treatment approach combining several nonpharmacological strategies and possibly medication for more chronic and difficult cases, is recommended for the management of sleep difficulties in SLE.

Introduction

Many patients with systemic lupus erythematosus (SLE) report difficulty sleeping even when their illness is well controlled. This chapter aims to provide a better understanding of the nature of sleep difficulties in persons with SLE and the factors associated with poor sleep in this patient population. The prevalence of sleep difficulties in SLE will be reviewed. Determinants of sleep difficulties emerging from published SLE studies will be described, along with potential physiological and psychological mechanisms that may explain sleep difficulties in SLE. Although there are no evidence-based guidelines for managing sleep problems in patients with SLE, assessment methods and treatment strategies will be addressed. Finally, this chapter will conclude with recommendations for future empirical studies.

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Systemic Lupus Erythematosus

Epidemiology

SLE is a chronic autoimmune disease that can affect multiple organs and systems. The annual incidence of SLE, depending on the population studied (i.e. age, gender, race) ranges from 2.0 to 7.6 per 100,000 persons per year (1). Prevalence rates also show a wide variability with rates reported to range between12.5 and 52.0 per 100,000 persons (1). Although SLE can develop at any age, the highest incidence is found in young women with a peak onset between the ages of 20–40 years. The female to male ratio is 9:1, and SLE is more common in persons of African and Asian descent (2, 3). The survival rate for SLE has improved significantly over the last four decades from less than 50% at 5 years to a 20-year survival of 68% in the 1990s (4, 5). Consequently, the spectrum of morbidity features for patients with SLE has evolved.

Etiology

No single cause for the development of SLE has been identified. Findings suggest that the pathogenesis of SLE is multifactorial, including a complex involvement of genetic, environmental and hormonal factors that interact to cause a state of immune hyperactivity (6, 7).

Clinical Features and Diagnosis

SLE is a chronic, recurrent disorder with a broad spectrum of clinical and immunological manifestations. Common symptoms include fatigue, malaise, fever, weight loss, skin rash, photosensitive skin, hair loss, pleuritic chest pain, arthritis and symptoms of dry eyes and mouth. The disease can also affect one or more tissue and organ systems including renal, gastrointestinal, neurological and cardiovascular. SLE is highly heterogeneous, affecting different target organs in different individuals. Organ involvement can also change in the same patient. Its clinical course is unpredictable and characterized by exacerbation of symptoms or "flares" (potentially accompanied by significant organ involvement) followed by periods of remissions.

Given the diversity of organs that can be possibly involved and the wide range of manifestations, it is not surprising that diagnosis is difficult and often delayed particularly for patients presenting with low grade disease (8). Currently, there is no single diagnostic marker to determine whether a person has SLE. The diagnosis of SLE is based on a combination of clinical and laboratory criteria. The American College of Rheumatology (ACR) in 1982 established a list of 11 criteria (9), which has since been revised (10), to assist in the diagnosis of SLE (see Table 45.1). This widely used criteria indicates that the diagnosis of SLE requires the presence of four or more symptoms, which do not necessarily have to occur during the same period.

Treatment

An individualized treatment approach is used to manage the patient with SLE due to the wide range of clinical manifestations and level of illness severity found across patients. Pharmacological management can include one or a combination of the following: nonsteroidal anti-inflammatory drugs (NSAIDS); corticosteroids; antimalarials; and/or immunosuppressives (e.g., azathroprine, cyclophosphamide). Long-term morbidity has been associated with the side effects of medications, particularly corticosteroids (coronary artery disease, osteoporosis, osteonecrosis) and cyclophosphamide (infection, infertility, malignancy, bladder toxicity). An important goal in the comprehensive management of SLE is to prevent co-morbid conditions such as atherosclerosis and osteoporosis and improve health status and overall quality of life (11).

SLE and Sleep Difficulties

Sleep disturbances are more common in persons with chronic conditions (12). Despite the probable negative impact of sleep disturbance on daily functioning and quality of life among

TABLE 45.1. American College of Rheumatology classification criteria for systemic lupus erythematosus.

Criterion	Definition
1. Malar rash	Fixed, flat or raised rash over the cheeks
2. Discoid rash	Red, raised patches anywhere on the body
3. Photosensitivity	A skin rash that develops as a result of exposure to sunlight
4. Oral ulcers	Ulcers in the mouth or nose, usually painless
5. Arthritis	Nonerosive arthritis involving two or more peripheral joints
6. Serositis	Inflammation around the lining of the lung (pleuritis) or the heart (pericarditis)
7. Renal disorder	Persistent excessive protein in the urine and/or cellular casts
8. Neurologic disorder	Seizures and/or psychosis occurring in the absence of drugs or metabolic disturbances known to cause such effects
9. Hematologic disorder	Hemolytic anemia or leucopenia (white blood count < 4000 cells per cubic millimeter or more on teo occasions) or lymphopenia (<1500 lymphocytes per cubic millimeter on 2 or more occasions) or thrombocytopenia (<100,000 platelets per cubic millimeter, detected in the absence of drugs known to trigger it)
10. Antinuclear antibody (ANA)	Positive laboratory test for ANA in the absence of drugs known to trigger it
11. Immunologic disorder	A positive laboratory test for anti-double-stranded anti-DNA or positive antiphospholipid antibody

Any combination of 4 or more of the 11 criteria occurring simultaneously or serially are required for a diagnosis of SLE (9, 10).

persons with SLE, sleep problems in lupus remain underrecognized, understudied and undertreated. Sleep difficulties have recently been found to be among the 10 highest unmet needs reported by SLE patients (13). Much of what has been reported on sleep problems in SLE is based only on a handful of studies, with most relying exclusively on subjective measures of sleep (see Table 45.2).

The Nature of Sleep Difficulties in SLE

Only two studies in SLE have used objective measures of sleep, i.e. polysomnography (PSG), and both have found evidence of sleep disturbances in SLE patients compared with that in healthy controls (14,15). SLE patients have been found to spend a larger amount of time in stage 1 sleep (lighter sleep stage), less time in slow-wave sleep and show a high percentage of alpha frequency intrusion into non-REM sleep (15). A similar alpha–delta pattern has been reported in other forms of arthritis (i.e. fibromyalgia and rheumatoid arthritis). This pattern has been correlated with patient reports of unrefreshing sleep and tiredness upon awakening (16, 17). Robb-Nicholson and colleagues (18) found that 61% of SLE patients report not feeling refreshed from sleep.

Sleep fragmentation refers to the disruption of continuous sleep by frequent and often lengthy awakenings at night. Using the Pittsburgh Sleep Quality Index (PSQI) (19), a standardized self-report measure of subjective sleep quality, evidence of sleep fragmentation, with reduced total sleep time (TST) (6.9 $\pm$ 1.6 h; range= 1.5–11) has been reported in SLE (20). More recently, Iaboni and associates (15), using PSG found a similar range of TST in their sample of SLE patients. However, they did not find TST in the SLE group to differ significantly from the healthy control comparison group. While a TST in the range of 5–7 h may not be uncommon in the general population, it is lower than the 8 h recommended as ideal by the National Sleep Foundation (21). This study did find evidence of sleep fragmentation, as the SLE group had significantly higher number of arousals per hour of sleep (4.26 $\pm$ 2.6) compared with healthy controls (2.6 $\pm$ 1.7) (15).

Sleep efficiency is the ratio of total sleep time (TST) to time in bed (TIB) (TST/TIB $\times$ 100) and represents an overall index of how well a person sleeps (22). A sleep efficiency greater than 90% is indicative of good sleep (23). Sleep efficiency has been found to range between 75.0 and 84.5% in patients with SLE (15,20), which is considerably lower then the 90% cutoff. *Sleep latency* reflects time elapsed between going to bed and the onset of sleep. Although there is little data published on sleep latency in SLE, initial evidence suggests that it appears to be more prolonged in persons with SLE. Da Costa and colleagues (20) using the PSQI found a mean sleep latency of 25 $\pm$ 24.1 min in SLE patients, which is more prolonged than the 10 min reported by healthy persons (22). In this study, poor sleep quality was found in 56% of SLE patients (20), which is similar to the 60% reported by Tench and colleagues (24) in their SLE sample using the same sleep index. Together, these findings suggest that sleep disturbance is more prevalent in SLE compared with that in the general population (9–40%) (19, 25, 26).

Sleep apnea refers to periodic cessation of breathing during sleep either by disruptions of the respiratory drive or by intermittent obstruction of the airway effects 1–5% of the adult population (27). Restless leg syndrome (RLS) is characterized by unpleasant sensations, such as tingling, crawling and pulling in the legs, resulting in an urge to move the legs (28). RLS symptoms are worsened by rest, relieved by movement and most severe at night. RLS occurs in 10–15% of the general population and is more common in women and in certain chronic conditions (28). Evidence for both respiratory and movement disorders during sleep has been reported in SLE. One study conducted in Mexico with 14 SLE patients found that 3 of the 14 patients (21.4%) had moderate sleep apnea (quantified as a respiratory disturbance index between 10 and 30) and 4 patients (28.6%) showed slight abnormality in respiration during sleep (defined as respiratory disturbance index greater than 5 but less than 10) (14). Five patients (35.7%) of the sample fulfilled objective criteria for movement disorder during sleep (14). Recently, Iaboni and colleagues (15) found that 57% of SLE patients had some degree of sleep respiratory disturbance, with 26% found to have sleep apnea and 23% periodic leg movement disorder. Both respiratory and movement problems during sleep have been associated with difficulties initiating sleep, frequent sleep fragmentation and daytime sleepiness in other populations (29). Iabono and colleagues (15) did not find daytime sleepiness to be associated with a higher rate of sleep problems. The limited studies published to date using PSG data suggest that respiratory and movement disorders are prevalent in SLE patients.

TABLE 45.2. Sleep difficulties in systemic lupus erythematosus.

Sleep difficulty	Subjective evidence	Objective evidence
Prolonged sleep latency	√	
Longer sleep time in stage 1 and less in stage 3 and 4		√
Numerous arousals	√	√
Decreased total sleep time	√	
Reduced sleep efficiency	√	√
Unfreshed sleep upon wake time	√	
Restless legs		√
Sleep respiratory problems		√

Determinants of Sleep Difficulties

Sleep problems in SLE are most likely multi-determined, modulated by factors such as disease status, behavioural and psychosocial variables. Evidence for each of these factors will be examined, along with a biopsychosocial model using the existing knowledge base to better understand the interplay between potential contributing factors and sleep disturbance in persons with SLE.

Disease-Related Factors

Disease Activity

Several studies, mostly aimed at better understanding fatigue, have indirectly examined the relationship between disease activity and sleep problems in SLE. Disease activity has been assessed in these studies with standardized measures including the Systemic Lupus Activity Measure (SLAM) (30) and the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) (31). Valencia-Flores and associates (14) in the small cohort of SLE patients (n = 14) found that those with active disease reported significantly poorer sleep efficiency, longer stage 1 sleep, shorter slow-wave sleep and more number of arousals compared to patients with inactive disease. Another study found sleep complaints were more frequently reported by SLE patients who had more active disease, especially those with central nervous system involvements (CNS), compared to patients with less active disease (32). In contrast, Tench and associates (24) reported only a weak correlation between disease activity and sleep quality in SLE. The studies thus far described were restricted by utilizing only univariate or bivariate statistical analyses. Da Costa and colleagues (20) when using bivariate analyses, also found an association between disease activity and sleep quality assessed with the PSQI. However, this association did not remain significant in the multivariate analysis, suggesting that the relationship between sleep and disease activity may be weak and nonlinear.

Cytokines

Cytokines which are secreted by immune cells, play an important role in maintaining the balance of the body during infectious challenges and inflammation. Proinflammatory cytokines when secreted in high levels can cause damage, including inflammation, cellular injury and potential debilitation of the organs involved. Various cytokines have been shown to be highly elevated in persons with SLE (33, 34). Researchers believe that the altered cytokine milieu may be crucial to the variety of clinical manifestations found in SLE (35, 36).

Accumulating evidence suggests that cytokines play a role in physiological sleep regulation. Several cytokines are somnogenic, including interleukin 1 (IL-1), a and b, tumour necrosis factor (TNF) a and b, interferon-a (IFN-a), while interleukin 10 and interleukin 1 receptor antagonist inhibit sleep (37). When altered in response to inflammation, higher levels of cytokines can alter sleep architecture (37). In autoimmune diseases, the elevated levels of proinflammatory cytokines may influence daytime sleepiness and disrupt nocturnal sleep (38). This pathway remains to be explored in SLE. Importantly the relationship between cytokines and sleep has been found to be bidirectional, with altered sleep also influencing cytokine levels in other populations (39–41) which may further impact the inflammation process in at risk populations. Taken together, the findings to date highlight the need to elucidate the potential link between cytokines and sleep patterns in SLE.

Pharmacological Agents

Corticosteroids, which are commonly used in the treatment of SLE, can induce depressed mood and sleep disturbances (42). In a recent review addressing psychiatric adverse effects of corticosteroid therapy, Warrington and Bostwick (42) conclude that dosage is the most important risk factors for the development of adverse effects, with patients receiving less that 40 mg/day at minimal risk, those taking 40–80 mg/day at moderate risk, and patients taking more than 80 mg/day at higher risk. In SLE, the evidence is inconsistent regarding the role of corticosteroid treatment on sleep impairment. Use of prednisone in the Da Costa and associates (20) study was marginally associated with sleep disturbances. However, others have not shown a relationship between use of corticosteroids and sleep disturbance in SLE (14, 24, 32). While fewer patients in the Da Costa (20) SLE sample were using corticosteroids, a greater proportion were taking higher doses of corticosteroids compared to previous studies (14, 24, 32), which may partially explain their results. Collectively, the findings to date regarding the effect of prednisone on sleep disturbance in SLE suggest that it does not play a major role in disrupting sleep among persons with SLE, but in high doses may play a secondary role.

Fibromyalgia

Secondary fibromyalgia (FM) has been reported in 9.5–25% of SLE patients (14, 43–45). FM is characterized by symptoms of widespread musculoskeletal pain and multiple tender points at specific anatomical sites (46). Fatigue and nonrestorative sleep, while not essential for diagnosis of FM according to established criteria, are also common features. The presence of FM has been associated with poor sleep quality in SLE patients (14, 20). Valencia-Flores and colleagues (14) found that SLE patients with co-morbid FM reported having more sleep fragmentation and poor sleep compared with SLE patients without FM. However, Da Costa and colleagues (20) found no relationship between the presences of FM and sleep problems in their SLE sample.

Although there are limited studies to make a definitive conclusion on the role of FM to sleep disturbances in SLE, it seems unlikely that FM is a major determinant.

Pain

Pain related to arthritis and arthralgias has been reported in up to 95% of SLE patients (47–49). In other rheumatic conditions (i.e., RA and FM), the relationship between pain intensity and sleep problems has been firmly documented (50). Only a few studies have examined the relationship between pain and sleep in SLE. Tench and associates (24) reported a moderate correlation between pain and poor sleep quality in SLE, noting that pain from joints or muscles may be a factor disturbing sleep. Another study found patients with SLE reported significantly more pain when trying to fall asleep and during the night compared with age-matched controls (32). Both Valencia-Flores and colleagues (14) and Da Costa and associates (20) using multivariate analyses found very weak relationships between pain and sleep disturbance, suggesting that this factor unlikely plays a primary role in sleep problems in SLE.

In summary, the cross-sectional nature of the data published to date and the weak or insignificant relationships found between disease-related parameters and sleep difficulties, indicate not only that the pathogenesis of sleep remains poorly understood and that factors in addition to disease expression likely influence the sleep problems experienced by persons with SLE.

Behavioral and Psychosocial Factors

Physical Activity

There is a general belief among sleep exerts (51, 52), primary care physicians, exercise scientists (53, 54), and the general public (55) that regular physical activity promotes sleep. Yet, recent reviews have concluded that the empirical evidence to support the sleep-promoting effects of exercise is not compelling (56, 57). This is likely attributable to the numerous methodological limitations in published experimental studies to date (56, 57). In a most recent review of exercise and sleep, Driver and Taylor (57) suggested that in clinical populations regular exercise is a useful modality for improving sleep quality and managing difficulties initiating and maintaining sleep. The mechanisms by which exercise may improve sleep quality is not well understood. There is some evidence to suggest physiological pathways including muscular relaxation, decreases in sympathetic tone, or thermal changes induced by exercise, which may promote sleep (58–60). Exercise has also been associated with improvements in depressed mood and anxiety levels (61–63) both of which also influence sleep quality.

Evidence for physical deconditioning including reduced aerobic capacity and muscle strength has been reported in patients with SLE (18, 64–67). Although physical deconditioning has been associated with increased levels of fatigue in SLE (64, 67), no study has examined its relation to sleep parameters. Only one study has examined the relationship between self-reported physical activity and sleep quality. In an observational study, Da Costa and colleagues (20) found, using multivariate analyses, that engaging in less leisure time physical activity was associated with poorer sleep quality. Interestingly, greater exercise participation was associated with less depressive symptoms in this SLE sample, suggesting that this may be an important psychosocial mechanism involved in the sleep-enhancing effects of exercise. Although preliminary, there is some initial evidence to suggest that lack of physical activity may be contributing to poor sleep quality in a subgroup of patients with SLE. The potentially beneficial effect of exercise has important clinical implications, as moderate-intensity exercise has been shown to be a useful nonpharmacological intervention for enhancing sleep quality (68) and psychological well-being in other patient populations (61–63).

Depression

The co-morbidity of sleep disturbances and depression has been well documented (69). The relationship between sleep difficulties and depression is likely bidirectional. Epidemiological studies estimate that 50–90% of persons diagnosed with depression report impaired sleep quality (69, 70). Sleep impairments commonly reported by depressed patients include sleep fragmentation and prolonged sleep latency (71). It has also been consistently demonstrated that disturbed sleep is an important independent risk factor for a new or recurrent depressive episode (71–74).

Among the psychological symptoms that can emerge secondary to a chronic medical condition, depression is the most common. The prevalence of major depression in patients with SLE, using structured psychiatric interviews ranges between 22.5 and 35% (18, 75). Much higher rates (up to 80%) have been observed when using standardized self-report instruments (76–80). These rates are much higher than in the general population (81), but similar to patients with other chronic diseases (82). Depression in SLE is likely related to multiple factors including the stress of living with a chronic illness, stressful life events, emotional coping, and more active disease (75, 78–79).

Several studies in SLE have reported an association between depressive symptoms and sleep disturbances assessed by PSG or self-report (14, 20, 83, 84). Valencia-Flores and colleagues (14) using PSG data found depressed mood to be correlated with various parameters of respiratory disturbances during sleep, but not with REM sleep latency. Da Costa and colleagues (20) using multivariate analyses with key demographic, clinical, behavioural and psychosocial variables in the model found depressed mood to be the strongest

predictor of poorer sleep quality in SLE patients. Collectively, the findings to date suggest a relationship between depressed mood and impaired sleep in SLE. The direction of the relationship in SLE is unknown, but there is preliminary evidence that similar to findings in other populations, the link is likely bidirectional. McKinley and associates (83), in a series of meditational analyses to understand fatigue in SLE, found evidence to support a reciprocal relationship between sleep disruption and depression. Together, these findings underscore the importance of screening and adequately managing both depression and sleep problems in SLE.

Stress

Clinicians note and patients often report that stressful events or experiences provoke exacerbations of SLE symptoms. Wekking and colleagues (76) explored this relationship in a small sample of SLE patients and found a significant relationship between daily stressful experiences and illness-related variables (e.g., renal function, pain, physical ability, and autoantibodies). Our own work has shown a prospective relationship between negative life events in the preceding 6 months and increased physical disability in women with SLE (85). In the sleep research, stress has been consistently linked to disturbed sleep patterns (86–88). For instance, Morin and colleagues (88) found that while poor and good sleepers reported similar numbers of minor stressful life events, the appraisal of stressors differed, with poor sleepers evaluating both daily minor events and major life events as more stressful compared with good sleepers. Poor sleepers also relied more on emotion-oriented coping strategies and showed higher presleep arousal, which together may mediate the relationship between stress and sleep. Like with depression, the relation between stress and sleep problems is likely bidirectional, with stress interfering with sleep and sleep disruptions eliciting more stress (87). These findings highlight the need to investigate of the role of stress on sleep problems in SLE, which to date remain unexplored.

Sleep disturbance in SLE appears to be multifactorial, with behavioural and psychosocial factors likely being important in the maintenance of the sleep problem. Although specific disease-related, behavioural and psychosocial factors have been associated with sleep problems in SLE, the exact mechanisms underlying the observed relationships remain at an embryonic state of knowledge. The few studies conducted to date at times have shown discrepant findings, which may be due to methodological differences in the assessment of sleep parameters and potential contributing factors which limit generalizability of the findings and make comparisons across studies difficult. Few studies have used PSG to objectively assess sleep parameters in this patient population. Even the two that have used PSG (14, 15) have had small sample sizes and did not control for first night sleep effects. Additional limitations in the SLE sleep research include inadequate inclusion of behavioural and psychosocial variables, cross-sectional designs hindering inferences about the causal sequence of the relationships observed, and the lack of a theoretical framework to guide the selection of potentially important variables and underlying mechanisms.

Proposed Biopsychosocial Model of Sleep Disturbance in SLE

Figure 45.1 depicts a model guided by a biopsychosocial conceptual framework that can be applied to help elucidate variables influencing sleep disturbance in SLE. The variables included in this model were derived from existing sleep studies in SLE and from studies in the sleep area. The model includes three broad components that can trigger and/or influence the maintenance of sleep problems. Certain relationships in the model are considered to be more hypothetical than others, and the strength of the relationships are not assumed to be equivalent. The model depicts the complex interplay between variables and sleep disturbance in SLE. It is important to note that given the current state of knowledge, it is unknown whether these components directly or indirectly influence sleep disturbance through their impact on other variables. For instance, disease activity may directly result in disturbed sleep. Alternatively, disease activity may influence sleep indirectly by decreasing physical activity participation, increasing depressed mood, and stress. Finally, a factor may moderate the effect of a specific variable on sleep. For example, pain severity may influence sleep only for patients who are physically inactive.

Clearly, more studies are needed to clarify the factors that influence sleep in SLE. A biopsychosocial approach should be used to guide future sleep studies in SLE. Clinically, the model also depicts the importance of assessing and addressing potentially important behavioural and psychosocial factors to improve sleep in SLE.

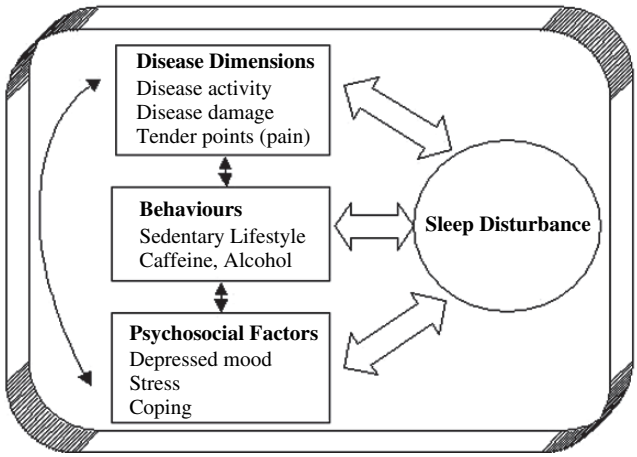

FIGURE 45.1. Biopsychosocial framework adapted to elucidate factors related to sleep disturbances in systemic lupus erythematosus.

Recognizing and Managing Sleep Difficulties in SLE

Patient complaints of sleep problems tend to be dismissed by primary care physicians (89). Given the numerous and complex symptom manifestations that can arise in SLE, it is not surprising that sleep complaints tend to be underrecognized and undertreated in this patient population. However, physicians involved in the care of SLE patients should recognize that sleep problems can complicate the management of SLE by further impairing patient quality of life (90), increasing fatigue (83), triggering or worsening depression (72), increasing work absenteeism (91), and increasing health care costs (92). Moreover and of particular relevance to SLE, experimental studies inducing a partial night of sleep deprivation typical to what patients with chronic medical diseases experience show alternations in immune function, which may negatively influence inflammatory disease progression and cardiovascular risk (93–95). For instance, partial night sleep deprivation has been associated with abnormalities in nocturnal secretion of IL-6 (96, 97). Irwin and colleagues (97) recently found more than a threefold increase in transcription of IL-6 messenger RNA and a twofold increase in tumor necrosis factor-α messenger RNA in the morning following a partial night of sleep loss. Taken together, these findings suggest that adequate sleep is essential to the maintenance of health status and quality of life in persons with SLE.

Routine screening and adequate treatment of sleep problems should be an important component of the comprehensive care of SLE patients. A clinical assessment can be done to ascertain the nature of the sleep problem. Culpepper (98) outlined key questions to ask patients in order to better define the sleep problem and the need to proceed further with assessment and treatment. These include:

- Does the patient have difficulty falling asleep or maintaining sleep?
- Does the patient feel refreshed upon awakening in the morning?
- Is the sleep problem occurring every night or is it occasional?
- Is the problem recent?
- How has the patient coped with the problem?
- What does the patient perceive to be the cause of the problem?
- Does the patient feel an intervention is required?

Physicians should also inquire about any agents that could impair sleep including, caffeine, tobacco, alcohol, and certain medication classes (98). Qualitative and quantitative self-report scales of sleep can also be administered to further clarify the nature of the problem. For example, The PSQI (19) assesses sleep quality and disturbances over a 1-month time interval. It includes subscales assessing subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. By summing the subscales, a global score is generated to represent a composite of sleep quality and quantity (19). The PSQ has previously been used in SLE patients (20, 24).

Referral to a sleep clinic for an overnight PSG is useful for providing objective evidence for the complaint of unrefreshing sleep and to ascertain diagnosis when there is uncertainty or when the patient has failed to respond to treatment (98, 99).

To date, no studies have been conducted to evaluate specific treatments for managing sleep problems in SLE. As such, there are currently no recognized guidelines available to manage sleep problems for patients with SLE. Much of what is reviewed herein comes from the literature with other chronic musculoskeletal conditions (i.e., fibromyalgia, rheumatoid arthritis) or insomnia patients. Pharmacological agents intended to promote sleep may help for a subgroup of patients. Triazolam, for example, has been shown in RA patients to improve TST, reduce daytime sleepiness, and improve morning stiffness (100). The lasting effects of these agents in SLE are unknown, and many patients may refuse to take sleep-promoting medications for fear of side effects, interactions with other medications, and dependency. Nonpharmacological interventions may be an effective and more feasible treatment option for the management of sleep problems in SLE.

Nonpharmacological treatments that may be useful include sleep hygiene, cognitive behavioural therapy, relaxation and aerobic exercise (101–103). Controlled studies with SLE patients are needed to determine whether the benefits of these sleep-enhancing interventions extend to this patient population. With respect to aerobic exercise, it has been documented in SLE patients with low to moderate disease activity that low to moderate intensity exercise does not exacerbate symptoms or disease activity (18, 77, 104–107). Although a handful of randomized clinical trials have shown that moderate intensity exercise improves fatigue, depression, physical functioning, cardiovascular capacity and health-related quality of life in SLE (18, 77, 105–107), no study to date has evaluated whether exercise can also improve sleep in this patient population. Given its beneficial impact on factors influencing sleep, i.e. depression, it appears that exercise shows promise for the management of sleep problems in SLE. The evidence already discussed suggests that sleep disturbance is multidetermined in SLE, therefore likely requiring a range of nonpharmacological management strategies.

Future Studies

It is clear that more studies using objective measures of sleep parameters are needed to better characterize sleep pattern in SLE. To date, all the sleep studies in SLE have assessed sleep at one single point in time. Hence, the temporal stability

and severity of sleep problems in SLE remains to be investigated. Furthermore, prospective designs would also allow for clarification of the factors that contribute to the maintenance and improvement of sleep in SLE. Although PSG is considered the gold standard, the actigraph which estimates sleep parameters based on limb motor movement, compared with PSG is less expensive, less invasive, and more conducive to repeated measures in ambulatory settings (108, 109). Moreover, the actigraph in other populations has been extensively used in intervention studies to track changes in sleep over time (110). A comparison of subjective and objectively derived sleep parameters such as the actigraph, in a large enough sample of SLE patients with repeated assessments over a number of days, is needed to fully understand sleep problems in SLE and to evaluate the strength and stability of the relationship between these two methods. Validation of this sleep assessment method could provide a useful adjunct in clinical and empirical evaluations of sleep problems in SLE. There is also a need to integrate immune system (i.e. cytokines) measures and biological measures of stress to help elucidate pathophysiological mechanism of sleep disturbances in SLE. Future studies should apply a comprehensive biopsychosocial framework to more clearly elucidate the complex interplay between disease-related, behavioural and psychosocial factors to sleep disturbance in SLE. Clinical trials are needed to evaluate pharmacological and nonpharmacological interventions for improving sleep in this patient population. In accordance with other recent reviews, there is a need to examine more comprehensively the impact of disturbed sleep in SLE and how these disturbances influence disease activity, fatigue and quality of life (14, 111).

Conclusion

Sleep problems are highly prevalent among patients with SLE. Most patients rarely discuss sleep problems with their physicians making it imperative that sleep be routinely assessed in this patient population, along with possible contributing factors in order to better guide management. SLE patients report sleep problems as a health need that remains unmet, suggesting inadequate management in cases where sleep problems are reported to health care providers. As such, there is a need for educational initiatives to inform both patients and physicians on the nature of sleep problems in SLE, their consequences, and possible treatments. Although the specific mechanisms involved remain to be clarified, numerous factors which can interact among each other contribute to sleep problems in SLE. Disease expression is likely an important factor triggering sleep problems in SLE. Additionally, an array of behavioural and psychosocial factors including physical inactivity, depressed mood and stress contribute to the sleep disturbances experienced by patients with SLE. Given the importance of depressed mood to sleep disturbances in SLE, treatment strategies aimed at alleviating depression have the potential to improve sleep and its negative impact on quality of life. A biopsychosocial approach should be used to guide future sleep studies in SLE. A better understanding of the factors involved in triggering, maintaining and improving sleep problems in SLE will help improve detection, management and guide the development of evidence-based interventions tailored specifically to this patient population.

Issues that need to be addressed by future research:

- Prospective studies are needed to determine the temporal stability of sleep problems in SLE.
- The actigraph may be a promising, less expensive objective tool to track changes in sleep over time in patient's real-life setting.
- Biological measures of immune system function (cytokines) and stress need to be studied to better understand the pathophysiology of sleep problems in SLE.
- A biopsychosocial model should be applied to guide the design of future studies aimed at elucidating the interplay between disease-related, behavioural and psychosocial variables to sleep disturbance in SLE.
- Clinical trials are needed to evaluate the efficacy of specific nonpharmacological and pharmacological interventions aimed at improving sleep in patients with SLE.
- Studies are needed to determine the impact of sleep problems on disease activity, fatigue and quality of life in persons with SLE.

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Sleep and Quality of Life in Obesity

Bharati Prasad and James J. Herdegen

Summary Obesity is a global problem now affecting more than 60% of the US population. It is associated with a wide range of co-morbidities including depression, diabetes, cardiovascular, hepatic, and rheumatologic conditions. Sleep disturbances are also common and include breathing disorders such as obstructive sleep apnea, obesity hypoventilation, upper airway resistance syndrome, and REM-specific sleep-disordered breathing. Obesity may account for more than 50% of sleep apnea cases. Although sleep apnea is an important and common complication of obesity, other sleep diagnoses have been associated with obesity. These include insomnia, hypersomnia, sleep fragmentation, and non-restorative sleep. The overlap of obesity, medical co-morbidities, and sleep disturbances results in a significant reduction in quality of life as measured by various self-report scales. The benefits of weight loss are also discussed as there can be a significant improvement of both obesity and associated health problems.

Keywords Obesity · metabolic syndrome · diabetes · sleep apnea · insomnia · bariatric surgery · non-alcoholic fatty liver disease · depression · chronic pain · degenerative disc disease

Learning objectives:

- Obesity is a highly prevalent condition.
- Obesity co-morbidities include diabetes, hypertension, malignancy, cardiovascular conditions including coronary artery disease and stroke, fatty liver disease, depression, and chronic pain from degenerative joint disease.
- Sleep disturbances associated with obesity include sleep apnea, insomnia, non-restorative sleep, and hypersomnia.
- Medical or surgical weight loss may significantly alter the prevalence and severity of these co-morbidities.

Epidemiology

Obesity has gained prominence as a major cause of preventable illness and death in the developed world. In fact, obesity is now a global epidemic with a WHO estimate of 300 million people being affected worldwide. The World Health Organization estimated that 22 million children are overweight worldwide in 2005. Obesity is defined by body mass index (BMI): a BMI of 25–30 kg/m^2 being overweight and $>$30 kg/m^2 being obese (see Table 46.1).

According to the National Health and Nutrition Examination Survey conducted in 2003–2004, an astounding proportion (66.3%) of the US adults are overweight or obese (BMI $\geq$ 25 kg/m^2), 32.2% are obese (BMI $\geq$ 30 kg/m^2), and 4.8% are morbidly or severely obese (BMI $\geq$ 40 kg/m^2). Foreign-born immigrants have a low incidence to start with that approaches that of the American population with longer residence (1).

As noted above, as many as 5% of adults in developed nations now have extreme obesity, characterized by a BMI of 40 kg/m^2 or more. These individuals have a mortality rate that is at least double that of individuals with a BMI in the desirable range of 18.5–24.9 kg/m^2 (2). According to another survey, the Behavioral Risk Factor Surveillance System, conducted from 1986 to 2000, the prevalence of severe obesity has increased twice as fast as the prevalence of obesity.

Health Complications of Obesity

The health consequences of obesity are increasingly recognized and have raised awareness of obesity as a medical disorder. There are now more than 40 distinct disorders,

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TABLE 46.1. Classification of obesity by BMI, waist circumference, and risk of associated disease occurrence (NHLBI Consensus, 1998).

Weight	BMI	Class of obesity	Men <40 inch; Women <35 inch	Men >40 inch; Women >35 inch
Underweight	<18			
Normal	18.5–24.9			
Overweight	25–29.9		Increased risk	High risk
Obesity	30–34.9	I	High risk	Very high risk
	35–39.9	II	Very high risk	Very high risk
Morbid/extreme Obesity		III	Extremely high risk	Extremely high risk

1998 National Heart, Lung, and Blood Institute obesity treatment guidelines. From Dalton: Top Clin Nutr, 2006. 21(2):p. 76–94

which are caused, exacerbated, or made substantially more likely by obesity. These medical complications can be classified into categories of metabolic (diabetes, hypertension, fatty liver disease, etc.), anatomical/structural (sleep apnea, GERD, pseudotumor cerebri, deep venous thrombosis, etc.), degenerative (atherosclerosis, degenerative joint disease, vertebral disc disease, etc.), neoplastic (breast, ovarian, colorectal cancer, etc.), and psychological (anxiety, depression, eating disorders, etc.). Many of these health consequences can directly or indirectly contribute to impaired quality of life and sleep complications such as insomnia, daytime sleepiness, sleep fragmentation, periodic limb movements, and sleep apnea.

These various co-morbidities associated with obesity are significant including the estimate that between 280,000 and 325,000 annual deaths in the USA can be attributed to obesity (3). More than 80% of these deaths occur among people with a BMI >30 kg/m^2 with the impact of the excess body weight higher among younger subjects (4). Obesity and cardiovascular disease are strongly linked to hypertension, coronary heart disease, stroke, and dyslipidemia. For example, a Finnish women study found that for each increase of about 1 kg in body weight, the risk of coronary mortality increased by 1–1.5% (5). Obesity has also increased in pediatric age groups and, in the Bogalusa Heart Study, nearly 60% of obese children had one risk factor for cardiovascular disease and 20% had two or more risk factors (6). Type 2 diabetes mellitus is strongly associated with obesity in all ethnic groups, and more than 80% of type 2 diabetes cases can be attributed to obesity. A study of 51,000 male health professionals in the USA found that the relative risk for diabetes in men with a BMI of 35 kg/m^2 was 40 times higher than that for men with a BMI of 23 kg/m^2 (7). A similarly strong curvilinear relationship between BMI and type 2 diabetes risk has been found in women (8). Non-alcoholic fatty liver disease (NAFLD) has become recognized as one of the most common abnormalities observed in obese individuals. Overall, NAFLD has been reported to affect 10–24% of populations of various countries and up to 74% of obese individuals (9). It has also been estimated that severe fibrosis occurs in up to 50% of obese individuals and cirrhosis develops in 7–16% (10–12). The incidence of osteoarthritis is increased in obese subjects and accounts for a major component of the cost of obesity (13). A twin study found that each kilogram increase in body weight (compared to a twin control) was associated with an increased risk of radiographic features of osteoarthritis at the knee and carpometacarpal joint (14). These and other co-morbidities influence general health and sleep quality and are discussed below.

Economics of Obesity

Overweight (BMI 25–29.9) and obese (BMI > 30) states confer a significant increase in mortality even after adjusting for variables such as age, race, education, chronic disease, smoking, and alcohol consumption (15). Severe obesity particularly in young adults is associated with a markedly reduced life expectancy (16). The socioeconomic impact of morbid obesity persists long after a reduction in weight and improvement in quality of life. Majority of these patients, despite radical measures such as bariatric surgery, do not return to gainful employment (17). Severe obesity impacts the quality of life in all domains such as mobility, hygiene, emotions, social interaction, sexual life, and eating behavior (18). Women suffer a disproportionate burden of disease attributable to overweight and obesity states as compared with men. This disparity is mostly due to differences in the health-related quality of life (19).

Today, obesity is the second most important public health problem in the USA second only to tobacco. The US department of health and human services in 2001 estimated the economic cost of obesity at 117 billion (6% of US health care dollars), again second only to tobacco-related cost. Obese individuals' cost of prescription drug treatment is twice compared with non-obese individuals', and their hospitalization rate is almost four times greater (20). Obesity is also associated with higher rates of sick days off work (21).

The increasing incidence of childhood obesity has been attributed to the same lifestyle factors as adult obesity. Childhood obesity is defined by the CDC as >95th percentile of the growth charts. According to the Institute of medicine website fact sheet, the incidence of obesity in the 6- to 12-year age group has tripled in both boys and girls of all ethnicities from 1970 to 2004. The rise of childhood obesity is of significant concern given the fact that as many as 80% of obese children become obese adults. Risk factors for the persistence of obesity into adulthood include the persistence of obesity over 7 years of age and the presence of an obese parent. The

health problems of childhood obesity are similar to adults and include hypertension, hyperlipidemia, hyperinsulinemia, along with orthopedic and liver problems. Sleep apnea has been documented in up to 7% of obese children, and up to 37% have an abnormal polysomnogram (22).

Obesity and Sleep Disorders

Although genetics has a role to play in the pathogenesis of obesity, it is not thought to be a major factor in the current epidemic. Various studies have documented lifestyle factors that have emerged as important contributors, such as reduced sleep time, number of hours of the day spent watching TV, and activity level at work among others. In a cross-sectional study from Spain statistically significant dose responses were observed, such that the prevalence odds ratio of obesity was 30% higher for each hour of increased TV viewing and 24% lower for each additional hour of sleep time (23). Another cross-sectional study of a heterogeneous primary care population found significantly less self-reported sleep in the overweight and obese population, again in a nearly linear relationship (24). The Japanese Toyama Birth Cohort Study, evaluated obesity-related factors in 3-year-old preschoolers and a 6- to 7-year age group. They found a significant inverse relationship between short-sleep time and obesity (25, 26). In adolescents, this association is weak and present only in males (27).

Many large epidemiologic studies published since 2000 have linked hours of sleep and weight. This association appears to get progressively weaker with aging (28). The proposed mechanisms for gain with sleep restriction are thought to be through increased sympathetic activity, elevated cortisol secretion, and decreased glucose tolerance (29). Reduced levels of leptin and elevated levels of ghrelin, with a corresponding increase in hunger, have also been demonstrated with sleep restriction (30). Therefore, obesity in sleep-deprived individuals may simply be a result of having more available time to eat with increased hunger. Sleep debt has a harmful impact on carbohydrate metabolism and endocrine function. The effects are similar to those seen in normal aging and, therefore, sleep debt may increase the severity of age-related chronic disorders, such as sleep-disordered breathing (31).

Obesity is known to affect sleep quality, besides its influence on sleep-disordered breathing. A prospective study of obese patients without sleep apnea compared with normal weight controls without sleep apnea, were compared regarding symptoms and polysomnographic data. Obese patients were noted to have lower percent of REM sleep ($p < 0.01$) and lower sleep efficiency ($p < 0.05$). All sleep-related symptoms were significantly more frequent in obese patients than in controls, including observed or reported apnea, awakenings, choking, unrefreshing sleep. Loud snoring was present in 46.7% of obese patients and 8.1% of control subjects. Excessive daytime sleepiness was reported by 34.7% obese patients and 2.7% of controls. The Epworth sleepiness scale was also significantly higher in the obese group (32). Overall, these findings may partially explain the lower quality of life in the obese.

In a multivariate logistic regression analysis of a prospective cohort, BMI was found to be strongly linked to complaint of excessive daytime sleepiness, independent of the AHI. This relationship was exponential beyond a threshold BMI of >28 (33). Another prospective control study looked at sleep disturbances in 73 obese patients (referred to a weight loss center) without Obstructive sleep apnea (OSA), Upper airway resistance syndrome (UARS), or Obesity hypoventilation syndrome (OHS) compared with 45 age-matched controls. They were assessed in the sleep laboratory by an 8-h polysomnography (PSG) followed by two nap opportunities of 1 h each. During nap's sleep latency, wake after sleep onset, total wake time were significantly lower, whereas percent sleep time was higher in obese patients.

Nocturnal PSG revealed a higher wake after sleep onset, total wake time, and lower percent sleep time, suggesting an underlying circadian rhythm abnormality in the obese (34).

Obesity and Sleep Apnea

As discussed in the following section, there is a strong correlation between Obesity and OSA. A 10% increase in weight predicts a sixfold increase in the odds of developing moderate to severe OSA (35). Excess weight may be responsible for more than 50% of OSA (36). OSA may be associated with poor personal relationships and work performance (37). Obesity and symptoms of OSA, i.e., snoring, witnessed apnea, and excessive daytime sleepiness, have major impact on psychosocial function and quality of life. These groups have been found to have poorer self-rated health, higher divorce rate, and more sick leave. This effect is accentuated in women (38). Obesity affects the upper airway size (independent of the bony craniofacial structure).The size of the upper airway as measured by lateral cephalometry has been shown to be correlated to the severity of sleep-disordered breathing (39). In a recent paper, certain characteristics of obese patients were predictive of sleep apnea-witnessed apnea, older age, BMI, waist and neck circumference (40).

Sleep apnea has been associated with impairment in work efficiency, increased automobile accident rates, and decrements in quality of life. One study reported more limitations in function caused by physical and emotional reasons, and a lowered sense of well-being for mental health and energy in sleep apnea patients compared with that in normal subjects (41). These patients also reported a poorer adjustment than normal subjects in their domestic, vocational, and social environments, including family relationships. Other clinical features associated with sleep apnea that can influence quality of life include a higher prevalence of depression (37, 42) and

variable effects on neurocognitive dysfunction and performance impairment. In addition, gastro-esophageal reflux is common in patients with sleep disorders, is associated with increased arousal, decreased duration of time spent in deeper stages of sleep, and poorer sleep-related quality of life (43).

Obesity and Insomnia

A relationship between symptoms of depression and obesity has been consistently noted in studies of the psychological correlates and sequelae of obesity. Insomnia is present in about 10–16% of the general population but is much more common in patients who have mood disorders. A number of studies have described a relationship between obesity and depression symptoms. Complaints of sleep disruptions are common preceding and during major depressive or manic episodes. At least 65% of patients who have major depressive disorder report at least one of the following sleep complaints: difficulty falling asleep or early morning awakening (44). Other common complaints include more frequent nocturnal awakenings, non-restorative sleep, disturbing dreams, or decreased total sleep. The 2002 Canadian Community Health Survey reported that 17% of obese class I and 22% of obese class II/III people reported insomnia, compared with 12% of people in the normal weight range (45). Physical activity is generally thought to be beneficial to sleep by contributing to psychological well-being, muscle relaxation, thermal effects, and energy conservation. The Canadian survey found that people who were moderately active had low odds of insomnia, compared with sedentary individuals.

Obesity, Chronic Pain, and Sleep

The incidence of osterarthritis is increased in obese subjects and accounts for a major component of the cost of obesity. Osteoarthritis commonly develops in the knees and ankles, but it also occurs more frequently in non-weight-bearing joints. In one study of more than 1000 women, the age-adjusted odds ratios of unilateral and bilateral osteoarthritis at the knee, determined from x-ray films of the knees comparing the high and low tertiles of BMI, were 6.2 and 18, respectively (46). Another study of 129 middle-aged men found that a BMI above 25 kg/m^2 increases the risk of lumbar disc degeneration (47). This study also found that being overweight at a young age was a stronger predictor of an increase in the number of degenerated discs during follow-up than being overweight in middle age. Chronic pain is a common condition that has been reported to affect sleep in as many as 70% of patients (48–50). A Gallup poll sponsored by the National Sleep Foundation reported that 25% of US adults have pain that disrupts their sleep for at least 10 nights per month (51). A Norwegian study of 457 patients with chronic low back pain found a threefold increase in reported sleep problems compared with a control population (52).

Obesity and Hypersomnia

Hypersomnia, generally defined as daily sleep in excess of 9–10 h and reported in 3–8% of the general population, is also commonly reported in major depression with atypical features or a seasonal pattern (53,54). Although obese patients are vulnerable to major depression and therefore insomnia or hypersomnia, a recent study found that reduced amounts of sleep are associated with overweight and obese subjects (55). This trend of decreasing sleep time was reversed in the extremely obese patients.

Obesity, Metabolic Syndrome, and Sleep

Obesity by definition is linked to the metabolic syndrome, which has received considerable attention in the recent years. The predominant underlying risk factors for the syndrome appear to be abdominal obesity, insulin resistance, physical inactivity, aging, and hormonal imbalance. Risk factors not related to weight appear to be first degree relatives of type II diabetics and individuals of South Asian ethnicity. The importance of the metabolic syndrome lies in its association with increased cardiovascular morbidity, besides other organ effects such as non-alcoholic steato-hepatitis. These medical co-morbidities can lead to significant sleep disturbances primarily through the pathway of sleep-disordered breathing.

The prevalence of metabolic syndrome in sleep apnea patients has been estimated impressively at between 50 and 90% (56, 57). It is associated with abdominal obesity, even in the absence of significant BMI elevation (58).

The metabolic syndrome diagnostic criteria updated in 2005 by the National cholesterol education panel/Adult treatment panel III as meeting three of the following five criteria (Table 46.2).

According to NHANES III data, as many as 47 million adult Americans are affected with the Metabolic syndrome. One million of these are aged 12–19 years. About 4.2% of all teenagers and 28.7% of the obese adolescents are affected. Mexican-Americans have the highest age-adjusted prevalence of the metabolic syndrome (31.9%). It is also more common in women than in men. A prospective analysis of the Framingham offspring study found a clustering of three or more metabolic syndrome risk factors to account solely for 20% of

TABLE 46.2. NCEP Metabolic syndrome diagnostic criteria.

1. Abdominal obesity	Waist circumference in men >102 cm, in women >88 cm
2. Dyslipidemia	Triglycerides >150 or drug treatment for it
3. Dyslipidemia	HDL cholesterol <40 in men, <50 in women or drug treatment for it
4. Hypertension	BP >130/85 or drug treatment for it
5. Insulin resistance	Fasting plasma glucose >110 or drug treatment for it

the cardiovascular events in men and 48% of the events in women (59).

Visceral obesity is thought to cause an elevation in inflammatory cytokines, hyperleptinemia, and hyperinsulinemia. This leads to progressive worsening of sleep apnea; that may then accelerate worsening of visceral obesity/metabolic syndrome by providing a stress stimulus and causing nocturnal elevations of hormones such as cortisol and insulin. A prospective study has shown that AHI/presence of sleep-disordered breathing is an independent risk factor for insulin resistance after controlling for obesity. In this study, each additional AHI increased the fasting insulin levels by about 0.5% (60). The same author among others has also shown a fall in serum leptin level after 6 months of CPAP treatment. Another study of middle-aged, Caucasian adults found that poor global sleep quality, as measured by the Pittsburgh Sleep Quality Index (PSQI), was significantly related to the metabolic syndrome (61). After adjusting for independent effects of sex and age on the metabolic syndrome, an individual was 1.44 times more likely to meet the criterion for the metabolic syndrome with every increase of 2.6 points on the PSQI.

Obesity, Sleep, and Weight Loss

It is now clear that weight loss improves symptoms of OSA and AHI (62).

Medical Weight Loss

This is difficult to achieve and even more difficult to sustain long term. Our current best treatment option is a combination of drug therapy and lifestyle modification. This type of therapy at 1 year has shown to be modestly effective resulting in a weight loss of 12.1 ± 9.8 kg in a group of 60 patients with baseline weight of 108.5 ± 18.6 kg (approximately 10% of baseline weight) (63). Longer term data on weight maintenance and degree of weight loss with other measures such as diet alone is scarce. In a series of 216 obese patients with OSA, a reduction in OSA by means of dietary weight loss alone was 11.1% (n = 24). This modest benefit however was short lived with only 3% patients showing long-term relief of OSA at 3-year follow-up. Patients (13 of 24) in this series maintained their lower weight, despite which 6 of these 13 patient's had recurrence of their OSA (64). Medical weight loss may not always lead to an improved psychological state. In a small study of obese males undergoing depression, quality of life, and sleep quality questionnaires during a weight loss program, a substantial improvement in the psychobiological profile was found with a 5 kg weight loss. However, additional weight loss showed a small but significant increase in depression that appeared to be associated with the increase in rigid restraint of eating (65).

Obesity, Sleep, and Surgical Weight Loss

Bariatric surgery is indicated for severe obesity, BMI >40 kg/m^{2}or BMI of 35 kg/m^2, with co-morbidities. The number of bariatric surgeries performed in the USA increased from 10,000 to 15,000 per year to 75,000 in year 2002. This is likely due to the introduction of laparoscopic techniques in 2002.

NIH criteria for bariatric surgery eligibility

BMI	Co-morbidity
35–39	Type II diabetes, hypertension, hypoventilation, sleep apnea, venous stasis, pseudotumor cerebri, polycystic ovary, degenerative joint disease, NASH, others
>40	None or any

According to a recent abstract, the prevalence of sleep apnea in this population is about 50% or greater and clinical tools predict sleep-disordered breathing poorly (66).

A recent meta-analysis suggests that depending on the surgical technique an excess body weight loss of 47–61% can be achieved (67). Long-term data are now available for patients undergoing bariatric surgery. The 10-year follow-up data from the SOS study showed the intervention group had a 16.1% weight loss at 10 years, with the control group having a 1.6% increase in weight (68). The SOS study also showed lower incidence rates of diabetes and dyslipidemia at 2 and 10 years. The recovery rates from diabetes, dyslipidemia, and hypertension were also more favorable in the surgical group. Surgical treatment does not increase mortality. In this study, a high likelihood for sleep apnea syndrome was observed in 23% of the surgically treated patients at baseline, but in only 8% after 2 years. In the control group, these numbers were 22 and 20%, respectively. The surgically treated group had improvements in health-related quality of life, and this group was more active on follow-up. However, the surgical group was found to at higher risk for biliary tract disease.

Few studies have looked at the long-term effects of weight loss on sleep quality or sleep-disordered breathing. A prospective study looked at self-reported sleep symptoms in a group of 313 patients with BMI > 35 referred for bariatric surgery. Patients filled out sleep questionnaires preoperatively and 12 months post-surgery. The group lost an average of 48% (SD 16%) of excess weight by 12 months. At baseline, 59% men and 45% women had disturbed sleep. Witnessed apnea was more common in men, and excessive daytime sleepiness was the same in both gender. Over the 12-month period, habitual snoring changed from 82 to 14%, witnessed apnea from 33 to 2%, excessive daytime sleepiness from 39 to

TABLE 46.3. Effect of Bariatric surgery on weight loss and sleep apnea. Adapted from CHEST (70).

Source	Number of patients	Follow-up months	BMI before	BMI after	AHI before	AHI after	p Value
Charuzi et al.	13	6	222.5%	150%	88.8	8.0	<0.0005
Sugerman et al.	40	Mean 69.6	56	40	64	26	0.0001
Scheuller et al.	15	12–144	160 kg	105 kg	96.9	11.3	<0.0001
Guardiano et al.	8	Mean 28	49	34	55	14	0.01
Rasheid et al.	11	3–21	62	40	56	23	¡0.05
All	87	3–144	56.2	39.2	71.5	19.3	

4%, and poor sleep quality from 39 to 2% ($p < 0.001$ for all) (69).

Surgical intervention, particularly the gastric bypass, therefore today has emerged as the treatment of choice for extremely obese individuals who cannot control their weight with traditional methods, such as lifestyle modification or pharmacotherapy.

Table 46.3 summarizes the effect of bariatric surgery,weight loss, and sleep apnea.

In addition to the above data, in 2005, a prospective study noted not only similar benefit in AHI after bariatric surgery-induced weight loss but also a significant improvement in CPAP requirement, Epworth sleepiness scale scores, metabolic syndrome, and quality of life by the SF-36 as well as Becks Depression inventory scores (71).

Long-term follow-up has lead to recognition of cases that despite weight maintenance have recurrence of their OSA (72). Intragastric balloon placement, now regarded as standard procedure for weight reduction, has also been demonstrated to have beneficial effects on severity of OSA. This procedure is associated with less morbidity and mortality compared with bariatric surgery and has comparable efficacy (73). There is well-recognized morbidity associated with bariatric surgery that includes intraoperatively iatrogenic splenectomy, perioperatively anastomotic leaks, bowel obstruction, GI hemorrhage, pulmonary embolism, wound infection, pneumonia, and late complications including bowel obstruction, incisional hernia, stomal stenosis. Factors placing patients at high risk for these complications include BMI >50, FEV1 <80%, prior abdominal surgery, and abnormal ECG (74). Despite these potential complications, adjustable gastric banding has improved OSA symptoms in addition to asthma and gastroesophageal reflux symptoms (75, 76). Thus, both patient-reported sleep disturbance and daytime sleepiness significantly improve with weight loss.

Summary

Obesity is associated with a number of co-morbidities, which directly or indirectly influence sleep and quality of life. These co-morbidities include increased mortality, malignancy, cardiovascular, metabolic, rheumatologic, and psychological problems. Many of these co-morbidities influence sleep and quality of life issues, which are related to the degree of obesity. These co-morbidities can be reduced or eliminated by weight loss.

Issues that need to be addressed by future research:

- Understanding the genetic and psychosocial predisposition to obesity.
- Understanding the complex inter-relationships between obesity, metabolic syndrome, and sleep apnea.
- Additional research is needed to determine the optimal preventive strategies for obesity.
- Additional research is needed to determine the optimal medical management programs for obesity.

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Sleep and Quality of Life in Endocrine Diseases

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Summary It is well established that a close relationship exists between sleep and hormones of the hypothalamic–pituitary axis. Sleep has an electrophysiological component and an endocrine component, i.e., the distinct patterns of hormone secretion. Both the electrophysiological and the hormonal component interact bi-directional. Sleep-endocrine rhythms are closely interrelated, and sleep is an important regulator of (neuro)endocrine function. The secretion of growth hormone (GH), prolactin (PRL), and thyrotropin (TSH) is markedly increased during sleep, whereas the secretion of adrenocorticotrophic hormone (ACTH) and cortisol is inhibited. Sleep deprivation is associated with decreased GH and PRL secretion, and increased cortisol and TSH secretion. The decrease of GH secretion, which occurs with advancing age, is strongly associated with impaired quality of sleep. Increasing age is associated with increased levels of cortisol, which is significant after age 50 years when sleep is more fragmented and REM sleep declines. GH deficiency in adults (AGHD) is a well-recognized clinical syndrome, which is characterized by abnormal body composition and most notably, impairment of quality of life (QoL). Recent studies on long-term treatment of adult GH-deficient patients have convincingly shown that GH replacement therapy improves QoL in association with a reduction in healthcare utilization. Chronic excess of glucocorticoids, Cushing's syndrome, is associated with sleep disturbances, mood alterations, depression, and impaired QoL. Patients with thyroid disease have sleep disturbances and a significantly reduced health-related QoL.

Keywords Neuroendocrine function · sleep · quality of life · growth hormone · cortisol · thyroid hormone

Learning objectives:

- Sleep endocrine rhythms are closely interrelated, and sleep is an important regulator of (neuro)endocrine function. The secretion of growth hormone, prolactin, and thyrotropin increases, whereas the secretion of adrenocorticotrophic hormone and cortisol decreases during sleep.
- Growth hormone secretion decreases with advancing age and is strongly associated with impaired quality of sleep after age 50 years.
- Chronic excess of glucocorticoids, Cushing's syndrome, is associated with sleep disturbances.
- Subjects with growth hormone deficiency, Cushing's syndrome, or thyroid disease have a severely impaired quality of life, which markedly improves with treatment.

Introduction

Recent studies have convincingly shown a close relationship between sleep and hormonal function. Sleep has an electrophysiological component, usually divided into two major states, the non-rapid eye movement (NREM) and rapid eye movement (REM) cycle, and an endocrine component, i.e., the distinct patterns of hormone secretion. Polygraphic sleep recordings such as the polysomnogram are scored in stages I, II, III, IV, REM and Wake; NREM sleep comprise stages I and II, followed by stages III and IV, often referred to as slow wave sleep (SWS).

Within the past decades, it has become clear that both the electrophysiological and the hormonal component interact bi-directional. Sleep-endocrine rhythms are closely interrelated, and sleep is an important regulator of (neuro)endocrine function. The secretion of growth hormone (GH) and prolactin (PRL) is markedly increased during sleep, whereas the secretion of adrenocorticotrophic hormone (ACTH) and cortisol is inhibited. Sleep deprivation inhibits nocturnal GH and PRL

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secretion, and increases cortisol and TSH. Furthermore, sleep has also modulatory effects on the hormonal control of carbohydrate metabolism, and water and electrolyte balance (1, 2). On the contrary, in recent years, several sleep regulatory hormones have been identified (3).

In this brief review, we will focus on the interrelationship of sleep with neuroendocrine function, and particularly with hypothalamic–pituitary-dependant hormone release of GH, cortisol, and thyroid hormone.

GH, Sleep, and Quality of Life

GH Regulation

GH regulates growth and affects somatic cells directly regulating tissue metabolism. It is the main factor to stimulate the release of insulin-like growth factor-I (IGF-I) locally in tissues, and in the liver. Many of the actions of GH on growth and metabolism are mediated by IGF-I.

The somatotropic system includes GH, GH-releasing hormone (GHRH), somatostatin, ghrelin, and IGF-I and IGF-binding proteins.

GH is secreted in a pulsatile fashion by the anterior pituitary gland. The frequency of the GH pulses occurs at approximately 3-h intervals. GH secretion is maximal during (late) puberty, occurring mostly during deep SWS during the night. GH production rate falls progressively with advancing age at a rate of about 14% per decade of adult life (4). GH secretion is tightly regulated by the interaction of a wide range of central and peripheral somatotropic signals, which converge on a final common trilogy of regulatory peptides at the hypothalamic and pituitary levels (5). GHRH and somatostatin exert opposing (i.e., stimulatory and inhibitory) actions on somatotrope cells.

Ghrelin, a 28 amino acid peptide mainly produced in the stomach, is the natural ligand for the GHS receptor type 1a, which is widely expressed in brain areas that affect mood, cognition, memory, learning, feeding, and sleep. Apart from its well-recognized orexigenic properties and effects on energy homeostasis, ghrelin is a powerful GH secretagogue. The GHS receptor is expressed at relatively high levels in the suprachiasmatic nucleus (SNC), an area important in the regulation of circadian rhythmicity (6). Indeed, an increase of 50% in REM sleep was found in elderly subjects treated with a GHS receptor-stimulating agent (7). Feedback regulation of GH occurs directly by GH itself. There are potent negative feedback effects of IGF-I on GH secretion at both pituitary and hypothalamic levels.

Metabolic factors such as glucose, amino acids, free fatty acids (FFA), and thyroid hormones, glucocorticoids, and gonadal hormones are also involved in the secretion of GH.

Association Between GH Release and Sleep

GHRH and other members of the somatotropic system are involved in non-rapid eye movement (NREM) sleep regulation. In healthy subjects, the plasma 24-h GH pattern shows stable low levels interrupted at approximately 3-h intervals by small bursts of GH secretion.

Shortly after sleep onset a large GH pulse occurs, which comprises most of the daily secretion of GH in men; in women, daytime GH pulses are more frequent and the sleep-associated pulse is generally less marked and does not account for the majority of the daily GH secretion. The increased daytime GH levels and GH bursts in women have been found to be associated with endogenous oestradiol concentrations. Oestradiol lowers the production of IGF-I in the liver resulting in a decreased feedback effect of IGF-I on GH secretion (8,9).

Extensive research has shown that the relationship between sleep-onset and increased GH secretion is maintained notwithstanding severe manipulations of the sleep–wake cycle such as sleep-onset delay, daytime recovery sleep following continuous wakefulness, transmeridian travel, temporal isolation without time cues, and interrupted sleep or night shift (10–14).

The strong relationship between sleep onset and the robust increase in plasma GH concentrations has been known for more than 30 years. More recent studies have shown that the robust rise of GH is strongly associated with the NREM sleep cycle.

Furthermore, it has become clear that hypothalamic mechanisms, which are operative in sleep regulation, are associated with the regulation of GH. Accordingly, recent studies in humans indicate that activation of hypothalamic GHRH is involved in the control of both NREM and SWS, and nocturnal GH release (15).

Indeed, pharmacological manipulation of SWS sleep has been found to affect GH secretion. Thus, it has been reported that a bedtime administration of gamma-hydroxybutyrate (GHB), a metabolite of gamma-amino butyric acid (GABA) increased GH secretion, which was quantitatively correlated with the increase in the amount of stage IV SWS sleep. Also, the administration of ritanserin, a selective 5HT2 receptor antagonist resulted in a highly correlated increase between SWS activity and nocturnal GH increase. On the contrary, flumazenil, a benzodiazepine antagonist, was found to be associated with a reduction of SWS and in parallel a decrease in nocturnal GH (16). So far, studies in humans regarding the effects of somatostatin and ghrelin have yielded inconsistent data.

Sleep-Related GH Secretion During Lifespan

GH secretion undergoes an age-related decrease. During puberty, daily GH secretion and peak amplitude are greatly increased, particularly at night. The relationship between sleep and nocturnal GH secretion is very robust in (pre)

pubertal children. Daily GH secretion in adults varies inversely with age. Twenty-four-hour integrated GH concentrations are lower in older versus younger subjects. Both nighttime and daytime mean pulse amplitude and duration but not pulse frequency are reduced in aging humans. In parallel with the fall in GH secretion, serum levels of IGF-I also decline. The pronounced decrease in GH and IGF-I with advancing age is strongly associated with alterations of sleep quality. These effects of aging on sleep quality and GH and IGF-I secretion occur early in adulthood and are essentially complete by the beginning of the 50th decade (17, 18).

Sleep and Quality of Life in Acromegaly and GH Deficiency

There are few studies that have examined the relationship between sleep and quality of life (QoL) and pathological GH secretion. In patients with active acromegaly who suffer from GH hyper secretion, the absence of nocturnal GH pulses despite the presence of SW sleep was found, whereas another study reported a reduced SWS and REM sleep (19, 20).

GH deficiency in adult patients with hypopituitarism on adequate replacement therapy with adrenal, thyroid, and gonadal hormones is well recognized as a specific clinical syndrome, characterized by abnormal body composition, reduced bone mineral density, dyslipidemia, and most notably impairment of QoL. The most consistent findings are related to compromised energy levels, vitality, lack of stamina and drive, poor memory and concentration, and (mental) fatigue.

In children with GH deficiency, a reduction in REM sleep and partial normalization after GH therapy has been described (21, 22). In one study in AGHD patients, a partial normalization of prolonged sleep and reduced SWS during short-term (6 months) GH replacement therapy has been reported. Concerning the long-term effects of GH replacement therapy on sleep, there are only few data, which indicate no significant change. Schneider et al. studied night sleep electroencephalogram (EEG) and daytime sleep propensity in adult hypopituitary patients with GH deficiency before and after 6 months of GH replacement. They found that GH replacement does not affect night sleep nor daytime sleep propensity in GH deficient hypopituitary adults, indicating that GH deficiency has no sleep disturbing effects (23).

Many studies have shown an improvement of QoL in AGHD patients during short-term replacement therapy with GH. Recently, several studies on the long-term effect of GH replacement therapy on QoL of life in AGHD patients have been reported. Gilchrist et al (24), demonstrated small but significant declines in QoL of AGHD patients who remained untreated for 9 years. In contrast, those patients who received GH replacement continuously during 9 years showed improvements in QoL.

Koltowska-Häggström et al. (25) studied whether QoL in AGHD patients is reversible with long-term therapy. QoL was measured by the Quality of Life-Assessment for Growth Hormone Deficiency in Adults (QoL-AGHD) in general population samples in England, Wales, The Netherlands, Spain, and Sweden and compared with corresponding patient data from KIMS (Pfizer International Metabolic Database) for 4–6 years at follow-up. The analyses at baseline showed significant impairment in patients on all QoL dimensions measured. The order of dimensions by degree of impairment severity was memory and concentration, tiredness, self-confidence, tenseness, and social isolation. Improvement during GH replacement therapy occurred in the reverse order. The most dramatic improvement was observed in the first 12 months treatment with a gradual amelioration later leading eventually to approximate the population reference level. The recent study by Saller et al. (26), confirmed that long-term treatment with GH is associated with a significant improvement in QoL. Furthermore, they showed that the improvement in QoL was associated with a reduction in healthcare utilization.

Obesity is associated with low basal plasma GH levels, reduced spontaneous GH secretion, and a blunted response to all known GH secretory stimuli; IGF-1 levels in the obese are usually reported in the low to normal range. The underlying pathophysiological mechanisms of the hyposomatotropic state in obesity have not been elucidated, but alterations in the balance between GHRH and somatostatin, possibly as a consequence of changes in circulating FFA, ghrelin, insulin, or changes in the GH clearance are likely to play a role (27–29). In patients with obstructive sleep apnea, a condition that rather frequently occurs in obese subjects, decreased GH secretion has been reported (30). In obese subjects without sleep apnea, also a much lower amount of GH secretion has been found, however a normal relation between the SWS and the GH nocturnal secretion profile (31). Treatment of patients with obstructive sleep apnea with continuous positive airway pressure (CPAP), clearly increased nocturnal GH secretion (32) (Figure 47.1), whereas in children correction of sleep apnea next to increased nocturnal GH secretion, growth rate normalized (33).

Glucocorticosteroid Hormone, Sleep and QoL

Glucocorticoid secretion by the adrenal cortex is characterized by feedback inhibition of stress-induced and circadian hypothalamic–pituitary axis activity (HPA).

In the brain, glucocorticoid and mineralocorticoid receptors are highly expressed. The hippocampus has much corticoid receptors and is thought to play an important role in most aspects of HPA activity.

Hypothalamic corticotrophin-releasing hormone (CRH), in combination with vasopressin (VP) and oxytocin (OT), stimulates corticotrophin (ACTH) from the corticotroph cells of the anterior pituitary. ACTH stimulates glucocorticoid secretion by the adrenal cortex.

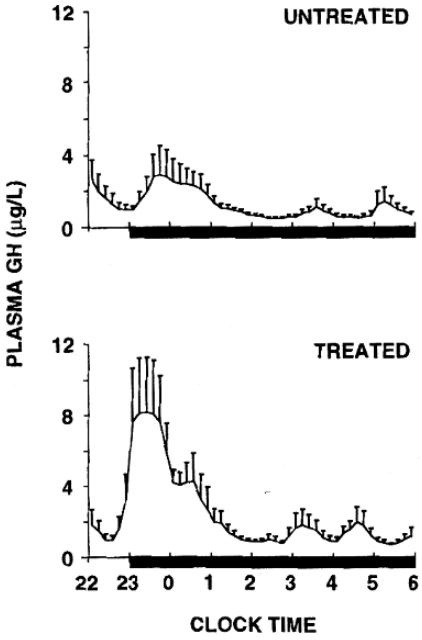

FIGURE 47.1. Mean (±SEM) noctural plasma growth hormone (GH) profiles in patients with sleep apnea before (top) and after (bottom) continuous positive airway pressure (CPAP) treatment. Black bars represent the scheduled sleep periods. [adapted with permission from (32)].

Both physical and psychological stressors increase HPA activity, with stimulus specific inputs to the hypothalamus. Thus, a physical stressor stimulates HPA activity by afferent sensory pathways, whereas a predominant psychological stressor stimulates HPA activity through the forebrain (34).

HPA activity varies in a circadian rhythm with peak glucocorticoid levels 2–4 h around waking and nadir levels around sleep onset. In case of activity during daytime, peak glucocorticoid levels occur in the early morning after waking, whereas trough levels occur around 11 p.m.; in case of activity during the night, the cycle is reversed (35).

The central control of the circadian rhythm in HPA activity depends on the SNC, the master circadian pacemaker in mammalian and human brain. But, there is also much evidence to indicate that the hippocampus by its high content of corticoid receptors plays an important role in the feedback regulation of circadian HPA activity. Thus, studies in rats have shown that lesions of the hippocampus disinhibit HPA activity at the circadian nadir, whereas corticosterone implants in the hippocampus inhibit circadian nadir activity of ACTH in adrenalectomized rats (36).

Glucocorticoid hormones play a role in the regulation of clock genes involved in the generation of circadian rhythms. There is evidence that clock genes in the SNC are influenced by glucocorticoid signaling. Indeed, in a recent study in rats, it has been shown that the adrenal glucocorticoid corticosterone controls the rhythm of expression of the circadian clock protein Period 2 (37).

Sleep disturbances and sleep deprivation result in lower cortisol levels the next day and the recovery night (Figure 47.2). It has been hypothesized that awakening salivary cortisol might be a biological marker for sleep disturbance as the awakening cortisol was found to be correlated negatively with the frequency of nightly awakenings. Furthermore, the lower morning and daytime cortisol levels are supposed to be due to nightly cortisol activation with a decreased HPA activation after awakening (38, 39).

The combined data from a series of studies show that increasing age is associated with an increased evening cortisol, which is significant after age 50 years when sleep is more fragmented and REM sleep declines (40).

Corticosteroids play an important role in the function of the central nervous system. Chronic excess of glucocorticoids, Cushing's syndrome, is associated with an increased prevalence of sleep disturbances, mood alterations, cognitive impairments, psychiatric diseases, and anatomical brain changes. Loss of brain volume is highly prevalent in patients with endogenous hypercortisolism (Cushing's syndrome) as well as in patients treated with supraphysiologic doses of exogenous glucocorticoids (41,42). Furthermore, cortisol also seems to reduce neural interactions between different areas of the brain. Using EEG coherence analysis, we found an inverse relationship between basal cortisol levels and neural interaction between the frontal and parietal cortex (43). Furthermore, reductions in cortico-cortical cross-talk as quantified by EEG coherence together with increases in depression were observed in moderate and severe, as compared with mild Cushing's syndrome (44).

Cushing's syndrome is often accompanied by depression, which is at least partially mediated by hypercortisolaemia. Support for this notion is provided by reports, which show amelioration of depression and psychosis after treatment of Cushing's syndrome with the glucocorticoid antagonist mifepristone (RU 486) (45, 46).

Thyroid Hormone, Sleep, and QoL

Thyroid hormone production and secretion is controlled by the hypothalamus–pituitary–thyroid regulatory system. Thyrotropin-releasing hormone (TRH) produced in the hypothalamus stimulates the synthesis and secretion of thyrotropin (TSH) of the thyrotrophic cells in the anterior pituitary gland. TSH stimulates the uptake of iodide and organification, the synthesis and release of thyroxine (T4), triiodothyronine (T3), and thyroglobulin (Tg). Circulating T4 secreted by the thyroid is activated to T3; at about 20% of circulating T3 is directly secreted from the thyroid. Most of the biologic effect of thyroid hormone is due to T3 derived from the peripheral deiodination of T4. TSH is secreted in pulses and follows a circadian pattern: the lowest values are between 14.00 and 19.00 h. Thereafter, the values increase during the evening, reaching maximal values between 23.00 and 04.00 h.

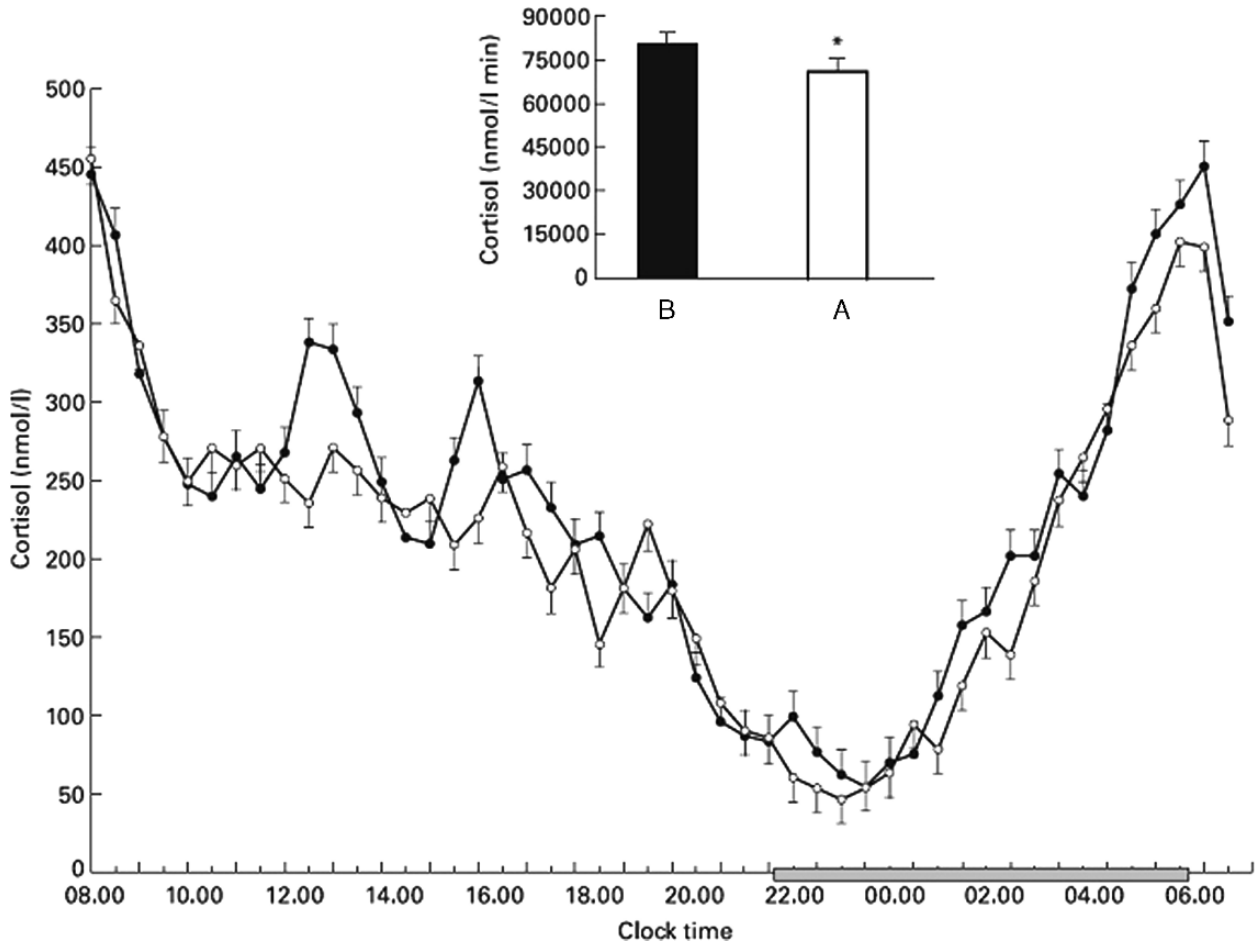

FIGURE 47.2. Diurnal variation (mean ±SE) in plasma cortisol concentrations in 10 healthy men pre- (●) and post- (○) sleep deprivation. Samples were taken every 30 min through an indwelling IV catheter. Inset, integrated nighttime AUC pre- (B) and post- (A) sleep deprivation. *$p < 0{\cdot}05$. [adapted with permission from (83)].

TSH pulses occur at about 8–14 per 24 h. An increase in pulse amplitude accounts for the nocturnal increase of TSH secretion. Hypothalamic stimulatory regulation of thyroid function is balanced by feedback inhibition by thyroid hormones, which inhibit TSH secretion, and to a lesser extent TRH secretion (47).

A number of studies have been published on the influence of sleep deprivation on the hypopituitary–thyroid axis both in healthy subjects and in patients with a major depressive disorder. In healthy subjects, sleep deprivation is associated with increases in the TSH levels, T4, and T3. A survey on studies regarding therapeutic (partial) sleep deprivation in depressed patients revealed consistent increases of TSH, but divergent findings with respect to changes in thyroid hormones (48). Kuhs et al. studied TSH and thyroid hormones in patients with major depressive disorder who were treated with serial therapeutic partial sleep deprivation late in the night during a 4-week course therapy with amitriptyline. They found that the levels of TSH and T3 were significantly elevated on the first day after partial sleep deprivation throughout the study, but T4 less regularly (49).

Only limited data are available on health-related QoL in patients with thyroid disorders. Bianchi et al. recently published a study based on SF-36 (Medical Outcome Study Short-Form-36) and NHP (Nottingham Health Profile) questionnaires in 368 patients with thyroid disorders. They compared the final scores of the domains with age- and sex-adjusted normative values. All domains of SF-36, except bodily pain, were reduced in patients with thyroid disorders. The domains of NHP were less severely affected. Mood and behavior disturbances were present in a large proportion of patients and were significantly associated with poor health-related QoL. Sleep disturbances were equally distributed among groups. Taken together, the data of this large study show a significantly reduced health-related QoL in patients with thyroid diseases. The authors conclude that perceived health status should be considered an additional outcome of management and therapy of thyroid disorders (50).

Issues that need to be addressed by future research:

- Increased awareness of the prevalence of sleep disturbances and impaired health-related quality of life in subjects with endocrine disease is needed.
- Further research is required to determine in more detail the mechanisms underlying the close association of sleep and endocrine rhythms in health and disease.
- More research is needed to assess the long-term effects of treatment of endocrine disease not only with respect to morbidity and mortality, but also on sleep quality and health-related quality of life.

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Sleep and Quality of Life in Diabetes

Robert P. Skomro

Summary Diabetes mellitus is one of the most common chronic medical conditions. It affects all age groups, has a variety of presentations, a range of complications, and numerous therapeutic interventions. Its impact on patients' quality of life is dependent on factors such as demographics, the level of glycemic control, and the presence of co-morbidities and diabetic complications. Some of these complications, such as painful diabetic peripheral neuropathy and nocturia, can cause sleep onset and sleep maintenance problems resulting in poor sleep quality, daytime fatigue, and somnolence. Co-morbidities, such as depression, are common in diabetes and may affect sleep and quality of life. Sleep complaints and sleep disorders, such as restless legs syndrome and sleep-related breathing disorders, are very common among adult diabetics. Their impact on the health-related quality of life (HRQoL) of the diabetics, however, has not been extensively studied. Even though there is a multitude of validated quality of life measures that have been used in the diabetic population, few generic and disease-specific questionnaires include sleep-related items. The results of the studies using instruments that incorporate sleep-related questions indicate that sleep complaints contribute significantly to the overall impairment of quality of life in this population. This chapter will review the literature on the relationship between diabetes, some of its complications, HRQoL and sleep quality. It will focus on the most common sleep disorders and describe their impact on quality of life. Finally, it will provide suggestions for further research in this area.

Keywords Diabetes mellitus · health-related quality of life · sleep disorders · obstructive sleep apnea · restless legs syndrome

Learning objectives:

- Sleep disorders are common in adult diabetics.
- Adult diabetics have decreased HRQoL and poor sleep quality, increased rates of insomnia, restless legs syndrome, and sleep-disordered breathing.
- The relative contribution of sleep disorders to the impaired HRQoL in diabetics is not well known.
- Majority of disease-specific HRQoL measures do not include sleep questions.
- There is substantial evidence that some sleep disorders increase the risk of impaired glucose tolerance and diabetes.

Introduction

Diabetes mellitus (DM) is one of the most common chronic illnesses affecting 5% of Canadians over the age of 20 years and 16 million people in the USA alone (1, 2). Its impact on the health status of general population and on health care costs cannot be overestimated; it lowers the survival by as much as 15 years and costs the US economy up to $100 billion annually. The age-adjusted death rate from diabetes in the USA has increased by 30% between 1980 and 1996 (2). Furthermore, the prevalence of diabetes is projected to increase by as much as 122% by 2025 and as much as 170% in the less-developed countries. Diabetes is often undiagnosed for years, has a multitude of complications affecting major organs, and is often not managed effectively. Approximately 90% of cases of diabetes are type II, which affects primarily adults (2). There has been a lot of interest in health-related quality of life (HRQoL) of diabetics as the researchers and funding agencies try to evaluate the impact of this disease and its therapy on individual patients and health care costs.

DM affects patients in all age groups, has a variety of clinical presentations, and a spectrum of therapeutic options ranging from diet and lifestyle modification to intense insulin therapy. Its impact on HRQoL is therefore dependent on a host of factors such as age, sex and socioeconomic status, access to health care, type of diabetes, presence of co-morbidities,

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complications, and therapeutic intervention. The literature characterizing the HRQoL in DM is difficult to summarize; there is a multitude of epidemiological and intervention studies using different instruments in different populations.

The relationship between sleep and diabetes is complex. Not only is the diabetes associated with sleep disorders, but there is emerging evidence that sleep disorders may affect glucose homeostasis and may even be a risk factor for the development of diabetes. This area has recently attracted a considerable amount of research interest resulting in a large number of original studies and review articles. As our knowledge of sleep and sleep disorders increases, so does the understanding of the role of sleep in regulation of function of major organs including the endocrine system. A review of the interaction between sleep, glucose homeostasis, and diabetes is beyond the scope of this manuscript. This chapter, rather, will provide the reader with an overview of current evidence regarding the relationship between sleep and quality of life in diabetes.

Sleep and Sleep Disorders in Diabetes

Sleep disorders in general population are very common. Recent studies indicate that up to 30% of general adult population have sleep complaints. Chronic insomnia affects 10–15% of adults, up to 20% have obstructive sleep apnea (OSA), and 7–11% have restless legs syndrome (RLS) (3–7). Sleep disorders have been associated with worse scores on generic HRQoL measures, and their treatment has been shown to improve HRQoL (8, 9). Adult subjects with RLS, for example, have significant deficits in all 8 scales of SF-36 compared with hypertensive patients, and have lower scores than diabetics on 7 scales (9). Therapy of RLS has been shown to improve sleep quality and quality of life (10–13); CPAP therapy of OSA has been demonstrated to improve daytime somnolence and HRQoL (8). The relationship between OSA and quality of life is described in chapter 9.

There is substantial evidence that some sleep disorders, namely sleep-related breathing disorders and sleep deprivation, may adversely impact glucose homeostasis and insulin sensitivity and may be an independent risk factor for the development of diabetes. Although a detailed discussion of the influence of sleep, sleep restriction, and fragmentation on glucose homeostasis and weight control is beyond the scope of this chapter, some of the most important developments in this area are summarized in this section.

Emerging epidemiological evidence suggests that sleep duration may be an important risk factor in the development of diabetes. A 12-year follow-up study of 1244 middle-aged men and women in Sweden reported an association between short sleep duration or sleep maintenance problems in men and risk of development of diabetes (14). Data from the Nurses Health Study and the Massachusetts Male Aging Study suggest that in middle-aged men and women short (i.e., <5 h/night) and long self-reported sleep duration (over 9 h/night in women and 8 h/night in men) significantly increases the risk of developing diabetes (15, 16). In women, the risk of developing diabetes appears to be reduced after adjusting for BMI, but in men, an adjustment for waist circumference did not alter that relationship. In another recent study of 6599 Swedish men followed for 15 years, the incidence of diabetes was higher in those reporting the use of hypnotics or difficulty with sleep onset even after adjustment for known confounders (17). Recent evidence from the Sleep Heart Health Study indicates that self-reported sleep duration of 5 h or less or 9 h or more is associated with increased odds ratio of DM or impaired glucose tolerance even when subjects with insomnia are excluded and adjustments are made for age, sex, race, body habitus, and apnea-hypopnea index (AHI) (18).

In addition to these epidemiological trials, recent experimental studies indicate that sleep deprivation in healthy humans alters glucose homeostasis, appetite regulation, decreases insulin sensitivity, and increases the risk of obesity (19, 20). While it is not known whether short or long sleep duration in the diabetics affects long-term glycemic control and the risk of diabetic complications, these trials indicate that sleep and sleep disorders play a significant role in glucose homeostasis.

Sleep Complaints in Diabetics

Sleep complaints are common in adult diabetics. In a study of 184 diabetics and age- and sex-matched controls, difficulty initiating or maintaining sleep occurred in 33.7% of patients and was more common than in controls (21). Skomro et al. described sleep complaints and symptoms of RLS in a group of 58 adult type 2 diabetics (22). When compared to age- and sex-matched controls, the diabetic subjects had higher rates of daytime somnolence, insomnia, nighttime musculoskeletal discomfort, nocturia, and hypnotic use. The prevalence of RLS in diabetics was 24% and was not related to anemia, iron deficiency, uremia, or glycemic control. In another study of 100 type 2 diabetics, poor sleep quality (as measured by the Pittsburgh Sleep Quality Index, PSQI) affected 45% of subjects, whereas daytime somnolence was present in 26% (23). The prevalence of RLS was 27% and was related to the presence of peripheral neuropathy (PN). Patients with RLS had worse sleep quality, shorter sleep duration, less sleep efficiency, and more use of sedatives than those without RLS. An association between RLS and DM has recently been suggested by an epidemiologic study of RLS in the US adults (4).

Sleep disorders in diabetics have a significant impact on quality of life. In a study of 894 dialysis patients, of whom 46.4% were diabetics, severe RLS was found in 15% of patients and was independently associated with diminished quality of life and sleep and shorter survival (24). In another study of diabetic patients undergoing hemodialysis chronic insomnia was present in 68.2% of subjects and was associated

with age, nutritional status, and depression (25). Subjects with insomnia had higher rate of snoring suggesting that sleep-disordered breathing may be contributing to poor sleep quality in this population.

Results form a large Finnish study of 1804 adult diabetics revealed that over 50% of subjects reported early awakening, 28% reported sleep onset insomnia, and 32% hypnotic use (26). One report suggested that the association between poor sleep and type 2 diabetes was mediated by nocturnal pain and nocturia (27). In a recent cross-sectional study of 161 African American type 2 diabetics, poor sleep quality (PSQI score > 5) was reported by 71% of the subjects. There was a significant although weak association between glycemic control and PSQI score in subjects with at least one diabetic complication (28).

These results indicate that insomnia, excessive daytime somnolence, and RLS are very common in type 2 diabetics and that RLS is affecting sleep quality and HRQoL in these patients and is likely related to PN.

Assessment of Sleep in Diabetics

While there is a number of epidemiological trials evaluating sleep complaints in the diabetics using questionnaires, there are few studies that use an overnight polysomnography (PSG) to study sleep in diabetics. Overnight PSG is the current gold standard for investigating sleep and sleep disorders (29). Data from the Sleep Heart Health Study on 5874 adults (including 692 diabetics) who underwent an overnight PSG at home suggest that subjects with diabetes have increased unadjusted rates of sleep-disordered breathing and less slow wave sleep (SWS) and rapid eye movement (REM) sleep. After controlling for age, sex, race, BMI, and neck circumference however, almost all these differences were eliminated except for increased OR for periodic breathing and slightly decreased REM (30). These results indicate that diabetes has little effect on sleep architecture but is associated with central sleep apnea.

All of the above-mentioned investigations were performed in diabetic adults. There is less data on sleep in children with diabetes. Matyka et al. (31) studied sleep in children with IDDM compared with that in controls. Diabetic children had a significant increase in wakefulness after sleep onset and number of wake episodes, but no other differences in sleep architecture were seen. Sleep has been shown to reduce physiologic responses to hypoglycemia (32), but in this study, there was no impact of hypoglycemia on sleep quality. In another investigation, however, Pillar et al. (33) demonstrated inhibition of sympathetic and arousal responses to hypoglycemia during sleep in children with diabetes. Rapid declines in the glucose levels were associated with arousals from sleep. Episodes of hypoglycemia were also associated with increased SWS and delta power in the EEG.

OSA and Diabetes

OSA is a very common and still under-recognized disorder affecting up to 20% of adults (3). Because DM is also common in the adult population and because the two conditions share some common risk factors (such as obesity), it is likely that both conditions will coexist in a substantial proportion of general adult population. Recent evidence indicates that the rates of obesity in the USA are increasing rapidly reaching what some authors called epidemic proportions (34, 35). If allowed to continue unabated the epidemic of obesity will undoubtedly contribute to the increase in the prevalence of OSA and DM.

The relationship between glycemic control, insulin resistance and DM had been the subject of exciting research, but the scope of this chapter precludes a comprehensive analysis of this subject. Nevertheless a few recent key epidemiologic studies in this area deserve a mention.

Using the database of Sleep Heart Health Study (SHHS) Resnick et al. examined the relationship between sleep-disordered breathing and diabetes (30). There was no difference between the diabetic and non-diabetic groups in respiratory disturbance index (RDI), sleep architecture and nocturnal oxygen saturation after adjustment for age, sex, BMI, race and neck circumference; however, a significant association was noted between DM and central apnea. The results of this large cross-sectional trial suggest that there is no independent association between OSA and DM, but that there is an association between DM and central apnea. In a subsequent study also using the SHHS data, however, Punjabi et al. determined that sleep-related hypoxemia was independently associated with glucose intolerance and insulin resistance (36). When this relationship was examined prospectively in the Wisconsin Sleep Cohort however, Reichmuth et al. (37) did not find evidence of a significant causal relationship between these two conditions at 4 years of follow up. Even though diabetes is more common in moderate to severe OSA, thus far there is no conclusive evidence that OSA predisposes to DM.

There is however considerable evidence that OSA negatively impacts HRQoL. Using the data from Wisconsin Sleep Cohort Study in 737 subjects, Finn et al. demonstrated that sleep-disordered breathing (SDB, defined as AHI > 5) was significantly and independently associated with lower general health status as evaluated by SF-36 in six of eight scales (38). The decrements observed in mental health and social function in subjects with moderate to severe SDB were of similar magnitude to those seen in other chronic conditions including diabetes. Severe sleep apnea was associated with significant decrements in multiple SF-36 scales in the Sleep Heart Health Study (39). Significant improvements in HRQoL have been described in OSA patients after CPAP therapy (8). These results indicate that presence of SDB is associated with lower HRQoL and that treatment of SDB improves HRQoL. The presence of SDB in subjects with diabetes may be an additional factor contributing to the lower HRQoL in this population.

HRQoL in Diabetes

Generic and Disease-Specific HRQoL Instruments Used in DM

The definition of HRQoL has been a subject of considerable debate and is provided elsewhere in this book. According to Polonsky, disease-specific HRQoL "refers solely to patients' sense of how the disease in question is compromising their well-being in the three broad areas of physical, psychological and social functioning" (Diabetes Spectrum, 2000). He identifies two categories of distress: (i) intrinsic, where the disease itself is intrusive and (ii) attributional, where the disease is "perceived as being responsible for distress in one or more of the three broad areas of functioning."

The impact of diabetes on all of these areas can be profound. Diabetic complications such as vision impairment, renal dysfunction, neuropathy, amputation, and heart disease result in a significant decrease in HRQoL. Short-term fluctuations in glycemic control and the demands of the diabetes regimen can also affect patient's QoL. Measuring all of these effects with a single instrument is a daunting task. It is therefore not surprising that Polonsky concludes: "at this time there is no well-accepted measure that comprehensively evaluates the many aspects of diabetes-specific HRQoL."

Considerable interest in the effects of DM on HRQoL has led to the development and validation of numerous instruments including generic, disease-specific, and symptom-specific measures. Generic HRQoL instruments are typically used in studies comparing HRQoL in different conditions, but these instruments are less sensitive to within-subject changes. Disease-specific instruments are used to assess the effect of therapy on a given condition and are often developed for the purpose of clinical trials. Their content therefore varies and is often dictated by the aims of a parti cular study. HRQoL is usually measured with a combination of generic and disease-specific instruments.

Some of the generic measures commonly used in DM include the Sickness Impact Profile, the Nottingham Health Profile (NHP), the SF-36, and the SWED-QUAL questionnaires (40–43). Recent reviews provide in-depth analysis of some commonly used HRQoL measures in subjects with diabetes (44, 45).

There is a considerable body of evidence documenting impairment of HRQoL in DM. Most studies reveal that, when compared with general population, adult diabetics have a significant decrease in quality of life particularly in areas such as physical functioning and well-being. Wandell (45) provides a review of 19 recent Scandinavian studies evaluating HRQoL in diabetic patients in primary health care. All of these studies used generic instruments such as Medical Outcomes Study–derived instruments (SF-36, SF-20, SWED-QUAL), NHP, General Health Questionnaire (GHQ), and the Goteborg Quality of Life Instrument (GQL). Most of these studies revealed a significant decrease in HRQoL in patients with diabetes when compared with that in non-diabetic controls. Older type 2 diabetics with poor metabolic control and diabetic patients with depression suffered from lower HRQoL. Patients with type 1 DM generally reported better physical functioning and energy than those with type 2. In this review, factors such as age, sex, psychosocial factors, social support, and type of therapy also influenced the HRQoL. When the adult diabetics are compared with age- and sex-matched controls with another chronic condition, the effects of DM on HRQoL are less apparent. Studies comparing HRQoL in DM with other chronic conditions such as angina pectoris demonstrate that the impact of uncomplicated DM on HRQoL is rather small (46).

Current evidence therefore indicates that adult diabetics have worse HRQoL than age- and sex-matched controls and that the most important predictors of HRQoL in DM are macrovascular disease, number of co-morbidities, type of treatment, psychosocial factors, old age, and female sex.

Studies of Sleep and HRQoL in Diabetes

Although there is a multitude of studies describing HRQoL in diabetes, the relationship between sleep quality and HRQoL in diabetes is still unclear. A recent review summarizes twelve commonly used diabetes-specific HRQoL measures (47). These measures vary greatly in their content; most do not include questions regarding sleep quality or sleepiness. A report to the UK Department of Health (July 2000) provided a review of diabetes-specific measures of symptoms and HRQoL and identified 20 instruments only 8 of which contained sleep questions. The number of items used by these instruments ranged from 7 to 234.

Some of the commonly used disease-specific instruments including the Diabetes-39, the Diabetes Quality of Life (DQoL), and the Diabetes Impact Measurement Scales (DIMS) (48–50) contain very few sleep-related items. The DQoL instrument, for example, has 46 items only two of which deal specifically with sleep, whereas both the Diabetes-39 and the DIMS instruments have only one question about sleep. This apparent lack of attention to sleep complaints in this population likely leads to an underestimation of the impact of sleep disorders on HRQoL in this population.

When the disease-specific instruments that include sleep items are used the results indicate that sleep problems contribute to poor HRQoL in the diabetics. In a Swedish study, type 2 diabetics demonstrated significant decrements in HRQoL (using Swedish Health-related Quality of Life Survey) in a number of categories including sleep problems and satisfaction with physical health (51). The authors followed the sample of diabetic patients for 3 years and noted a significant decrease in physical functioning scale between 1992 and 1995. There was a correlation between a decrease in general health status over the 3-year study period and sleep problems. The study, however, was limited by its small sample size (n = 48), included only type 2 diabetics, and

lacked detailed characterization of sleep disorders and objective measurement of sleep.

A cross-sectional study of 117 adults with type 2 diabetes in Iran, also using SWED-QUAL, found a correlation between a measure of sleep quality and employment status (52) suggesting that employment status may affect sleep in diabetics.

A large Finnish study of 1804 adult diabetics compared HRQoL in diabetics with age- and sex-matched general population using NHP (26). The NHP contains five sleep-related questions: (i) "I take tablets to help me sleep," (ii) "I lie awake for most of the night," (iii) "I sleep badly at night," (iv) "It takes me a long time to get sleep," and (v) "I am waking up in the early hours of the morning." Significant differences were found in the proportion of diabetics reporting early morning awakening (49 vs. 39%) and sleep onset problems (28 vs. 25%) compared with controls. Diabetics had higher use of sleeping pills than general population (32 vs. 14%). When the diabetic population was classified on the basis of therapy (diet, tablet, insulin, and combination groups), the diet group had significantly worse HRQoL indices in sleep and social isolation scales while the other diabetic groups had worse scores in almost all NHP dimensions suggesting that sleep may be impaired early in diabetes and that sleep problems are common in all types of diabetic treatment groups.

In another Scandinavian study, HRQoL of the elderly diabetic patients was studied using the SWED-QUAL questionnaire (53). Diabetics had lower HRQoL life scores on 7 of 13 scales including sleep. Poor glucose control was not a predictor of sleep problems; there was however a significant relationship between vascular complications of diabetes and sleep.

A large cross-sectional study of 3484 patients with chronic illnesses (which included 577 subjects with type II diabetes) utilized SF-36 Health survey to determine the relationship between sleep problems and well-being, work, and health care utilization (54). Significant decreases in SF-36 scores were found in those with sleep problems. For all scales of SF-36, decreases in scores were associated with higher severity of sleep problems. Four scales (role physical, vitality, role emotional, mental health) had the most significant decrease in those reporting severe sleep problems. The authors concluded that "sleep problems, therefore, may be a significant confounding factor in the interpretation of health outcomes among patients with chronic diseases" (54).

The majority of studies that incorporate HRQoL instruments containing sleep questions reveal significant decrements in sleep-related subscales in diabetics. Because there is such a variety of methods and a variety of questions used in these instruments, drawing definitive conclusions regarding the impact of sleep quality on HRQoL in diabetics is difficult. The existing evidence, however, indicates that subjective sleep complaints in the diabetics are common and that these complaints contribute to the decrease in both generic and disease-specific measures of HRQoL.

Diabetic Complications, Sleep, and HRQoL

Diabetes is a life-long condition with varying impact on QoL. Because it typically takes years to develop diabetic complications, the impact of this disease on QoL depends, amongst other factors, on subject's age and duration of diabetes. In one study comparing the HRQoL of older and younger diabetics using insulin, Trief et al. (55) found that elderly patients reported more physical limitations but better social function, less diabetes-related emotional distress, and better ability to cope. In another study of 177 elderly diabetics in which HRQoL was assessed using SWED-QUAL and was compared with age- and sex-matched non-diabetic controls (53), there were significant decreases among the elderly diabetics in 7 of 13 scales including " sleep problems."

It has been demonstrated that co-morbidities and diabetic complications have a significant impact on HRQoL. Nevertheless, it is difficult to summarize the impact of DM and its complications on HRQoL as the disease may be asymptomatic, its progression is quite variable and the treatment modalities range from lifestyle modification to intense insulin therapy. The level of glycemic control, the most commonly used physiologic outcome in diabetes management, correlates well with HRQoL in some (56), but not in other studies (57). Both hypo- and hyperglycemia have been demonstrated to impair cognitive function in DM with most of the evidence coming from studies in type 1 DM patients (58). The impact of either acute or chronic fluctuations in glucose control on HRQoL has not been extensively investigated. The data from the DCCT trial showed no difference in HRQoL between intensive and conventional insulin treatment (57).

Intensification of therapy of type 2 DM from diet to oral agents to insulin is associated with a decrease in QoL; an improvement in frequency of hyperglycemic episodes and glycemic control, however, has been shown to improve general and emotional health and vitality (59, 60). Current evidence suggests that the relationship between DM and HRQoL is mediated predominantly by the presence of macro- and microvascular complications and not by short-term fluctuations in glucose control. Some of these complications have been associated with poor sleep quality. Two of these are described below.

Painful Diabetic Polyneuropathy

The most common type of diabetic neuropathy is diabetic PN (DPN) affecting up to 54 and 45% of patients with type 1 and type 2 DM, respectively. While only 10.9–15% of diabetics have symptomatic neuropathy, painful neuropathy is often worse at night resulting in significant impairment of sleep quality (61–63). In one study of 105 subjects with painful diabetic neuropathy, 57% of subjects reported substantial interference with daily activities, but the largest impact of pain associated with polyneuropathy was on sleep. The

impact of DPN on sleep was higher than on other activities such as mobility, mood, work, and recreational activities (63). In a study of 41 diabetics with painful DPN and 38 age-, sex-, and treatment-matched diabetics and non-diabetic controls Benbow and colleagues (64) assessed HRQoL using NHP. The diabetic group with DPN had significantly elevated NHP scores in 5/6 domains (indicating worse QoL) than the diabetics without DPN. Interestingly, even the diabetic group without DPN had a higher score on the sleep domain of the NHP than the healthy controls suggesting that painful neuropathy alone does not explain the decrements in sleep quality observed in adult diabetics. This study suggests therefore that diabetic neuropathy negatively impacts sleep and quality of life.

Treatment of painful diabetic neuropathy with gabapentin improves sleep and bodily pain, vitality, and mental health scores of the SF-36 (65, 66). In another study, treatment of painful PN with tramadol resulted in improvement in pain but not in sleep quality (67).

Nocturia

Sleep is one of the important physiologic mechanisms affecting urinary output; under normal conditions the urine volume decreases during sleep. Nocturia, defined as "waking once or more at night to urinate," is a frequent symptom in subjects with DM and is particularly common in the elderly (68). Nocturia has also been reported with increased frequency in OSA, likely an effect of increased ANP secretion, and improves when OSA is treated with CPAP (68). The effects of nocturia on sleep quality are well documented and consist of reports of insomnia, non-refreshing sleep, and nightmares (69). Patients with nocturia have increased frequency of awakenings, increased fall risk, and difficulty falling asleep after voiding. Women with three or more episodes of nocturnal voiding are four times more likely to report decreased sleep duration and daytime sleepiness (69). The use of hypnotics is increased among women with nocturnal voiding. Sleep duration improves when nocturnal micturition is treated with desmopressin in subjects with nocturia and nocturnal polyuria (70). In subjects with OSA and nocturia, CPAP therapy results in a significant decrease in the number of nocturnal voids and in 60% of patients nocturia is completely abolished (71).

The Effect of Diabetic Treatment on HRQoL

There is limited information on the impact of diabetic treatments on HRQoL. The best evidence comes from the Diabetes Control and Complications Trial (DCCT), which, despite demonstrating significant improvement in glycemic control and diabetic complications, did not find a significant difference in HRQoL between the intense insulin therapy and standard treatment in insulin-dependent DM (57). It is likely that any potential improvements in HRQoL that may have been due to improved glycemic control were offset by a decrease associated with the intense insulin regimen. One has to be cautious however, in applying these findings to other therapeutic interventions, age groups, or populations of diabetics.

In a 12-week study of the effect of glipizide on glycemic control in type 2 diabetics, significant improvements in measures of symptom distress, general perceived health, and cognitive functioning were demonstrated in the glipizide treatment arm. There was also a significant improvement in sleep quality as measured by a VAS scale in the active therapy arm (72). This study provides evidence that control of hyperglycemia using glipizide results in an improvement in sleep and HRQoL. It is not clear whether these benefits are sustained after longer treatment duration or whether they can be demonstrated in other treatment modalities.

Summary

DM is a complex chronic disease affecting all age groups and leading to serious complications, decreased quality of life, and shortened survival. The impact of this disease on HRQoL is related to factors such as age, sex, type of diabetes, presence of complications, co-morbidities, and depression as well as types of therapy. Current evidence suggests that uncomplicated type 2 diabetes has a small impact on HRQoL, whereas DM complicated by micro- and macrovascular disease is associated with substantial reduction in HRQoL. Despite the fact that sleep disorders are common in the adult diabetics, sleep-related items do not feature prominently in most disease-specific HRQoL instruments. The impact of sleep disorders on HRQoL of the diabetics is therefore largely unknown; there is also very little information regarding the effect of therapy of sleep disorders on HRQoL in this population. Furthermore, there are few studies in children, the elderly, and pregnancy. The discovery of the importance of sleep in the regulation of glycemic control and recent studies demonstrating an association between sleep duration and diabetes should stimulate further research in this area. It is important that future studies pay more attention to the impact of sleep disorders on long-term complication and HRQoL in diabetes.

Issues that need to be addressed by future research:

- There is a need to further investigate the relationship between sleep quality, sleep disorders, and HRQoL in diabetics.
- Further research is needed to assess the effect of therapy of sleep disorders on HRQoL in diabetics.
- Further studies should focus on the relationship between sleep and HRQoL in the elderly, in children, and in pregnancy.

- Population-based epidemiologic and intervention studies assessing HRQoL in diabetes should include validated sleep questionnaires.

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Sleep and Quality of Life in Cancer Patients

Ora Paltiel and Randi Greenwald

Summary Current clinical practice and research in cancer patients has focused on supportive care needs as well as tumor control. Sleep disorders are commonly observed in cancer patients but they are under-reported by the patients, and infrequently elicited by their physicians. The prevalence of sleep disorders ranges from 30 to 60% in cancer patients and of insomnia from 18 to >50%. In the oncology population, insomnia often forms part of a symptom cluster consisting of pain, depression, anxiety, and most importantly fatigue. The pathophysiological basis of sleep disorders in cancer has not been fully elucidated but includes circadian rhythm disturbances and alterations in cortisol, melatonin, and cytokine secretion. Risk factors for sleep disorders can be categorized as predisposing, precipitating, and perpetuating factors, some of which are related to personal traits of the patients, and others which are related to the disease, its treatment, or reactions to it. Measurement of sleep-related problems has varied from objective observation to a variety of sleep-specific questionnaires, to quality of life (QOL) instruments, the latter usually containing very few items regarding sleep. The most accepted and efficacious treatment for sleep difficulties in cancer patients is cognitive behavioral therapy. However, in some subgroups (e.g., palliative care patients) medications may be preferred. A combined pharmacological and behavioral approach may be necessary for some patients. Methodological problems are frequent in the literature on sleep and QOL in cancer patients. There is a need for consensus on definitions, instruments for measurement, and high-quality trials to assess the efficacy of therapies.

Keywords Cancer · quality of life (QOL) · insomnia · sleep disorders · prevalence · pharmacotherapy · cognitive-behavioral therapy (CBT)

Learning objectives:

- Sleep disorders are frequently encountered in cancer patients, but infrequently reported in clinical practice, resulting in undertreatment.
- The most frequently used QOL scale for cancer contains only one item concerning sleep difficulties.
- Sleep disorders are often part of a symptom cluster of pain, anxiety, depression, and fatigue in this patient population.
- Cognitive behavioral therapies are the primary mode of treatment for these disorders in this population; however, pharmacotherapy still has a role to play.

Scope of the Problem

It has long been recognized that cancer patients are required to cope with many challenges besides the control of their tumors. When the "war on cancer" was the prevailing paradigm, the tumor itself was the target of the fight. More recently, cancer care and the corresponding literature have become more holistic and have focused on accompanying symptoms and supportive care needs of patients with cancer. Symptoms that often accompany cancer include pain, fatigue, depression, and sleep disturbances. These are often inter-related but may be experienced individually. Other complaints such as nausea, diarrhea, constipation, and breathlessness may also influence quality of life (QOL) as well as sleep quality in cancer patients. These symptoms may predate the cancer diagnosis or accompany the phase of active treatment and may continue months or even years beyond the initial diagnosis and treatment. Furthermore, caregivers of cancer patients may experience sleep disorders of variable duration (1).

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In this chapter, we will review the prevalence of sleep disorders in cancer patients. We will explore the various instruments and questionnaires used to explore this phenomenon, focusing on the distinctions, interactions, and overlap between sleep disturbance and cancer fatigue, as well as the relation to pain and depression. Finally, we will review the literature regarding treatment of sleep disorders in cancer patients using pharmacologic and behavioral means.

Definitions and Mechanisms of Sleep Disorders in Cancer Patients

Cancer patients may experience the entire spectrum of sleep disorders (2) ranging from insomnias (defined by the American Academy of Sleep Medicine as disorders that produce repeated difficulty with sleep initiation, duration, consolidation, or quality that occurs despite adequate time and opportunity for sleep and results in some form of daytime impairment) to daytime sleepiness, circadian rhythm disorders, and sleep-related movement disorders.

The pathophysiologic basis of sleep disturbances among patients with cancer is not completely understood. Mechanisms contributing to these disorders include, circadian rhythm disturbances (3), abnormalities in the circadian production of cortisol (4–6), and melatonin (7, 8), as well as cytokine production (9). There is evidence that as cancer becomes more advanced and performance status deteriorates, the circadian disturbances are exacerbated (10, 11). Besides biologic etiologies for sleep disorders, sleep quality of hospitalized cancer patients may be affected by extrinsic disturbances caused by medical staff entering their room at night, and performing procedures, some of which require the participation of the patient him/herself (12).

Subjective Versus Objective Assessment and Under-Reporting of Sleep Disturbances in Cancer Patients

Most of the studies examining sleep in cancer patients have relied on questionnaires and subjective assessments of sleep quality. Relatively few studies have included direct observation of the sleep of participants. In fact, Silberfarb and colleagues (13) found poor correlations between self-assessed quality of sleep and objective measures of sleep latency, REM latency, and percentage of time spent in Stage I versus Stage II in patients suffering from lung cancer. The main factor determining the perceived quality of sleep for these patients was the amount of time spent in delta sleep. This is in contrast with non-cancer patients who generally rate their sleep based on percent of time in bed spent asleep (sleep efficiency) rather than sleep architecture (13). This early study has important implications regarding the interpretation of the large body of work based on subjective perceptions of sleep quality. A later study by this same group (14) compared the sleep efficiency of breast and lung cancer patients in a sleep laboratory. Although 15 of 17 lung cancer patients thought they had *no* sleep problems, they were objectively found to have poorer sleep efficiency, longer time to fall asleep, and more difficulty remaining asleep than controls and patients with breast cancer. This discrepancy between subjective and objective assessment, and particularly its direction (under-reporting), was considered by the study's authors to be unique to cancer patients.

Studies examining the supportive care needs of cancer patients have identified the need for information as an important concern (15). A Canadian survey found that 37% of cancer patients had sought information on problems with sleep although only 13% were successful in finding the information (16). Moreover, it is unlikely that this information will be provided unless it is directly elicited. Velikova and colleagues (17) found that while over half of cancer patients reported at least mild sleep disorders according to the EORTC QLQ-C30 questionnaire (18), only 5% of these had this problem mentioned in their medical notes; the corresponding values for moderate sleep disturbance were 23% and 7% respectively. Similarly, a study at our center found that although 25.7% of cancer patients reported taking sleeping pills or tranquilizers in the past week, fewer than one tenth had these drugs recorded in their oncology clinic chart (19). Engstrom (20), in a study of breast cancer patients found that although half of breast and lung cancer patients reported sleep problems, 85% had never spoken to their physicians about them. Two patients reported that they "didn't think it was enough of a problem" to discuss with their doctor or that "it was not as important as the cancer itself". Reporting was more likely to occur if the attributed cause of the sleep problem was physical rather than psychological (20).

Thus, although sleeping difficulties are common among cancer patients, the phenomenon appears to follow a pattern of "don't ask, don't tell" in the clinical oncology setting, and remains largely a research issue rather than a routine clinical concern.

Prevalence of Sleep Disorders among Cancer Patients

The prevalence of sleep disorders has recently been extensively reviewed (21, 22). Table 49.1 expands and updates the data collated in Savard and Morin's comprehensive review (21). When taken as a group, sleep disorders have been described in approximately 30–60%, and insomnia in 18 to>50%, of cancer patients with prevalence varying according to cancer site, time from diagnosis and stage of disease. These rates are approximately twice the rates in the general population (23–25) according to some but not all (26, 27) scholars and point to a large unmet need among oncology patients.

TABLE 49.1. Prevalence of Insomnia in Cancer Patients [Adapted from Savard and Morin (21)].

First author and year	n	Cancer site/stage	Time of assessment	Sleep assessment method	Results
Ancoli-Israel, 2006 (107)	85	Breast Stage I–IIIA	Before adjuvant chemotherapy	Actigraphy, questionnaire, Pittsburgh Sleep Quality Index	Average sleep 6 h/night, napping >1 h during day. 1.8 wake h after sleep onset; no significant correlation between circadian rhythm disturbance and PSQI.
Anderson, 2003 (108)	354	Multiple sites/stages	Not indicated	3-item sleep disturbance scale	62% showed moderate/severe sleep disturbanceMean score 5.6 for cancer patients (higher than depressed or community dwelling adults)
Beszterczey, 1977 (109)	47	Not indicated	Not indicated	18-item questionnaire	Total sleep time per week < 50 h in 45% of the patients; < 40 h in 23% of the patients; insomnia associated with depression and anxiety but not pain
Brandberg, 1995 (110)	144	Melanoma/stage I	Postsurgery and 7 and 13 months later	6-item questionnaire	More sleep problems in patients with thicker tumor at the 3 time points
Brandberg, 2000 (111)	99	Posterior uveal melanoma	2 and 12 months post-diagnosis	1 item QLQ-C30	Insomnia 43% in patients treated with radiotherapy and 58% in enucleated
Couzi, 1995 (33)	190	Postmenopausal breast/in situ or invasive locoregional	2–6 years after diagnosis	1-item questionnaire	Difficulty sleeping in 44% of the patients; severe insomnia symptoms in approximately 1/3 of them; difficulty sleeping associated with severity of hot flashes and night sweats
Davidson, 2002 (26)	982	All	34 months (median)	42-item sleep survey	Insomnia prevalence(%)
			66.7 months		37.8
		Breast	32.2 months		32.4
		GI	39.7 months		18.4
		GU	34.2 months		29.4
		Gyn	11.0 months		36.8
		Lung	73.1 months		22.8
		Non melanoma skin cancer			Insomnia in 30.5% of the patients who received recent treatment; 29.6% without recent treatment
Degner, 1995 (35)	434	Mixed/all stages	Within 6 months after diagnosis	1-item questionnaire	Moderate to severe insomnia in 30.9% of the patients
Engstrom,1999 (20)	150	Breast, lung/all stages	99% within 4 years after diagnosis; 74% within 2 years	82-item questionnaire	Sleep disturbances in 44% of the patients; relationship between report of sleep problems before diagnosis and at interview; no relationship with naps, pain, nausea, cancer site, stage, or treatment modality
Ginsburg, 1995 (29)	52	Lung/all stages	Within 5 months after diagnosis; under radiotherapy or chemotherapy	Diagnostic interview schedule	Insomnia in 52%; severe insomnia in 29%
Harrison, 1997 (112)	29	Tongue/all stages	5 year follow-up (median)	3 items of the Memorial Symptoms Assessment Scale	Insomnia in 41% of the patients; 78% of them reported moderate to severe distress associated with insomnia
Kaye, 1983 (113)	30	Mixed/inoperable	Not indicated	38-item questionnaire	Difficulty falling asleep in 40% (no difference with healthy controls). Difficulty staying asleep in 45% (significantly higher than in healthy controls). And waking up earlier than intended in 24% of the cancer patients (no difference with healthy controls)

TABLE 49.1. continued.

First author and year	n	Cancer site/stage	Time of assessment	Sleep assessment method	Results
Krech, 1991 (114)	39	Pancreas/unresectable	25 within 12 months after diagnosis	1-item questionnaire	Sleep problems in 54% of the patients
Kurtz, 1993 (115)	279	Mixed/not indicated	79% within 3 months after treatment	1-item of McCorkle Symptoms Distress Scale-modified	Insomnia in 54.3% at first assessment; 53.2% 6 months later
Lindley, 1998 (116)	86	Breast/ stage I and II	2–5 years after initiation of chemotherapy or hormonal therapy	1-item of the McCorkle Symptom Distress Scale	Insomnia in 23.3% of the patients. Fatigue in 31.4%
Malone, 1994 (117)	212	Mixed/not indicated	During treatment	1-item of the United Kingdom Sickness Impact Profile	39.6% of the cancer patients reported sleeping less at night compared with 15.2% of the control (healthy) participants
Mercadante, 2004 (118)	123	All sites/advanced palliative care	1–2 days after admission to palliative care unit	Pittsburgh Sleep Quality IndexTotter questionnaire	30% slept less than 5 h per night
Owen, 1999 (119)	15	Mixed/not indicated	During treatment	Pittsburgh Sleep Quality Index	Significantly poorer sleep quality, sleep duration, sleep efficiency, and increased medication use among cancer patients compared with an historical comparison healthy group
Portenoy, 1994 (120)	243	Prostate,colon,breast, ovarian/all stages, (2/3 metastatic)	Not indicated	3 items of the Memorial Symptoms Assessment scale	Difficulty sleeping in 52.3% of the overall sample; prevalence rates of insomnia varying from 48.6% (breast cancer) to 60.0% (ovarian cancer) across cancer sites
Sarna, 1993 (121)	69	Lung/ all stages	Within 5 years after diagnosis (86% within 2 years)	1 item of the Symptom Distress Scale modified	Insomnia in 24.6% of the overall sample and in 30.8% of the patients experiencing serious fatigue
Savard 2001 (58)	300	Breast non-metastatic treated with radiotherapy	After radiotherapy	Insomnia screening questionnaire and interview	19% insomnia (pre-existing sleep difficulty aggravated by cancer)
Savard, 2005 (28)	327	Prostate-radical prostatectomy	Within 10 years of surgery	Insomnia Severity Index	31.5% sleep difficulties; 18.0% insomnia

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The table demonstrates some of the shortcomings in research performed thus far on sleep and QOL in cancer patients. Firstly, the sample sizes of the studies are very variable and many of the studies had fewer than 50 participants, with heterogeneous patient populations. Furthermore, scales and instruments used to assess sleep difficulties were almost as numerous as the studies themselves. Insomnia was not consistently defined. All of these factors make it difficult to draw conclusions from these works.

One study deserves particular attention because of its large sample size, use of a 42-item questionnaire, and consistent definition of insomnia (26). Davidson and colleagues performed a cross-sectional survey of almost 1000 cancer patients in six site-specific oncology clinics. Insomnia was defined as trouble sleeping in the past 4 weeks, in at least seven of the last 28 days and interfering with daytime functioning including "ability to carry out usual activities, ability to concentrate, emotions, physical well-being or ability or cope with stress." In addition to insomnia, the authors reported the prevalence of sleep-related phenomena such as daytime napping, frightening and unpleasant dreams, fatigue, restlessness in legs or repetitive leg movements and others and assessed their relation to insomnia. Sleep difficulties were more prevalent among lung and breast cancer patients than those with tumors at other sites, and sleeping pill use was most frequent among lung cancer patients. Sleeping difficulties were consistently more prevalent among patients who had received cancer treatment in the previous six months, and insomnia was related to cancer surgery within the past 6 months [Odds ratio (OR) 1.87, 95% confidence interval (CI) 1.08–3.24]. Insomnia was also related to increasing age and being fatigued (OR 2.49, 95% CI 1.75–3.55) and having low spirits (OR 4.95%CI 1.69–2.94). The relation with pain was not specifically reported although 45% of patients with insomnia attributed the symptom to pain and discomfort. Among patients with insomnia, 75.3% of cases experienced this symptom for six months or longer. About half of the participants with insomnia reported that the onset of the disorder coincided with the period six months preceding the cancer diagnosis until 18 months post-diagnosis. Interestingly, a substantial proportion of participants first experienced insomnia 5 years prior to their cancer diagnosis or 5 years following it.

Another large study focusing specifically on prostate cancer patients who underwent radical prostatectomy had contrasting findings (28). In this patient population, young age, rather than older age, was related to insomnia, and 45.8% of those with insomnia reported the onset of the disorder more than 6 months preceding the diagnosis. One might question whether some of these patients suffered insomnia because of symptoms (e.g., nocturia) related to prostatic hypertrophy.

Risk Factors for Sleep Disorders in Cancer Patients

Savard and Morin (21) have divided the etiologic factors related to sleeping difficulties in cancer patients to the 3 Ps; predisposing, precipitating, and perpetuating factors (21). The first group includes traits such as female gender (26), older age (26), marital status (21, 28), personal or family history of insomnia, and psychiatric symptoms such as anxiety and depression. Many cancer patients with sleep problems do not exhibit frank psychiatric disturbances (29), although the rate of psychological distress exhibited by cancer patients puts them at higher risk for sleep disorders.

Precipitating factors for insomnia include the stress associated with the diagnosis of cancer itself, symptoms of the disease as well as treatments and their side effects. As noted, a large proportion of cancer patients reporting insomnia date its onset to the time of diagnosis (26). Disease symptoms such as pain (5), depression (5, 28) and delirium contribute to sleep disturbances (21, 24). Recently, Vena and colleagues (30) showed that among lung cancer patients, insomnia was associated with physical health problems (cough, breathing difficulty etc) while daytime sleepiness was related to mental health difficulties. In terms of specific treatments, insomnia has been associated with recent surgery (26), radiation therapy (31), hospitalization (12) and some types of chemo- and hormonal therapy. For example, the nausea and vomiting associated with chemotherapy, and antiemetics used to treat these symptoms, specifically corticosteroids, are associated with disturbed sleep (21). Women taking tamoxifen (32) and especially those experiencing hot flashes (33, 34) report an increased frequency of sleep disturbances. Similarly, men with prostate cancer who experience symptoms of androgen blockade are more likely to report non-specific sleep difficulties and insomnia (28).

Finally, although stressful events, symptoms and treatments may precipitate the onset of sleep disturbances, these are for the most part self-limited. In contrast, as reported by Davison and colleagues, three-fourths of cancer patients with sleep disturbances report that these are long term or chronic (26). Factors which are related to a prolonged duration of insomnia (perpetuating factors) include habits which themselves perpetuate insomnia. For example, daytime resting, although a possible antidote to cancer fatigue, may contribute to sleep disturbance. The practice of resting or taking naps during the day may itself lead to an irregular sleep wake cycle. Furthermore if the bed or bedroom becomes the main venue for daytime wakeful activities such as reading, eating, watching television etc, the conditioned reflex of bed-relaxation-sleep will be broken (21).

Individuals with cancer may also harbor faulty beliefs about sleep requirements and about factors associated with sleep difficulties, which may, themselves, contribute to the perpetuation of insomnia (21).

The Impact of Sleep Disorders on QOL and Other Symptoms Among Cancer Patients

The main consequence of disturbed sleep for cancer patients are fatigue, impaired daytime functioning and mood disturbances (21). The relation with fatigue will be discussed below. The effects of sleep disturbances have been mainly studied in the non-cancer population and include impaired cognitive and psychomotor functioning as well as increased irritability, anxiety and depressive disorders (21). Some authors also claim an association between insomnia and survival in cancer patients (24). Evidence for this claim comes from a single study (35), which reported that cancer patients who were distressed by symptoms such as insomnia, nausea, appetite and pain had a lower 5 year survival after controlling for disease stage. Further support for this hypothesis comes indirectly from a study which demonstrated that women with breast cancer and altered patterns of cortisol levels had a lower level of natural killer (NK) cells and experienced a higher mortality rate compared with women with normal cortisol patterns (36).

When directly questioned by Davidson and colleagues about the impact of insomnia on their lives, cancer patients reported that it affected how they felt physically (89%), their ability to cope with stress (76.3%), their emotions (72.3%), their ability to carry out usual activities and their ability to concentrate (65%) (26). Similar findings were reported by Fortner and colleagues in a sample of breast cancer patients (37).

As noted previously, the most common correlate of sleep disturbance in cancer patients is fatigue. Fatigue is reported in over 60% (reviewed in 38) and as many as 78% (16) of cancer patients. It is defined by the National Comprehensive Cancer Network (NCCN) as an unusual, persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning (39). Cancer related fatigue has received much attention in recent years because of the development of instruments specifically designed to measure the phenomenon as well as specific treatments and management strategies. One important element of cancer-related fatigue is that it is generally not relieved by rest (38) or only moderately so. In spite of this, cancer patients with fatigue are often encouraged to rest or choose on their own to nap and sleep as a fatigue-reducing strategy (40). As noted, this can perpetuate sleep disturbances and impair the sleep-wake cycle. Furthermore, even among cancer survivors sleep disorders are important predictors of fatigue and depression (41).

Although fatigue and insomnia often go hand-in-hand, this is not always the case. For instance, Ahlberg et al. (42) in a study of women undergoing radiotherapy for uterine cancer, found that although fatigue scores substantially increased during and after completion of therapy there was no concomitant rise in insomnia scores. Furthermore, global QOL was shown to decrease as treatment progressed. Another study of cancer patients involved in a variety of clinical trials showed that those who received dexamethasone had significantly less fatigue, although they suffered from more sleeplessness (43). Redeker performed a multivariate regression analysis and found that fatigue and insomnia explained only 4% of the variance in QOL after controlling for psychological variables including anxiety and depression (44).

In general, pain, fatigue, sleep disorders, and depression or distress can be viewed as a common symptom cluster in oncology patients. Even among non-cancer patients suffering from pain, sleep disturbance is commonly reported, although not necessarily in combination with mood disturbances (45). The pharmacologic and non-pharmacologic treatment of one of these symptoms (e.g., rest for fatigue, narcotics for pain, antidepressants) can precipitate or aggravate existing sleep disturbances (46). To further elucidate a mediation pathway between these inter-related symptoms, Beck and colleagues administered questionnaires measuring pain, sleep quality, and fatigue among 84 patients with cancer. The multivariate models constructed demonstrated that pain influences fatigue directly as well as indirectly through its effect on sleep (47).

Instruments Used to Measure Prevalence of Sleep Disturbance in Cancer Patients

Specific Sleep Questionnaires

Many studies that have examined sleep in cancer patients have utilized accepted scales for the assessment of sleep disturbances. These have been extensively reviewed by Berger and colleagues (48). Tools that have been used in the clinical assessment of sleep include Clinical Sleep Assessment for children and sleep diaries. The Insomnia Severity Index (ISI) (49) is a brief 7-item instrument that has been validated in 1670 breast and prostate cancer patients (50). In the research setting, validated tools include the Pittsburgh Sleep Quality Index (51), Epworth Sleepiness scale (52) as well as objective or semi-objective measures such as polysomnography, actigraphy as well as specific instruments for children. A detailed discussion of these methods is beyond the scope of this chapter.

QOL Questionnaires

Questions about insomnia, sleep quality, and fatigue are included in a number of QOL instruments, some of which are specifically oriented to cancer patients. Donovan and colleagues pointed out a number of characteristics of QOL scales that should make them acceptable to patients, health providers, and researchers. These include (i) short completion time; (ii) ease of administration and scoring; (iii) comprehensibility to the majority of the population; and (iv) perceived relevance (53). Aaronson and colleagues (54) pointed out that by focusing on particular dimensions of QOL such as pain,

nausea and vomiting, insomnia and psychological distress, significant improvement in symptom control among cancer patients has been achieved. As noted above, the recent focus on cancer-related fatigue has also spurred research interest as well as therapeutic strategies.

As opposed to sleep-specific questionnaires, QOL questionnaires commonly used in cancer patients have very limited questions regarding sleep quality. Of 40 studies assessing interventions for sleep disturbances and QOL for cancer patients reviewed by Berger and colleagues (2), only four used multi-item sleep questionnaires and 31 used the EORTC QLQ-C30 (18), which uses a single question. It simply asks, "In the past week have you had difficulty sleeping?"—measured on a 4-point scale ranging from "not at all" to "very much." This query may be regarded as a screening question regarding sleep disturbances but, obviously, a detailed analysis of sleep difficulties, such as daytime sleepiness, poor sleep efficiency, etc., would not be assessable using this scale. Furthermore, even insomnia per se cannot be measured using this scale because basic questions fitting its definition are lacking. The revised Rotterdam symptom checklist asks about difficulty falling asleep on a 4-point scale (55). Other commonly used QOL instruments, such as the FACT-G (56), have no specific sleep question, although its fatigue-related spin-off (FACIT-F) includes statements such as "I feel tired" or "I need to sleep during the day"' with a 5-point scale ranging from "not at all" to "very much." Interestingly, the Nottingham Health Profile (57), an instrument intended for the primary care (non-oncological) setting, includes a number of sleep-related items ranging from difficulty falling asleep, poor sleep quality, to use of sleeping pills.

Some studies focusing on sleep and QOL in cancer patients have used sleep-specific questionnaires in combination with accepted QOL instruments (28, 30). It is evident that specific sleep questionnaires are required in order to define and evaluate sleep disturbances among cancer patients; on the other hand, general QOL questionnaires including a single item regarding sleep quality can alert clinicians to sleep difficulties among their patients, their impact on global QOL, as well as providing a basis for ongoing or repeated measurements of sleep problems after specific interventions.

Interventions for Sleep Disorders in Cancer Patients

Research on the treatment of sleep disorders in the cancer population has focused principally on insomnia and the related but distinct problem of fatigue (26, 38, 58–61). Treatment guidelines for co-morbid insomnia in oncology patients are derived from research on primary insomnia in the general population (21, 60). The latter studies have usually excluded patients with sleep disorders related to medical illness (62), pain, or depression, which are commonly found in oncology patients (63). Given that sleep disturbances are frequently undetected in the cancer population, it follows that these patients often are not offered effective interventions. When insomnia comes to the attention of the clinician, medications and benzodiazepines, in particular, are the most frequent treatment provided (19, 21, 26, 60, 64). Although benzodiazepines demonstrate short-term effectiveness for primary insomnia in the non-cancer population, medications have a number of disadvantages. One major weakness of pharmacotherapy is that sleep improvement is not maintained after cessation of treatment (65–67). In contrast, cognitive-behavioral therapy (CBT) has demonstrated satisfactory long-term benefits (68, 69). As a result, CBT has garnered recommendations as the primary treatment for insomnia in the general population (66). Although CBT may be the preferred approach, the complexity of the oncology patient's medical condition requires that the clinician consider the advantages and disadvantages of each intervention when selecting treatment.

Pharmacological Interventions

Benzodiazepines have been the primary medication used to treat insomnia in both the general and the oncology populations along with anti-depressants and anti-histamines. There are a number of disadvantages in treating insomnia with benzodiazepines and, to a lesser extent, with the newer selective benzodiazepine receptor agonists (BRZA) such as zolpidem, zaleplon, and eszopiclone. These disadvantages include next day sedation resulting in memory and cognitive impairment, falls due to psychomotor impairment, and psychological and sometimes physiological dependence (21, 69–71) and rebound insomnia (72). These side effects further burden cancer patients contending with additional illness-related symptoms and treatment side effects. An additional problem is that patients with chronic insomnia frequently use medication for long periods, often for years, despite tolerance or the lack of evidence of long-term effectiveness, and the risk of side effects. Furthermore, medications for insomnia have the potential to interact with other pharmacological interventions for the treatment of the cancer or for symptom management. For example, benzodiazepines can exacerbate the respiratory-suppressant effects of opioids that are used to treat cancer pain (24, 73). Often, patients are reluctant to add medications when they are already receiving chemotherapy or radiation (60, 62).

Recommendations to use reduced dosages for older adults may apply to advanced stage cancer patients, who are often older and/or more fragile (74). When life expectancy is short, medication is recommended as the treatment of choice for sleep disorders both because the results are more rapid and because palliative patients are often less able to participate in CBT (73). However, it should be noted that sleep problems may foreshadow delirium, which is common in end-stage cancer patients, and in these situations, benzodiazepines are contraindicated and anti-psychotic medication may be appropriate.

If sleep disorders accompany depression, it is preferable to prescribe antidepressants rather than benzodiazepines or BRZAs. Here, too, standard recommendations must be tailored to the needs of cancer patients. In their study of the treatment of depression in cancer patients, Grassi et al. (75) note the advantage of reboxetine over tricyclic antidepressants and SSRIs that can exacerbate GI distress due to chemotherapy. Cancer patients often turn to complementary therapies as well as over-the-counter medications (e.g., antihistamines) for symptom control, including sleep disorders, and these therapies are of limited proven benefit (71, 76).

About 41% of cancer patients report leg restlessness (26). If restless leg syndrome or periodic leg movement of sleep (RLS/PLMS) are the cause of insomnia, a different treatment regimen is required (74, 77).

Non-pharmacological Treatments: Cognitive Behavioral Treatment for Insomnia

An increasing body of research has emphasized that CBT is as effective as medication for the short-term treatment of primary insomnia (62, 78–80). Early studies of behavioral interventions for primary insomnia demonstrated improvements in approximately 70–80% of patients and resulted in large effect sizes for a number of sleep parameters (81–83). When considering the options, the advantage of the rapid onset of effect from medication must be weighed against the benefits of long-term maintenance of sleep improvement (up to 2 years) from CBT (68, 78, 83). Recent studies have focused on the effects of combining or varying the sequence of medication and CBT. Long-term results were best for CBT alone (67, 84). It appears that patients sustain sleep improvements for longer periods after learning the skills involved in CBT without the aid of medication (65). One explanation is that patients who received combined therapy, who attributed their improvement to medication rather than to the skills learned in CBT, were more likely to relapse (65). In another study, starting treatment with CBT alone or in combination with medication produced better results post-treatment and at follow-up when compared with beginning treatment with medication and subsequently adding CBT (84). However, CBT alone tended to result in an initial reduction in total sleep time, which was not found in patients starting with the combined approach. For cancer patients who may also be struggling with fatigue, a reduction in total sleep time may be too much of a burden and may reduce the likelihood of adherence to CBT treatment (65, 84). In those cases, the combined approach may be the preferred initial course of treatment. It may also be possible to temporarily utilize stimulant medication, such as methylphenidate (24,85) or modafinil (24,38,86), to assist patients with fatigue in adhering to CBT guidelines.

In summary, CBT is the preferred first line of treatment for insomnia. Research suggests that when medication must be given, it is preferable that its administration be short term and concurrent with CBT, and that CBT be continued beyond cessation of medication to consolidate the patients' newly learned sleep behaviors and maximize maintenance of sleep improvement.

The Components of CBT for the Treatment of Insomnia

The four main behavioral components of CBT developed over the past 25 years, which provide patients with skills to counteract the cognitive and behavioral factors postulated to trigger and perpetuate insomnia are (78, 79): relaxation therapy, stimulus control, sleep restriction therapy, and sleep hygiene. These components of CBT focus on: (i) cognitive and/or physiological arousal at bedtime or during periods of wakefulness, (ii) the association of bedtime and the bedroom as a place of anxiety, (iii) the problem of fragmented sleep, and (iv) education about behaviors and conditions that promote sleep (78, 79). The usual behavioral guidelines include limiting time in bed only to sleep and sex (no reading, TV, radio, eating, or worrying), going to bed only when sleepy, leaving the bed if awake for more than 20 min, waking up at a standard time, and avoiding daytime napping. Sleep restriction limits time in bed to actual sleep time based on sleep logs. Although sleep restriction has an important impact on sleep maintenance, compliance with restrictive guidelines is sometimes problematic because of initial increased sleepiness (78,86) and may prove particularly difficult for cancer patients already struggling with fatigue.

In addition to the behavioral components, cognitive therapy has been shown to alter the dysfunctional beliefs and attributions about sleep that can lead to increased arousal and anxiety that can exacerbate and perpetuate insomnia (78, 87, 88). In studies of cancer patients, those with insomnia had significantly higher levels of dysfunctional sleep-related thoughts (e.g., excessive rumination about the consequences of sleep loss) (89, 90). In these patients, it is also important to teach ways of coping with the anxiety and uncertainty surrounding cancer and its treatment, which often surfaces at bedtime (91). There is a well-developed body of research that addresses the treatment of anxiety and depression in cancer patients through CBT (92, 93). CBT for cancer patients with insomnia also needs to focus on the frequent problem of fatigue because the tendency to nap and reduce activity levels can interfere with nighttime sleep (61, 94).

Evidence for the Efficacy of Non-Pharmacological Interventions for Insomnia in Cancer Patients

Early studies, focusing on relaxation treatment for insomnia in cancer patients, found modest improvements in both a single case study (95) and a randomized trial (96). A study of breast cancer patients, which included behavioral strategies but no cognitive component, found mixed results (97). Other strategies such as mindfulness meditation (98, 99), yoga (100), and

expressive writing (101) have also resulted in improved sleep in cancer patients.

Four recent studies utilizing various components of multi-modal CBT group therapy have shown positive results (91, 102–104). However, it must be noted that two patients dropped out of one study because of difficulties adhering to sleep restriction guidelines (102), and another patient had increased pain from bone metastases during relaxation training (91). Although only one study used a randomized control design, taken together, these four studies provide evidence for the efficacy of CBT group treatment of insomnia in cancer patients and demonstrated benefits on QOL measures as well. Furthermore, positive immunological effects of CBT have been demonstrated (105). It must be noted that all these patients were post-treatment, with a high performance status. It is uncertain how these results would apply to patients during chemotherapy or radiation or with more progressive disease. One study of cancer patients receiving CBT during treatment to aid in symptom management (including insomnia), found that patients suffering from neutropenia and/or from pain, fever, and fatigue were less able to benefit from CBT (106). This raises the question as to whether a more intensive CBT intervention might be more helpful at such a time or whether medication management for insomnia might be more appropriate.

Although most research has isolated and focused on the treatment of insomnia in cancer patients, in clinical practice insomnia is often part of a complex set of problems. Gielissen et al. (94) showed positive results in the treatment of fatigue in cancer using a multi-modal CBT approach. CBT for insomnia, along with other modules, were offered based on individualized assessment of patients needs. Improvements in insomnia resulted in diminished fatigue (94, and Gielissen, personal communication) Intervention models in which insomnia treatment forms one part of a modular CBT treatment, which also includes components for treating anxiety, depression, fatigue, and pain, may bring us closer to meeting the needs of the individual cancer patient.

Quality of the Evidence on Sleep and QOL in Cancer Patients and Future Research

Although it is evident from the data presented in this chapter that sleep problems are a common concomitant of cancer, many problems exist with the quality of the evidence available to date. Clark et al. (22) have critically reviewed some of the problematic issues in the existing literature that hamper clinical decision-making in this area. The four main issues identified were (i) lack of conceptual clarity—including a lack of standardized definitions making comparison across studies difficult, and hampering communication as well as identification of specific sleep–wake disturbances; (ii) failure to identify a conceptual model that guided the study; (iii) use of subjective and objective measures that have not undergone evaluation for validity or reliability, and lack of relation between subjective and objective measures; and (iv) lack of randomized controlled trials evaluating assessment instruments and interventions. All of the above limit our ability to wisely and confidently advise patients with cancer and sleep–wake difficulties.

It is hoped that the future will bring large-scale studies evaluating sleep difficulties using validated questionnaires and objective measures. Interventions that have been evaluated in adequately powered multi-centered trials will then be offered to cancer patients suffering from these problems. Further research should evaluate preventive interventions in cancer patients. Finally, once simplified and automated, ongoing QOL evaluation, including an assessment of sleep quality, should become routine parts of clinical care for cancer patients, allowing for swift and effective responses to their unmet needs.

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Issues that need to be addressed by future research:

- The pathophysiological basis of sleep disorders in cancer patients has not been fully elucidated.
- Additional research is needed to examine the efficacy of specific treatments for sleep disorders, especially the role of multi-modal therapy that recognizes the multiple needs of cancer patients.
- The optimal tool for ascertaining sleep disorders in this population and for assessing effects of treatment has not been determined.

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Sleep and Quality of Life in Head and Neck Neoplasm

Roy Rada

Summary What is the relationship between obstructive sleep apnea (OSA) and head and neck neoplasms (HNN)? For relevant articles identified through MEDLINE, thirty-three were about neoplasms (often benign) presenting first as OSA, and five were about head and neck cancer (HNC) treatment causing OSA. Three of these articles gave incidences for HNC treatment causing OSA, but these incidences varied widely, as they went from 8 to 92%. A few, older case studies described individual patients treated for HNC who developed OSA, particularly after extensive radiotherapy. However, those case studies did not stimulate much further investigation. Handling of OSA caused by HNN fits the classic, medical pattern of a symptom that is traced to a disease for which treating the disease removes the symptom (the treatment typically is to remove the HNN). OSA secondary to treatment for HNC may be missed, in part, because patients have many, permanent, adverse effects, such as xerostomia, from HNC treatment, and those adverse effects camouflage the OSA symptoms. OSA that has been caused by the treatment for HNC has been managed by tracheostomy or Continuous Positive Airway Pressure (CPAP), although patient complications may require additional steps. Quality of life surveys confirm that patients with HNC have sleep problems. Xerostomia may contribute to these sleep problems, and the role of salivary mucins deserves consideration. HNN and their treatments create special situations for studying the causes of OSA and for caring for patients.

Keywords Obstructive sleep apnea · head and neck cancer · radiation · head and neck benign tumors · tracheostomy

Learning objectives:

- Develop a methodology for systematically searching the literature related to head and neck neoplasms and obstructive sleep apnea.
- Recognize that head and neck neoplasms can cause obstructive sleep apnea.
- Identify signs and symptoms that obstructive sleep apnea may be present in patients secondary to treatment for head and neck cancer.

Introduction

This review addresses the conditions under which a head and neck neoplasm (HNN) is related to obstructive sleep apnea (OSA). The obvious relationship is that a neoplasm can obstruct the airway and cause OSA. If the neoplasm is not obvious, then these can be challenging cases to diagnose. On the other hand, unfortunately, the treatment of HNN may lead to OSA. This chapter will investigate both these situations, namely when an HNN causes OSA and when treatment of an HNN causes OSA.

OSA occurs when an obstruction in the upper airway blocks breathing (1). The Apnea-Hypopnea Index (AHI) is the number of apneas or hypopneas per hour of sleep. The patient has no disease when AHI is less than 5 but has severe disease when AHI exceeds 30. One of five adults has an AHI between 5 and 30 and has mild to moderate OSA (2).

HNN refers to "any new and abnormal growth" in the "head and neck" region. For operational purposes, this review will include under "head and neck" those anatomical locations specified in the Medical Subject Headings (MeSH), which is the National Library of Medicine's hierarchical thesaurus for indexing and retrieving journal articles (3). The term 'HNN' is sometimes used to refer to only "malignant neoplasms" or "cancers," but in this review the subset of neoplasms that are malignant may be distinguished with the term "Head and Neck Cancers" (HNC).

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Methods

One expert way to search MEDLINE is to use MeSH. The hierarchical relationships in MeSH go approximately 10 levels deep from parent to child to grandchild and so on (4). The concept of Sleep Apnea Syndromes appears in MeSH with three children:

- Pickwickian Syndrome,
- Central Sleep Apnea, and
- OSA.

The concept of HNN has 23 descendant concepts of which the two most prominent are

- Mouth Neoplasms and
- Otorhinolaryngologic Neoplasms.

The child "Otorhinolaryngologic Neoplasms" has itself these children:

- Ear Neoplasms,
- Laryngeal Neoplasms,
- Nose Neoplasms,
- Pharyngeal Neoplasms, and
- Tonsillar Neoplasms.

The three descendants of "Pharyngeal Neoplasms" correspond to nasopharyngeal, oropharyngeal, and hypopharyngeal neoplasms. Each MEDLINE citation includes about a dozen MeSH concepts. Furthermore, for each citation, about two concepts are indicated as the major concepts for that article. In querying MEDLINE, one can request citations for which a concept was a major concept by qualifying the query term with the expression "MeSH Major Topic" abbreviated as "majr." The query by default includes the MeSH concept and all its descendants in the hierarchical thesaurus. A MEDLINE query in June 2006 on "head and neck neoplasms(majr) AND sleep apnea syndromes(majr)" returned 41 citations.

Of the 41 articles retrieved for the aforementioned MEDLINE query, 38 fell into two categories:

- 33 articles were about OSA caused by HNN and
- 5 articles were about treatment of HNC causing OSA.

These two categories of articles constitute the headings for the next sections of this chapter. Of the three remaining articles, one was a journal review of both OSA caused by HNN and treatment of HNC causing OSA (5), one showed a high proportion of HNC patients to have OSA immediately prior to surgery for HNC (6), and the other article did not address the relationship between HNN and OSA (7).

Tumor Causes Apnea

The most common cause of OSA in the general population is obesity (8). Thirty-four of the retrieved articles are about the presentation of a patient with OSA who is subsequently found to have a neoplasm (and not obesity) causing the OSA. Sometimes, no treatment of the OSA occurs:

- In Hockstein et al. (9), worsening OSA led to identification of a lipoma causing the OSA but no treatment, given other conditions of the patient.
- Koopmann et al. (10) report a lipoma causing OSA but do not report on the resolution of the OSA.

In the majority of the articles, diagnosis of the neoplasm secondary to OSA is the main point but resolution of the OSA is addressed. Typically, resolution of the OSA is achieved by treatment of the neoplasm or continuous positive airway pressure (CPAP), as evidenced in these three cases:

- A patient presented with OSA from a right parapharyngeal lipoma and removal of the lipoma cured the OSA (11).
- Hunter's syndrome causing myxoma presented as OSA, and the OSA was successfully treated with surgery and CPAP (12).
- A patient presented with OSA, was diagnosed and treated for pharyngeal non-Hodgkin's lymphoma, and the OSA resolved (13).

Several articles claimed to be the first report of a neoplasm causing OSA:

- Abdullah et al. (14) say "A parapharyngeal space lipoma causing obstructive sleep apnea has not been previously reported."
- Kimura et al. (15) say "To our knowledge, this is the first report of OSA associated with hemangiomas involving the upper airway."

The difference between cases may be subtle; for instance, Alobid et al. (16) report the first case of a patient with OSA caused by a left parapharyngeal angiolipoma, whereas Pellanda et al. (11) report the first case of right parapharyngeal lipoma causing OSA.

Indexers assign not only the concept, such as "lipoma," to an article but also add a qualifier, such as "complications," "etiology," or "treatment." Most of the retrieved citations reflected a "neoplasm complication" and a "sleep apnea etiology." The classification of each neoplasm by its anatomic location reveals that the most frequently mentioned locations are salivary gland, larynx, nasopharynx, and oropharynx. In terms of histological type, the distribution of MeSH concepts in the indexing of the articles shows more benign neoplasms than malignant neoplasms. Of the benign neoplasms, frequently indexed ones are "lipomas" and "papillomas." The most frequently indexed malignant neoplasm is non-Hodgkin's lymphoma, whereas in the general population 95% of HNC are squamous cell carcinoma (17).

Tumor Treatment Causes Apnea

A summary of the five articles in which the treatment of HNN gave rise to OSA as follows:

- Twenty-four patients treated for HNC were studied for OSA. All patients received surgery and 10 additionally

received radiation. All the radiated patients developed OSA, and the overall incidence of OSA post-HNC treatment was 92%. CPAP was prescribed for the OSA patients, and eight of those patients improved with CPAP (18).
- Forty patients underwent reconstructive laryngectomy for glottic carcinoma. In the post-operative period, three of them presented for the first time clinical evidence of OSA—making for an incidence of 3 of 40 or 8%. One of the patients was effectively treated with CO_2 laser vaporization and the other two were effectively treated with CPAP (19).
- Four of 33 patients (15%) developed OSA after treatment for HNC (20).
- One patient with squamous cell carcinoma of the base of tongue was treated with chemotherapy and radiation followed by surgery and 2 months after surgery developed OSA; CPAP was started, and the OSA resolved (21).
- Jasper et al. (22) note that surgical treatment of lymphangioma can produce the paradoxical effect of OSA.

The 92% incidence OSA post-HNC treatment in one study versus 8% in another study is not solely explained by the conditions of the two studies (as explained later). Although a small minority of the articles address treatment of HNN causing OSA, this relationship is one of the most interesting. In discussing this relationship with a sleep specialist, the author was introduced to four articles that were not retrieved by the query "head and neck neoplasms(majr) AND sleep apnea syndromes(majr)." Each article is a case study of a single patient and a summary of those articles follows:

- Baker and Ross (23) in 1980 described the possible mechanisms of OSA and a case study of a patient who was treated for squamous cell carcinoma of the left pyriform sinus with radiation and a neck dissection. Fifteen months after treatment, the patient reported severe sleep problems that were diagnosed as OSA secondary to a swollen epiglottis secondary to radiation. The patient was successfully treated with a permanent tracheostomy that the patient plugs during the day unplugs at night.
- Polnitsky et al. (24) in 1981 reported a case in which a patient with squamous cell carcinoma of the base of tongue was treated exclusively with radiation. The patient reported to the doctor 5 years after treatment and had severe OSA. The patient was treated with tracheostomy. The authors say, "Fibrosis and edema may be more prevalent than previously appreciated."
- In a 1989 paper, Herlihy et al. (25) present a case in which a patient with HNC treated with first surgery and then radiation developed OSA. Tracheostomy was first used to treat the OSA but was not enough. Then the doctors recognized that the patient also had hypothyroidism secondary to the cancer treatment and added thyroxine to the treatment regimen. The tracheostomy plus thyroxine stopped the patient's OSA.
- In 1999, Loube et al. (26) presented a case in which a patient with HNC treated with surgery and radiation developed OSA. The patient was successfully treated with CPAP.

Examination of the MEDLINE indexing of these four articles shows that the indexers did not specify a neoplasm as a major topic of the article, and thus, these articles were omitted from the retrieved set of citations to the query "head and neck neoplasms(majr) AND sleep apnea syndromes(majr)."

Discussion

Clearly, HNN can cause OSA. Although a minority of the articles address treatment of HNN causing OSA, this relationship is particularly interesting. The conditions under which treatment of HNC causes OSA are not clear.

Disparity

The frequency of OSA secondary to treatment of NHC is 96% in Friedman et al. (18) but 8% in Rombaux et al. (19). The criteria and methods of the two studies are compared next. In Friedman et al. (18), patients are considered to have OSA if their AHI is greater than 15, and Rombaux et al. (19) use a similar criterion.

Friedman et al. (18) prospectively selected 24 patients who had previously been treated for HNC involving the tongue base, pharynx, or supraglottic larynx. The treatment always included surgical resection, and in 10 of the 24 patients, radiation was also used. The radiated patients were more likely to have T3 or T4 disease. Unspecified are 1) the population of patients from which these 24 were selected, 2) whether the patients had sleep problems before the cancer treatment, and 3) the time between the cancer treatment and the appearance of OSA.

In the Rombaux et al. (19) study, 40 patients were retrospectively analyzed of whom three had developed clinical symptoms of OSA within 3 months of surgery. The patients had all undergone curative reconstructive laryngectomy with bilateral neck dissection (no radiation or chemotherapy was used) for glottic squamous cell carcinoma. Review of the medical record suggests that no evidence of OSA had presented itself in these patients before surgery.

In the Friedman et al. (18) study, some of the patients had more advanced disease and received more extensive treatment (radiation and surgery) than those in the Rombaux et al. (19) study. Anatomically, the cancers were in different parts of the neck. These attributes of the disease and treatment may account for the differences in the incidences of OSA.

One way to explore the likely upper limits on OSA incidence would be through results of "Quality of Life" studies on HNC patients. The MEDLINE query "quality of life(majr) AND head and neck neoplasms(majr)" retrieves 331 citations. A frequently used questionnaire in the articles of the past few years comes from the European Organization for Research and Treatment of Cancer (EORTC). The EORTC "Quality

of Life Questionnaire" (QLQ-C30) is intended to be used in conjunction with site- or disease-specific modules, to provide more comprehensive assessment of patients' difficulties. The EORTC head and neck module goes by the label "QLQ-H&N35" (27). The QLQ-C30 contains exactly 30 questions of which one is about sleep; the sleep question asks "During the past week, have you had trouble sleeping?" The QLQ-H&N35 has 35 questions and goes into depth on certain topics introduced in the QLQ-C30. For instance, the QLQ-C30 asks one question about eating, but the QLQ-H&N35 asks eleven questions about eating. Interestingly, the QLQ-H&N35 asks no questions about sleep. The responses to the sleep question are mapped to a 0–100 scale where the 0 represents "not at all" and the 100 represents "very much."

Three studies with the ECORT questionnaires and HNC patients show

- 120 patients reported on average a 30 for sleep quality before, during, and after sleep treatment (28).
- 129 patients received surgery or surgery followed by radiotherapy for oral cancer, and the QLQ-C30 was administered before surgery and after surgery but before radiotherapy (29). The sleep value was again 30 before and after surgery.
- In 40 patients with cancer of the larynx, the sleep value dropped from 25 at diagnosis to 19 one year after diagnosis (30).

None of these studies differentiated the kind of sleep problem—patients could have had anxiety-based insomnia one time and OSA another time. Only the third study was long term.

Some "Quality of Life" questionnaires administered to HNC patients do not address sleep, see Smith et al. (31). Some reviews of Quality of Life studies for NHC patients do not mention sleep, see Hecker et al. (32). However, some work on intensity-modulated radiation therapy (IMRT) specifically addresses sleep. For instance, in one survey of post-IMRT, HNC patients, 33% of the patients reported occasional sleep problems and 10% reported frequent sleep problems (33). The frequency of OSA secondary to treatment for HNC merits further study.

Radiation and Mucins

The literature is unclear on the etiology of OSA secondary to HNC treatment. Rada (5) reports an HNC patient treated only with radiation who developed xerostomia and then OSA (but no anatomical narrowing of the upper airway). A search on MEDLINE for "Head and Neck Neoplasms/ radiotherapy(majr) AND xerostomia/ etiology(majr)" retrieved 40 citations; one of which stated that (34):

> 59 patients followed on average 47 months after radiotherapy for HNC were given a mucin spray and asked about its impact. They reported sleeping significantly better when using the mucin spray.

The same search but with "radiotherapy" replaced with "surgery" retrieved only one citation, and that article was about Sjorgen's syndrome. The same search with "radiotherapy" replaced with "drug therapy" also retrieved only one citation, and that article also did not address sleep.

The relationship between mucins and sleep is subtle. Saliva provides mucins that serve as mucosal lubricants (35). Mucins bind water effectively, and their presence on the mucous membrane surface helps maintain these tissues in a hydrated state. Surface tension forces are associated with the mucins and play a role in upper airway luminal patency. A low surface tension may reduce the tendency for functional narrowing by inhibiting surface tension-mediated mucosal fold apposition (36). Topical instillation of mucin-like materials into the upper airway decreases the intraluminal pressure required to reopen a closed pharyngeal airway (37) and could be used therapeutically for patients with OSA (38).

As previously noted, the query "Head and Neck Neoplasms/surgery(majr) AND xerostomia/etiology(majr)" returned one article about Sjorgen's syndrome. In seeking further evidence from the literature for the role of saliva in OSA, one may look to Sjorgen's syndrome because it damages salivary glands. Forty-nine of 65 patients with primary Sjorgen's syndrome reported moderate or severe sleep problems (39). These sleep problems in Sjorgen's syndrome patients support the contention that radiated salivary glands could contribute to sleep problems.

Conclusion

Thirty-three articles were identified about HNN first presenting as OSA. Physicians should be aware that certain neoplasms, such as a lipoma of the pharynx, might cause OSA. Far fewer articles address the treatment of HNC causing OSA and the ones that do introduce controversial incidence results.

Mucin production from various salivary glands may be impaired by radiation, and the resulting deficit of mucin could tip the balance in airway patency in favor of OSA. Accordingly, radiation oncologists might want to avoid mucin-producing salivary glands in their IMRT fields. Patients who present with sleep problems post-treatment for HNC should be assessed for OSA.

HNC accounts for 60,000 new cancer cases per year in the United States. Whether the frequency of OSA secondary to treatment of NHC was the 96% reported in Friedman et al. (18) or the 8% reported in Rombaux et al. (19), thousands of patients would be affected. Quality of Life studies indicate that sleep is a problem for HNC patients. Oncologists should be aware of relationships between HNC treatment and OSA. Further research is needed on the precise relationship between HNC and OSA.

Issues that need to be addressed by future research:

- The incidence of obstructive sleep apnea secondary to treatment for head and neck cancer needs to be better understood.
- The mechanisms by which obstructive sleep apnea arises from treatment for head and neck cancer should be elaborated.
- Treatments for head and neck cancer need to be developed with consideration of their possible impact on the ability of the patient to sleep.

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51
Menopause, Sleep, and Quality of Life

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Summary Health-related quality of life does not appear to be substantially worsened during menopause. Although women increasingly report difficulty sleeping during this period, laboratory physiological studies do not bear this out. Rather, women who report higher levels of anxiety also report difficulty sleeping. The prevalence of insomnia in the general population is highly dependent upon the definition employed and may account for the reports obtained in menopausal women.

Keywords Hot flashes · sleep · menopause · arousals · awakenings · sleep disruption

Learning objectives:

- The menopausal transition per se is not necessarily related to a decreased quality of life. Rather, women who report depression and anxiety before this period, also report these symptoms during menopause.
- Similarly, neither menopause nor hot flashes produce objective sleep disturbance. Rather, the prevalence of some sleep disorders, such as apnea, do increase during menopause and, in turn, produce disturbed sleep.

Introduction

At this point in time, about 50% of the women in Western societies have reached the median age of menopause, which is 51 ± 5 (SD) years. Thus, issues of quality of life during the menopausal transition are relevant to a very large segment of the population.

The effects of menopausal status on health-related quality of life (HRQOL) have been examined using cross-sectional and longitudinal methods. The cross-sectional studies, reviewed by Matthews and Bromberger (1), have generally found that perimenopausal women reported more pain and role limitations due to emotional problems or physical health and more physical symptoms compared with premenopausal women. The studies that statistically controlled for emotional symptoms no longer showed the effect of menopause on physical symptoms. That is, women who report high levels of emotional symptoms, such as depression and anxiety, are the women who report poor QOL during menopause. Thus, although menopause may be related in some way to HRQOL, it is probably not its main determinant.

Among longitudinal studies, the Melbourne Women's Mid-life Health Project (2) found no effect of change in menopausal status on perceived health. In fact, well-being increased across the menopausal transition. The Australian Longitudinal Study of Women's Health found that women who changed from pre- to perimenopausal status reported only declines in physical function, but not in pain and vitality (3). These two studies and a third, the Pittsburgh Healthy Women Study (4), found that reported sleeping difficulty increased across the menopausal transition. This will be examined in more detail in the next section.

Menopause and Sleep

Subjective Reports

Many epidemiologic studies have been done in which reports of poor sleep during the menopausal transition were assessed using cross-sectional or longitudinal methods (Table 51.1). Most of these found that reports of poor sleep, usually assessed by a single question, increased during this period.

The most extensive of these studies, the Study of Women's Health Across the Nation (SWAN) (18), found the overall prevalence of self-reported sleep difficulty to be 38%, with the highest rate being during late perimenopause (45%). These

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TABLE 51.1. Do hot flashes and sleep disturbance occur with menopause?

Study	Type	HFs	Sleep Disturbance
(5) McKinlay 74	Cross-sectional	+	+
(6) Ballinger 76	Cross-sectional	ND	+
(7) Bungay et al. 80	Cross-sectional	+	+
(8) Hunter 86	Cross-sectional	+	+
(9) Anderson et al. 87	Clinic	+	+
(10) Matthews 90	Longitudinal	+	–
(11) Hunter 92	Cross-sectional	+	+
(12) Holte 92	Longitudinal	+	–
(13) Shaver 93	Cross-sectional	+	–
(14) McKinlay 94	Longitudinal	+	+
(15) Baker 97	Clinic, Cross-sectional	+	+
(16) Kuh et al. 97	Longitudinal	+	+
(17) Owens 98	Cross-sectional	ND	–
	Longitudinal	ND	+
(18) Kravitz 03	Longitudinal	+	+

ND = not done

rates were based on reponses to the question: "Over the past 2 weeks, have you experienced difficulty sleeping?"

These findings have generally been attributed to disruptive effects of menopause, hot flashes, or both upon sleep. However, research discussed below challenges this assumption.

Hot Flashes

Because hot flashes are experienced by up to 80% of menopausal women and are one of the most commonly posited causes of menopausal sleep disturbance, their physiology will be briefly described here.

The symptoms of a hot flash are characteristic of a heat-dissipation response and consist of sweating on the face, neck, and chest, peripheral vasodilation, and feelings of intense heat. Although hot flashes clearly accompany the estrogen withdrawal at menopause, estrogen alone is not responsible because levels do not differ between symptomatic and asymptomatic women (19, 20). Until recently, it was thought that hot flashes were triggered by a sudden downward resetting of the hypothalamic setpoint, because there was no evidence of increased core body temperature. However, we recently obtained such evidence, using a rapidly responding ingested telemetry pill (21, 22). We then found that the thermoneutral zone, within which sweating and shivering do not occur, is virtually nonexistent in symptomatic women but normal (about 0.4°C) in asymptomatic women (23). Thus, we believe that small temperature elevations preceding hot flashes acting within a reduced thermoneutral zone constitute the triggering mechanism. We also demonstrated that sympathetic activation is elevated in symptomatic women, which, in animal studies, reduces the thermoneutral zone (24). Clonidine reduces central sympathetic activation, widens the thermoneutral zone, and ameliorates hot flashes (25). Estrogen virtually eliminates hot flashes and does so by widening the thermoneutral zone (26).

Physiological Sleep Studies

Early physiological sleep studies lent some support to the idea that hot flashes cause disturbed sleep. Erlik et al. (27) found a significant correlation between the occurrence of hot flashes and waking episodes in 8 of 9 postmenopausal women. This association was not found in premenopausal women. In the postmenopausal women, 45 of 47 of the hot flashes were associated with a waking episode, but 31 waking episodes (40%) were not accompanied by a hot flash. On average, the waking episodes preceded the hot flashes by about 36 s.

Our group recorded hot flash and sleep measurements in symptomatic and asymptomatic postmenopausal women using ambulatory monitoring (28).We found significantly increased time awake, poorer sleep efficiency, and more stage changes in the former group, as well as more Stage 4 sleep. We also found significantly more arousals in the symptomatic women. Of 55 hot flashes recorded in this group, 73% occurred concurrently with an arousal. Additionally, there were 53 arousals that occurred without hot flashes.

A third study recorded sleep parameters in postmenopausal women but relied on self-reported hot flashes (29). There were no significant correlations between hot flashes and sleep, but self-reported hot flash counts during sleep are not reliable.

It is important to note that none of these studies screened women for other sleep disorders or for factors that could alter sleep, such as drug use. This is important because the incidence of some sleep disorders such as apnea (30) increases during menopause.

We then conducted a study in which we controlled for these factors (31). We screened 49 women to eliminate those with sleep disorders (n = 3), drug use (n = 7), physical and mental illness (n = 1), and risk factors for primary sleep disorders, such as obesity and smoking (n = 2). We performed physiological recordings of sleep and hot flashes in asymptomatic, pre- and postmenopausal women and symptomatic postmenopausal women of similar ages. We also obtained objective and subjective measurements of daytime sleepiness,

fatigue, and psychomotor performance. We hypothesized that hot flashes would produce increased arousal and awakening frequencies in the symptomatic women leading to disrupted sleep architecture, increased daytime sleepiness, and poorer performance, relative to the other two groups.

There were no significant differences among the three groups on any sleep variable (Table 51.2). Of awakenings occurring within 2 min of a hot flash, 55.2% occurred before the hot flash, 40.0% after the hot flash, and 5% simultaneously. Of arousals occurring within 2 min of a hot flash, 46.7% occurred before, 46.7% after, and 5.6% simultaneously. There were no significant group differences on any self-report measure or on any performance measure. There were also no significant group differences on any quantitative EEG measure (Table 51.3).

This study provides no support for the notion that hot flashes produce sleep disturbance in postmenopausal women. No significant group differences whatsoever were found on objective or subjective measure of sleep architecture, sleepiness, fatigue, or psychomotor performance. These measurements were obtained in controlled laboratory conditions, using validated procedures. Furthermore, the majority of awakenings preceded rather than followed hot flashes, and the arousal frequencies before and after hot flashes were identical. If hot flashes produce awakenings and arousals, one would expect most of them to precede the sleep disruptions. Our findings are most likely because we eliminated women with other disorders likely to disturb sleep. It is also possible that some reports of menopausal sleep disturbance are due to misattribution.

Our findings are supported by those of the Wisconsin Sleep Cohort study (32), which measured sleep quality by complete laboratory polysomnography (PSG) and by self-reports in a probability sample of 589 pre-, peri-, and postmenopausal women. Sleep quality was not worse in peri- or postmenopausal women not in symptomatic versus asymptomatic women on any physiological measure. The study *did* find significant elevations in reported sleep dissatisfaction in post versus pre- and peri- versus premenopausal women.

As described earlier, hot flashes constitute an exaggerated heat dissipation response and are thought to be triggered by small elevations in core body temperature acting within a reduced thermoneutral zone in symptomatic postmenopausal women. During the day, hot flashes are less frequent in cold relative to warm ambient temperatures (33). In this investigation, we utilized this phenomenon to manipulate hot flash occurrence during sleep and observe whether sleep disturbance would emerge at a warm ambient temperature. Because hot flashes are a thermoregulatory effector response and thermoregulation is absent during REM sleep, hot flashes do not occur during REM sleep (31). Thus, we analyzed halves of the night separately, because more REM sleep occurs in the second half. Finally, we performed quantitative EEG analyses, which have shown to be sensitive to thermal manipulations in previous studies.

Eighteen postmenopausal women with hot flashes, six without them, and twelve cycling women, all healthy and medication-free and of similar ages, were then run in the laboratory (34). PSG, skin and rectal temperatures, and skin conductance to detect hot flashes were recorded for four nights. Nights 2, 3, and 4 were run at 30, 23, and 18°C in randomized order.

With the exception of awakenings, there were no significant Group, Night, or Group × Night effects for any sleep stage parameter over the night as a whole. The symptomatic women had significantly more awakenings than the cycling women. There was also a significant Night effect for awakenings:

TABLE 51.2. Sleep parameters (average of nights 2 and 3, means ± SD).

	Group			
(2-5) Variable	Cycling (n = 11)	Symptomatic (n = 12)	Asymptomatic (n = 8)	*p* for ANOVA
Total sleep (h)	6.9 ± 0.7	7.0 ± 0.4	7.0 ± 0.4	0.765
Sleep efficiency (%)	87.2 ± 7.5	87.6 ± 5.5	88.5 ± 5.7	0.907
Number of awakenings (≥1 min)	4.8 ± 3.3	6.7 ± 2.1	6.9 ± 3.5	0.208
Number of arousals (3–14 s)	89.6 ± 30.1	111.9 ± 45.8	99.4 ± 22.2	0.348
Sleep latency to PS (min)	18.3 ± 16.8	20.2 ± 14.3	17.2 ± 13.9	0.906
Intermittent awake (min)	12.8 ± 7.5	12.4 ± 5.5	11.5 ± 5.7	0.906
Number of stage changes	147.1 ± 28.8	154.7 ± 32.3	145.6 ± 27.4	0.755
Entrances to wake & stage 1	34.5 ± 9.6	38.5 ± 11.5	37.8 ± 9.8	0.640
Stage 1 (min)	38.1 ± 17.4	43.7 ± 11.6	44.4 ± 18.5	0.607
Stage 1 %	9.3 ± 4.2	10.4 ± 2.5	10.5 ± 3.9	0.701
Stage 2 (min)	230.9 ± 21.3	224.4 ± 39.3	236.0 ± 27.4	0.704
Stage 2%	54.0 ± 10.2	53.6 ± 8.0	55.9 ± 4.0	0.810
Stage 3 (min)	30.0 ± 17.5	28.1 ± 6.4	25.6 ± 5.7	0.723
Stage 3 %	7.2 ± 4.2	6.7 ± 1.5	6.4 ± 1.7	0.813
Stage 4 (min)	31.0 ± 25.6	40.2 ± 31.6	30.3 ± 19.6	0.634
Stage 4 %	7.2 ± 5.7	9.8 ± 8.3	8.0 ± 5.3	0.650
Stage REM (min)	81.8 ± 18.4	81.2 ± 22.5	84.8 ± 15.3	0.912
Stage REM %	19.9 ± 4.4	19.5 ± 5.4	20.0 ± 3.0	0.952
MSLT latency (min)	12.8 ± 6.8	7.7 ± 6.0	11.0 ± 2.9	0.115

TABLE 51.3. Percent time in band (means ± SD).

Group Band (HZ)	Cycling (n = 11)	Symptomatic (n = 12)	Asymptomatic (n = 8)	p for ANOVA
Percent Time in Band (means ± SD)				
Delta (0.5–4)	54 ± 7.7	57.6 ± 8.6	55.4 ± 8.7	0.583
Theta (4–8)	22.3 ± 2.9	21.3 ± 3.2	22.6 ± 2.7	0.563
Alpha (8–12)	14.3 ± 3.8	12.8 ± 3.9	13.2 ± 5.0	0.713
Sigma (12–16)	4.8 ± 1.4	4.2 ± 1.3	4.6 ± 1.1	0.541
Beta (16–32)	4.6 ± 1.3	4.3 ± 1.3	4.8 ± 0.8	0.618
Power in Band (μV^2 – means ± SD)				
Delta (0.5–4)	978.7 ± 468.7	1271.5 ± 1083.7	998.9 ± 542.2	0.620
Theta (4–8)	136.7 ± 56.3	113.7 ± 41.0	159.1 ± 152.8	0.525
Alpha (8–12)	53.2 ± 23.8	48.4 ± 27.6	101.3 ± 90.7	0.066
Sigma (12–16)	12.7 ± 6.9	11.6 ± 5.9	16.9 ± 8.6	0.256
Beta (16–32)	25.4 ± 46.8	54.6 ± 100.1	38.4 ± 60.7	

Warm = 11.1 ± 1.2 SE, Neutral = 10.5 ± 1.0, and Cold = 8.6 ± 0.6.

During the first half of the night, the women with hot flashes had significantly more arousals and awakenings than the other two groups, and the 18°C ambient temperature significantly reduced the number of hot flashes. These effects did not occur in the second half of the night. In the first half of the night, most hot flashes preceded arousals and awakenings. In the second half, this pattern was reversed ($p < 0.000$, see Figure 51.1). The average skin temperatures, and delta, and theta EEG activity differed significantly among the three nights, but there were no differences among the three groups.

Thus, using a thermal manipulation, we uncovered some evidence of sleep disturbance in symptomatic women in the first half of the night. This finding may have been overlooked in other studies, because none analyzed data by halves of the night.

We recently completed a study to determine the characteristics of peri and postmenopausal women who reported difficulty sleeping. One hundred and two such women, 44–56 years old, received complete laboratory recordings of sleep and hot flashes and the Hamilton Anxiety and Depression questionnaires. The two major endpoints were laboratory sleep efficiency (objective sleep quality) and the global score on the Pittsburgh Sleep Quality Index (PSQI) (subjective sleep quality).

The average BMI of the sample was 29.3 ± 6.3. Fifty-six per cent demonstrated hot flashes. The sleep recordings showed that 53% of the women had clinically significant apnea (n = 23), restless legs syndrome (RLS) (n = 31), or both (n = 6). Regression analysis showed that the significant predictors of sleep efficiency were apnea/hypopnea index, RLS index, and number of arousals ($R^2 = 0.44$, $p < 0.0001$) but not hot flashes. In contrast, the only significant predictors of PSQI scores were Hamilton Anxiety and hot flashes in the first half of the night ($R^2 = 0.20$, $p < 0.005$). Thus, *all* of the factors determining objective sleep disturbance in these women were due to primary sleep disorders.

Estrogen and Sleep in Menopause

Because hormone therapy (HT) is the most effective treatment for hot flashes, its effects upon sleep in menopausal have been extensively studied. There are seven published studies of the effects of estrogen on laboratory-recorded sleep in

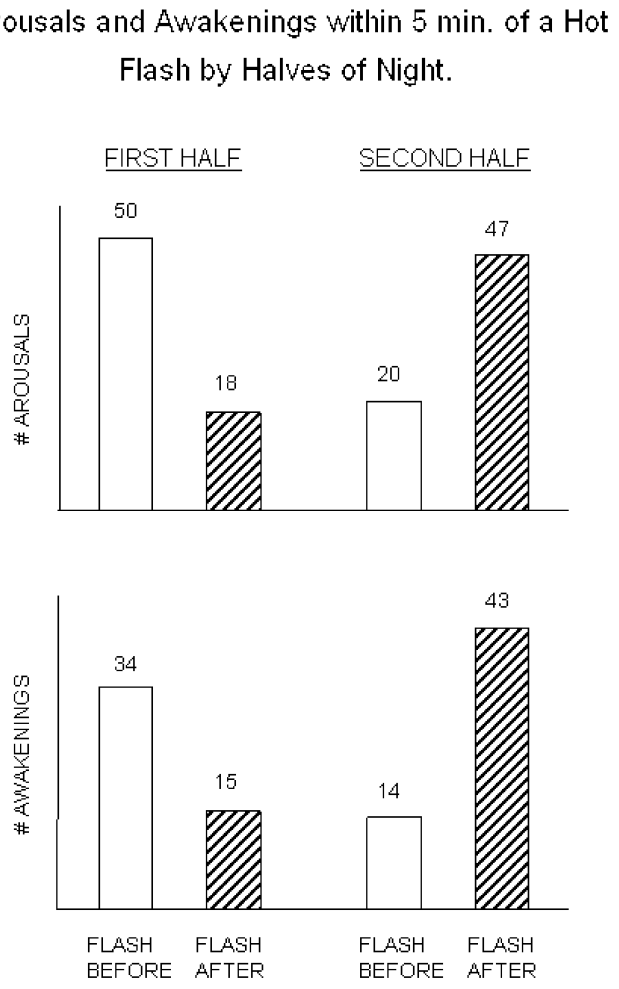

FIGURE 51.1. Arousals and Awakenings within 5 min of a hot Flash by Halves of Night.

TABLE 51.4. Effects of estrogen on hot flashes and sleep.

Study	HFs	Objective Sleep	Subjective Sleep
(35) Thomson	No difference	↓wake time, ↓ arousals ↑ REM	No difference
(36) Schiff	↓	↓ sleep latency, ↑ REM	No difference
(27) Erlik	↓	↓ awakenings	Not done
(37) Purdie	↓	no difference (room at 16°C)	No difference
(38) Scharf	↓	↓ awakenings & stage changes ↑ sleep efficiency (no control group)	↑ sleep quality
(39, 40) Polo Kantola	↓	↓ movement arousals ↑ alpha arousals	↑ sleep quality
(29) Antonigevic	Not done	↓ wake time, ↑ REM	↑ sleep quality

postmenopausal women. Table 51.4 summarizes that these effects were variable: some studies reported decreased wake time and arousals whereas one found decreased sleep latency. Three studies found increased REM sleep. Interestingly, the single study reporting no objective sleep improvement recorded subjects at an ambient temperature of 16°C. Previous research showed that hot flashes are suppressed at ambient temperatures <19°C. Half of the studies in Table 51.2 found that estrogen improved subjective sleep quality, whereas half did not. No study used an objective assessment of subsequent sleepiness, such as the multiple sleep latency test (MSLT).

Although not utilizing laboratory sleep recordings, the Women's Health Initiative (WHI) studied the effects of HT (estrogen plus progestin) and ET (estrogen only) on HRQOL in very large randomized clinical trials. In the first study (41), 16,608 women, 50–74 years of age, were randomly assigned, in double-blind fashion, to receive HT or placebo. After 1 year, there were no significant effects on general health, vitality, mental health, depressive symptoms, or sexual satisfaction. There were statistically significant, but small and not clinically meaningful, effects upon sleep disturbance, physical functioning, and bodily pain. The mean benefit on sleep disturbance was 0.4 point on a 20-point scale. At 3 years, there were no significant benefits whatsoever.

In the second study (42), 10,739 women, 50–79 years of age, were randomly assigned to receive conjugated estrogens or placebo. The identical effect upon sleep was obtained: a 0.4 point improvement on a 20-point scale. Other than a significant negative effect on social functioning, there were no statistically significant effects. Thus, neither HT nor ET have significant effects on HRQOL, although most of the subjects were long past the onset of menopause.

Insomnia in the General Population

In examining the role of the menopausal transition in sleep disturbance, it is instructive to consider the prevalence of insomnia in the population as a whole. With one exception, all of the epidemiologic studies of sleep disturbance in menopause have employed the broadest definition of insomnia: the simple report of poor sleep (yes/no). Ohayon (53) has shown that the prevalence of insomnia in the general population is strongly dependent on the definition employed: the broadest definition yields the highest rate. When the definition of insomnia is taken into account, it can be seen that the prevalence of insomnia reported in studies of menopause is similar to that in the general population (Table 51.5). Thus,

TABLE 51.5. Prevalence of insomnia by definition.

Population		
Definition	General	Peri- and Postmenopause
1. Presence of symptoms, no criteria	(43) Klink – 38% (44) Mallon – 36% (45) Quera-Salva – 48% (46) Klink – 34% (47) Bixter – 35%	38% – Swan (18) 36% – McKinley (5) 38–45% – Dennerstein (3) 32–40% – Bungay (7) 42% – Owens (17)
2. With frequency criteria	(48) Karacan – 28% (49) Vela–Bueno – 27% (50) Leger – 25%	25% – Owens (17)
3. Symptoms with daytime consequences	(51) Breslau – 21% (52) Ohayon – 9% (52) Ohayon – 8 % (53) Hoffman – 11%	7% – Owens (17)
4. DSM-IV	(54) Ohayon – 4% (54) Ohayon – 5% (55) Ohayon – 6% (55) Ohayon – 6%	Not done

it is possible that the prevalence of insomnia in women of menopausal age may have nothing to do with menopause or with HFs, but may simply reflect the prevalence in the general population.

Conclusions

It appears that menopause per se has little effect upon HRQOL or on sleep disturbance. Matthews observed that women reporting poor QOL during menopause were those reporting high levels of depression and anxiety. Similarly, in our most recent sleep study, women reporting poor sleep were those scoring high on the Hamilton Anxiety Scale. Women demonstrating poor objective sleep in that study were those suffering from apnea, RLS, or both. Because apnea does increase with menopause, this may account for some findings of poor physical sleep during that period. Thus, the prevalence of disturbed sleep during menopause may simply reflect the prevalence of sleep disorders in the general population.

The effects of hot flashes on sleep in menopausal women are unclear. We found that hot flashes in the first half of the night only predicted subjective but not objective sleep disturbance. The mechanism through which this occurs is not known and should be an area of further research.

Issues that need to be addressed by future research:

- Why do hot flashes in the first half of the night contribute to subjective but not objective sleep disturbance?
- A screening algorithm not requiring PSG should be developed to detect apnea in the population at large.

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Sleep and Quality of Life in Pregnancy and Postpartum

Magdie Kohn and Brian James Murray

Summary Sleep fragmentation and disruption during the normal physiological changes of pregnancy are as significant as some medical diseases. Sleep disorders during pregnancy are an even further complication. These changes, which persist not only over the course of the pregnancy, but also into the postpartum period, are significant enough to affect quality of life. Measures specific to the quality of life associated with sleep disorders are limited in pregnancy. Sleep disruption affects quality of life in a significant way. Those with insomnia suffer significant distress during that period, and those with poor sleep suffer the daytime consequences such as excessive daytime sleepiness. The literature regarding sleep and quality of life during pregnancy is limited. This review outlines the sleep characteristics typical of a normal pregnancy, including physical and emotional changes, and then the quality of life implications. We present some preliminary data that have been collected on quality of life in a study of normal pregnancy, and how sleep disruption may have an impact. Then, we explore sleep disorders such as restless legs syndrome and sleep-disordered breathing in pregnancy and assess how they may impact quality of life. Finally, we discuss sleep changes in the postpartum period, and how they may impact quality of life. The implications for perinatal depression may be particularly important. It becomes clear that for such a significant change in life, physically and emotionally, further studies exploring the impact of sleep on quality of life in pregnancy are required. The potential treatment of sleep disorders in pregnancy could lead to significant quality of life improvements during this time.

Keywords Sleep · sleep disorders · quality of life · pregnancy · postpartum

Learning objectives:

- Sleep disruption is common in pregnancy and is associated with the normal physiological changes of pregnancy.
- Sleep disorders during pregnancy are surprisingly common and likely impair quality of life.
- Measures specific to the quality of life associated with sleep disorders in pregnancy are currently limited.
- Identifying sleep disruption and sleep disorders may be particularly important to improving quality of life in pregnancy and postpartum, as many are treatable.

Introduction

Although this book focuses on medical illness, sleep fragmentation and disruption during the normal physiological changes of pregnancy are as significant as some medical diseases. Sleep disorders during pregnancy are an even further complication. These changes, which persist not only over the course of the pregnancy but also into the postpartum period, are significant enough to affect quality of life.

Quality of life has emerged as a logical outcome measure for the treatment of various medical conditions (1). Measuring quality of life is complex. A number of scales have been developed such as the commonly used Medical Outcomes Study 36-item Short Form General Health Survey (SF-36) (2, 3), which attempts to quantify various components of a multidimensional model of quality of life in a number of diseases and conditions. Measures specific to the quality of life associated with sleep disorders are limited (4). Others have noted that quality of life is unique to an individual's personal values (5) and can be studied with qualitative research, or if quantitative data are required, on the basis of a person's quality of life scale.

Sleep disruption affects quality of life in a significant way. Sleep constitutes approximately one-third of a typical life. Those with insomnia suffer significant distress in that time.

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Individuals with poor sleep often suffer daytime consequences such as excessive daytime sleepiness, which can impair one's quality of life in the remaining two-thirds (6).

The literature regarding sleep and quality of life during pregnancy is limited. Studies for this review were identified from OVID Medline (1966 to November Week 2, 2006), EMBASE (1980 to 2006 Week 46) and CINAHL (1982 to November Week 2, 2006). The search terms employed included pregnancy AND (sleep OR sleep disorders OR sleep deprivation OR insomnia) AND (quality of life OR health-related quality of life OR SF-36). This search strategy yielded 68 articles in total. Other relevant articles were included when known to the authors.

This review will outline the sleep characteristics typical of a normal pregnancy and then the quality of life implications. We will present some preliminary data that have been collected on quality of life in a study of normal pregnancy. Then, we will explore sleep disorders in pregnancy and assess how they may impact quality of life. Finally, we will discuss sleep changes in the postpartum period and their impact. It becomes clear that for such a significant change in life, physically and emotionally, further studies exploring the impact of sleep on quality of life in pregnancy are required. The potential treatment of sleep disorders in pregnancy could lead to significant quality of life improvements during this time.

Physical Changes and Sleep Characteristics During Normal Pregnancy

Pregnancy is time associated with numerous physiological changes. Hormonal and mechanical changes predominate. These changes may have significant effects on respiration and sleep.

Hormonal changes can significantly alter sleep in pregnancy (7). Progesterone levels, which are typically elevated, trigger the ventilatory drive, which often results in a respiratory alkalosis (8). This hormone also has an effect on sleep architecture, resulting in an increase in non-rapid eye movement (NREM) sleep (9, 10). Higher estrogen levels tend to decrease the quantity of REM sleep (11–13). Hormonal changes in women have been noted to have at least some effects on sleep and quality of life in situations such as menopause (14).

Many of the hormonal changes during this time can also affect sleep in an indirect manner. For example, estrogen levels often result in increased blood flow to the nose and upper airway, thereby resulting in localized narrowing and edema (15). This can cause nasal congestion and contribute to snoring and sleep-disordered breathing.

Blood flow is also increased to other organs throughout the body during pregnancy, with an increase in overall total blood volume (16, 17). This is an important factor in urinary frequency and nocturia. This symptom is also affected by the mechanical changes within the pelvis during pregnancy. The upper abdomen is also subject to increased pressure from the expanding uterus and gastroesophageal reflux symptoms often present or worsen (18). All of these changes can have a significant impact on sleep quantity as well as sleep quality.

Throughout the course of pregnancy, many of these hormonal and mechanical factors tend to progress (19). In addition to their potential disruption of sleep, there are many changes to sleep during pregnancy that are not as completely understood and vary as the pregnancy progresses.

During the first trimester, many women complain of increasing fatigue and daytime sleepiness (20). The total sleep time often increases as a result. However, many women also note the onset of insomnia (21). These effects may be a primary effect of the pregnancy, perhaps related to the effects of hormones on sleep–wake circuitry in the brain (22), or represent the unmasking of a sleep disorder.

Once the second trimester begins, there tends to be a normalization of the total sleep time (23). However, women often report nocturnal awakenings that are presumed to be due to the onset of sleep disturbances such as nocturia and gastroesophageal reflux.

These symptoms often become worse during the third trimester at which time the frequency of nocturnal awakenings increases further with a subsequent reduction in total sleep time (24). Stage 1 sleep increases as a marker of sleep disruption, sleep efficiency drops (25), and REM sleep is curtailed (26). Slow wave sleep also declines through pregnancy (27). Many women find it difficult to become comfortable and may complain of worsening insomnia.

In summary, sleep characteristics are often altered considerably during pregnancy and can vary significantly amongst the different trimesters. Although mechanical and hormonal effects can explain many of these changes, further research is required to understand the causes of these changes and their consequences.

Sleep and Quality of Life During Normal Pregnancy

The physical and emotional changes that occur in pregnancy may affect quality of life, and many have great effects on sleep. Most of the physical changes can cause discomfort, which would also be expected to disrupt sleep continuity. Mood changes, which could represent effects of the pregnancy, or effects of sleep changes would be expected to have a pervasive effect over a person's daily experience. As suggested, the literature examining quality of life during normal pregnancy is quite limited, especially with respect to how sleep enters into this picture. Both sleep and quality of life may be affected by physical, hormonal, and emotional changes during pregnancy.

There are only a few studies that have been published looking at general quality of life in pregnancy and a few that

explore the effects of specific physical symptoms such as back pain and depression.

As this book has outlined, health-related quality of life can be measured in various ways, and one of the most widely used instruments is the SF-36. In one study, 125 women with a normal pregnancy were followed throughout the course of their pregnancy with this tool to determine whether there were any significant changes in their quality of life as pregnancy progressed (28). The study found that only the physical health status aspects of this assessment changed significantly during normal pregnancy. Physical function, role limitation due to physical complaints, and pain scales deteriorated during the course of pregnancy. Many of these physical factors would be expected to affect sleep.

Many physical factors may interfere with sleep and quality of life in pregnancy. Some degree of nausea and vomiting occurs in 50–90% of pregnant women (29). Hyperemesis gravidarum is the term used to describe severe cases of nausea and vomiting during pregnancy. This condition may result in significant morbidity (30, 31). In early pregnancy, nausea and vomiting has been associated with impairments in quality of life (32). In some individuals, sleep may actually represent respite from this condition, although nocturnal gastroesophageal reflux may worsen. Gastroesophageal reflux in sleep has also been associated with poor quality of life (33–35) in non-pregnant populations. In pregnancy, gastroesophageal reflux has been noted to impair quality of life (36). Recent reviews note that rhinitis is associated with impaired quality of life and may be associated with reduced quality of life in pregnancy (37, 38). Urinary frequency is another of the most common new physical complaints during pregnancy, beginning as early as the first trimester (23). Nocturia has been associated with reduced quality of life in other studies (39).

A study of 30 patients noted that headaches may present in pregnancy and that there was a trend for headaches to decrease throughout pregnancy and to increase during the birth week (40). There was also a tendency in multiparous women for headaches to increase in the third trimester, whereas primiparous women noted fewer headaches. Sleep may actually provide relief from headaches, as many headaches such as migraine resolve with sleep (41). Headaches have a significant impact on quality of life and can lead to lost professional and personal time (42).

To the best of our knowledge, the only other physical problem during pregnancy that has been studied in relation to its effect on quality of life is back pain (43). Back pain is relatively common during pregnancy and may occur in up to 41% of women (44). In this study population, back pain significantly affected quality of life. One hundred and sixty women were studied in the third trimester and reported a reduced quality of life, as compared with published reports in healthy women of similar age. Women who had the most reduced quality of life were more likely to report back pain, and the factors impacting quality of life were mostly related to physical symptoms.

Other common physical complaints during pregnancy include dyspnea, and constipation, which would certainly not be expected to improve quality of life (19).

Fatigue and sleepiness are common complaints during the first trimester and in some cases can continue throughout pregnancy (20). We know that insomnia, fatigue, and daytime sleepiness are commonly reported during this time. In the general population, these complaints, regardless of their cause, have been associated with an impairment in quality of life (4, 45). These findings suggest that pregnant women with sleep disruption are also more likely to have a reduction in quality of life. A further understanding of the mechanism of how these symptoms develop is necessary, as some may be amenable to intervention.

In addition to the numerous physical complaints that are common during pregnancy, there are several psychological changes during this time. The SF-36 instrument has been used to explore the extent to which quality of life can change during pregnancy and has been found to be sensitive to the affective status of subjects when administered during early pregnancy (46). A different study using further quality of life assessment instruments found significantly higher levels of emotional distress and changes in psychological health status (47). This study of 393 women in their third trimester noted that on the Short Form-36, pregnant women in the third trimester had significantly poorer levels of physical and psychological functioning. Given the impact of sleep deprivation on mood (48), it is tempting to suspect that there may be a causal relation between sleep loss in pregnancy and subsequent mood changes.

It was previously believed that pregnancy was protective against depression. However, recent data suggest that the new onset of depression or a relapse of a previous depressive disorder is more common than previously thought (49–52). Depressive symptoms in early pregnancy have been associated with a poor health-related quality of life. In one study, women with such symptoms had significantly lower quality of life scores in all domains of the SF-36 except for physical functioning (53). Similar findings were also found in another study (54). Depression has also been associated with significant impairment in health-related quality of life in the postpartum period (55). Given that health-related quality of life has been found to be poor in non-pregnant or postpartum individuals with depression, these results are not entirely surprising (56, 57).

In summary, the limited number of studies that have examined quality of life in pregnant women have indicated that it is indeed impaired. There are numerous physical changes that occur during a normal pregnancy. Many of these physical complaints have the potential to affect quality of life, and certainly sleep. Similarly, mood changes are prominent in pregnancy, and may be at least partially related to sleep disturbance, and can detrimentally affect quality of life.

Pilot Data in Quality of Life During Normal Pregnancy

As part of a larger study of sleep changes in pregnancy, our group collected pilot information about quality of life in this time period, given the paucity of sleep-related quality of life data. All subjects provided informed consent for study, and the local ethics review board approved our project. We had a sample of 219 healthy pregnant women, recruited from obstetrician and family practice offices. Our overall response rate was 88%. We were unable to use an extended instrument such as the SF-36 because of the scope of the other data collected, and had to have a quick measure. Subjects were simply asked: "Overall, how would you rate your present Quality of Life? Please use a number: (scale: 1 = very bad, 10 = perfect)."

The mean reported quality of life was 8.0 (SD 1.5). We then asked the same subjects 2 months later what their quality of life was at that point, and no significant differences were noted. What was impressive to us was that the number of self-reported awakenings while still pregnant was inversely correlated with quality of life ($r = –0.23$, $p = 0.001$). This suggested that sleep disruption, or underlying sleep disorders, may indeed be significant in impairing quality of life, and warrants further exploration.

Sleep Disorders in Pregnancy

Normal physiological changes in pregnancy can precipitate a number of sleep disorders. Two major conditions that are aggravated in pregnancy are sleep-disordered breathing and restless legs syndrome. The effects of pregnancy on other conditions are less well studied. However, treatment of other sleep disorders is often altered during pregnancy. To avoid fetal developmental complications, patients with a number of pre-existing sleep disorders often have to discontinue medication treatments, which can lead to aggravation of their underlying sleep problems.

Sleep-disordered breathing increases throughout pregnancy and is most likely a consequence of increasing mucosal edema, weight gain, and reduced diaphragmatic excursion (58). Patients often report that snoring increases during this time, particularly women who are obese (59–61). Approximately 14–46% of pregnant women report snoring during this period, which often increases as pregnancy progresses (62, 63). Snoring has been associated with poor maternal and fetal outcomes. The development of hypertension, pre-eclampsia, intrauterine growth retardation, and low APGAR scores have been reported in pregnant snorers (64).

As the incidence of snoring increases during pregnancy, so does the amount of sleep fragmentation. This may at least partially account for increased daytime sleepiness sometimes observed in this population (62). Although snoring is more common in pregnant versus non-pregnant women, the incidence of upper airway resistance and sleep apnea in this population is unknown. Witnessed apneas are more common during this time (64). In women with upper airflow limitation and pre-eclampsia, nasal PAP has been shown to eliminate abnormal airflow and result in a reduction in blood pressure. There are limited studies examining this intervention in pregnant women, but it is considered to be a safe modality at this time (65).

In addition to sleep-disordered breathing, restless legs syndrome is surprisingly common in pregnancy—occurring in approximately 20% of otherwise healthy young women (66, 67). Restless legs syndrome is aggravated or, in some cases, caused by iron deficiency (68–70). Iron deficiency is common in young women (71). One-third of pregnant patients in one study had iron stores that were in the range where restless legs syndrome was particularly prominent (72). The ongoing development of the fetus consumes more iron than is typically taken during pregnancy and current iron supplementation protocols may be insufficient (73). Restless legs syndrome can be disruptive to the initiation of sleep and result in severe sleep onset insomnia (74). The reduction in iron stores likely also directly contributes to the increasing fatigue noted in this patient population. Mechanical changes in the spine can even precipitate radiculopathies, which are also associated with the restless legs syndrome (75). Nocturnal leg cramps are often noted in pregnancy, and our group has observed that they are occasionally the culmination of a series of occult periodic limb movements noted on polysomnography of pregnant women.

Many women have to, or choose to, modify treatment of their sleep disorders during pregnancy, particularly in the first trimester when organogenesis is of particular concern. For example, we often counsel our patients with narcolepsy to take a medication holiday during this period of time, and use strategic napping (76), rather than expose the fetus to the risk of malformation. This may be a very effective strategy in these patients, but the consequences of an untreated sleep disorder may be significant—such as the temporary loss of employment due to the inability to drive. When medications need to be avoided during pregnancy, behavioral interventions assume an even more important role. Fortunately, some sleep disorders, such as parasomnias, have been reported to decrease in pregnancy (77).

Interaction Between Sleep Disorders in Pregnancy and Quality of Life

Direct studies of the effects of sleep disorders during pregnancy on quality of life are not published. Therefore, some information must be extrapolated from studies of quality of life and sleep disorders outside of pregnancy.

Several scales have been developed to assess quality of life in the obstructive sleep apnea syndrome (78) but are not necessarily applicable to, or validated in, pregnancy. Sleep

apnea is associated with impaired quality of life, as documented elsewhere in this book. Overt obstructive sleep apnea is not common in pregnancy but is important to identify as it is associated with impaired fetal outcome (60), which could affect not only the quality of life of the mother but also the newborn. Sleep apnea is also important to identify as it is associated with a treatment (continuous positive airway pressure) that can improve quality of life (79).

There are no published studies of restless legs syndrome and quality of life in pregnancy. It would not be surprising that restless legs syndrome would affect quality of life in pregnancy because studies of quality of life in the restless legs syndrome have found a significant impact because of this condition. This impairment has been comparable to that of the quality of life in diabetes or heart disease (80). Scales have been developed to follow quality of life as a primary outcome in the treatment of restless legs syndrome, but again have not been validated in pregnancy (81–83).

Given that women may need to come off sleep medications during their pregnancy, this may leave a number of sleep disorders untreated. Therefore, the impact of insomnia, narcolepsy, parasomnias, and other conditions become unmasked. Further chapters in this book address the quality of life impact of these and other conditions. A special consideration in this population, however, is the impact of an untreated (at least from a medication perspective) sleep disorder such as narcolepsy in the context of the care needs of a young family.

Postpartum Physiology and Sleep Disturbance

Sleep difficulties in the infant and mother tend to be most marked during the first month of life. The sleep disturbance related to infant care following delivery can produce significant demands on sleep and contribute to significant sleep loss and consequent daytime sleepiness. Sleep disruption has been tracked with actigraphy in this population (84), and this may represent a very useful tool for following changes over time. In addition to the infant's sleep–wake cycle, other contributing factors to sleep disruption in this period include parity, method of feeding, and co-sleeping (85, 86). Although sleep disruption related to infant care is an obvious factor, others have suggested that sleep disruption is fundamental to the biological changes following pregnancy independent of care of the baby (24, 87).

Many women believe that reduced sleep during the postpartum period is a contributing factor in the development of postpartum depression (88). This claim has been further substantiated by a number of studies, which have shown that interventions aimed at improving infant sleep patterns also have a positive effect on maternal mood (89, 90). When sleep quality is preserved despite infant sleep problems, women are less likely to suffer from depression, thereby suggesting that the sleep deprivation itself plays a significant role in mood disturbances during this time of life (91).

Links Between Sleep Disturbance, Perinatal Mood Disorders, and Quality of Life

Mood changes in pregnancy are frequent and can be seen along a spectrum from the "baby-blues" (which is surprisingly common), to depression, or even suicide (92). Anxiety is also higher in this population (93). Mood disorders are a significant problem for some new mothers, and these problems have not been given much attention in the past, as pregnancy was traditionally presumed to be a positive time in a person's life. The silent burden of this condition is significant.

Mood disorders are associated with significant quality of life changes. Only one recent study looked at health-related quality of life in 78 women with postpartum depression (55). Women with postpartum depressed mood scored significantly lower on all components of the SF-36. Poor sleep quality was noted to predicted poorer mental health, even after controlling for mood, suggesting a significant effect of sleep changes.

Given that sleep changes are common in depression (94), and that mood and sleep are closely related (95), it is not surprising that the significant sleep changes of pregnancy and perinatal depression might be linked. This may be particularly significant in the postpartum period, where sleep changes are most dramatic. Similarly, given the high incidence of both sleep disruption and mood changes in the postnatal period, one could speculate that there may be sleep mechanisms that may be amenable to interventions that could potentially prevent serious perinatal mood disorders. Underlying sleep disorders in particular need to be identified so that they can be treated aggressively to reduce morbidity in this situation.

Conclusion and Future Directions

In summary, quality of life is altered in normal pregnancy. Furthermore, sleep disruption during this time is very common and may represent a spectrum from normal physiological changes to overt and potentially serious sleep disorders. A number of sleep disorders can produce insomnia and excessive daytime sleepiness, which are associated with a poor quality of life in non-pregnant populations. Although this association likely holds true as well in pregnant women, the current studies addressing these issues, specifically, are limited. We also need better quality of life measurements during pregnancy that are also able to address the effects of sleep changes. Further work in exploring sleep disruption as a contributor to peripartum mood disorders is particularly warranted given the burden of perinatal depression, which is associated with a significant reduction in quality of life and significant concerns for both maternal and fetal wellbeing.

The impact of sleep disorders on maternal and fetal medical complications are also of great significance. The possibility of treating underlying sleep disorders in this population may be a means to intervene and improve health-related quality of life in pregnancy and postpartum.

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Issues that need to be addressed by future research:

- Quality of life measures specific to pregnancy that address sleep disruption and sleep disorders need to be developed and validated.
- The magnitude of the impact of sleep disorders on quality of life in pregnancy needs to be clarified.
- We need to better understand the impact of sleep disruption and sleep disorders on perinatal mood.
- Treatment trials to intervene in sleep disruption and sleep disorders during pregnancy and postpartum should be pursued, and use quality of life as an outcome measure.

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Sleep and Quality of Life in HIV and AIDS

Louise McGrath and Steven Reid

Summary Insomnia is a common complaint in people living with HIV and AIDS. It contributes to fatigue, functional impairment, and an overall reduction in the quality of life; yet, there remains considerable uncertainty about its cause and significance. Early reports of sleep-specific EEG changes related to HIV infection, in particular an increase in slow wave sleep, have not been confirmed in later controlled studies. Sleep disturbance is reported at all stages of HIV infection, but the presence of cognitive impairment or an AIDS-defining illness is a significant risk factor. Antiretroviral medications have not demonstrated a class effect, but plasma levels of the non-nucleoside reverse transcriptase inhibitor, efavirenz, do correlate with insomnia. Amongst the recognized risk factors, the most notable is psychological morbidity which has shown a consistent and strong association with insomnia in seropositive patients. Insomnia in HIV infection is associated with a reduced quality of life, but in this population, it remains both under-recognized and under-treated. This may in part be a reflection of uncertainty about approaches to management, as there is little data on treatment of insomnia in this population. Insomnia in HIV presents a considerable challenge for the clinician and requires careful evaluation, in particular screening for anxiety and depression, and a familiarity with non-pharmacological interventions as well as drug treatments for sleep disturbance.

Keywords HIV infections · acquired immunodeficiency syndrome · sleep disorders · insomnia · anxiety · depression · antiretroviral medication · cognitive impairment

Learning objectives:

- Insomnia is common in people living with HIV and AIDS, but is under-recognized and under-treated.
- Psychological morbidity is a major determinant of insomnia in HIV infection.
- The presence of cognitive impairment, an AIDS-defining illness, and treatment with efavirenz are significant risk factors for insomnia in this population.

Introduction

Insomnia is a common complaint in individuals with chronic disease including HIV infection (1, 2). It is reported at all stages of HIV disease yet often receives little attention. This may be because it is considered a normal consequence of the disease and its treatment, or the consequences of insomnia may be considered insignificant in comparison with other complications of HIV infection. Furthermore, when recognized, clinicians often find sleep disturbance a difficult problem to manage, with uncertainty about the most appropriate treatment options. A number of factors have been implicated in the aetiology of insomnia in HIV infection. Early studies suggested that somnogenic cytokines, such as tumor necrosis factor alpha (TNF-α) and interleukin-(IL)-1β, were involved (3). As well as immune dysregulation, other factors such as virus progression, psychological morbidity, substance misuse, and the adverse effects of antiretroviral treatment have been considered (2). What is clear however is that disrupted sleep in people living with HIV contributes to fatigue, functional impairment, and an overall reduction in the quality of life (4).

HIV and AIDS

The acquired immunodeficiency syndrome (AIDS) was first recognized 25 years ago, and infections with HIV are now seen throughout the world, with an estimated 15,000 new infections per day (5). The first documented cases of AIDS were reported in the USA in 1981 when reports appeared

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of young men presenting with uncommon diseases including Kaposi's sarcoma and *pneumocystis carinii* pneumonia (6, 7). Initially, investigators assumed that AIDS was related to a homosexual lifestyle, but cases were soon reported in intravenous drug users, blood transfusion recipients, and then increasingly in both adults and children in sub-Saharan Africa. The human immunodeficiency virus (HIV)-1 was isolated in 1983, and Gallo and colleagues provided the first evidence that it was the infectious transmissible agent responsible for AIDS. Subsequently, a less common variant of the virus, labeled HIV-2, has been isolated, although this is largely confined to West Africa (8).

An estimated 40 million people were living with HIV/AIDS in 2006 (5). In 2005, there were 4.1 million new HIV infections and 3 million AIDS deaths. Currently, 95% of all infections occur in developing countries with the majority occurring in sub-Saharan Africa and Southeast Asia, but numbers are increasing rapidly in both China and India. The virus is transmitted most commonly by sexual intercourse, with heterosexual transmission accounting for about 85% of HIV infection worldwide (9). Other modes of transmission are through the reuse of contaminated needles by intravenous drug users or for therapeutic procedures, and the receipt of infected blood or blood products, donated organs, and semen. Perinatal transmission of HIV accounts for virtually all new infections in children, although infants may also become infected through ingesting breast milk of a seropositive mother.

HIV disease progresses through a continuum beginning with acute seroconversion (primary HIV infection) and ending with AIDS and death (Figure 53.1) (10). The HIV targets CD4 T lymphocytes that are an integral component of the normal immune response. Other cells targeted by HIV include macrophages and microglial cells in the central nervous system. HIV infection is characterized by the gradual destruction of the CD4 cell population. During the chronic phase of the disease, although minimal symptoms may be experienced, there is an extremely rapid turnover of plasma virus; the half-life of a single viral particle is so short that half the entire plasma virus population is replaced within 30 min (5). The clinical course is highly variable, but depends on the host immunology, viral properties, and genetic factors (11). Progression to AIDS is predicted both by CD4 count and by plasma HIV viral load. The CD4 count remains the primary marker for the development of opportunistic infections and other complications, particularly when lower than 200 cells per microliter. The time from initial infection to the development of AIDS varies from 6 months to over 15 years. The Centers for Disease Control and Prevention (CDC) developed the HIV disease classification system based on a combination of clinical signs, the presence of certain conditions, and investigative findings (12):

Group I Primary HIV infection
Group II Asymptomatic phase
Group III Persistent generalized lymphadenopathy
Group IV Symptomatic infection

Primary HIV infection represents the stage of infection when antibodies are developing to the virus. Signs of infection include flu-like symptoms, lymphadenopathy, poor appetite and weight loss, as well as insomnia. There may be signs of late-stage disease, such as oral candidiasis, due to a high rate of viral replication, but this is uncommon. Once these symptoms subside, the person with HIV begins a chronic asymptomatic or minimally symptomatic state with CD4 lymphocyte counts generally above 350 cells per microliter. This phase may persist for 10 years or more before the onset of overt immunodeficiency (10). Some otherwise well patients may present with persistent generalized lymphadenopathy, but there is no evidence that this has an effect on outcome. Eventually, the replication of the virus rapidly accelerates leading to a decline in immune competence. The precipitants for this change remain unclear. With the onset of symptomatic HIV infection, patients commonly develop constitutional symptoms such as fever, diarrhoea, weight loss and night sweats. Profound immunodeficiency leads to the appearance of opportunistic infections, wasting, neurological disorders and neuropsychiatric disorders, and malignancies (5, 10) (Table 53.1).

Sleep and the Neuropathology of HIV

From the earliest clinical descriptions of HIV, insomnia has been recognized as a frequent complaint, and descriptive studies of seropositive patients using polysomnography indicated abnormalities of sleep pattern (13–15). As it was recognized that the HIV penetrates the blood brain barrier by infecting microglial cells and macrophages, it was suggested that the reported deterioration in sleep architecture was a direct consequence of HIV neurotoxicity (3). A particular area of interest was the role of the proinflammatory cytokines, particularly TNF-α and IL-1, which are released by infected cells. Studies in animal models and trials of cancer chemotherapy using TNF-α and IL-1 have shown that exogenous administration of these cytokines may cause excessive sleepiness and fatigue (16). In particular, an increase in slow wave sleep was observed; similar changes to those reported in studies of otherwise asymptomatic seropositive individuals. Norman and colleagues in a series of small polysomnography studies noted a significant increase in slow wave sleep, particularly during the late sleep cycles (14, 17, 18). There were also reports of an increased frequency but reduced duration of periods of rapid eye movement (REM) sleep (19). The cytokine studies supported the hypothesis that these changes in sleep architecture were a direct consequence of HIV disease progression. Notably, these studies lacked controls and made comparisons with normative population data. Later, controlled investigations challenged these observations, finding no differences when compared with

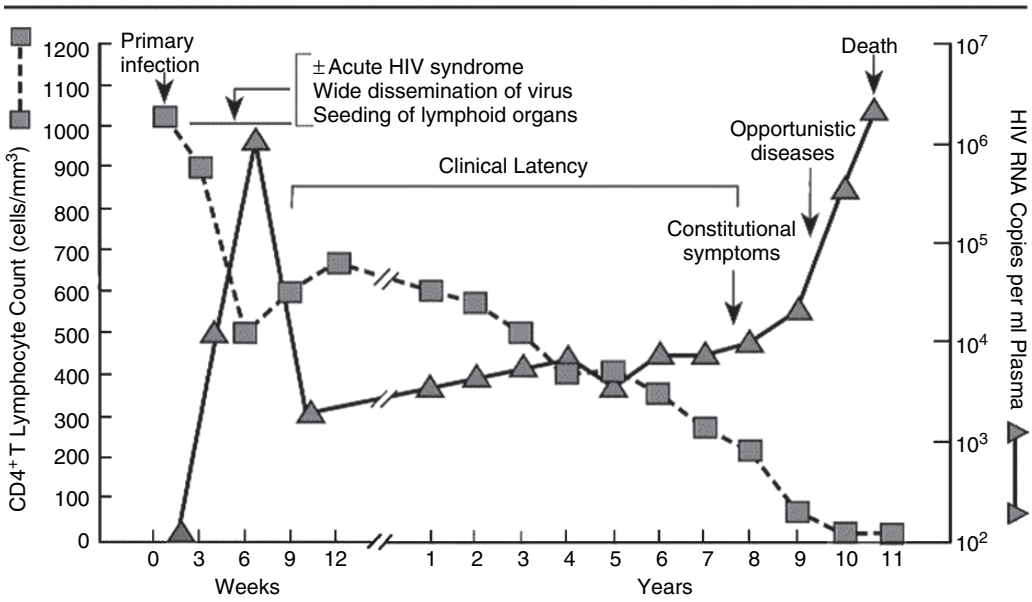

FIGURE 53.1. Typical course of HIV infection. *Adapted from* Pantaleo G, et al. Mechanisms of disease: the immunopathogenesis of human immunodeficiency virus infection. *The New England Journal of Medicine* 1993;328:327–35, with permission.

TABLE 53.1. Complications of HIV infection.

Infectious complications	Non-infectious complications
Pneumococcal and other bacterial pneumonia	Persistent generalized lymphadenopathy
Pulmonary tuberculosis	Guillain–Barré syndrome
Herpes zoster	Aseptic meningitis
Thrush (oropharyngeal candidiasis)	Cervical carcinoma
Kaposi's sarcoma	B-cell lymphoma
Oral hairy leukoplakia	Anaemia
Pneumocystis carinii pneumonia	Mononeuritis multiplex
Disseminated histoplasmosis	Idiopathic thrombocytopenic purpura
Coccidioidomycosis	Hodgkin's disease
Military/extrapulmonary TB	Peripheral neuropathy
Progressive multifocal leukoencephalopathy	HIV-associated dementia
Disseminated herpes simplex	Cardiomyopathy
Toxoplasmosis	Vacuolar myelopathy
Cryptococcosis	Progressive polyradiculopathy
Microsporidiosis	Non-Hodgkin's lymphoma
Candida oesophagitis	CNS lymphoma
Disseminated CMV	
Disseminated mycobacterium avium complex	

seronegative individuals (20–22). Furthermore, no consistent relationship was found between changes in sleep architecture and CDC staging for HIV or CD4 count (23–26). The notable exception is late-stage symptomatic illness (stage IV), often associated with manifest cerebral pathology (27, 28). Insomnia at this stage may be a direct consequence of an AIDS-defining illness, and the abnormalities are generally similar to those found in other disorders of the central nervous system. Sleep architecture becomes severely disrupted, and EEG studies show a reduction in slow wave sleep with increased fragmentation, leading eventually to a complete destruction of the normal pattern. Kubicki and colleagues (29) found a striking absence of sleep spindles in a case series of 5 patients with AIDS and cerebral complications. A reduction in sleep spindle activity was also noted in a case-controlled EEG study of patients with AIDS (30). Although the significance is unclear, this finding has not been observed in other cerebral diseases or disorders of sleep. Cognitive impairment is a potential marker of CNS infiltration, and Rubinstein and Selwyn (1) in a cross sectional study found that it was the best predictor of insomnia (odds ratio 1.4; 95% confidence interval 1.1–1.7). In the 10% of their sample with cognitive impairment, sleep disturbance was universal, although it should be acknowledged that chronic insomnia itself may lead to cognitive impairment.

Prevalence of Insomnia in HIV Infection

The prevalence of insomnia in HIV and AIDS has been measured in a number of studies using the Pittsburgh Sleep Quality Index (PSQI), a self-rated questionnaire that assesses sleep quality and disturbance over the preceding month (31). As well as yielding several subscales, including subjective sleep quality, sleep latency and sleep efficiency, it provides a global score which is used to distinguish good from poor (PSQI > 5) sleepers. Rubinstein and Selwyn (1) found that 84 of 115 (73%) seropositive outpatients were poor sleepers. This group required more than 1 h to fall asleep compared with less than 15 min in good sleepers ($p < 0.001$) and slept for 2 h less ($p < 0.001$). Two further studies reported a prevalence for initial insomnia alone of 29 and 56% (32, 33). Persistent insomnia is associated with a number of adverse consequences including chronic fatigue, mood disturbance, cognitive impairment, impaired job performance and increased healthcare utilization (4, 34). As well as having an impact on quality of life, it may also compromise treatment adherence, which is of particular importance in HIV infection (35).

The role of immune dysregulation and the neurotropic effects of the HIV in the development of insomnia remain unclear, but a number of other risk factors have been identified as of importance: psychiatric illness, drug and alcohol use, the constitutional symptoms associated with HIV infection, such as fatigue and pain, and antiretroviral therapy (2).

Insomnia and Psychiatric Disorders

Insomnia is a well-recognized feature of psychiatric disorders. It is one of the diagnostic criteria for both anxiety and depression that creates an association by definition. This complicates attempts to measure sleep disturbance in the context of HIV infection, given the increased prevalence of both these disorders (36). However, when the criteria for depression and anxiety are restricted to mood symptoms, excluding sleep-related questions, the association with insomnia remains (25).

A systematic review of correlates of insomnia in HIV infection found that psychological morbidity was a major determinant of insomnia, more so than other factors such as disease progression or antiretroviral therapy (2). This was demonstrated in two epidemiological studies (1, 25). Perkins and colleagues followed up 98 HIV-positive men over a period of 6 months and found that an increase in depression scores predicted worsening severity of insomnia (25). This association was not apparent with changes in CD4 count or clinical disease progression. Rubinstein and Selwyn examined a mixed population of seropositive clinic attenders and found that among patients complaining of insomnia, both anxiety (65 vs. 26%; $p < 0.01$) and depression (41 vs. 10%; $p < 0.01$) were more common (1). These findings suggest that in a population of otherwise asymptomatic seropositive individuals, complaints of disturbed sleep are likely to be related to psychological morbidity. Similar findings have also been observed in studies of fatigue in HIV-positive populations. Not surprisingly, fatigue is a common and debilitating symptom in HIV infection, but notably, it has been found to be more strongly associated with psychological morbidity than viral or immune factors, or HAART (37).

Insomnia and Substance Misuse

The HIV Cost and Services Utilization Study, estimating the prevalence of psychiatric disorders and drug dependence in people with HIV infection, found that half of the sample of over 2500 people receiving care for HIV reported illicit drug use in the previous 12 months, and 12% were positive for drug dependence (36). As well as the myriad recognized adverse health outcomes, substance misuse is associated with unsafe sexual and needle-sharing behaviors that increase the risk of HIV infection. Treatment adherence may also be affected. All psychoactive drugs may have a disruptive effect on the sleep–wake cycle. Alcohol, in particular, is frequently used by people with chronic insomnia as it has a transient sedative effect (38). However, as alcohol is metabolized rapidly rebound wakefulness is likely to follow after 3–4 h. Also, gastric irritation and a full bladder may cause frequent wakening. There is limited available evidence on the effects of substance misuse in HIV infection as these patients are often excluded from studies (1, 2). Furthermore, participants are likely to under-report illicit drug use because of fear of criminal prosecution, making such information unreliable (39).

Insomnia and Pain

Clinical experience suggests that any painful condition will lead to sleep disturbance. The more severe the pain, the greater the likelihood of insomnia and this was demonstrated in the 1991 General Social Survey by Statistics Canada where 44% of people with a painful disorder reported sleep problems (40). Pain may disrupt sleep directly through the mechanism of emotional arousal, which disrupts the initiation and maintenance of sleep. It also has a close association with depression, and insomnia may be mediated through this pathway. Pain is commonly reported by HIV-positive individuals with prevalence figures ranging from 40 to 60%, and may be due to HIV infection itself or complications such as Kaposi's sarcoma, opportunistic infections affecting the intestines or skin, arthritides, or myopathies (41). Peripheral neuropathy, characterized by a sensation of burning and numbness in the affected extremity, affects up to 30% of seropositive people and is particularly severe at night. Several antiretroviral drugs, notably nucleoside analogue reverse transcriptase inhibitors (NRTIs), and prophylactic agents such as dapsone can also cause a toxic neuropathy (41). Despite these problems, as

with pain in other medical disorders, it is both underestimated and undertreated (41–43). Paradoxically, treatments for pain may themselves induce sleep disturbance. Notably, opioids can disrupt the sleep–wake cycle and induce a delirious state.

Insomnia and Antiretroviral Treatment

Although no current treatment eradicates HIV infection, antiretroviral medications are the best option for viral suppression and have transformed the clinical course of the disease. Before the development of highly active antiretroviral therapy (HAART), the average life expectancy was 12 years, but now, at least in the developed world, for many patients HIV infection is considered a chronic manageable illness (44, 45). Antiretroviral therapy works by inhibiting viral replication, which allows the partial reconstitution of the immune system. High rates of viral replication, the rapid development of viral resistance and concerns about adverse effects led to the development of different classes of antiretrovirals (Table 53.2). There are several potential targets for antiretroviral drugs in the viral replication cycle, and the combined effect of different mechanisms of action (HAART) suppresses replication to such low levels that the emergence of viral resistance is delayed (Figure 53.2) (5).

Although the benefits of treatment outweigh the potential adverse effects in patients with late-stage illness or a CD4 count of less than 200, in asymptomatic patients, there remains considerable uncertainty about the optimum time to start treatment (46). Most clinicians would consider starting treatment when the CD4 count is 200–350/μL, the aim being to both achieve a substantial increase in the CD4 count and reduce the plasma viral load to less than 50 copies per milliliter. HAART improves life expectancy and quality of life, but rigorous adherence to treatment is essential for maintaining suppression of the viral load. Partial or poor adherence can lead to a resurgence of rapid viral replication, and adherence rates of less than 95% are associated with the emergence of drug resistance, the development of opportunistic infections and increased mortality (47, 48).

Although insomnia is commonly regarded as an adverse effect of antiretroviral medications, in Phase II and III drug trials, the proportion of subjects complaining of disturbed sleep is less than 10% (49). Few studies have systematically examined the risk of insomnia associated with antiretroviral drugs either individually or as a group, and to date, there is an absence of evidence to support a class effect of antiretroviral drugs (1, 24). One antiretroviral drug that has been subject to particular scrutiny is the non-nucleoside reverse transcriptase inhibitor efavirenz (50). Efavirenz was introduced as an effective alternative to protease inhibitors that was particularly easy to use, as it required once daily administration. In general, it exhibits good tolerability, but the most frequent adverse effects are central nervous system symptoms including drowsiness, hallucinations, vivid dreams and nightmares. Severe depression, aggressive behavior and psychotic symptoms may also occur (51, 52). Neuropsychiatric complications have also been reported with nevirapine,

TABLE 53.2. Currently approved drugs for HIV.

	Generic name	Common/Trade name
Reverse transcriptase inhibitors		
Nucleoside/Nucleotide (NRTIs)	Zidovudine	Retrovir
	Stavudine	Zerit
	Lamivudine	Epivir
	Didanosine	Videx
	Abacavir	Ziagen
	Emtricitabine	Emtriva
	Tenofivir DF	Viread
	Abacavir + Lamivudine	Epzicon or Kivexa
	Emtricitabine + Tenofivir DF	Truvada
	Lamivudine + Zidovudine	Combivir
	Lamivudine + Zidovudine + Abacavir	Trizivir
Non-nucleoside (NNRTIs)	Nevirapine	Viramune
	Delavirdine	Rescriptor
	Efavirenz	Sustiva
	Efavirenz + Tenofivir DF + Emtricitabine	Atripla
Protease inhibitors	Saquinavir	Invirase
	Ritonavir	Norvir
	Indinavir	Crixivan
	Nelfinavir	Viracept
	Darunavir	Prezista
	Atazanavir	Reyataz
	Fosamprenavir	Lexiva or Telzif
	Tipranavir	Aptivus
	Lopiniavir + Ritonavir	Kaletra
Entry inhibitors	Enfuvirtide	Fuzeon

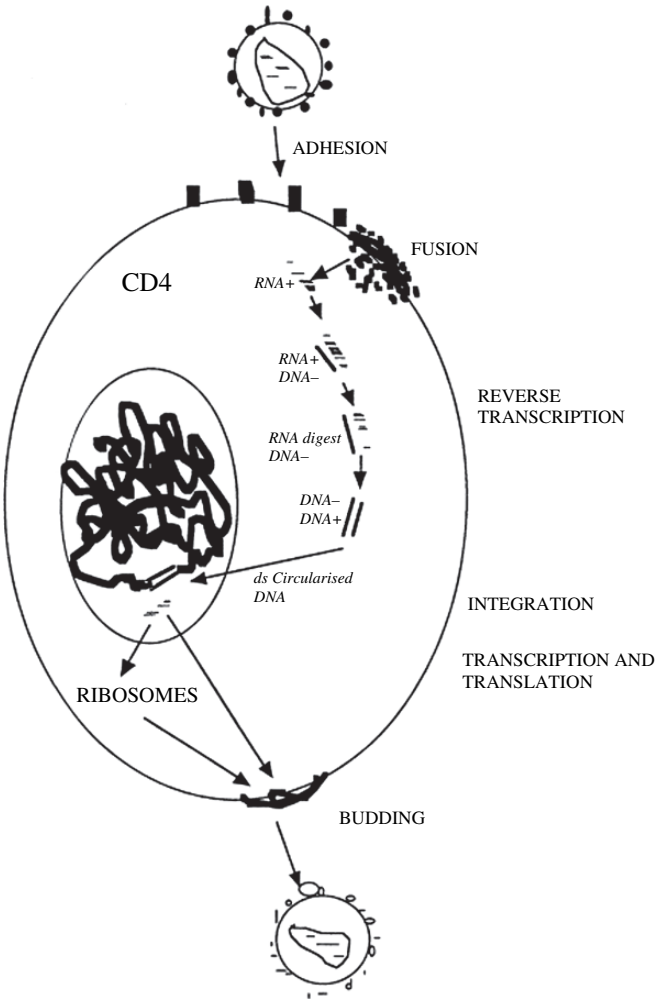

FIGURE 53.2. HIV viral replication. *Adapted from* Weller IVD & Williams IG. ABC of AIDS: Antiretroviral drugs. *BMJ* 2001;322:1410–2, with permission.

another non-nucleoside reverse transcriptase inhibitor (53). A number of case reports describe nevirapine-induced insomnia and vivid dreams, but the evidence for a consistent effect is limited (54). The reported rates of efavirenz discontinuation because of nervous system adverse effects vary between 2 and 12% (50). As a consequence, efavirenz has been examined closely for its effect on sleep and a correlation with insomnia has been well established. One study compared efavirenz with a protease inhibitor and found that 4 weeks after treatment initiation 35% of those prescribed efavirenz reported difficulty sleeping, compared with 4% in the protease inhibitor group (55). Controlled studies using EEG monitoring in HIV-infected subjects treated with efavirenz have found that efavirenz-treated patients have longer sleep latencies and shorter duration of deep sleep (56). The effects appear to be dose-dependent; Nunez and colleagues compared 15 patients experiencing significant insomnia with 36 patients receiving efavirenz without experiencing any CNS adverse effects found a clear correlation between efavirenz concentration in plasma and the number of patients suffering CNS side effects (56). In a multivariate analysis, an efavirenz plasma level greater than 3.5 μg/mL was an independent predictor for insomnia (OR 6.3; 95% CI, 1.2–32.9). For the majority of patients, however, the adverse effects associated with efavirenz appear within 2 weeks of starting treatment and then decline. Furthermore, for some patients, the disadvantages of insomnia may be outweighed by the advantages afforded by treatment with efavirenz, i.e., the ease of use and infrequency of other adverse effects. This was borne out in two studies demonstrating the disruptive effect efavirenz may have on the sleep–wake cycle but also showing paradoxically an improvement in quality of life overall (55, 57).

Antiretroviral therapy may lead to metabolic changes, and in particular, weight gain and a redistribution of fat, referred to as lipodystrophy. This is characterized by peripheral lipoatrophy of the face, limbs and buttocks. There is also a central accumulation of fat in the regions of the abdomen, breasts, and dorsocervical spine (58). A cohort study of people starting treatment with HAART found that after a median follow-up of 18 months, 85 (17%) of 494 patients developed some type of lipodystrophy (59). The increased fat deposition around the neck and upper airway may increase the risk of obstructive sleep apnoea (60). Sleep apnoea should be considered in patients complaining of daytime somnolence, fatigue and snoring, as well as insomnia. The presence of obesity and an increased neck circumference should prompt investigation with overnight polysomnography.

Management of Insomnia in HIV Infection

In patients with HIV infection, self-reported complaints of insomnia will depend on the degree of concern a patient attaches to the level of sleep disturbance. This complaint may include difficulty in initiating sleep, frequent or early awakening, poor sleep quality or daytime fatigue and somnolence (61). An adequate sleep history is necessary, which should include the duration of the sleep disorder. Short-term insomnia is mostly due to situational stressors and may respond to simple sleep hygiene measures (62). Despite the recognized association of psychiatric disorder and insomnia, they are often missed in medical settings, so it is important that attempts are made to identify and treat anxiety and depression (63). Daytime sleepiness should also be evaluated, with consideration given to driving and occupation-related hazards.

A sleep diary is especially useful in the clinic setting for collecting information on precipitants, and the pattern of sleep disturbance. Checking with the bed partner for snoring or pauses in breathing may indicate sleep apnoea. For patients with habitual or chronic insomnia, or in circumstances where causal factors such as pain are not fully manageable, specific treatments for insomnia may be required.

Psychological Treatments

A number of behavioral strategies have been developed and shown to have a good effect in insomnia, but they have not been evaluated in populations with HIV infection, and remain under-used in clinical practice. Sleep hygiene measures are easy to implement and, as noted above, may be particularly effective in people with sleep disturbance of recent onset (Table 53.3). A randomized controlled trial of caffeine withdrawal and abstinence found a 35% improvement in sleep in seropositive patients with a reduced intake (64).

Sleep hygiene measure is often used in combination with the two more structured interventions, stimulus control and sleep restriction (65). Stimulus control consists of providing a set of instructions that curtail behaviors incompatible with sleep and ensures that the patient does not spend time in bed awake. The aim is to redevelop the association between bedtime cues and rapid sleep onset. The patient is instructed to

- go to bed only when sleepy;
- use the bed only for sleep and sexual activity;
- if unable to fall asleep within 10 min, get up and leave the bedroom;
- return to bed only when sleepy and repeat the routine;
- arise at a regular time each morning.

Sleep restriction may be helpful for patients with severe persistent insomnia (66, 67). This technique induces a degree of mild sleep deprivation and involves two interventions. The patient is initially instructed to curtail the amount of time spent in bed to no more than they spent asleep the previous night. The time in bed is then progressively increased in 15-min increments as their sleep efficiency improves (sleeping approximately 85% of the time that they spend in bed).

Drug Treatments

Clinical experience suggests that despite the lack of evidence for major benefits and the potential for harm, benzodiazepines and other hypnotics are the most frequently used treatment for insomnia in people with HIV infection. Whilst there is good evidence that in the short term (<4 weeks) benzodiazepines increase sleep duration, their effects on sleep efficiency particularly in the long term are uncertain (68, 69). Tolerance, rebound insomnia, prolonged sedation and dependence are all recognized problems with both benzodiazepines and newer hypnotics (zopiclone, zaleplon). There is also good evidence for the association of long-term benzodiazepine use with an increased risk of falls, road traffic accidents and cognitive impairment. Therefore, it is recommended that when used hypnotics should be prescribed at the smallest effective dose for the shortest period of time. Benzodiazepines with a short half-life are indicated when the problem is one of initial insomnia, and longer-acting drugs may be beneficial for those who experience frequent awakening. Importantly, protease inhibitors have been shown to raise the plasma levels of alprazolam, midazolam, triazolam, with the potential for respiratory depression, so these drugs should be avoided (70).

When prescribed for patients with major depression, sedative antidepressants improve subjective and objective measures of insomnia. However, there is little evidence in support of their efficacy in insomnia unrelated to depression (71). Tolerance and dependence are of less concern with antidepressants, although they do have a range of adverse effects including anticholinergic effects, cardiac toxicity, orthostatic hypotension and sexual dysfunction. Despite this, drugs such as trazadone, amitriptyline and mirtazapine are commonly used and may be helpful for selected patients. They are typically prescribed at lower doses than would be indicated for depression.

TABLE 53.3. Sleep hygiene measures.

Maintain regular wake time
Avoid excessive time in bed
Avoid daytime naps
Exercise daily, finishing at least 4 h before bedtime
Take a hot bath within 2 h of bedtime
A hot drink without caffeine
Avoid caffeine, nicotine, and alcohol in the evening
Avoid large meals soon before bedtime
Develop a relaxing bedtime ritual

Conclusions

Although insomnia is a frequent complaint in people living with HIV, there is considerable uncertainty about its cause and significance. Sleep disturbance is reported at all stages of HIV infection, but the presence of cognitive impairment or an AIDS-defining illness is a significant risk factor. Antiretroviral medications have not demonstrated a class effect, but efavirenz has consistently been found to be an independent predictor of insomnia. Psychological morbidity has been shown to have a consistent and strong association with insomnia in seropositive patients.

Chronic insomnia is associated with a reduced quality of life; yet, in this population, it remains both under-recognized and under-treated. This may in part be a reflection of uncertainty about approaches to management, as there is little data on treatment of insomnia in this population. The management of insomnia in HIV is a considerable challenge for the clinician. It requires careful evaluation, screening for anxiety and depression, and a familiarity with non-pharmacological interventions as well as drug treatments for sleep disturbance.

Issues that need to be addressed by future research:

- The effects of alcohol and substance abuse on insomnia and quality of life in people living with HIV and AIDS need to be examined.
- Further epidemiological study is needed of the correlates of insomnia in HIV infection in differing populations.
- Research is needed to examine the effects of pharmacological and psychological treatments for insomnia in people living with HIV and AIDS.

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