Clinical Handbook of Insomnia

Second Edition

Edited by

Hrayr P. Attarian

Catherine Schuman

Humana Press

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Current Clinical Neurology

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ISBN 978-1-60327-033-5 e-ISBN 978-1-60327-042-7
DOI 10.1007/978-1-60327-042-7
Springer New York Dordrecht Heidelberg London

Library of Congress Control Number: 2010924279

Printed on acid-free paper

Humana Press is a part of Springer Science+Business Media (www.springer.com)

To my mentor and friend Mark Mahowald, with gratitude for helping launch my career …and as always to my soul mate and wife Diana with unending love.

Hrayr P. Attarian

To my parents, Carole and Warren Schuman, for a lifetime of love and support.

Catherine Schuman

Series Editor's Introduction

It has been 5 years since publication of the first edition of Dr. Attarian's C*linical Handbook of Insomnia* which at the time was the first significant clinical textbook dedicated to insomnia, an often overlooked but important medical problem. The book was very well received. There has now been sufficient new information on the subject to warrant a second expanded edition of this very useful volume. Then, as now, the approach is to emphasize the frequent biological causes of insomnia rather than to attribute it primarily to underlying psychological and emotional factors. This new edition is an impressive major effort, having been expanded from 14 to 23 chapters including an extensive revision and updating of previous chapters with new references and the addition of many new authors. An entirely new section of the book deals with insomnia in special populations including teenagers, pregnancy, menopause, and the geriatric population. Other new topics include insomnia as encountered in primary care practice, the role of circadian rhythms, the contribution of sleep related movement disorders to insomnia, insomnia in pain disorders, and the interesting entity of paradoxical insomnia, in which there is a large discrepancy between the objective and subjective estimation of quantity of sleep. This collection within a single volume of practical information concerning a common but often neglected disorder remains a very useful addition to the armamentarium of the general or specialty physician who wishes to properly address insomnia in an informed and responsible manner.

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Preface

Insomnia is the second most common complaint, after pain, in the primary care setting. Persistent insomnia affects roughly more than one-third of the population and is a risk factor for significant psychiatric morbidity.

Insomnia also leads to overutilization of health care services, decreased productivity in the workplace, more accidents, and more absenteeism from work. All this costs about $100 billion annually. Hence, persistent insomnia is both a public health and an economic problem. Insomnia is not, however, one distinct illness. There are many causes and each naturally requires a different method of evaluation and treatment. Patients with insomnia frequently self-treat with alcohol or over- the-counter medications. There is no scientific evidence for the efficacy of these medications in insomnia. Additionally, those taking these medications may suffer impaired daytime functioning caused by lingering feelings of sedation.

Most medical school curricula suffer a dearth of material on sleep medicine as well as insomnia. Primary care text and reference books often do not include chapters that address the evaluation and treatment of insomnia. When we published The Clinical Handbook of Insomnia 5 years ago, it represented the first clinically oriented, easily readable textbook dedicated to the evaluation and treatment of insomnia in the primary care setting. Our goal was to provide practitioners in general and primary care providers specifically with an easily accessible handbook to serve as a reference for the evaluation and treatment of this important yet poorly recognized medical problem. The volume was very well received by the medical community, so we decided to update and expand it with this current edition.

The second edition of The Clinical Handbook of Insomnia is divided into five sections. The first includes updated chapters on definitions, differential diagnosis, the epidemiology and the pathophysiology of insomnia, and a new chapter geared for midlevel providers as a quick reference guide when confronted with patients complaining of poor sleep. The second section is entirely new in this edition and it focuses on the insomnias in special populations: preadolescents, teens, pregnant women, menopausal women, and the elderly. Part III discusses the primary insomnias with updated chapters and Part IV has updated and expanded chapters on secondary insomnias with a new chapter on the relationship between chronic pain and insomnia. The last

section reviews the pharmacological and behavioral treatments of insomnia. Most of the chapters are illustrated by case studies, charts and graphs to better elucidate the points conveyed.

We hope the Clinical Handbook of Insomnia, Second Edition, will continue to fill an important niche in the medical literature by providing the first comprehensive publication that addresses insomnia in its multiple forms, summarizes the findings published in different medical journals, and presents these to the practicing health care provider in an easily accessible format.

Chicago, IL — Hrayr P. Attarian, MD
Malden, MA — Catherine C. Schuman, PhD

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Part I

Overview

1

Defining Insomnia

H.P. Attarian and M.L. Perlis

Abstract

In the early 1980s, insomnia was thought to be a symptom, not a disorder. After two decades or more of sleep research and sleep medicine, insomnia is considered a distinct nosological entity. Perhaps what is different in the modern era is that initially the distinction between primary insomnia and secondary insomnia allowed for difficulty initiating and maintaining sleep to be both a disorder in its own right and symptom of other disorders, while the most recent international classification of sleep disorders divides up the category of insomnia into 11 diagnostic entities based on etiological and pathophysiological criteria. Thus, it is no longer either a symptom (secondary) or a diagnosis (primary) but both. This is a more accurate definition especially given the large proportion of insomniacs with comorbid medical conditions, the most common being psychiatric illnesses. We are fortunate to have several nosologies that recognize insomnia as a primary disorder. The various classification systems provide us the wherewithal to differentiate types of insomnia both by presenting complaint as well as by the factors that are thought to precipitate or perpetuate the illness.

Keywords: Primary insomnia, Comorbid insomnia, Secondary insomnia, Nosology, Diagnostic entities

Introduction

In the early 1980s, as the sleep medicine movement was just gathering steam, there was perhaps no rallying cry as popular as "insomnia is a symptom, not a disorder." Presumably, this position was taken in part for medico-political reasons, but also because it was genuinely believed that the polysomnographic study of sleep was destined to reveal all the underlying pathologies that give rise to the "symptoms" of insomnia, fatigue, and sleepiness. After two decades or more of sleep research and sleep medicine, it is interesting to find that "all things old are new again": Insomnia is once again considered a distinct

From: *Clinical Handbook of Insomnia,* Current Clinical Neurology
Edited by: H.P. Attarian and C. Schuman, DOI 10.1007/978-1-60327-042-7_1,

nosological entity. Perhaps what is different in the modern era is that initially the distinction between primary insomnia and secondary insomnia allowed for difficulty initiating and maintaining sleep to be both a disorder in its own right and a symptom of other disorders; and the most recent international classification of sleep disorders divides up the category of insomnia into 11 diagnostic entities based on etiological and pathophysiological criteria [1], so it is no longer either a symptom (secondary) or a diagnosis (primary) but both. This is a more accurate definition especially given the large proportion of insomniacs with comorbid medical conditions, the most common being psychiatric illnesses; about 40% [2].

Historical Perspectives

The first references in the western culture to insomnia, the inability to initiate and/or maintain sleep, date back to the ancient Greeks. The earliest mention of it is in the pre-Hippocratic Epicurean tablets that list 70 cases one of which is a patient with insomnia. The first scientific approach is found in the writings of Aristotle from circa 350 BC, and the first records of treatment of insomnia come from the first century BC Greek physician, Heraclides of Taras, who lived in Alexandria and recommended opium for the treatment of insomnia. Although there had been a significant amount of research and interest in insomnia in the twentieth century, it was not until the 1970s that distinct diagnostic criteria were created to describe different forms of insomnia.

Over the years insomnia has featured in the writings of several prominent literary figures including William Shakespeare, who alluded to it in several of his plays, to the pop culture icons the Beatles who referred to it in their song "I am so tired." Prominent historical figures that have suffered from insomnia include Churchill, Charles Dickens, Napoleon Bonaparte, Marcel Proust, Alexander Dumas, and Benjamin Franklin to name just several.

Definitions of Insomnia

Insomnia is the most common sleep-related complaint and the second most common overall complaint (after pain) reported in primary care settings with about 50% of adults reporting sleep trouble in a given year [3]. The general consensus based on many population studies is that one third of adults have frequent trouble falling sleep, staying asleep, or overall poor sleep quality [2]. An NIH State-of-the-Science Conference held in June 2005 concluded that the prevalence of chronic, persistent insomnia that also causes daytime fatigue and impairment is 10% [4] and is a cause of significant morbidity [1]. It costs the American public about $100 billion annually in medical expenses, ramifications of accidents, and reduced productivity due to absenteeism and decreased work efficiency [5].

Insomnia is not defined by total sleep time but by the inability to obtain sleep of sufficient length or quality to produce refreshment the following morning [6]. For example, a person who needs only 4 h of sleep does not have insomnia if he or she is refreshed in the morning after 4 h of sleep, whereas someone who needs 10 h of sleep may have insomnia if he or she does not feel refreshed after 8 h of fragmented sleep. Previously, the underlying psychiatric or

psychological condition was thought to be the most common cause of insomnia, but newer studies have refuted this theory. In fact untreated insomnia may adversely affect the course of the associated disorder [6].

Classifications

There are three major classification systems used by professionals: The International Classification of Diseases (ICD) by the World Health Organization (WHO), The International Classification of Sleep Disorders, 2nd Edition, by the American Academy of Sleep Medicine (AASM) in 2005, and the American Psychiatric Association's (APA) the Diagnostic and Statistical Manual on Mental Disorders, fourth edition (DSM-IV TR).

WHO-ICD: The WHO defines insomnia as a condition of unsatisfactory quantity and/or quality of sleep, which persists for a considerable period of time, including difficulty falling asleep, difficulty staying asleep, or early final wakening [7].

APA-DSM-IV TR: The APA defines two types of insomnia, primary and secondary.

The term "primary insomnia," which is adopted by the APA's diagnostic nomenclature (DSM-IV TR [8]), is used to distinguish insomnia that is considered to be a distinct diagnostic entity from insomnia that is a secondary symptom of an underlying medical and/or psychiatric condition. The American Psychiatric Association specifies a duration criteria of 1 month and stipulates that the diagnosis be made when the predominant complaint is difficulty initiating or maintaining sleep or nonrestorative sleep. In either case, the complaint must be associated with significant distress and daytime impairment, and not due to other medical, psychiatric, or sleep disorders (Table 1.1).

AASM: The American Academy of Sleep Medicine's nosology (the International Classification of Sleep Disorders, 2nd edition [ICSD-2]) does not have a distinct category of primary insomnia but instead discusses 11 free standing insomnia disorders: three of which are roughly equivalent to primary insomnia because of the absence of other diagnostic entities and medical conditions causing the sleep disturbances. These are psychophysiologic insomnia, paradoxical insomnia, and idiopathic insomnia [1]. There are also eight others that are roughly equivalent to secondary insomnia as they are either due to another medical or psychologic disorder or due to acute stressors or sleep disruptive practices.

Table 1.1 Diagnostic criteria for primary insomnia (the Diagnostic and Statistical Manual on Mental Disorders, fourth edition TR).

The predominant symptom is difficulty initiating or maintaining sleep or nonrestorative sleep, for at least 1 month
The sleep disturbance (or associated daytime fatigue) causes clinically significant distress or impairment in social, occupational, or other important areas of functioning
The sleep disturbance does not occur exclusively during the course of narcolepsy breathing-related sleep disorder, circadian rhythm sleep disorder, or a parasomnia
The disturbance does not occur exclusively during the course of another mental disorder (e.g., major depressive disorder, generalized anxiety disorder, a delirium)
The disturbance is not due to the direct physiological effects of a substance (e.g., drug abuse, medication) or a general medical condition

Psychophysiologic Insomnia

The ICSD-2 definition of psychophysiologic insomnia is directly tied to the etiologic underpinnings of the disorder. Psychophysiologic insomnia is described as "a disorder of somatized tension and learned sleep-preventing associations that results in a complaint of insomnia and associated decreased functioning during wakefulness" [1]. "Somatized tension" refers to either the patient's subjective sense of, or objective measures of, somatic hyperarousal while attempting to sleep. Somatic arousal is characterized by peripheral nervous system activity which is commonly marked by increased muscle tension, rapid heart rate, sweating, etc. "Learned sleep-preventing associations" refer to the pattern of presleep arousal that appears to be classically conditioned to the bedroom environment, where intrusive presleep cognitions, racing thoughts, and rumination are often taken as indicators of presleep arousal (Table 1.2).

Idiopathic, or Childhood-Onset, Insomnia

This condition presents as a chronic, serious inability to initiate and maintain sleep, which can often be traced back to the first few weeks of life [9]. Sleep latency (i.e., the time it takes to fall asleep after going to bed) may be very long, and sleep is riddled with awakenings. Daytime features typically include decreased attention and vigilance, low levels of energy and concentration, and deterioration of mood that is usually described as grim and subdued rather than obviously depressed or anxious.

The presumed underlying neurologic abnormality may vary from mild to severe, so the range of insomnia encountered also may vary from mild (essentially, the patient is a light sleeper) to severe and incapacitating. In mild or moderate idiopathic insomnia, psychological functioning is remarkably intact.

Table 1.2 Diagnostic criteria for psychophysiological insomnia (adapted from The International Classifications of Sleep Disorders Revised: Diagnostic and Coding Manual).

The patient's complaint meet the criteria for insomnia
The insomnia is present for at least 1 month
The patient has evidence of conditioned sleep difficulty and/or heightened arousal in bed as indicated by one or more of the following:
Excessive focus on and heightened anxiety about sleep
Difficulty falling asleep in bed at the desired bedtime or during planned naps, but no difficulty falling asleep during other monotonous activities when not intending to sleep
Ability to sleep better away from home than at home
Mental arousal in bed characterized either by intrusive thoughts or a perceived inability to volitionally cease sleep-preventing mental activity
Heightened somatic tension in bed reflected by a perceived inability to relax the body sufficiently to allow the onset of sleep
The sleep disturbance is not better explained by another sleep disorder, medical or neurologic disorder, mental disorder, medication use, or substance use disorder

Table 1.3 Diagnostic criteria for idiopathic insomnia (adapted from The International Classifications of Sleep Disorders Revised: Diagnostic and Coding Manual).

The patient's symptoms meet the criteria for insomnia
The insomnia is present for at least 1 month
One or more of the following criteria apply:
The patient reports a chronic pattern of little or no sleep most nights with rare nights during which relatively normal amounts of sleep are obtained
Sleep-log data during 1 or more weeks of monitoring show an average sleep time well below published age-adjusted normative values, often with no sleep at all indicated for several nights per week; typically there is an absence of daytime naps following such nights
The patients show a consistent marked mismatch between objective findings from polysomnography or actigraphy and subjective sleep estimates derived either from self-report or a sleep diary
At least one of the following is observed:
The patient reports constant or near constant awareness of environmental stimuli throughout most nights
The patient reports a pattern of conscious thoughts or rumination throughout most nights while maintaining a recumbent posture
The daytime impairment reported is consistent with that reported by other insomnia subtypes, but it is much less
The reported sleep disturbance is not better explained by another sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder

In severe cases, daytime functioning may be severely disrupted, and affected patients may be unable to hold a job. During childhood and adolescence, idiopathic insomnia is often associated with such neurologic signs as dyslexia and hyperactivity. In many cases, diffuse, nonspecific abnormalities are seen on an electroencephalogram (EEG) [1] (Table 1.3).

Paradoxical Insomnia

In this fascinating disorder, complaints of insomnia occur without any objective evidence of sleep disturbance. Patients may report that they have not slept at all in weeks, months, or years. However, on objective sleep studies, they sleep several hours per night [10]. When results of sleep evaluation are presented, patients with sleep-state misperception may vehemently insist that the studies are in error, because they are convinced that they sleep very little, if at all (Table 1.4).

Interestingly, none of the nosologies formally embrace the older descriptive clinical characterizations of insomnia in terms of initial, middle, and terminal (late) insomnia. Trouble falling asleep is often referred to as "initial," early, or sleep-onset insomnia. Trouble with frequent or prolonged awakenings is often labeled "middle" or sleep maintenance insomnia. Waking up earlier than desired and being unable to fall back asleep is referred to as "late," "terminal," or early morning awakening insomnia. Waking up feeling unrefreshed is commonly

Table 1.4 Diagnostic criteria for paradoxical insomnia (adapted from The International Classifications of Sleep Disorders Revised: Diagnostic and Coding Manual).

The patient's symptoms meet the criteria for insomnia
The course of the disorder is chronic, as indicated by each of the following:
Onset during infancy or childhood
No identifiable precipitant or cause
Persistent course with no periods of sustained remission
The sleep disturbance is not better explained by another sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder

referred to as "nonrestorative" sleep. Patients often report some combination of the above descriptions, which is generally referred to as "mixed" insomnia. For the purpose of this chapter, although we consider the International Classification system to provide a more precise definition of the disorder, we will use the term "primary insomnia" since it is the most widely embraced in clinical practice in the USA. We will adopt the more descriptive terminology when a more specific characterization of the presenting complaint is required.

Classification Based on Duration and Severity

Apart from presenting a specific definition of the disorder/disease entity, there is the need to qualify the duration and severity of the defined illness. Typically, duration is framed dichotomously in terms of acute and chronic stages. Severity can be construed in one of two ways. In one case, standards are set for what constitutes significant deviance from population norms with respect to frequency and intensity of presenting symptoms. In the other case, standards are set by "setting the bar" for "pathologic" at a level which is modal for patients who are help-seeking.

Duration of Illness

Insomnia lasting less than 3 months is generally considered "acute," or by the ICSD-2 criteria adjustment insomnia. It is often associated with clearly defined precipitants such as stress, acute pain, or substance abuse. Insomnia is characterized as being chronic when symptoms persist unabated for a duration of at least 3 months, and more typically for durations of time which are 6 months or greater. Please note that these cutoffs are relatively arbitrary and correspond to traditional medical definitions of what constitutes short and long periods of time. At this time there are no studies which use risk models to evaluate the natural course of insomnia. Thus, there is no way of definitively defining "chronicity" in terms which are related to when the disorder becomes severe, persistent, and (for want of a better expression) "self-perpetuating." One clinical cue for differentiating between acute and chronic insomnia resides in the way patients characterize their complaint. When patients stop

causally linking their insomnia to its precipitant and instead indicate that their sleep problems seem "to have a life of their own," this change in presentation may (1) serve to define the "cut point" between the acute and chronic phases of the disorder and (2) suggest when CBT should be indicated.

Severity of Illness

Intensity

Although there are no formal diagnostic criteria, most investigators consider 30 or more minutes to fall asleep and/or 30 or more minutes of wakefulness after sleep onset to represent the threshold between normal and abnormal sleep. Recent work by Lichstein and colleagues suggests that this criterion should be set at "more than 30 min," as this definition is better related to the occurrence of complaint in population studies [11, 12]. With respect to "how much sleep," many investigators are reluctant to fix a value for this parameter. Of the investigators that are inclined to set minimums, most specify that the amount of sleep obtained on a regular basis be equal to or less than either 6.0 or 6.5 h per night. The reluctance to establish total sleep time parameters is due, in part, to the difficulty in establishing precisely what one considers to be abnormal. Representing what is pathological with a single number is too confounded by factors like age, prior sleep, and the individual's basal level of sleep need. The lack of an established total sleep time cutoff is also related to the possibility that profound sleep initiation or maintenance problems may occur in the absence of sleep loss. This is an important distinction, because it is often assumed that insomnia is synonymous with sleep deprivation. While it is certainly the case that the daytime symptoms associated with insomnia might be explained, in part, by partial chronic sleep loss, daytime symptoms need not be ascribable only to lack of sleep. For example, it has been shown that patients with insomnia reliably exhibit sleep micro-architectural disturbances such as enhanced high-frequency activity during NREM sleep [13–17]. This type of activity, which appears to be independent from sleep continuity and architecture parameters, has been shown to be correlated with patient perceptions about their sleep quality and quantity [13, 18, 19].

Frequency

There is also no fixed benchmark for "frequency" of symptoms. Most clinical researchers, in this case, require that subjects experience problems on three or more nights per week, but this may have more to do with increasing the odds of studying the occurrence of the disorder in laboratory than an inherent belief that less than three nights per week is "normal."

Commonalities and Problems with Current Definitions

All of the above definitions show a degree of consistency, both in terms of what "is" and "is not" delineated. Common to all is that (1) insomnia is defined as a subjective complaint, (2) patients must report compromised daytime

functioning, (3) there are no specific criteria for how much wakefulness is considered pathologic (prior to desired sleep onset or during the night), and (4) there are no criteria for how little total sleep must be obtained to fall outside the normal range. The latter two of these issues have already been explicated above (lack of quantitative criteria for SL, WASO, and TST). The former two require further discussion.

Insomnia as a Subjective Complaint

Defining insomnia as a subjective complaint without requiring objective verification of signs and symptoms has advantages and disadvantages. The advantage of having subjective criteria is that it recognizes the primacy of the patient's experience of distress or disease. That is, ultimately patients seek, comply with, and discontinue treatment based on their perception of wellness. The disadvantage is that such measures, when used alone, do not allow for a complete characterization of either the patient's condition or the disorder in general.

Insomnia and Daytime Impairment

The reason that daytime complaints are required for diagnosis is that in the absence of such complaints, it is possible that the phenomena of "short sleep" may be misidentified as insomnia. Frequent complaints associated with insomnia include fatigue, irritability, problems with attention, and concentration and distress directly related the inability to initiate and/or maintain sleep.

Comorbid, Formerly Secondary, Insomnia

Secondary insomnia was a term coined to refer to insomnia that was due to another disorder. In a landmark review paper from 2001, Lichstein correctly argued that, from a practical point of view the conditions needed to assert causality for the insomnia are almost never identified. Since the main diagnostic tool is history and most people present with the insomnia lasting at least 6 months if not more, they are unable to provide a reliable accounting of the course and their relative sequence of the two disorders [20].

Since comorbidity without necessarily implying causality can easily be established and since from a treatment standpoint both conditions need to be treated together the tide started turning in favor of abandoning secondary insomnia and adopting the term comorbid insomnia. This trend became further solidified in the AASM report on the Research Diagnostic Criteria (RDC) for insomnia. The suggested criteria used a slightly different language than before. Instead of saying insomnia due to a certain disorder they stated that the onset and the temporal course of the insomnia should coincide with the course of the specific disorder for the insomnia to be considered comorbid [21].

In conclusion, the term comorbid insomnia more accurately describes the conditions formerly known as secondary insomnia and it has no negative impact on treatment since regardless of causality both conditions need to be treated for a successful outcome.

Summary

We are fortunate to have several nosologies that recognize insomnia as a primary disorder. The various classification systems provide us the wherewithal to differentiate types of insomnia both by presenting complaint as well as by the factors that are thought to precipitate or perpetuate the illness. Perhaps what remains to be accomplished in the present decade, from a definitional point of view, is for scholars and scientists to complete the characterization of this important disorder by providing for the formulation of the ultimate definition, one which formally lays out the RDC and does so based on the force of empirical research.

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2

Epidemiology of Insomnia

Ritu Grewal and Karl Doghramji

Abstract

Insomnia is a prevalent complaint and often encountered by health care practitioners. It is costly and can cause significant morbidity if not addressed appropriately. Women and the elderly tend to suffer from insomnia more than other groups of the population. Other risk factors include psychosocial stressors, psychiatric and medical problems, low income, unemployment, excessive environmental noise, not having a life partner, and job-related stressors among others.

Keywords: Prevalence of insomnia, Hypnotic use, Economic impact, Sociodemographic determinants

Sleep accounts for one third of human life and insomnia is the most common sleep-related complaint and the second most common overall complaint (after pain) reported in primary care settings [1].

Estimates of the prevalence of insomnia are variable owing, in part, to inconsistencies in definitions and diagnostic criteria for insomnia. These issues also make it difficult to define other dimensions of the condition, such as incidence and remission rates, as a uniform characterization of episode lengths is lacking; a positive finding of insomnia at baseline and at 1-year follow-up may reflect unremitting chronic insomnia or two episodes of transient insomnia [2, 3]. Currently, there are three distinct diagnostic nosologic systems for insomnia: The Diagnostic and Statistical Manual of Mental Disorders [4], The International Classification of Sleep Disorders [5], and The ICD-10 Classification of Mental and Behavioral Disorders [6].

Mellinger et al. presented data from one of the first attempts to quantify the prevalence of the disorder. Their 1979 US survey, utilizing a nationally representative sample of 3,161 people whose ages ranged from 18 to 79, found that insomnia affected 35% of the general adult population in 1 year [7]. About half of these people experienced the problem as severe [7], yet only 15% were

From: *Clinical Handbook of Insomnia,* Current Clinical Neurology
Edited by: H.P. Attarian and C. Schuman, DOI 10.1007/978-1-60327-042-7_2,

treated with hypnotic medications [7]. In 1996, another study by Ohayon in Montreal examined the prevalence of insomnia in a representative sample of 5,622 French subjects of 15 years of age or older. 20.1% of the participants stated that they were unsatisfied with their sleep or taking medication for sleeping difficulties [8]. A 2000 study by Leger and colleagues, in France, noted that the prevalence of frequent insomnia was 29% in a representative sample of the population that included 12,778 individuals [9]. Twenty-four percent of the Canadian English-speaking population aged 15 and above reported insomnia according to a 2001 study by Sutton et al. [10]. In a representative selection of German citizens who were older than 13 years of age, 1,997 were asked about their sleep complaints. Twenty-five percent of people suffered at least sometimes from difficulties in falling asleep and/or staying asleep, which was not due to external factors, and 7% frequently or always [11]. A similar survey in Japan, conducted in a group of 6,277 new outpatients from 11 hospitals, revealed a prevalence of 20.3% with 11.7% of the people suffering from insomnia for over a month. Only 37% were treated with hypnotics [12]. A second study in Japan, done in a representative sample ($n = 3{,}030$) of the general population, reported almost identical results: 21.4% during the month preceding the survey [13]. A representative adult sample (18 years and above) of the Norwegian population, comprising 2,001 subjects, participated in telephone interviews, focusing on the 1-month point prevalence of insomnia and use of prescribed hypnotics. Employment of DSM-IV inclusion criteria of insomnia yielded a prevalence rate of 11.7% [14]. A prior Norwegian study had queried 14,667 subjects and reported 41.7% of the women and 29.9% of the men complaining of occasional insomnia [15].

Another study in Austria in a sample of 1,000 revealed a prevalence of 26% with 21% of them being severe and chronic with duration of 1 year or more [16]. In a representative sample of the South Korean general population composed of 3,719 noninstitutionalized individuals aged 15 years or older, the prevalence of insomnia symptoms occurring at least three nights per week was reported to be 17.0% [17]. In Mexico, the prevalence of insomnia in a group of a 1,000 subjects, aged 18–84, was found to be 36% with 16% reporting severe insomnia [18]. In Finland, an early study reported a severe insomnia (daily of several times a week) prevalence of 5–14%, depending on age group, in subjects between ages of 15 and 64. In Singapore, the prevalence of persistent insomnia for over a year was 15.3% in subjects between the ages of 15 and 55 [19]. Hyyppa and Kronholm reported a male/female prevalence of 9.6/12.8% of frequent or nightly insomnia and 57.6–62.7% of occasional insomnia in a group of 1,099 subjects representative of the Finnish population [20].

There are fewer studies in the pediatric population yet they reveal, in general, similar prevalence rates. In preadolescent children, one of the earliest studies noted that 14% of an outpatient US pediatric population between the ages of 6–12 had insomnia with a mean duration of 5 years [21]. Archbold et al. at Ann Arbor surveyed parents of 1,038 unselected children (554 boys) aged 2.0–13.9 years. Forty one percent of the children had at least one symptom of insomnia and 18% had two or more symptoms [22]. The prevalence of frequent insomnia in 1,413 schoolchildren aged 6.2–10.9 years in Sweden was reported to be 13% [23].

In adolescent groups, the prevalence of insomnia appears to be similar to that of younger children. In a Chinese study, a total of 1,365 adolescents

between the ages of 12 and 18 years were surveyed and 16.9% reported insomnia [24]. A multinational study in Europe, in a representative sample of 1,125 adolescents aged 15–18 years, from four countries (France, Great Britain, Germany, and Italy) reported insomnia symptoms in approximately 25% and DSM-IV insomnia disorder in approximately 4% [25]. Previous studies had reported prevalence rates of 4–5% for persistent insomnia in a group of 574 (aged 7–17) [26], 10.8–33.2% for frequent insomnia (at least twice a week) in a group of 40,202 children aged 11–16 [27], 11–12.6% for frequent insomnia [28–30], 23–38% for occasional insomnia, and 1–2% for persistent insomnia [31]. In summary, various from different countries suggest that insomnia is a universal complaint, and that it is commonly expressed, making it a major health issue.

In a recent review by Ohayon [32], an attempt was made to determine the prevalence of insomnia based on four categories; (1) Insomnia symptoms of difficulty in initiating and maintaining sleep or nonrestorative sleep; (2) Insomnia symptoms accompanied by daytime consequences; (3) Dissatisfaction with sleep quality or quantity; (4) Insomnia diagnosis based on definitions established by DSM-IV or ICSD. The first category based on insomnia symptoms alone revealed a prevalence of 30–48%. This dropped to 16–12% when frequency modifiers were added to symptoms such as presence of symptoms to at least three nights a week or "often" or "always." When severity criteria were added to insomnia symptoms the prevalence of insomnia ranged from 10 to 28%. The prevalence of insomnia based on insomnia symptoms with daytime consequences (category 2) was around 10%. The prevalence of insomnia based on dissatisfaction with sleep quality and quantity (category 3) was 8–18% with a higher prevalence being consistently reported in females. The prevalence of insomnia based on DSM-IV classification varied from 4.4 to 6.4%. Primary insomnia was the most frequent diagnosis, its prevalence ranging between 2 and 4%.

Sociodemographic Determinants

Most epidemiological studies indicate that women, the elderly, and people with coexisting health problems are more likely to suffer from insomnia [33].

Gender

All of the available epidemiological studies that compare the prevalence of insomnia between the genders report a higher prevalence in women [8]. The female to male ratio is roughly 1.5/1 [33]. This is especially true when comparing peri- or postmenopausal women with age-matched men. One of the most common perimenopausal symptoms in women ranging in age from 35 to 55 is insomnia [34, 35].

There are, however, other studies that report an increased prevalence of insomnia in younger women, and even in adolescent girls, when compared with age-matched male counterparts. When studying a group of children and adolescents between ages of 3 and 14 ($n=452$), Camhi et al. found that the complaints of insomnia were much higher in adolescent girls (aged 11–14) than in the rest of the group (30.4–16.8%) [36]. This suggests that insomnia or the processes that produce it are operant in women as early as adolescence.

The increased prevalence of insomnia in adult women of all ages when compared with men seems to be a universal phenomenon. Studies from Hong Kong [37, 38], Germany [39], Canada [8, 13], the USA [2, 40], Norway [15], Scotland [41], and other countries [42, 43] have all reported increased prevalence in adult women when compared with age-matched male counterparts.

Age

Advancing age is thought to be a risk factor for developing insomnia. The odds ratio was noted to be 1.3 in one study [33]. Despite other reports of increased prevalence of insomnia with aging [13, 14], a few studies that involve elderly populations exclusively have failed to demonstrate this effect [42, 44, 45]. In 2001, Ohayon et al. surveyed 13,057 subjects, whose ages were above 15 years, from three different countries (United Kingdom, Germany, and Italy). Insomnia symptoms were reported by more than one-third of the population aged 65 and older. Multivariate models showed that age was not a predictive factor for insomnia symptoms when controlling for activity status and social life satisfaction. The authors concluded that the aging process per se is not responsible for the increase of insomnia often reported in older people. Instead, inactivity, dissatisfaction with social life, and the presence of organic diseases and mental disorders were the best predictors of insomnia, with the contribution of age being insignificant. In this study, the prevalence of insomnia symptoms in healthy seniors was similar to that observed in younger individuals [46].

Ethnocultural Factors

The few studies that have looked at the impact of ethnocultural variables on insomnia have shown that, among the elderly, European Americans more frequently complained of insomnia than African Americans [47, 48] and had a greater reliance on sleep medications [48].

Shift Work

Several studies have demonstrated that rotating daytime shift workers report sleep onset insomnia more frequently than the fixed daytime schedule workers (20.1% vs. 12.0%) [49], with the complaints of insomnia increasing in proportion to the number of shifts worked. Insomnia and other sleep complaints are significantly more common in three-shift workers than in two-shift workers. By the same token two-shift workers complain more of insomnia than straight-day shift workers [50]. Working the night or third shift may not only acutely cause insomnia but may have persistent deleterious effects on sleep quality, when adhered to for prolonged periods of amount of time, even after reversion to day or evening shifts [51].

Other Factors

Occupation, socioeconomic status, marital status, mental and physical health also impact the prevalence of insomnia. A few studies have reported a direct relationship between unemployed status [8, 13, 38, 52], lower socioeconomic status [33, 38] and lower educational level [38], and increased prevalence of insomnia. Higher prevalence of complaints of insomnia has also been reported

among single, widowed, or divorced adults as compared with ones who were in a marital relationship [8, 12, 52]. Noisy environments are associated with increased reports of poor sleep particularly in women [38, 53]. Psychosocial stressors appear to be a risk factor for insomnia as well [24]. Poor physical health is also associated with a higher prevalence of insomnia [12, 24, 33, 37, 43–45] as is poor mental health [12, 43–45]. Medical problems associated with insomnia include depressive disorders [44, 54], anxiety disorders [54, 55], substance abuse [55], schizophrenia [54], congestive heart failure, obstructive airway disease and other respiratory illnesses [56], back and hip problems, and prostate problems [57].

Seasonal differences have been reported in patients suffering from chronic insomnia. In Norway, a survey of a representative sample of 14,667 adults living in the municipality of Tromso, north of the Arctic Circle, revealed increased incidence of complaints of insomnia during the dark period of the year than during any other time [15].

Psychiatric Disorders

In 1989, Ford and Kamerow utilized standardized questionnaires in 7,954 subjects at baseline and a year later. Of this community 10.2% had insomnia at baseline. The risk of developing new major depression following the course of 1 year was much higher in those who had insomnia at baseline, and in those in whom insomnia had not resolved by the time of the second visit [58].

In 1997, Chang et al. published a landmark paper on the subject of insomnia and its relation to the development of depression. A total of 1,053 men provided information on sleep habits during medical school at The Johns Hopkins University (classes of 1948–1964) and were followed since graduation. During a median follow-up period of 34 years (range 1–45), 101 men developed clinical depression (12.2%) and 13 committed suicide. A Cox proportional hazards analysis adjusted for age at graduation, class year, parental history of clinical depression, coffee drinking, and measures of temperament revealed that the relative risk of subsequent clinical depression was greater in those who reported insomnia in medical school [59]. In the same year, Weissman et al. published a study that reported data from a survey of over 10,000 adults living in three US communities. Psychiatric disorders were assessed utilizing a structured diagnostic interview, and the prevalence of insomnia, not due to medical conditions, medication, drug or alcohol abuse, during the subsequent 1-year of follow-up was assessed. The results revealed that 8% of subjects who had primary insomnia had sought psychiatric help at the end of that year for different psychiatric problems vs. 2.5% of the normal controls. Uncomplicated or primary insomnia was also associated with an increase in risk for first onset of major depression, panic disorder, and alcohol abuse over the following year [54]. These and similar studies have suggested that insomnia is a risk factor for the development of major depression and other psychiatric disorders [60].

Morbidity and Mortality

A number of studies have demonstrated a decreased quality of life as a direct consequence of the insomnia. Chevalier et al., using the SF-36, demonstrated that the degree of impairment in quality of life was directly proportional to

the severity of insomnia. They also demonstrated that individuals with severe insomnia showed a higher level of healthcare utilization [42]. Hajak and the SINE group (Study of Insomnia in Europe) in Germany and Leger and colleagues in France reported very similar results regarding quality of life and health care utilization [39, 61]. Zammit et al. and Hatoum et al., independently, reported similar results in the USA [62, 63]. Cognitive deficits identified on objective testing have been associated with chronic, persistent, insomnia as well [64, 65].

The limited numbers of studies that have examined the association between insomnia, its treatment, and mortality have been inconsistent. Kripke et al. followed 1.1 million subjects for 6 years. Insomnia alone was not associated with increased mortality [66]. However, another study showed that mortality risk over a 6-year follow-up period was significantly elevated in older adults who used medications other than traditional hypnotics for improved sleep [67]. There is an association between difficulties falling asleep and mortality due to coronary artery disease in men [68].

Epidemiology of Hypnotic Use

The use of hypnotics increases with age, particularly among middle aged and elderly women [69, 70]. Sleeping pill use varies with occupation. According to one study, the rate of frequent or habitual hypnotic use among male gardeners, female social office workers, and male construction workers was higher than the rate in other surveyed occupations [71]. Alcohol is the most commonly used hypnotic among insomniacs (roughly 15% have reported using alcohol for insomnia) [55, 72]. Between 1987 and 1996 there was a dramatic shift, in the USA, toward the use of antidepressants instead of hypnotics for the symptomatic treatment of insomnia, despite a paucity of data regarding their efficacy, and despite the potential for serious side effects [73]. Antidepressants and over-the-counter sleep aids remain the most commonly recommended and prescribed treatments for insomnia complaints [73]. Despite the safety profile of benzodiazepine receptor agonists they remain less utilized in the USA, possibly owing to concerns regarding their potential for dependence and abuse and their DEA status as “scheduled” agents [74].

Economic Impact of Insomnia

Insomnia costs the American public $92.5 to $107.5 billion annually, in both direct and indirect expenses, due to medical procedures and medications, accidents, and reduced productivity associated with absenteeism and decreased work efficiency [75]. Insomnia sufferers place a significant burden on both the health care system and their employers [76]. Weissman et al. noted that insomnia sufferers were more prone to access medical and psychiatric care providers during a 1-year follow-up period [54]. In 1995, Walsh and Engelhardt reported a total direct cost of $13.9 billion in the USA [77].

Conclusion

Insomnia is a prevalent complaint and often encountered by health care practitioners. It is costly and can cause significant morbidity if not addressed appropriately. Women and the elderly tend to suffer from insomnia more than other groups of the population. Other risk factors include psychosocial stressors, psychiatric and medical problems, low income, unemployment, excessive environmental noise, not having a life partner, and job-related stressors among others.

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3

Physiological Basis of Insomnia

Michael H. Bonnet and Donna L. Arand

Abstract

Forty years of psychophysiological research have shown that patients with primary insomnia have elevated levels of physiological arousal as indicated by a wide range of variables including brain and whole-body metabolic measures, cardiac measures, and hormone and endocrine measures. Current research has attempted to refine our understanding of the relationship between physiological arousal, poor EEG sleep, psychological status, and subjective report of insomnia. Experimentally induced chronic physiological arousal in normal adults produces mood and personality changes seen in insomnia patients and therefore provides a model of how chronic insomnia could develop in physiologically susceptible individuals. Studies showing that poor sleep, as found in insomnia patients, by itself does not produce the arousal, mood, and personality characteristics found in clinical insomnia and imply that (1) the symptoms produced by chronic physiological arousal are not mediated by the poor sleep itself and (2) the symptom complex associated with psychophysiological insomnia is not really a sleep disorder but rather an arousal disorder. Finally, the importance of physiological arousal as the harbinger of insomnia has been enhanced by the finding that normal adults with no reported sleep disorder who were found to have EEG-defined situational insomnia also had elevated heart rate and cardiac spectral activity – an indication of predisposition to the later development of insomnia. In total, such studies show the primary importance of physiological activation as the harbinger of both the poor sleep and subjective dysphoria that characterize primary insomnia.

Keywords: Insomnia, Physiology, Metabolic rate, Heart rate, Sympathetic nervous system

Introduction

Patients with insomnia often have symptoms that include tension, anxiety, depression, fatigue, and irritability [1–4]. Frequently insomnia begins in conjunction with a significant stress [5]. As a result, many investigators

From: *Clinical Handbook of Insomnia,* Current Clinical Neurology
Edited by: H.P. Attarian and C. Schuman, DOI 10.1007/978-1-60327-042-7_3,

have hypothesized that insomnia is the result of internalization of emotions producing emotional arousal. Others have hypothesized that insomnia can develop entirely from physiological activation, as in phase shift insomnia or in individuals predisposed to physiological activation. More recently, it has become evident that insomnia often begins in individuals with a physiological disposition who experience stress. This chapter will examine evidence for physiological activation in patients with primary insomnia and describe research that implicates physiological activation as a key in the production of situational insomnia and as a possible cause of anxiety and subjective malaise that underlie the insomnia complaint.

Historical (Prior to 1990) Literature

Following the development of modern recording methods, many studies reported comparisons of poor sleepers or insomnia patients with controls on a range of physiological measures. Monroe [6] reported increased rectal temperature, heart rate, basal skin resistance, and phasic vasoconstrictions 30 min prior to and during sleep in poor sleepers as compared with normal sleepers. Other studies have shown that patients with sleep-onset insomnia had increased frontalis [7] and mentalis EMG [8, 9], increased heart rate [10], increased finger temperature, and more beta and less alpha frequencies in the EEG [8, 9]. However, significantly elevated body temperature was not reported in all studies of poor sleepers [11, 12]. Poor sleepers had increased secretion of corticosteroids and adrenaline [11, 13] compared with good sleepers in most but not all studies [14]. The inconsistent results in some of these studies was taken to indicate that either physiological activation was not a major factor in all patients [15] or that wide variability and small sample sizes may have made it difficult to show clear physiological differences. The lack of control of daytime activity in the studies might also have obscured differences. Finally, it was also possible that the involved physiological system(s) differed from patient to patient and more global measures, such as whole-body oxygen use, heart rate variability, or brain metabolic activity in arousal areas, would more consistently show differences.

Other research examined daytime function in insomnia patients to verify their subjectively reported deficits in performance, mood, and alertness. The cumulative partial sleep deprivation assumed to occur in chronic insomnia should have produced daytime sleepiness or increased susceptibility to acute sleep loss in insomnia patients. However, studies consistently found that these patients were not sleepier than normal controls on Multiple Sleep Latency Tests (MSLT) [12, 16, 17] or after sleep loss [18] and actually had longer MSLT latencies [19, 20]. Studies did find that insomnia patients made more errors on a line tracing task [21], produced fewer responses in a word category test [12], and performed worse on the Romberg (balance) test [22]. However, these results may also be viewed as demonstrating that patients have poor performance on tests where too much arousal reduces steadiness or blocks higher order associates. Studies comparing daytime performance in insomnia patients to normal controls generally did not find differences on tests that are sensitive to sleep loss [17, 22]. On the basis of these results and patient reports that they were fatigued or "washed out" during the day, it was hypothesized that standard sleep and sleep loss tests were confounded in that they "simultaneously

measure sleep need and hyperarousal, which is interfering with sleep onset" ([19], p. 59). This concept is supported by studies [17, 19, 21] reporting significant negative correlations between total sleep at night and MSLT values on the next day.

With this background in mind, we planned a series of experiments to try to define more general measures of physiological activity in patients with psychophysiological insomnia and to try to differentiate causal factors in the production of both poor nocturnal sleep and compromised daytime function. This chapter will review our work to define metabolic and cardiac changes in insomnia patients and the relationship of such physiological changes to poor sleep and the report of insomnia. The chapter will also provide an update of current findings of physiological activation in patients with primary insomnia.

Metabolic and Cardiac Change in Insomnia Patients Compared with Normal Controls

Several studies were performed to compare sleep and physiological measures in patients with psychophysiological insomnia and paradoxical insomnia (sleep state misperception) with matched normal sleepers. It was hypothesized that both patients with psychophysiological insomnia and paradoxical insomnia would differ from controls by having increased physiological activation independent of their sleep stage parameters. The same general screening criteria were used for all of the studies. Subjects (Ss) were required to be healthy, 18–50-year-old males and females.

Insomnia subjects: Individuals who indicated that they had a sleep problem, and that it took them 45 min or more to fall asleep at least four nights each week or that they were awake for 60 min or more each night after falling asleep for at least four nights each week for at least 1 year were considered. Insomnia patients were also required to have EEG sleep latencies greater than 30 min on two consecutive lab nights or to have a sleep efficiency of less than 85% on both nights.

Paradoxical Insomnia Patients

Patients with a complaint of insomnia who demonstrated normal sleep (sleep latency <30 min and sleep efficiency >90%) despite their claim of insomnia, overestimated their sleep latency by at least 100% on both sleep laboratory nights, and had sleep latency estimates of 20 min or more on both nights were considered.

Normal controls: Ss with reported normal sleep were selected to match a qualified insomnia patient by sex, age (within 5 years), weight (within 25 pounds), and general time in bed characteristics. Ss were also required to have EEG sleep latencies of less than 30 min on two consecutive laboratory nights and to have a sleep efficiency greater than 90% on both nights.

Exclusions: Potential subjects who indicated excessive caffeine consumption (more than 250 mg of caffeine per day), who were using psychoactive medication or drugs, or who had completed a drug or alcohol abuse program within the previous year were excluded. Ss with a history of depression or psychiatric hospitalization were excluded. Potential Ss who had histories strongly suggestive of circadian desynchrony (e.g., shift workers), sleep apnea, or periodic leg movements were excluded. Subjects with an apnea/hypopnea index greater than 10 or a periodic leg movement arousal index greater than 10 were disqualified.

Design: Subjects spent two nights and the intervening day in the laboratory. On both nights, a standard clinical polysomnogram was performed. On the second night, metabolic measures including were recorded.

On the day spent at the laboratory, Ss had a 20-min metabolic observation after awakening, performed computer tests, took an MSLT test followed by 20-min resting metabolic observations, and completed an MMPI and a sleep history. They were fed the same daily menu of food prepared at the laboratory. Caffeinated beverages were not available.

Metabolic Rate in Psychophysiological Insomnia

Groups of ten patients with psychophysiological insomnia and matched normal sleepers who did not differ in age, weight, or time usually spent in bed per night were identified [23]. As expected by selection criteria, insomnia patients had significantly longer objective sleep latencies (20.5 min vs. 12.5 min) and shorter total sleep per night (342 min vs. 442 min) compared with the matched controls.

Metabolic data: The initial analysis was based on mean data for each minute across the night. Each subject was compared with his/her matched control minute by minute across the night by *t*-test. The *t*-values from each of the ten subject pairs were in the same direction and 9 of 10 were statistically significant ($p < 0.01$). The average *t*-value was 13.10 ($p < 0.0001$). The respective means for for insomnia patients and normals were: 296 and 266 ml/min. In a second set of ten *t*-tests with data associated with awakenings, movements, and arousals eliminated, 8 of 10 were statistically significant ($p < 0.02$), and the average *t*-value was 13.38 ($p < 0.0001$). The overall mean sleep metabolic rates for the insomnia and normal groups respectively were: 280 and 256 ml/min. When only slow wave sleep was examined, only the eight pairs of subjects who all had SWS were included. In the set of eight *t*-tests comparing metabolic values from slow wave sleep observations between matched insomnia patients and normals, 5 of 8 were statistically significant, and the average *t*-value was 5.57 ($p < 0.0001$). The overall mean sleep metabolic rates for the insomnia and normal groups respectively were: 266 and 250 ml/min. It was concluded that whole-body metabolic rate was significantly increased in the insomnia patients when all data points were compared, when epochs with sleep disturbance were eliminated, and even when only SWS was examined.

Paradoxical Insomnia

Groups of nine patients with paradoxical insomnia and matched normal sleepers who did not differ in age, weight, or time usually spent in bed per night were identified [24]. As expected by subjective historical report of sleep, patients with paradoxical insomnia reported significantly longer sleep latencies (98 min vs. 18 min) and shorter total sleep per night (5.3 h vs. 7.4 h).

In the sleep laboratory, the paradoxical insomnia patients estimated that their sleep latency was significantly longer than the normals (52 min vs. 24 min), that their sleep time during the night was significantly shorter than the normals (6.8 h vs. 7.5 h), and that their sleep quality was significantly worse than the normals. However, the paradoxical insomnia patients did not differ significantly from the normals on any EEG sleep variable. In fact, total sleep time was nonsignificantly longer in the patients as compared with the normal sleepers.

Metabolic data: The mean for each of the eight waking metabolic measurements and the mean for each hour during the sleep period were entered into a repeated measures ANOVA with terms for the matched subjects (1 df) and time (15 df). The time by group interaction was not significant, but the main effect for group was significant ($F_{1,143}=45.22$, $p<0.001$). The means for the insomnia and control groups were respectively 304 ml/min (s.d. 26) and 286 ml/min (s.d. 34). These data indicated that patients with a complaint of insomnia had elevated metabolic rate despite the fact that their EEG sleep parameters did not differ from the controls.

Heart Rate and Heart Rate Variability

Groups of 12 patients with psychophysiological insomnia and matched normal sleepers who did not differ in age, weight, or time usually spent in bed per night were identified [25]. As expected by selection criteria, insomnia patients had significantly longer sleep latencies (16.4 min vs. 6.6 min) and shorter total sleep per night (382 min vs. 445 min) compared with normal sleepers.

Heart Rate Data

Nocturnal heart data were examined in both groups by dividing each night into 5-min blocks based upon sleep stage and calculating means across sleep stages [25]. No significant interaction was found between group and sleep stage for beat to beat interval. There was a significant main effect for Group for both beat to beat interval ($F_{1,44}=44.67$, $p<0.001$) and the standard deviation ($F_{1,44}=56.16$, $p<0.001$). The intervals were significantly longer (i.e., heart rate was lower) and the variability was greater in the normal Ss as compared with the insomnia patients. Heart rate during wake, stage 2 and REM was respectively 61, 58, and 59 BPM in controls and 68, 64, and 68 BPM in the insomnia patients. Several previous studies have shown increased heart rate in insomnia patients as compared with controls during the night. Monroe [6] reported a nonsignificant 3.9 BPM increase in insomnia patients, Stepanski [26] reported a significant 4.4 BPM increase in insomnia patients, Haynes [10] reported a significant 4.6 BPM increase, and Varkevisser [27] reported a nonsignificant 4.1 BPM increase in insomnia patients compared with normal sleepers. These reported differences agree well with the data from the present groups where the overall mean difference in heart period translated to a heart rate difference of 6.9 BPM.

Spectral Analysis Data

The same 5-min blocks of digitized heart data were analyzed by spectral analysis to provide estimates of low-frequency and high-frequency spectral power. These data were used to construct low-frequency power (LFP) and high-frequency power (HFP) ratios that are respectively associated with sympathetic and parasympathetic nervous system activity [25]. The interaction F-value for Group by Stage was not significant for either LFP or HFP ratios. There was a significant main effect for Group for both LFP ($F_{1,32}=12.93$, $p<0.001$) and HFP ($F_{1,44}=12.21$, $p<0.001$). These results indicated that LFP was increased and HFP was decreased in insomnia patients as compared with normals across all sleep stages.

These metabolic and heart rate data replicated previous studies indicating elevated levels of physiological arousal in patients with insomnia. The finding of elevated , elevated heart rate, and altered heart rate variability within sleep stages strengthened the case that the elevated levels of arousal were not simply a by-product of poor sleep. Finally, elevated metabolic rate in paradoxical insomnia patients showed that these patients truly do have an objective, physiological problem as the basis of their complaint in spite of the fact that their sleep stage distributions were normal. These physiological findings were supported by spectral analysis of EEG in patients with sleep state misperception [28] that showed increased higher frequency EEG in these patients. Such physiological findings support underlying hyperarousal as a causal mechanism in the sleep complaints presented. The findings of significant changes in heart rate variability in insomnia patients also are consistent with elevated sympathetic nervous system activity and decreased parasympathetic nervous system activity.

Implications of These Physiological Arousal Data

As an entity, insomnia is rarely viewed as a significant medical problem. However, if insomnia is associated with chronic sympathetic hyperactivity, long-term consequences of the sympathetic activation associated with the insomnia may exist. Many risk factors for coronary heart disease are related to increased sympathetic activity. For example, hypertension; elevated plasma insulin [29] and its related decrease in HDL cholesterol; increase in triglyceride and cholesterol [30]; increased hematocrit [31]; decreased plasma volume [32]; increased plasma thromboglobulin [33]; increased plasma angiotensin [34]; and increased cardiac arrhythmias [35, 36] are all signs of increased sympathetic and decreased parasympathetic tone that could also be associated with the physiological activation of chronic insomnia.

In recent years, many studies have examined the relationship between poor sleep and hypertension and other cardiac events [37]. For example, in one study of 8,000 Japanese male middle-age telecommunication workers, individuals with sleep onset or sleep maintenance insomnia and normal sleepers were followed [38]. Four years later, it was found that 40% of the workers who were identified as having sleep-onset insomnia at the first time point and 42% of the workers who were initially identified as having difficulty staying asleep had developed hypertension while 31% of workers without a sleep problem at the initial time point had developed hypertension (both significant). After adjusting for age, BMI, smoking, alcohol consumption, and job stress, difficulty maintaining sleep was associated with increased hypertension with an odds ratio of 1.88 (95% CI: 1.45–2.45). The authors [38] speculated that this increase in hypertension might be related to activation of the hypothalamic-pituitary-adrenal axis [39, 40].

In a 1999 review, Schwartz [41] performed a meta-analysis of ten studies that had examined links between insomnia and cardiovascular disease and reported a combined risk ratio of 1.92 (95% CI = 1.62–2.31). At least four additional studies have been reported since that 1999 review and have continued to show significant links between various definitions of insomnia and general cardiac outcomes [37]. Odds or risk ratios for these studies for the relationship between general insomnia variables and heart disease outcomes ranged from 1.21 to 3.1 [37]. In one study of note, Taylor et al. [42] used sleep logs to carefully refine the insomnia diagnosis and several additional

questions were asked about snoring, sleep associated breathing problems, and limb movements or restlessness to adjust for other sleep disorders. Despite adjustment for sleep disorders in addition to depression and anxiety, the odds ratio for the association of insomnia with both heart disease and high blood pressure was still significant (2.27; CI: 1.13–4.56 and 3.18; CI: 1.90–5.32, respectively).

This literature is criticized because it is possible that there is a coincidental relationship between insomnia and cardiovascular disease through the relationship of insomnia to sleep apnea (and links of apnea to cardiac disease) [43]. However, the possibility of this association is greatly reduced by the fact that many studies have shown a relationship between difficulty falling asleep, not a correlate of sleep apnea, and cardiovascular outcomes. In addition, many of the studies linking insomnia with cardiovascular outcomes have statistically controlled for BMI, snoring, breathing disorders during sleep and restlessness to eliminate sleep apnea as an underlying correlate.

The Effects of Physiological Activation

In addition to poor sleep, it has been established that many patients with insomnia will (a) report daytime fatigue or dysphoria; (b) have normal or longer than normal MSLT values; (c) report increased stress; (d) have abnormal Minnesota Multiphasic Personality Inventory (MMPI) values; and (e) subjectively misperceive their sleep process. These findings are summarized in Table 3.1 (left column).

Because insomnia patients typically display both mood alteration and evidence of physiological activation, differentiation of cognitive vs. physiological pathology as the primary causal factor has been difficult. Production of consistent and long-lasting mood changes in normal individuals to test the effect of mood change on sleep and daytime function presents ethical problems. However, it is possible to produce a state of chronic physiological activation and to follow these hyperaroused normals for the development of both nocturnal and daytime symptoms of insomnia.

In a study that examined the impact of this physiological activation [44], caffeine 400 mg TID was given to 12 normal young adult sleepers for a week as a means of increasing physiological arousal, and standard insomnia outcome variables were measured. As expected, the chronic use of caffeine significantly increased whole-body metabolic rate, which was used as the objective measure of arousal level, and sleep efficiency was found to decline significantly.

It is well known that caffeine can produce poor sleep. However, the major question in this study was whether caffeine would also produce the other secondary effects seen in chronic psychophysiological insomnia.

Responses from the Profile of Mood States (POMS) suggested increasing dysphoria as caffeine administration progressed (see Table 3.1 center column for a summary of caffeine effects). Significant main effects for condition were found for all six POMS scales. Initial caffeine administration produced an immediate significant increase in Vigor and Tension (anxiety) followed by a decrease as caffeine administration continued (significant for Vigor). Fatigue was significantly increased at the end of caffeine administration compared with placebo. These results were of considerable interest because they showed that the chronic daytime dysphoria and fatigue reported by insomnia patients could be paradoxically produced by unrelenting physiological arousal.

Table 3.1 Variables that differentiate insomnia patients vs. normal sleepers given caffeine 400 mg TID or the sleep on an insomnia patient.

	True	Hyperaroused	"Yoke" insomnia situational	
	Insomnia	Normals	Normals	Insomnia
MSLT	Increased	Increased[a]	Decreased[b]	Increased[c]
Metabolic rate/ heart rate	Increased	Increased[a]	Increase PM[b]; Decrease AM	Increased[c]
Body Temperature	Increased	Increased	Decreased[b]	No measure
Mood (tension, confusion)	Increased	Increased[a]	Decreased[b]	No change
Vigor	Decreased	Decreased[a]	Decreased[b]	No change
Personality Disturbance	Increased	Increased MMPI PT[a]	No change	No change
Subjective sleep Latency/wake	Overestimated	Mild overestimation	No change	No change

Data from normal sleepers who had situational insomnia are also reported.
[a]Significant differences reported in [44].
[b]Significant differences reported in [45].
[c]Significant differences reported in [54].

The MSLT data revealed that sleep latencies were significantly increased throughout caffeine administration as compared with baseline and withdrawal, which did not differ. The mean latency after early caffeine use was significantly longer than the latency after chronic caffeine use. Respective means for baseline, early caffeine, late caffeine, and withdrawal were 10.7, 17.9, 13.4, and 11.3 min. Again, these increased sleep latencies were similar to those seen in insomnia patients compared with normals.

The MMPI is a nontransparent measure of relatively stable personality characteristics. It was administered before caffeine use and at the end of the caffeine administration primarily because it had been used as a measure in many previous insomnia studies. At baseline, as expected, all of the MMPI values were characteristic of normal young adults. However, after a week of caffeine administration, there was movement toward increased pathology on all the clinical scales except MF, and the change was statistically significant for the PT (anxiety) scale. These findings were also surprising because they indicated that even stable aspects of personality could shift significantly toward pathology in a short period secondary to a relatively simple physiological manipulation.

As can be seen from Table 3.1, Ss given caffeine had significant changes in the direction of chronic insomnia patients on MSLT, metabolic rate, negative moods, and personality. The data indicate that chronic hyperarousal with no predisposing psychological component can produce the typical pattern of poor sleep, mood change, and personality change commonly seen in patients with psychophysiologic insomnia. However, it could not be determined from this data if the mood and personality symptoms were produced by the hyperarousal or secondarily from the poor sleep that was also produced.

The Effects of Poor Sleep

It has been implied that increased physiological arousal, possibly even as an innate phenomenon, produces an environment in which an individual is prone to report insomnia. Many insomnia patients, however, feel that their sleep is the central problem and that the poor sleep leads to their symptoms of fatigue and dysphoria. To test whether the insomnia sleep pattern by itself could produce hyperarousal and the other symptoms of primary insomnia, the poor sleep found in insomnia patients was produced for a week in normal young adults, and subjects were followed for the development of insomnia symptoms [45]. Primary insomnia patients were identified by the standard sleep criteria mentioned earlier, and the sleep parameters of those patients were used in a yoke-control fashion to produce comparable sleep in a group of matched normal sleepers. It was hypothesized that if the yoked normal sleepers developed the spectrum of secondary symptoms seen in the "true" insomnia patients after sleeping like the patients, then those symptoms could be seen as secondary to the poor sleep. On the other hand, if the yoked normal sleepers did not develop the symptoms seen in the "true" insomnia patients, then some factor other than poor sleep itself would be responsible for those secondary symptoms.

In this study, the EEG sleep characteristics of primary insomnia patients were reproduced in matched normal sleepers for a week. Sleep patterns were matched by making experimental arousals and awakenings throughout the night in normal sleepers to match the pattern of wake time and arousals seen in the patients with insomnia. Since the EEG sleep produced in the study was similar to that found in patients reporting insomnia, changes in the outcome variables should have reflected the consequences of pure "poor" sleep. Table 3.1 provides a summary of typical findings in patients with insomnia and compares those findings with the results of this yoke-control study (right column). Changes secondary to the poor sleep produced in the yoke-control study were clearly different from the symptoms most frequently reported by insomnia patients. Insomnia patients typically have difficulty falling asleep both at night and during the MSLT [19–21, 23]. However, both sleep latency and MSLT data from the yoke-control study supported significantly increasing ease of falling asleep as the nights of insomnia increased. Insomnia patients frequently have elevated body temperature and whole-body metabolic rate [6, 13, 23]. Except for an increase in nocturnal metabolic rate probably associated with the experimental sleep disturbance itself [46], the trends in the yoke-control study showed lower metabolic rate and decreased body temperature during the day (both of these are increased in insomnia patients). Insomnia patients typically report increased stress, anxiety, or depression [1, 23]. However, in the yoke-control study, the state measures of tension and depression decreased significantly during the study. Insomnia patients typically have elevated MMPI scales, but the MMPI measures were unchanged in this study. Insomnia patients report increased fatigue and decreased vigor, and similar changes were found in the yoke-control study. However, these changes are also found during simple sleep deprivation. Finally, insomnia patients overestimate their time spent awake during the night. Despite increased awakenings and wake time in the yoke-control study, the normal sleepers continued to estimate their wake time during the night correctly.

The most parsimonious explanation for the results was that the insomnia sleep pattern resulted only in partial sleep deprivation when imposed upon

normal sleepers. This interpretation is supported by rebounds of REM and SWS during the recovery night after the seven nights of yoke-insomnia along with decreasing MSLT values. These changes are classic signs of sleep loss. Decreases in vigor and body temperature also suggested simple sleep loss. Since total sleep time in the study was reduced to 6 h for a week, this could easily have resulted in partial sleep deprivation. For example, a study by Rosenthal et al. [47] has shown increased sleepiness on the MSLT after just one night of 5.6 h of sleep.

The data from this study showing that normal sleepers with the insomnia sleep pattern became more sleepy suggest that some patients with insomnia may suffer from mild partial sleep deprivation. As in normal subjects, however, the degree of deficit should be related to the amount of sleep lost and should typically recover after an occasional night of improved sleep. In fact, one could hypothesize that poor sleep in response to hyperarousal is an adaptive response that acts as a homeostatic mechanism to cause partial sleep deprivation and reduce the impact of hyperarousal. Unfortunately, in patients with chronic insomnia, a night of relatively good sleep would remove a portion of the chronic partial sleep deprivation and leave the patient more susceptible to the effect of hyperarousal on the next day. This situation leaves patients in the uncomfortable situation of either suffering from hyperarousal or from hyperarousal masked by sleep deprivation.

If the poor sleep of insomnia patients produces only mild sleep loss in matched normal sleepers, how does one explain the consistent secondary symptoms reported by insomnia patients? As can be seen from Table 3.1, the secondary symptoms of insomnia patients appear in normal sleepers who are hyperaroused [44] but not in normal sleepers actually given the poor sleep experienced by patients with insomnia. The major implication of such data is that it is the increased arousal and not the poor sleep per se that is responsible for the symptoms. Another possibility is that the development of these insomnia symptoms in patients is actually dependent upon poor sleep interacting with personality variables in the insomnia patient. If this is the case, then one would expect that insomnia patients having particularly poor nights of sleep would experience an exacerbation of their insomnia symptoms.

Poor Sleep in Insomnia Patients

In the next study [48], it was hypothesized that, if nocturnal sleep parameters produced the daytime dysphoria reported by patients with insomnia, then sleep maintenance insomnia patients who were kept awake even longer than usual during the night should have increased dysphoria during the following day. To test this hypothesis, patients with sleep maintenance insomnia were allowed only 80% of their already reduced total sleep each night for seven consecutive nights. This sleep reduction was accomplished by waking patients up at the end of each quarter of the night if they accumulated more than 80% of their baseline sleep for that quarter of the night (while holding time in bed for the entire night at the baseline level). This paradigm produced very poor sleep (average total sleep of 4.2 h on each night for the week).

This reduction of total sleep time by experimental awakenings resulted in a significant decrease in daytime MSLT values in these insomnia patients. After seven nights of 4.2 h of sleep, MSLT values had decreased from 15.6 to 11.1 min.

While this reduction was statistically significant, the 11.1-min value is still within the normal range for the MSLT. In a study where total sleep was reduced to 5 h per night in normal young adults [49], MSLT was reduced to 41% of baseline compared with a reduction to 71% of baseline in our insomnia patients. These results indicated that when the sleep of insomnia patients was experimentally reduced, they displayed some increased sleepiness during the day in agreement with the expectancy in normals but not a further increase in latency that would be expected from insomnia becoming more severe (i.e., being associated with greater sleep loss). Despite the large reduction in total sleep, the insomnia patients did not become pathologically sleepy on the MSLT, and this probably indicated the degree to which their hyperarousal was successful in masking their sleep tendency. Of equal interest, patients did not report significant decreases in their sleep quality or show changes in their personality or physiological parameters consistent with more severe insomnia when their wake time during the night was increased by 2 h. One conclusion from such data is that the reports of poor sleep quality and daytime dysphoria from insomnia patients are not directly related to their EEG sleep at all but rather to their level of arousal [50]. In support of these results, Chambers and Kim [51] reported a significant negative correlation between state anxiety at bedtime and reports of feeling rested the next day in insomnia patients despite the fact that neither anxiety nor reports of feeling rested were significantly correlated with sleep values.

Level of Arousal and the Perception of Sleep

Insomnia patients commonly overestimate how long it takes to fall asleep at night and underestimate their total sleep time. Is such misperception related to personality or to underlying physiology? We decided to look at several physiological manipulations to determine if they produced changes in the perception of sleep onset [52] independent of an insomnia complaint. Insomnia patients subjectively estimate that it takes much longer for them to fall asleep than EEG measures indicate [53]. One means of examining this phenomenon is to divide the subjective estimate of sleep latency by the EEG estimate to derive a unitless indicator of degree of estimation difference. For example, sleep deprivation or the use of benzodiazepines decreases the level of arousal and was hypothesized to decrease this subjective to objective ratio of sleep latencies. Conversely, administration of caffeine, which increases arousal level, or sleep during the daytime, when level of arousal is higher, should increase the ratio. Specifically, results from several studies [52] indicated that the ratio of subjective to objective sleep latency decreased when subjects were given triazolam or diazepam to decrease level of arousal, and the decreases tended to be dose related. Similarly, the ratio of subjective to objective sleep latency decreased during sleep deprivation, and, again, the decreases were related to the amount of sleep lost. In two tests of increased arousal, the ratios of subjective to objective sleep latencies increased after an initial night of caffeine consumption and were greater during sleep periods that began midday than in sleep periods that began later in the evening. These data support the contention that the perception of falling asleep is related to the level of physiological arousal at sleep onset. The consistency of the findings with six different experimental manipulations supports the argument that estimates of sleep latency may also be dependent upon level of physiological arousal.

These data support the idea that subjectively reported poor sleep or insomnia is a physiological phenomenon that can be controlled by varying the level of arousal. The point is that poor sleep, whether it is acute or chronic, is a physiologic (as opposed to a psychological) event that is amenable to physiologic exploration and modification.

The Development of Insomnia

It is well known that the incidence of insomnia increases with age. This increase could be associated with increasing sympathetic nervous system dominance that is also associated with age, or the increased insomnia could be associated with cognitive or behavioral changes. Unfortunately, very little empirical work has examined how insomnia starts or develops. One theory holds that individuals placed in a situation of temporary stress develop poor sleep hygiene or inappropriate conditioned responses to their sleep environment. Then, the poor hygiene or inappropriate responses continue to produce poor sleep after the period of stress passes.

If this is true, one way to understand the development of insomnia would be to take normal young adults, expose them to a temporary stress, and evaluate the insomnia produced.

We have specifically followed this methodology in a recent study where 50 normal sleepers were exposed to a series of stressful experiences including first night in a sleep laboratory, 3-h phase advance of sleep time, 6-h advance of sleep time, and sleep following administration of caffeine 400 mg 30 min prior to bedtime [54].

It was found that there was both wide variability and remarkable consistency in the responses. The variability was in the between subject response to the situational stress – some Ss continued to have nearly normal nights of sleep even after a 6-h phase advance of bedtime or caffeine while other Ss had poor sleep following all of the stresses. A large number of Ss participated in this study so that it was possible to form "extreme" groups – in this case the 25% of the population that slept best on the first night in the laboratory ("super" sleepers) and the 25% who had the worst sleep on that night (situational insomnia). Significant correlations were found between sleep efficiency on the first night and on the other stress nights in the complete data set and also by comparing sleep values in the extreme groups.

Subjects who had poor sleep on their laboratory adaptation night (and were therefore called the "Situational Insomnia" or SI group) also had increased MSLT latencies on the day that followed. They had normal sleep on the baseline night that followed but then had significantly worse sleep on the phase advance nights and after caffeine administration. Their sleep was so bad after the 6-h phase advance (about 4.5 h compared with about 7 h in the super sleepers) that their MSLT was significantly reduced on the day that followed. The SI group also had very poor sleep after caffeine administration but surprisingly, their MSLT after caffeine administration was significantly increased. The super sleep group did not have any significant changes in their MSLT throughout the study. The implication is that the SI group was both more sensitive to all of the stresses in terms of the production of poor sleep and was also more sensitive to the arousing effect of caffeine.

This study also examined other differences between the SI and good sleeping groups (see Table 3.1, far right column). No significant differences were found on the MMPI or mood measures. Whole-body metabolic rate was nonsignificantly increased in the SI group. The SI group was found to have increased heart rate, increased low-frequency EKG spectral power, and decreased high-frequency EKG spectral power compared with the good sleepers. These physiological findings in "pre-insomnia" patients suggest that their existing hyper-reactivity to sleep-related stress and caffeine could be secondary to elevated sympathetic nervous system activity and that this could be a marker for the development of chronic insomnia at a later date. The finding of elevated physiological activity prior to mood change, personality change, or complaint of chronic insomnia provides another clue that underlying physiology could be the key to the later development of additional insomnia symptoms.

Recent Studies of Physiological Activation in Insomnia

Studies of physiological activation in insomnia were reviewed recently [55]. In studies published since 1990, numerous physiological variables have been assessed in patients. Elevated heart rate has been reported in three of four studies [25–27, 54]; cortisol was elevated in all four studies [39, 40, 56, 57], and EEG beta activity was elevated in three of four studies [58–61]. Some other physiological findings of note have included reports of increased corticotropin [39] and norepinephrine [62]; decreased melatonin [57, 63]; and decreased natural killer cell activity [62].

Some of the most interesting physiological findings in recent years have included the observation that patients with insomnia have specific changes in brain metabolism that are consistent with their insomnia complaint. A study using positron emission tomography (PET) showed that insomnia patients had higher glucose metabolism during sleep and wakefulness. Of equal importance, insomnia patients had a smaller decrease in glucose metabolism compared with controls in arousal areas of the brain during NREM sleep [64]. The same authors have reported more recently that both subjective and objective wake time during sleep are significantly correlated with brain glucose metabolism in several pontine and thalamocortical areas [65]. A new study, using brain MRI images from patients with insomnia and controls, has reported that insomnia patients have significant bilateral reductions in hippocampal volumes [66]. Similar changes have previously been described in patients with several psychiatric disorders including depression and post-traumatic stress. At the observational level, of course, it is not known if these changes are a consequence of poor sleep or are related to chronic physiological activation. However, it is known that reduced volume in the hippocampus is also related to increased cortisol production [67], and this suggests an underlying physiological mechanism.

Discussion

It is generally accepted that there are changes in several physiological systems in association with psychophysiological insomnia. Current research has attempted to refine our understanding of the relationship between physiological

arousal, poor EEG sleep, psychological status, and subjective report of insomnia. The finding that experimentally produced chronic physiological arousal in normal young adults produces the mood and personality changes seen in insomnia patients provides a compelling description of how chronic insomnia could develop in physiologically susceptible individuals. The studies showing that the poor sleep of insomnia patients by itself does not produce the arousal, mood, and personality characteristics of patients and that the production of much worse EEG sleep in insomnia patients does not magnify symptoms lead to the conclusions that (1) the symptoms produced by chronic physiological arousal were not mediated by the poor sleep that was produced and (2) the symptom complex that was associated with psychophysiological insomnia is not really a sleep disorder but rather an arousal disorder. Finally, the importance of physiological arousal as the harbinger of insomnia was enhanced by the finding of elevated heart rate and cardiac spectral activity in normal subjects with no sleep complaint who were found to have EEG-defined situational insomnia. These several approaches to the question of insomnia identify tangible physiopathology that should be open to identification and amenable to treatment.

We have recognized for many years that some patients have lifelong problems with excessive sleepiness secondary to disorders such as narcolepsy or idiopathic hypersomnolence. The extent to which these disorders demonstrate a failure of the sleep system vs. a failure of the arousal system can be debated. Certainly, these disorders are commonly treated with medications that have direct impact by increasing CNS arousal. Recognition that another group of patients suffer from the opposite lifelong problem (hyposomnolence or hyperarousal) has been more difficult. At this point, much work has identified the physiological markers of chronic hyperarousal in patients. Behavioral relaxation techniques can provide help for some patients with situational hyperarousal, but just as behavioral techniques like sleep extension fail in many patients with idiopathic hypersomnolence, behavioral techniques may also fail in patients suffering from chronic hyperarousal. Identifying abnormal arousal as a major component of both hypersomnolence and insomnia can help direct research toward more effective pharmacological control of the underlying physiologic arousal disorder.

Acknowledgment. Supported by the Dayton Department of Veterans Affairs Medical Center, Wright State University School of Medicine, and the Sleep-Wake Disorders Research Institute.

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4

Differential Diagnosis of Insomnia

Michael Saletu and Bernd Saletu

Abstract

Insomnia is both a symptom and a clinical entity in itself. There are three well-defined insomnia conditions that are often referred to as primary insomnias. In addition, there are a number of medical, psychiatric, and social factors that can lead to comorbid insomnia.

While formulating a differential diagnosis one must think of the mental and medical conditions the person with insomnia has, in addition to medications they may be taking, social environment, habits, exposure to toxins, and other sleep disorders.

Keywords: Psychophysiological insomnia, Sleep hygiene, Paradoxical insomnia, Insomnia due to mental and medical conditions, Insomnia due to drug or substance use

Definition

Insomnia is defined as a complaint of difficulty initiating sleep, difficulty maintaining sleep, waking up too early, or sleep that is chronically nonrestorative or poor in quality [1]. Depending on the definition (i.e., insomnia symptoms, with or without daytime consequences, dissatisfaction with sleep), prevalence rates have varied extensively from as low as 5% to as high as 50% [2].

Classification of Insomnia

Currently, the three most widely used insomnia classification schemes are those included in the *International Classification of Sleep Disorders* (ICSD-2) [1], the fourth edition of the American Psychiatric Association's *Diagnostic and Statistical Manual* (DSM-IV) [3], and the World Health Organization's *International Classification of Diseases* (ICD-10) [4]. The original ICSD included over 40 diagnostic categories that could be applied to insomnia sufferers.

From: *Clinical Handbook of Insomnia,* Current Clinical Neurology
Edited by: H.P. Attarian and C. Schuman, DOI 10.1007/978-1-60327-042-7_4,

This number has been slightly reduced in the ICSD-2 system, but this nosology continues to provide a high degree of specificity in the subtyping of insomnia disorders. It is this classification system that will be referred to throughout this article. In contrast, the DSM-IV and ICD nosologies include substantially fewer and more global diagnostic categories for insomnia. The first versions of the ICSD and the DSM-IV systems list insomnias that are primarily sleep/wake disturbances or dyssomnias along with the so-called secondary or comorbid insomnias that arise as a function of psychiatric conditions, medical diseases, or substance abuse. In contrast, the ICD-10 system provides a limited number of disorders of sleep of nonorganic origin and sleep disturbances with a presumed organic basis, whereby the specific sleep disorder is listed along with as many pertinent diagnoses as necessary to adequately describe the psychopathology or pathophysiology involved in a given case. The ICSD-2 includes insomnia disorders as one of six major categories of sleep disorders. Both the "primary" and the "comorbid" forms of insomnia are listed in this section.

Types of Insomnia

Adjustment Insomnia (Acute Insomnia)

Alternate Names
Acute insomnia, transient insomnia, short-term insomnia, stress-related insomnia, transient psychophysiological insomnia, adjustment disorder.

Essential Criteria [1]
The sleep disturbance is temporally associated with an identifiable stressor that is psychological, psychosocial, interpersonal, environmental, or physical in nature and is expected to resolve when the acute stressor resolves or when the individual adapts to the stressor.

Differential Diagnosis
Psychophysiological insomnia, circadian rhythm sleep disorders, sleep disorders due to medical conditions or drug or substance use, mental disorders.

Psychophysiological Insomnia

Alternate Names
Learned insomnia, conditioned insomnia, functionally autonomous insomnia, chronic insomnia, primary insomnia, chronic somatized tension, internal arousal without psychopathology.

Essential Criteria [1]
The patient has evidence of conditioned sleep difficulty for at least 1 month and/or heightened arousal in bed as indicated by one or more of the following:

- Excessive focus on and heightened anxiety about sleep
- Difficulty falling asleep in bed at the desired bedtime or during planned naps, but no difficulty falling asleep during other monotonous activities when not intending to sleep
- Ability to sleep better away from home than at home

- Mental arousal in bed characterized either by intrusive thoughts or a perceived inability to volitionally cease sleep-preventing mental activity
- Heightened somatic tension in bed reflected by a perceived inability to relax the body sufficiently to allow the onset of sleep

Polysomnographic and Other Objective Findings

Sleep monitoring may show increased sleep latency or increased wake time after sleep onset coupled with reduced sleep efficiency. Some patients demonstrate altered sleep architecture with an increase in stage 1 sleep and a decrease in slow-wave sleep. Patients with a pronounced conditioned sleep difficulty in the home environment may show a reverse first-night effect in the sleep laboratory. Actigraphy produces overestimates of sleep time and underestimates of wake time, presumably due to a propensity for patients suffering from this condition to remain relatively motionless while awake in bed. Results of heart-rate and metabolic monitoring, respectively, show increased heart-rate variability and metabolic rate across the 24-h day relative to normal sleepers.

Differential Diagnosis

Idiopathic insomnia, paradoxical insomnia, inadequate sleep hygiene, circadian rhythm sleep disorder, delayed sleep-phase type, insomnia due to drug or substance use or insomnia due to mental disorder.

Paradoxical Insomnia

Alternate Names

Sleep state misperception, subjective insomnia, pseudo-insomnia, subjective complaint of sleep initiation and maintenance difficulty without objective findings, insomnia without objective findings, sleep hypochondriasis, subjective sleep complaint.

Essential Criteria [1]

- The patient reports a chronic pattern of little or no sleep most nights with rare nights during which relatively normal amounts of sleep are obtained.
- Sleep-log data during one or more weeks of monitoring show an average sleep time well below published age-adjusted normative values, often with no sleep at all indicated for several nights per week; typically there is an absence of daytime naps following such nights.
- The patient shows a consistent marked mismatch between objective findings from polysomnography or actigraphy and subjective sleep estimates derived either from self-report or a sleep diary.
- The patient reports constant or near-constant awareness of environmental stimuli and thoughts or rumination throughout most nights.
- The daytime impairment reported is consistent with that reported by other insomnia subtypes, but it is much less severe than expected given the extreme level of sleep deprivation reported; there is no report of intrusive daytime sleep episodes, disorientation, or serious mishaps due to marked loss of alertness or vigilance, even following reportedly sleepless nights.

Differential Diagnosis

Psychophysiological insomnia, idiopathic insomnia, mental disorders.

Idiopathic Insomnia

Alternate Names
Childhood-onset insomnia, life-long insomnia, insomnia first evident during infancy or childhood.

Essential Criteria [1]
The course of the disorder is chronic, as indicated by:

- Onset during infancy or childhood
- No identifiable precipitant or cause
- Persistent course with no periods of sustained remission.

Polysomnographic and Other Objective Findings
Polysomnography shows sleep-continuity impairments involving prolonged sleep-onset latency, increased time awake after sleep onset, and reduced total sleep time and sleep efficiency. The percentage of time spent in different sleep stages is also altered with increased stage 1 and stage 2 sleep and decreased stages 3 and 4 sleep.

Differential Diagnosis
Behavioral insomnia of childhood, psychophysiological insomnia, paradoxical insomnia, insomnia due to medical condition, insomnia due to mental disorder, short sleepers.

Insomnia Due to Mental Disorder

Alternate Names
Insomnia related to psychopathology, psychiatric insomnia, insomnia due to depression, insomnia due to anxiety disorder.

Essential Criteria [1]
- A mental disorder has been diagnosed according to standard criteria (i.e., formal criteria as provided in the *Diagnostic and Statistical Manual of Mental Disorders*).
- The insomnia is temporally associated with the mental disorder; however, in some cases, the insomnia may appear a few days or weeks before the emergence of the underlying mental disorder.
- The insomnia is more prominent than that typically associated with mental disorders, as indicated by causing marked distress or constituting an independent focus of treatment.

Differential Diagnosis
Psychophysiological insomnia, inadequate sleep hygiene, paradoxical insomnia.

Mood Disorders

In sleep architecture, depressed patients usually exhibit a decrease in deep sleep and an increase in light sleep and REM sleep, particularly in the first half of the night [5, 6]. Shortened REM latency is considered a “psychobiologic marker” for primary depression [7]. Approximately 70% of depressed patients

Table 4.1 Polysomnographic differences between mental disorder patients and controls as well as between drug treatment and placebo.

	Polysomnography – sleep variables								
Mental disorders	**SE %**	**E min**	**M min**	**L min**	**S1 %**	**S2 %**	**S3+4 %**	**SREM %**	**REML min**
Anxiety disorder	–	+	+	+		–	+		
Depression	–	+	+	+			–	+	–
Mania	–	+	+	+			–	0/+	0/–
Schizophrenia	–	+	+			–	–	(–/+)	0/–
Obsessive-compulsive disorder			+				–		0/–
Posttraumatic stress disorder	–	+						–	+
Borderline personality					+		–	+	–/0
Anorexia	–	+	+				–		(–)
Bulimia									
Alcohol – acute use		–	+	+			+/	–/+	
– subacute use	–							–	
– chronic use	–		+	+			–	+	
– abstinence		+	+	+	+	–	–	–	
Opiates – acute use	–						–	–	
Hypnotics – chr. use					–	+	–	–	
Cocaine – acute use	–	+	+	+	+	–	–	–	+
Treatment									
Anxiolytics	+	(–)	–	–		+	(–)		+
Hypnotics	+	–	–	–		+	–/+	–	+
Antidepressants –sedative	+	–	–	–			+	–	+
Antidepressants – nonsedative	–	(+)	+		+			–	+
Neuroleptics – sedative	+	–	–	–	–	–	+	+	
Stimulants	–	+	+	+	+	–	–	–	+

SE sleep efficiency, *E* early insomnia, *M* middle insomnia (W_{TSP}), *L* late insomnia (W_{BB}), *REML* REM latency.

complain of insomnia, 30% of hypersomnia, with the latter seen particularly in bipolar disorder and atypical depressions [8]. Mania is characterized by a diminished total sleep time and other polysomnographic abnormalities (see Table 4.1). Sleep disorders are often ahead of mood disorders (in contrast to anxiety disorders) and may not resolve automatically with treatment of the comorbidity but rather require specific therapeutic attention.

Anxiety Disorders

Polysomnographic abnormalities have been documented in generalized anxiety disorder (GAD), panic disorder, posttraumatic stress disorder (PTSD), and obsessive-compulsive disorder (OCD) [8]. Benca et al. [9] described a decreased total sleep time, a decreased sleep efficiency index, and increased sleep latency as typical of insomnia in GAD, while findings were rather variable concerning slow-wave sleep, REM latency, REM density, and percentage REM. In our own studies in GAD and panic disorder, we observed a significant decrease in the percentage of S2 and a significant increase in deep sleep in home-recorded patients, but no differences in REM measures [6, 10]. Sleep panic attacks appear to be NREM phenomena. In OCD insomnia may be caused by worrying about the obsessions and time-consuming rituals. Nightmares are common in PTSD patients, who may develop phobic avoidance of sleeping. Simple phobia has little effect on sleep.

Psychotic Disorders

Untreated schizophrenics demonstrated reduced sleep efficiency, prolonged sleep latency, a fragmented sleep due to middle and late insomnia as well as reduced S2 and slow-wave sleep, while there were only few changes in regard to REM sleep (reduced REM cycles and attenuated single REMs) [11–14].

Keshavan et al. [15] postulated that slow-wave sleep alterations may, at least in part, reflect more invariant, perhaps trait-related alterations in schizophrenia.

In regard to REM latency, Benson and Zarcone [16] found shortened REM latencies in untreated schizophrenics as compared with controls in 7 of 12 studies.

Sleep problems in schizoaffective disorders are similar to those found in delusional depression. These patients tend to have fragmented sleep and many of the same sleep abnormalities as in affective disorders.

Eating Disorders

In patients with eating disorders such as anorexia and bulimia even subjective sleep complaints are inconsistent [8]. Anorectic patients may report a reduced need for sleep, while bulimic patients may complain of increased sleep following binge-eating episodes. Polysomnographic findings in anorexia have suggested reduced sleep efficiency, total sleep time, and slow-wave sleep [8]. REM latency may be reduced but REM density decreased. A specific sleep and eating parasomnia (sleep-related eating disorder, SRED) is characterized by involuntary eating episodes, which occur during partial arousal from deep sleep.

Inadequate Sleep Hygiene

Alternate Names

Poor sleep hygiene, sleep hygiene abuse, bad sleep habits, irregular sleep habits, excessive napping, sleep-incompatible behaviors.

Essential Features [1]

- Improper sleep scheduling consisting of frequent daytime napping, selecting highly variable bedtimes or rising times, or spending excessive amounts of time in bed.

- Routine use of products containing alcohol, nicotine, or caffeine, especially in the period preceding bedtime.
- Engagement in mentally stimulating, physically activating, or emotionally upsetting activities too close to bedtime.
- Frequent use of the bed for activities other than sleep (e.g., watching television, reading, studying, snacking, thinking, planning).
- Failure to maintain a comfortable sleeping environment.

Differential Diagnosis
Psychophysiological insomnia, idiopathic insomnia, paradoxical insomnia, environmental sleep disorder, circadian rhythm sleep disorders, insomnia due to mental disorder and insomnia due to drug or substance.

Behavioral Insomnia of Childhood

Alternate Names
Childhood insomnia, limit-setting sleep disorder, sleep-onset association disorder.

Essential Criteria [1]
1. The sleep-onset association type includes each of the following:
    - Falling asleep is an extended process that requires special conditions.
    - Sleep-onset associations are highly problematic or demanding.
    - In the absence of the associated conditions, sleep onset is significantly delayed or sleep is otherwise disrupted.
    - Nighttime awakenings require caregiver intervention for the child to return to sleep.
2. The limit-setting type includes each of the following:
    - The individual has difficulty initiating or maintaining sleep.
    - The individual stalls or refuses to go to bed at an appropriate time or refuses to return to bed following a nighttime awakening.
    - The caregiver demonstrates insufficient or inappropriate limit-setting to establish appropriate sleeping behavior in the child.

Differential Diagnosis
Circadian rhythm sleep disorder/delayed sleep-phase type or irregular sleep–wake type, inadequate sleep hygiene, anxiety disorders, medical disorders, obstructive sleep apnea, RLS, and periodic limb movement disorder.

Insomnia Due to Drug or Substance

Alternate Names
Substance-induced sleep disorder, alcohol-dependent sleep disorder, alcohol-dependency insomnia, stimulant-dependent sleep disorder, drug-induced sleep disorder, substance abuse, insomnia related to drug abuse, rebound insomnia, medication side effect, medication reaction, food-allergy insomnia, toxin-induced sleep disorder.

Essential Criteria [1]
There is a current ongoing dependence on or abuse of a drug or substance known to have sleep-disruptive properties either during periods of use or intoxication or during periods of withdrawal.

Numerous agents are associated with insomnia, including:

- Alcohol
- Anticholinergics (ipratropium bromide)
- Anticonvulsants (lamotrigine, phenytoin)
- Antidepressants (bupropion, phenelzine, protriptyline, fluoxetine, tranylcypromine, venlafaxine)
- Antihypertensives (clonidine, beta-blockers, diuretics, methyldopa, reserpine)
- Antineoplastics (dalmonibicin, goserelin, interferon alpha, leuprolide)
- Bronchodilators (albuterol, metaproterenol, salmeterol, terbutaline, theophylline)
- Corticosteroids (prednisone)
- Cough and cold medications/decongestants (phenylpropanolamine, pseudoephedrine)
- Hormones (progesterone, thyroid hormones)
- L-Dopa and dopamine agonists
- Nicotine
- Stimulants (caffeine, dextroamphetamine, methamphetamine, methylphenidate, modafinil, pemoline).

Polysomnographic and Other Objective Findings

Polysomnographic findings vary as a function of the substance involved [1]. Stimulants increase sleep latency and arousals and decrease total sleep time. REM latency may be prolonged, and total REM time may be decreased. During stimulant withdrawal, sleep latency is reduced, total sleep time is increased, and REM rebound may be observed.

Studies of individuals who have used benzodiazepines on a long-term basis show relatively low percentages of stages 1, 3, 4, and REM sleep. Electroencephalographic waveform alterations including decreased K-complexes, decreased delta waves, increased 14 to 18-Hz waves, and increased alpha and beta activity have also been reported. Eye movements during REM sleep may be reduced in number.

Extended alcohol use is associated with decreases in stages 3 and 4 along with REM-sleep fragmentation. Frequent awakenings and sleep-stage transitions are common in the latter part of the sleep period as the blood ethanol level declines. Chronic alcohol use with later abstinence may produce patterns of light and fragmented sleep for months to years after alcohol consumption is discontinued.

Differential Diagnosis

Inadequate sleep hygiene, psychophysiological insomnia.

Insomnia Due to a Medical Condition

Alternate Names

Sleep disorder due to a general medical condition, medically based insomnia, organic insomnia, insomnia due to a known organic condition.

Essential Criteria [1]

- The patient has a coexisting medical or physiological condition known to disrupt sleep.

- The insomnia is clearly associated with the medical or physiological condition. The insomnia began near the time of onset or with significant progression of the medical or physiological condition and waxes and wanes with fluctuations in the severity of this condition.

Differential Diagnosis
Insomnia due to drug or substance, psychophysiological insomnia or inadequate sleep hygiene.

***Classification* [17]**

Insomnia Associated with Sleep-Induced Respiratory Impairment

Complaints of insomnia occur in patients with central-type sleep apnea and obstructive-type sleep apnea, in which brief awakenings follow the termination of apneic events.

Insomnia Associated with Sleep-Related Movement Disorders

Periodic limb movement disorder and restless legs syndrome.

Insomnia Associated with Other Neurological Disorders

A variety of neurological diseases result in sleep fragmentation through indirect, nonspecific mechanisms or impairment of central neural structures involved in the generation and control of sleep itself [17]. Dementia from any cause, for example, has long been associated with disturbances in the timing of the sleep–wake rhythm. Polysomnographic features include sleep fragmentation, prolonged sleep latency, reduced sleep efficiency, and decreased total sleep time, delta sleep, and NREM sleep [17]. The sleep of dementia patients is also often disturbed by respiratory and periodic limb movement disorders. In moderate-to-severe forms of Alzheimer's disease and other dementias, disturbed sleep at night and excessive sleepiness by day, night wandering, disorientation and confusion (called sundowning), and problems of behavioral management are common reasons for institutionalization and for disruption in the lives of family caregivers. Epilepsy may rarely present as a sleep complaint. Often the history is of abnormal behavior, at times with convulsive movements during sleep, and the differential diagnosis includes REM sleep behavior disorder, sleep apnea, and periodic limb movement disorder (see above). Diagnosis requires nocturnal EEG recording. Other neurological diseases associated with abnormal movements [17], such as Parkinson's disease, Huntington's disease, and Gilles de la Tourette syndrome, are also associated with disrupted sleep, presumably through secondary mechanisms. However, the abnormal movements themselves are greatly reduced during sleep. Headache syndromes (migraine or cluster headache) may show sleep-associated exacerbations by unknown mechanisms.

Fatal familial insomnia is a rare hereditary disorder caused by degeneration of anterior and dorsomedial nuclei of the thalamus. Insomnia is a prominent early symptom [17]. Progressively, the syndrome produces autonomic dysfunction, dysarthria, myoclonus, coma, and death.

Insomnia Associated with Other Medical Disorders

A number of medical conditions are associated with disruptions of sleep [17]. The association is frequently nonspecific, e.g., that between sleep disruption and chronic pain from rheumatologic disorders. Attention to this association is important as sleep-associated symptoms are often the presenting complaint. Treatment of the underlying medical disorder or symptom is the most useful approach. Important medical conditions are asthma, chronic obstructive pulmonary disease, hyperthyroidism, gastroesophageal reflux, chronic renal failure, and liver failure and cardiac ischemia.

Sleep Problems During Pregnancy

The first trimester is generally associated with increased daytime sleepiness, possibly as a result of the sedating effects of progesterone [17]. However, physical discomfort may disrupt sleep at any stage of gestation. Evidence suggests that insomnia and daytime fatigue due to pain and discomfort peak in the third trimester.

In addition to the normal sleep effects of pregnancy, many gravid women develop onset or worsening of PLMS. Mechanical, physiological, and hormonal effects of pregnancy are also associated with increased incidence and severity of snoring, and obstructive sleep apnea develops in some cases.

Sleep Problems Postpartum

The sleep-disrupting effects of babies are well known; however, the postpartum period is a time of potential risk for more serious conditions (e.g., affective disorders and psychosis) that may include insomnia [17].

Sleep Problems During Menopause

Polysomnography demonstrated significantly deteriorated sleep initiation and maintenance, increased S1 and decreased S2 in insomniac postmenopausal syndrome patients. Subjective sleep and awakening quality, well-being, morning drive, wakefulness, memory, and reaction time performance were deteriorated too [18].

Insomnia not Due to Substance or Known Physiological Condition, Unspecified (Nonorganic Insomnia, NOS)

This diagnosis is used for forms of insomnia that cannot be classified elsewhere but are suspected to be related to an underlying mental disorder, psychological factors, or sleep-disruptive practices [1].

Physiological (Organic) Insomnia, Unspecified

This diagnosis is used for forms of insomnia that cannot be classified elsewhere but are suspected to be related to an underlying medical disorder, physiological state, or substance use or exposure [1].

Diagnostic Tools

A thorough understanding of insomnia necessitates the assessment of multiple components such as evaluation for other sleep disorders or comorbid conditions, quantitative and qualitative sleep measures, and daytime function and consequences of insomnia [19]. This evaluation involves a comprehensive history and physical examination, with sleep logs/diaries and structured questionnaire(s). This could be further supplemented by specific structured interviews and questionnaire(s), polysomnography and actigraphy.

(A) Sleep History

Only an in-depth sleep history will allow the clinician to discover concomitant medical or psychiatric disorders that may contribute to the insomnia. During the interview process also other primary sleep disorders (e.g., obstructive sleep apnea or restless legs syndrome) may be identified. A review of all medications the patient is currently receiving (as well as any past medications used to facilitate sleep) should be performed. The sleep history should include the following components outlined by Summers et al. [19]. An important key feature in differentiating primary insomnias (psychophysiological, paradoxical, and idiopathic) from other types is the total lack of hypersomnolence during the day in these patients despite profound fatigue. They bitterly complain of inability to nap and usually do not fall asleep unintentionally during the day.

Sleep Pattern

What is the problem: difficulty initiating sleep, difficulty maintaining sleep, waking up too early, feeling poorly rested despite adequate sleep? When did the problem begin? What was its course (severity, remissions)? Was there a precipitating factor associated with the onset of the insomnia?

What time does the patient go to bed? How long does it take him to fall asleep? Does he have awakenings? What wakes him up (see other components of sleep disruption such as reflux, dyspnea, choking, nightmares, uncomfortable leg sensations, urination, pain, noise, uncomfortable environmental conditions such as the bed or temperature)? What time does he wake up? Does he do it spontaneously or with an alarm or bed partner? What time does he eventually get out of bed? How long does he think he was asleep? How long does he think he needs to sleep to feel better? How does he feel in terms of sleepiness, alertness, or fatigue?

Behavioral Factors

Does he do anything else in bed other than sleep such as watch TV, read, work, or eat? Is he awakened by noise or light or bed discomfort? Does he sleep better away from home, or more easily in anything other than his bed such as a couch? Does he nap during the day? Does he look at the clock?

Cognitive Factors

Does the patient feel tense when he sees the bedroom? Does he think about his sleep problems during the day? Is he afraid of sleeping? What does he perceive are the consequences of his poor sleep?

Medical Disorders
What other medical conditions does the patient have which can potentially affect sleep (asthma/COPD/congestive heart failure; awakenings with shortness of breath; pain conditions; reflux; neuropathy)? What medications is the patient taking that can potentially affect sleep (diuretics, stimulants, β-blockers)?

Psychiatric Disorders
Has the patient been treated for emotional or psychological problems? Has the patient seen a mental health provider (therapist, psychologist, psychiatrist, social worker)? Does the patient feel depressed? How is the patient's appetite? Has the patient's weight fluctuated? Does the patient have panic attacks or phobias? How is the patient's marriage or relationship? Does the patient have an active sex life? Does he have any personal/familial stress? Does the patient have any work/school-related stress?

Alcohol and Medication
Does the patient drink alcohol? At what frequency, amount, and how long? Does he take any sedative or hypnotic agent prescribed, over the counter or herbal? Does he take any illicit/recreational drugs that either stimulate or sedate? Does he drink any caffeinated beverages? How much and how often? How late during the day does he drink this beverage?

Other Primary Sleep Disorders
Does he have uncomfortable sensations in his legs that prevent him from sleeping or wake him up? Has the bed partner noted leg movements during sleep (restless legs syndrome)? Does the patient snore loudly and frequently? Does he awaken gasping for breath? Has the bed partner noted any breathing irregularity or pauses in his breathing? Does the patient have a dry mouth in the morning or problems breathing through his nose (obstructive sleep apnea)? Does the patient experience difficulty waking up in the morning? Does he sleep later on weekends? Does he work shifts?

(B) Laboratory Evaluation
Results of a medical history and examination may uncover the need for laboratory testing (e.g., thyroid function, prostate-specific antigen, ferritin levels in suspected sleep movement disorders).

(C) Sleep Logs
A sleep log is a graph on which the patient records bedtime, approximate sleep time, times and duration of awakenings during the sleep period, final awakening time, and naps taken during the day over a period of 2–3 weeks. Although subjective, this record summarizes the patient's perception of the amount and quality of sleep he or she is getting [20].(Figure. 4.1)

(D) Actigraphy
Actigraphy is a recently developed technique to record activity during waking and sleeping without application of any electrodes. An actigraph is worn on the wrist and is about the size of a watch. It comprises a movement detector and has considerable storage capacity. Thus, it is able to record movement and

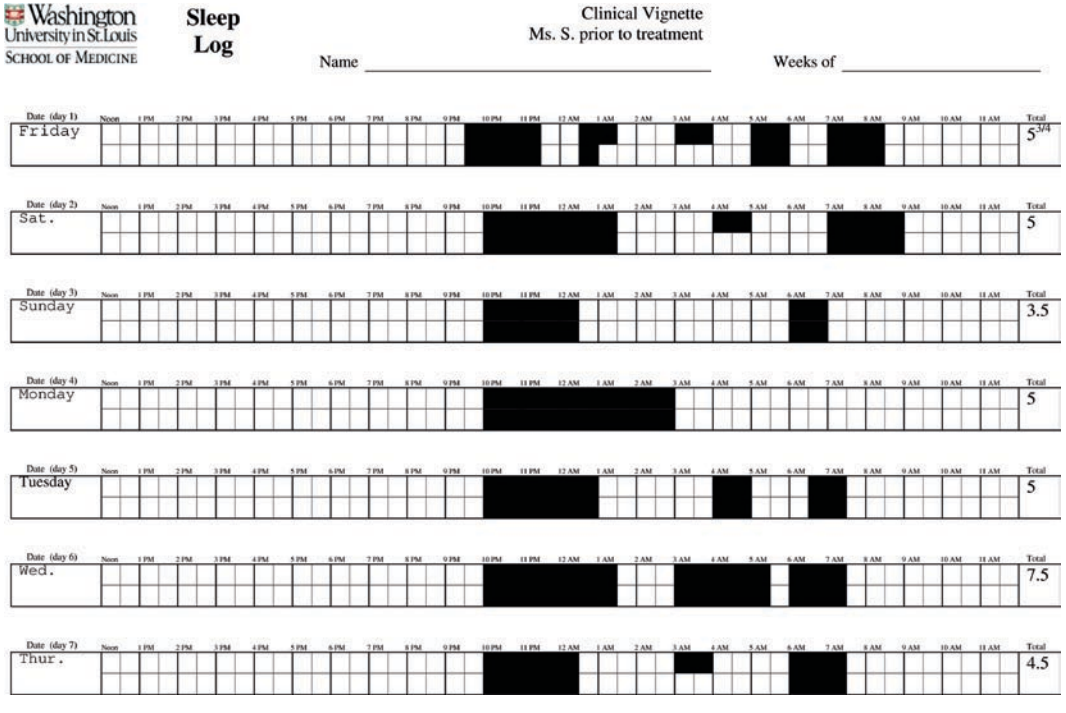

Figure 4.1 Example of a 1-week sleep log. The shaded areas indicate sleep and the white areas wakefulness

Figure 4.2 Picture of an actigraph (Used with permission. Courtesy of Mini Mitter® Co. Inc)

nonmovement data plotted against time for a week or two. The patient wears it continuously during sleep and when performing routine daily activities. Actigraphy is ideally suited for an extended examination of the sleep/wake cycle in the patient's home environment. It is convenient and readily accepted by patients. It can be used to supplement sleep logs and to evaluate incredible complaints, such as, "I have not slept for several nights"(Figures. 4.2 and 4.3).

(E) Polysomnography

PSG is the only method that provides a comprehensive measurement of sleep and is essential in diagnosing a number of sleep disorders. Recent practice parameters for the evaluation of insomnia published by the American Academy of Sleep Medicine [21] state that PSG "is not indicated for the routine evaluation of chronic insomnia," unless there exists "valid indication and clear rationale." PSG should be considered in situations where the patient presents with pathologic levels of sleepiness, reports symptoms of other sleep pathologies (e.g., sleep-disordered breathing, periodic limb movements, parasomnias, narcolepsy), or does not respond to insomnia treatment.

Last but not least, polysomnography is the essential instrument in the "key-lock principle" in diagnosis and treatment of nonorganic insomnia. Sleep laboratory investigations in patients for diagnostic purposes and in normals for the evaluation of drug effects suggest that alterations in the sleep architecture of patients with nonorganic insomnia due to psychiatric disorders as compared with normal controls are opposite to the changes induced by psychotropic drugs intended for their treatment as compared with placebo

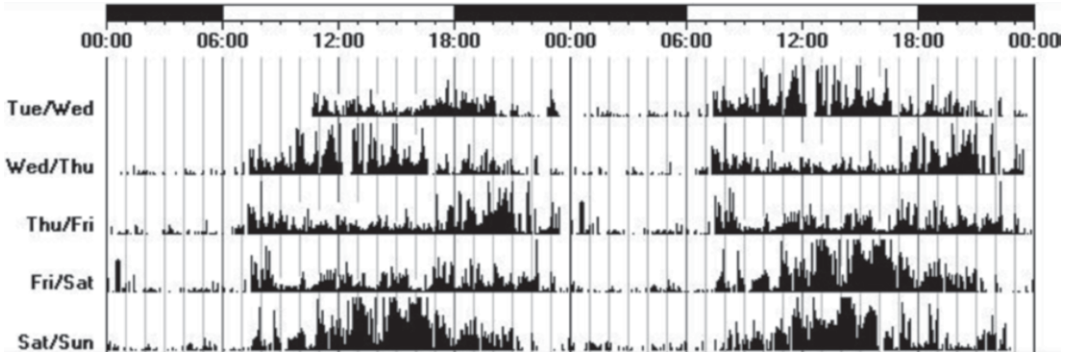

Figure 4.3 One-week printout of an actigraph. The *high bars* reflect wakefulness, the *low bars* sleep. (Used with permission. Courtesy of Mini Mitter® Co. Inc)

("key-lock principle"). Evidence for this principle was found regarding nonorganic insomnia related to GAD or panic disorders and benzodiazepines, nonorganic insomnia related to depressive episodes, recurrent depression or dysthymia and sedative antidepressants and finally schizophrenia and sedative neuroleptics. PSG findings of other mental disorders are rather scarce and often depend upon the subtype and stage of the disease. In conclusion, sleep laboratory studies may be helpful for choosing the right drug for an individual insomniac patient.

A Multiple Sleep Latency Test (MSLT) is an instrument to objectively evaluate daytime sleepiness. It provides a series of four or five opportunities to take a 15–20-min nap, each separated by a 2-h interval. It is used to assess daytime sleep pressure in various sleep disorders such as sleep-disordered breathing and narcolepsy. In primary insomnia, results of the MSLT are usually normal [22].

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5

Insomnia in Primary Care Practice with a Special Focus for the Midlevel Practitioner

Nancy I. Resi

Abstract

Insomnia is the most common sleep complaint in a primary care setting and the second most overall complaint after pain. The 2005 Sleep in America Poll by the National Sleep Foundation, however, found that less than one-third of patients were asked about sleep by their primary care provider and only 45% of responders said they would think to discuss sleep issues with their provider, even though 75% said they had experienced problems with sleep several nights a week within the past year. For these reasons, it is incumbent upon the provider to evaluate and treat sleep complaints. Since midlevel providers (NPs and PAs) are being represented in larger numbers in today's health-care field especially in primary care, it is important for them to realize the importance of insomnia as a complaint and what to do about it.

Keywords: Midlevel provider, Primary insomnias, Secondary insomnias, Sleep logs, Actigraphy, Behavioral treatments, Pharmacological treatments

Insomnia is a condition in which individuals have difficulty falling asleep, staying asleep, or awakening too early. The end result is a poor quality of sleep which does not allow the individual to feel refreshed upon awakening. It can lead to significant mood disturbances and psychological stress, accidents, decreased work productivity and efficiency, and absenteeism [1].

Of all sleep disorders, insomnia is the most common sleep complaint in a primary care setting [2], and the second most overall complaint after pain [3]. The 2005 Sleep in America Poll by the National Sleep Foundation, however, found that less than one-third of patients were asked about sleep by their primary care provider and only 45% of responders said they would think to discuss sleep issues with their provider, even though 75% said they had experienced problems with sleep several nights a week within the past year [3, 4]. For these reasons, it is incumbent upon the provider to evaluate and treat sleep complaints.

From: *Clinical Handbook of Insomnia,* Current Clinical Neurology
Edited by: H.P. Attarian and C. Schuman, DOI 10.1007/978-1-60327-042-7_5,

Definition

Insomnia is a disturbance of sleep. This may include sleep-onset insomnia when it takes greater than 30 min to fall asleep. Sleep maintenance insomnia occurs when sleep is disrupted during the night and one is unable to fall asleep readily. Insomnia may also be related to early morning awakening which occurs when the individual is unable to resume sleep [5]. Lastly, insomnia may manifest as nonrestorative sleep [2, 5].

Acute insomnia may be caused by many different factors which impact on ones ability to sleep and it may last for up to 4 weeks. The most common cause is a psychosocial or physical stressor. Some examples of this are environmental conditions nonconducive to sleep, such as hot, humid weather, noisey or excess light. Circadian rhythm issues such as: shift work or jet lag due to air travel traveling over multiple time zones which are inconsistent with ones biological rhythm. Though anyone can have difficulty with jet lag, the adjustment of time zone changes are often more difficult in the elderly [5]. The jet itself may also be detrimental to ones sleep. It may cause headache, fatigue, limited mobility, nasal congestion and dry air [6, 7]. Stressors of daily life, minor and major, whether good or bad, also become triggers for acute insomnia. These can range from a bad day at work or worrying over an upcoming exam to loss of a loved one or the birth of a child.

Chronic insomnia occurs for a length of time of greater than 4 weeks. It persists after the acute stressor has dissipated. Major causes of perpetuation of the insomnia are inherent tendency to be a light sleeper and maladaptive bedtime behaviors that have developed during the acute phase. Chronic insomnia is characterized by poor quality of sleep which often presents with daytime symptoms such as excessive daytime fatigue, malaise, irritability, and limited ability to concentrate and recall information [8].

Insomnia can further be classified as primary and secondary. Primary insomnia occurs without a coexisting disorder. It is the major symptom. The primary insomnias include: idiopathic, paradoxical and psychophysiological insomnias. Factors such as anxiety, stress, poor sleep hygiene, and behavioral conditioning contribute to primary insomnia [5].

Secondary insomnia is due to a multitude of causes. This might include psychiatric disorders such as anxiety and depression or other sleep disorders such as restless legs syndrome, periodic leg movements of sleep, obstructive sleep apnea, narcolepsy and circadian rhythm abnormality. Other causes such as menopause, insomnia in medical (asthma) and neurologic conditions (dementia, fatal familial insomnia), pain, or medication-induced insomnia or poor sleep hygiene (Table 5.1).

Primary Insomnias

Idiopathic Insomnia

Idiopathic insomnia is a rare disorder. It is characterized by a chronic and serious inability to sleep that can be traced back to the first few weeks of life. It takes patients a long time to fall asleep; sleep is fragmented by many awakenings

Table 5.1 Primary vs. secondary or comorbid insomnia.

Primary insomnia	Secondary or comorbid insomnia
Idiopathic insomnia	Insomnia with:
Paradoxical insomnia	Psychiatric disorders
Psychophysiological insomnia	Restless legs syndrome
	Periodic leg movements of sleep
	Obstructive sleep apnea
	Narcolepsy
	Circadian rhythm abnormality
	Pain
	Menopause-related insomnia
	Insomnia in medical and neurologic conditions
	Medication-induced insomnia
	Fatal familial insomnia
	Poor sleep hygiene
	Substance abuse-related insomnia

and has multiple sleep-stage abnormalities [3, 9]. Although it manifests in childhood most children with insomnia do not have this rare disorder. For detailed account of both this condition and childhood insomnias see Chaps. 6, 7, and 12.

Paradoxical Insomnia

Patients with this disorder complain of an inability to sleep over varying lengths of time perhaps from weeks to years. However they do not have any objective evidence of a sleep disorder. When studied in the laboratory, they are found to sleep [10] although they become adamant that they have not slept at all. This condition may be called sleep hypochondrias and individuals may develop both anxiety and depression over time [6].

Psychophysiological Insomnia

This is the most common form of insomnia and may be caused by life stressors such as loss of a loved one, move to a new location or work stressors. This type of insomnia occurs after several nights of poor sleep. Following that the individual's anxiety becomes exacerbated and the cycle of being unable to sleep continues, even in the absence of other psychiatric disorders [7, 10].

Case Example

A 51-year-old woman presented with complaints of difficulty sleeping over the past several months. Since early retirement from her career as an educator, she had moved to Vermont to be near her aging parents. Simultaneously,

she began work on her first novel. She has had difficulty falling asleep for the last 2 months. She often awakens during the night and finds that her mind is racing at which point she will often begin writing again. She has not had difficulty with sleep prior to this and readily admits to feeling quite frenzied and frantic about the upcoming deadline in 6 weeks and feels she will be able to get back to her routine sleep habits after that.

She generally goes to bed around 11 pm and as she is writing in bed she falls asleep with the lights still on in about an hour. She awakens once spontaneously between 2:30 and 3:00 am and resumes writing. She may or may not fall back asleep. She generally gets up for the day between 7:30 and 8:00 am without an alarm, estimating a total sleep time of 4–5 h per night. She denies napping. Her sleep patterns are the same 7 days a week. She denies any other sleep complaints and denies falling asleep unintentionally during the day despite being profoundly fatigued.

She drinks one cup of caffeinated coffee in the morning and has a second cup later in the day. She drinks one glass of wine at night, prior to bed as it helps her fall asleep.

Past medical history and past surgical history is unremarkable. She does not take any prescription or OTC medications. Review of systems is unremarkable. Her physical exam is completely normal.

Intervention

Patient is advised to eliminate any form of caffeine after noon and stop alcoholic beverages at bedtime. She is further advised to work in another room and adhere to a strict sleep and rise time. If she wakes during the night, she should get up, go into another room and spend time doing a leisurely, nonwork-related activity until she feels sleepy again. A prescription for zolpidem 10mg at bedtime to be taken on an as needed basis is given as well.

Results

At the 4 weeks follow-up appointment she reports that she implemented all the recommendations above and that her sleep has returned to normal 7½ h per night and she is rarely taking the zolpidem.

Secondary Insomnias

Poor Sleep Hygiene

Poor sleep habits are a common problem. Individuals with poor sleep hygiene often have variable wake and sleep times. For someone who has difficulty sleeping, it is important to go to bed and arise at the same time 7 days per week. Both caffeine and nicotine are stimulants which should be avoided 4–6 h before bed time. For some, the stimulants should be avoided all together. Exercise should also be avoided before bed time as it can decrease ones ability to fall asleep, though exercise in the earlier part of the day will help to deepen sleep. Napping should be considered “poison” for individuals having difficulty with sleep as it can mean being unable to sleep at night. The bedroom should be used only for sleep and sex. Activities such as reading, watching television, work, hobbies or any other activity should be done elsewhere in the home.

Fatal Familial Insomnia

This is a very rare autosomal dominant neurodegenerative condition [3]. Early in the disorder, severe insomnia becomes problematic. It is characterized by the loss of neuroendocrine regulation and vegetative circadian rhythms causing progressive insomnia with excessive sweating, lacrimation, salivation, increased body temperature agitation, confusion which, in turn, leads to coma and death. This unfortunate condition is fatal within 6 months to 2 years and there is no treatment for it [11, 12].

Psychiatric Disorders

Psychiatric history is closely related to the severity and chronicity of insomnia. Chronic insomnia may also be a residual symptom of a prior mental health disorder and place one at a higher risk of relapse [13, 14]. Depression and anxiety are common causes of insomnia. In adults with depression, early morning awakening is common; however, in adolescents and young adults sleep-onset insomnia is more problematic. There is a high prevalence of depression amongst the elderly with insomnia [13]. Anxiety disorders will also disrupt sleep. Examples of this are panic attacks and posttraumatic stress disorder characterized by nightmares and flashbacks [13].

In schizophrenia, the severity of sleep complaints is related to the intensity of the psychotic symptoms. In acute phases, sleep onset becomes problematic and there is an overall decrease in total amount of sleep.

Restless Leg Syndrome and Periodic Leg Movements of Sleep

Restless leg syndrome (RLS) has been described as pain, burning, and a creepy, crawly sensation which makes the individual want to move their legs to alleviate the sensation [6]. If one moves their legs, or gets up and walks, the sensation disappears, only to return when the legs are quiet again. Symptoms of RLS can be mild to severe and are often more apparent in the afternoon or evening when the individual is still and when they are trying to fall asleep. It has been reported in 5–15% of the population [15, 16].

Approximately 80% of individuals with RLS will also have Periodic limb movements of sleep (PLMS). In this disorder, limb movements occur every 20–90 s, lasting 2–6 s. Most commonly it consists of flexion of the knees and hips, dorsiflexion of the foot and great toe, though it can occur in the arms as well [6]. PLMS occurs during non-REM sleep. The movements may cause arousals into a lighter stage of sleep or a full awakening. The bed partner will often report the movement problem. This condition typically increases with aging. It can be exacerbated by iron deficiency, pregnancy, renal failure, diabetes, and by some medications such as tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRI's) [15, 16].

Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is perhaps the most common sleep disorder. It is often associated with aging, obesity, snoring, and excessive daytime sleepiness. The primary complaint by patients with OSA is often hypersomnia; however, patients will also report difficulty maintaining sleep. This may be due to frequent arousals associated with apneic events.

Narcolepsy

Narcolepsy is a chronic neurologic disorder which is caused by the brain's inability to regulate the sleep–wake cycle. The onset of this disorder typically occurs in adolescence and early adulthood. Though it affects only 0.05–0.1% of the population, its effects can be devastating. Individuals with this disorder are excessively sleepy, have periods of irresistible sleep, cataplexy, sleep paralysis and hypnagogic hallucinations and often disturbed night time sleep [17].

Circadian Rhythm Abnormality

These disorders are characterized by ones ability to sustain sleep during abnormal hours. They include shift work and jet lag, delayed sleep phase, and advanced sleep phase.

- Shift work and jet lag: These are perhaps the most common circadian rhythm abnormalities. They occur when travel or work precludes the individual from sleeping at their normal times [18–20].
- Delayed sleep phase: Sleep onset is delayed in comparison to conventional bedtimes. Patients will fall asleep late, and awaken late. This is often prevalent in younger patients such as high school and college age individuals [18–20].
- Advanced sleep phase: This sleep disturbance is characterized by sleep onset moving to an earlier hour. Individuals will fall asleep and awaken earlier. It is frequently seen in the elderly [18–20].

Menopause-Related Insomnia

During menopause women may experience vasomotor symptoms such as hot flashes and hot flushes, night sweats, and depression. Forty three percent have poor sleep quality, often with midnight awakening [21, 22].

Insomnia in Medical and Neurologic Conditions

Medical conditions such as gastro esophageal reflux, allergies, asthma, pain syndromes, and neurodegenerative diseases may cause insomnia. Insomnia may be caused either directly or indirectly by the illness. An example of this is the asthmatic who awakens dyspneic, treats the symptoms with a short acting beta agonist and is unable to resume sleep due to the medication side effects [7, 8].

Substance-Induced Insomnia

A number of substances are known to disrupt sleep. These include caffeine which causes sleep-onset insomnia, alcohol which though it helps one fall asleep, will lead to mid-night awakening. Other substances include stimulants, theophylline, steroids, some antihypertensive, and antidepressants, illicit substances, anticonvulsants, nicotine, and MAOI's (Table 5.2).

Diagnostic Workup

The diagnosis of insomnia begins with the patient history to analyze the onset, frequency, duration, and severity as well as the progression and fluctuations of

Table 5.2 Commonly used medications and substances that can cause insomnia.

Antiseizure	Beta adrenergic blockers	Central nervous system stimulants
Felbatol	Atenolol	Amphetamines
Lamotrigine	Metoprolol	Methylphenidate
	Pindolol	Modafinil
	Propranolol	
	Sotalol	
Centrally acting alpha adrenergic agonists	Monoamine oxidase inhibitors	Nonsteroidal antiinflammatories
Clonidine	Phenelzine	Celecoxib
	Selegiline	
	Tranylcypromine	
Corticosteroids	Over the counter decongestants	Selective serotonin Reuptake inhibitors
	Ephedrine	Citalopram
	Pseudoephedrine	Escitalopram
		Fluoxetine
		Paroxetine
		Sertraline
Theophylline	Opiates	Antiemetics
		Metoclopramide
		Prochlorperazine
Alcohol	Caffeine	Nicotine

symptoms [23]. Include both the patient and bed partner or caregiver whenever possible. Screen for any treatable, coexisting, illnesses which may be the underlying cause. Identify any events which may have occurred prior to insomnia, i.e., did it begin with the onset of a new job, has the insomnia been transient, intermittent, or persistent. Does the individual have difficulty falling asleep, staying asleep, or both. Identify events which may have precipitated the time insomnia became problematic. A sudden onset might suggest a stressful life event such as the loss of a job, or developing a medical problem such as asthma (See Table 5.3).

Carefully review the sleep–wake cycle for any evidence of sleep phase delays or advances, problems with sleep hygiene, timing of medications, and stimulants such as caffeine, alcohol, tobacco, or environmental triggers.

Family history will provide insight into medical, neurologic, and psychiatric disorders associated with sleep. Laboratory testing may help with diagnosis of medical conditions; however, routine testing is not indicated for insomnia. Physical exam should include will assist with identifying other medical conditions such as cardiovascular, respiratory, gastrointestinal, endocrine, and neurologic problems.

Table 5.3 Insomnia sleep history.

- Chief complaint
- HPI
  - o When did symptoms of difficulty sleeping begin?
  - o Are symptoms transient, intermittent or persistent?
  - o Where do they sleep? In the bedroom?
  - o Difficulty falling asleep, maintaining sleep or early am awakening?
  - o Is rest restorative?
  - o Are there any daytime consequences? of insomnia?
  - o What occurred prior to complaints of insomnia?
  - o What makes it worse, i.e., stress, being away from home?
  - o What were previous treatments and response?
  - o Snoring episodes, witnessed pauses or gasps
  - o Paresthesias
  - o Nocturnal symptoms GERD, SOB, chest pain
  - o Nightmares, or terrors
  - o Cataplexy, sleep paralysis, hypnagogic hallucinations, excessive daytime sleepiness
  - o Night sweats or hot flashes
- Sleep–wake Cycle
  - o What time one goes to bed?
  - o When do the lights go out?
  - o What are the normal rituals before bed, i.e., reading, television, paying bills?
  - o How long does it take to fall asleep?
  - o How many arousals and what specifically causes them?
  - o How long to fall back asleep?
  - o Is their mind racing?
  - o What do they do during this time?
  - o What time one awakens in the am? To an alarm or spontaneously?
  - o Is rest restorative?
  - o Are there any naps?
  - o Do sleep patterns change weekday versus weekend?
- Past medical history
  - o Respiratory, cardiovascular, gastrointestinal, endocrine, neurologic, chronic pain, psychiatric, other sleep disorders
- Medications and or substance use
  - o Including diuretics, bronchodilators, steroids, alcohol, tobacco, caffeine, antidepressants, hypnotic agents
- Family history
  - o Psychiatric, medical or neurological illnesses
- Social history
  - o Level of education
  - o Occupation including shift work
  - o Bed partner
  - o ETOH, tobacco use, caffeine intake
- Review of systems
  - o Systematic review of all systems

Diagnostic Tools

Sleep Log

Sleep logs are very useful in evaluation of all sleep disorders. They are best when kept over a 2–3-week period. Included in the logs should be drowsiness state, time in bed, sleep onset and any awakenings, as well as any naps in the 24-h period. Caffeine intake, nicotine use and a list of all medications should also be included. Please refer to Chap. 4 for an example of sleep log.

Polysomnogram and Multiple Sleep Latency Testing

According to the American Academy of Sleep Medicine, a polysomnogram (PSG) or Multiple Sleep Latency Testing (MSLT) are not indicated in the evaluation of insomnia [24]. However, if the diagnosis is uncertain, or an underlying primary diagnosis of sleep disorder is suspected these tools may be helpful. The PSG is most useful in evaluation of sleep-breathing disorders. It will measure stages and periods of sleep, cardiogram, positioning and oxygenation.

A MSLT may be indicated for excessive daytime sleepiness including disorders in the narcolepsy family. During a MSLT 4–5 opportunities are provided for napping during daytime hours. The environment is darkened and the individual allowed 20 min to fall asleep while in bed. They are monitored for sleep-onset latency and any rapid eye movements to document pathologic sleepiness.

Actigraphy

Wrist actigraphy is a tool which monitors and records wrist movements. Increased wrist movement is associated with wakefulness and decreased wrist movement is associated with sleep. This is often helpful in circadian rhythm disorders [25]. It will also confirm how much sleep the individual is getting. It is important to remember that this is a tool to aid in diagnosis, not a standalone diagnostic or screening tool. Its results should be interpreted in the setting of the entire clinical picture.

Management

Insomnia is a syndrome, not a disorder. Therefore, treatment will depend on the underlying cause. Both pharmacologic and nonpharmacologic treatments are useful for insomnia. However, the mainstay of treatment for insomnia is nonpharmacologic [26].

Nonpharmacological Treatment Methods

Cognitive behavioral therapies for insomnia include sleep hygiene measures, stimulus control, sleep restriction/consolidation, and relaxation.

Sleep Hygiene

Sleep hygiene is the cornerstone to a good nights sleep. Sound, consistent habits for sleep are necessary for the insomniac 7 nights per week. All factors which might be harmful to a good nights sleep should be addressed and eliminated [27]. (Table 5.4)

Table 5.4 Some basic sleep hygiene rules.

- Maintain a regular sleep schedule: to bed at the same time, up at the same time 7 days per week
- Avoid any activity other than sleeping or sex in the bedroom
- Avoid napping during the day
- Exercise no later than 3 h before bedtime
- Avoid caffeine 6-9 hours before bedtime
- Avoid alcoholic beverages
- Avoid smoking
- If not asleep within 30 min, get out of bed, go to another room and do something calming. Return to bed only when sleepy.

Stimulus Control

The primary goal of this therapy is to reassociate the bed and bedroom with rapid onset of sleep [28]. Any activity such as reading, watching TV, paying bills, etc in the bedroom should be avoided. If unable to fall sleep within 30 minutes, get out of bed, go to another room and participate in a nonstimulating activity. When sleepy, return to bed. This can be repeated as many times as necessary. It is also important to maintain a consistent bedtime and rise time 7 nights per week.

Sleep Restriction/Consolidation

Individuals with poor sleep will often increase their time in bed hoping to sleep. With sleep restriction therapy it is first necessary for the individual to determine how many hours of sleep they are getting by averaging their sleep from at least 7 days of sleep logs or sleep diaries. Then they are limited to those number of hours in bed as long as the total number of hours is not less than 5. The individual must maintain a strict sleep schedule, regardless of whether or not they achieve any sleep. It is also important for them to avoid napping. The premise is when one is sleep deprived, they will fall asleep more quickly and increase their sleep efficiency [29]. Sleep logs should be evlauated every 2-4 weeks. If at least 90% of total time in bed is spent sleeping, a half hour is added to either end of the sleep period. This continues until the person is sleeping 7–8 h a night.

Relaxation

Relaxation therapy is based on the perspective that patients with insomnia have anxiety both during the day and nighttime which may interfere with initiation of sleep. Techniques for this include abdominal breathing, yoga, meditation, and progressive muscle relaxation [28].

Pharmacological Treatment Methods

Hypnotics have been the mainstay of pharmacological treatment for insomnia. Benzodiazepines such as clonazepam, estazolam, flurazepam, lorazepam,

temazepam, and triazolam have been used for years. However, they also run the risk of addiction and tolerance. Three nonbenzodiazepine are also used for sleep [30]. These include eszopiclone, zaleplon, and zolpidem. These are shorter acting than most of the benzodiazepines and have less chance of addiction and may be preferable for this reason [31]. They do have a higher incidence of sleep-related behaviors.

Antidepressants such as amitriptyline, mirtazepine, and trazodone have sedative prosperities and may be used in patients with a coexisting depression. They have not been shown to be effective in treatment of insomnia not associated with depression [2].

Ramelteon, a melatonin receptor agonist, is a somewhat newer agent proposed to treat sleep-onset insomnia. It has been shown to be more effective than melatonin itself [31].

First generation antihistamines such as diphenhydramine, which are over the counter, have sedating effects [32]. Unfortunately their half lives are 8½–10 h and will decrease daytime alertness. They have a number of side effects, primarily related to their anticholinergic properties and often cumulative therefore they are not useful in the treatment of chronic insomnia.

Herbal remedies such as valerian root and melatonin have been very popular for treatments for insomnia. Despite this, none of the studies with these medications have shown definite efficacy as first line hypnotic in primary insomnias [32]. Additionally, they are not controlled by the FDA.

Conclusion

Insomnia is a common problem in primary care which impacts the individual's mood, safety, and daily performance. Routine screening of patients during health examinations will identify those requiring further evaluation. Insomnia is often associated with psychiatric and medical illnesses. Treatment is available which may significantly impact the lives of those affected.

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Part II

Insomnia in Special Populations

6

Behavioral Insomnias of Childhood: Assessment and Treatment

Daniel S. Lewin and Edward Huntley

Abstract

The Behavioral Insomnias of Childhood (BIC) include a series of problems of sleep initiation, continuity, maintenance, and bedtime resistance. These sleep problems can place a significant burden on the parents who may be required to attend to a child at the beginning or in the middle of the night. The resulting sleep loss can impact parents' and children's daytime functioning and can increase bedtime-related conflict. Even when sleep problems do not meet criteria for a disorder, they can increase parental stress and parent–child conflict. Childhood sleep problems can be an indicator of poor regulatory capacity in the infant or child, and there is some evidence that sleep problems presenting in the first few years of life can be a marker of a diathesis for psychopathology. Even though sleep problems in early childhood are quite common and there are well-established interventions for these problems, little is understood about the pathophysiology of childhood sleep disorders. This chapter will review common causes of sleep problems in infants and young children that can persist into the later school years and adolescence. This will be followed by a detailed practical approach to evaluating and treating childhood insomnias.

Keywords: Behavioral insomnias of childhood, Sleep-onset association type, Limit-setting type, Parental reinforcements, Children's sleep habits questionnaire, Gradual extinction, Positive routines

Introduction

The Behavioral Insomnias of Childhood (BIC) include a series of problems of sleep initiation, continuity, maintenance, and bedtime resistance. These sleep problems can place a significant burden on the parents who may be required to attend to a child at the beginning or in the middle of the night. The resulting sleep loss can impact parents' and children's daytime functioning and can increase bedtime-related conflict. Even when sleep problems do not meet

From: *Clinical Handbook of Insomnia,* Current Clinical Neurology
Edited by: H.P. Attarian and C. Schuman, DOI 10.1007/978-1-60327-042-7_6,

criteria for a disorder, they can increase parental stress and parent–child conflict. Childhood sleep problems can be an indicator of poor regulatory capacity in the infant or child, and there is some evidence that sleep problems presenting in the first few years of life can be a marker of a diathesis for psychopathology [1, 2]. Even though sleep problems in early childhood are quite common and there are well-established interventions for these problems, little is understood about the pathophysiology of childhood sleep disorders. This chapter will review common causes of sleep problems in infants and young children that can persist into the later school years and adolescence. This will be followed by a detailed practical approach to evaluating and treating childhood insomnias.

Definitions

While most children have at least minor or transient problems initiating and maintaining sleep, a smaller percentage of children, between 15 and 20%, have a persistent sleep disorder [3, 4]. The BIC as defined in the International Classification of Sleep Disorders [5] are divided into two overlapping diagnoses, Sleep-Onset Association Type and Limit-Setting Type. The specific features of BIC subtypes are presented in Table 6.1. It is important to note that the criteria for diagnosing BIC are nonspecific, particularly when compared to Psychophysiological Insomnia which includes specific time periods for sleep-onset latency (SOL) and wake time after sleep onset (WASO) as well as duration criteria that differentiate chronic and acute subtypes [5]. While the primary focus of this chapter is on the BIC subtypes, there will also be some discussion of the causes of Psychophysiological Insomnia and Idiopathic Insomnia. Psychophysiological Insomnia, generally considered a disorder only occurring in adults, has a subtype called Idiopathic Insomnia that has its origins in childhood. At this time there is little or no specificity regarding how these symptoms present in childhood. Instead it is based on a retrospective report of a "lifelong history" of sleep problems.

The primary features of both subtypes of BIC that are targets of treatment are parent reports of bedtime resistance, involvement of the parent in wake-to-sleep

Table 6.1 Estimated normative values for total sleep time form birth to 18 years [55–57].

Estimated norms for 24-h sleep duration		
Age group	**Poll finding NSF '05 & '06**	**Population Iglowstein '03 (Switzerland)**
Infants (3–11 months)	12.7	13.9–14.2 (1.7)
Toddlers (12–35 months)	11.7	12.5–13.5 (1.2)
Pre-K and K (3–5 years)	10.4	11.4–12.5 (0.9)
School-aged (6–10 years)	9.5	9.9–11 (0.6)
11–15	7.2–8.4	8.1–9.6 (0.7)
16–18	6.9–7.2	

transitions at the beginning and the middle of the night, and sleep/wake schedule conflicts with environmental demands. In children younger than 6 years, it is a parent who typically identifies the sleep problem and brings it to the attention of a pediatrician, mental health provider or sleep specialist. On occasion, an educator or childcare provider will report that a child appears tired and has an atypical need for sleep during the day. While even very young children can describe sleep problems, their sleep complaints seldom lead to a referral.

Pathophysiology of BIC

For both adults and children, and perhaps all species of animals, the transition from wake to sleep is a vulnerable period as it requires the letting down of vigilance. While most people live in relatively safe and secure environments and have the luxuries of strong locks, lights, and secure homes, this was not the case for most of human history. Bedtime routines facilitate the letting down of vigilance by assuring that the sleep environment is free of threats. Repetitive and planned behavior sequences can allay fears and worries. Across all species routinized behavior at bedtime involves checking the immediate environment for threats and referencing indicators of safety such as a being in close proximity to one's clan or pack. Infants and young children are dependent on their parents for the implementation of routines and maintenance of a safe environment. When individual or environmental factors interfere with routines or cause chronic Psychophysiological arousal or hypervigilance at bedtime, delayed, and middle-of-the-night wake-to-sleep transitions can also be affected.

The origins or BIC and Psychophysiological insomnia that persist into the school age years are heterogeneous. In some cases, it is important to understand the cause as it can maintain the sleep problem. In other cases, the causes are remote and less relevant to intervention. These initial causes, which may occur alone but often co-occur and can sometimes be compounding, can be divided into several categories. The most common cause is *parental reinforcement* of a child's dependence on the parent's involvement in the wake-to-sleep transition. Included in this category are feeding problems and poor sleep hygiene. Children who have *medical problems,* such as postpartum complications, gastroesophageal reflux, or colic, may have an increased risk of developing sleep problems. A *sentinel event* such as a separation from parents, the birth of a sibling or an accident can precipitate a subsequent sleep disturbance that then persists. Children with a diathesis for *psychopathology*, *temperamental hyperarousal, or hyperreactivity* often have increased anxiety and hypervigilance at bedtime. Conflict between *environmental demands* (e.g., child care or parent work schedules) and the child's intrinsic *circadian phase* may result in delayed sleep onset and insufficient sleep during the day. Finally, *sleep disorders* such as Obstructive Sleep Apnea Syndrome and Restless Leg Syndrome can cause insomnia. Further explanation of these categories is warranted as their contributions to the sleep problems may inform the treatment approach.

Parental Reinforcement

Parental reinforcement refers to routines established at wake-to-sleep transitions and to parental responses to a child's bids for parental attention. The wake-to-sleep transition is the first significant separation for the child–parent

dyad and can lead to heightened arousal and ambivalence on the part of the parent and child. Therefore, an assessment of the child and parent interaction is critical to understanding the nature of sleep disturbances in young children. Parents' contributions to the child's problematic sleep-to-wake transitions and bedtime resistance may occur for a variety of reasons. For example, parents may simply prefer to be present when the child is falling asleep or may learn that their presence results in a faster and easier transition to sleep. When the bedtime routines and the wake-to-sleep transition involve parental presence (e.g., feeding the child, rocking the child, etc.), the child may become dependent on this very powerful indicator of safety and security. If the parent attempts to leave the room when the child is awake, or is not present for any or all of the multiple awakenings that occur during a normal night of sleep, the child may have difficulty returning to sleep if the child has not learned to initiate sleep independently. When the child protests being left alone and the parent repeatedly returns to the child's room, the parent's repeated visits reward the child for calling out and reinforce the child's dependence on the parent. The parent is also reinforced by the child's rapid calming and relatively rapid return to sleep. It is a widely accepted assumption that by teaching the child to transition to sleep independently at the beginning of the night, the child generalizes this learning to middle of the night awakenings.

Parental reinforcement is probably the most important root cause of BIC and perhaps an initiating cause of insomnia that persists into childhood and adolescence. Parents may quickly modify routines and their children will generally adapt quite quickly. When chronic and more severe bedtime and nighttime conflict between the parent and child are present, these interactions can become part of the learned bedtime ritual and can impact the quality of parent–child interactions during the day. Over time, the child may be labeled and then self identify as a "poor" or "bad sleeper." One of the goals of treatment is to break this cycle of conflict and to replace impressions that the child is inherently a poor sleeper with the knowledge that the child can learn to be a "good sleeper."

While not always directly related to parental reinforcement, an infant and young child's feeding patterns can contribute to irregular sleep/wake patterns. It is common for a mother to nurse or feed her infant at the transition to sleep and the infant may fall asleep while feeding. This association between feeding and sleep onset is quite powerful and can become problematic when the infant becomes dependent on parental presence at the wake-to-sleep transition. After 6 months of age, most normally developing infants do not need to feed in the middle of the night. Modifying the feeding pattern prior to a sleep intervention is sometimes necessary before fully implementing the sleep plan.

Medical Problems

Various medical problems can contribute to a child's sleep problems and can shape parents' patterns of responding to their child that can, in turn, complicate the wake-to-sleep transition. Medical problems associated with pain and physical discomfort can result in a child's developing negative associations with the crib or bed. Parents' responses to their child's illnesses can be quite complex. Parental worry that arises from ongoing illness or that is conditioned based on a prior illness can result in some parents having ambivalent feelings

about separating from their child at bedtime. Parental guilt, a common and normal response to a child's illness, can also result in parents having ambivalent or conflicting feelings about separating from their child at bedtime. For example, a child who has gastroesophageal reflux or colic, and consequently has long bouts of screaming and crying at bedtime that cannot be soothed, can cause parents to develop a negative association with bedtime, which is a problem that needs to be addressed. While the well-established behavioral treatments for BIC are effective for children with medical illnesses, it is usually optimal to aggressively treat the underlying illness before implementing a behavioral sleep intervention.

Sentinel Events

A sentinel event in the child's or family's life may cause short- or long-term sleep problems. The event may cause increased vigilance and worry or a short-term change in routine that could lead to dependence on parental presence at the wake-to-sleep transition. A short-term positive adaptation in a family that has suffered a trauma might involve the parents taking the child into their bed during the acute response phase. Once the trauma becomes more remote and the parents attempt to shift the child back to her bed, the separation at bedtime may reignite childhood fears, parental guilt and/or parental ambivalence about cosleeping or being present when the child transitions to sleep. In these cases, treatment may focus on fears that are related to a past event, parental ambivalence, and a behavioral intervention involving a gradual approach to establishing an independent wake to sleep transition. If the trauma is severe, or is associated with sleep or bedtime (e.g., sexual abuse or a nighttime home fire), a referral to a pediatric mental health specialists for assessment and treatment of Post Traumatic Stress Disorders would be warranted.

Psychopathology and Temperament

There are now well-established links between child sleep disturbances and anxiety disorders [6] as well as the later emergence of mental health problems [7]. There are also significantly increased rates of sleep problems among children with developmental disorders (e.g., autism) [8–10], attention deficit hyperactivity disorder (ADHD) [3, 11], and other psychiatric disorders [12]. Therefore, a psychiatric history and assessment of the mental status is of particular importance. If a comorbid sleep and psychiatric disorder is suspected, a referral for treatment is in order. However, there is some evidence that an intervention for the child's sleep problems may improve the psychiatric symptoms.

The wake-to-sleep transition is one of the first significant separations that a child experiences in her development. The ability of the child to self sooth in order to regulate her internal states during these separations may be mediated by the attachment between child and parent. Attachment as conceptualized by Bowlby [13] is a biologically based bond between the child and parent that ensures safety and survival of the child and over the course of development has components of both physiological and psychological bonds [14]. Attachment patterns develop though a series of separations and reunions with the child and parent and over time lead to a stable and predictable relationship that the child internalizes. This internal model of the parent facilitates increasing self-regulatory capacity and independence over time. During infancy, the sleep–wake

cycle involves multiple separations and reunions. Thus, the wake-to-sleep transitions represent a critically important phenomenon in the emerging patterns of parent–child interactions [15]. A transactional model of sleep–wake development proposed by Anders et al. [15] illustrates how intrinsic (e.g., biomedical factors, infant temperament) and external contexts (e.g., cultural and social norms, family stress, parental psychopathology, SES) interact bidirectionally. When problems arise in the attachment relationship, they may appear first as BIC symptoms of the child but in some instances may also be understood as a function of problems of the child–parent dyad. For example, overidentification with the child and/or guilt over neglect and abandonment may trigger parental separation anxiety, which subsequently becomes generalized by the child as bedtime resistance from and/or difficulty initiating sleep onset. Therefore the child–parent dyad plays an essential role for establishing and maintaining healthy sleep behaviors early in life and assessment of the child–parent relationship is essential for understating the complex transactions that occur within the context of a family system.

Some children with stable personality characteristics involving avoidance, hyperarousal and hyperreactivity to environmental stimuli may have increased rates of sleep problems [16]. These children may be overly attentive to cues in their environment that threaten their sense of safety and may have difficulty letting down vigilance. Attachment disorders may also increase risk for sleep problems in children [17]. For example, children who have been adopted from other countries and have been raised in nurseries may be overly attached to parents or may be unable to accept nurturance and calming offered by parents. Criteria for diagnosing these types of problems can be found in the Zero to Three Diagnostic Manual [18]. In addition, there is some evidence that suggests children adopted from overseas may experience increased rates of sleep problems [19].

There are also some established links between postpartum depression and mother–infant sleep problems. Specifically, maternal depression may be worsened by inadequate sleep which is common during the infant's first 6 months of life, and maternal depression may result in irritability, withdrawal, and/or impairment in mother–child bonding [20, 21]. A behavioral–educational intervention designed to promote maternal and infant sleep resulted in increased maternal nighttime sleep time and longer infant nighttime sleep periods with fewer infant nighttime awakenings [22].

Cosleeping can also be linked to marital and family relational problems. In a marriage in which there is conflict, sexual, or emotional abuse, or avoidance of sexual relations, a child in the parental bed or a parent cosleeping in a child's bed may facilitate avoidance or serve as a buffer against further conflict. These parental psychiatric problems and marital problems can contribute significantly to the maintenance of a child's sleep problems, and referral to an adult psychiatrist or a family therapist may be a necessary adjunctive approach.

Environmental and Circadian Factors

There are a variety of environmental demands that may have a negative impact on the child's sleep period. Based on preference, economic or career demands, some parents enforce a sleep schedule on the infant. For example, parents who have to return to work soon after the birth of their child and initiate childcare

when the child is at 6 weeks of age may be required to wake their child early or put them to bed late. There is currently no consensus on the impact of sleep training or scheduling. Some infants may take easily to an enforced day and nighttime sleep schedule as a result of their being adaptable and having flexibility in mechanisms regulating their circadian phase. Other infants may have difficulty adapting. If the scheduled sleep periods are in direct conflict with the infant's homeostatic and circadian drive, then sleep problems may immerge. Either the infant has difficulty falling asleep at the required time or extended periods of wakefulness lead to poor regulatory capacity and the infant has difficulty settling. While there is no scientific evidence that children who are overtired and who have had insufficient sleep have more difficulty settling and do not sleep as well, this is accepted in clinical practice as a relatively robust phenomena [23–25].

The timing of sleep and nap periods can be difficult to navigate as there are vast individual differences in children's sleep needs: the timing of their day and nighttime periods of highest sleep propensity; their intrinsic flexibility to tolerate sleeping at different time periods; and, their ability to tolerate varying durations of wakefulness between sleep periods during the day. There is a good deal of variability in published normative trends regarding the timing and sleep needs in infants and children (refer to Table 6.1.) and no validated or clinically feasible approaches for their evaluation. Actigraphy and sleep logs provide the best approximation of key variables (i.e., number and duration of sleep periods, sleep-onset latency, wake time after sleep onset), but interpretation of these data and the development of a treatment plan require consideration of circadian and homeostatic factors as well as assessment of a child's behavior regulation during the day, and environmental demands.

Sleep Disorders

Several sleep disorders can cause symptoms of insomnia and should be evaluated as part of the assessment. These sleep disorders which cause or are associated with inadequate sleep may account for increased irritability and poor regulatory capacity that can delay sleep onset. For example, Obstructive Sleep Apnea Syndrome has been associated with behavioral problems and poor sleep regulation [26, 27]. Restless legs syndrome (RLS) has been estimated to occur in as many as 17% of children [28]. RLS involves limb discomfort that tends to occur in the early evening and can delay sleep onset. In some cases, parents are called upon to rub the child's legs to relieve sensations. The child's over activity at bedtime may relieve RLS sensations. Parents can misinterpret their child's activity as oppositional or another behavior problem which can result in parent–child conflict. Parasomnias (e.g., confusional arousals and night terrors), while not a cause of insomnia, can be confused for full awakenings. It is important to consider that sleep disorders can both have a direct effect on a child's sleep and can lead to the initiation of problematic bedtime routines that result in more persistent insomnia symptoms.

In summary, behavioral sleep problems in young children can present with varying levels of severity, ranging from transient problems with sleep onset to a diagnosable disorder, and their causes are usually multifactorial. While the vast majority of cases are relatively straightforward and can be evaluated and managed by general practice pediatricians or child mental health or behavioral

specialists, persistent problems require a comprehensive evaluation and consideration of sleep/wake mechanisms, child-specific factors, developmental and psychiatric status, family function, and environmental demands.

Insomnia Pathophysiology

The literature on the evaluation and treatment of Psychophysiological Insomnia in adults and BIC are quite large and there are several excellent review articles that summarize this literature [3, 4, 29]. However, there are only a few published reports that describe insomnia symptoms in children ages 6–18 years and no studies and few theoretical papers that link childhood insomnia to adult insomnia. There is only one treatment study of adolescents [30] and there are no criteria for making a differential diagnosis between BIC, Psychophysiological Insomnia and Idiopathic insomnia. The definition of insomnia in childhood is a topic that has lacked consensus among pediatric sleep specialists. Some argue that sleep problems during the school age and adolescent years are best attributed to other causes, such as parental reinforcement of poor sleep habits, anxiety and depression or circadian phase delays. Others contend that there is at least a small subgroup of children with sleep problems who have Psychophysiological Insomnia. The relationship between child and adult insomnia has not been studied.

We propose that there are three subgroups of patients between 6 and 18 years of age who meet criteria for Psychophysiological Insomnia as defined in the ICSD (Table 6.2). The first group is composed of children who will have lifelong difficulty initiating and maintaining sleep that supersedes BIC and will eventually be diagnosed with idiopathic insomnia. The second group is composed of children who have temperamental problems and may meet criteria for a psychiatric disorder and who also have chronic sleep problems that persist even when psychiatric problems remit. The third group is composed of children who have persistent symptoms of insomnia that may be attributed to an initiating cause (e.g., BIC, a medical illness, sentinel event, etc.), but their symptoms persist into childhood or adolescence and they are not responsive to established treatment for BIC.

Table 6.2 Definition of behavioral insomnias of childhood [58].

Behavioral insomnias of childhood	
• Sleep-onset association disorder	• Limit-setting sleep disorder
– Prevalence: 25–30%	– Prevalence: 25–30%
– Age group: 6–36 months	– Age group: 18–60 months
– Clinical features	– Clinical features
o Delayed sleep onset & nighttime awakenings	o Delayed bedtime
o Sleep onset becomes associated with exogenous cues	o Parents reinforce undesirable behavior at bedtime
o Sleep onset at bedtime or the middle of the night will not occur w/out cue	o Inconsistent limit setting
	o Otherwise normal nocturnal sleep

Assessment

Most sleep problems in young children are relatively straightforward to evaluate and treat, and are often addressed by pediatricians who provide general recommendations. Other problems require a comprehensive evaluation and a nuanced interpretation of data derived from sleep logs, actigraphy, and sleep questionnaires. Assessment of sleep problems in primary pediatric practices almost exclusively relies on parental report. When children present to a pediatric sleep specialist, they have typically failed other interventions and require more extensive assessment and an individually tailored treatment plan. This thorough assessment typically takes between 60 and 90 min.

The presenting complaint generally involves a conflict at bedtime or bedtime resistance, disrupted child and parental sleep (multiple middle-of-the-night awakenings and/or early morning awakenings), daytime impairment (e.g., irritability, impaired attention) or general concern that the child's sleep quality is poor. The first steps in the assessment are refining the presenting complaint and establishing a consensus treatment goal. The specific domains of assessment are provided in detail in Table 6.3. During the interview, observation of parent–child interactions in the examination room can also be useful in understanding the child's developmental status, regulatory capacity (i.e., their ability to maintain attention or deal with frustration), and their parents' attentiveness to their needs. When taking a history, some assessment of each of the categories discussed above is optimal. The remainder of the evaluation should focus on the five categories of potential causes and facilitators of sleep problems presented in the section above on Pathophysiology.

Table 6.3 Assessment domains.

Assessment domain	Area of focus	Example
Daytime routine	Time out of bed	Variability; parental role; child's mood & alertness
	Difficulty waking	Frequency; duration; parental role
	Daytime sleep propensity	Nap frequency; duration; time of day; planned/unplanned
	Academic difficulties	Poor performance; disruptive behavior; irritability
Sleep routine	Transition to sleep	Child's behavior (bedtime resistance, curtain calls or call outs); parental involvement
	Time to bed	Variability (weekday/weekend); sleep-onset latency
	Sleep hygiene	Activity leading up to scheduled bedtime; use of electronic media; caffeine
	Sleep environment	Light; temperature; noise; where and with whom; transitional object
	Nighttime sleep activities	Awakenings; differentiating full and partial arousals; snoring; restlessness

Sleep logs or diaries and sleep questionnaires are well-established assessment tools that have been used in the vast majority of assessment and treatment studies. Sleep logs used over a 2-week period provide more objective data for sleep patterns and can be used to establish a baseline to evaluate clinical interventions [31]. They have been shown to have relatively good reliability with actigraphy [32] and are a necessary complement to actigraphs. Optimally, a family should come to their initial assessment session with a completed 2-week sleep log that would document the timing of sleep periods: time in bed, SOL, WASO, time out of bed, and schedule and unplanned naps. It is often helpful to compare sleep periods from school schedules to those obtained on weekends, holidays or vacations. Two of the most widely used sleep questionnaires, the Sleep Habits Questionnaire [33] and the Pediatric Sleep Questionnaire (PSQ) [34], can be used to identify potential sleep problems in children and adolescents.

The Children's Sleep Habits Questionnaire (CSHQ) [33] is a comprehensive, parent-report measure for assessing children's sleep with good psychometric properties for both community and sleep-disordered samples for children 4–12 years of age. It yields both a total score and eight subscales scores reflecting key sleep domains that encompass a range of medical and behavioral sleep problems including sleep-disordered breathing, sleep-related anxiety, bedtime refusal, insomnia, parasomnias, and daytime sleepiness. However, it should be noted that the CSHQ does not have established normative values for the total or subscale scores. Items are rated on a 3-point scale. The CSHQ has shown adequate internal consistency in both clinical and community samples of children [33]. Two-week test–retest estimates also have been shown to be acceptable (0.62–0.79). The CSQH has been primarily used for research to assess sleep at baseline and postintervention.

The PSQ [34] is a validated 74-item questionnaire assessing children's sleeping habits and behaviors in children 2–18 years of age. The PSQ includes a 22-item sleep-related breathing disorder subscale (PSQ-SRBD) that has been shown to predict risk for PSG-confirmed SDB [35]. In addition, the PSQ includes a 4-item Sleepiness Scales (PSQ-SS) that contains items assessing the degree to which sleepiness is a problem rather than perceived sleep propensity in different situations. The PSQ-SS had low-to-moderate validity against an objective measure of sleepiness, the Multiple Sleep Latency Test, which is comparable to what has been observed in the adult literature assessing associations between the Epworth Sleepiness Scale and Multiple Sleep Latency Test [36].

Wrist actigraphy is a cost-effective tool that has a broad array of applications in research and in clinical settings. It estimates sleep by utilizing the difference between the reduced activity during a sleep period relative to waking behavior. The actigraph itself is a small battery-operated device (size of a watch) that is worn on the wrist 24 h a day (for up to 2 or more weeks) and records movement sampled several times per second with an accelerometer and stores the sampled data in epochs (typically 1 min). After downloading raw movement data, a computer program applies an algorithm to score sleep/wake periods. Actigraphy has been validated against PSG with agreement rates for minute-by-minute sleep/wake identification of higher than 90% [37–39]. Actigraphy has been used extensively in clinical and research assessment with children, and there are no risks associated with its use. In addition, actigraphy provides

the clinician with the opportunity to collect data from an individual sleeping in her natural sleep environment. Dependent variables derived from actigraphy include total sleep time (TST), sleep efficiency (SE; a ratio of minutes asleep to time in bed), and WASO. While SOL is also important, actigraphy does not afford reliable measures of this variable.

To aid the assessment of behavioral problems and psychiatric symptoms several of the following validated questionnaires utilizing parent or teacher report may help a clinician characterize behavioral problems and psychiatric symptoms that may be associated with BIC symptoms: (a) general behavioral problems – Child Behavior Checklist (CBCL); (b) depression – Child Depression Inventory (CDI); (c) anxiety – Screen for Child Anxiety-Related Emotional Disorders (SCARED); (d) ADHD – (Connors). If a co-occurring sleep and psychiatric disorder is suspected, a referral for treatment is in order.

The CBCL [40, 41] is a 113-item parent-report scale assessing a broad range of behavioral problems and social and academic functioning. The CBCL is one of the most extensively tested rating scales available and possesses excellent psychometrics. The measure yields Total, Internalizing and Externalizing Behavior scales, and eight subscale scores. In addition, there are a youth self-report version and teacher-report form that have been validated and may be considered to supplement the parental report. The measures take about 10 min to complete and 2 min to score.

The SCARED [42, 43] is a 42-item measure of childhood anxiety that includes a child and parent form. Birmaher et al. [44] found that the SCARED was able to differentiate between clinically anxious and nonanxious psychiatrically ill youth. Test–retest reliability coefficients and internal consistency coefficients of the subscales were found to be acceptable.

The CDI [45] is the most widely used self-report measure of depressive symptoms in children and is used extensively in pediatric sleep and affective research. The CDI consists of 27 items and yields five factors plus a total score normed according to age and gender. Published reports on the reliability and validity of the CDI are extensive with internal consistency coefficients ranging from 0.71 to 0.89 and the test–retest coefficients range from 0.74 to 0.83 (time interval 2–3 weeks).

The Connors Rating Scale – Revised (CRS-R) [46] is an 80-item observer (parent or teacher) or self-report questionnaire used to assess attention deficit/hyperactivity disorder (ADHD) and evaluate problem behavior in children and adolescents. Short versions of the CRS scales are also available. The CRS-R is comprised of seven factors: cognitive problems, oppositional, hyperactivity-impulsivity, anxious-shy, perfectionism, social problems, and psychosomatic. The CRS-R factors have high internal reliability (alphas = 0.75–0.94) but poor to adequate 6-week test–retest reliability (rs = 0.13 – parents and 0.78).

Treatment

There are several straightforward behavioral interventions that have established efficacy as treatments of the BIC [4, 29, 44, 47]. The primary interventions involve simple and graduated extinction techniques, sleep scheduling, positive routines, sleep hygiene training, and parent education. The number of sessions and the order in which these interventions are implemented has not

been adequately studied, and the demands of the specific case generally dictate priorities. Based on discussions with pediatric sleep specialists, the most common course of treatment involves a thorough in-person assessment and initial treatment recommendations, and then phone or E-mail follow-up.

Initial recommendations should focus on the treatment of medical problems and feeding schedules. Symptoms of untreated gastroesophageal reflux, and recurrent ear infections and other ailments involving pain and discomfort can undermine usually efficacious interventions. Special attention may need to be given to parents of children who have had medical problems as they may be, with good reason, hypersensitive to their child's condition. Children with illnesses involving pain may have developed an aversion to their crib or bed. When this is suspected, and when possible, a change in the bedroom or the type of bed may break this association. Other behavioral techniques such as systematic desensitization or graduated exposure may be most effective.

Ferber [25] recommends addressing feeding schedules prior to implementing a sleep intervention. Common feeding schedules and issues that interfere with an infant's independent wake-to-sleep transitions can include nursing or bottle feeding the infant. The association between feeding and direct contact with the parents is exceedingly powerful. Middle-of-the-night feedings are equally problematic. While a middle-of-the-night feeding usually results in the infant returning to sleep very rapidly and is rewarding for the overtired parent, it reinforces the child's dependence on the parent and may disrupt daytime feeding schedules. Specifically, after 6 months of age normally developing infants do not need to feed at night. The one caveat is that an infant whose sole nutrition is mother's milk may have difficulty going a whole night without a feeding. In this case the introduction of cereal for infants prior to bedtime can help to sustain the infant throughout the night.

Behavioral Interventions

A thorough evaluation establishes the priorities for interventions and specifically the identification of behaviors that are targets for change. An understanding of the behavioral cues that precede it (antecedents) and the responses or consequences that follow the behavior must be understood as critical components of the behavioral plan to eliminate the problematic behavior. Other considerations, which have been discussed in detail above, involve child, parent and environment-specific factors, and the history and course of the sleep problem.

Extinction

Extinction techniques involve removal of reinforcers that maintain or cue an undesirable behavior. *Simple or unmodified extinction* involves the immediate removal of reinforcers [48, 49]. For example, parents ignore the child's bids for attention at bedtime and the middle of the night and over the course of 3–5 days the child learns that crying, call outs and sometimes more extreme behavior (e.g., throwing toys or other objects and vomiting) do not elicit the desired response from the parent. The child no longer depends on the parents to be present at bedtime because he develops new associations or self-soothing skills, and the attempt to gain the parents attention cease. This

approach both breaks the chain of interactions between parent and child, and the sleep-onset association (i.e., parental presence) is transferred to an object or a self-soothing behavior that decreases or eliminates the child's dependence on the parent. Simple extinction has also been called the "cry-it-out" or cold turkey method. This is generally very effective, although not all parents feel comfortable implementing this plan. The child's crying and call outs can be quite persistent, and it is not uncommon for a child to vomit in their crib as a result of long episodes of crying and upset. If a child vomits during the course of an intervention plan, parents are instructed to cleanup immediately, and to provide their child with support but to minimize strong emotional responses (e.g., anger, frustration, physical comforting, etc.) that could be reinforcing. Parents who fail to implement simple extinction techniques often inadvertently reinforce longer crying spells and poorer self-regulation.

Graduated Extinction (GE) techniques are far easier for parents to tolerate because they involve less crying and more flexibility for parents to regulate the pace of the intervention. The trade-off is that GE can take longer to implement. There are some manualized approaches [49], but most interventions are tailored to the specific needs and preferences of the parent and child. The general principle of a GE intervention is that reinforcement is gradually withdrawn on a set schedule. The variables that are modified over time can include: physical contact with the child (e.g., breast feeding, holding, patting, etc.), verbal responses, proximity to the child, and frequency and duration of check-ins. Any combination of these variables can be gradually modified. For example, if the parent typically lies in bed with the child until the child falls asleep, the recommendation could involve: 3 nights of sitting next to the child's bed and holding his hand until he falls asleep; followed by 3 nights of sitting further away from the child and using verbalizations to calm the child; followed by 3 nights sitting in the room and refusing interactions; followed by 3 nights of check-ins every 5 min as long as the child stays in bed; followed by 3 nights of check-ins every 10 min.

There are several types of modifications that can be included in a GE intervention. *Fading* refers to a gradual decrease in the intensity or quality of parental reinforcement of the child's behavior. *Shaping* refers to the parents' reinforcement of qualitative changes in the child's behavior. For example, if the child cries for extended periods of time, the parent might only enter the room when there is a pause in the child's crying, thereby reinforcing calming behavior. *Chaining* refers to the parent gradually modifying the child's behavioral response. For example, the parents may tell the child that they will check in with the child as long as the child does not cry, then the parents may tell the child that they will check in as long as the child does not call out. *Thinning* refers to a gradual decrease in the frequency of parental reinforcement of child calming behavior.

Positive Routines

Positive Routines involve modification of parent–child interactions and behaviors at bedtime to decrease stress and conflict and to establish a relaxed environment that is conducive to a smooth transition to sleep. Positive routines also establish new wake-to-sleep associations. This may be coupled with a shift in the time to bed so that the child has an increased sleep propensity but is not

overtired and hyperaroused. In adjusting time to bed, it is also important to consider that there is a naturally occurring increase in arousal level also called the "danger zone." When a regular sequence of activities is established, the child knows what to expect and the sequence should involve increasing calm and relaxing behaviors like reading, close time with parents, quiet singing, etc. Parental warmth and calm, and positive and supportive statements reinforce the child's participation in the quiet activities, set the tone, model appropriate behavior, and reinforce and facilitate learning. Once the child learns the routine and transitions to sleep more quickly, the parents can gradually advance the bedtime with the goal of increasing the child's total sleep time. After about 6 months of age, the introduction of a transitional object (a blanket, a plush toy) can become an important part of the bedtime routine and can take the place of the parent or other sleep-onset associations that are problematic. The choice of an object is important because it will sometimes be with the family for years. It should be washable and made of a nontoxic material and parents may want to purchase a duplicate in the event that the object is lost.

Schedule Modification

Schedule Modification is sometimes necessary when the child's bedtime is exceedingly early or late or when the timing of naps interferes with bedtime. Schedule problems can arise when a child's optimal sleep time (controlled by their circadian phase) conflicts with parental or other environmental demands. Some young infants have very rigid early morning awakenings that chronically disrupt parents' sleep. While small shifts in the sleep phase can sometimes be achieved, parents' may need help in adjusting their schedule or agreeing on an alternating care plan for their child. Helping parents identify the optimal nap times based on the child's age and daytime sleep needs can be complicated. A late afternoon nap for some children over the age of 3 can erode their ability to fall asleep at night while others need a nap. Eliminating a morning nap between 18 and 24 months of age can extend the duration and improve the quality of the afternoon nap.

Sleep Hygiene Training

Sleep Hygiene Training involves changes in behaviors, sleep-related activities, or the environment that precede sleep and that interfere with sleep or the process of decreasing arousal. Sleep hygiene education is a common component of behavioral interventions used to address adult sleep problems such as insomnia and is routinely included in behavioral interventions targeted in pediatric populations [30, 50, 51]. Sleep hygiene education begins with an assessment of daytime and bedtime routines that delay sleep onset (e.g., exercise, use of electronic media, pets in the bedroom) and degrade sleep quality (e.g., caffeine use, environmental factors like light, noise, and temperature). The clinician works with parents and their child to establish guidelines that are feasible and within reference to developmental norms. During the hour leading up to the child's scheduled bedtime parent and children are instructed to engage in calm and relaxing activities that the child enjoys (e.g., reading). This may require some negotiation between child and parent and activities that have the potential to cause conflict should be avoided. The timing of bedtime routine activities

should be consistent and predictable and the scheduled bedtimes should not deviate significantly from day to day. The bed should only be used for sleeping; therefore, activities other than sleep (e.g., play) should be avoided to strengthen the association between the bed and sleep. A later bedtime may be warranted especially if a child appears alert and functions well with slightly less sleep. To the extent possible light (e.g., use of a nightlight) and noise should be reduced to promote an optimal sleep environment.

Other Treatment Considerations

Another intervention that can be useful with older children, involves the use of a bedtime pass [52, 53]. The child is provided with a token or piece of paper that allows them one opportunity to engage the parent after bedtime. This technique provides the child with more control and helps them to weigh their actual need to see the parent. If passes are not used on successive nights then the child can turn them in for a reward. As part of the intervention, parents should also be informed that following the initial implementation of the intervention, an extinction burst [54] commonly occurs. This phenomena, that occurs in many behavioral interventions, involves a temporary return to the undesired behavior. If parents are unaware of the phenomenal they may assume that the intervention has failed. They are generally instructed to persist in the treatment plan.

Conclusion

Behavioral sleep problems during childhood represent a complex group of problems ranging from short-term delays in sleep onset and parental reinforcement of problematic behavior to chronic problems with sleep initiation and maintenance. Thorough assessment is required to define the causes of course of the problems, particularly when they are chronic and disrupt the family and/or the child's daytime behavior. There is currently no research on the developmental pathophysiology of behavioral sleep problems in childhood, particularly those that are chronic and persist into later childhood and early adolescence. There is a relatively large literature and several good reviews of behavioral treatment strategies for BIC occurring in infants and children under the age of 7. In most cases parents can implement these interventions independently or with the assistance of a pediatrician or pediatric nurse. However persistent problems require the expertise of a sleep specialist.

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Two-Week Sleep Record

Patient's Name _____ Study ID _____

Patient's Date of Birth _____ Date of Sleep Record: From _____ To_____

Instructions:

1. Leave wake periods blank **2. Mark bedtimes with down arrows**

Example:

Day	12a	1a	2a	3a	4a	5a	6a	7a	8a	9a	10a	11a	12p	1p	2p	3p	4p	5p	6p	7p	8p	9p	10p	11p
Friday	sleep			sleep				↑					↓	nap		↑				↓	sleep			

3. Fill in Sleep Periods **4. Mark wake-up times with up arrows**

⇓ Midnight **⇓ Noon**

Day of the week	12a	1a	2a	3a	4a	5a	6a	7a	8a	9a	10a	11a	12p	1p	2p	3p	4p	5p	6p	7p	8p	9p	10p	11p

Special Observations and Notes: _____

_____

_____

7

Insomnia in Teens

John Garcia

Abstract

This chapter explores the causes for insomnia in teens: delayed sleep phase syndrome, insomnia as a symptom of psychiatric disorders, and insomnia as a symptom of substance abuse.

Other forms of insomnia occur in the adolescent population. These include psychophysiologic insomnia, neuro-endocrine/hormonal influences on sleep patterns, which pertain to women's health, restless legs syndrome, insomnia after traumatic brain injury, medical conditions including hyperthyroidism, and genetic disorders.

Keywords: Delayed sleep phase syndrome, Substance abuse, Restless legs syndrome, Hyperthyroidism, Traumatic brain injury

Introduction

This chapter explores the causes for insomnia in teens: delayed sleep phase syndrome (DSPS), insomnia as a symptom of psychiatric disorders, and insomnia as a symptom of substance abuse.

Other forms of insomnia occur in the adolescent population. These include psychophysiologic insomnia, neuro-endocrine/hormonal influences on sleep patterns, which pertain to women's health, restless legs syndrome, insomnia after traumatic brain injury, medical conditions including hyperthyroidism, and genetic disorders. These disorders are similar to those in adults. Please refer to the appropriate chapters in this book for further details.

Delayed Sleep Phase Syndrome

The prevalence of DSPS in teens is much higher than in adults. In adults, the prevalence range is 0.13–0.17% [1] One author found that the prevalence of DSPS in teens is 7% [2].

From: *Clinical Handbook of Insomnia,* Current Clinical Neurology
Edited by: H.P. Attarian and C. Schuman, DOI 10.1007/978-1-60327-042-7_7,

DSPS is defined as a misalignment between a teen's sleep phase and societal expectations. Teens often experience this as either an inability to get to sleep or an inability to awaken in time for school. Their sleep is continuous once sleep onset has been achieved. The sleep history during holiday and summer breaks is often revealing. During this time, they reveal their intrinsic circadian phase. After a few weeks in this schedule, during which they pay off their sleep debt, they report that they are without daytime sleepiness. Teens may adapt their environment to create social and photic isolation. They frequently change their sleep environment to the basement. They may cover their windows with cardboard or foil. Some even go to the extent of painting the walls in dark color (Box 7.1).

Box 7.1

1. There is an intractable delay in the phase of the major sleep period in relation to the desired clock time, as evidenced by a chronic or recurrent complaint of inability to fall asleep at a desired conventional clock time together with the inability to awaken at a desired and socially acceptable time.
2. When not required to maintain a strict schedule, patients will exhibit normal sleep quality and duration for their age and maintain a delayed, but stable, phase of entrainment to local time.
3. Patients have little or no reported difficulty in maintaining sleep once sleep has begun.
4. Patients have a relatively severe to absolute inability to advance the sleep phase to earlier hours by enforcing conventional sleep and wake times.
5. Sleep–wake logs and/or actigraphy monitoring for at least 2 weeks document a consistent habitual pattern of sleep onsets, usually later than 2 a.m., and lengthy sleeps.
6. Occasional noncircadian days may occur (i.e., sleep is "skipped" for an entire day and night plus some portion of the following day), followed by a sleep period lasting 12–18 h.
7. The symptoms do not meet the criteria for any other sleep disorder causing inability to initiate sleep or excessive sleepiness.
8. If any of the following laboratory methods is used, it must demonstrate a delay in the timing of the habitual sleep period: (1) 24-h polysomnographic monitoring (or by means of two consecutive nights of polysomnography and an intervening multiple sleep latency test), (2) Continuous temperature monitoring showing that the time of the absolute temperature nadir is delayed into the second half of the habitual (delayed) sleep episode.

American Academy of Sleep Medicine (2005). *International Classification of Sleep Disorders: Diagnostic & Coding Manual*. ISBN 0-9657220-2-3

Diagnosis and Differential Diagnosis of DSPS

Currently, the diagnosis of DSPS is made clinically but as laboratory measurement of salivary melatonin becomes more standard, it will be used to further confirm clinically suspected DSPS. Quoting Pandi-Perumal, "A substantial number of studies have shown that the onset of melatonin secretion under dim light conditions (the dim light melatonin onset or DLMO) is the single most accurate marker for assessing the circadian pacemaker" [3]. Still further in the future lies the hope of using genetic testing to inform the clinical evaluation. A link has been found between a length polymorphism in the *PER3* clock gene and DSPS.

Actigraphy is useful in the evaluation of DSPS especially when the patient or parent is not able to keep an accurate sleep log. It may also be useful when schools, truancy officers, or other officials want documentation of the sleep pattern. The American Professional Sleep Societies recommend the use of actigraphy in the diagnosis of circadian rhythm disorders [4].

The confidential teen interview (with the parent absent) is invaluable. It provides the necessary environment for the teen to divulge sensitive information that might otherwise remain hidden in the presence of a parent. It is good to share with the teen that the examiner will guard the confidentially of this part of the clinic visit as long as the information shared is not potentially life threatening to the teen or others. Topics explored with regard to sleep may include abuse of sedative hypnotics, stimulants or both, late-night internet addictions, or illegal activities such as gang related activities, burglary or theft.

The differential diagnosis of DSPS is not long and deserves mention (see Box 7.2). It includes restless leg syndrome, school avoidance/refusal, poor sleep hygiene, lifestyle issues, psychiatric disorders, and substance abuse.

Sleep onset insomnia as a symptom of anxiety, depression, posttraumatic stress disorder (PTSD), or other psychiatric disorder. As Drs. Owens and Mindell point out in their book "Pediatric Sleep; a Practical Guide," sleep onset insomnia caused by these disorders present no matter what time the teen goes to bed.

School avoidance/refusal. In this case, there may be a history of learning disability. The sleep/wake schedule may be more flexible. There may be nights where the youth goes to sleep early. This rarely happens in DSPS. Also in school avoidance, there is anxiety or fear of school. In contrast, in DSPS, school is perceived by the youth as occurring at an acutely inconvenient time, but the content of school is not onerous [5].

Box 7.2 DSPS differential diagnosis

Restless legs syndrome: Youth present with the "four R's"
- Symptoms occur at Rest
- There is an uRge to move the legs in response to the discomfort
- The discomfort is Relieved by movement
- Since RLS is autosomal dominant, a Relative can often be found with RLS

Treatment of DSPS

Treatment of DSPS includes four modalities; phototherapy, pharmacotherapy, chronotherapy, and adapting the environment. Phototherapy involves using light in the appropriate spectrum at the most appropriate time in the phase response curve. Each person responds to phototherapy differently. The amount of time the sleep phase is shifted depends on the person's intrinsic ability to respond to phototherapy, the amount of light provided, the timing of the light, and wavelength of light. Each person's intrinsic ability to respond to phototherapy at a specific time during the 24-h cycle has been graphically represented by the phase response curve. Blue light (460–470 nm) changes the sleep phase most effectively [6, 7]. Small doses of melatonin (in the study cited here as little as 0.05 mg to as much as 5 mg) given 5 h before sleep onset may help phase advance [8]. Chronotherapy involves requiring the teen to awaken 15 min earlier each morning. This eventually leads to sufficient sleep debt increasing the strength of the homeostatic drive to overcome the circadian clock's dominance and promote earlier sleep onset.

Case History 1

Gerald is a 14-year-old male with a chief complaint of, "I can't wake up for school." Mother shares that he has "never been an easy one to get to bed." About 1 year ago, he began to have more and more trouble getting to sleep. He currently is required to go to bed no later than 10 pm. He complains that he lies in his bed and is quite bored. He denies anxiety; although his mind wanders to plan the day to come or to review the day just finished. He is clear that these thoughts are not what keep him awake. He further denies pain, restless legs, and shortness of breath. His mother has not heard him snore or have observed apnea. Gerald's mother has gone to great lengths to get Gerald out of bed. Gerald complains that he wants to get out of bed but cannot. He often does not get out of bed until 11 am. If he makes it to school on time, he often sleeps in his first three classes. He is failing these first three classes. Prior to this difficulty, he was an A–B student. He has missed more than 40 days of school. Truancy office of the public school has been notified. He tried drinking large amounts of caffeine several months ago but has stopped as it did not help. He sleeps in the basement of the family's home. He has painted the walls dark blue. He has a TV and computer in his room. When interviewed in the absence of his mother, he shares that he often text messages until 2 or 3 am with another friend with similar problems. He has had no difficulty with the law. He denies use of illicit substances. He agrees to a urine toxicology screen. It is negative. Mother enjoys a normal sleep phase. Father, on the other hand, has always been a "night owl" by mother's report. His difficulties with "night-owlish-ness" were worse as a teen but improved in father's early twenties. Gerald's past medical history is unremarkable. Specifically, he has no history of head injury, depression, or anxiety [9].

After explanation of DSPS, Gerald is encouraged to awaken 15 min earlier every other day. Sleeping in on the weekends is discouraged. Early morning bright light exposure either with the use of a commercially available light box or ambient light is described. A small dose of melatonin (0.5–1 mg) at 5 pm is recommended. Asking the schools to make a reasonable accommodation such

as a 9 am start time by putting a study hall that he does not attend as his first class may be considered in some extreme cases.

Gerald returns in 1 month. He gradually phase advanced himself over 2 weeks. He is improving his grades in school. He shares that he is willing to continue the hard work of maintaining good sleep hygiene. He and his family have spoken with the vice principal in hopes of a later school start time beginning next semester.

The prognosis for teens with DSPS is good. The intensity of DSPS generally wanes in the early 20s though a tendency toward DSPS persists through life. If teens are coached to respect their biologic clock, they are generally much happier. This may take some negotiation between the family and the school system. The availability of online high schools has provided some flexibility in school start times.

There are several common pitfalls with regards to making the diagnosis of DSPS. Lack of awareness of the diagnosis leads parents, peers, and school officials to identify teens with DSPS as "lazy." Family and teens are relieved when it is shared that "lazy" is not a diagnosis. It is a sloppy designation that often signifies depression, anxiety, a sleep disorder, or a learning disability. Secondly, being vigilant for comorbid conditions is recommended. Depression and DSPS often travel together. It is nearly impossible to treat the DSPS if depression is not addressed. Finally, as mentioned above in the differential diagnosis portion, other diseases may masquerade as DSPS including RLS, school avoidance, anxiety, and depression.

Psychiatric Disorders

Teens often present with insomnia as the primary complaint of a psychiatric disorder. It is important to identify the root psychiatric cause of the insomnia. Without treatment of the root psychiatric disorder, a patient often returns requesting more effective medication. Insomnia is often seen as a symptom of depression. It is clear that insomnia serves as a marker for an increased risk of suicide in adolescents though the link between suicidality and insomnia appears to be mediated by depression [10]. Using a standardized tool like the Beck's depression inventory is helpful. This author usually recommends that the psychiatrist manages both the antidepressant and sleep inducer. If there are side effects, the patient then has one doctor to call. The sleep consultant remains in the role of helping rather than taking over care.

Teens with anxiety may present with sleep onset insomnia. Insomnia is an independent risk factor for suicide attempt in patients with anxiety [11]. Reports of fears at bedtime or the self-fulfilling prophecy of "I don't want to be the last one in the house awake" cause a curious sleep doctor to pursue the diagnosis of anxiety with a tool such as the Children's Manifest Anxiety Scale.

There is evidence that mild insomnia caused by the everyday stressors of being a teenager without evidence of severe psychiatric disorders may be adequately addressed by the primary care provider [12, 13] The primary care provider may become even more effective by consulting a licensed provider of integrative medicine therapies such as self hypnosis, biofeedback, and relaxation imagery [14]. Other studies have questioned the effectiveness of integrative medicine therapies in treatment of insomnia [15, 16].

Case History 2

Aaron is a 16 year old presenting with sleep onset insomnia. His mother shares that as a school age child, he had many "curtain calls" at bedtime. He would often come to his parents after being put down to bed requesting another story, a drink of water, or reporting some fear. Now, as a teen, things are worse. He does not want to be the last one awake in the house. He slept in his older sister's room until she left for college last year. Even when he gets to sleep after midnight, he is unable to sleep in past 8 am. He is a straight-A student. Mother describes him as a worrier. He is without symptoms of snoring, reflux, or restless legs. His past medical history is notable for tension headaches.

The history describes a child with childhood anxiety manifesting as sleep onset insomnia. A trial of biofeedback/relaxation imagery/self-hypnosis were quite effective in promoting sleep. Once every 2 weeks, if he is not asleep by midnight, he will take 10 mg of zaleplon.

Insomnia as a Symptom of Drug Abuse

"Insomnia and substance abuse are bi-directional" [17]. Teens burdened with untreated insomnia may pursue illicit drugs in attempt to treat themselves. Stimulants abused in self-treatment of insomnia related daytime sleepiness include amphetamine, methylphenidate, fenfluramine, pemoline, cocaine, methamphetamine ("speed") phenmetrazine, 3,4-methylenedioxymethamphetamine ("ecstasy"), and propylhexedrine [18]. Drug abusing teens may suffer more insomnia and pursue more illicit drugs. Whether the insomnia is primary or a side effect of drug abuse, it acts as an early warning for vulnerability to addictions. Consequences of untreated combined sleep-addictive behavior are costly to society [19, 20].

Insomnia as a symptom of substance abuse may represent withdrawal from prescription or illicit sedating agents, abuse of stimulants, or even overuse of caffeine. Insomnia in illicit sedating agents may present in withdrawal. Abuse of stimulants may produce profound insomnia and rebound hypersomnia. The international classification of sleep disorders describes polysomnographic findings associated with stimulant-dependent sleep disorder. These include "(1) sleep disruption with reduced sleep efficiency and increased number and duration of awakenings; and upon withdrawal of the stimulant or (2) an MSLT that demonstrates a mean sleep latency less than 10 min" [21].

The plethora of commercial hyper-caffeinated energy/sports drinks as well as the cultural acceptance of caffeine overconsumption can lead to caffeine abuse. In fact, one quarter of college students report mixing energy drinks and alcohol. Teens who mix energy drinks and alcohol have a significantly higher incidence of being taken advantage of sexually, being injured and requiring medical attention and riding with an intoxicated driver [22].

Adolescents reporting insomnia report more depression, anxiety, as well as increased drug and alcohol use [17, 23, 24]. Fifty percent of adults with alcohol dependence and sleep problems report the onset of sleep problems preceded the onset of alcohol dependence [24]. Teens who use alcohol have a high prevalence of self reported sleep problems. Teens who drank 1–11 times in the previous year were 2.3 times more likely to report sleep problems [23].

Sleep problems increased in prevalence as the number of days of alcohol use increased [23]. Targeting poor sleepers with additional counseling and education regarding the risks of substance use, it may be possible to prevent addiction [25].

From the above, it is clear that insomnia can be a marker preceding drug abuse. This requires that clinicians include questions regarding insomnia in their routine interview. Adolescents underutilize mental health services, so the burden of identification lies with pediatricians [17]. If a provider identifies insomnia, a confidential interview with the teen separated from the parents is recommended. During this interview, mental health and substance abuse should be explored. The clinician should have a low threshold for requesting a urine toxicology screen. It is suspicious when a teen refuses this test. Appropriate referrals to mental health and chemical dependency programs hinge on the clinical interview.

A common neurophysiologic pathway for insomnia and addictive behaviors is suspected and deserves further research [17].

Case History 3

Alan, 17 years old, is required by his mother to attend an evaluation by the family's pediatrician. Mother is concerned that Alan's sleep/wake pattern have become what mother describes as "bizarre" over the past 9 months. Alan stays out late with his friends. When his mother "puts her foot down" and requires him to stay home, he will fall asleep around 9 or 10 pm. He has missed many days of school and the truancy office is involved now in the second half of the school year. Mother filled out a sleep log though she is not exactly sure what time Alan has been getting home.

In the confidential interview, Alan is inappropriately unconcerned about his failing school performance. He is irritated because his mother has forced him to the meeting and answers most questions with "I don't know" or shrugs his shoulders. He refuses a urine toxicology screen. He denies restless legs symptoms, anxiety, and depression. Before 9 months ago, he was a B student.

Back in the room with mother and Alan, the discussion becomes more heated with mother accusing Robert of using marijuana and "other stuff." Alan denies the accusations. The pediatrician narrowly avoids Alan stomping out of the office and persuades him to meet with a community social worker familiar with teen issues including substance abuse. Fortunately, the social worker and Alan strike up a trusting relationship. Over several weeks, Alan begins to be more honest about his multiple substance abuse. It is discovered that the problem began when he was 13 years old.

Clinical Red Flags

1. The insomnia in conjunction with suspicions of substance abuse are concerning as mentioned above.
2. This is not standard DSPS as Alan can go to sleep at a reasonable time when he is forced to stay home. Teens with DSPS (with or without secondary substance abuse) do not fall asleep at a normal time.
3. Alan's behavioral clues include his inappropriate unconcern for his own well-being and his passive behavior.
4. Alan's refusal of the urine toxicology screen is suspicious at best.

Summary

This chapter has reviewed common causes of insomnia in teenagers, including delayed sleep phase syndrome, insomnia associated with psychiatric disorders, and insomnia in substance abusing teens. It is the author's hope that the early identification of insomnia may create novel approaches to working with teens previously misidentified as lazy, noncompliant, or other pejorative labels. It is hoped that the early identification of insomnia may alert mental health providers to depression, anxiety, and substance abuse.

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8

Insomnia During Pregnancy

Beth Ann Ward

Abstract

Pregnancy is a time of extensive physiologic, physical, and hormonal changes. These changes can significantly disrupt a woman's sleep and can result in symptoms of daytime sleepiness and fatigue. Understanding how sleep is altered during pregnancy and recognizing sleep disorders that commonly develop during pregnancy may enable healthcare professionals to identify and treat sleep problems. Sleep is vital to the health and well-being of pregnant women. By counseling women on strategies to optimize sleep, healthcare professionals may improve the quality of nighttime sleep and reduce daytime sleepiness and fatigue.

Keywords: Estrogen, Progesterone, Pregnancy, Insomnia, Sleep-disordered breathing, Restless legs syndrome

Introduction

Pregnancy is a time of extensive physiologic, physical, and hormonal changes. These changes can significantly disrupt a woman's sleep and can result in symptoms of daytime sleepiness and fatigue. Understanding how sleep is altered during pregnancy and recognizing sleep disorders that commonly develop during pregnancy may enable healthcare professionals to identify and treat sleep problems. Sleep is vital to the health and well-being of pregnant women. By counseling women on strategies to optimize sleep, healthcare professionals may improve the quality of nighttime sleep and reduce daytime sleepiness and fatigue.

Influence of Hormonal Changes on Sleep

The vast changes in hormonal levels that occur during pregnancy may impact sleep architecture. Most notably, progesterone and estrogen levels steadily rise throughout the pregnancy [1]. Progesterone has been shown to have a sedating

From: *Clinical Handbook of Insomnia,* Current Clinical Neurology
Edited by: H.P. Attarian and C. Schuman, DOI 10.1007/978-1-60327-042-7_8,

effect, decreasing sleep latency, and increasing non-REM sleep [2, 3]. Daytime sleepiness and fatigue are often the early symptoms of pregnancy, and these symptoms may be directly attributable to the soporific effects of progesterone. Progesterone may also potentiate the effects of anesthetics and sedative–hypnotic medications [4]. The effects of estrogen on sleep are still not fully understood. In animal studies, estrogen has been shown to suppress REM sleep [5–7]. However, in human studies, estrogen appears to increase REM sleep [2].

In addition to the direct effects of estrogen and progesterone on the central nervous system, these hormones have systemic effects that may impact sleep. For example, progesterone relaxes smooth muscle, which can lead to increased urination, even in the first trimester of pregnancy [4]. Estrogen can cause vasomotor rhinitis, characterized by nasal and pharyngeal mucosal edema, with resultant airway narrowing and increased airflow resistance [8]. These direct effects of estrogen can lead to snoring, and may predispose to obstructive sleep apnea.

Changes in the Sleep–Wake Cycle During Pregnancy

Sleep disturbances are an almost universal experience during pregnancy. Survey studies of pregnant women reveal that the duration and quality of sleep varies through the course of the pregnancy. During the first trimester, sleep duration increases by an average 0.7 h [9]. However, despite the increase in sleep time, women describe a decrease in the quality of their sleep and complain of nocturnal awakenings [9–11]. A prospective study of 25 pregnant women demonstrated a 1.4-fold increase in nocturnal arousals during the first trimester as compared to prior to conception [12]. Moreover, during the first trimester, many women complain of increased daytime sleepiness and fatigue.

For many women, sleep and daytime levels of energy and alertness improve during the second trimester of pregnancy. However, 19% of women will continue to report sleep difficulties [13]. Additionally, total sleep duration decreases late in the second trimester, as compared with the first trimester.

The third trimester represents the period of most disturbed sleep for pregnant women. The greatest change in the sleep patterns at this time is due to increased wakefulness after sleep onset [14–17]. During the third trimester, both the number and duration of nocturnal awakenings increase [10]. Several studies have demonstrated that over 90% of women experience nocturnal awakenings during the third trimester [9–11]. On average, women have 2–5 awakenings per night [11, 17], and during the third trimester, women remain awake for an average of 20 min with each arousal [12]. As the pregnancy progresses, women also report longer sleep onset latencies and often complain of waking too early in the morning [11]. Although decreased sleep efficiency in the third trimester leads to reduced amount of sleep as compared with earlier in the pregnancy, overall total nocturnal sleep times are similar to pre-pregnancy levels [9]. Moreover, 78% of pregnant women report taking naps in the third trimester [18], with an average nap duration of approximately 1 h [11, 18]. As a result, total sleep in a 24-h period may exceed pre-pregnancy levels. Nevertheless, although total duration of sleep is increased as compared with prior to pregnancy, the quality of sleep declines in the third trimester [9, 19]. Many women have impaired daytime alertness during the third trimester, with 67% reporting “moderate” to “very great” daytime sleepiness [11].

Changes in Sleep Architecture During Pregnancy

Polysomnographic studies evaluating how sleep architecture changes during pregnancy have been limited by small sample size, few nights of polysomnography, and little longitudinal data. However, these studies have confirmed many of the changes in sleep patterns that women report in the survey studies. Polysomnographic studies demonstrate that sleep disruption in pregnant women is even greater than they subjectively report, with objective recordings revealing that women obtain approximately 30 min less of total sleep time than they report [20]. Among the most consistent finding in polysomnographic studies is a decrease in sleep efficiency during pregnancy. This reduction in sleep efficiency is present by 11–12 weeks' gestation, and continues to decline throughout the course of pregnancy [16]. The reduced sleep efficiency is primarily due to increased wakefulness after sleep onset [14, 15]. In one study of 7 pregnant women during late pregnancy, pregnant women were observed to have 37–50 min of wakefulness during the night, as compared with only 5 min of wakefulness in non-pregnant controls [21]. In addition to increased wakefulness after sleep onset, pregnant women also demonstrate prolonged sleep onset latencies. On average, pregnant women take 21.9 min to fall asleep as compared with 10.9 min in non-pregnant women [21].

Longitudinal studies that have followed women through the course of pregnancy have shown that during the first trimester, total sleep time increases by approximately 34 min as compared with prior to pregnancy [16]. By 23–24 weeks' gestation, total sleep time decreases, and at 35–36 weeks' gestation, total sleep time is similar to prior to pregnancy [16].

Polysomnographic studies have yielded inconsistent results regarding the impact pregnancy has on sleep stage distribution. Some studies have demonstrated a decline in REM sleep through the course of pregnancy [15, 17], as well as a reduction in REM sleep in pregnant women as compared with non-pregnant controls [14]. However, other studies have failed to demonstrate a decrease in REM sleep during pregnancy [16, 21]. Similarly, studies investigating the impact pregnancy has on slow wave sleep (SWS) have produced conflicting data. Some studies have observed a decrease in SWS during pregnancy [16, 21–23], while other studies have revealed an increase in SWS during pregnancy [15], and still other studies have found no change in SWS during pregnancy [14, 17].

Causes of Nocturnal Arousals During Pregnancy

Many of the physical and hormonal changes that occur during pregnancy can account for the fragmented sleep that women experience. The causes of the frequent nocturnal arousals change as the pregnancy progresses. During the first trimester, one of the most common causes of night awakenings is nocturia. In one study of 25 pregnant women, 51.4% of all awakenings during the first trimester were attributed to the need to urinate [12]. This is likely related to progesterone's inhibitory action on the smooth muscle of the bladder [4]. Furthermore, during the first trimester, as the fetus grows within the pelvis, it can place pressure on the bladder, resulting in an urge to urinate. Other causes of awakenings during the first trimester include nausea, vomiting, and backaches [12, 13].

Nocturnal awakenings often decrease during the second trimester, and many women report more energy during the day. As the growing fetus moves out

of the pelvis, it exerts less pressure on the bladder, and urinary frequency consequently improves [24]. However, during the second trimester, women begin to wake up due to general discomfort, perhaps related to weight gain and increased abdominal size [12]. It is during the second trimester that women can begin to sense fetal movements, and these movements may awaken women [12]. Approximately one-third of women report the onset of snoring during the second trimester, which may disrupt their sleep [24]. Heartburn may also arise in the second trimester, due to the development of gastroesophageal reflux, which can cause frequent brief arousals during sleep [12, 25].

Sleep during the third trimester of pregnancy is marked by an increased number of arousals at night [12], and women frequently report a decrease in the quality of their sleep [9, 19]. As the uterus enlarges, it again exerts pressure on the bladder, causing urinary frequency. Nearly 85% of women report frequently waking in the third trimester in order to urinate [26]. The enlarging uterus displaces the intestines and lower esophageal sphincter, and the lower esophageal sphincter pressure progressively declines throughout the pregnancy [27]. Thus, heartburn and gastroesophageal reflux become more common and of increased severity in the third trimester, and may fragment sleep [12]. The expanding uterus also elevates the diaphragm, which can reduce lung capacity and lead to shortness of breath, another commonly cited source of arousals [12, 26].

Women in the third trimester frequently report discomfort at night that interferes with their sleep. Specifically, backaches and joint pain represent a common source of arousals at this stage in the pregnancy [11, 12, 14, 26]. Approximately 70% of women report that their sleep is disrupted because they are unable to find a comfortable position [11, 26], and 45% of women awaken due to a sensation of being too hot or perspiring [26].

Leg discomfort often disturbs sleep in pregnant women. The frequency of women who awaken due to leg cramps steadily increases during the pregnancy, affecting 12–21% of women in the first trimester, and impacting up to 75% of women during the third trimester [28]. Furthermore, approximately one-quarter of pregnant women develop restless legs syndrome by the third trimester of pregnancy, which can result in prolonged sleep-onset latencies [29, 30]. Periodic limb movements in sleep have also been demonstrated in pregnant women and can cause frequent night awakenings [31].

Fetal movements, frightening dreams, and anxiety about labor, delivery, and upcoming lifestyle changes may also disrupt sleep during the third trimester. [12, 19, 26] Furthermore, attention should be paid to the sleep environment of women throughout pregnancy. Many pregnant women report that their sleep is disturbed by co-sleepers, children, and outside noises [12].

Restless Legs Syndrome in Pregnancy

Restless legs syndrome (RLS) is a neurologic disorder characterized by an overwhelming urge to move the legs, usually associated with an uncomfortable or painful sensation in the legs [32]. The urge to move the legs is worse at rest, worse at night, and relieved with movement [32]. Restless legs syndrome becomes more common with advancing age, and is rare in young, healthy individuals without a family history of RLS [33, 34]. However, RLS frequently develops during pregnancy, with a peak incidence of symptoms occurring in

the third trimester. A prospective study of 41 American women, none of whom had RLS prior to pregnancy, found that 12.5% of women developed RLS symptoms in the first trimester of pregnancy, and observed that by the third trimester, 23% of women had developed symptoms [29]. A cross-sectional study of approximately 16,500 pregnant women in Japan yielded similar results, reporting a prevalence of restless legs syndrome of 15% at 3–4 months gestation, and a prevalence of 23% at term [30]. Women who develop RLS during pregnancy have more difficulty falling asleep, more nocturnal arousals, shorter sleep duration, and a higher incidence of excessive daytime sleepiness than those women who do not have RLS [30, 35]. Risk factors for developing RLS during pregnancy include primiparity, sleep duration of less than 7 h in the night, lack of daytime naps, employment, and use of alcohol or tobacco [30].

Iron deficiency is a risk factor for RLS in non-pregnant individuls, with ferritin levels less than 50 mcg/l correlating with more severe symptoms [36, 37]. Although pregnant women with RLS have indeed been demonstrated to have low ferritin levels, this is a non-specific finding, as pregnant women without restless legs syndrome had similar reductions in ferritin levels [29]. In contrast, there appears to be an association between reduced folate levels and RLS in pregnant women. Women who develop restless legs syndrome have consistently lower folate levels than women who do not develop restless legs syndrome [29].

Metabolic demand for folate and iron is high during pregnancy in order to maintain fetal growth and red blood cell formation. Thus, dietary intake is often insufficient, and ferritin and vitamin B_{12} levels decline beginning in the second trimester [24]. Because of the high metabolic demand, it is difficult to replenish iron or folate stores during pregnancy, and women who have low folate or ferritin levels prior to pregnancy are most at risk for developing restless legs syndrome [24]. Thus, during pre-conceptual counseling folate and iron levels should be assessed, and if levels are low, patients should be given appropriate supplementation.

When RLS develops during the pregnancy, consideration should be given to checking a serum ferritin level, as iron supplementation may be helpful [38]. Given the association of low folate and restless legs syndrome in pregnancy, folate supplementation may also be helpful. Although there is only limited data evaluating folate therapy for treatment of restless legs syndrome in pregnancy [39], folate supplementation of 400–800 mcg daily is recommended for all women for prevention of neural tube defects. Thus, ensuring that women are receiving adequate folate supplementation is a reasonable treatment approach.

For individuals who are not pregnant, dopamine agonists are considered the treatment of choice for RLS [40]. Of the dopamine agonists, only pergolide has been labeled by the Food and Drug Administration (FDA) as Class B in pregnancy (presumed safety based on animal studies). However, use of pergolide has been associated with valvular heart abnormalities in non-pregnant individuals [41]. Other dopamine agonists such as ropinirole and pramipexole, are classified by the FDA as Class C in pregnancy (uncertain safety; no data from human studies and animal studies show an adverse effect). Among other pharmacologic agents used to treat RLS, only oxycodone is labeled as Class B in pregnancy. Other opioids, as well as most benzodiazepines and anticonvulsants, are associated with significant concerns regarding safety during pregnancy and thus have been classified as Class C, D, or X in pregnancy.

Given the risks associated with pharmacologic treatment of restless legs syndrome during pregnancy, consideration should be given to non-pharmacologic therapy. Anecdotally, massaging the limbs, stretching, walking, applying heat to the limbs, and relaxation techniques have all been reported to reduce symptoms [42]. Women should be reminded to dedicate an adequate amount of time for sleep, as total sleep durations less than 7 h are associated with restless legs syndrome [30]. Alcohol and tobacco use are both associated with an increased risk of RLS during pregnancy, and pose other risks to the developing fetus, and thus women should be counseled to abstain from both during pregnancy [30]. If conservative measures and iron and folate supplementation prove insufficient in controlling restless legs syndrome symptoms, short-term use of oxycodone or pergolide may be warranted when symptoms are severe.

Sleep Disordered Breathing in Pregnancy

Sleep disordered breathing (SDB) is a general term used to describe respiratory disturbances in sleep; this can include primary snoring, upper-airway resistance syndrome, and obstructive sleep apnea syndrome [43]. SDB can disrupt sleep and may lead to daytime sleepiness [44]. During pregnancy, there are vast physiologic and hormonal changes that occur. Some of these changes theoretically should protect against the development of SDB, while others may predispose to SDB. Throughout pregnancy progesterone levels steadily rise [45], leading to increased respiratory rate and increased minute ventilation [46, 47]. The increased respiratory drive may reduce the risk for central apneas [48]. Progesterone also increases pharyngeal muscle tone, reducing the risk of upper airway closure [47]. As pregnancy progresses, women are encouraged to sleep in the lateral position to reduce uterine compression on the inferior vena cava and maintain venous return. Sleeping in the lateral position may reduce the risk for SDB, since obstructive events tend to be more frequent in the supine position as compared with the lateral position [49]. As reviewed above, some studies suggest that the percent of REM sleep diminishes during pregnancy [14, 15]. Obstructive sleep apnea is frequently more severe during REM sleep, particularly in women [50]; thus, if REM sleep is reduced during pregnancy, this may reduce the risk of obstructive sleep apnea.

Despite some of the physiologic and hormonal changes of pregnancy which reduce the risk for SDB, many other changes that occur during pregnancy may precipitate the development of SDB. Excess body weight is the strongest risk factor for obstructive sleep apnea, with the risk of sleep apnea increasing relative to the degree of excess weight [44]. Moreover, moderate increases in weight have been demonstrated to significantly increase the risk of sleep apnea [51]. In a large prospective study evaluating the impact of weight change on SDB, a 10% weight gain resulted in a sixfold increased risk of developing moderate–severe sleep apnea, and a 20% weight gain predicted an approximately 70% increase in the apnea–hypopnea index [51]. The average weight gain during pregnancy is 25–35 lb, often resulting in an increase of 20% or more of the total body weight. This degree of weight change, over a relatively short period of time, may predispose to the development of SDB. Elevated estrogen levels during pregnancy can cause vasomotor rhinitis, nasopharyngeal hyperemia, and mucosal edema [45]. These changes can result in airway narrowing, increased resistance to airflow, and ultimately, airway obstruction.

The increase in nocturnal awakenings and sleep fragmentation that occurs during pregnancy may also augment the risk for SDB. Sleep onset is associated with an irregular ventilatory pattern, typically characterized by oscillating, periodic breathing [52]. When sleep is fragmented, the increased frequency of wake–sleep transitions can amplify this unstable breathing pattern, heightening the risk for SDB.

Snoring commonly develops in pregnant women. Prior to pregnancy, only 4% of women report snoring [53]. The prevalence of snoring increases throughout the pregnancy, and by the end of pregnancy, approximately 25–30% of women describe regular snoring [11, 12, 18, 53, 54]. Obese women are more likely to snore during pregnancy than women who are not obese [55], and it has been suggested that both the initial BMI as well as the amount of weight gain during the pregnancy impact whether sleep-disordered breathing develops [34]. Snoring may contribute to sleep complaints, as it can lead to arousals and fragmented sleep. Moreover, snoring is one of the most common symptoms of obstructive sleep apnea [56], and thus the onset of snoring may herald the development of sleep apnea.

The true prevalence of obstructive sleep apnea in pregnancy is not known, as large population-based studies utilizing polysomnography to evaluate for sleep apnea have not been performed. However, in addition to the increase in snoring, pregnant women report an increase in other symptoms of sleep apnea, including gasping, choking, difficulty breathing, and apneic events [11, 57]. A small case-control study utilizing polysomnography evaluated for SDB in obese and non-obese pregnant women [55]. Obese pregnant women had a higher apnea–hypopnea index (AHI) than non-obese pregnant women, as measured during both the first trimester and during the third trimester [55]. Furthermore, the mean AHI in obese pregnant women significantly increased during the course of pregnancy (1.7 vs. 2.6 events/h, $p<0.01$). The clinical significance of this increase in AHI is unclear, however, as both values were within the normal clinical range. One obese woman in the study did develop mild sleep apnea, whereas none of the non-obese women developed sleep apnea. Another study performed polysomnograms on 35 women during the third trimester of pregnancy, all of whom endorsed symptoms of sleep apnea [58]. Obstructive sleep apnea was diagnosed in 11.4% of these women. The women found to have obstructive sleep apnea had a significantly larger neck circumference than women who did not have sleep apnea. The women with obstructive sleep apnea were obese and were noted to have higher BMI than those women without sleep apnea (37.5 vs. 30.6), although this difference was not statistically significant ($p=0.062$). These studies reveal that some women do develop obstructive sleep apnea during pregnancy. Thus, it may be prudent to screen for symptoms of sleep apnea in pregnant women, particularly among obese women. If symptoms of sleep apnea are present, further evaluation with polysomnography may be warranted.

The impact of sleep-disordered breathing on pregnancy remains uncertain, as studies thus far have yielded conflicting results. A link between SDB and adverse fetal outcomes was first proposed based on case reports of intrauterine growth retardation in women with obstructive sleep apnea [59, 60]. Subsequent studies have reported that snoring is associated with a greater than twofold increased risk of gestational hypertension, preeclampsia, fetal growth retardation, and perinatal complications [54, 61]. Habitual snorers

have also been found to be more likely to have infants with low Apgar scores [54]. However, other studies have failed to reveal an increased risk of maternal or fetal complications among women who snore during pregnancy [9, 53, 62–64]. Thus, it is unclear whether snoring during pregnancy truly poses an increased risk for adverse outcomes. It is possible that it is not primary snoring, but rather obstructive sleep apnea, which increases the risk for unfavorable pregnancy outcomes. Because the above referenced studies which examined the relationship between snoring and pregnancy outcomes did not utilize polysomnography, it is not possible to discern whether the adverse outcomes were attributable to snoring alone versus obstructive sleep apnea.

Studies utilizing polysomnography to assess for sleep apnea in pregnant women have been limited. In a study by Sahin et al. polysomnograms were performed on 35 women, all of whom endorsed symptoms of obstructive sleep apnea [58]. Four of the women (11.4%) met diagnostic criteria for obstructive sleep apnea. Infants born to the women with obstructive sleep apnea had lower Apgar scores ($p=0.006$) and lower birth weights ($p=0.126$) than infants born to women without sleep apnea, although none of the infants were diagnosed with intrauterine growth restriction. Three of the infants born to women with obstructive sleep apnea (75%) were treated in the newborn healthcare unit due to respiratory distress. Nonstress test (NST) recordings were performed during the diagnostic polysomnograms. Three of the women diagnosed with obstructive sleep apnea (75%) were noted to have fetal heart rate decelerations in conjunction with maternal oxygen desaturations. In comparison, only one woman without obstructive sleep apnea (3.2%) was observed to have late decelerations on the NST recording. In this study, none of the four women diagnosed with obstructive sleep apnea had pregnancy-induced hypertension or preeclampsia [58]. Two of the four women with sleep apnea (50%) had gestational diabetes, whereas only two of the 31 women (6.5%) without sleep apnea had gestational diabetes. This study was limited by small numbers, as only four women were diagnosed with sleep apnea. Larger prospective randomized-controlled studies of obstructive sleep apnea in women are still needed to determine the impact obstructive sleep apnea has on maternal and fetal outcomes.

Given that it is unclear whether sleep apnea in pregnant women increases the risk for adverse outcomes, it is impossible to determine whether treatment of sleep apnea can modify these potential risks. However, small case-series have been reported in which pregnant women with documented SDB have been effectively treated with continuous positive airway pressure (CPAP) [65, 66]. In these case-series, the women who were treated with CPAP delivered healthy infants of normal birth weight. Thus, the limited data available at this point suggests that treatment of sleep apnea in pregnant women should be considered as it may improve outcome. Moreover, treatment of sleep apnea during pregnancy should be considered in any woman who has complaints of disturbed nighttime sleep or daytime sleepiness.

During pregnancy, conservative treatment measures may be effective in controlling symptoms of sleep-disordered breathing. Women should be counseled to avoid excessive weight gain, particularly if they are obese or have a large neck circumference prior to conception. Some individuals demonstrate a significant positional dependence to their obstructive sleep apnea symptoms, experiencing considerable symptoms when supine and minimal symptoms while in the lateral position [49]. For such individuals, sleeping in the lateral position

may provide sufficient treatment. Women should abstain from alcohol during pregnancy, as this can worsen sleep-disordered breathing, as well as increase the risk for fetal complications [67]. CPAP has been shown to be the most effective therapy for sleep apnea in the non-pregnant population, and should be considered when conservative measures fail to control symptoms. Although there are been theoretical concerns that CPAP could lead to decreased cardiac output and placental blood flow, CPAP has been shown to be a safe treatment for SDB in pregnant women [64]. As weight increases during pregnancy, CPAP settings may need to be adjusted [64]. Thus, women who are being treated with CPAP should be followed closely for symptoms of recurrent snoring, waking up gasping for air, witnessed apneas, or increased daytime sleepiness, as these symptoms may indicate that the current CPAP settings are suboptimal. Surgical treatments for sleep apnea are not recommended during pregnancy, given the potential risks associated with anesthesia [34]. Moreover, procedures such as uvulopalatopharyngoplasty are often unsuccessful in treating sleep apnea, with the highest success rates being only 66% [68]. Oral appliances are also unlikely to be a practical treatment option for sleep apnea in pregnant women, as multiple calibrations of the device are typically required. Thus, it may take several weeks or months before optimal treatment is achieved.

Treatment of Sleep Problems in Pregnancy

Sleep disruption is an almost universal experience during pregnancy, however, few women complain to their physicians about sleep problems [11, 34]. Because it is such a common occurrence, perhaps women come to accept this sleep disruption as an unavoidable circumstance. However, poor sleep during pregnancy may have an impact on the health of both the mother and the newborn baby. Sleep restriction during the last month of pregnancy increases the risk for a prolonged labor or a cesarean delivery [69]. Poor sleep at the end of pregnancy may also increase the risk of postpartum blues [26, 70], although further research needs to be done to verify the role that sleep disruption plays in the subsequent development of postpartum depression.

Given the impact that sleep problems can have on the health and well-being of individuals, healthcare professionals should inquire about symptoms of disturbed sleep during pregnancy. Pregnant women should be instructed on principles of good sleep hygiene. Women should be advised to dedicate sufficient time for sleep and to ensure that their sleep environment is quiet and conducive to sleep. During the first and third trimester, when nocturia is one of the most common causes of nighttime awakenings, women should be counseled to limit fluid intake for several hours prior to bedtime. Women should avoid food that is likely to provoke heartburn, and limit food intake several hours prior to bedtime to reduce gastroesophageal reflux. Supportive pillows may be used to help women sleep comfortably. Massage and local heat application may also help reduce low back pain. Cognitive behavioral therapy, including relaxation techniques and stimulus-control therapy may also be helpful. Healthcare professionals should screen for symptoms of restless legs syndrome or sleep-disordered breathing; when symptoms are present the appropriate diagnostic work-up and treatment should be provided, as detailed above.

If conservative measures prove to be insufficient in managing symptoms, consideration can be given to short-term pharmacologic treatment. The risks and benefits of treatment should be discussed in detail, as pharmacologic therapy during pregnancy holds potential risk of adverse outcomes for the fetus. No pharmacologic therapy for insomnia is designated by the FDA as Class A in pregnancy (documented safety). Diphenhydramine is the only agent categorized as Class B in pregnancy, indicating that it appears safe based on animal studies, although adequate human data is lacking. Zolpidem was previously categorized as Class B, but in 2008 was re-categorzied as Class C, based on studies in rats and rabbits that revealed evidence of adverse effects on fetal development. Of note, the adverse effects were only observed at doses higher than the maximum recommended human dose. Controlled studies of zolpidem in pregnant women have not been performed. When symptoms of insomnia are severe and are refractory to conservative measures, treatment with diphenhydramine, or possibly zolpidem, may be warranted. However, extreme caution should be taken as diphenhydramine can produce significant anticholinergic side effects, and both agents can cause next morning drowsiness, and impaired ability to manage complex tasks such as operating a motor vehicle [71, 72].

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9

Menopausal Insomnia

Tarja Saaresranta, Päivi Polo-Kantola, and Olli Polo

Abstract

Four major categories of sleep disorders associated with menopause may present with insomnia: "pure" menopausal insomnia, psychophysiologic insomnia, sleep-disordered breathing, and fibromyalgia. The subset of women with vasomotor symptoms has lower sleep efficiency, more sleep complaints, and higher risk of insomnia and depression. Subjective sleep quality may be poor even when the objective sleep quality is normal. Menopausal sleep disruption can aggravate other pre-existing sleep disorders including the restless legs syndrome (RLS) or circadian disorders. Co-morbidities without direct link with menopause as well as stressful changes in social environment coinciding with menopause should not be overlooked when exploring the etiology of insomnia in middle-aged women.

Keywords: Vasomotor changes, Hormones, Menopause, RLS, Circadian disorders, Fibromyalgia, Sleep related breathing disorder

Introduction

Sleep problems are one of the hallmarks of menopause. Fifty to eighty percent of peri- and postmenopausal women report about suffering from sleep problems. Comments like "She is at that age" or "It's due to hormones" too often prevent careful investigation of causes and active therapeutic interventions in postmenopausal women with sleep disorders.

Four major categories of sleep disorders associated with menopause may present with insomnia: "pure" menopausal insomnia (often related to menopausal vasomotor symptoms), psychophysiologic insomnia (frequently related to depression), sleep-disordered breathing (SDB), and fibromyalgia (FM). The subset of women with vasomotor symptoms has lower sleep efficiency, more sleep complaints, and higher risk of insomnia and depression. Subjective sleep quality may be poor even when the objective sleep quality is normal [1]. SDB increases markedly after menopause due to weight gain and hormonal changes.

From: *Clinical Handbook of Insomnia,* Current Clinical Neurology
Edited by: H.P. Attarian and C. Schuman, DOI 10.1007/978-1-60327-042-7_9,

SDB is generally considered as a condition of middle-aged obese men. Therefore, SDB is severely under-recognized in peri- or postmenopausal women. Health care providers should not assume that sleep complaints are due to vasomotor related insomnia or depression without considering SDB. FM has gender, age, and probably hormonal associations. Sleep complaints with associated objective findings in sleep recordings are common in FM. Menopausal sleep disruption can aggravate other pre-existing sleep disorders including the restless legs syndrome (RLS) or circadian disorders. Co-morbidities without direct link with menopause as well as stressful changes in social environment coinciding with menopause should not be overlooked when exploring the etiology of insomnia in middle-aged women.

Characteristics of the Climacterium

The menopause is the time when there is constant cessation of menstruation following the loss of ovarian hormonal activity. The average age of menopause is 51–52 years with the range of 45–55 years [2]. Perimenopause is the period of time immediately before and after the menopause. The menopause can be diagnosed retrospectively after 12 months of permanent amenorrhea and the time thereafter is called postmenopause [3]. The climacterium covers the perimenopause and the part of postmenopausal period, indicating the course of time when a woman passes through a transition from the reproductive stage to postmenopausal years, the era when climacteric symptoms occur.

During climacterium, women suffer from several symptoms with wide variation in severity. Vasomotor instability, hot flashes, and sweating are the most typical symptoms with the feature of thermoregulatory events: peripheral vasodilatation especially in the upper body, around the face and the chest, is usually followed by sweating causing evaporative cooling [4]. Using core temperature measurements, a lower sweating temperature threshold and higher shivering threshold have been shown in vasomotorically symptomatic postmenopausal women compared to asymptomatic women [5, 6]. The symptoms are supposed to be mediated through the preoptic area of the anterior hypothalamus. In spite of these findings, the comprehensive understanding of reasons for variability in symptom frequency and response are uncertain. Approximately 75% of postmenopausal women and 40% of perimenopausal women experience vasomotor symptoms [7, 8]. Similar to severity, the duration of symptoms alters among individuals. In average, the occurrence of vasomotor symptoms is 1–2 years, but about 25% of women report them for 5 years and 9% suffer from them practically the entire time after menopause [9, 10].

Climacteric symptoms include also other symptoms, both physical and mental. Palpitations may occur during the daytime and at night and are closely related to vasomotor symptoms as a supplementary mark of autonomic nervous system dysfunction [11]. Dizziness, deterioration in postural balance, headache, numbness, muscle and joint pain, dry eyes and mouth, and decreased skin elasticity also enhance and are often related to menopause, although they do not correlate to the reduced estrogen levels [11]. Vaginal dryness, as well as nocturia and other urinary tract symptoms are female sex-hormone dependent and clearly deteriorate after menopause, normally with some years' delay [11]. Mental symptoms such as anxiety, depression, lack of concentration, memory impairment or decline of libido take place, and these symptoms may even

exceed the severity of vasomotor symptoms. Furthermore, sleep problems are common, occurring either solely or more typically in relation to other climacteric symptoms [12]. After menopause 50–80% of women report mental symptoms and sleep problems [7, 13].

Female Sex-Hormones and the Brain

Estrogen and progesterone receptors are found in several brain areas, such as in the cerebral cortex, hippocampus, hypothalamus, amygdala, basal forebrain, midbrain raphe nuclei, pituitary gland, locus coeruleus, and cerebellum [14–16], areas which are involved in sleep regulation [17]. In the brain estrogen increases blood circulation and thus diminishes oxidative stress. It also increases excitability of neurons, activation of intracellular signaling pathways, as well as modulation of proteins, and protection against neuronal damage [14]. Sex-steroids are involved in various neurotransmitter systems. During climacterium cholinergic-, serotonergic-, dopaminergic-, and noradrenergic systems are essential [18]. An imbalance, especially in levels of serotonin and noradrenalin in the hypothalamic thermoregulatory centers, caused by decrease in circulating estrogen levels, has been suggested to lead to hot flashes [19, 20]. Also glutamate-, gamma-amino-butyric acid (GABA)-, opiate- and vasopressin-systems as well as insulin-like growth factor 1 (IGF-1), transforming growth factor alpha (TGF-α), protein kinase activators, and various other neurotransmitters are probably involved [21]. These neurotransmitters are also important for sleep [17]. Therefore the disturbance in their secretion or actions associated with menopausal changes in female sex-hormone levels may contribute to sleep problems.

Although central nervous system (CNS)-related circadian hormones, like growth hormone (GH), prolactin (PRL), cortisol or melatonin, are mainly age-dependent, menopause and reduced sex-hormone levels may contribute to the alterations [21]. After menopause, diurnal GH and PRL levels decrease [22, 23], whereas cortisol levels increase [24]. Unopposed estrogen therapy (ET) increases serum GH levels [25, 26], but results on the effects with combined hormone therapy (HT) are inconsistent [23, 27, 28]. The diurnal secretion of PRL is higher in younger women than in postmenopausal women [29]. ET alone or combined to progestogen has found to elevate serum PRL [30]. Studies on the effect of HT on cortisol levels are conflicting [31, 32].

Estrogen and Sleep

According to sleep surveys, women report more sleep problems compared to men [33–35]. After 50 years of age 25% of women suffer from moderate and 15% from severe insomnia [34]. However, several factors such as respiratory disorders, cardiovascular, neurological and endocrinological diseases, mood disorders, psychosocial factors and medications, may contribute to sleep problems and therefore determining the true effect of menopause and decreased hormonal levels is often complex [36].

Sleep quality is frequently deteriorated already during perimenopause due to gradual cessation of female sex-hormone secretion. Many studies have ensured the increase of sleep problems in the menopausal transition.

Compared to premenopausal women, odds ratios for sleep problems in perimenopausal women have found to be 1.3–1.5 [37, 38]. In postmenopausal women, odds ratios from 1.5 to even 3.4 have been reported [37, 39]. According to a study carried out among menopausal clinical patients, almost 80% suffered from insomnia and 90% experienced fatigue. The most frequent complaints were waking too early in the morning or discontinuous sleep [40].

Climacterically symptomatic women often report sleep problems. Those with vasomotor symptoms typically have perspiration or palpitation after falling asleep, or sleep is interfered with frequent awakenings caused by sweating [7, 38, 41]. In a study with 12,600 women, an odds ratio for sleep problems in women with climacteric symptoms was 2.0 compared to asymptomatic women [38]. Further, those with climacteric mood symptoms have sleep difficulties [42]. Despite these clear clinical observations, the studies with objective sleep measurements are not exclusive for these associations. In a study with skin conductance measurements along with subjective vasomotor symptoms scoring and sleep diary, subjective hot flashes and sleep problems were connected, but no relation between measured hot flashes during sleep and sleep problems were found [43]. Data about the relationship between objectively measured sleep quality (polysomnography (PSG), actigraphy, or quantitative analysis of EEG) and climacteric symptoms is even more incongruent. When relying on subjective sensations of vasomotor symptoms more time in bed and longer REM latency [44] have been found in symptomatic women compared to asymptomatic women, although studies with no differences have also been published [41, 45, 46].

Some PSG studies have been conducted with objective measures of vasomotor symptoms (skin conductance or core body temperature). In a previous study by Freedman and colleagues, vasomotor symptoms caused nocturnal awakenings, increased sleep stage changes, and lower sleep efficiency [47]. Subsequently, in an other study comparing symptomatic postmenopausal women with asymptomatic or premenopausal women, no association with symptoms and PSG findings were shown [48] and finally in two other studies hot flashes intruded with sleep quality in the first half but not in the second half of the night causing arousals and awakenings [49].

The Effect of Hormone Therapy on Sleep

At present the principal indication to prescribe HT is alleviation of climacteric symptoms, especially vasomotor symptoms [50]. Observational as well as controlled clinical studies have shown the protection against osteoporosis and bone fractures during HT [51]. A cardioprotective action of HT has also been suggested when initiated at menopause [52], although all data do not support this assumption [53] and further, initiation with years delay has reverse effects [54]. As complications due to HT are mostly associated to high doses and long duration of treatment or use in older women [50, 55], the counseling for therapy includes short duration of the treatment with the lowest potent dosage.

Controlled clinical trials have shown a definite improvement on subjective sleep quality during menopause by HT [7, 13, 55–59]. The results have been beneficial regardless of dose [13, 57–59], administration route [55–58], or duration [13, 56, 58] of the treatment. The only prospective controlled study up to now which discriminated the effect of estrogen on different subjective

sleep problems found also an unquestionable advantage in sleep quality [57]. In that trial, 63 postmenopausal women, both vasomotorically symptomatic and asymptomatic, went through a 7-month cross-over study. Compared to placebo, estrogen facilitated falling asleep and decreased nocturnal restlessness and awakenings, as well as decreased tiredness in the morning and during the daytime. Furthermore, the general sleep quality was improved. Although the degree of improvement in vasomotor symptoms was an important predictor for the degree of improvement in sleep disturbance, the vasomotorically asymptomatic women with insomnia also benefit from estrogen. The Women's Health Initiative (WHI) study, which evaluated the long-term effects of HT on the quality of life in asymptomatic or mildly symptomatic older postmenopausal women, found an improvement of sleep quality as well after 1 year's follow-up [55]. In that study, however, only the overall sleep quality was determined without detailed estimates.

Different mechanisms account for the favorable effects of HT on sleep quality. Female sex-hormones have potent direct CNS effects in brain areas responsible for sleep regulation [18]. In addition to this primary effect, secondary mechanisms via alleviation of climacteric symptoms, especially vasomotor symptoms, seem to more probably explain the positive alterations, since changes in sleep quality associate with alleviation in vasomotor symptoms [56, 57]

Despite the results in subjective sleep studies have been convincing and in line with clinical experience, the inconsistent findings using objective measurements of sleep quality have confused the view towards HT. HT has been shown to increase REM sleep [60–62], to decrease stage 1 sleep [63] and to reduce awakenings [60, 64–66], nocturnal wakefulness during the entire night [60, 67] or in the first sleep cycle [62]. In addition, a shortening in sleep latency [61, 68], an improvement in sleep efficiency [63, 65, 67], and a reduction of the rate of cyclic alternating patterns of sleep [65] have also been reported. According to some studies, HT has no effect on PSG sleep measures [69–72]. Besides, in an observational study without a placebo group, the postmenopausal HT users had worse sleep quality compared to nonusers, since they had less slow wave sleep, more stage 1 sleep, and their sleep was more fragmented [45].

The definite conclusions on the effect of HT on objectively measured sleep quality are impossible to draw, since the study designs, subject enrolment, and treatments (form, dose and duration) have varied considerably. Some studies have enrolled both peri- and postmenopausal women without hormone level measurements [60] or both naturally and surgically menopausal women [61]. This has led to a wide age range or differences in biological circumstances and clinical symptoms [73]. In observational studies, self selection of HT [45, 67] has presumably caused some bias. In controlled studies, the follow-up time has been short, from 4 weeks to 7 months and thus the long-term effects of HT are lacking. The incongruence in objective sleep studies calls in question the PSG techniques. Sleep laboratory studies are needed to ascertain possible underlying sleep disorders, such as sleep apnea, narcolepsy, or sleep movement disorders, but in clinical practice evaluation of subjective sleep quality by questionnaires is generally sufficient to diagnose insomnia. And last but not least, PSG changes seem to be more age than hormone dependent, since in a recent PSG study, sleep measures were similar between pre- and postmenopausal women with various hormonal status but differed significantly when comparing to young women [74].

The Management of Menopausal Sleep Problems

The etiology of climacteric sleep problems is often complex, challenging the management. In women with climacteric vasomotor symptoms, the first line treatment is HT, which is clearly shown the most effective therapy for reducing vasomotor symptoms and related secondary insomnia [7, 13, 55–57, 59]. In addition, HT often reduces sleep problems if they are associated with climacteric mood symptoms [57]. The window for initiation of HT is crucial: the treatment should be started when entering menopause, not after menopause. Delay with initiation of HT after menopause may increase the risk for cardiovascular complications. The lowest effective doses should be used and the necessity of the treatment reconsidered yearly [50]. The mammography examination with at least two dimensions should be performed every second year, and women should be encouraged to self-palpate their breasts. If no symptom relief has been achieved in a few months, further medical examinations are necessary. In women over 60 years, the side-effects may surpass the benefits [54, 55] and thus initiation of HT is not recommended.

Some symptomatic women choose to refuse to use HT or HT is contraindicated. For these women, the treatments which directly affect thermoregulatory mechanisms, such as adrenergic and serotoninergic systems, may be an option [20]. Clonidine, an α_2 adrenergic agonist [20, 75] or serotonin-reuptake inhibitors (SSRI) [20] have shown to decrease climacteric symptoms and related sleep problems. The antiepileptic drug gabapentin may also reduce vasomotor symptoms [20]. With all these treatments, the benefits must always be weighted against possible side-effects. Albeit debatable, dietary phytoestrogens (isoflavones found in soy and red clover) may alleviate vasomotor symptoms [76] and thus improve sleep quality. The response is individual and safety data of the drugs are lacking. Some women evidently benefit from hypnotic therapy, which should be used for short periods under frequent controls.

A cornerstone for good sleep quality is adequate sleep hygiene. The bedroom should be dark, quiet, comfortable, and often with low temperature. Avoiding daytime napping and irregular bedtimes, as well as use of beverages (tea, coffee, some soft drinks, and herbal drinks), smoking, and alcohol intake before bedtime often alleviates sleep problems [77]. Some women profit from relaxation or cognitive sleep therapies.

Menopausal Depression and Sleep Problems

Women report mood symptoms, such as depression, anxiety, and lack of initiative more often than men [78, 79]. In some of the cases, female sex-hormone fluctuations play an important role, since mood symptoms are in connection with the female reproductive cycle (premenstrual tension syndrome, postpartum depression, or climacteric depression). During climacterium depressive symptoms are reported in up to 70–90% of women [33]. Sleep disturbance is a sensitive marker of mood disturbance, [42, 80] and impaired sleep can be the first sign of affected mood. Especially, difficulties in falling asleep and too early morning awakening commonly originate from depressive mood.

Progestogens and Sleep

Progesterone has sedative, benzodiazepine-like agonistic effects on $GABA_A$ receptor [81]. The sedative effects on sleep appear to be mediated via the conversion of progesterone to its major metabolite allopregnanolone [82]. However, the effects of progesterone on sleep are controversial. Premenstrual syndrome occurs during the luteal phase of the menstrual cycle, when progesterone levels are increased. Premenstrual syndrome presents with hypersomnolence in some and with insomnia in others.

There is surprisingly scarce data of the effects of progestogens on sleep in postmenopausal women. Medroxyprogesterone acetate, a progesterone derivative, did not affect objective or subjective sleep quality in postmenopausal women with SDB [83] or end-stage stabile chronic obstructive pulmonary disease (COPD) [84]. Although progestogens seem not to affect subjective or objective sleep quality in postmenopausal women, these findings have to be interpreted cautiously because of small study samples and lack of randomized controlled studies.

Sleep-Disordered Breathing

Partial or total periodical collapses of the upper airway during sleep is the most common cause of SDB. The classical clinical presentation includes excessive daytime sleepiness, loud snoring, and witnessed episodes of apnea during sleep. Male to female ratio of the obstructive sleep apnea syndrome (OSAS) ranges from 2:1 to 4:1 in community based populations [85–88] and up to 10:1 in sleep clinic samples [89]. The male predominance of OSAS suggests that sex hormones have a role in the pathogenesis of SDB. Female hormones are supposed to protect premenopausal women from SDB. Most, although not all, community-based and clinic-based cross-sectional studies show increased prevalence estimates of sleep apnea after menopause [86, 87, 90–93]. A prospective 4-year study of 305 premenopausal women showed a 19-fold increase in risk for SDB in women who became postmenopausal [88]. In a large community-based study, 1.9% of postmenopausal and 0.6% of premenopausal women had OSAS, defined as an apnea–hypopnea index (AHI) of at least 10 per hour and occurrence of daytime symptoms [91]. This study was criticized for not taking into account the effects of age or BMI. A couple of years later, another study showed that the proportion of those with AHI > 5 was higher among peri- and postmenopausal than in premenopausal women when adjusted for age or BMI [92].

A number of hormones, including female sex steroids, have been suggested to play a role in SDB [94]. High lipid solubility enables circulating sex steroids to easily cross the blood–brain–barrier [95]. Sex steroids act directly or via central neuromodulatory systems [95] but also peripherally by contributing to upper airway patency [96]. Sex steroids influence neuromodulatory serotonergic neurons [95], which are essentially involved in the neural control of breathing [97]. Treatment with estrogen and/or progesterone can upregulate 5-hydroxytryptamine (5-HT) levels [98]. In humans, estrogen influences 5-HT synthesis and $5\text{-}HT_{2A}$ receptor binding in a gender specific manner [99–101]. Serotonin also increases excitation of the upper airway and phrenic motoneurons [102, 103].

Progesterone is a powerful respiratory stimulant, acting via central and peripheral chemoreceptors [104, 105]. In healthy women, upper airway resistance is lower during the luteal (high progesterone levels) than the follicular phase of the menstrual cycle both during wakefulness and sleep [106]. Co-administration of estrogen and progesterone enhances progestin-induced ventilatory effects [107, 108], although contradictory findings have been reported [109]. The enhancement of ventilatory effects by combination therapy is likely to be associated with estrogen-induced upregulation of progesterone receptors [110].

In a cohort of 53 women, higher AHI was associated with lower levels of estradiol, progesterone, and 17-OH-progesterone, when adjusted for BMI, age, phase of the menstrual cycle, and postmenopausal status [111]. However, the cross-sectional study design does not allow drawing conclusions on causality.

The apnea–hypopnea index (AHI) i.e., number of episodes of apnea or hypopnea per hour of sleep, is commonly used to describe the severity of SDB. In women, the AHI grossly underestimates the clinical severity of SDB. High frequency of symptoms with low AHI suggests that women have other factors contributing to their symptoms [85]. We have shown that partial upper airway obstruction is far more common than "conventional" sleep apnea. Out of 62 "healthy" postmenopausal women, 17% had significant amount of partial upper airway obstruction during sleep [119]. In a clinic-based population, 50% of breathing abnormalities were due to obstructive non-periodic breathing, i.e., partial upper airway obstruction, which results in low AHI [113]. Especially in women, it is of great importance not to look at only AHI, when defining the clinical severity of SDB. The clinical severity of SDB has to be specified with two components: objective PSG findings (AHI plus flow-limitation) and subjective daytime sleepiness with functioning disability. According to the American Academy of Sleep Medicine Task Force severity criteria, the rating should be based on the most severe component of these two [114]. Patients with mild, i.e., asymptomatic, SDB have poor adherence to nasal continuous positive airway pressure (CPAP) therapy [115, 116]. Partial upper airway obstruction is often misclassified as mild SDB because of low AHI. However, patients with significant percentage of partial obstruction during sleep frequently complain of excessive daytime sleepiness and morning headaches in particular. Their symptoms usually respond well to nasal CPAP therapy and their long-term adherence to CPAP is compatible with that of patients with conventional OSAS [117].

The classical clinical picture of OSAS includes complaints of excessive daytime sleepiness, loud snoring, breathing pauses during sleep, and waking up with gasping or choking. However, the gender differences in clinical presentation may result in under diagnosis or misdiagnosis of SDB in women [117, 118]. Women tend to report snoring less frequently than men even with the similar levels of AHI [86, 119, 120]. Males are more likely to report their nocturnal apneas than females, and females more frequently report their bed partner's apneas than males do [86, 117, 121]. Male SDB patients express sleepiness whereas females tend to use words like fatigue, lack of energy, or tiredness [122, 123]. Women with SDB complain more frequently for morning headaches than male patients [119, 122] although not confirmed in all studies [124]. Hypothyroidism is more prevalent in women than in men. Hypothyroidism per se may induce SDB [94].

Sleep problems like difficulties falling asleep, awakenings during the night, nocturia, dry mouth when awakening, nightmares, or sweating during night are also symptoms of SDB. These symptoms are more common among female than male SDB patients complicating the diagnosis in women presenting with these symptoms [120, 124].

Women seem to have insomnia as a presenting symptom of SDB more frequently than men [120, 124, 125]. Guilleminault and colleagues observed that 80% of 394 postmenopausal women with chronic insomnia had sleep apnea [125]. PSG recordings confirmed insomnia in 68% of 38 normal weight postmenopausal women complaining insomnia and revealed sleep apnea in 50%, periodic leg movements during sleep (PLMS) in 7.8%, and bruxism in 2.6% of the subjects [126]. PLMS in women with SDB seem to be more common than in men with SDB possibly leading to insomnia [120].

Depressive mood and depression are highly prevalent among patients with SDB. Females with SDB express these symptoms or are treated for depression more often compared to males, and women with severe SDB have higher depression scores compared to those with mild SDB [119, 120, 124, 127].

Weight control and nasal CPAP therapy form the basis for treatment of SDB. Some patients benefit from oral appliances or different types of surgical interventions. Postmenopausal HT might prevent or alleviate SDB – but the effect size is modest. The current body of data does not allow us to give any recommendations for using HT to prevent or treat SDB. In a cohort study, the prevalence estimates of sleep apnea in postmenopausal non-users of HT were compatible with those in men, whereas in HT users they were compatible with those in premenopausal women [91]. Combination therapy with estrogen plus progesterone was not superior to unopposed ET. Short-term administration of progesterone alone [83, 128], unopposed estrogen [112, 129] or combination therapy [130, 131] has induced some but clinically insufficient improvement of SDB.

Fibromyalgia

Fibromyalgia (FM) is a poorly understood, chronic disorder characterized by nonarticular, widespread musculoskeletal pain. It affects 2% of the population, and is seven times more frequent in women than in men [132]. The time of onset or the increase in intensity of FM symptoms often coincides with perimenopausal or postmenopausal period suggesting that the endocrine changes at menopause may play a role in the pathophysiology of FM [133, 134]. Disturbed sleep, including sleep onset or sleep maintenance insomnia or persistent nonrestorative sleep, are especially distressing to FM patients [132, 135–138].

Some but not all studies have suggested misalignment of the phase of the circadian pacemaker. Circadian pacemaker influences both melatonin secretion and activity of the hypothalamic–pituitary–adrenal (HPA) axis. Studies comparing FM patients with healthy controls have shown normal [139], decreased [140], or increased [141] melatonin levels in FM patients. A blunted rise in ACTH has been reported in women with FM during a hypoglycemic–hyperinsulinemic clamp performed in the morning [142] and a delayed rise in ACTH in response to infused interleukin-6 [143]. Some, but not all, studies have shown blunting of the normal diurnal cortisol rhythm, with elevated evening cortisol levels in FM [142, 144, 145]. One study done under the constant

routine conditions did not find any difference between the women with fibromyalgia and controls in the circadian amplitude or phase of rhythms of melatonin, cortisol, and core body temperature [146].

There are associated, although not specific, findings in PSG recordings. Three distinct patterns of alpha sleep activity have been detected in FM [147]. Phasic alpha simultaneously with delta activity is found in 50% of FM patients, tonic alpha continuously through NREM sleep in 20% of patients, and low alpha activity in the remaining 30% of patients compared to low alpha detected in 84% of healthy controls [147]. All patients with phasic alpha, 58% of those with low alpha and 12% of patients with tonic alpha reported poor perceived sleep. Patients with phasic alpha also showed lower sleep efficiency and shorter total sleep time.

FM patients have increased CNS levels of the nociceptive neuropeptide substance P (SP) and lower serotonin levels resulting in a lower pain threshold to normal stimuli. High SP and low serotonin have significant potential to affect sleep and mood. Treatment of sleep itself seems to improve, if not resolve FM.

Sedating antidepressants, zolpidem tartrate, and sodium oxybate have shown a short-term efficacy for treating FM-associated fatigue and insomnia, but the beneficial effects often decrease over time [148–151]. Recently cognitive-behavioral therapy (CBT) has shown promising responses in the treatment of FM-related chronic insomnia [152]. In a randomized clinical trial of 42 FM patients with chronic insomnia, sleep logs showed that CBT-treated patients achieved almost a 50% decrease in their nocturnal wake time compared to 20% with sleep hygiene instructions and 3.5% with usual care. Actigraphy findings were in line with sleep log findings.

Other Sleep Disorders

RLS is characterized by urge to move and unpleasant sensations in legs. These symptoms begin or worsen at rest, especially in the evening and at night. Symptoms are partially or completely relieved by movement. The limb movements may be present during sleep and are virtually identical to the PLMS without any symptoms of the RLS. Both RLS and PLMS have high genetic predisposition. The majority of cases are primary RLS. The secondary causes include iron deficiency, pregnancy, renal failure, rheumatoid arthritis, and certain drugs. The most important drugs which aggravate RLS and PLMS are glucocorticoids, tricyclic antidepressants, SSRIs, antipsychotics, antihistamines, calcium channel blockers, dopamine antagonists, and caffeine [17].

RLS is estimated to occur in 2.5–15% in general population. The prevalence of RLS increases with age and has a female preponderance [153–156]. RLS affects women twice as often as men, the gender difference being explained mostly by parity [155]. About 80% of those with RLS have PLMS and about 35% of those with PLMS have RLS. The prevalence of PLMS is thought to be 30% between the ages of 50 and 65 years, and 45% in the population over the age of 65 [17].

Estrogen has been suggested to have antidopaminergic action, and therefore could play a role in RLS and PLMS. However, ET in a study of 62 postmenopausal women had no effect on frequency of PLMS [157].

RLS is strongly linked with insomnia [156]. PLMS, urge to move, and abnormal sensations in legs prevent falling asleep, cause brief arousals or prolonged awakenings during the night. In general, pharmacological treatment should be limited to individuals who meet the diagnostic criteria of RLS, and especially to those who suffer from insomnia and/or excessive sleepiness due to RLS. According to the guidelines of the American Academy of Sleep Medicine, dopaminergic agents are the first-line therapy, followed by opioids, anticonvulsants, and benzodiazepines [158].

Physiologic changes in the timing of the circadian clock easily affect sleep in mid-life women. Circadian clock is advancing with age resulting in early morning awakening. This may be misperceived as insomnia or a symptom of depression. It also becomes more and more difficult to adjust with shift-work leading to aggravation of shift-work related insomnia.

Medical Disorders

Medical disorders become more frequent with aging. A careful history is essential to accurately assess medical disorders and their influence on sleep. A wide array of diseases and disorders may directly or indirectly disturb sleep. Indirect mechanisms including anxiety and depression are often linked with chronic diseases as well as drug-induced sleep problems. Several commonly used drugs such as glucocorticoids, statins, theophylline, beta blockers, alpha-2 agonists, calcium antagonists, and angiotensin-converting enzyme inhibitors affect sleep.

Nocturnal and early morning headaches (the latter frequently linked with partial upper airway obstruction during sleep), neurological diseases such as Alzheimer's and Parkinson's disease affect sleep, asthma, COPD, gastroesophageal reflux, hypertension, nocturnal angina and heart failure, musculoskeletal disorders, and hypothyroidism are frequently revealed as contributing factors in sleep problems.

It is well established that patients with COPD have a poor sleep quality not only during acute exacerbations of the disease but also during the stabile phases. However, despite often having very short and fragmented sleep (Figure 9.1), i.e., maintenance insomnia, these patients lack excessive daytime sleepiness [159]. Treatment with benzodiazepine derivatives should be avoided because of the risk of ventilatory depression and carbon dioxide retention. Antidepressive agents help some patients with insomnia related with COPD. Those with high carbon dioxide levels may benefit of nocturnal non-invasive ventilation. The possible role of CBT in the treatment of COPD-related insomnia is not known. However, CBT is unlikely to benefit insomnia related to nocturnal respiratory impairment but might be beneficial for anxiety or depression induced components of insomnia.

Nocturia means need for voiding twice or more often at night. It is often underdiagnosed. Nocturia, sometimes more than vasomotor symptoms, may disrupt sleep in postmenopausal women. Not only diuretics, estrogen depletion, changes in the structure, and position of uterus and structures are related to it but SDB also has to be taken into account in the differential diagnostics of possible causes behind this troublesome disorder.

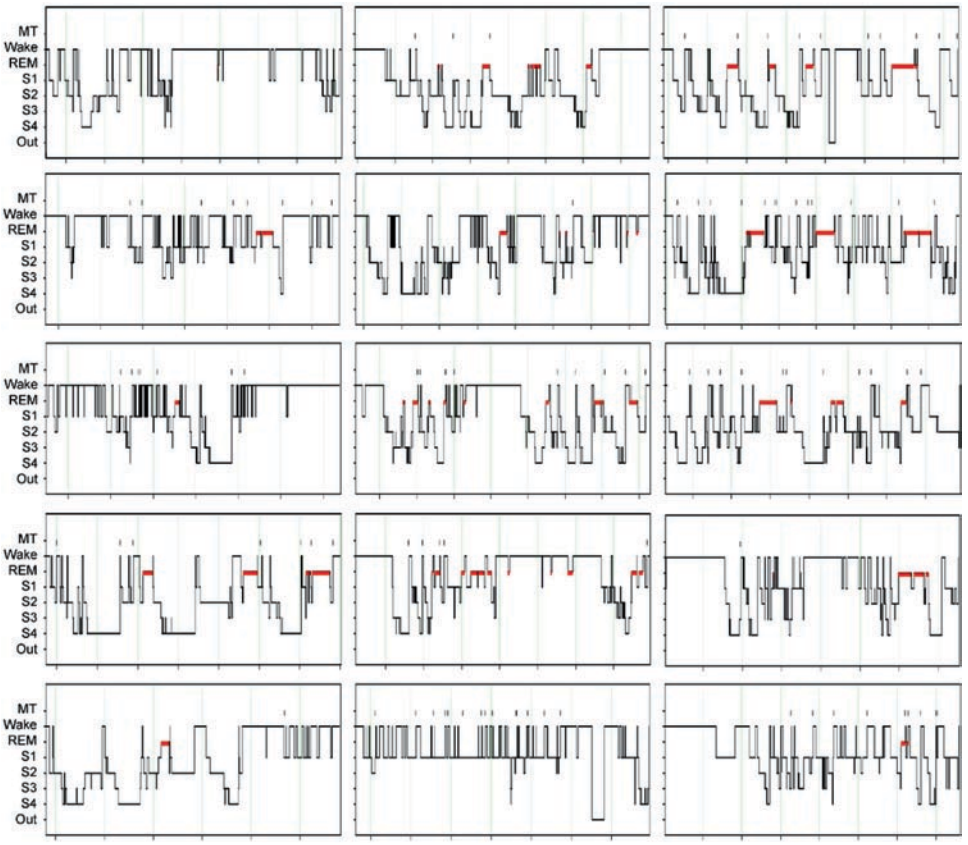

Figure 9.1 Hypnograms of the 15 postmenopausal women with end-stage stabile COPD. Their mean total sleep time is 4 h 41 min and sleep structure is markedly destroyed. *MT* movement time; *REM* rapid eye movement sleep; *S1* and *S2* sleep stages 1 and 2 (light sleep); *S3* and *S4* sleep stages 3 and 4 (slow-wave sleep, deep sleep). With permission from ref. [159]

Social Factors

Postmenopausal period often coincides with several stressful life events and changes in social environment. Concerns of teen-age children, empty nest syndrome, caring of aging and disabled family members, divorce or widowhood, demands of the rapidly changing work life, and deaths of friends and family members frequently contribute to sleep problems including insomnia.

Conclusions

Menopausal insomnia is not a single entity but comprises a wide spectrum of conditions initiated or aggravated by menopause. The etiology of menopausal insomnia may be a psychiatric disorder, SDB, FM, co-existing sleep problem such as RLS, climacteric vasomotor symptoms, overwhelming demands of the

social environment, or a dynamic interaction among one or several of these conditions. Careful history forms the basis for appropriate diagnostics and successful therapeutic interventions. Menopausal insomnia is most often a disorder with specific treatment and deserves to be taken seriously by health care providers.

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10

Sleep and Aging: Insomnia in the Geriatric Population

Clifford Singer and Francine Nanda

Abstract

Sleep complaints are common among older adults. About 20% of older adults who responded to the 2003 National Sleep Foundation poll admitted taking a sleep pill prescribed by a doctor or use over-the-counter sleep pills or drink alcohol, wine, or beer to promote sleep with 15% admitting using these aids every or almost every night. Overall, those who report a good health have a better quality of sleep than those who estimate having a fair or poor health. Sleep patterns are affected by age-related changes in circadian rhythms, medications, pain and medical conditions, neurodegenerative diseases, excessive daytime sleep, and specific sleep pathologies. Inadequate quality and quantity of sleep impact daytime alertness, physical, mood, and cognitive function. Neuropsychiatric disorders (e.g., depression and dementia), digestive system diseases (e.g., esophageal reflux), pain, heart disease, and chronic pulmonary problems increase risk of insomnia. Insomnia itself may increase risk of chronic disease.

Keywords: Elderly, Insomnia, Depression, Dementia, Pain, Medications, Neurodegenerative conditions, Daytime alertness

Introduction

Sleep is a topic likely to animate any conversation in a gathering of older adults. Even healthy, "optimal" aging is accompanied by changes in subjective sleep quality, and objectively measured duration and architecture. The prevalence of insomnia in primary care patients was 69%, with 50% reporting occasional insomnia and 19% reporting chronic insomnia [1]. About 20% of older adults who responded to the 2003 National Sleep Foundation poll admitted taking a sleep pill prescribed by a doctor or use over-the-counter sleep pills or drink alcohol, wine, or beer to promote sleep with 15% admitting using these aids every or almost every night [2]. Although 79% of the older adults (65–84 years old) evaluated their sleep as excellent, very good, and good, 25% estimated their

From: *Clinical Handbook of Insomnia,* Current Clinical Neurology
Edited by: H.P. Attarian and C. Schuman, DOI 10.1007/978-1-60327-042-7_10,

sleep has gotten somewhat or much worse over the past 10 years. Interestingly, the NSF poll observed a higher rate (34%) of older persons of 55–64 years old who find their sleep has gotten worse as compared to older persons (25%), 65–84 years old over the past 10 years, suggesting that subjective sleep quality begins to decline in midlife for many people. Overall, those who report a good health have a better quality of sleep than those who estimate having a fair or poor health.

Sleep patterns are affected by age-related changes in circadian rhythms, medications, pain and medical conditions, neurodegenerative diseases, excessive daytime sleep, and specific sleep pathologies (e.g., sleep-related breathing problems, periodic limb movements). Inadequate quality and quantity of sleep impact daytime alertness, physical, mood, and cognitive function [3]. Neuropsychiatric disorders (e.g., depression and dementia), digestive system diseases (e.g., esophageal reflux), pain, heart disease, and chronic pulmonary problems increase the risk of insomnia. As will be reviewed later in the chapter, insomnia itself may increase risk of chronic disease.

Sleep Changes with Aging

The ability to initiate and maintain nighttime sleep declines with aging [4–9]. Sleep becomes more fragmented with aging and with more nighttime awakenings and greater tendency for daytime sleepiness. Increased sleep onset latency and time awake after sleep onset (WASO) are reflected in reduced total nighttime sleep time. However, daytime sleep tends to increase in old age, suggesting no overall change in actual sleep requirement [10]. Poor sleep continuity has the most impact on the quality of life of seniors. Increased WASO and low sleep efficiency (from increased number of nighttime awakenings) likely have several causes: decreased nocturnal "sleep drive" due to intrinsic changes in circadian rhythms, polynocturia, periodic leg movements, sleep-related breathing problems (including obstructive apneas and hypopneas), esophageal reflux, pain, and depression. Decreased activity and excessive time in bed during the day are also major factors. Dew et al. found long sleep latency (>30 min) and lower sleep efficiency (<80%) to be associated with a doubling of annual mortality rate [11]. Increased daytime sleep may be an even stronger indicator of poor health and increased mortality rate likely due to its association with obstructive apnea, obesity, and chronic diseases (Fig. 10.1).

Figure 10.1 Sleep histograms of two healthy adults, one old and one young. Starting at the left, the graphs show rapid descent through the stages of non-REM sleep into stage 3/4 for the young adult, but only to stage 2 for the older adult. REM periods are shown by the dark-top plateaus and come earlier in the older adult's night. The high spikes are awakenings and represent the most striking difference between old and young sleep

Table 10.1 Sleep changes commonly seen in normal aging.

Increased nocturnal wake time
Increased daytime sleep time
More time in bed with decreased time spent sleeping (i.e., lower sleep efficiency)
Earlier sleep times (i.e., "phase advance" in circadian sleep–wake cycle)
Increased time to fall asleep
Decreased deep sleep (slow wave sleep, NREM 3/4)

Polysomnographic studies of adults across the lifespan reveal precipitous declines in slow-wave sleep (NREM stages 3 and 4) with proportionate increases in NREM stages 1 and 2 starting early in middle adulthood [12]. Little or no change in REM sleep occurs in healthy elderly [13], although declines are pronounced in patients with dementia, especially Alzheimer's disease (AD) [14].

Aging is also associated with changes in the timing and circadian structure of sleep. Circadian rhythms (circadian = "about a day") such as the sleep–wake cycle are regulated by the hypothalamus. The circadian clock is located in the hypothalamic suprachiasmatic nucleus (SCN) that receives input from the retinohypothalamic tract. Timing and duration of the sleep–wake cycle depend on its synchronization with the light–dark cycle [15]. Reduced exposure to sunlight, reduced production of the nocturnal hormone melatonin, and degenerative changes in the SCN may affect daytime alertness and nighttime sleep in older adults, especially those with neurodegenerative diseases, such as AD [16, 17]. In addition, older adults may be more sensitive to shift work and travel across time zones, and there is an increasing tendency to earlier sleep and wake times. Sometimes, this tendency to early sleep times can lead to clinical complaints of late afternoon sleepiness and very early morning awakening (Table 10.1).

Insomnia and Age-Related Disease

At any given time, over 40% of seniors will report subjective sleep complaints, many of whom may be diagnosable with insomnia [18]. An insomnia prevalence study in individuals ranging in age from 20 to 79 years found more sleep symptoms in old as compared to young, and in women as compared to men, especially within the 70–79 years age range [19]. Sleep disturbances in elderly are strong predictors of concurrent morbidity with many of the chronic diseases associated with aging [20]. Chronic sleep deprivation (≤5 h/night) as well as long nighttime sleep (≥9 h/night) are both associated with higher mortality in older adults [21].

A bidirectional relationship exists between health and sleep. Chronic diseases such as cardiovascular disease, diabetes mellitus, pain syndromes, AD, and depression are among the disorders that may both lead to sleep disturbance but also be exacerbated by them. In fact, there is substantial evidence that insomnia increases risk for these diseases [22–29]. Sleep loss is associated with increased activation of the hypothalamic–pituitary–adrenal axis increasing cortisol secretion and impairing immune function, tissue repair, and glucose tolerance [30–34], suggesting at least one mechanism by which age-associated diseases may be accelerated by insomnia.

The relationship of insomnia and degenerative dementia is particularly illustrative of the complex relationship of chronic disease and sleep in old age. Functional brain imaging of insomniacs reveals reduced glucose metabolism in frontal cortex, thalamus, and hypothalamus during the wake period [35] similar to metabolic activity observed in studies of cognitive impairment associated with acute sleep deprivation [36]. Insomnia appears to not only contribute to benign cognitive impairment in older adults [37], but also may be a strong predictor of developing a progressive degenerative dementia over a 3-year follow-up period [27]. That is, insomnia not only causes mild problems with cognition, but may even accelerate neurodegenerative processes that lead to progressive dementia, most likely from AD. Beyond this, most degenerative dementias are themselves associated with progressive disruption of sleep–wake cycles, leading to more nighttime awakenings and daytime sleep episodes.

Sleep Changes of Menopause

Although the focus of this chapter is sleep in old age, we do want to mention menopause as one aspect of aging sleep. Aging of the neuroendocrine system in women produces profound sleep effects in midlife. While some sleep symptoms of menopause are depression-related [26], vasomotor symptoms also play a significant role in subjective sleep complaints of middle-aged women. Nocturnal hot flashes awaken menopausal women at night [38, 39]. Hormone replacement therapy has been shown to improve sleep quality [40, 41]. Estrogen and its receptors have been localized in brain regions and neurotransmitter systems involved in sleep regulation, including acetylcholine, serotonin, and dopamine [42, 43]. There is evidence that even middle-aged people suffer more cognitive impairment from sleep disturbance than do younger individuals [44].

Daytime Sleepiness in Old Age

Patients are less likely to complain of excessive daytime sleepiness than insomnia, but it may actually be more common. Tractenberg et al. found that over 60% of very healthy octogenarians reported excessive daytime sleepiness when screened with a sleep symptom questionnaire [45]. In clinical encounters, patients are likely to complain of poor concentration, fatigue, low energy and initiative than sleepiness per se. Daytime sleepiness is more likely to be associated with nighttime sleep disturbance and sleep duration in healthy seniors [46], but its association with poor health status is strong [44, 47]. Excessive daytime sleepiness is associated with depression, less physical activity, obesity [44, 47, 48], heart disease [44], and general poor health status [49]. Daytime sleepiness contributes to mild cognitive impairment, including problems with attention, concentration, praxis, delayed recall, difficulties in orientation, and recent recall [50]. The association between excessive sleepiness and cardiovascular disease may be stronger in women than in men [51], although overall, the prevalence of sleepiness is probably higher in men [52].

Sleep disordered breathing is common in older adults and is likely a major factor in many if not most cases of excessive daytime sleepiness [53–55].

Obstructive apnea may be the link between daytime sleepiness and poor health status in seniors, particularly men, but other diseases of aging, including diabetes, depression, and dementia, are important variables too. In late-stage dementia, daytime sleeping becomes so prevalent that we think nothing of seeing such patients dozing in chairs. At any given hour of the day, one-third of nursing home residents are asleep [6, 56–58]. Daytime sleep increases as dementia progresses, although not necessarily as a function of poor nighttime sleep [59, 60]. Given its association with obstructive apnea, metabolic syndrome, cerebrovascular and cardiovascular diseases, depression and dementia, it is not surprising that daytime sleepiness and excessive napping may be an even greater predictor of mortality insomnia [61–65].

Daytime sleepiness in older adults appears to be influenced by both genetic and nongenetic variables [66]. Genetic influences of sleep disordered breathing may be particularly strong, although modest genetic associations have been seen with depressive symptoms [67], snoring and restless sleep [52]. Common reasons of nighttime awakenings in the elderly is to go to the bathroom, but other reasons such as pain, noise can be disturbing factors as well [62]. A cognitive impairment was found in the elderly suffering from daytime sleepiness in these different subscales: attention–concentration deficits, praxis, delayed recall, difficulties in orientation for persons, difficulties in temporal orientation, and difficulties in prospective memory with a higher tendency for napping coming with age [50].

A Clinical Approach to Insomnia in Older Patients

Questions regarding nighttime sleep and daytime sleepiness should be part of every review of systems for older adults. Open-ended questions such as "How are you sleeping?" and "Are you as alert and active as you need to be?" are good screening questions for the patient, although a spouse, family member, or caregiver should be asked these questions regarding the patient as well. Follow-up questions will be necessary to define the problem and develop a working diagnosis. To help understand the frequency and severity of the sleep problems, a validated sleep-rating instrument, such as the Pittsburgh Sleep Quality Index, is extremely useful. This tool is completed by the patient and is in the public domain to be found on several websites. A simple sleep log maintained for 2 weeks will also clarify frequency and severity of the insomnia. People's memory for sleep quality tends to be short and a prospectively completed daily sleep diary provides much more accurate information than spontaneous recall. Samples of sleep logs are also available on line. The National Sleep Foundation Website has one that is easy for older adults to use. The diagnosis of insomnia does not require a quantitative measure of sleep, only a subjective complaint, so more objective data are not required. However, it is overtreatment of insomnia that is potentially risky in these patients who take many medications and are at high risk for adverse drug reactions, especially instability and falls. By documenting a sleep disturbance two or more nights per week and sleep deprivation that is severe enough to affect daytime function, we can avoid unnecessary treatment of "nuisance" but clinically insignificant awakening. Sometimes, simple education about the normal sleep–wake cycle changes of aging can be reassuring to those who manage to sleep well enough to function well during the day. Being told that

Table 10.2 Elements of sleep history [68].

Obtain sleep history (from patient, family members, caregivers)
Determine characteristics of sleep disturbance
Time required to fall asleep
Times of going to bed and waking up
Total sleep time
Number and duration of nighttime awakenings
Quality of sleep (restorative, refreshing?)
Level of daytime alertness (hypersomnolent?)
Napping pattern
Recent changes in sleep pattern
Previous history of sleep problems
History of snoring, sleep-disordered breathing, abnormal limb movements
Exclude potential external factors
Use of drugs, alcohol, caffeine
Diet
Activity level, exercise
Symptoms of dysfunction of other organ systems
Situational stressors
Sleep hygiene
Assess impact of problem
Duration of sleep disturbance
Degree of functional impairment caused by sleep difficulties

brief nighttime awakenings and daytime sleep periods are as much a part of aging as not running as fast or jumping as high may put this into perspective. However, remember that people do not get old over the course of weeks or months, so acute and subacute symptoms always should be addressed as a potentially remediable situation. Table 10.2 summarizes elements of the sleep history in seniors. Table 10.3 presents the major differential diagnoses of old age insomnia.

Once medical causes of sleepiness are ruled out by history, exam, and lab tests (see Table 10.3), identifying problems with sleep hygiene is helpful. People with insomnia often develop maladaptive habits that can exacerbate and perpetuate the sleep problem. Spending excessive time in bed, insufficient activity, insufficient exposure to daytime light, excessive alcohol and caffeine intake are frequent issues.

If secondary causes of insomnia, such as poor bedding, GERD, alcohol dependence, depression, and pain, are ruled out, then a diagnosis of primary insomnia or "psychophysiologic" insomnia may be made. Treatment can be initiated with a brief discussion of the benefits of cognitive-behavioral and pharmacologic treatments. Cognitive-behavioral therapy (CBT) compares well with drug treatment of insomnia, especially in the long run. CBT for insomnia has been shown to be as effective in older adults as in younger adults. It can be provided in abbreviated form in the medical office, with a few simple guidelines.

Table 10.3 Differential diagnosis of insomnia.

Insomnia diagnosis	History, clinical course
Transient Insomnia from stress, illness, etc.	Recent stressor, illness, travel, etc.Usually self-limited
Primary psychophysiologic insomnia	Insidious onset, often lifelong, sometimes worsening over time, more common in women, can wax and wane but typically chronic and recurrent
Pain and discomfort (e.g., GERD, incontinence, musculoskeletal, nocturia, asthma, etc.)	Acute or subacute onset in association with physical symptoms
Chronobiological disorders	Chronic insomnia, usually lifelong pattern of extreme morning lark or night owl, may be acute or subacute onset with travel or shift work, may develop with new onset in blind individuals
Medications (e.g., antidepressants, L-dopa, steroids, cholinesterase inhibitors, etc.)	Acute or subacute onset in association with new medications

Drug treatment of insomnia has the benefit of rapid response and easy acceptance by most patients frustrated by sleep, but not all. Patients will often be self-treated with aspirin, acetaminophen, alcohol, and over-the-counter remedies containing diphenhydramine, melatonin, or valerian root. Of these, alcohol and diphenhydramine carry the strongest contraindications in seniors. Dependency, abuse, mood disorders, falls, and early morning awakenings are some of the risks of alcohol. Anticholinergic effects such as urinary retention, tachycardia, and confusion are the risks of diphenhydramine, along with morning hangover and rapid loss of efficacy. The most promising evidence of efficacy of OTC sleep remedies in seniors is for melatonin, which has been studied extensively in controlled trials. Reports of efficacy have been mixed, however, although some people will respond well. Factors associated with response have not been reliably defined. Endogenous melatonin production has been hypothesized to be the key factor, but this has not been well established empirically.

At the time of this writing, only one melatonin agonist (ramelteon) is available by prescription in North America. Data support the use of the agent for older adults with sleep-onset insomnia. Ramelteon appears to be a safe alternative to other sedative-hypnotics in terms of tolerance, ataxia, cognitive impairment, and exacerbation of sleep-related breathing problems. It outperforms placebo in clinical trials. Clinical consensus suggests that it works very well in some patients, but not the majority. Patients should be told that they may not feel a robust sedative effect from it (although some certainly do!), and they should also be encouraged to try it for at least 2 weeks before giving up on it.

Benzodiazepine and benzodiazepine-receptor agonist (BzRA) sedative-hypnotics are the most commonly prescribed treatments for old and young alike. These drugs have a narrow risk–benefit ratio in seniors and problems such as daytime rebound anxiety, increased hypopneas and apneas, morning hypersomnolence, ataxia, and cognitive impairment are significant risks, more so than dependency and addiction. Tolerance and dose escalation are common, even with the BzRA. These medications are covered in other chapters, and the same principles apply to seniors as in younger adults. Short and medium half-life agents are generally better tolerated. Patients should be seen with in

a few weeks of initiating treatment to be sure they are tolerating and benefiting from the drug. At that visit, counseling regarding sleep hygiene and CBT strategies will need to be reinforced. On-going surveillance for pain, cognitive impairment, depression, gait instability, and alcohol abuse should be documented. Although only two of the BzRA and none of the benzodiazepines are FDA-approved for prolonged treatment, insomnia is often a chronic and recurrent problem, even in people who practice enlightened sleep hygiene, so these medications are frequently prescribed on an on-going basis. This is generally acceptable so long as persistent benefit and tolerability are assessed and documented.

Benzodiazepines that are approved for anxiety disorders rather than insomnia are also commonly used for sleep disturbance. For example, diazepam, alprazolam, and lorazepam are frequently used for this purpose. The efficacy, risks, and benefits are likely similar to the insomnia-approved benzodiazepines. Sedating antidepressants, such as trazodone, mirtazapine, doxepin, and amitriptyline, are the most commonly used. These last two agents are tricyclic antidepressants with robust anticholinergic side effects, so the doses must be kept very low. The tolerability of trazodone and mirtazapine are likely better, but neither has been extensively studied in controlled trials in young or old adults for insomnia. Clinical consensus is that safety and efficacy of these agents is acceptable for many patients, but the clinician must remember that despite widespread use, these drugs are being prescribed "off label" and in the absence of compelling data when used for sleep. In their favor, these medications may help treat comorbid anxiety and depression, are safer for patients with COPD and apnea, and restore more physiologic sleep architecture than do the benzodiazepines and BzRA.

Nocturnal awakenings in patients with Parkinson's disease, AD, and other dementias can be particularly challenging and has been extensively investigated. There are data to suggest that increased exposure to daytime light and nighttime melatonin can have modest effects. We have presented preliminary data that the atypical antipsychotic quetiapine can have robust effects relative to placebo in a mixed dementia population, but do not recommend this class of agents specifically for sleep disturbance in the absence of other neuropsychiatric syndromes such as psychosis and severe mood symptoms.

Other Sleep Disorders and Aging

Sleep Disordered Breathing

Twenty-five percent community-dwelling seniors experience trouble falling asleep once per week, and 39% have episodes of excessive daytime sleepiness at least once a week [55]. Sleep-disordered breathing, hypopneas, and apneas are a major cause of daytime sleepiness in this population. Sleepiness affects not only the quality of life of persons suffering from obstructive sleep apnea but also their overall health conditions [69, 70]. A poor sleep efficiency, severe snoring, and increased arousals are all strong predictors of daytime sleepiness [71]. Also, age, sex, and body mass index are all predictors of sleep-disordered breathing [72]. The apnea–hypopnea index increases with age [73] with the prevalence of sleep apnea ranging around 5.6–70% in elderly [53, 54] with middle-aged adults having a high tendency to develop sleep-disordered breathing with a stronger prevalence among men compared to women [74].

However, a strong association remains between the aging process and prevalence of OSAS [74]. Age–apnea condition differences exist between older and middle-aged adults [75] with the occurrence of certain diseases such as diabetes, stroke, obesity, and heart failures considered as specific risk factors of developing sleep-disordered breathing in older adults [76]. Nevertheless, association of obesity and snoring with sdb remain stronger in younger adults [77]. Some specific OSAS symptoms are observed in elderly and seem to be age-related. Diabetes seems also to be associated with sleep-disordered breathing with a high prevalence in diabetic [78]. A decreased respiratory effort during apnea episodes has been observed and must certainly be caused by physiologic changes occurring with age [79]. However, although older adults experience more OSAS disorders than younger adults, common symptoms are found in both middle-aged and elderly persons [76]. For instance, sleepiness remains the strongest factor associated with cardiac dysfunction in middle-aged patients with OSAS in comparison to other factors such as age, blood pressure (hypertension), and other sleep variables including sleep efficiency and awakening duration [80]. Nocturnal increase in blood pressure, hypertension, obesity, and cardiac problems are strongly associated with sleep apnea. Mild sleep apnea in older patients showed no significant risk of morbidity or mortality even after 7 years of follow-up but for persons with more severe apnea, it is even likely that death might occur during sleep [81]. Severe sleep apnea with a respiratory disturbance index over 50 is an independent risk factor for mortality in elderly women [82]. Older women with severe RDI experience the most inadvertent naps, longer nap times, higher number of awakenings, and longer wake time after sleep onset associated to a higher risk for mortality [82]. Some mechanisms are underlying factors appearing with aging and might be worsened in aged patients with OSAS. Increases in RDI have shown some association with increase in cognitive impairment [83]. Deficit in attention and reaction time are significant in older patients with OSAS [84] but overall, cognitive performance in patients with OSAS does not necessarily get worse with age [85].

In the clinic, patients can be quickly screened for daytime sleepiness by using the Epworth Sleepiness Scale [86]. This tool, easily administered and available on line, quizzes the patient (and preferably the spouse, bed partner, or caregiver) about the likelihood of dozing in eight hypothetical situations: lying down in the afternoon, while watching TV, while reading, during conversation, sitting up after lunch, in a public place such as theater or waiting room, as a passenger in a car for an hour, and sitting in a car stopped in traffic. Each situation is scored 1–3, 0 = not at all likely to doze, 1 = slight chance of dozing, 2 = moderate chance of dozing, and 3 = high chance of dozing. A cumulative score ≥10 suggests pathological sleepiness that should prompt a referral to a sleep center where OSAS can be ruled out. Other features observed in OSAS include numerous nighttime arousals affecting sleep efficiency.

Periodic Limb Movements

Periodic limb movements during sleep (PLMS), also called nocturnal myoclonus, can have onset before the age of 20 [87], but prevalence is strongly age-related with increasing prevalence through midlife [88–91]. The prevalence ranges from 25 to 37% in the elderly [92, 93], although the prevalence does not seem to increase markedly through old age

through follow-up periods from 1 to 18 years [94–97]. The presence of restless legs symptoms and nonrestorative sleep should prompt referral to a sleep center for polysomnographic rule out of PLMS.

REM Sleep Behavior Disorder

Rapid-eye-movement sleep behavior disorder (RBD) is a dissociated form of REM sleep or parasomnia characterized by dream enactment behavior due to disruption in normal muscle atonia of REM sleep [98]. Patients with RBD may complain of frighteningly vivid dreams, and can physically act out violent dream-directed behaviors as if they were awake [98]. RBD is prevalent in male older adults [98], and the RBD idiopathic form is associated with Parkinsonian disorders such as Parkinson's disease and Diffuse Lewy Body Disease (LBD). In fact, RBD may precede the hallmark symptoms of LBD such as Parkinsonism and dementia [98–101]. Treatment with low-dose clonazepam can provide dramatic relief.

Sundowning

Sundowning is a descriptive term that refers to the circadian pattern of increased agitation and confusion that occurs in the late afternoon or early evening in many patients with dementia. A controversy remains to accurately define the sundowning phenomenon and its prevalence, and the term is sometimes applied to the sleep disturbance of dementia [10, 102–105]. Given the fact that the symptoms of sundowning follow a clearly circadian pattern, it has been hypothesized that disruption of the brain biological clock, called SCN that may occur with aging and AD might relate to sundowning symptoms [106]. Investigators have attempted with little success to demonstrate improvement in afternoon agitation with bright light exposure. The roles of fatigue and neurotransmitter (e.g., acetylcholine) depletion in the circadian delirium that comprises sundowning need to be investigated.

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Part III

The Primary Insomnias

11

Psychophysiological Insomnia

Mary B. O'Malley and Edward B. O'Malley

Abstract

Of all the forms of chronic insomnia, perhaps the most insidious is Psychophysiologic insomnia, also called Primary Insomnia in the DSM-IV. This sleep disorder is a final common pathway for many people who initially develop sleeplessness in the context of acute stressors (e.g., pain, job loss), but then acquire a form of "learned" sleeplessness as they become increasingly overconcerned about their unsatisfying sleep patterns. Patients report reduced total sleep time, with increased sleep latency (greater than 30 min), or increased wake after sleep onset time, though these findings are not always corroborated on PSG studies. Patients with this form of chronic insomnia are often vexed by its seemingly unpredictable nature from night to night, but to be diagnosed symptoms must be present on three or more nights per week, for more than 1 month (DSM-IV) or 6 months (ICSD-2). The essential feature of this form of insomnia is a pattern of sleep disturbance that evolves over time as a result of psychological distress that triggers unhelpful behaviors and physiological arousal. This chapter will summarize the current understanding of the development of this disorder, and the clinical approaches that may be useful to resolve it.

Keywords: Psychophysiological insomnia, Primary insomnia, Cognitive behavioral therapy, Sedative-hypnotic medications, Biofeedback

Introduction

Of all the forms of chronic insomnia, perhaps the most insidious is Psychophysiologic insomnia, also called Primary Insomnia in the DSM-IV. This sleep disorder is a final common pathway for many people who initially develop sleeplessness in the context of acute stressors (e.g., pain, job loss), but then acquire a form of "learned" sleeplessness as they become increasingly overconcerned about their unsatisfying sleep patterns. Patients report reduced total sleep time, with increased sleep latency (greater than 30 min), or increased wake after

From: *Clinical Handbook of Insomnia,* Current Clinical Neurology
Edited by: H.P. Attarian and C. Schuman, DOI 10.1007/978-1-60327-042-7_11,

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Etiology of Psychophysiologic Insomnia

The process of transitioning from wake to sleep involves many steps, most of which we do not usually consider. Given the right circadian timing, and a reasonably accommodating sleep environment, most adults fall asleep within 30 min [1]. For many, the added pressure of chronic sleep deprivation makes sleep onset that much easier and faster. However, when circumstances are unfavorable for sleep, or there is added psychophysiologic tension, falling asleep, or returning to sleep may be delayed. Given several difficult nights of sleep, some people develop conscious as well as unconscious negative associations to their bed and bedroom environment that heighten arousal levels, making it more likely that the trend will continue with successive nights of "failure". Unfortunately, in frustration and despair, these individuals often make poor choices that may further worsen their sleep disturbance. Using alcohol to facilitate sleep, or going to bed extra early to try to "catch" some sleep may seem like reasonable approaches to the patient, but tend to exacerbate insomnia [2]. Thus the model for this disorder described by Spielman and colleagues (Figure 11.1) rests on the role of perpetuating factors such as these that lead to a chronic, vicious cycle of tension and arousal around sleep in predisposed individuals [3]. This model, "The 3 P's: Predisposing, Precipitating, and Perpetuating Factors," works well to account for much of what we see clinically in the development and recovery from Psychophysiologic insomnia.

One concept widely embraced in the insomnia literature is that some people are more likely to develop Psychophysiologic insomnia than others. These "predisposing factors" are still unclear, however. A large majority of patients in treatment for chronic insomnia have increased levels of anxiety and/or depression [4–6], though these symptoms do not often meet the diagnostic criteria for disorders. A distinguishing characteristic of Psychophysiologic insomnia is that anxiety symptoms and dysphoria or hopelessness tends to be nearly exclusively (or disproportionately) about sleep patterns, rather than other life issues.

Current research consistently identifies elevated levels of arousal in adults with chronic insomnia. Insomnia sufferers have been found to have elevated electromyographic activity [7], increased cortisol levels [8] and metabolic rates [9], and higher resting heart rates [10] compared with normal sleepers. Further, the electroencephalographic (EEG) activity of insomniacs during sleep is characteristically too "awake" – beta activity is increased, and delta (slow wave) activity is diminished throughout the night compared with normal sleepers [11]. Recent neuroimaging studies have also added evidence that insomniacs display overactivation of many brain areas that regulate body and emotional tone, and underactivation of executive functioning areas [12]. It is

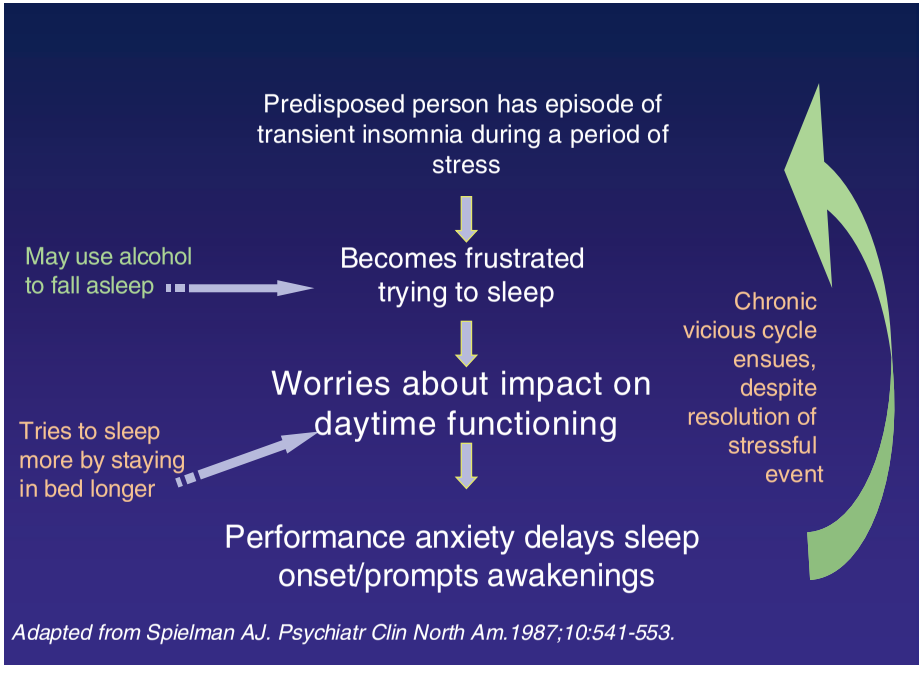

Figure 11.1 The evolution of psychophysiologic insomnia. Predisposed individuals enter into a vicious cycle of perpetuating factors that lead to Psychophysiologic insomnia

unclear whether these changes are what predispose individuals before their insomnia develops, or arise as a consequence of the disturbed sleep pattern, but the current research suggests that physiologic hyperarousal is a common profile among adults with chronic primary insomnia. Indeed, these altered physiologic patterns may be part of the perpetuating factors that undercut the patient's ability to get sleep back on track.

Clinically, we see these insomniacs as individuals who are primed to be more physically and emotionally reactive to stress, and sleep disruption tends to be a barometer for how stressed they are feeling. Individuals who are predisposed to this stress-reactivity report that a wide range of life events, physical and psychological stressors act as triggers that precipitate sleep disruption [13]. Higher subjective stress burden has been shown to be inversely correlated with the delta power of non-REM sleep [14]. In fact, insomniacs differ from other sleepers most clearly in their poor response to stressful events, not the severity or frequency of exposure to stressors [15]. A wide range of physiologic factors may contribute to the vulnerability to sleep disturbance in this population: a hypersensitive HPA axis, dysfunction in the sleep homeostatic system; or dysregulation of emotional control mechanisms [16]. One or more of these specific mechanisms may be involved in the generation of Psychophysiologic insomnia. Ultimately it appears that these insomniacs are biased toward chronicity by their fundamental difficulty in regulating physiologic arousal levels.

Identification of Patients with Psychophysiologic Insomnia

The most important element in the clinical assessment of individuals with insomnia complaints is a thorough sleep and medical history. Insomnia symptoms may be complex, emerging from different sources from night to night, and across time. Medications, substances, medical disorders, sleep environment, or scheduling issues may add to the symptoms of insomnia that patients present. The features of Psychophysiologic insomnia must be discerned between, with and among all the patients' presenting sleep complaints. A systematic clinical assessment to identify intrinsic or extrinsic conditions that may be contributing to sleeplessness is essential, and insomnia secondary to other conditions should be addressed directly.

A history of escalating overconcern regarding sleep is usually able to be identified outright. Indeed, many patients are desperately aware that their anxiety about sleep is effectively sabotaging their ability to sleep. Occasionally, a patient may be completely unaware that they are anxious or tense, and misattribute sleeplessness to other causes. A fairly typical history for Psychophysiologic insomnia is a patient who has had occasional problems initiating sleep in the past when stressed, but always managed to stay asleep once sleep began. Then, during an extended bout of initial insomnia 2 years ago, the patient became preoccupied with their problem sleeping and began having trouble returning to sleep after waking to urinate. These normal awakenings were perceived as problematic, and as the patient's focus on sleep intensified, their sleep initiation problem expanded to include sleep maintenance symptoms.

What makes Psychophysiologic insomnia different from the other Insomnia conditions is the essential role of the patient's psychological and physiological

arousal levels in the creation of the symptoms. So in addition to the routine elements of a sleep and medical history, the clinician should develop a longitudinal picture of the patient's ability to sleep in novel or stressful situations. The patient may recognize themselves as someone who tends to get "revved up" by life events in general, but many observe their trouble unwinding only in relation to their attempt to sleep. Still other patients do not perceive themselves to be anxious or "wound up," but simply "too awake." The clinician should explore whether the sleep complaints arise in the context of background of stress-reactivity, and how much insight the patient has about this aspect of themselves. Did this patient have difficulty transitioning to sleep as a child? Was this patient a "light" sleeper, sensitive to variations in their sleep environment? Did this patient feel sleep came easily before the problem of insomnia began, or have they always second-guessed their ability to sleep well? How was their sleep affected on nights before stressful or exciting events? Are they aware of the timing for sleep that really suits them (i.e., morningness vs. eveningness) or do they feel they "never sleep well"?

A comprehensive approach to understanding both the behaviors and the attitudes and beliefs around sleep issues has been demonstrated to be very important to adequately address chronic insomnia symptoms ([17] Morin 2004). Morin and colleagues have developed a variety of assessment tools that identify the cognitive distortions (e.g., "if I don't sleep 8 hours, I won't be able to function at all"), and misperceptions related to sleep. Most insomniacs carry dysfunctional patterns of thinking and feeling about sleep that represent a real inner barrier to improved sleep. Informed clinicians can readily identify these patterns, and help patients to change them by using these assessment tools (see Appendix for Dysfunctional Beliefs and Attitudes about Sleep). This type of history takes time, and not all clinicians may feel able or willing to use this approach. However, the investment of time to identify this information will usually allow the clinician to more quickly and precisely correct a patient's approach to sleep, and develop a more effective treatment plan.

As important element of an insomnia assessment is the use of outpatient self-report forms to document sleep patterns over the 24-h day. Patients may be annoyed by the task, but sleep logs (sleep diaries) are essential to the process of ongoing assessment of their sleep at home, and its response to treatment. There are many formats that can be used; the authors prefer a format that shows blocks of sleep visually, and includes a way to indicate what time a patient got into bed relative to when they first attempted to fall asleep (i.e., would show the time spent reading in bed before "lights out"). It is not necessary to have patients complete an exhaustive diary of meals, activities, and mental states, but patients can include relevant details when they recognize the potential to affect their sleep (e.g., "was very stressed after phone call"). Patients' subjective reporting on sleep logs is well-supplemented with actigraphy. Wrist-worn actigraphs are inexpensive, durable and lightweight devices that sensitively and continuously record movement activity and rest periods that correspond well to wake and sleep on polysomnography. The patient wears the actigraph on the nondominant wrist like a wrist watch, and objective measurements of activity levels can be collected for up to 4 weeks, allowing an objective assessment of their longitudinal sleep patterns at home [18]. Sleep logs, even without actigraphy, are more accurate and informative than a verbal report of their sleep patterns, particularly because patients tend to overestimate

or globalize their lack of sleep (e.g., "It always takes me 3 h to fall asleep"). With consistent use, sleep logs will facilitate collecting data on circadian, sleep hygiene, and sleep-timing patterns that will guide the treatment process. In fact, weekly logs may initially provide the only "proof" to a patient that there are incremental improvements in their sleep patterns.

If the diagnosis of Psychophysiologic insomnia is clear, a nocturnal polysomnogram is not needed. However, one may be needed to rule out other underlying sleep disorders. Patients with chronic insomnia are often surprised when they are able to sleep in the testing environment, and this can be a useful outcome measure as well – to reassure them that their brain can generate effective sleep, even under potentially adverse conditions. This information is useful for the clinician as well – Psychophysiologic insomnia is generally associated with less difficulty sleeping in new environments. Polysomnograms may reveal physiologic clues to the patient's history of sleeplessness: surges in heart rate with awakenings may correspond with anxiety or pain; shortened REM sleep-onset latency may be seen in patients with residual (or prodromal) major depression; a relative excess of light NREM sleep (N1, N2) and "spindling" will betray exposure to benzodiazepines. Patients may focus upon the findings for clues that their brain is "not broken," and the clinician should be aware that patients may really benefit from hearing the good news about a relatively normal polysomnogram.

Finally, if a behavioral treatment program has not produced significant improvement after several weeks of patient-compliant therapy then a polysomnogram would be indicated to rule out underlying organic disturbance that may have been missed or underreported by the patient. These studies sometimes reveal significant sleep apnea or other primary sleep disorders whose treatment may fully resolve the subjective sleep complaints or accelerate the patient's insomnia therapy.

Treatment of Patients with Psychophysiologic Insomnia

Nonpharmacologic Tools

Several longitudinal studies have demonstrated the most effective long-term treatment for Psychophysiological insomnia is Cognitive Behavioral Therapy (CBT) [19]. CBT protocols for insomnia are described in this text (Chap. 22) and comprehensive guides to treatment are also available elsewhere [17, 20]. A summary of the patient instructions and underlying core cognitive and behavioral strategies is outlined in Table 11.1. CBT treatment is used to systematically eliminate the beliefs and behaviors that undermine the patients' normal sleep process. Because the traditional CBT protocols developed for insomnia take several weeks, and there are a limited number of Behavioral Sleep Medicine clinicians trained in this therapy, clinicians have worked to develop an abbreviated version of CBT that is similarly effective, and can be delivered by primary care clinicians. Edinger and colleagues [21] have demonstrated that even two sessions of CBT delivered by family practitioners may also significantly improve sleep quantity and quality. Patients given this abbreviated version of CBT reported 50% less wake after sleep onset time 3 months after the intervention, a significant improvement over patients given

Table 11.1 Instruction and underlying purpose of sleep scheduling strategies.

Instruction: Restrict your time spent in bed to that spent sleeping
• Identify a regular rising time – given patient need and circadian preference
• Establish a bedtime no earlier than will provide hours of consolidated sleep
Instruction: Prepare for sleep by winding down
• Develops routines that promote regular sleep timing
• Incorporates relaxation into presleep period
• Can learn to identify and ameliorate presleep tension symptoms
Instruction: Go to bed only when you feel sleepy
• Learns to identify drowsiness as a sign they are ready for sleep
• Learns to identify conditions that postpone sleep onset
Instruction: Get out of bed when awake and getting frustrated
• Learns to deemphasize normal awakenings by remaining relaxed (and learns to eliminate clockwatching!)
• Reduces conditioned associations to bed when anxious/sleepless
Instruction: Keep a regular sleep schedule
• Learns to avoid creating exceptions after a "bad night"
• Helps to develop regular circadian signals to facilitate sleep and wake

sleep hygiene instructions alone. A more recent study that attempted to define the "dose–response" curve of CBT for insomnia suggests that four individual, biweekly sessions may represent the optimal dosing for the CBT intervention tested [22]. It is clear that even brief courses of CBT can translate into a valuable tool for the long-term recovery from insomnia.

In addition to CBT, many insomnia patients may greatly benefit from practices designed to evoke states of relaxation. Herbert Benson described the "relaxation response" and its benefits for reducing stress on the cardiovascular system many years ago [23]. Similarly, relaxation techniques have been applied in the treatment of insomnia to reduce the somatic and/or cognitive hyperarousal coincident with their sleep disturbance. Some studies have demonstrated that relaxation therapy is moderately effective for sleep maintenance insomnia [24, 25], while other studies have shown more robust benefits for insomniacs [26]. There is little evidence that one method is superior to others, and it is likely that the most critical determinant to success is that no matter what type of method used, the patient must learn to master the technique before applying it to the presleep period. One validated instrument specific to insomnia is the Pre-Sleep Arousal Scale (Table 11.2) which may used to assess a patient initially, and as they begin to apply relaxation tools during the sleep period [27]. Recent research has demonstrated there is value to combining CBT for insomnia with mindfulness-meditation [28] in reducing sleep symptoms, as well as presleep arousal levels. In addition, the overall level of arousal was subjectively reduced with this intervention in these insomniacs.

Another nonpharmacologic tool that may be useful in treatment of insomnia is EEG-Biofeedback, or Neurofeedback (NFB) training [29]. There are several

Table 11.2 The presleep arousal scale.

Instructions to patient

This scale is fairly self-explanatory. We are interested to find out about how you are feeling in your mind and in your body before you fall asleep. Please describe how intensely you experience each of the symptoms mentioned below as you attempt to fall asleep, by circling the appropriate number.

Further instructions to clinician

Two separate scores can be obtained for the PSAS. The sub-scale score for cognitive arousal comprises the total of items 1 to 8, and the sub-score for somatic arousal comprises the total of items 9 to 16.

	Not at all	Slightly	Moderately	A lot	Extremely
1. Worry about falling asleep	1	2	3	4	5
2. Review or ponder the events of the day	1	2	3	4	5
3. Depressing or anxious thoughts	1	2	3	4	5
4. Worry about problems other than sleep	1	2	3	4	5
5. Being mentally alert, active	1	2	3	4	5
6. Can not shut off your thoughts	1	2	3	4	5
7. Thoughts keep running through your head	1	2	3	4	5
8. Being distracted by sound, noise in the environment	1	2	3	4	5
9. Heart racing, pounding or beating irregularly	1	2	3	4	5
10. A jittery, nervous feeling in your body	1	2	3	4	5
11. Shortness of breath or labored breathing	1	2	3	4	5
12. A tight, tense feeling in your muscles	1	2	3	4	5
13. Cold feeing in your hands, feet or your body in general	1	2	3	4	5
14. Have stomach upset (knot or nervous feeling in stomach, heartburn, nausea, gas, etc.)	1	2	3	4	5
15. Perspiration in palms of your hands or other parts of your body	1	2	3	4	5
16. Dry feeling in mouth or throat	1	2	3	4	5

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From Appendix E in [17] (pp 141–142).

types of NFB training currently available, all of which measure cortical EEG in patients while awake, and provide real-time visual or auditory feedback to the patient about their EEG patterns to facilitate a renormalization of their brain states. For instance, patients can learn to produce more alpha waves in their EEG when their success is coupled to an arrow's movement toward a target on a graphic display. The majority of NFB systems are modeled after the pioneering work of Barry Sterman [30] who demonstrated that cats can learn to voluntarily enhance their sensorimotor rhythm (SMR, 12–14 Hz activity) in their wake EEG through operant conditioning paradigms. These cats demonstrated significant changes in their sleep EEG (increase in sleep spindles, and in quiet sleep time), suggesting that strengthening the thalamocortical rhythms through NFB training can benefit sleep systems.

To date however, only two studies have evaluated the effect of NFB training on sleep in insomniacs. In 1981, Hauri and colleagues applied three biofeedback methods to a group of 48 insomniacs that he randomized as follows: (1) frontalis muscle EMG feedback, (2) frontalis muscle EMG training followed by theta frequency band EEG NFB; (3) SMR NFB training; or (4) control [31]. Thus, this study intended to evaluate the efficacy of somatic relaxation (frontalis muscle EMG) training, and two types of NFB training or both, on insomniacs. As with Sterman's cats, the amount of learning in SMR NFB training correlated significantly with sleep improvement. Interestingly, the initial somatic tension levels (frontalis EMG measured 5 min after lights out on NPSG) correlated positively with sleep improvement for the EMG-training groups, but negatively with sleep for the SMR group. Essentially, the authors identified that this group of insomniacs were not uniformly tense, and that the benefits of the biofeedback measures were evident only when patients were randomized to the group appropriate to their specific deficiencies. A replication study conducted by the same group [32] further corroborated that insomniacs who were tense and anxious benefited from theta frequency band EEG-biofeedback (NFB training that facilitates relaxation), while those who were relaxed at intake but still could not sleep benefited only from SMR training (NFB training that strengthens the sleep system). These studies were the first to characterize that insomniacs have distinct pretreatment physiologic profiles, and that selective application of appropriate biofeedback protocols may significantly benefit their sleep.

Recently, we have applied a new type of NFB training in insomnia patients that utilizes a more global approach to EEG training (Zengar, Neurocare system). This NFB system is based on nonlinear dynamical (chaos) control theory that predicts that reducing "turbulence" in EEG will lead to renormalization of brain states. This system measures EEG across the entire range of frequencies (0.5–60 Hz), and provides real-time feedback about the degree of emergent variability ("revving" or "turbulence") to the patient as brief interruptions in music being played. This NFB system has several advantages, including eliminating the need for a diagnostic quantitative EEG, and there is less potential for side effects than with traditional targeted EEG-biofeedback. We have seen significant clinical improvement in a diverse array of insomnia patients such that the majority of patients' sleep symptoms are resolved after 16–20 thirty-minute training sessions [33]. Further research is needed to validate this and other more traditional NFB protocols for insomnia treatment, but it is likely these nonpharmacologic tools represent potent technologies that may greatly enhance physiologic recovery from chronic insomnia.

Pharmacologic Treatments

Hypnotic medications may initially be necessary to help a patient begin sleeping regularly again. Anxious patients make poor students, and compliance with CBT and other behavioral regimens will be a challenge for patients desperate to sleep. For these patients, a nightly hypnotic may be the best first step in treatment so that the patient may experience regular, predictable sleep periods again. The choice of hypnotic medications should be made based upon the patient's pattern of insomnia: short-acting hypnotics for initial insomnia, hypnotics with longer half-lives for problems with sleep maintenance. For a complete discussion of hypnotic medications and their use in insomnia patients, the reader is referred to Chap. 23 of this text. Once the patient is sleeping again, they can successfully participate in CBT protocols, and hypnotics can then be gradually tapered off and discontinued. Of course, there are many patients who have already tried an exhaustive list of hypnotics, but are still not sleeping well. Though these patients may also be desperate to sleep, their despair may actually make them more likely to commit to nonpharmacologic practices if offered in a supportive and systematic way. Ultimately, the challenge for many insomniacs is to rediscover the confidence they have lost that they can sleep, and deal with occasional bouts of sleeplessness on their own. For many chronic insomniacs, successful treatment may be predicated on having access to a suitable hypnotic as a "back-up plan" for the rare night they feel beyond their limit to tolerate sleep issues.

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12

Idiopathic Insomnia

Garrick Applebee

Abstract

Idiopathic insomnia (Childhood-onset insomnia) is defined as the lifelong inability to get adequate amounts of sleep. It is presumably due to dysfunction in the sleep–wake centers in the brain. Idiopathic insomnia patients are thought to have hyperactivity in the wake center or hypoactivity in the sleep center. These patients have sleep disturbances such as inability to fall asleep, frequent awakenings, and early morning wakefulness since early childhood. Psychologically, most patients with idiopathic insomnia are remarkably healthy, given their chronic lack of sleep. Management strategies are rather disappointing in their effectiveness, but include behavioral techniques to prevent the worsening of the insomnia and medications.

Keywords: Idiopathic insomnia, Sleep–wake center, Childhood onset, Benzodiazepines, Zolpidem, Melatonin, Tricyclic antidepressants

Many things – such as loving, going to sleep, or behaving unaffectedly – are done worst when we try hardest to do them.

C.S. Lewis

Definition

The *International Classification of Sleep Disorders* defines idiopathic insomnia, alternatively referred to as childhood-onset insomnia, as a lifelong inability to get adequate amounts of sleep. Beyond the temporal onset of the insomnia symptoms, there are two other distinct features which distinguish idiopathic insomnia from psychophysiological insomnia; there should be no identifiable precipitating factor for the insomnia, and the course is usually sustained in symptom severity.

From: *Clinical Handbook of Insomnia,* Current Clinical Neurology
Edited by: H.P. Attarian and C. Schuman, DOI 10.1007/978-1-60327-042-7_12,

The etiology of idiopathic insomnia is unknown, but there is presumably an underlying abnormality in the neurologic control of the sleep–wake system [1]. There continues to be debate, however, that this disorder is a separate and unique type of insomnia. For example, the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* classifies idiopathic insomnia as a component of a broader entity named "primary insomnia," which also includes psychophysiological insomnia and paradoxical insomnia (formerly known as sleep state misperception) [2, 3].

Historical Note

The Association of Sleep Disorders Centers, now the American Academy of Sleep Medicine, developed and published Sleep Nosology in 1979. In that publication, a new category entitled "childhood-onset insomnia" was presented. It was described as "sleep-onset and sleep-maintenance insomnia, resulting in daytime symptoms of inadequate sleep, which is characterized by a distinctive history of (unexplained) development before puberty, and persistence into adulthood." It was postulated that this new entity represented "a CNS shift or dysfunction of the sleep-arousal equilibrium" [4]. The existence of this disorder was confirmed by research done in the 1980s. It was also documented that this is a distinct form of insomnia by showing that childhood-onset insomnia was different from adult-onset insomnia on polysomnographic grounds [5] and that it could be distinguished from other types of insomnia in a cluster analysis [6].

Epidemiology

Idiopathic insomnia is rarely seen in its pure form at the time of diagnosis. In children, it can be difficult to isolate idiopathic insomnia from contributing behavioral factors. Evaluation in the context of other medical conditions, such as learning disabilities and attention-deficit/hyperactivity disorder, can also be challenging. This is especially true in the latter, as there is evidence that idiopathic insomnia occurs frequently in this population [1], and sleep difficulties are often contributed to by treatment with stimulants.

By the time idiopathic insomnia is identified in adults, a lifetime of chronic and serious insomnia has almost always led to confounding factors of poor sleep hygiene and emotional disturbance that further complicate the diagnosis [7]. Also, a baseline predisposition toward poor sleep exists in many insomniacs. It is estimated that true idiopathic insomnia represents less than 5% of all insomniacs, with a prevalence of approximately 0.7% in adolescents and 1.0% in young adults [1, 8].

Etiology

Idiopathic insomnia may be due to a dysfunction in the brain sleep–wake centers, representing either hyperactivity in the wake center or hypoactivity in the sleep center [5, 9]. Another commonly accepted theory is that patients with idiopathic insomnia are organically hyperaroused [10]. Evidence also suggests that idiopathic insomnia may have familial patterns of inheritance, though this may be generalized to all types of insomnia [1].

Pathogenesis and Pathophysiology

The sleep-promoting centers are located in the anterior hypothalamus, the raphe nuclei and medial forebrain area, and the wake-promoting centers in the ascending reticular activating system, including the posterior hypothalamus [7, 9]. Whether a person is awake or asleep depends on the neurophysiological balance between the reticular activating system and the sleep-promoting system [11]. Idiopathic insomnia presumably is due to a shift of this balance toward arousal, with either hyperactivity in the arousal system or hypoactivity in the sleep system [9]. Patients suffering from idiopathic insomnia may have a neurochemical, neuroanatomical, or neurophysiological dysfunction, or have anatomic lesions interfering with normal sleep [11]. Despite animal data showing the creation of insomniac animals with medial forebrain and medial preoptic area lesions [12], no direct human evidence for structural neuropathology exists [13].

The theory of hyperarousal is supported by idiopathic insomnia patients exhibiting hyperarousal during wakefulness on questionnaires, auditory evoked potentials, and EEG [14]. Physiologic hyperarousal in many systems (cardiac, metabolic, neuroendocrine) is not confined to idiopathic insomnia patients, but is frequently found in all primary insomnias [15]. This suggests there may be a variation in the degree of hyperarousal amongst insomnia subtypes.

Clinical Manifestations

Idiopathic insomnia is a chronic and serious inability to initiate and maintain sleep that can be observed as early as the first few weeks of life. Parents often report that the patient slept much less, or required less sleep, than their siblings when they were infants. Sleep latency is long and tends to be longer than the sleep latency in adult-onset insomnias. Sleep is fragmented by many awakenings and may show sleep stage abnormalities, such as infrequent eye movements in REM sleep or ill-formed sleep spindles during stage II sleep [5]. Patients can also report an increased propensity for nightmares as children and adults [16]. Paradoxically, idiopathic insomniacs may show fewer body movements per unit of sleep than normal sleepers do [13]. The spectrum of severity of insomnia in this condition varies from mild to severe and incapacitating, as the presumed underlying neurological abnormality varies from mild to severe [13]. Daytime features typically include decreased attention and vigilance, low levels of energy and concentration, and a deterioration of mood commonly described as grim and subdued, rather than obviously depressed or anxious. In mild or moderate idiopathic insomnia, wake quality of life is remarkably intact. In some cases, daytime functioning may be severely disrupted and affected patients may have significantly reduced quality of life and daytime functioning. During childhood and adolescence, idiopathic insomnia has been associated with neurological issues such as dyslexia or hyperactivity [1].

The *International Classification of Sleep Disorders*' diagnostic criteria for idiopathic insomnia are: (a) the patient's symptoms meet the criteria for insomnia, (b) the course of the insomnia is chronic as indicated by: (1) onset during infancy or childhood, (2) no identifiable precipitant or cause, (3) persistent

course with no periods of sustained remission, and (c) the sleep disturbance is not better explained by another sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder [1].

Case History

Mr. C. was a 23-year-old male college student who reported a lifelong history of difficulties with falling asleep and staying asleep. Since childhood, he had taken 1-2 h to fall asleep and frequently awakened at night for 30–60 min. He had also never been able to take naps. Despite this, he had rare daytime sleepiness, until 3 months prior to his visit, when his sleep schedules were significantly altered due to a trip from Vermont to Singapore. With the significant changes in time zones, it took him almost a month to resume a "normal" sleep schedule after returning to Vermont. During this time his sleep was minimal and his insomnia and daytime fatigue prompted a referral to a psychiatrist. Mr. C. was diagnosed with depression and placed on bupropion, which disrupted his sleep even further. This was discontinued and sertraline was started, although the patient noticed little improvement in his daytime fatigue. His lack of improvement prompted a sleep referral. He directly correlated a worsening in daytime fatigue with sleepless nights. The patient had tried zolpidem intermittently, and although it helped him fall asleep somewhat faster, he still experienced disrupted and nonrefreshing sleep. The patient reported being very sensitive to light and so wore shades over his eyes at night. He was also very sensitive to sound and had difficulties living in a dormitory secondary to the frequent ambient noise at night. This prompted him to move to a single occupant room partway through the semester.

He had no other sleep complaints.

He did not have any family history of insomnia.

Physical exam was normal.

Polysomnography was performed and the patient reported a better night's sleep than usual. The sleep latency was 23 min, with a sleep efficiency of 87%, and arousals averaging 23/h. There was no sleep-disordered breathing.

Cognitive behavioral therapy for insomnia and sleep restriction therapy were initiated for treatment.

Differential Diagnosis

Not all insomnia in childhood is idiopathic or childhood-onset insomnia. Although complaints of insomnia are seen in up to 41% of children [17], uncomplicated idiopathic insomnia is rarely seen. Idiopathic insomnia is diagnosed when insomnia predates the development of the other complicating factors (emotional problems, ill adaptive associations or poor sleep hygiene) and when an imbalance of the sleep–wake system plays a paramount role [1].

Idiopathic insomnia should be differentiated from the behavioral insomnias of childhood, either the sleep-onset association or limit-setting types. In the former, habits, objects, or conditions become associated with the transition to sleep and need to be reestablished after normal awakenings, otherwise periods of waking are prolonged [18]. The latter is characterized by normal sleep ability, with deliberate attempts to remain awake at bedtime or after nighttime awakenings using a variety of requests, demands, and stalling tactics (stories,

drinks, bathroom trips, blanket adjustments, television, etc.) [18]. A careful history of the child's bedtime behavior usually can distinguish these disorders from idiopathic insomnia.

Idiopathic insomnia is differentiated from short sleep requirement by the lack of accompanying symptoms of fatigue and daytime performance impairment. Short sleepers should feel and function well during waking hours. They therefore rarely present for sleep evaluation, as they have no subjective sleep complaints.

In adults, idiopathic insomnia is most difficult to distinguish from psychophysiological insomnia, which is also accompanied by an innate predisposition toward poor sleep. In idiopathic insomnia, the presumed sleep–wake imbalance is enough to cause the insomnia by itself; in psychophysiological insomnia, the inherent sleep–wake disturbance needs the addition of maladaptive conditioning to trigger the insomnia [1]. Psychophysiological insomnia would be suggested if the onset is in adulthood, if an inciting event prior to developing insomnia is identified, and if the symptomatology has a waxing and waning character relatable to stressors in the patient's life.

Psychologically, most patients with idiopathic insomnia are remarkably healthy, given their chronic lack of sleep [1]. However, as in other primary insomnias, patients with idiopathic insomnia tend to be emotional repressors. Although the insomnia is persistent, relentless, and almost unvaried through both poor and good periods of emotional adaptation, patients may experience occasional worsening of their sleep under stressful situations [7].

Diagnostic Workup

Idiopathic insomnia is a diagnosis of exclusion. A careful history identifies the exact onset of the insomnia and is important in defining any maladaptive behaviors, sleep hygiene issues, and extrinsic factors. A thorough psychiatric interview reveals no psychological reason severe enough to explain the insomnia. Specifically, no psychological distress explains the early onset. A general medical evaluation reveals no causative medical factors such as allergy, pain, thyroid, or neurological abnormalities that might have been operative since early childhood. A polysomnogram, if performed, may reveal severely impaired sleep. However, because idiopathic insomniacs often show a "reverse first-night effect" (sleeping better in a different environment than at home) [6], more than one night in the sleep laboratory may be necessary. Nonspecific EEG abnormalities have been seen, but are highly idiosyncratic and not diagnostic. Overall, polysomnography adds little diagnostic value in idiopathic insomnia.

Another way of bypassing the "reverse first-night effect" is through actigraphy. An actigraph is a small wrist-mounted device that records the activity plotted against time, usually over 1–2 weeks. A close correlation exists between recorded rest or activity and the sleep–wake pattern, and has been validated in conjunction with polysomnography [19]. Actigraphy is a valuable tool in evaluating insomnia, especially in patients with severe complaints, and can supplement subjective sleep logs. Its ability to record sleep in the patient's home environment over long periods can be an objective measure which helps both the physician and patient better analyze disrupted sleep patterns.

Prognosis and Complications

The suspected neurological abnormality underlying idiopathic insomnia is presumably lifelong. Therefore, the symptom of insomnia to a certain degree persists for the person's entire life. Complications, like with other primary insomnias, include depression [20], attempts to treat the condition either by self-medication (such as alcohol) or by prescriptions (high doses of benzodiazepines or barbiturates), excessive use of stimulants to promote alertness, or the development of maladaptive behaviors and poor sleep hygiene.

Management

No guidelines for a consistent treatment approach to idiopathic insomnia are available. Impeccable sleep hygiene is essential, including regular, somewhat curtailed sleep hours, relaxation skills, and an active waking lifestyle [11]. Behavioral treatments such as sleep restriction consolidation and biofeedback can be helpful. Pharmacologically, benzodiazepines and the nonbenzodiazepine GABA agonists (e.g., zolpidem, eszopiclone) are effective as hypnotics [9]. Long-term use of medication has raised the question of tolerance and dependence [9]. Multiple studies have shown, however, that the risk for tolerance, dependence, and addiction is minimal in patients using long-term benzodiazepines for insomnia or for other sleep disorders [21–23]. According to sporadic case reports, some patients with idiopathic insomnia have responded to low-dose tricyclics, antipsychotic medications, or to opiates [7, 24, 25]. Melatonin has also been shown to be helpful in treating chronic insomnia in school-age children, particularly if their dim-light melatonin onset is significantly delayed [26, 27].

Case History

A 36-year-old, right-handed man presented to the sleep center clinic for a first time evaluation concerning his long-standing inability to fall asleep or stay asleep. He stated that as far back as he could remember, even as a child in grade school, he had trouble falling asleep. His mother had told him that even as a newborn he slept much less than his siblings had. He went to bed around 10 o'clock and tossed and turned for an hour or so before he fell asleep. He stated that his sleep was very light, and he tended to wake up once or twice in the middle of the night and stayed awake tossing and turning in bed. Whenever he was unable to fall asleep, he became restless, constantly watching the digital clock on his bedside table, and only rarely got out of bed to watch TV. He went to bed every night anticipating not falling asleep. As a result, he got about 4–5 h of sleep a night, and did not feel refreshed. Rarely, after a few nights of minimal sleep, he would sleep continuously for 7 h and feel significantly better and refreshed the next morning. He denied excessive daytime sleepiness, and denied falling asleep in inappropriate situations. He was unable to take naps. He stated that whether he slept at home or somewhere else, he was still unable to fall asleep or maintain sleep. He denied symptoms of restless legs or of periodic limb movements. He denied snoring, heartburn, cataplexy, sleep paralysis, hypnagogic hallucinations, or symptoms of apnea. In the past, he had tried zaleplon and trazodone. Zaleplon was ineffective, and

trazodone had somewhat shortened his sleep latency, only to produce excessive daytime tiredness, grogginess, and fatigue. He had also tried over-the-counter sleeping aids that did not make his sleep satisfactory in length or quality. He did not drink caffeinated beverages after the early afternoon, or alcohol in the late afternoon, but he did chew tobacco throughout the day even into the late evening. He had no other complaints.

Family history was significant for a similar type of insomnia in his grandmother and mother, but not in his father or siblings.

Physical exam was normal.

Overnight polysomnography revealed increased sleep latency and a 48% sleep efficiency due to prolonged unexplained awakenings. An Actigraph, worn for a week, confirmed his subjective reports of 4–5 h of fragmented sleep a night.

With strict compliance to sleep hygiene regulations and 1 mg of estazolam at bedtime, he was able to improve his sleep efficiency to a considerable degree, but this did not resolve his insomnia entirely [28].

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13

Paradoxical Insomnia

Hrayr Attarian

Abstract

A fascinating yet poorly understood disorder, paradoxical insomnia refers to a condition of gross discrepancy between objective sleep quantity per night and the subjective perception of sleep. Generally, people suffering from this condition complain bitterly, and sincerely, of not being able to sleep at all, yet when studied show sleep of normal duration and quality. Pathophysiology of paradoxical insomnia remains largely poorly understood. Increase in faster EEG activity during sleep and increase in physiological arousal seem to be prevalent in these patients, but whether they have direct causative impact remains to be seen. Management starts with education and other than psychotherapy no other techniques have been shown helpful.

Keywords: Paradoxical insomnia, Psychotherapy, Fast EEG activity, Physiological arousal

Introduction

A fascinating yet poorly understood disorder, paradoxical insomnia refers to a condition of gross discrepancy between objective sleep quantity per night and the subjective perception of sleep. Generally, people suffering from this condition complain bitterly, and sincerely, of not being able to sleep at all, yet when studied show sleep of normal duration and quality.

Historically, the first case report of this condition was published in 1959 shortly after the advent of polysomnography. In 1976, differences of large magnitude between subjective and objective sleep were described as a common occurrence in a study of 122 patients with chronic insomnia.

In 1990, the term sleep state misperception was adopted by the American Sleep Disorders Association (ASDA) as a diagnostic term in the first edition of International Classification of Sleep Disorders (ICSD). In 2005, the American

From: *Clinical Handbook of Insomnia,* Current Clinical Neurology
Edited by: H.P. Attarian and C. Schuman, DOI 10.1007/978-1-60327-042-7_13,

Academy of Sleep Medicine (AASM) changed the name to Paradoxical Insomnia in the second edition of the ICSD or ICSD-2.

Definition

The patient should have at least 1 month duration of persistent complaint of insomnia, often severe and extreme, and daytime fatigue without any objective evidence, from polysomnography or actigraphy, to support it.

Epidemiology

The prevalence of paradoxical insomnia in the general population has never been reported. In sleep-center patient population, the prevalence has ranged between 5 and 9%. One multicenter trial of diagnostic systems discovered that 6.6% of cases were diagnosed with either primary or secondary sleep state misperception. An older study reported that 9% of sleep clinic patients complaining of insomnia and 5% of patients complaining of sleepiness met criteria for sleep state misperception [1].

Etiology

Paradoxical insomnia's etiology has not been clearly defined. There are, however, several theories on its causation. The earliest paper on the topic theorized that presleep cognitive arousal and worry over sleep gave the person the impression of being awake even though they were asleep [2]. Kuisk et al. on the other hand, in their 1989 paper, theorized that the impression of being awake is due to excessive mentation in sleep [3]. A more recent study discovered a direct correlation between spontaneous sleep disruptions and the likelihood of underestimating one's sleep in a group of insomnia patients [4].

Salin-Pascual and colleagues suggested in their 1992 paper that paradoxical insomnia may be a transitional pathophysiological state from healthy sleep to primary or psychophysiological insomnia [5]. Lending more credence to this theory is the well-established fact that most insomniacs misperceive the amount of objective sleep they get and tend to unintentionally exaggerate their condition [6, 7]. This may be due to the fact that people suffering from psychophysiological or primary insomnia tend to have an attenuation of the normal-sleep-onset-associated amnesia [8]. Psychological distress that accompanies chronic insomnia also influences perception of sleep; MMPI scores of Psychasthenia are positively correlated with misperception of sleep time [9]. All these theories suggest that paradoxical insomnia may be an extreme form of primary psychophysiological insomnia which, in turn, is on a spectrum with normal sleep. Of note, a certain percentage of healthy sleepers also underestimate their sleep latency, especially, if woken up shortly after having fallen asleep [10].

Another set of theories has focused on the possibility that there may actually be a certain number of physiological arousals from sleep that are not detectable by available conventional diagnostic tests [11, 12]. Excessive sleepiness can result from frequent auditory stimuli, delivered during sleep, that are of an intensity sufficient to increase pulse and mean arterial blood pressure but not loud enough to cause a traditional EEG arousal [13]. One actigraphic study

showed increased movement in sleep of patients with paradoxical insomnia [14], potentially supporting the above hypothesis.

Sleep Misperception is not limited to patients with insomnia. Patients with obstructive sleep apnea (OSA) tend to overestimate sleep-onset latency and underestimate total sleep time [15, 16], so do patients with Chronic Fatigue Syndrome [17]. Even one-third of healthy sleepers may misperceive sleep as wakefulness when awakened form consolidated sleep [18].

In 2004, we reported a case of a 71-year-old woman who repeatedly grossly underestimated sleep latency and physiologic wakefulness by polysomnographic and actigraphic criteria, as subjective sleep, at the time we, tentatively, called it Reverse Sleep State Mispercerption [19]. A few years later, Dr. Schneider-Helmert published a case series of 27 patients with similar presentation as ours [20], this was followed, in the same year, by another case series of 27 patients reported by Trajanovic and colleagues [21]. Three separate terms have been used to describe this new variant including; disturbed perception of wakefulness within sleep [22], asymptomatic insomnia [20] and positive sleep state misperception [21].

All these variations on the presenting "theme" of paradoxical insomnia raise the possibility that the cause is more multifactorial and not a single theory alone can explain the etiologic whole.

Pathophysiology

The key pathophysiological feature of the paradoxical insomnia is the relatively normal objective measures of sleep and wakefulness despite subjective, often severe, sleep complaints.

As to why this is remains to be elucidated. There are few papers primarily exploring abnormalities in EEG measures. There were no strong correlations between changes in sleep stages, sleep onset latency, wake after sleep onset or WASO, spindle density, arousal index, and EEG frequency either individually or in combination [23]. Another paper found a possible link between decreased alpha frequency activity in sleep and underestimation of sleep time [24]. Quantitative EEG studies have also found an increase in the high-frequency (over 14 Hz) activities during sleep in patients with paradoxical insomnia [25–27].

Bonnet and Arand used a different approach by looking at physiological measure of arousal in the form of metabolic rate. They found higher metabolic rates both during wakefulness and sleep in patients with paradoxical insomnia as compared to healthy controls and to primary insomniacs with objectively documented sleep disruptions [28].

In short, the pathophysiology of paradoxical insomnia remains largely poorly understood. Increase in faster EEG activity during sleep and increase in physiological arousal seem to be prevalent in these patients but whether they have direct causative impact remains to be seen.

Case 1

A 70-year-old woman presents to the sleep medicine clinic complaining of 30-year history of insomnia. Her insomnia started rather abruptly following a partial hysterectomy. Prior to the surgery she slept heavy and soundly. She

states that for the first 27 years she did not sleep at all. She lays down every night and get up every morning at the same time and without having slept at all. She states that during the day she does not feel fatigued and she is not excessively sleepy. Her Epworth sleepiness scale score is zero. She states that her husband keeps telling her that she is actually sleeping at night, but she knows that she is not; she is just lying there quietly. She does not nap during the day. Three years ago she started taking triazolam 0.375 mg two or three nights a week. When she takes the medication then she sleeps through the night without interruptions. During the day she feels the same level of energy whether she takes the triazolam or not. She has no other medical problems and only takes an aspirin tablet a day. Her exam is normal. A week of sleep diary and simultaneous actigraphy is done and the results are shown in Figs. 13.1 and 13.2.

The two nights when she took triazolam she slept an hour longer but all seven nights showed solid sleep on the actigraphy while on the sleep log she had only the two nights marked as sleep and the rest of the time she had marked as awake.

The diagnosis is presented to her and she is referred for cognitive behavioral therapy to the Sleep Center's psychologist. Although, she appears to be accepting the diagnosis she cancels her appointment with the psychologist and does not reschedule it and does not return to the Sleep Center for follow-up.

Clinical Manifestations

The cardinal symptom of Paradoxical Insomnia is the complaint of long-standing, often severe, insomnia and nonrestorative sleep that is either partially responsive or completely unresponsive to standard treatment. Generally, the patients are not as impaired during the day or as fatigued than one would expect with the little amount of sleep they report getting at night. Polysomnography (PSG) or other objective measures are often normal showing normal sleep latencies and sleep durations despite patient's claims of the contrary. There have been rare cases where patients have complained of disabling sleepiness but Multiple Sleep Latency Tests have not shown any signs of physiologic hypersomnia. Recently, there have been a few papers describing patients who presented with unexplained fatigue and reported normal nighttime sleep but on PSG and actigraphy recordings they had severely curtailed amount of sleep.

Another key feature of paradoxical insomnia and, to a lesser degree, its hypersomniac variants, is the absence of any psychiatric and medical conditions that impact, are related, or explain the sleep complaints. These patients are not malingering or generally looking for a conscious or subconscious secondary gain from their symptoms. They are genuinely distressed over their perceived lack of sleep. Often they dismiss reports of their bed partners who report that the patient was actually sleeping when they were sure they were awake.

Diagnosis and Differential Diagnosis

The diagnosis is usually established by demonstrating on an objective measure of sleep, either PSG or actigraphy, at least 6.5 h of sleep a night with a minimum sleep efficiency of 85–90% [29]. When using PSG it is important to ascertain that the patient felt the night in the lab to be a typical night and that they

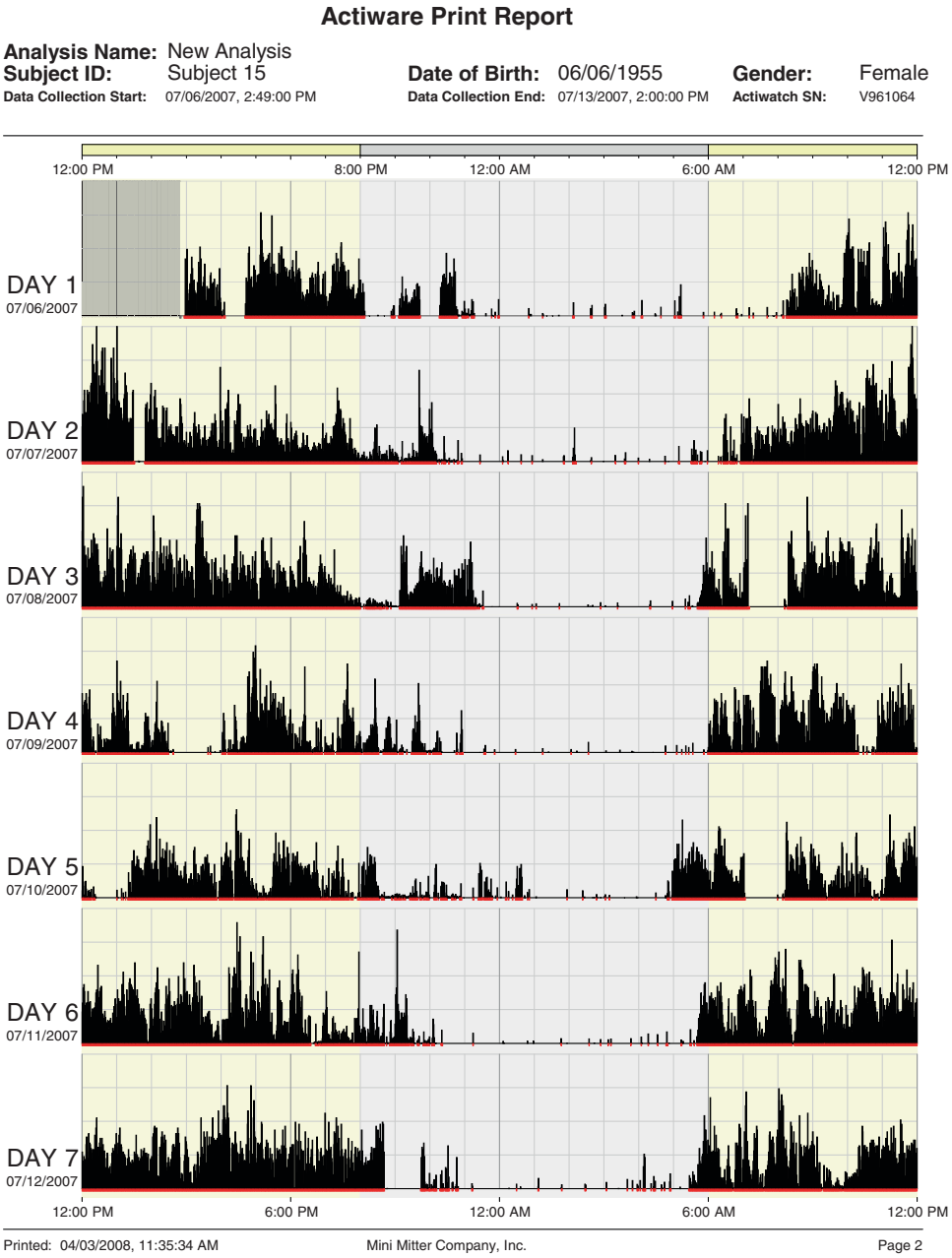

Figure 13.1 Actiware print report

still think they only slept as little as usual. Often patients with other forms of insomnia sleep better when they are not at home, so a relatively normal night's sleep in the sleep lab may be because of a "reverse" first-night effect and unless the patient is asked about their perception on that particular night they may get misdiagnosed with paradoxical insomnia[30]. Actigraphy comes in handy as well because it allows the patient to be studied in their own home

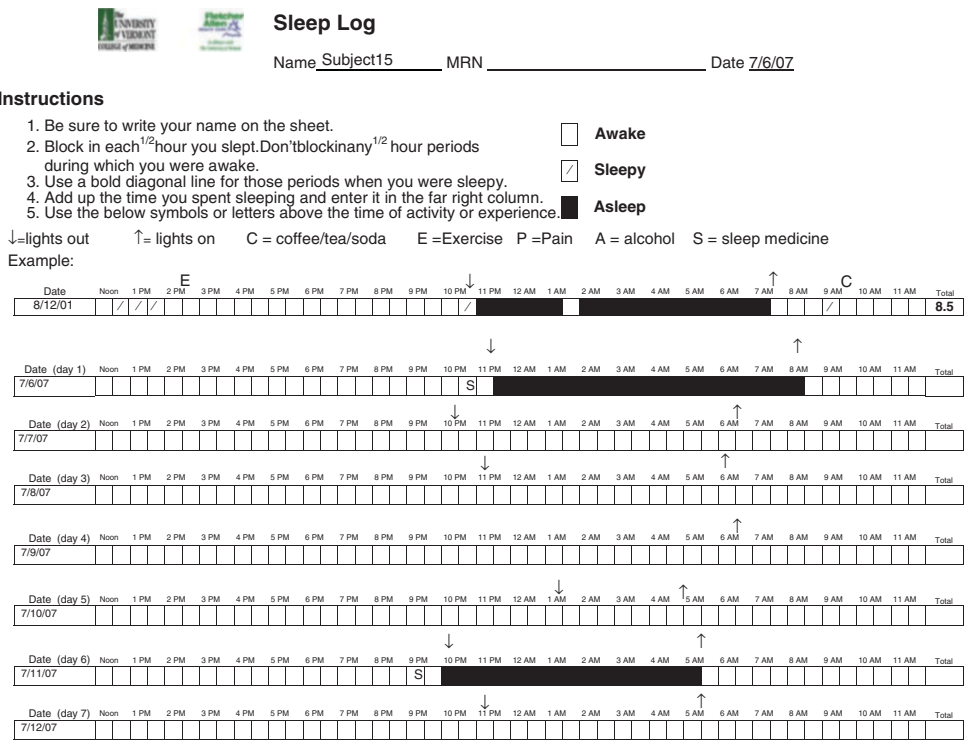

Figure 13.2 Sleep log

over a few weeks and those findings to be correlated with the patient's own subjective sleep logs.

Before paradoxical insomnia diagnosis is made, psychiatric and psychological causes should be ruled out as well as malingering and other forms of primary or secondary insomnia. Patients with psychophysiological and idiopathic insomnia often have some degree of misperception but it is not extreme as ones with paradoxical insomnia. A survey of patient's sleep hygiene, medications, medical conditions, and other symptoms are important to determine whether they have a form of secondary insomnia.

Prevention, Management, and Prognosis

Since paradoxical insomnia is relatively poorly understood and we do not know the risk factors for it prevention is not possible. Management starts with education about the spectrum of sleep–wake patterns, validation of the patients concerns, presenting the objective data and reassurance. CBT and/or hypnotic medications are sometimes, but not always, helpful at least for a period of time[10]. This population of patients responds differently to sedative hypnotic medications and often report significant subjective improvement without objective change in sleep [31, 32]. Recently, there was a report of severe paradoxical insomnia without other psychiatric diagnoses responding to electroconvulsive therapy (ECT) [33]. The prognosis is not well-studied because

most cases are lost to follow-up but it appears to be a persistent problem with occasional relapses even in the successfully treated group. The key concern is avoiding drug dependance. The benefits of prescribing sedative hypnotics should be weighed carefully against risk of dependance and the fact that the medications are not changing objective sleep measures.

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14

Sleep Hygiene

Hrayr Attarian

Abstract

Inadequate sleep hygiene is an insomnia associated with daily living activities that are inconsistent with the maintenance of sleep and daytime alertness. Not everyone who practices poor sleep hygiene develops insomnia. In patient's suffering from chronic insomnia there is a complex interplay of internal factors and poor sleep hygiene behaviors. Diagnosis is made by history and treatment is based on education.

Keywords: Sleep hygiene, Napping, Caffeine, Alcohol, Drug use, Ambient noise

Definition

The American Academy of Sleep Medicine (previously the American Sleep Disorders Association) classifies poor sleep hygiene-induced insomnia as one of the 11 insomnias in the 2005 second edition of the *International Classification of Sleep Disorders* [1]. Inadequate sleep hygiene is an insomnia associated with daily living activities that are inconsistent with the maintenance of sleep and daytime alertness. For example, intake of caffeinated beverages very close to bedtime produces insomnia due to the stimulating properties of caffeine and so does nicotine. Alcohol close to bedtime interferes with sleep maintenance by causing awakenings during the major sleep period. These constitute poor sleep hygiene. Setting aside relaxation or "down time" prior to going to bed facilitates sleep; therefore, it is an element of good sleep hygiene.

Grossly apparent poor sleep hygiene practices like the above and others such as excessive time in bed, exercising before bed or major variations in bedtime and rise-time on a daily basis are easy to spot but more subtle effects of practices such as a single daily nap may go undetected. Clinical judgment is needed when determining how long a nap should be and how close to bedtime to prevent it from interfering with nighttime sleep [1] (Table 14.1).

From: *Clinical Handbook of Insomnia,* Current Clinical Neurology
Edited by: H.P. Attarian and C. Schuman, DOI 10.1007/978-1-60327-042-7_14,

Table 14.1 Sleep hygiene guidelines used at University of Vermont Sleep Center.

1. Go to bed only when sleepy
2. Use the bed only for sleeping; do not read, watch television, or eat in bed
3. If unable to sleep, get up and move to another room. Stay up until you are definitely sleepy and then return to bed
4. Set the alarm and get up at the same time every morning, regardless of how much you have slept through the night
5. Do not nap
6. Don't exercise just before going to bed
7. Don't engage in stimulating activity just before bed
8. Avoid caffeine in the afternoon
9. Don't drink alcohol close to bedtime
10. Eliminate clocks in the bedroom
11. Before bedtime, schedule a period to review stressful events of the day
12. Focusing on quiescent tasks that occupy the mind such as reading, watching television, or listening to music promotes relaxation and sleep

Epidemiology

There are no ethnic or racial predilections identified and men and women are affected almost equally; however, there are cultural differences [2]. Older teenagers and young adults are one of the two groups especially affected by poor sleep hygiene. Manni et al., studied a large group of Italian high school students aged 17. In their cohort, 19% of girls and 11.6% of boys had persistent insomnia due to poor sleep hygiene [3], this was better than their American counterparts whom complained more of insomnia due to poor sleep hygiene (Italians: 18%; Americans: 25%), according to a newer study [2]. The other group that is affected by poor sleep hygiene is the elderly, especially those dwelling in nursing homes [4]. This is due to the level of noise and ambient light at night [5]. Although recently, a sample of community dwelling elderly insomniacs were surveyed and other than greater amounts of napping, they did not engage in poorer sleep hygiene behaviors than their age-matched noninsomniac counterparts [6]

In patient's suffering from chronic insomnia there is a complex interplay of internal factors and poor sleep hygiene behaviors. It is impossible to tease out the magnitude of the roles each element plays in the development of the insomnia. Most patients suffering from chronic and persistent insomnia have at least some features of inadequate sleep hygiene admixed with the features of their primary disorder. It is not known whether the sleep hygiene components are a result, or a partial cause, of the main sleep problem. There is, however, evidence that suggest that sleep hygiene education is at least partially effective in patients with primary insomnia [7] even though it is not recommended as a standalone treatment for primary insomnia [8]. In a survey conducted among 3,600 adult Japanese women to identify external factors causing insomnia, the prevalence of insomnia was found to be 11.2% [9]. Most of the complaints of insomnia were related to street noise at night. More recently, studies have

shown that chronic insomniacs do engage in poor sleep hygiene activities that tend to perpetuate the problem. Among these, the most prevalent are smoking and drinking alcohol close to bedtime as well as "sleeping in" to make up for missed sleep during the night [10].

Etiology

As we discussed above, the main cause of poor sleep hygiene insomnia is the set of behaviors that the patients voluntarily engage in, that produces increased arousal or in some way disrupts normal sleep [1]. These behaviors are normal when practiced in moderation but cause insomnia when they occur in susceptible people or in conjunction with other factors that disrupt sleep. Common poor sleep hygiene practices include going to bed when not feeling sleepy, consuming moderate amounts of alcohol, caffeine, or nicotine close to bedtime, night-to-night variability in bed- and wake-times, excessive napping especially when done in close proximity to the major sleep period, stimulation near bedtime (psychosocial stress, excitement, physical exercise, stimulating mental activity, etc.) [11], poorly regulated environmental elements such as ambient noise [9], light, or temperature [11], or disturbing household members [12]. A study done in community dwelling Japanese women found that living near streets with high nighttime traffic was the most important external risk factor for developing poor sleep hygiene insomnia. Others included experiencing major life events, having young children under the age of 6 years and having an irregular bedtime [9] (Table 14.2).

Pathogenesis and Pathophysiology

Not everyone who practices poor sleep hygiene develops insomnia. Persons diagnosed with inadequate sleep hygiene insomnia have an underlying hypersensitivity to changes in their sleep schedules and minute amounts of external stimuli. They have exaggerated physiological responses to even small amounts of stimulants (caffeine, nicotine), alcohol, exercise, excitement, or strong environmental disruptions, such as noise, shift work and ambient light. It is thought that these persons' circadian control centers (suprachiasmatic nucleus) [12] also seem to be sensitive to even minimal variations in their sleep schedules or to daytime napping [1]. Others, who suffer from inadequate sleep hygiene insomnia, because of psychological or physical illness or due to an innate predisposition, may have a particularly low tolerance to the effects of even infrequent sleep deprivation and, in good faith, in an attempt to remedy

Table 14.2 Amount of caffeine in common beverages.

Beverage	Amount of caffeine
8 oz of brewed coffee	100–150 mg
8 oz of instant coffee	85–100 mg
8 oz of tea	65–75 mg
12 oz of cola	40–75 mg
8 oz of cocoa	50 mg

the situation may resort to such poor sleep hygiene behaviors as extra naps or bedtime alcohol. A combination of behaviors that are nonconducive sleep and an innate physiological hyperarousal leads to the development of poor sleep hygiene insomnia [13, 14].

Clinical Manifestations

The main clinical symptom of inadequate sleep hygiene is insomnia. Other symptoms may include dysphoric mood, fatigue, irritability, occasionally hypersomnia, and poor concentration.

The time course of poor sleep hygiene-induced sleep problems may vary from self limiting and transient, to occasional or even frequent but intermittent, or persistent. It may be the cause of insomnia or may exacerbate an already existing one or itself may be the result of a preexisting primary or secondary insomnia. The insomnia may be sleep onset, sleep maintenance, or terminal resulting in early morning awakenings. In some cases it may present as irregular sleep patterns. The activities that constitute poor sleep hygiene and lead to poor sleep hygiene insomnia, usually, are common activities of daily life, which produce sleep disturbances in people with an innate susceptibility. Behaviors that are considered nonconducive to sleep include intake of caffeine late in the afternoon or evening, intake of alcohol at night (often in an attempt to self-medicate) psychological stress or excitement in the evening, obsessive clock watching while awake at night, exercise or smoking late at night or close to bedtime, use of the bed for activities unrelated to sleep (other than sex), variable bedtime and rise-time, going to bed when not sleepy poorly regulated comfort measures in the bedroom such as temperature, light, noise, uncomfortable bed, pets, family members or house mates that may engage in behaviors that is disruptive to one's sleep [15]. In addition to an innate susceptibility, a combination of these behaviors and extrinsic factors is needed, any one of which might be considered acceptable behavior in most people.

Case Study 1

A 46-year-old engineer comes in with the complaint of sleep maintenance insomnia. The patient goes to bed between 10 and 11 p.m., and has no difficulty initiating sleep. He awakens everyday at around 3 a.m. He, subsequently, is unable to go to sleep for the rest of the morning. This problem has been of about 2–3 years duration. Over-the-counter hypnotics have not helped. The patient denies experiencing pain or worry or anxiety at night, history of snoring or witnessed apneas, falling asleep unintentionally during the day or any caffeine intake after his early morning cup of coffee. He denies any neurovegetative symptoms of anxiety and depression.

Medications: Zestril, Lipitor.

Exam is normal and his Beck's Depression Inventory score is 4 (not depressed).

When further questioned, he reveals that he drinks on a nightly basis, over the past several years, three glasses of wine or some other type of liquor just before he goes to bed. He does this out of habit and denies having had problems falling asleep prior to him engaging in this nightly alcohol consumption.

He is asked to reduce his alcohol intake and to drink lesser amounts earlier in the evening.

At the next visit 6 weeks later his insomnia has resolved.

Case Study 2

A 26-year-old right-handed psychology student presents to the Sleep Medicine Center's clinic for initial evaluation of recent onset sleep initiation insomnia. In the past, she had only rare problems falling and staying asleep until 6–7 months ago when this problem became persistent.

Currently she goes to bed exhausted, sleepy, around 12 midnight or 1 a.m. and is still unable to fall asleep. She lays there anywhere from half an hour to 3–4 h tossing and turning, but does not leave the bed or the bedroom. She usually gets up in the morning at 7 a.m. with an alarm and on weekends when she doesn't have to go to work she sleeps into late morning, and sometimes till early afternoon.

During the day she takes a 45 min to 1½h nap. She also uses her bedroom during the day to study, to eat, to watch television, read, and sometimes works late into the night shortly before retiring. She does not abuse caffeine and only uses alcohol socially. She does not abuse recreational drugs and does not smoke. She denies cataplexy, hypnagogic hallucinations, snoring, choking spells, falling asleep unintentionally during the day or symptoms of restless legs. The only symptom she states that she's experienced rare periods of sleep paralysis, maybe twice to three times in her life time.

Past medical history: ADHD.

Medications: Dexedrine. Ambien PRN.

Exam is normal and his Beck's Depression Inventory score is 6 (not depressed).

Differential Diagnosis

The differential diagnosis of poor sleep hygiene insomnia falls under three main categories. The first consists of the other environmental sleep disorders, e.g., adjustment insomnia, behavioral insomnia of childhood, behaviorally induced insufficient sleep syndrome, high altitude periodic breathing, insomnia due to drug or substance, insomnia due to alcohol use, nocturnal eating or drinking syndrome, food allergy insomnia, and toxin-induced sleep disorder (the last three disorders no longer exist in the ICSD2) [1].

Sometimes, it is hard to differentiate individual disorders from each other because of significant overlap among them.

The second main category consists of the primary insomnias that include psychophysiological insomnia, childhood onset or idiopathic insomnia and paradoxical insomnia [1]. Any of these may coexist with poor sleep hygiene may cause it or be exacerbated by it.

The third includes insomnia due to other sleep disorders such as obstructive sleep apnea, restless legs syndrome, periodic limb movement syndrome, and even narcolepsy. Insomnia due to neurological, psychiatric, and other medical causes such as due to degenerative neurological illnesses, anxiety disorders, asthma etc. When the symptoms of the underlying disorder are prominent then

secondary insomnias are usually suspected and diagnostic testing appropriate to the circumstance may elucidate the underlying cause of the insomnia.

Diagnostic Workup

The diagnosis of inadequate sleep hygiene is best made through careful and detailed history of the patient's daily sleep-related habits [16]. These include bedtime, rise-time, time spent in bed awake, different nonsleep-related activities that the patient does in the bed and the bedroom including watching TV, reading etc., the timing of exercise, activities engaged in prior to bedtime and while awake at night, amount and timing of caffeine or alcohol ingestion, and daytime napping. In short, trying to identify any activity that is incompatible with sleep.

A useful diagnostic tool is a detailed sleep questionnaire completed by the patient and the bed partner [17, 18]. In 2006, Mastin et al., developed a well-validated short questionnaire called the Sleep Hygiene Index for the better assessment of poor sleep behaviors [19] (Table 14.3). As in most primary insomnias, sleep diaries are an essential tool in identifying sleep problems and charting their evolution and response to treatment. In a paper published in 1998, Blake and Gomez introduced a simple but useful questionnaire by which to measure compliance with sleep hygiene education [20].

A thorough psychiatric and medical evaluation including a physical exam should be done to rule out medical or psychiatric causes of the insomnia, as is true for most insomnias. Polysomnography is only recommended if the patient has symptoms suggestive of other primary sleep disorders or they do not respond to behavioral modification. Below are the AASM guidelines for the use of polysomnography in the evaluation of insomnia [21] (Table 14.4).

Table 14.3 Sleep Hygiene Index.

1. I take daytime naps lasting 2 or more hours
2. I go to bed at different times from day to day
3. I get out of bed at different times from day to day
4. I exercise to the point of sweating within 1 h of going to bed
5. I stay in bed longer than I should two or three times a week
6. I use alcohol, tobacco, or caffeine within 4 h of going to bed or after going to bed
7. I do something that may wake me up before bedtime (for example: play video games, use the internet, or clean)
8. I go to bed feeling stressed, angry, upset, or nervous
9. I use my bed for things other than sleeping or sex (for example, watch television, read, eat, or study)
10. I sleep on an uncomfortable bed (for example, poor mattress or pillow, too much or not enough blankets)
11. I sleep in an uncomfortable bedroom (for example, too bright, too stuffy, too hot, too cold, or too noisy)
12. I do important work before bedtime (for example, pay bills, schedule, or study)
13. I think, plan, or worry when I am in bed

Table 14.4 Practice parameters for evaluation of chronic insomnia.

1. The health-care practitioner should screen patients for symptoms of insomnia
2. An in-depth sleep history is essential in identifying the cause of insomnia. Additionally, a physical examination is an important element in the evaluation of insomnia patients with medical symptoms
3. Polysomnography is not indicated for the routine evaluation of chronic insomnia. However, symptoms of insomnia do not exclude polysomnographic evaluation in assessing the complaint. There should be a valid indication and a clear rationale, based upon specific elements of the history, to support use of polysomnographic evaluation
4. Instruments which are helpful in the evaluation and differential diagnosis of insomnia include self-administered questionnaires, at-home sleep logs, symptom checklists, psychological screening tests, and bed partner interviews
5. The multiple sleep latency test (MSLT) is not routinely indicated for the evaluation of insomnia
6. There is insufficient evidence to make recommendations about the diagnostic role of other portable equipment

Adapted from ref. [21].

Prognosis and Complications

As in most extrinsic sleep disorders, once the underlying cause is removed, the symptoms resolve completely. The sooner treatment is started the more complete the resolution of symptoms, the better the prognosis. If poor sleep hygiene is allowed to continue it may lead to psychophysiological insomnia in susceptible individuals.

Some recent publications find a high correlation between poor sleep hygiene, especially among younger drivers, and high rates of accident [22, 23].

Prevention

Education is the cornerstone for the prevention of poor sleep hygiene insomnia. Almost all of us engage in poor sleep hygiene at various times in our life. There are also a large number of external sleep disruptors such as noise, ambient light etc., outside of one's control. Although it is extremely important to educate people about sleep hygiene, these rules do not strictly apply to everyone. A short daily nap is part of the lifestyles of some cultures and does not necessarily constitute poor sleep hygiene if it does not result in symptoms of insomnia or sleep disturbances. Similarly a cup of coffee or a drink with dinner or even reading in bed may not negatively impact some people's sleep. In some people, however, either because of their predisposition or due to the additive effect of different factors may develop significant insomnia.

It is essential to inform people early on, at the first appearance of symptoms, the potential sleep problems poor sleep hygiene can cause, and help identify and stop them.

Treatment

Like all extrinsic sleep disorders the mainstay of treatment needs to be modification or complete removal of the external factors causing the insomnia. Sleep hygiene must be taught and reinforced in patients suffering with this disorder [24]. It may be overwhelming for patients to follow every single sleep hygiene regulation at once and, if tried, could lead to noncompliance. It is best to isolate two or three key factors individualized to the patient and ask them to concentrate on those [16]. Other cognitive behavioral treatment modalities may be helpful in select cases. These include relaxation therapy, biofeedback, sleep restriction consolidation, and stimulus control [16]. Usually, sleep hygiene education is simpler and easier to follow and as effective as the more elaborate and difficult to follow cognitive behavioral treatment. In fact, of all the nonpharmacological/behavioral treatments, sleep hygiene education is one of the most effective methods and one of the easiest to follow [7].

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Part IV

The Secondary Insomnias

15

Insomnia Caused by Medical Disorders

Kenneth Plotkin

Abstract

Virtually any medical condition can cause sleep disruption. The incidence of insomnia increases with age as medical problems increasingly occur, and patients with chronic insomnia are more likely to develop adverse health outcomes due to medical disease. There are multiple ways in which insomnia may be caused or aggravated by medical illness or bodily injury. Unpleasant stimuli can directly impede initiation of sleep, or they may cause frequent arousals or awakenings. Changes in basic systemic physiology (such as disorders of ventilation) may produce similar disruption in sleep continuity. There may be humoral changes that have direct neurochemical or neurophysiological effects, augmenting vigilance and lowering the threshold to arousal from sleep. The effects of acute and subacute sleep disruption can lead to chronic psychophysiological insomnia by creating the anticipation of disturbed sleep and by altering circadian entrainment, further accentuating the disruptive effects of the underlying medical condition. Difficulties with insomnia may persist long after the causative medical condition has been effectively managed.

Keywords: Eczema, End-stage renal disease, Gastroesophageal reflux disease, Congestive heart failure, Asthma, Allergies, Hyperthyroidism, Arthritis

Introduction

Virtually any medical condition can cause sleep disruption. The incidence of insomnia increases with age as medical problems increasingly occur [1], and patients with chronic insomnia are more likely to develop adverse health outcomes due to medical disease [2]. There are multiple ways in which insomnia may be caused or aggravated by medical illness or bodily injury. Unpleasant stimuli can directly impede initiation of sleep, or they may cause frequent arousals or awakenings. Changes in basic systemic physiology (such as disorders of ventilation) may produce similar disruption in sleep continuity. There may be humoral changes that have direct neurochemical or neurophysiological

From: *Clinical Handbook of Insomnia,* Current Clinical Neurology
Edited by: H.P. Attarian and C. Schuman, DOI 10.1007/978-1-60327-042-7_15,

effects, augmenting vigilance and lowering the threshold to arousal from sleep. The effects of acute and subacute sleep disruption can lead to chronic psychophysiological insomnia by creating the anticipation of disturbed sleep and by altering circadian entrainment, further accentuating the disruptive effects of the underlying medical condition. Difficulties with insomnia may persist long after the causative medical condition has been effectively managed.

When describing the medical causes of insomnia, the most frequently recurring theme is the disruptive influence of painful or unpleasant stimuli on sleep initiation and maintenance. The polysomnographic appearance of sleep disturbance caused by medical conditions is nonspecific, and most times is no different than any other form of insomnia [3, 4]. The diagnosis is most often made by clinical correlation, requiring a thorough review of a patient's general medical profile and a complete physical examination. After a polysomnogram has been recorded to evaluate for any detectable cause of sleep disruption, an empirical approach to treatment can begin.

Treatment of secondary insomnia draws upon all of the commonly utilized behavioral, pharmacological, and alternative medical approaches utilized in primary insomnia [5, 6]. Optimizing the treatment of the underlying medical condition is the cornerstone of effective insomnia management, along with attempts to improve the quality of sleep. Ultimately, the treatment must also take into consideration potential complications produced by the medical condition(s), either a change in the natural course of the disease, or an untoward response to well-intended pharmacological insomnia therapy. In cases where the medical condition has an intermittent character, short-term or intermittent pharmacotherapy for insomnia may be the best approach. In progressive medical disorders, the management of associated insomnia may require elaboration over time, with an evolving pharmacotherapeutic approach. More complicated cases should compel frequent review of the applied management strategies, in order to avoid the maintenance of suboptimal therapy, the continuation of pernicious medications, and the ultimate surrender of the patient to decline in level of function as sleep disruption becomes more profound.

An attempt to comprehensively review major medical disorders is bound to leave some conditions unaddressed. For most conditions there is only anecdotal information or brief mention of insomnia as a feature of the disease process. Perhaps the best way to frame the discussion is an approach to each organ system, allowing for the collection of related disorders that may share a common overall effect on sleep continuity. This parallels the method used by physicians to categorize the symptomatic profile (the Review of Systems) for a given patient, allowing for an orderly review of potential medical issues during a general medical examination. The unique role of each organ system in sleep disruption can be reviewed, even for disorders of completely disparate etiology (for example, a neoplastic versus inflammatory cause of disease), along with the shared treatment issues.

Skin Conditions and Insomnia

The skin is the body's largest organ, serving to sequester and protect the internal environment from the outside world, and providing some of the most profound early alerts of important environmental issues. It has the densest collection of nerve terminals outside of the central nervous system. Any condition that imposes damage, pressure, or irritation on the dermis will cause pain

through dermal nerve endings, and the pain will disturb the integrity of sleep. Infectious, allergic, or inflammatory skin conditions are common potential causes of disturbed sleep initiation and maintenance.

A recent pilot study reported that 93.75% of adults surveyed with active dermatological issue had insomnia [7].

Pain due to minor or major burns frequently delay sleep initiation, and may become aggravated by involuntary body shifting during sleep. The acute phase of burn healing may be incredibly painful and last several months in severe cases, and this is the time of greatest sleep disturbance. The healing process may leave scar tissue that is unusually sensitive or restrictive, prolonging the negative influence on sleep quality. In a cohort suffering from herpes zoster reactivation, insomnia was one of the most bothersome symptoms reported (25%), second only to pain [8]. Lacerations have a shorter time of healing, but may produce nerve injury, and the subsequent reinnervation can cause paroxysms of sharp pain, burning pain, or dull aching pain. Swelling of soft tissues due to edema may be transient, intermittent, or chronic, but causes epidermal discomfort that delays sleep onset and impairs sleep maintenance. Pathological diaphoresis may be sufficiently severe to cause awakening due to cold, damp bedclothes or sheets [9]. The use of occlusive dressings, bandages, or splints may produce discomfort and restrict movement during sleep. Oral corticosteroid medications may produce insomnia [10], particularly at higher doses, especially during the initial period of use.

Atopic dermatitis is a known cause of insomnia especially among children. Pruritus and scratching are the main causes of sleep disturbances in this condition [11].

A recent study showed that watching comedic films prior to going to sleep reduced the amount of awakenings at night in patients with atopic dermatitis as compared to watching nonhumorous films [12].

Interestingly, insomnia appears to be the most important psychosomatic symptom that is a predisposing factor for chronic urticaria, a condition characterized by skin weals and pruritus, which can itself disrupt sleep thus creating a vicious cycle [6].

Amelioration of a skin condition may require a relatively short duration of treatment, causing only short-term sleep disruption. The use of hypnotic medication, especially shorter-acting medications that are unlikely to produce daytime sedation, may be ideally suited to a skin condition that has brief course (such as poison ivy dermatitis) or intermittent exacerbation (such as eczema). Many of the antihistamine medications used to reduce allergic response and reduce itching are sedating, improving sleep initiation and maintenance somewhat, but there may be residual daytime effects on alertness and cognitive performance [13]. The use of medications such as amitriptyline or trazodone, which may improve the component of insomnia caused by depression and pain, should be considered if the duration and severity of insomnia warrants their use, and if other medical conditions do not preclude their use.

Upper Airway Problems and Insomnia

Problems in the nasopharynx, oropharynx, and larynx are a common cause of sleep disruption. The most widely recognized condition that can be caused by the pharyngeal tree is obstructive sleep apnea (OSA). Mass lesions, hyoid

pathology, and cervical spine degenerative changes [14] can also cause obstructive apnea. For a detailed discussion of insomnia due to OSA the reader is referred to Chap. 19 of this book.

Postnasal drip caused by chronic allergic rhinitis or chronic/recurrent sinusitis may cause frequent awakening by stimulating cough during sleep [15]. Severe allergic rhinitis impairs all dimensions of sleep, causing severe insomnia and reduced quality of life regardless of whether the rhinitis is intermittent or chronic [16]. Allergic, infectious, or inflammatory pharyngitis can impair sleep continuity through the occurrence of local pain, which may be worsened upon swallowing, or may stimulate frequent reflexive swallowing. Sleep-related laryngospasm or choking is a rare sleep disorder first described by Chodosh in 1977 [17]. Its symptoms include periodic and sudden awakenings with the feeling of choking and a brief period of stridor that progresses to normal breathing [18]. It may cause sufficient distress that the security of sleep is threatened [18]. Most common contributor to nocturnal laryngospasm is gastroesophageal reflux disease [19] but other factors include postnasal drip, otolaryngological tumors, metabolic factors such as hypoparathyroidism [20], multisystem atrophy (MSA) [21], iatrogenic factors such as postextubation [22], and psychological disturbances [19]. These conditions lead to the irritation of the superior laryngeal nerve hence causing the spasm [19]. Prevention and treatment in most cases is focused on treating the underlying cause. In rare cases (with MSA) CPAP [23] and acupuncture [22] have been helpful

Any painful condition affecting the airway can negatively affect the quality of sleep, and when present for a sufficient duration or with sufficient frequency, can cause insomnia [24]. Assessment of the head and neck may not provide sufficient evidence of pathology in some cases. The diagnostic clue on a routine PSG would be frequent bursts of submental myogenic activity, which in isolation could also be interpreted as bruxism or a reflection of a nocturnal periodic movement disorder. In this case, the bed partner's observations or the use of good quality video/audio during PSG may help to identify the cause of sleep disruption, and help to appropriately direct treatment.

Pulmonary Disorders and Insomnia

Pulmonary disorders frequently cause some degree of sleep disruption, which can develop over time into secondary insomnia. Nocturnal Asthma causes poor efficiency sleep and secondary impairment of cognitive function even when the asthma symptoms are fairly stable; more frequent attacks of bronchospasm at night would worsen insomnia as well [25, 26]. Since nocturnal asthma attacks can be fatal, aggressive treatment is warranted which in of itself can lead to insomnia. Medications used to treat asthma, including bronchodilators such as albuterol, the methylxanthines derivatives theophylline and caffeine, and even inhaled steroid medications have an activating effect on the central nervous system, which may prolonged sleep initiation and increase the likelihood of arousal from sleep. Some suggest using theophylline in the early evening or steroids in the afternoon improve both nocturnal lung function and sleep as opposed to conventional schedules [27, 28]. Chronic obstructive pulmonary disease (COPD) [29] can also lead to significant insomnia. For a detailed discussion of COPD and insomnia the reader is referred to Chap. 19. Other pulmonary conditions such as restrictive changes in the pulmonary bed [30],

bronchitis, pneumonitis, pleuritis, and neoplasia of the pulmonary tree can cause disruption of ventilation, waxing/waning hypoxia [31], cystic fibrosis [32], chest wall pain, and cough that lead to frequent arousal and poor sleep continuity. Chronic hypoxia and hypercarbia gradually desensitize carotid and CNS medullary chemoreceptors, causing central apnea that can worsen the magnitude of ventilatory pathology, and thereby the chronic nature of sleep disruption. The appearance of sleep-disordered breathing in association with pulmonary disease is well-appreciated by the medical community, but optimal sleep quality may not immediately return despite effective management of the pulmonary problem. The medications used in the treatment of secondary insomnia due to pulmonary dysfunction must be chosen carefully. The level of oxygenation and the persistence of ventilatory drive may be challenged by even the short-acting hypnotic medications, and hypnotics with more muscle-relaxing qualities may compromise the additional ventilatory effort offered by chest wall musculature. The use of tricyclic antidepressant medications is relatively contraindicated in asthma, due to their propensity to aggravate bronchiolar constriction. Nonpharmacological treatments (sleep restriction, light therapy) may be paired with very low doses of short-acting hypnotic medications to enhance sleep initiation and continuity, and the serotonin reuptake inhibitor paroxetine may have slightly sedating and anxiolytic properties that prove useful for the treatment of secondary insomnia due to pulmonary disease. Although nocturnal supplemental O_2 is the mainstay of treatment for COPD-related insomnia [31], its role in restrictive lung diseases has not studied. Careful bronchial hygiene is an important adjunct therapy modality in all cases.

Cardiovascular Diseases and Insomnia

Cardiovascular diseases cause sleep disruption through nocturnal angina [33, 34] abnormal sensations such as palpitations or tachycardia [35], paroxysmal dyspnea, or orthopnea related to congestive heart failure. More severe congestive heart failure produces ventilatory changes during sleep as well, with periodic breathing of Cheyne-Stokes character, or central apnea that produces frequent arousals from sleep [36]. Orthopnea may require that a patient is only able to recline slightly while sleeping, and the resulting disturbance of sleep continuity may be significant. Acute insomnia is a common sequela of myocardial infarction [33]. The medications used to treat cardiac disturbance may aggravate sleep disruption. Vasodilating agents may produce headache that disrupts sleep continuity, as may the rebound effects of morphine when it is used intermittently. Digoxin may produce side effects including insomnia and headache, especially at higher blood levels. Diuretic therapy at night causes frequent awakening to urinate. The symptoms of cardiac disease and potentially pernicious effects of its treatment are usually superimposed on the typical sleep fragmentation of elderly individuals, but the chronicity and severity of cardiac disturbance will largely determine whether secondary insomnia becomes sufficiently severe to require treatment. Once medical therapy has been optimized, the ideal approach will select therapy that has the least chance of casing medical complications. As with severe pulmonary disease, longer-acting hypnotic medications are more likely to cause ventilatory compromise. Tricyclic antidepressant medications can increase the possibility of cardiac arrhythmia, and are relatively contraindicated. Trazodone may be somewhat

less likely to cause arrhythmia, but like the tricyclic agents, its residual effects in the daytime may cause fatigue or hypersomnia. Creative treatment with shorter-acting hypnotic medications may be combined with efforts to maximize physical comfort through special furniture, such as a hospital bed, to promote blocks of restful sleep lasting a few hours at a time. Monophasic sleep may need to be sacrificed, in favor of two or three smaller blocks of sleep that take advantage of the natural periods of drowsiness that occur during the day. Treatment of disturbed ventilation may help sleep continuity, avoid hypoxia, and provide more refreshing sleep, but CPAP therapy is not well-tolerated, and can actually aggravate central apnea. Biphasic positive pressure ventilation may avoid exacerbation of central apnea, and may be more tolerable in its promotion of normal ventilatory tidal movement.

Digestive Disorders and Insomnia

Disorders of the gastrointestinal system may produce significant sleep disturbance leading to secondary insomnia [37]. The primary problem may remain occult, and if a sleep study shows only the typical features of insomnia, the benefit of insomnia management may be limited over the course of months or years. GERD worsens with reclining, especially if a person has eaten within an hour or two of sleep, and up to two-thirds of people with GERD have nocturnal symptoms that disturb their sleep [38]. GERD is also worsened by obstructive breathing, as the increase in intrathoracic pressure produces an increase in abdominal displacement, causing more pressure within the GI lumen and more tendency for reflux through a hypotonic or incontinent lower esophageal sphincter. The irritation of the esophageal mucosa causes arousal from sleep, which appears on PSG to be spontaneous, without correlation on ventilatory or EMG channels. Only the use of a nasogastric pH probe during PSG will provide definitive diagnosis, but most sleep laboratories do not routinely perform such testing. Insomnia is a particularly common symptom when GERD and irritable bowel syndrome overlap [39]. Peptic ulcer disease is likely to be identified due to its typical pattern of awakening in the early hours of sleep, with abdominal discomfort or nausea. The untreated condition could certainly produce chronic sleep disruption, but recurrent bouts of ulcer may eventually lead to chronic difficulties with sleep maintenance and persistent early awakening. Pain and discomfort in association with any infectious, inflammatory, allergic, or neoplastic intestinal disorders may cause frequent nocturnal arousal, which may also include prolonged awakenings for bathroom visits, requiring sleep to be reinitiated at a disadvantageous time during the night. Milk allergy [40] and other food allergies [41] have been suggested as a cause of poor sleep in infants. The absence of a specific finding on PSG makes it contingent on the clinician to infer the diagnosis from clinical history, and treatment of the underlying disorder can be combined with short-term or longer-term treatment of secondary insomnia, which is likely to require at least some pharmacotherapy. The symptoms of esophageal reflux may be reduced by smoking cessation, weight loss, avoiding fatty/spicy foods, reducing daily caffeine intake, and treatment with a variety of medications, including antacids, H2-receptor blockers, proton pump inhibitors, and agents that improve gastric motility. Flexible dosing of shorter-acting hypnotic medications may be most appropriate for disorders that have waxing and waning

symptoms (inflammatory bowel disease) that appear at different times of night. Longer-acting hypnotic medications may be required when symptoms are more severe or enduring on a given night. Note that nearly all of the hypnotic medications can aggravate intestinal problems, by dehydrating mucosal linings (tricyclic antidepressants, antihistamines), increasing motility (serotonin reuptake inhibitors), or decreasing motility (benzodiazepines, barbiturates).

Insomnia Associated with Renal Disorders

Poor sleep quality, insomnia, and restless legs syndrome (RLS) are quite common in patients with renal illnesses. Chronic renal disease commonly causes insomnia [42], even early in the development of the disease [43]. Sleep disturbances as defined by a score of higher than 5 on the Pittsburgh Sleep Quality Index (PSQI) occur in 74.4% of patients with renal disease [44].

Using the same scale, 53% of chronic kidney diseases sufferers rate the quality of their sleep as poor [45]. Insomnia occurs in 49% of dialysis patients making it the most common sleep disorder in this group [46]. An earlier study had reported the prevalence of insomnia to be 72% in a similar group of patients [47]. Restless legs syndrome is also quite common in these patients with 21.5% of patients with end-stage renal disease [48] and up to 84% on maintenance dialysis complaining of RLS [47]. Insomnia is worsened by electrolyte fluctuations caused by hemodialysis and the high incidence of PLMS [49] in addition and independent of RLS. Parathyroid hormone may be of particular influence in causing insomnia, and parathyroidectomy has been shown to alleviate insomnia in some patients on hemodialysis [50]. Kidney transplant significantly improves both sleep problems and RLS but does not necessarily resolve them despite eliminating all of the electrolyte shifts and lifestyle confounds of hemodialysis [51]. The prevalence of RLS is significantly lower, however, in kidney transplant patients than in patients on dialysis [52]. One study found that Cognitive behavioral therapy has been shown to be of benefit in a small-cohort study of patients undergoing chronic peritoneal dialysis [53].

Renal disease-associated RLS and resultant sleep disturbances respond to the same treatments that idiopathic RLS does. After correction of any iron deficiency a small dose of benzodiazepine might be beneficial; however, low doses of dopamine agonists are preferred [54]. The use of erythropoietin in patients with renal disease may improve restless legs [55]. If insomnia persists despite elimination of RLS, a small dose of a sedative antidepressant such as trazodone which does not have significant respiratory depressant potential and are primarily metabolized by the liver, may be of help.

Genitourinary System Disturbances and Insomnia

Urological disorders cause sleep disruption by compelling frequent awakening for urination and frequent arousal due to pain. Progressive prostatic hypertrophy compels frequent voiding of small urine volumes, ameliorated somewhat by medications that reduce the size of the prostate. Prostatic carcinoma may cause a similar pattern, and resection of the prostate may produce urinary urgency and incontinence, further exacerbating sleep dysfunction [56].

Pain or discomfort related to interstitial cystitis, prostatitis, bladder infection, or nephrolithiasis may cause awakening or occult nocturnal arousal, resulting in insufficient sleep. Neurogenic bladder dysfunction may produce a hypotonic (overfilled) bladder that requires intermittent catheterization to avoid overflow incontinence, or a hypertonic bladder that produces discomfort and the urge to void with the smallest amount of urine volume. Once the cause of urological dysfunction has been identified and appropriately addressed, the use of hypnotic medications tend to be benign, and the pharmacology of different medications can be chosen for the most practical solution. Tricyclic antidepressant medications tend to cause urinary retention and increase urinary hesitancy, and would not be an ideal choice.

Musculoskeletal Problems and Insomnia

The rheumatoid disorders, and musculoskeletal discomfort in general, are highly associated with chronic sleep disruption. Rheumatoid arthritis [57, 58], ankylosing spondylitis [59], systemic lupus erythematosis [60], vasculitis, polymyalgia rheumatica, and fibromyalgia [61] can produce sleep disruption, which may become a very debilitating aspect of the disease, complicating functional recovery. Insomnia is reported in up to half of the children who have chronic limb pain [62], and daytime pain is reported to be worse following unrefreshing sleep [63]. The pain certainly is a profound trigger of sleep disturbance, as are the effects of glucocorticoid medications [64] commonly used to treat the rheumatoid diseases. The EEG during NREM sleep may include considerable alpha range activity, even in deep sleep (the "alpha–delta" sleep pattern), which was decreased by treatment with sodium oxybate in patients with fibromyalgia [65]. Alpha intrusion is not specific to the rheumatoid disorders; the same pattern may be seen in chronic fatigue syndrome [66], with its cardinal symptoms of idiopathic fatigue, headache, arthralgia, myalgia, and insomnia [67]. Osteoarthritis may become more symptomatic as the morning approaches, after a night of relative immobility, and may result in early awakening. Degenerative change of the spine, scoliosis, and scleroderma may all cause impaired ventilation, leading to frequent arousals and impaired sleep. Cognitive behavioral therapy has been shown to be beneficial for the treatment of insomnia associated with fibromyalgia [68] and in older adults with comorbid conditions including arthritis [69]

Endocrine Causes for Insomnia

Various endocrine disturbances cause insomnia, due to either the activating effects of the hormones or somatic discomfort produced by their imbalances [70]. Insomnia is more prevalent in hyperthyroidism, in association with a globally activated behavioral state, and sleep studies have shown an overall increase in the percentage of deep sleep [71] once difficulties with sleep initiation are overcome. The return to a serological and clinical euthyroid state may not guarantee the resolution of insomnia. Hypothyroidism more commonly causes fatigue and lethargy, and PSG has shown an associated decrease in deep sleep. Parathyroid hormone has been mentioned as a potential cause of insomnia in ESRD hemodialysis patients [50], with insomnia dramatically

improved in some patients following parathyroidectomy. Insomnia symptoms were also improved in symptomatic secondary hyperparathyroidism after parathyroidectomy [72]. However, there was no improvement in subjective reports of insomnia after parathyroidectomy in otherwise asymptomatic primary hyperparathyroidism [73]. Perhaps the improvement in insomnia is not due to the change in parathyroid hormone itself, but because there is improvement in some of the somatic symptoms produced by hyperparathyroidism. Dysfunction causing catecholamine oversecretion will cause sympathetic activation and insomnia, and excessive glucocorticoid levels also cause insomnia [10, 64]. It has been suggested that elevated glucocorticoid levels may alter the production of endogenous GABA-related steroid production [35], causing some of the observed insomnia. Disruption of the hypothalamic–pituitary–adrenal axis has been found in association with chronic insomnia, though it is not clear whether the disruption of hormonal secretion is the cause or effect of insomnia [74, 75]. There is considerable clinical reporting of insomnia during menses [76], with or without associated somatic discomfort, and during menopause [77]. The symptom of insomnia and its management in pregnancy and menopause are discussed in depth in other chapters. Insomnia is reported in up to a third of patients with diabetes mellitus [78]. Treatment of sleep disruption in endocrine disturbance may be complicated by hormonal fluctuations and potential medical complications of therapy, and may require multiple modalities, spanning the pharmacological, behavioral, and alternative therapeutic realms.

Cancer and Insomnia

Cancer may produce insomnia due to pernicious effects on systemic physiology, painful tissue changes, therapeutic efforts, or the anxiety and depression accompanying the diagnosis. Insomnia has been found to occur in over half (53%) of the patients with newly diagnosed lung cancer, and was felt to be a severe symptom in over a quarter [79], especially in association with pain and fatigue [80]. Insomnia occurred in 19% of women with breast cancer, and was of chronic character 95% of the time [81]. There may be premorbid risks that contribute to the development of insomnia after the diagnosis of breast cancer [82, 83] such as depression, anxiety, and of course previous problems with insomnia. Chronic insomnia after treatment for breast cancer may also be influenced by physical discomfort, as would be associated with lymphedema [84]. Insomnia has been examined in a variety of cancer types [85], and has been found to occur in about a third of cases, along with reports of fatigue, leg restlessness, and excessive sleepiness. The fatigue associated with cancer treatment may be partly due to insomnia. [86]. The claudication associated with hematologic disorders such as sickle cell anemia causes severe intermittent sleep disruption [87], made worse by occult sleep-disordered breathing and PLMS. Treatment should take into consideration the anticipated duration of the underlying disease, and any potential medical issues that could complicate pharmacotherapy. Insomnia therapy should be directed to preserve the quality of daytime function, improving sleep with a minimum of residual cognitive dulling, lingering hypnotic effects, or uncomfortable side effects. There may be a role for medications that have antidepressant or anxiolytic characteristics,

especially in the early stages following cancer diagnosis. Chronic treatment may be better achieved by nonpharmacologic interventions [81, 83, 88] such as cognitive therapy, relaxation therapy, biofeedback, and behavioral approaches to improve sleep quality [89–91]. There is some evidence to suggest that cognitive behavioral therapy for the treatment of insomnia in breast cancer may actually enhance immunological function as well [92, 93].

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16

Insomnia in Neurological Diseases and Disorders

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Abstract

Insomnia is the most common sleep complaint. Insomnia is not a disease but a symptom arising from multiple environmental, medical, and mental disorders. Insomnia can be transient, short-term, or chronic in its presentation. Degenerative and vascular diseases involving the central nervous system (CNS) may impair sleep either as a result of the brain lesion or because of illness-related personal discomfort.

Chronic insomnia can be caused by neurological conditions characterized by movement disorders starting or persisting during sleep that hinder sleep onset and/or sleep continuity.

Three specific neurological conditions, Fatal familial insomnia, a human prion disease, Morvan's chorea, an autoimmune limbic encephalopathy, and Delirium tremens, the well-known alcohol or benzodiazepine withdrawal syndrome, share a common clinical phenotype characterized by an inability to sleep associated with motor and autonomic activation. Agrypnia excitata (AE) is the term which aptly defines this generalized overactivation syndrome, whose pathogenetic mechanism consists in an intralimbic disconnection releasing the hypothalamus and brainstem reticular formation from corticolimbic control.

Keywords: Insomnia, Degenerative diseases, Movement disorders, Fatal familial insomnia, Morvan's chorea, Delirium tremens, Agrypnia excitata

Introduction

Poor sleep quality is the most common sleep complaint. Insomnia is when sleep is insufficient, inadequate or nonrestorative. Its prevalence varies considerably depending on the definition adopted. Epidemiologic evidence concludes that while one-fourth to one-third of the general population report transient or occasional difficulty falling and/or staying asleep, about 10% of the adult population present chronic complaints and seek help for insomnia [1, 2]. Increasing age

From: *Clinical Handbook of Insomnia,* Current Clinical Neurology
Edited by: H.P. Attarian and C. Schuman, DOI 10.1007/978-1-60327-042-7_16,

and female sex are the most important risk factors for chronic insomnia [1, 3]. The inadequate identification and treatment of insomnia has significant medical and public health implications. Chronic insomnia impairs occupational performance and quality of life [4]. Objective sleep measures, EEG activity, and physiological findings suggest that insomnia is not a state of sleep loss, but a disorder of hyperarousal present during both night and daytime [4, 5]. Several psychological and physiological factors such as the association with other medical complaints and/or psychological symptoms, particularly anxious-ruminative personality traits, worry and depression can contribute to the onset and perpetuation of insomnia. Stressful life events (difficulties in interpersonal relationships, family discord, problems at work and financial troubles) may also determine poor sleep quality.

Insomnia is not always a specific illness or disease but can often represent a symptom or consequence of other primary disorders. Positive family history for insomnia is common in patients with a "poor quality of sleep." It is difficult, however, to fathom whether the emotional problems favoring the onset of a sleep disorder in adulthood are due to a genetic predisposition or the result of having lived in a family burdened by affective problems and/or interpersonal conflict [6]

The mechanisms regulating sleep and sleep architecture may be affected by neurological illness, but one should also bear in mind that neurological disorders and diseases are almost always accompanied by major psychological distress. In addition, the medications used in the treatment of medical and neurological diseases e.g., β-blockers, some Selective Serotonin Reuptake Inhibitors (SSRIs), some neuroleptics, amphetamines and others, may induce sleep fragmentation, reduce total sleep time and delay sleep onset. Hence, it is difficult to establish whether the onset of chronic insomnia in an individual patient with a neurological illness is due to the disease or to a psychosomatic disorder or an iatrogenic consequence of the neurological impairment.

The neurological diseases most commonly associated with chronic insomnia can be divided into three groups: (a) neurological diseases or disorders (degenerative and other) involving the central nervous system (CNS) impairing sleep mainly or exclusively because of illness-related personal discomfort (motor immobility, personal or family life disruption, depression, drugs); (b) neurological diseases characterized by movement disorders hindering sleep onset and/or sleep continuity; (c) CNS lesions (dysfunction) impairing the basic mechanisms of sleep generation (agrypnia or organic insomnia).

Insomnia in Neurological Diseases (Degenerative and Others)

Insomnia and Dementia

Good sleep is an important index of people's quality of life especially in the elderly. An inability to get to sleep, shorter sleep times, and changes in the normal circadian patterns can impact on an individual's overall well-being and they are increasingly common as people age. Sleep disturbances were present in 59.2% of people with dementia and insomnia is reported in 21.8% of patients [7]. In addition, the elderly often present high comorbidity and polytreatment. Many common chronic conditions, such as chronic

obstructive pulmonary disease, diabetes, dementia, chronic pain, and cancer, which are more common in the elderly, can also have significant effects on sleep, increasing the prevalence of insomnia compared with the general population.

Moreover, aging accompanied by mental deterioration caused by a degenerative (e.g., Alzheimer's) or vascular disease (multi-infarct dementia) may determine more pronounced alterations of the sleep–wake cycle than physiological aging. A 24-h actigraphic study performed in institutionalized dementia patients showed four types of abnormal rhythms: a free-running (phase delayed) type, an aperiodic type, an ultradian rhythm type with a cycle lasting 3–4 h, and a flattened amplitude type in which patients were largely bedridden [8]. *Sundowning* defines the tendency of demented people to have nocturnal agitation. Sundowning can be a primary factor leading to the decision to institutionalize a patient. Admission to a nursing home, in turn, exacerbates the behavioral disorder with mental confusion and hallucinations.

Less severe or better tolerated than nocturnal disruptive behavior are disorders arising during the day. Nursing facilities that routinely put patients to bed during the afternoon for naps had lower rates of agitation than facilities that did not employ this routine [9]. The cause of sundowning in dementia is unknown, but there is some evidence of impaired circadian fluctuations in body temperature and secretion of melatonin and cortisol in patients with dementia compared with an age-matched normal population [10]. It remains unsettled whether insomnia or sleep disruption in the elderly with dementia is due to an anatomical–functional impairment of the suprachiasmatic nucleus or to a more complex alteration of the neuronal network controlling circadian and homeostatic wake–sleep cycle regulation [10].

The treatment approach to the demented elderly patient with insomnia is difficult and largely based on clinical experience and empiric data rather than a large evidence-based studies. Using a "less is better" approach in attempting nonpharmacologic interventions before initiating a trial of drug therapy is the optimal first step.

Because of environmental and medical conditions, older adults are less likely than younger adults to receive prolonged, high intensity daily bright light. Keeping patients in well-lit rooms during the day and in dark and quiet sleeping rooms during the night may help to improve the wake–sleep cycle. Exposure to bright light may help to optimize the sleep–wake cycle in dementia, although optimal timing of such light exposure for older adults (i.e., morning, afternoon, or evening) is uncertain and there is no consensus on the optimum treatment protocol. In addition to sleep improvement, bright light therapy may be reducing unwanted behavioral and cognitive symptoms associated with dementia and depression in the elderly [11].

Although potentially effective, benzodiazepines must be used with care. Daytime sedation or worsening of the agitation, two common side-effects, may limit use of benzodiazepines. However, newer nonbenzodiazepine drugs appear to be promising [12]. Clozapine (12.5–25 mg twice a day to be used with care because of potential bone marrow suppression) and risperidone (1.0 mg a day) may be of value and the more recently atypical antipsychotics such as quetiapine (12.5–25 mg) and olanzapine (10–15 mg) showed improvements in nighttime behavior [13, 14]. Administration of 3–5 mg of melatonin 2–3 h before bedtime may also be of some benefit although large-scale studies showing unequivocal efficacy are not available.

Insomnia in Neurological Diseases with Motor-System Involvement

This group of diseases includes Parkinson's disease (PD) and Parkinsonian syndromes or synucleinopathies such as Multiple System Atrophy (MSA) and Dementia with Lewy body disease (DLB) and tauopathies such as Progressive Supranuclear Palsy (PSP) and Corticobasal Degeneration (CBD), Huntington's Chorea (HC), progressive dystonia, Tourette's Syndrome (TS), and Autosomal Dominant Cerebellar Ataxia (ADCA). Literature reports on insomnia in these diseases are fragmentary, controversial, and mainly anecdotal.

Polysomnographic (PSG) recording is not indicated for the routine evaluation of insomnia in these diseases, but video-PSG may be required in special cases in which motor, (REM sleep behavior disorder - RBD) or breathing disorders (laryngeal stridor) or excessive daytime sleepiness are prominent. Lacking appropriate therapy, treatment of sleep disturbance is often difficult and is confined to general measures to improve sleep quality (sleep hygiene, etc.).

Parkinson's Disease

Patients with Parkinson's disease (PD) experience major difficulties in maintaining sleep, and present painful nighttime abnormal movements, daytime sleepiness, sleep attacks and insomnia. According to a recent study, insomnia is present in 54–60% of PD patients [15]. Insomnia fluctuates over time in individual patients, and seems to be due to a complex interaction between movement disorders, side-effects of dopamine agents, depression and degeneration of sleep–wake regulating systems. A marked reduction of spindling, sleep fragmentation and a shorter total sleep time are common in the PSG recordings of PD patients.

Dementia with Lewy Body Disease

Sleep disturbances, in particular hallucinatory episodes and RBD, are very common in diffuse Lewy body disease (DLB) and are helpful in differentiating DLB from Alzheimer's disease early in the disease course [16–18].

Multiple System Atrophy

Sleep disorders are common manifestations in Multiple System Atrophy (MSA) and include reduced and fragmented sleep, motor events (RBD) and/or breathing difficulty (central and obstructive apneas and nocturnal stridor) [19]. RBD and nocturnal stridor may be the first symptoms of the disease. RBD occurs in virtually 100% of patients, sometimes preceding the onset of waking motor symptoms and autonomic failure by several years [20]. Nocturnal stridor is a life-threatening condition in MSA due to a sleep-related laryngeal dystonia [21]. PSG recordings in patients with Shy–Drager syndrome show a reduced amount of slow-wave sleep (SWS), reduced REM sleep, reduced total sleep time, increased sleep latency, and recurrent awakenings [22, 23]. The circadian rhythms of temperature and melatonin secretion are also impaired in both MSA and PSP reflecting a severe disruption of the mechanisms regulating autonomic and endocrine homeostasis [24].

Progressive Supranuclear Palsy and Corticobasal Degeneration

Progressive Supranuclear Palsy (PSP) and Corticobasal degeneration (CBD) have overlapping clinical features hampering the clinical distinction between these two entities. Insomnia is a common complaint [25, 26] in these patients. Axial rigidity, dystonia, and postural difficulties may contribute to sleep disruption. PSG recordings in patients with PSP show a prolonged sleep latency, decreased total sleep time, decreased sleep efficiency, repeated arousals and awakenings, a decreased percentage of stage 2, with a drastic reduction in the number and amplitude of sleep spindles, and less REM sleep [25, 27, 28]. REM sleep latency may be reduced in some patients. Isolated cases of RBD associated with PSP have been reported but RBD seldom occurs in PSP and CBD [29, 30].

Another characteristic feature of PSP seems to be daytime somnolence. However, subjective sleepiness in these patients may not coincide with objective measurements by multiple sleep latency test (MSLT).

Huntington's Chorea

Insomnia with impaired initiation and maintenance of sleep is a common complaint, especially in moderate-to-severe Huntington's chorea (HC). Longer sleep latency, lower sleep efficiency, frequent nocturnal awakenings and less slow-wave sleep increase as the disease progresses [31, 32]. Sleep efficiency is reduced with increased stage 1 sleep and less REM sleep. Anatomical lesions, involuntary movements, medication, and depression all contribute to the insomnia.

Progressive Dystonia

Sleep disturbances occur in many patients with torsion dystonia. Deterioration of sleep parallels disease progression. PSG studies in these patients disclosed increased sleep latency and frequent awakenings with reduced sleep efficiency [33]. REM sleep may be reduced in severely affected patients.

Tourette's Syndrome

The degree of sleep disturbance is correlated with disease severity. Around 40% of children with Tourette's syndrome (TS) also have a history of somnambulism, night terrors or enuresis and are prone to "confusional arousal." An increased number of awakenings and increased motor activity and body movements during sleep have been described in TS [34].

Autosomal Dominant Cerebellar Ataxia

Autosomal dominant cerebellar ataxia (ADCA) is a clinically and genetically heterogeneous group of disorders characterized by progressive ataxia, dysarthria and nystagmus. Sleep disturbances are common features in ADCA. In 1978, Osorio and co-workers reported the absence of REM sleep in two patients with spinocerebellar degeneration and described a peculiar EEG pattern characterized by an admixture of different elements of states of being with high-voltage slow waves and increased tonic EMG activity [35]. This nonconventional sleep stage probably represents an example of status dissociatus.

In two small pilot studies, PSG revealed REM sleep without atonia in the majority of patients with spinocerebellar ataxia type 2 (SCA2) [36, 37] and a reduction of REM density [37]. Impaired sleep is a frequent yet unrecognized symptom in SCA3 (Machado–Joseph disease) with a very high prevalence of RBD (>50%) [38, 39], appearing in some cases several years before ataxia [39]. RLS is present in about half of SCA3 patients but is rare in other types of SCA [40]. Stridor and nocturnal confusional states following sleepwalking have also been described in SCA3 patients [39, 41, 42]. Excessive daytime somnolence is prominent in ADCA and often the most significant clinical problem [38, 43].

Insomnia and Sleep-Related Movement Disorders

The main sleep-related movement disorders hindering sleep onset or interrupting SWS or REM sleep are: (1) restless legs syndrome (RLS) and periodic limb movement disorder (PLMD) (2) propriospinal myoclonus (PSM); (3) nocturnal frontal lobe epilepsy (NFLE); (4) REM Sleep Behavior Disorder (RBD).

Restless Legs Syndrome

Restless legs syndrome (RLS) is a common chronic sensorimotor disorder clinically characterized by a compelling urge to move the limbs, accompanied by uncomfortable and unpleasant sensations in the extremities [44, 45]. Typically, the legs are mostly affected but arm involvement has also been reported [45, 46] (Figure 16.1). The urge to move the legs or unpleasant sensations begin or worsen during periods of rest or inactivity and are worse in the evening, especially when the patient lies down trying to fall asleep [45]. Any limb movement, such as walking or stretching or rubbing the legs together, making cycling movements, and pacing across the room, partially or totally relieves symptoms, at least as long as the activity continues [44]. In milder forms, the disorder only briefly delays sleep onset and is not a true medical problem. However, more severe forms of RLS may cause severe insomnia by lengthening the time before sleep onset and provoking recurrent and prolonged awakenings throughout the night and impairing quality of life [47]. Idiopathic RLS is often familial with a genetically heterogeneous complex trait [48]. RLS may also occur in acquired forms associated with a variety of neurological disorders, (such as Parkinson disease and parkinsonian syndromes) and other medical conditions, (such as uremia and end-stage renal disease, iron-deficiency anemia, diabetes and familial amyloidosis). RLS may transiently appear during pregnancy (in most cases, symptoms are mild and they usually resolve after delivery), or intensify during treatment with various drugs (such as typical and atypical neuroleptics, metoclopramide, estrogens, tri- and tetracyclic antidepressants, serotonin reuptake inhibitors) [49].

Juvenile onset is the rule in inherited-familial forms. Children with RLS commonly report symptoms resembling “growing pains.” RLS was suggested to be highly associated with attention-deficit hyperactivity disorder [50]. Although RLS prevalence is high, only 11.9% of patients with the condition will be led to consult a physician [51]; severe forms leading patients to seek treatment are present in only about 3.4% of patients [52]. Older patients tend

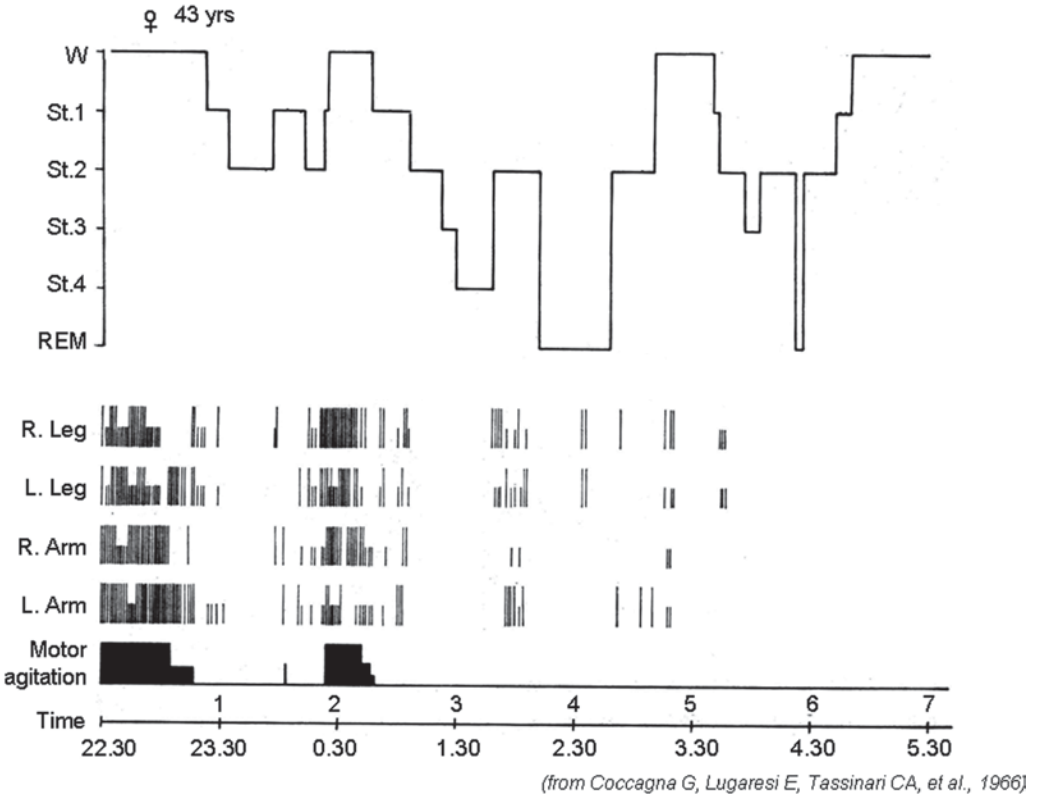

Figure 16.1 Polysomnographic recording in a patient with Restless Legs Syndrome. Hypnogram (*top*) and schematic representation (*bottom*) of myoclonic jerks, involving legs and arms and motor agitation. Delayed sleep onset and sleep fragmentation result from the motor disturbance (*R* right; *L* left) (reproduced from "Restless Legs," Coccagna G, Lugaresi E, Tassinari CA, Ambrosetto C. Omnia Medica et Therapeutica, 1966 vol 4)

to complain of more severe RLS symptoms indicating that the frequency and severity of symptoms tend to increase over time together with the progression of the disease. For patients with moderate-to-severe symptoms, drug therapy is required. First choice treatment relies on low doses of a dopamine agonist; opioids are a second line option. Clonazepam and Gabapentin are alternative treatment possibilities either alone or in combination with dopaminergic therapy [53].

Periodic Limb Movements in Sleep

Periodic limb movements in sleep (PLMS) occur in 80–100% of patients with RLS [46]. PLMS is characterized by periodic episodes of involuntary, repetitive and highly stereotyped dorsiflexion of the big toe and/or foot, sometimes associated with flexion of the leg on the thigh and of the thigh on the trunk. Both extremities are usually involved, but as a rule not simultaneously or symmetrically, predominating in one leg or alternating between legs. PLMS appear on falling asleep and continue in light sleep, recurring every 20–40 s. K complexes, increased muscle tone, heart and breathing rates, and raised systemic blood pressure appear simultaneously with PLMS during light

sleep, suggesting that PLMS are part of a periodic arousal involving cortical, somatic, and visceral functions [54, 55]. A dual mechanism consisting in an abnormal hyperexcitability of different and unsynchronized primary lumbosacral and, to a lesser extent, cervical spinal generators triggered by sleep-related factors located at a supraspinal but still unresolved level, could be the source for PLMS [56].

PLMS occur in a number of sleep disorders such as narcolepsy, sleep apnea syndrome and RBD. They can also occur as an isolated condition in otherwise healthy subjects, especially in the elderly [57] and in most cases PLMS are simply a causal PSG observation and are virtually never appreciated by the patient. It is currently controversial whether PLMS themselves cause insomnia or excessive daytime sleepiness [58]. Because the prevalence of PLMS does not differ significantly in people with insomnia, hypersomnia, or healthy subjects, except for very peculiar cases in which myoclonic jerks are so frequent and violent as to disrupt nocturnal sleep, PLMS are not the cause of insomnia [46].

Propriospinal Myoclonus

Propriospinal myoclonus (PSM) is a type of spinal myoclonus in which the myoclonic activity is generated within the spinal cord but does not remain restricted to segmentally innervated muscles and actually spreads up and down the length of the spinal cord along propriospinal pathways intrinsic to the cord [59]. PSM is characterized by violent muscle jerks in flexion or extension of the trunk and abdomen usually arising from the thoraco-abdominal/paraspinal muscles, or cervical muscles such as the sternocleidomastoideus muscle (Figure 16.2). In some patients and in some instances, jerks may involve only a restricted group of muscles (always including the originator muscle), propagating to more rostral and caudal levels only in the most intense jerks [60]. PSM is usually idiopathic, but is sometimes associated with spinal lesions (cervical trauma, thoracic herpes zoster, syringomyeilia, multiple sclerosis, HIV infection, etc.).

PSM typically arises at sleep onset, during relaxed wakefulness and drowsiness (with EEG characterized by diffuse alpha rhythm), and disappears as soon as the patient achieves sleep (with the appearance of the first sleep spindles in stage 2 NREM). Physiological sleep usually continues until the morning [61]. The jerks may recur quasi-periodically, every 10–20 s, several for minutes or hours, hindering sleep onset and, eventually, leading to a severe insomnia which can persist for years or even decades (Figure 16.2). The jerks quickly disappear also whenever the patient is aroused (by somesthesic stimuli, or when asked to perform mental calculation, make a fist, or simply speak) and EEG then changes to desynchronized activity. Clonazepam (at a dose of 0.5–2 mg) can reduce muscular jerks making sleep more restful. Opiates may also be effective but carry the risk of dependence [61].

Nocturnal Frontal Lobe Epilepsy

Nocturnal frontal lobe epilepsy (NFLE) is a peculiar form of partial epilepsy in which seizures are characterized by bizarre motor behavior or sustained dystonic posture. Seizures appear almost exclusively during sleep. The clinical spectrum of NFLE comprises distinct paroxysmal manifestations of

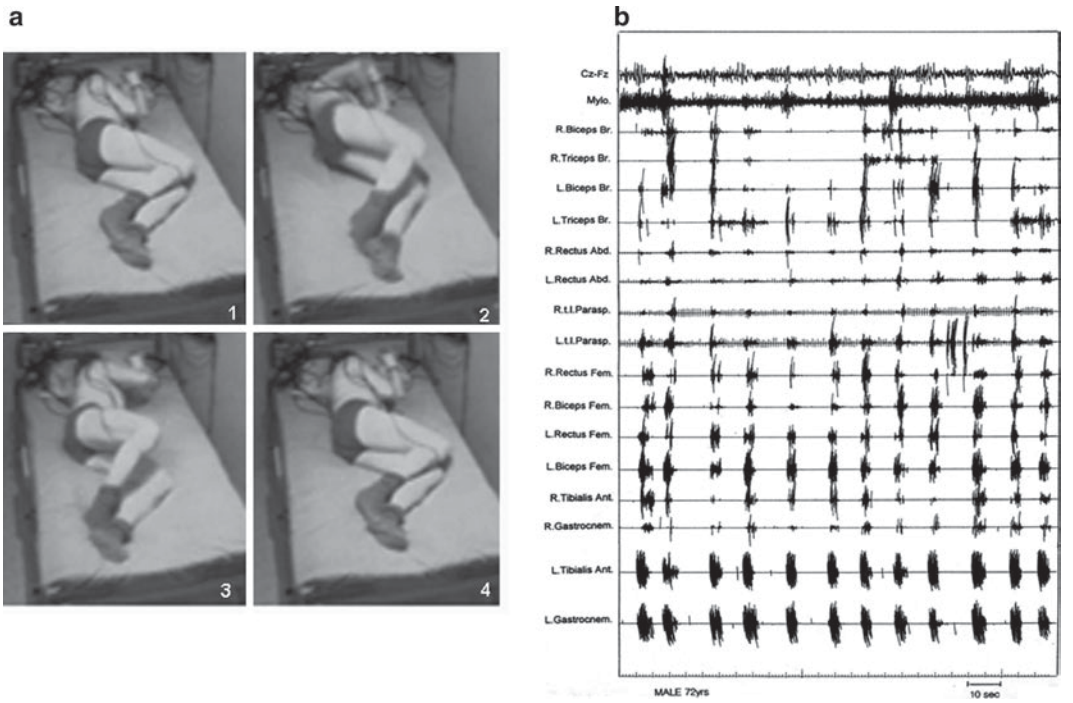

Figure 16.2 Propriospinal myoclonus. (**a**) Video recording of a jerk of propriospinal myoclonus in a 41-year-old man. (**b**) Excerpt from polysomnographic recordings in a 72-year-old man: myoclonic jerks recur at quasi-periodic intervals at sleep onset, and during relaxed wakefulness prior to falling asleep. The abnormal EMG activity originates in the right rectus abdominis muscle spreading thereafter to more rostral and caudal muscles (*mylo* mylohyioideus; *biceps br.* biceps brachii; *triceps br.* triceps brachii; *rectus abd.* rectus abdominis; *t.l. parasp.* thoracolumbar paraspinalis; *rectus fem.* rectus femoris; *biceps fem.* biceps femoris; *tibialis ant.* tibialis anterior; *gastrocnem.* gastrocnemius; *R* right; *L* left)

variable duration and complexity arising during SWS and usually consisting of: (1) *paroxysmal arousals* (PA), brief sudden awakenings associated with stereotyped and abnormal movements, recurring several times per night; (2) *nocturnal paroxysmal dystonia* (NPD), more complex motor episodes lasting 1–2 min, characterized by violent motor behavior (choreo-athetosic, ballic, and nearly rhythmic legs or arms movements), vocalization, screaming, fearful and repetitive movements of the trunk and limbs, and dystonic–dyskinetic postures (Figure 16.3); (3) prolonged episodes, named *episodic nocturnal wandering* (ENW), or *agitated somnambulism* [62]. The three types of seizures often coexist in the same patient. If seizures recur frequently every night, patients may feel tired and weary on awakening in the morning and complain of daytime sleepiness. NFLE can be inherited as an autosomal dominant disorder and some mutations linked to familial cases of NFLE have been identified [63].

Distinguishing NFLE from paroxysmal nonepileptic sleep disorders is often difficult and sometimes impossible on clinical grounds alone, because a reliable description of motor events occurring during the night is often difficult to collect from a sleep partner. Therefore, video-polysomnography monitoring together with careful history taking may represent the only tool to distinguish NFLE from other nonepileptic paroxysmal motor disorders in sleep [64]. Effective treatment controlling or reducing the amount of nocturnal seizures improves insomnia and daytime somnolence.

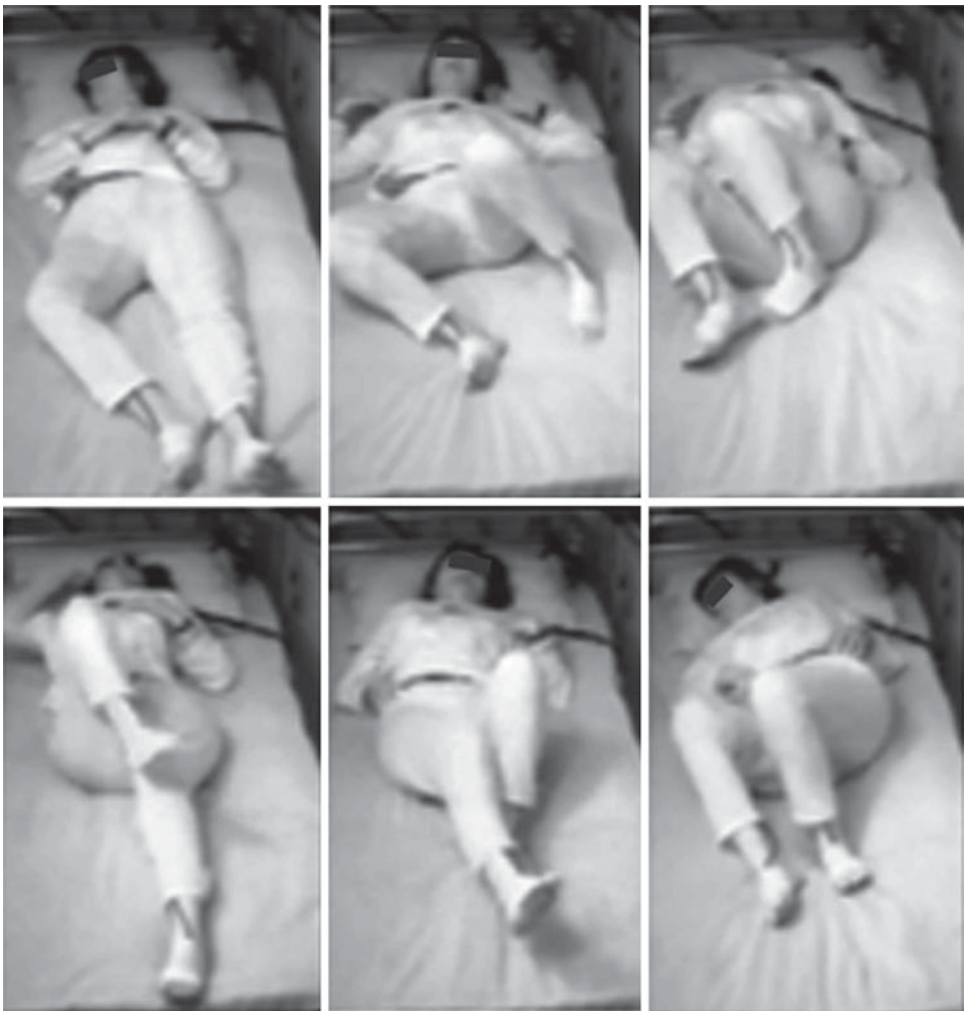

Figure 16.3 Nocturnal frontal lobe epilepsy (NFLE). Video recordings (excerpts taken at regular time intervals) of a NPD attack. During the attack, frantic wide-ranging movements display ballistic and dystonic patterns involving the trunk and limbs

REM Sleep Behavior Disorder

REM sleep behavior disorder (RBD) is a parasomnia characterized by abnormal and often violent motor agitation arising during REM sleep [65, 66]. Violent behavior can result in sleep disruption and severe injuries, including ecchymoses, lacerations, and fractures for the patient or bed partner have been described [67]. Patients with RBD have a high proportion of aggressive content in their dreams associated with more or less purposeful gestures enacting attack or defense reactions, despite normal levels of daytime aggressiveness [65]. RBD usually occurs in the middle of the night or early hours of the morning and are caused by the loss of the physiological muscular atonia during REM sleep (REM sleep without atonia) (Figure 16.4). RBD is more common in the older population; the mean age at onset is 60 years, with a male/female ratio of 9/1. At the moment, two main types of RBD are recognized: acute

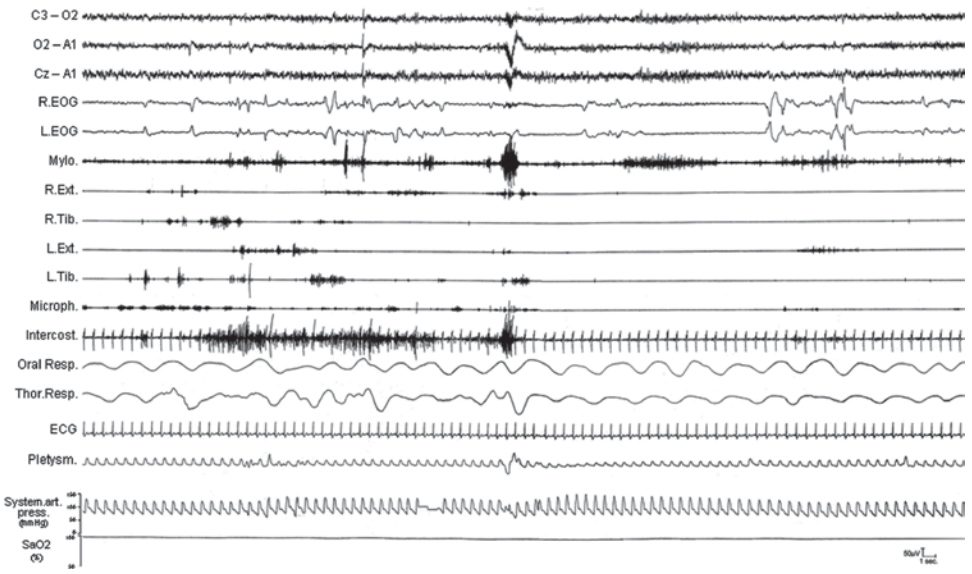

Figure 16.4 Polysomnogram of a patient with Rem sleep behavior disorder (RBD). The normal muscle atonia of REM sleep is disrupted (see sustained EMG activity of the mylohyioideus muscle)

onset and chronic RBD. Acute onset RBD is usually related to the effects of medications, such as the use of tricyclic antidepressant, SSRI or to withdrawal of barbiturates, benzodiazepines, alcohol or meprobamate. In this context, RBD is usually a transient manifestation, resolving spontaneously after a few days. Chronic RBD can present alone, without concomitant medical disorders, known as idiopathic (in about 40% of cases), or is commonly reported in patients with neurodegenerative disorders, especially synucleinopathy [68], sometimes as a heralding symptom [20]. Clonazepam (0.5–2 mg before bedtime) is highly effective and well-tolerated in 80–90% of cases [29, 67].

Other less common sleep-related movement disorders which may disrupt sleep include:

Excessive Fragmentary Hypnic Myoclonus

Excessive fragmentary hypnic myoclonus (EFHM) is a pathological motor activity consisting of small myoclonic twitches and fasciculation potentials during NREM sleep [69]. It is an abnormal intensification of the physiologic hypnic myoclonia and is characterized by sudden arrhythmic asynchronous and asymmetric brief twitches involving different body areas. EFHM may be an isolated phenomenon or associated with other sleep disorders such as sleep apnea, RLS, RBD and excessive daytime drowsiness. If severe, EFHM may disturb sleep onset and continuity, causing insomnia [70].

Facio-Mandibular Myoclonus

Facio-mandibular myoclonus is a rare sleep-related movement disorder and usually does not affect sleep. It consists of sudden forceful myoclonus of the masticatory muscles, evident only during sleep, often associated with biting

of the tongue and lips and, in such cases, simulating epileptic seizures during sleep [71–73]. The myoclonus usually starts in adult life, and may be familial. Rhythmic or prolonged tonic contractions of the masticatory muscles may damage the tongue and oral mucosa resulting in a burning pain that disturbs sleep [71].

Generalized Overactivity Syndrome (Agrypnia Excitata)

There are at least three neurological conditions (Fatal Insomnia, Morvan's chorea, and Delirium tremens) in which the inability to sleep is typically associated with motor and sympathetic or noradrenergic overactivation. Agrypnia (from the Greek "to chase sleep") and excitata (AE) are the terms aptly defining the clinical conditions in which organic insomnia is associated with a generalized activation syndrome [74–76].

Fatal Familial Insomnia

Fatal familial insomnia is an autosomal dominant disease caused by a point mutation at codon 178 of the prion protein gene (PRPN). Nearly 50 FFI kindreds have been described to date in addition to nine sporadic (nongenetic) cases (SFI) around the world in every ethnic group.

The disease begins, on average, at the age of 50 years with a variable duration from 8 months to 7 years. The early cardinal symptoms are apathy (attention deficit and indifference to surroundings), drowsiness, and stupor, accompanied by enacted dreams (gestures mimicking daily life activities with a dream content), autonomic hyperactivation (hyperhydrosis, sialorrhea, tachycardia, hypertension, mild fever, etc.) and motor signs (ataxia, dysarthria, evoked and spontaneous myoclonus) [77]. Signs and symptoms of sympathetic overactivity are associated with a marked and progressive increase in catecholamine secretion. In addition, 24 h serial studies document autonomic (blood pressure and body temperature) and hormonal (cortisol, norepinephrine) circadian oscillations that progressively subside until they disappear almost completely. On the contrary, melatonin secretion is reduced and lacks the nocturnal peak.

Longitudinal polysomnographic studies document that spindles and delta sleep, the typical EEG features of synchronized sleep, markedly reduced from disease onset, are completely absent in the most advanced stages (Figure 16.5), whereas wake or subwakefulness EEG patterns (stage 1 NREM) interspersed by recurrent brief REM sleep episodes without atonia persist throughout day and night, and actigraphic recordings performed during several weeks or even months preceding death document persistent motor activity throughout the 24 h (Figure 16.5). At this stage, even intravenous administration of barbiturates or benzodiazepines fails to generate spindle-like activity and delta rhythms [78].

PET scan in short-evolution FFI cases discloses a brain hypometabolism confined to the thalamus, while hypometabolism still predominates in the thalamus but is widespread to the cerebral cortex (namely frontotemporal cortex) and basal ganglia in long-evolution cases. FFI neuropathology is dominated by selective degeneration of the mediodorsal and anteroventral thalamic nuclei. Other thalamic nuclei and some limbic cortical regions (the caudal orbital cortex and anterior cingulate gyrus) are less consistently and less severely involved [78, 79].

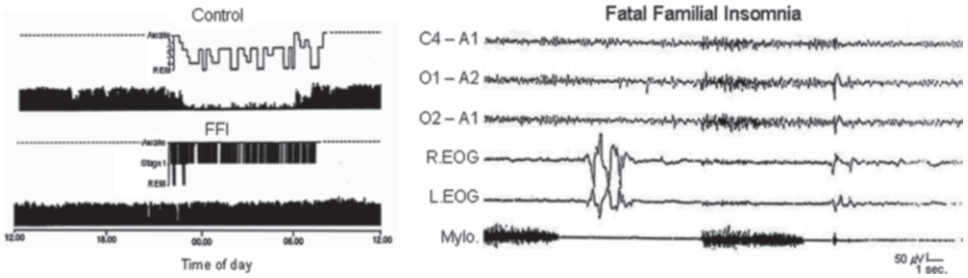

Figure 16.5 Fatal familial insomnia (FFI). *Left:* hypnograms and 24-h actigraphic recordings in a healthy control individual and in an FFI patient. *Right:* excerpt of polysomnographic recordings (PSG) in FFI. The hypnogram fluctuates from stage 1 NREM to REM sleep. Actigraphic recording shows continuous motor activity throughout the 24 h. The polysomnographic tracing is characterized by wake or subwake EEG patterns interspersed with short episodes of REM sleep

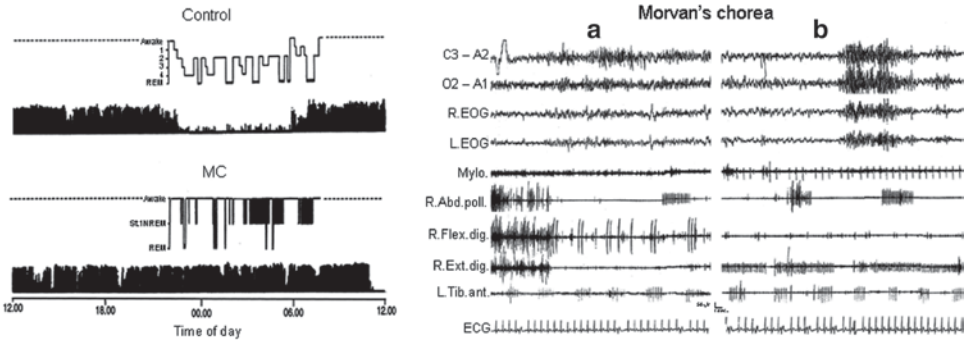

Figure 16.6 Morvan's chorea (MC). *Left:* hypnograms and 24-h actigraphic recordings in a healthy control individual and in an MC patient. *Right:* excerpts of polysomnographic recordings (PSG) in an MC patient. The hypnogram fluctuates from wakefulness to REM sleep. Actigraphic recording shows continuous motor activity throughout the 24 h. PSG: (**a**) the patient is agitated and presents dream-enacting behavior. Characteristic continuous muscle fiber activity on the electromyogram are also present. ECG shows multiple arrhythmic abnormalities; (**b**) sleep-like behavior: the patient is quiet, but the EEG lacks any characteristic sleep pattern

Morvan's Chorea

Morvan's chorea (MC), first described by Morvan in 1890, is an autoimmune limbic encephalopathy, characterized by severe insomnia accompanied by autonomic overactivity (profuse perspiration, tachycardia, hypertension, and fever), fasciculations, cramps, and motor agitation [80]. Mental confusion with vivid hallucinations and enacted dreams (behaviorally similar to those observed in FFI patients) appear in the most severe cases [81]. MC arises at any age and has a spontaneous remission, in a few weeks or months, in 80–90% of the cases. The remainder have a malignant progression of the disease until death. In 1974 Fischer-Perroudon and co-workers demonstrated that sleep disappeared at least 4 months before death in a typical case of MC [82]. We recently described serial polysomnographic recordings in a malignant evolution case documenting the abolition of spindle and delta sleep in the full-blown stage of the disease [81]. Short episodes of REM sleep recurring in clusters emerged from a subwake EEG pattern (stage 1 NREM) during day and night in the months before death (Figure 16.6). Enacted dreams

mimicking daily life activities coincided with REM sleep episodes as in FFI. Motor agitation persisting day and night, central sympathetic overactivation accompanied by persistently high norepinephrine levels and reduced melatonin secretion characterized the patient we observed. Serum IgG in our case bound strongly to neurons in the hippocampus, thalamus and striatum of rat brain, whereas direct immunochemistry on frozen sections of the patient's brain tissue showed areas of antibody leakage in the thalamus. Postmortem brain examination was unremarkable in our case, as in the few other cases. Silber et al., briefly reporting a case of MC with benign outcome, also emphasized the striking similarities between the polygraphic aspects in their cases and those observed in FFI [83].

Delirium Tremens

Delirium tremens (DT) is the well-known acute psychotic syndrome linked to sudden alcohol or benzodiazepine withdrawal after chronic abuse [84]. DT is clinically characterized by severe insomnia, anxiety, confusion associated with visual hallucinations, and dream enactment. Tremor and motor violent agitation associated with sleeplessness and sympathetic hyperactivity (perspiration, tachycardia, hypertension, mild fever) are other common signs. During the acute phase of the disease, polysomnographic recordings disclosed complete sleep–wake disruption with a drastic reduction of spindle and delta sleep. A state between subwakefulness (stage 1) and protracted REM sleep episodes (so-called Stage 1 + REM) becomes the predominant PSG pattern as Kotorii et al. reported [84] (Figure 16.7). Enacted dreams mimicked daily life activities as in FFI and MC and coincided with REM sleep episodes [85]. Even though the pathogenetic mechanism of DT is not fully understood, we can assume that sudden alcohol or benzodiazepine (BDZ) withdrawal results in a transient homeostatic imbalance within the limbic system, due to the sudden dramatic changes in GABAergic synapses, downregulated by chronic alcohol abuse [85].

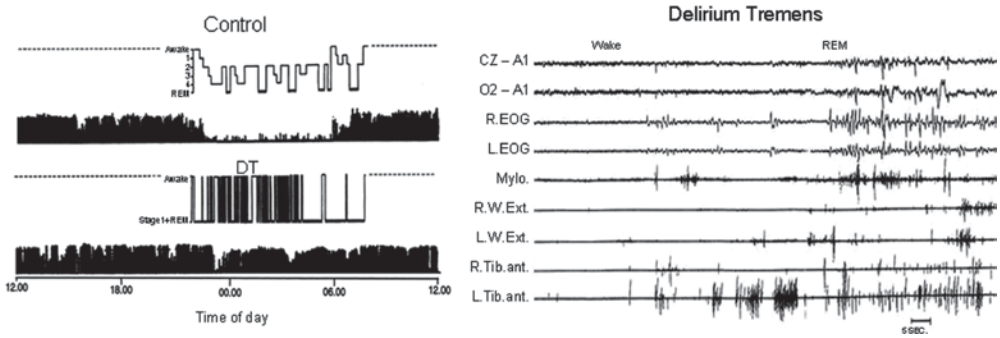

Figure 16.7 Delirium tremens (DT). *Left:* hypnograms and 24 h actigraphic recordings in a healthy control individual and in a DT patient. *Right:* excerpt of polysomnographic recording (PSG) in a DT patient. The hypnogram and PSG are characterized by fluctuation from wakefulness to Stage 1 + REM sleep. Actigraphy shows a continuous motor overactivity with a loss of the 24 h circadian rest-activity cycle

Agrypnia Excitata: A Generalized Activation Syndrome

The striking clinical and polygraphic similarities shared by FFI, MC, and DT suggest that they have a common pathogenetic mechanism, despite the widely different etiology and clinical course. Clinically, the picture is characterized by severe insomnia, hallucinations, dream-enacting behavior (oneiric stupor), motor agitation and sympathergic activation. Hormonal functions are consistently involved (cortisol and catecholamine secretion are high, melatonin secretion, at least in FFI and MC, is markedly reduced). Polygraphically, FFI, MC, and DT are characterized by the disappearance of SWS (spindle and delta activity) and EEG signs of "subwakefulness" alternating or intermingling with REM sleep episodes. The intralimbic disconnection caused by degeneration of the visceral thalamus triggers the generalized activation associated with the inability to sleep characteristic of FFI [86]. Auto-antibodies binding to the (voltage dependent) potassium channels of thalamo-limbic neurons, giving rise to a sort of autoimmune limbic encephalopathy, could explain the clinical picture of MC [81, 87]. Sudden alcohol (or BDZ) withdrawal generates the same clinical features because previous alcohol (or BDZ) abuse had strongly downregulated the inhibitory gabaergic synapses within the thalamo-limbic circuits [85]. Summing up, an anatomical or functional intralimbic disconnection resulting in the prevalence of activating over deactivating systems is the cause of the generalized activation syndrome – agrypnia excitata – shared by FFI, MC, and DT [88].

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17

Insomnia in Psychiatric Disorders

Samy S. Karaz

Abstract

Management of insomnia without a basic understanding of the possible underlying psychiatric disorders might result in an inadequate, if not hazardous outcome. Insomnia is listed in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)* as a symptom of several psychiatric disorders.

Insomnia related to other *DSM-IV* mental disorders was found to be as high as 77%. In more than 50%S of the cases, the diagnosis was a depressive disorder. In general, 57% of individuals reporting insomnia have a psychiatric disorder or will develop one within a year. Anxiety seems to play a key role in the development of insomnia. Second to anxiety disorders, depression is strongly associated with the development of insomnia. Depression is considered as a possible precipitating mechanism but even more likely as a consequence of insomnia.

Keywords: Anxiety disorders, Depressive disorder, Insomnia, Benzodiazepines, SSRIs, Prazosin, PTSD

The best bridge between despair and hope is a good night's sleep

E. Joseph Cossman

Introduction

Management of insomnia without a basic understanding of the possible underlying psychiatric disorders might result in an inadequate, if not hazardous outcome. Insomnia is listed in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)* as a symptom of several psychiatric disorders *(*see Table 17.1) [1].

Insomnia related to other *DSM-IV* mental disorders was found to be as high as 77%. In more than 50% of the cases, the diagnosis was a depressive disorder [2]. In general, 57% of individuals reporting insomnia have a

From: *Clinical Handbook of Insomnia,* Current Clinical Neurology
Edited by: H.P. Attarian and C. Schuman, DOI 10.1007/978-1-60327-042-7_17,

Table 17.1 DSM-IV diagnoses with insomnia as a symptom.

Diagnosis	DSM-IV criteria
Separation anxiety disorder	Reluctance or refusal to go to sleep without being near a major attachment figure and repeated nightmares involving the theme of separation
Alcohol withdrawal	Insomnia
Stimulant withdrawal (including cocaine, amphetamines, nicotine, or caffeine)	Insomnia or hypersomnia
Sedative withdrawal (including hypnotics, anxiolytics, and opiates antidepressants)	Insomnia
Major depression	Insomnia or hypersomnia
Dysthymia	Insomnia or hypersomnia
Posttraumatic stress disorder	Recurrent distressing dreams of the traumatic event leading to difficulty in falling or staying asleep
Acute stress disorder	Reexperiencing the trauma in recurrent nightmares
Generalized anxiety disorder	Insomnia
Primary insomnia	The predominant complaint is difficulty initiating or maintaining sleep or non-restorative sleep, for at least 1 month
Nightmares	Repeated awakening from any sleep period due to frightening and vivid dreams
Sleep terrors	Recurrent episodes of abrupt awakening from sleep, usually occurring during the first third of the major sleep episode
Sleep disorder due to another psychiatric	Insomnia
Sleep disorder due to another medical	Insomnia
Postconcussional disorder	Insomnia or hypersomnia
Premenstrual dysphoric disorder	Insomnia or hypersomnia

Adapted from ref. [1].

psychiatric disorder or will develop one within a year [3]. Second to anxiety disorders, depression is strongly associated with the development of insomnia. Anxiety seems to play a key role in the development of insomnia. Depression is considered as a possible precipitating mechanism but even more likely as a consequence of insomnia [4].

Sleep and Depressive Disorders

Patients with major depressive disorders present with depressed mood or loss of interest or pleasure. The full *DSM-IV* criteria of major depression are listed in Table 17.2 [5].

The most characteristic feature of insomnia seen in major depression is repeated awakenings leading to early morning or "premature" insomnia. Waking up early and not being able to return to sleep is a cardinal complaint [6]. Younger depressed patients might present with initial insomnia. The most characteristic sleep-tracing, polysomnographic, feature of major depression is

Table 17.2 Diagnostic criteria for a major depressive episode.

In the same 2 weeks, the patient has had five or more of the following symptoms, which are a definite change from usual functioning. Either depressed mood or decreased interest or pleasure must be one of the five
Depressed mood for almost all day nearly every day
Markedly decreased interests for almost all day nearly every day
Appetite and or weight increased or decreased for almost all day nearly every day
Decreased or increased sleep for almost all day nearly every day
Patient agitated or retarded for almost all day nearly every day
Fatigue or loss of energy for almost all day nearly every day
Patient feels worthless or inappropriately guilty for almost all day nearly everyday.
Trouble thinking or concentrating for almost all day nearly every day
Repeated thoughts about death (other than the fear of dying), suicide (with or without a plan). Or has made a suicide attempt
These symptoms cause clinically important distress or impair work, social, or personal functioning
This disorder is not directly caused by a general medical condition or the use of substances, including prescription medications
Unless the symptoms are severe (defined as severely impaired functioning, severe preoccupation with worthlessness, ideas of suicide, delusions, or hallucinations, or psychomotor retardation), the episode has not begun within 2 months of the loss of a loved one

earlier onset of the first rapid eye movement (REM) period. Other abnormalities include reduced delta sleep and increased REM sleep [6]. The severity of insomnia correlates with the severity of depression. Despite the overwhelming evidence of insomnia and sleep architecture abnormalities, patients with major depression do not usually present with symptoms of excessive daytime sleepiness. Patients with major depression frequently present with major depression frequently present with symptoms of tiredness and lack of energy.

Accordingly, it is of clinical importance to try to differentiate between tiredness with a lack of energy and excessive daytime sleepiness in patients with insomnia. On the other hand, as a part of bipolar disorder and seasonal affective disorder, depression is usually accompanied by increased sleep efficiency, frequent napping, and daytime sleepiness [6].

In hypomanic or manic phase of bipolar disorder, patients usually sleep as little as 2–4 h each night, yet they wake-up feeling subjectively refreshed. The absence of depression symptoms in the initial evaluation of insomnia should not rule out the risk of major depression in future visits. Patients with insomnia and no depression at intake were at approximately 40-fold higher risk of developing new episodes of major depression in comparison to individuals with no insomnia [7]. There is another group of insomnia patients who have major depression, yet their sole complaint is insomnia. The psychiatric literature described individuals with "Alexithymia" (patients without words to express their feeling state). These individuals are more likely to have "masked depression." They are particularly commonly seen in the primary care setting. Patients with masked depression substitute somatic complaints such as insomnia for the traditional core symptoms of depressed mood or loss of pleasure. Therefore, it is important to focus on the objective component of the mental status.

The general demeanor and posture of patients with depression may appear to be slowed. They may walk slowly, holding their heads down and lacking spontaneity. Patients with depression may respond to questions with long pauses and short answers [8]. Their facial expressions may be blunted and their eye contact may be poor. Focusing only on the contents of the patient's complaints may result in overlooking depression and, in turn, a poor treatment outcome. Severe insomnia is an independent risk factor for suicide during the first 2 years of an episode of major depression [9].

Treatment of Depression/Insomnia Symptoms

Selective serotonin reuptake inhibitors (SSRIs) like fluoxetine, paroxetine, sertraline, and fluvoxamine are commonly used for treatment of depression. SSRI antidepressants decrease total sleep time (TST), increase number of arousals, suppress REM sleep, and increase the number of phasic REMs. Despite their arousing effect on the sleep electroencephalogram (EEG), SSRI antidepressants improve subjective sleep quality in subjects with major depression and primary insomnia [10]).

Tricyclic antidepressants play a role in treatment of depression/anxiety symptoms. Tricyclic antidepressants decrease REM sleep and increase REM latency. EEG measures of sleep continuity may improve with tricyclic antidepressants [9].

The tertiary amine tricyclic antidepressants (e.g., Amitriptyline and Imipramine) have a more sedating effect than the secondary amine tricyclics like Desipramine and Nortriptyline. The secondary amines group has fewer adverse effects. Some clinicians believe that depressed patients with marked insomnia and anxiety obtain some immediate relief from the sedating antidepressants before the full antidepressant effect takes place, which might increase the likelihood of compliance during the acute phase of treatment [11].

One drawback of the tricyclic antidepressants is the risk of fatal effects if an overdose is ingested. Patients were randomly assigned to an initial prescription of the SSRI fluoxetine or the tricyclic Imipramine. The rate of improvement in insomnia was identical in both groups [12]. Serotonin receptor modulators like Trazodone and Nefazodone increase sleep continuity. However, Trazodone decreases REM sleep and may cause daytime sedation, whereas Nefazodone increases REM and has minimal daytime sedation [13].

Monoamine oxidase inhibitors (MAOIs), antidepressants like Tranylcypromine (Parnate) and Phenelzine (Nardil), still have a role in the treatment of depression. However, because of the necessity to regulate the diet and to continuously evaluate the concomitant medications, MAOIs are not used as a first line of treatment [11].

Insomnia is one of the most common residual symptoms after successfully treating depression with CBT or pharmacotherapy. This could result in greater risk of subsequent depression. This suggests that adjunctive treatment, specifically of insomnia, may be necessary for some MDD patients. [14]

Benzodiazepines like Lorazepam, Clonazepam, and Alprazolam are sedating, induce sleep, and have antianxiety and muscle relaxant effects. Newer medications like Zolpidem and Eszopiclone act selectively on the $\grave{u}_1$ benzodiazepine receptors and have a sedative effect without anxiolytic, anticonvulsant, and muscle relaxant effects. They do not cause rebound effects or withdrawal

when discontinued [13]. A double-blind study by Smith and co-workers found that patients taking fluoxetine for depression showed greater improvement in their psychiatric symptoms when taking Clonazepam concomitantly [13]. In a double-blind study by Rosenberg et al., Zolpidem was found to improve the quantity and quality of sleep without worsening depression when coadministered with antidepressants [13]. Eszopiclone was discontinued after 8 weeks of Fluoxetine/Eszopiclone cotherapy in patients with insomnia and comorbid MDD. It did not result in withdrawal symptoms, rebound insomnia or rebound depression and improvement of sleep and depressive symptoms were maintained [15].

Patient's individual susceptibility to certain side effects, personal and family history of previous response to specific antidepressants, history of alcohol or drug abuse, patient's age, and possible other concomitant underlying medical problems should all be factored in when an antidepressant and/or benzodiazepine are to be selected.

Case 1

A 52-year-old married male was referred to the sleep center by his primary care physician.

The patient presented with difficulties initiating and maintaining sleep.

He goes to bed at 10:00 PM and it takes him up to 1–2 h to fall asleep. He wakes up two to three times in the second half of the night. He stays awake for 15–20 min, up to an hour each time. Once or twice a week he wakes up around 2:00–3:00 AM and cannot fall asleep again. He ends up reading or watching TV. He gets out of bed in the morning at 6:00 AM feeling tired. He is unable to take naps. He drinks two to three beers in the evening one day per week on a weekend. He doesn't smoke.

He has a past medical history of hiatal hernia and was recently diagnosed with borderline hypertension. He is on no medications.

On physical exam, there was evidence of mild nasal septal deviation. Otherwise, his exam was essentially normal.

On mental status exam, his affect was euthymic and he had good eye contact. He denied any symptoms of depression or anxiety.

Sleep hygiene education and cognitive behavioral/medication management was utilized. The patient was advised to avoid wakeful activity during his scheduled sleep time. He was educated regarding the stimulus control technique and relaxation. He was started on Temazepam, 15 mg at bedtime. Four weeks later he reported improvement with residual insomnia.

He continued to comply with the cognitive behavioral therapy, sleep hygiene, and medication management.

Six months later, the patient called for an earlier appointment. He complained of recurrent insomnia despite his ongoing compliance. He complained that his poor sleep is even worse than before he started treatment. He weighed 7 pounds less than the previous visit. He denied dieting, yet admitted to decreased appetite. He complained that 4–5 days a week he wakes up 3–4 h earlier than his usual wake-up time and cannot fall asleep.

On mental status exam, he appeared to have dysthymic affect with poor eye contact. He complained of loss of interest and lack of energy. He denied suicidal ideation, yet complained of feelings of worthlessness. Temazepam was

continued and Sertraline was added to his treatment. He was scheduled for six sessions of cognitive behavioral therapy of depression.

Four weeks later, there was significant improvement of both his depression and insomnia. Three months later, Temazepam was eventually tapered and discontinued. He was kept on Sertraline and continued to be asymptomatic.

Insomnia and Anxiety Disorders

Sixteen million Americans suffer from anxiety disorders [16]. The interrelationship between anxiety disorders and insomnia is a very common finding in the clinical setting. Anxiety and related conditions (tension, psychic distress) were found to be quite prevalent among insomniacs in epidemiological studies of either the general population or the elderly. The vast majority of insomniacs manifested the symptoms of apprehension, rumination, multiple fears, and excessive worrying [17]. Core features of panic disorders and PTSD occur in relation to sleep (sleep panic attacks, and reexperiencing nightmares). [18]

Generalized Anxiety Disorder

Patients with generalized anxiety disorders (GADs) experience chronic and persistent anxiety and, not surprisingly, most report problems with insomnia [19]. Fifty to seventy percent of patients with GAD report trouble in sleeping [20]. Sleep disturbance is characterized by sleep onset or maintenance insomnia due to excessive anxiety and apprehensive expectations about one or more life circumstances. These patients may express intense anxiety during the daytime about the inevitability of each night's poor sleep. Patients display chronic anxiety with features that include trembling, muscle tension, restlessness, easy fatigability, shortness of breath, palpitations, tremors, sweating, dry mouth, dizziness, keyed up feelings, and exaggerated startle response [6]. The *DSM-IV* criteria of GAD are listed in Table 17.3 [5].

The polysomnographic features of GAD reveal the nonspecific findings of increased sleep latency (SL), decreased sleep efficiency, increased amount of stage 1 and stage 2 sleep and decreased slow-wave sleep. REM sleep was

Table 17.3 Diagnostic criteria for generalized anxiety disorder.

Worries and anxieties over several events and activities for 50% of the time or more for at least 6 months
The person experiences difficulty or trouble trying to control these feelings
In addition to the above there are at least three of the symptoms listed below for 50% of the time or more for at least 6 months:
Feels restless, edgy, keyed up
Tires easily
Trouble concentrating
Irritability
Increased muscle tension
Trouble sleeping (initial insomnia or restless, unrefreshing sleep)
The cause of the anxiety and the worry is not an aspect of another psychiatric illness. The anxiety is not the symptom of another medical condition. The anxiety is not the symptom of another psychiatric condition
The symptoms cause clinically important distress or impair work, social, or personal functioning

normal in GAD, in contrast to findings from major depression where REM sleep latency is reduced. [18] These changes are often mild. There is usually little to no physiologic sleepiness on the Multiple Sleep Latency Test of patients with GAD [5]. There are similarities between psychophysiologic insomnia and GAD in both their clinical presentation and the polysomnographic changes.

If anxiety permeates most aspects of functioning, a GAD is the usual diagnosis. In contrast, if anxiety is focused almost exclusively on poor sleep and its consequences on daytime functioning, psychophysiologic insomnia is the typical diagnosis [21].

On the other hand, patients with GAD experience pervasive anxiety during the day, which interferes with their level of functioning well beyond the consequences of poor sleep [11].

In contrast with GAD, sleep efficiency improves on the second night in patients with psychophysiologic insomnia when their nighttime sleep polysomnogram (PSG) is recorded in the sleep lab two nights in a row [5].

Treatment

Benzodiazepines like Alprazolam and Clonazepam continue to play a major role in the management of GAD. SSRI antidepressant medications like fluoxetine, paroxetine, sertraline, and a tricyclic antidepressant like Imipramine are found to be valuable options in the treatment of GAD. Cognitive behavioral therapy should be strongly considered as an important tool in the treatment of GAD and the related insomnia.

Panic Disorder

Sleep disturbances have been reported in 70% of patient's with panic disorder [22]. The panic attack is characterized by a sudden, intense fear or terror of dying. Symptoms include dizziness, choking, palpitation, trembling, chest pain, or discomfort, and sweating [5].

Symptoms of panic attack as listed in the *DSM-IV* are shown in Table 17.4.

Panic disorder can be associated with sudden awakening from sleep. Nocturnal panic attacks present with similar symptoms to daytime panic.

Table 17.4 Diagnostic criteria for panic disorder.

The patient suddenly develops a severe fear or discomfort that peaks within 10 min. During this discrete episode, four or more of the following symptoms occur:
Choking sensation
Chills or hot flashes
Chest pain or other chest discomfort
Fear of dying
Dizzy, lightheaded, faint, or unsteady
Derealization (feeling unreal) or depersonalization (feeling detached from self)
Fears of loss of control or becoming insane
Heart pounds, races, or skips beats
Nausea or other abdominal discomfort
Numbness or tingling
Sweating
Shortness of breath or smothering sensation
Trembling

Palpitation, dyspnea, and flushing are the most frequent symptoms of nocturnal panic attacks [22]. Thirty-three to seventy-one percent of panic disorder population reported having experienced sleep panic attacks [18]. Polysomnographic monitoring of nocturnal panic demonstrates an abrupt awakening with a sensation of panic out of stage 2 or 3 sleep. It also presents with marginally increased SL and decreased sleep efficiency.

Obstructive sleep apnea (OSA) may lead to awakening with panic-like symptoms. OSA usually presents with symptoms of snoring, sleepiness, and the absence of daytime anxiety, which distinguishes OSA from panic disorder [5].

Night terrors, which also emerge from nonrapid eye movement (NREM) sleep, are usually followed by no recollection of the events and there are no daytime panic symptoms. Nightmares differ from panic attacks as they usually cluster around the early morning and contain much more mental content [5].

It is important to note that panic disorder is associated with major depression in 50–94% of patients [22]. This comorbidity could result in alteration of the presentation of insomnia symptoms.

Treatment

SSRI antidepressants like paroxetine, fluoxetine, sertraline, fluvoxamine, or citalopram are the current consensus to start treating a patient with uncomplicated panic. Many patients with panic disorder have what is described as supersensitivity syndrome, which are an initial agitation and more frequent panic in the first 1–2 weeks of starting an SSRI medication. Further reduction of the dosage adding benzodiazepine, or switching to a different compound from the same family usually gets the patient through this relatively short period [11].

Benzodiazepines are powerful antipanic drugs. The major advantage of benzodiazepines is their quick onset of action. Follow-up studies suggest that benzodiazepine-responsive patients maintain their gain for several years and do not develop tolerance. Maintenance doses are usually lower than the dosages used for acute treatment [11].

MAOIs are potent antipanic drugs, yet their use is limited by the necessity to regulate the diet and continuously evaluate the concomitant medications.

Tricyclic antidepressants, particularly Imipramine and Clomipramine, are very effective antipanic medications.

Case 2

A 42-year-old married female was seen at the sleep center due to gradually progressive symptoms of insomnia.

The patient was frustrated due to increasing problems with tiredness during the day. She works as a bank teller, and she had difficulty functioning due to tiredness. She denied any daytime sleepiness.

She goes to bed at 10:00 PM. She lies in bed for a couple of hours frustrated and worrying about and planning for the next day, until she falls asleep. She wakes up a couple times during the night almost around the same time each night and is awake for about an hour to an hour-and-a-half each time. She denied any history of psychiatric problems. She smokes a half pack of cigarettes every 3 days, and she seldom drinks any alcoholic beverages.

She has a past medical history of allergic rhinitis and history of appendectomy. Her physical exam was essentially normal.

The patient was treated with cognitive behavioral therapy with focus on relaxation techniques including breathing exercises, scheduling the worry, and imagery.

The patient called shortly after the first visit and was very frustrated. She could not benefit from the relaxation techniques.

Eszopiclone, 3 mg at bedtime was prescribed. The patient was seen 3 weeks later, and she reported that the medicine helped mostly the first couple of days and the benefit gradually decreased over time. The improvement of her sleep at the time of the visit was minimal. She complained that she could not stop her racing thoughts during the night. She described the thoughts as repetitious and impossible to stop. Even without any specific worry, her thoughts would revolve around trivial matters. She complained of becoming increasingly anxious during the day. She occasionally feels tremulous and complained of poor concentration. She admitted that she had similar, yet milder symptoms over the last couple of years.

The patient was referred for a psychiatric consult. She was diagnosed with generalized anxiety disorder with obsessive compulsive comorbid symptoms. She was treated with Paroxetine, in addition to the Eszopiclone. She received cognitive behavioral therapy more extensively with focus on treatment of anxiety and obsessive rumination.

Her anxiety gradually improved and her obsessive rumination was better controlled. She was most pleased for being able to utilize the behavioral therapy recommended for insomnia, and her insomnia problems improved. She was continued on a combination of both medications. Her obsessive rumination decreased significantly, and her sleep became more restorative. She was no longer tired during the day. She continued follow-up appointments primarily in psychiatry, with appointments scheduled on an as needed basis at the sleep center.

Posttraumatic Stress Disorder

Insomnia and nightmares are common symptoms of posttraumatic stress disorder (PTSD). Of patients with PTSD or individuals exposed to major stress, 59–68% report frequent nightmares [20]. Insomnia is part of the hyperarousal complex of symptoms and nightmares are characteristic in the symptoms cluster of reliving the traumatic events [23]. The anxiety arousals in PTSD may emerge from both REM-related nightmares and may also arise from NREM sleep [20]. There is evidence of increased eye movement density and phasic motor activity in REM sleep. [2] Cognitive behavioral therapy for nightmares and insomnia was associated with improvement of the symptoms of PTSD [24]. SSRI antidepressants have also proven to be effective in the treatment of PTSD and insomnia. Fluvoxamine was found to be effective, particularly in the treatment of traumatic-related nightmares and sleep maintenance insomnia [10].

Trazodone was also found to be effective in the treatment of nightmares and insomnia associated with PTSD [23]. Benzodiazepines and tricyclic antidepressants were also found to be effective in the treatment of PTSD. Most recently several studies have shown that Prazosin (mean dose of 3 mg at bedtime), a central nervous system active alpha-1 adrenoreceptor antagonist, has reduced nightmares and sleep disturbances associated with PTSD, both subjectively and objectively [24–26].

Other Disorders

Other anxiety disorders (e.g., obsessive-compulsive disorder) and other psychiatric disorders (e.g., schizophrenia, eating disorders, dementia, and alcoholism) are accompanied by problems with insomnia and sleep architecture changes. Details of these changes are illustrated on Table 17.5 [19].

Insomnia and Substance Abuse

Alcoholism

Special attention needs to be given to alcoholism, as it is often associated with anxiety disorders, depression, and insomnia. Acute alcohol use reduces the amount of wakefulness for the first 3–4 h of sleep. The amount of wakefulness increases during the second half of the night and sometimes the numbers of dreams, particularly anxiety dreams, increase. Chronic, excessive alcohol use eventually results in fragmented and restless sleep [6].

Sleep problems due to alcohol abuse could be confused with insomnia due to psychiatric disorders or primary insomnia if the problem with alcoholism is overlooked or not addressed. Insomnia may predispose or perpetuate alcohol consumption. Compared with the general population, alcoholics have a greater tendency to choose alcohol over other means of alleviating sleep problems. [27]

It is advisable to avoid prescribing benzodiazepines if alcohol use is a problem. Benzodiazepine-prescribing decisions vary widely among physicians. Although some agreed with prescribing for patients with high probability

Table 17.5 Sleep abnormalities in psychiatric disorders.

Disorder	Symptoms	Objective findings
Major depression	Insomnia, vivid dreams, nightmares, and fatigue	~Total sleep ~sleep latency
Seasonal affective disorder/ bipolar depression mania	Hypersomnia	~Sleep efficiency ~wake time ~REM
Anxiety disorders	Insomnia	~Total sleep time
Posttraumatic stress disorder	Insomnia	~Total sleep ~sleep latency
Schizophrenia	Insomnia, flashback dreams	~Sleep efficiency ~wake time ~REM
Eating disorders	Insomnia, reversal of sleep–wake cycles	~ Sleep continuity
Alcoholism	Insomnia, sleep-related eating spells	Normal or ~REM
Dementia Alzheimer's type	Insomnia	~ Sleep continuity, normal or ~SWS, normal or ~REM sleep
	Insomnia, reversal of sleep–wake cycles	Normal or ~ sleep continuity, normal or ~REM sleep
		~ Sleep continuity, ~SWS, normal or ~REM sleep, normal or ~REM%
		~Total sleep ~sleep latency
		~wake time, ~SWS

Adapted from ref. [15].
REM rapid eye movement, *SWS* slow-wave sleep.

of alcohol abuse, other physicians avoided benzodiazepines unnecessarily, depriving certain insomnia patients from a viable treatment option [28, 29].

Caffeine

Caffeine is a stimulant that is consumed in coffee (85–150 mg per cup), tea (60–75 mg per cup), cocoa (50 mg per cup), chocolate, over-the-counter (OTC) cold preparations (15–60 mg per tablet), and OTC stimulants (100–200 mg).

Caffeine effects may last for 8–14 h. Caffeine consumption might induce or worsen insomnia, even if it is consumed as early as the late afternoon.

For most people, 1 g of caffeine may induce insomnia. Other more sensitive individuals may become overstimulated on as little as 250 mg [20].

The polysomnography changes with caffeine shows increased SL, decreased TST, increased wake after sleep onset (WASO), decreased REM sleep, and decreased delta sleep [30].

Nicotine

Nicotine can be consumed by smoking, chewing tobacco, snuff, nicotine patches, and nicotine gum. Nicotine is addictive. Withdrawal from nicotine starts 1–2 h after the last smoke [20]. Abrupt cessation or decrease of the nicotine consumption can result in insomnia in the following 24 h [5]. Cigarette smoking accelerates the metabolism of certain medications including Diazepam, Lorazepam, Oxazepam, and Imipramine. This could result in a decrease of the sedative effect of these medications among smokers. Nicotine polysomnography changes include increased SL, decreased TST, and decreased REM sleep [30].

Stimulants

Amphetamines such as methamphetamine "speed" are taken intravenously, by snorting, or by smoking "ice." PSG changes on amphetamines are decreased TST, increased WASO, increased movement during sleep, decreased REM sleep, and decreased delta sleep [30]. Cocaine is also taken intravenously, by snorting, or smoking (as free base "crack"). PSG changes on cocaine are increased SL, decreased TST, and decreased REM sleep [27].

Serious medical and psychiatric complications result from stimulant abuse and among these complications are a disruption of the sleep–wake pattern and insomnia. Stimulants (e.g., amphetamines and methylphenidate) are used therapeutically in the treatment of narcolepsy, attention deficit hyperactivity disorder, some causes of depression, and other related disorders. The availability of objective diagnostic tools and careful clinical monitoring helps decrease the risk of stimulant abuse among these patients population.

Anxiolytics and Sedative Hypnotics

The present major anxiolytics and sedative hypnotics include benzodiazepine, nonbenzodiazepines (Ambien, Zolpidem, and Eszopiclone) and other miscellaneous drugs like Chloral Hydrates and antihistamines. [20].

The older sedative hypnotics like barbiturates are less frequently used due to the higher risk of dependence and the more severe withdrawal symptoms like withdrawal seizures.

The benzodiazepines polysomnographic changes include increased TST, decreased WASO, decreased REM sleep, and increased sleep spindles in stage 2. Most benzodiazepines decrease the SL and decrease delta sleep [30]. Nonbenzodiazepines (Eszopiclone, Zolpidem, and Zaleplon) decrease sleep latency and have no effect on slow-wave sleep. Zaleplon and Zolpidem decrease REM and Eszopiclone does not change REM sleep. Nonbenzodiazepines have less effect on sleep architecture changes than benzodiazepines.

Chloral hydrate decreases sleep latency and improves sleep continuity. [31] The sedative hypnotics' abuse occurs predominantly in the context of polysubstance abuse [20]. Benzodiazepines with rapid onset of action (e.g., Alprazolam and Diazepam) are more likely to be abused than the longer onset of action type of benzodiazepine (Oxazepam or Chlordiazepoxide). Withdrawal from sedative hypnotics can result in a rebound insomnia or emergence of insomnia as a new symptom (in prolonged high-dose use). Anxiety is a common withdrawal symptom, which independently can initiate or worsen insomnia. In evaluating the risks versus benefits of the sedative hypnotic therapy in patients including those who have insomnia, it is helpful to distinguish between "drug-seeking behavior" from "therapy-seeking behavior" [20].

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18

Circadian Rhythms and Insomnia

Leon C. Lack and Helen R. Wright

Abstract

Because our circadian rhythms have a strong influence on sleepiness/alertness, inappropriate timing of these rhythms with respect to the attempted sleep period can produce insomnia. Relatively delayed circadian rhythms have been associated with sleep-onset insomnia and advanced or early timed rhythms have been associated with early morning awakening insomnia. Therefore, management of these insomnias need to include treatments, such as bright light and melatonin, that will retime the circadian rhythms to be more in synchrony with the timing of sleep.

Keywords: Circadian rhythms, Delayed sleep phase, Advanced sleep phase, Insomnia, Bright-light therapy, Melatonin

Introduction

When there is a disparity between the timing of an individual's endogenous circadian rhythm and their preferred sleep–wake schedule, persistent or recurrent sleep difficulties can occur [1, 2]. This mismatch can lead to insomnia, decreased total sleep time and impaired daytime functioning. Difficulty in initiating sleep is associated with a delayed or late-timed circadian rhythm relative to the intended sleep time, while early morning awakening is associated with a relatively early timed or advanced circadian rhythm.

Normal Biological Determiners of Sleep

The two major biological determiners of sleep are sleep homeostasis and circadian rhythms [3]. Sleep homeostasis simply refers to the build-up of sleep drive or pressure during continued wakefulness much as going without food increases hunger or food-seeking drive. Similarly, the process of

From: *Clinical Handbook of Insomnia,* Current Clinical Neurology
Edited by: H.P. Attarian and C. Schuman, DOI 10.1007/978-1-60327-042-7_18,

sleeping reduces sleep drive as eating reduces hunger drive. Independent of this determiner of sleep is the circadian rhythm system. Circadian rhythms (circa = about, dian = a day) refer to the 24-h oscillations in virtually every biochemical, hormonal, and physiological variable including core body temperature, cortisol, melatonin, sleep/wake cycle and sleepiness. An illustration of these rhythms is shown in Fig. 18.1, and indicates the normal relationship between the sleep period and two extensively researched circadian rhythms of core body temperature and melatonin hormone levels. All three rhythms (sleepiness, temperature, and melatonin) as well as almost every other biological and behavioral rhythm are being driven in synchrony by the central body clock, the suprachiasmatic nucleus (SCN). This is a small nucleus in the anterior hypothalamus that receives direct input from the retinas of the eyes [4]. The SCN controls the timing of the melatonin synthesis in the pineal gland [5] which then, through circulating plasma melatonin, feeds back to the SCN helping to maintain circadian rhythmicity [6].

In a controlled, constant environment the circadian rhythms oscillate unabated showing a strong endogenous origin. However, environmental stimuli and our own behavior can influence the timing of the rhythms and are called Zeitgebers or time givers.

Effects of Circadian Rhythms on Sleep

Our circadian rhythms exert a very strong effect on our subjective and objective sleepiness, that is, how sleepy we feel, how quickly we will fall asleep, and how likely we will awake. In a normally entrained person (e.g., someone with normally timed circadian rhythms) the sleep period occurs approximately between 11 P.M. and 7 A.M. Figure 18.1 indicates maximum circadian sleep propensity between 1 and 6 A.M., associated with high melatonin levels and the minimum core temperature (Tmin) [7]. Wake-up time usually occurs soon after the core body temperature begins to rise. Of particular relevance to circadian rhythm sleep disorders are two circadian periods of

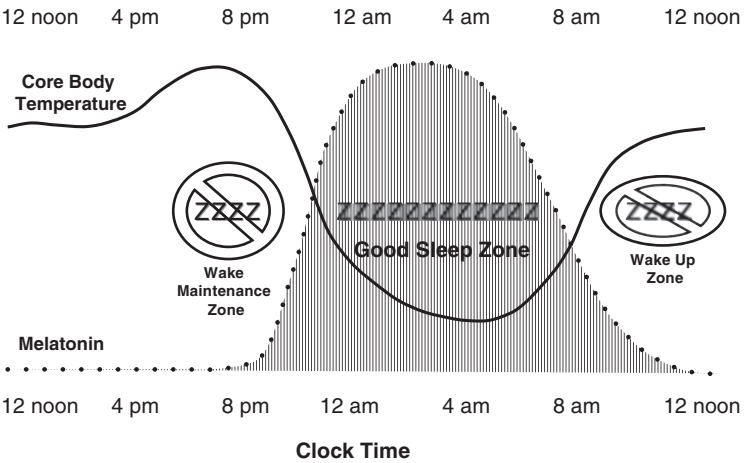

Figure 18.1 Graphical representation of the core body temperature (*solid line*) and melatonin (*dotted line*) rhythms over a 24-h period with the major sleep period indicated by the row of Zs and wake-maintenance and wake-up zones by "*not allowed*" signs over a short row of Zs

sleeping difficulty that surround the sleep-conducive period [8–11]. These are indicated in Fig. 18.1 as the wake-maintenance zone, a 3–4-h period normally between 6 and 10 P.M. when it is difficult to fall asleep and a less intense and longer wake-up zone when it is difficult to stay asleep.

Another important feature of our circadian rhythm is its period length, or time taken to complete one oscillation. Recent research has suggested that the endogenous period length of most young adults is somewhat longer than 24 h and is on an average 24.2 h [12] and considerably longer (over 25 h) for someone with a delayed sleep-phase disorder [13]. The clinical implication is that, in the absence of time cues or other entraining stimuli such as morning light, most young adults will have a tendency for their circadian rhythms to drift later, or phase delay, possibly resulting in sleep difficulty.

Insomnias Related to Circadian Rhythm Mistiming

Disturbances of the relationship between the endogenous sleep–wake rhythm and the preferred sleep–wake pattern within an individual can lead to chronic sleeping difficulties. If individuals have a delayed circadian rhythm but attempt to sleep during the earlier "normal" sleep time, they would be attempting to fall asleep during their evening wake-maintenance zone. Sleep initiation would be inhibited and, if the individual has to adhere to a normal awakening time, for example, to meet social or work obligations, total sleep time would be reduced. Several nights of reduced sleep will result in daytime impairment and distress.

Conversely, some individuals may have an early timed or phase-advanced circadian rhythm resulting in their wake-up zone occurring as early as 3 A.M. and therefore, sleep is curtailed earlier than desired. This also can lead to a reduced total sleep time, distress, and daytime impairment.

Circadian Rhythm Delay in Sleep-Onset Insomnia

The main feature of sleep-onset insomnia is difficulty of initiating sleep at the start of the sleep period. A delayed sleep phase can lead to chronic difficulties falling asleep at night as well as difficulty not being able to awake in the morning at a conventional time. If sleep onset is delayed over many nights and weeks, frustration and anxiety can develop and become associated with bedtime. This will lead to learned or psychophysiological insomnia (see Chap. 11) and contribute to the development of chronic insomnia [2].

There is increasing evidence for a circadian rhythm delay in sleep-onset insomnia. Morris and colleagues [14] found that sleep-onset insomniacs who took longer than 45 min to fall asleep also had a delay of their circadian core body temperature rhythm of approximately 2.5 h later than a control group of good sleepers. They were attempting to fall asleep within their predicted "wake-maintenance zone" in comparison to the control group who had bed times at least 2 h following this zone. More recent evidence supports this finding. In one study, 55% of individuals who experienced sleep-onset insomnia had markedly delayed (>2 h) melatonin rhythms [15]. In another study, sleep-onset insomniacs with average bedtimes at 12:25 A.M. and sleep latency of 60 min had an average melatonin onset at 12:15 A.M., over 3 h later than normal [16]. Therefore, sleep-onset insomnia appears to be associated with a

2–3 h delay of circadian rhythms as well as their associated wake-maintenance zone impairing the initiation of sleep.

Then the attempt to wake in the morning for work or domestic obligations, for example at 7 A.M., would be doubly difficult, because of insufficient sleep and trying to arise at the time of maximum circadian sleepiness, for that phase-delayed individual. In fact, when the opportunity arises, sleeping-in to a late time is made easier because the delayed circadian rhythm will have a delayed wake-up zone that, in this example, would not occur until about midday. However sleeping-in later in the mornings to catch up on lost sleep can further exacerbate the circadian phase delay because the removal of morning light while asleep releases the brakes on the tendency to phase delay [17–19].

Clinical Manifestations

Figure 18.2 shows the sleep pattern of an individual who presented to our clinic with sleep-onset insomnia. On weeknights the person was going to bed between 11:30 P.M. and midnight but taking between 60 and 90 min to fall asleep. Due to study commitments, he set the alarm for 7:30 A.M. and needed to be out of bed by 8 A.M. However, on most occasions he slept through the alarm. When he did get up earlier, he only obtained 5 h sleep. On the weekend, he stayed up on Friday and Saturday nights and slept in very late on Saturday and Sunday mornings. These sleep-ins typically result in greater difficulty falling asleep on Sunday night and difficulty in awaking Monday morning.

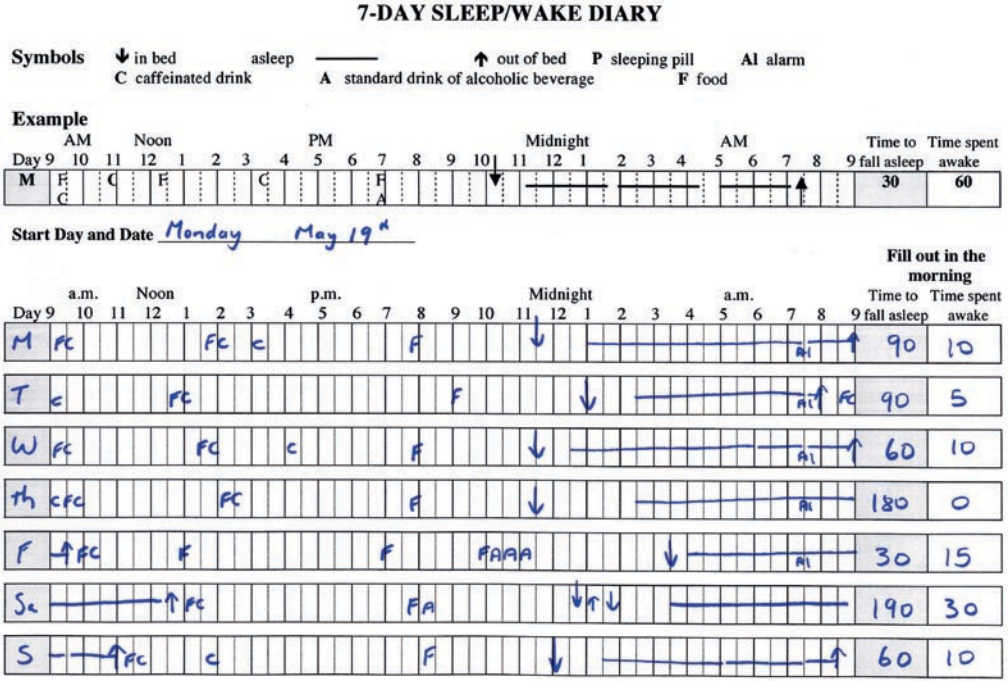

Figure 18.2 Example of a 7-day sleep/wake diary illustrating a typical client with mild-moderate circadian rhythms phase delay who experienced sleep-onset insomnia. Symbols are explained at the top of the diary

Apart from difficulty getting up in the morning, the client was beginning to feel very anxious and restless after going to bed. Individuals with sleep-onset insomnia often report being unable to "switch off" due to a racing mind. They can also feel as though they have lost control over their ability to fall asleep and feel frustrated and/or anxious. Repeatedly experiencing these feelings while attempting sleep can produce a conditioned or learned (psychophysiological) insomnia (see Chap. 11). Management of this type of insomnia will, therefore, require a multifaceted approach.

Circadian Phase Advance in Early Morning Awakening Insomnia

Chronic early morning awakening insomnia has been associated with an advanced circadian rhythm and with wake-up times ranging from 4:29 to 5:53 A.M., and total sleep times reduced to about 5 h [20–23]. Participants also experienced symptoms of daytime tiredness. Circadian rhythm timing of both temperature and melatonin rhythms was found to be advanced with temperature minima between midnight and 2:20 A.M. and urinary dim light melatonin onset (DLMO) ranging from 8:20 to 10:00 P.M. [21–23]. When compared to age-matched control groups, the insomniacs' temperature rhythms were significantly earlier by nearly 4 h and DLMO times earlier by more than 2 h.

Clinical Manifestations

People with chronic early morning awakening insomnia tend to experience overwhelming evening sleepiness and morning awakenings earlier than desired [2]. Although they could fall asleep in the early evening, they usually attempt to delay bedtime to a more socially acceptable time. Despite this, they will still awaken early and be unable to fall back to sleep. The total amount of sleep obtained can then be as little as 5–6 h leading to daytime sleepiness, fatigue, and other symptoms of sleep loss such as impaired motivation and concentration.

Figure 18.3 shows the sleep/wake pattern of a sleep clinic client who experienced early morning awakening insomnia. In the evening she experienced overwhelming sleepiness and, on four evenings, she unintentionally fell asleep briefly in front of the television. After going to bed, she experienced no difficulty falling asleep. However, after only 5– 6 h sleep, she woke and was unable to fall back to sleep. On average, she lay in bed for over an hour before getting up. Again, this can cause anxiety, frustration, and helplessness. During the day she felt fatigued, irritable, and unable to concentrate.

Management

Insomnia associated with delayed or advanced circadian rhythms needs a multifaceted approach combining behavioral, cognitive, and circadian-directed therapies. For those with sleep-onset insomnia and concomitant delayed circadian phase, appropriate treatments would include strategies to advance their circadian rhythms and sleep/wake pattern as well as psychological therapies for possible concomitant psychophysiological insomnia. Similarly, therapies to improve the sleep and daytime functioning of those with early morning awakening insomnia would include strategies to delay the circadian rhythm as well as cognitive behavior therapy.

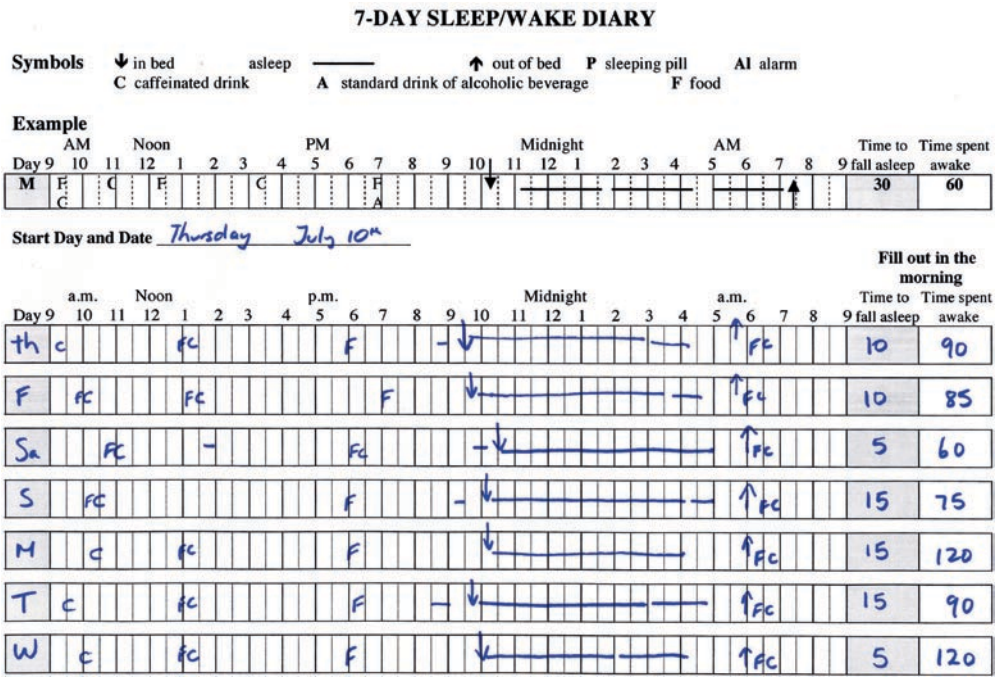

Figure 18.3 Example of a 7-day sleep/wake diary illustrating a typical client with an advanced circadian rhythm who experienced early morning awakening insomnia. Symbols are explained at the top of the diary

Retiming the Circadian Rhythm

The retiming of an individual's circadian rhythm may be achieved via zeitgebers (time givers) such as bright-light and exogenous melatonin or melatonin agonists.

Bright Light

Light entering the eye is the most powerful zeitgeber for retiming circadian rhythms. As a therapeutic tool, the light source may be sunlight or an artificial light device such as a commercially available light box. The timing of the light stimulus is crucial for effective treatment [24–27]. Studies have shown that bright light before the temperature minimum will produce a phase delay and bright light after the temperature minimum will produce a phase advance, that is, a shift to an earlier time. Therefore, bright morning light (after the Tmin) is recommended for those with an abnormally late rhythm and evening bright light (before the Tmin) for those with an early circadian rhythm and sleep pattern.

Morning outdoor light is recommended for those with sleep-onset insomnia. If an artificial light source is needed, broad spectrum white light boxes have been used to retime circadian rhythms. However, more recently it has been shown that shorter wavelength light, (blue–green light between 450 and 525 nm) is the effective part of the white light spectrum [28–30] with one study showing a phase-advancing effect in a group of mildly delayed sleepers [31]. However, clinical studies using these light wavelengths for sleep-onset insomnia have not yet been conducted.

Morning Light Therapy for Sleep-Onset Insomnia

In therapy, we suggest that the bright-light stimulus of about 1-h duration initially be administered immediately after awakening at the unconstrained ad lib wake time. The timing of awakening and the start of bright-light therapy should then be advanced earlier each morning by 15 min until the desired wake-up time has been reached. In our example (Fig. 18.2), the initial light exposure would start at 9 A.M. and then advanced by 15 min each day to the target wake-up time of 7:30 A.M. From our experience [31] we suggest continuing with 30 min of light exposure each morning with light therapy at that target wake time for at least 2 weeks. This will allow time for the apparently slower advancing sleep-onset time to "catch up" and finally result in adequate total sleep time. After therapy we suggest that clients continue to maximize light exposure in the morning, for example, by not wearing sunglasses on their way to work. We also advise dim light and quiet activities in the evening to avoid possible phase-delaying effects of evening bright light.

Evening Light Therapy for Early Morning Awakening Insomnia

Two studies have administered evening bright light to adults experiencing early morning insomnia [32, 33]. In these studies, light was administered for 4 h until midnight or 1:00 A.M. This produced delays in circadian rhythms as well as final wake-up times and increased total sleep time. As a long-lasting therapeutic intervention, we suggest that clients stay up for an hour later than their habitual bedtime with maximum ambient light. If available, an artificial light source of higher intensity would be recommended to achieve quicker results. We advise keeping active in the evening to prevent unintentional napping. We also advocate that clients, in this case, avoid bright morning light and may need to wear dark glasses or blue light blocking glasses if they wish to go outside in the first hours after awakening.

Melatonin

Other zeitgebers that have been shown to phase change circadian rhythms and sleep/wake schedules are exogenous melatonin and more recently melatonin agonists. As with light therapy the timing of melatonin ingestion is important. A recent study [34] suggested that the effects of melatonin administration and bright light are additive. However, to complement the effects of light therapy the timing of Melatonin administration must be 180 degrees or about 12 h different than that of light administration [35]. For phase advancing those with sleep-onset insomnia, melatonin ingestion should be in the evening approximately 4 h prior to the onset of endogenous melatonin or 6 h prior to habitual sleep-onset time [34–37]. For assisting phase delays in early morning awakening insomnia melatonin can be ingested at first awakening during the night [35, 38].

Although exogenous melatonin appears safe with short-term use, there is scant information about its long-term administration [39]. Some adverse side effects that have been reported following melatonin administration include headaches, dizziness, nausea, and drowsiness. [39]

More recently, Melatonin receptor agonists also have been shown to produce a phase change in healthy adults [40–42] and can also decrease sleep-onset

latency in those with insomnia [43–47]. However, their efficacy in treating insomnia associated with circadian rhythm disorders is yet to be evaluated.

Cognitive-Behavioral Therapy

In addition to morning bright-light therapy to address the circadian delay of sleep-onset insomnia it would be efficacious to use Stimulus Control Therapy instructions to address the conditioned insomnia likely to be present with this chronic insomnia [48, 49] (see Chap. 22). This will minimize the amount of time spent awake in bed trying to fall asleep and reassociate the bed with sleep rather than wakefulness and worry. As the circadian rhythm advances, the time of evening sleepiness and sleep onset will also gradually advance. Avoiding sleeping-in by keeping a consistent wake-up time is also necessary to reduce the likelihood of another phase delay.

For those experiencing early morning insomnia, in addition to evening bright-light therapy we suggest including a form of Bedtime or Sleep Restriction Therapy to minimize time in bed awake [50] (see Chap. 22). Staying up an hour later than habitual bedtime to administer evening bright light would be one part of this bed-restriction therapy. In addition, the client should get out of bed after their habitual sleep duration if they have already awoken or get out of bed at their first awakening if that has exceeded their habitual sleep duration. For example, the recommended protocol for our client in Fig. 18.3 would be evening light until 11–11:30 P.M. and "out of bed time" either on awakening if it is later than 5:30 A.M. or at 5:30 A.M. if already awake. Over the week(s), spontaneous wake-up time will get later and total sleep time will increase.

Conclusions

Circadian rhythm phase delays and phase advances are suggested as etiological factors for chronic sleep onset and early morning awakening insomnia, respectively. Circadian rhythm timing can be altered with Zeitgebers such as bright blue/green light or melatonin/melatonin agonists. Morning bright light and evening melatonin can advance or time earlier the circadian rhythms, thus serving as a treatment for the phase-delayed rhythms of sleep-onset insomnia. Evening bright light and morning melatonin administration can phase delay circadian rhythms and thus serve as treatment for early morning awakening insomnia. Because chronic insomnia from any etiological beginnings is likely to be perpetuated by learned or psychophysiological insomnia, treatment needs to be multifactorial and, in this case, include the appropriate cognitive/behavioral therapies.

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19

Insomnia Secondary to Sleep-Related Breathing Disorders

Brooke G. Judd

Abstract

Patients with sleep-disordered breathing, particularly obstructive sleep apnea, may present with insomnia-predominant symptoms rather than classic sleep apnea symptoms. As polysomnography is not typically performed in the evaluation of insomnia, it is the challenge of the clinician to obtain a thorough history to determine if there are other signs or symptoms that may lead one to consider the diagnosis of sleep-disordered breathing in this group of patients. Treatment of concurrent sleep-disordered breathing and insomnia may also pose a challenge, as both disorders may need to be addressed for successful resolution of symptoms.

Keywords: Insomnia, Obstructive sleep apnea, Sleep-related breathing disorders

Sleep-related breathing disorders are frequently associated with insomnia complaints. The sleep-related breathing disorders as defined by the *International Classification of Sleep Disorders*, 2nd edition (ICSD-2) [1] include the obstructive sleep apnea syndromes, central sleep apnea syndromes, and sleep-related hypoventilation/hypoxemia syndromes. Often, patients with sleep-related breathing disorders have more obvious respiratory symptoms (such as loud snoring or observed pauses in breathing) and it is assumed that the insomnia is due to the disrupted sleep precipitated by the underlying breathing disorder. In other cases, however, patients may present predominantly with insomnia symptoms. Polysomnography is not typically indicated in the evaluation of insomnia and thus, one could miss the diagnosis of sleep-disordered breathing, which may affect quality of life as well as potentially increasing long-term medical morbidity.

From: *Clinical Handbook of Insomnia,* Current Clinical Neurology
Edited by: H.P. Attarian and C. Schuman, DOI 10.1007/978-1-60327-042-7_19,

Obstructive Sleep Apnea Syndromes

There has been little research to date that has specifically investigated the link between sleep-disordered breathing and insomnia, although the work that has been done has primarily focused on the associations between obstructive sleep apnea (OSA) and insomnia symptoms. Studies indicate that 40–50% of patients with OSA may present with one or more symptoms of insomnia [2–4]. OSA (and its variants; namely upper airway resistance syndrome) may intuitively be thought of as contributors to poor sleep, as these disorders cause disrupted sleep by definition. In fact, the ICSD-2 lists a patient complaint of insomnia as a possible presenting symptom for OSA [1]. Despite this association, clinicians are typically taught that most patients with insomnia do not need polysomnography. Moreover, the majority of insurance carriers will not pay for a sleep study if it is ordered as part of an insomnia evaluation.

OSA is typically described as a disorder causing excessive daytime sleepiness, although not all patients complain of overt hypersomnia. Often there may only be more vague complaints of fatigue. Furthermore, patients with OSA are typically unaware of their nocturnal respiratory symptoms; rather, bed partners or other observers of the patient's sleep raise suspicion for the disorder. Patients who sleep alone may therefore be less likely to seek evaluation for OSA based on the typical symptoms (such as snoring or observed pauses in breathing), but may seek evaluation of other less specific symptoms such as fatigue or insomnia symptoms.

There also appears to be particular populations of patients prone to complaints of insomnia in association with OSA. In particular, there is evidence of an association of the more subtle forms of sleep-disordered breathing with insomnia symptoms. A number of studies have demonstrated higher rates of insomnia as the presenting symptom in patients with a predominantly upper airway resistance syndrome (UARS) picture and a low apnea–hypopnea index (AHI) [4–7]. Furthermore, patients with UARS and milder forms of sleep-disordered breathing are more likely to present with sleep initiation complaints as well as sleep maintenance complaints, while patients with more overt OSA and concurrent insomnia symptoms are more likely to complain of disrupted sleep and maintenance problems only, with fewer sleep initiation complaints [2, 5].

As women tend to have higher rates of insomnia in general, it is not surprising that it has also been demonstrated that women present with more prominent insomnia symptoms in association with OSA/UARS than men [6, 8].

Another group of patients with obstructive sleep apnea that may be more likely to present with insomnia symptoms are the elderly. Both insomnia and OSA increase in prevalence with advancing age. An early report studying older adults with insomnia symptoms found prevalence rates of OSA ranging from 29–43%, depending on the AHI threshold used to define OSA [9]. A more recent study [10] also found a prevalence rate of 29% in older adults with presenting with insomnia symptoms. Therefore, it may be prudent to have a lower threshold to perform polysomnography on these groups of individuals, despite lack of the more common symptoms of sleep-disordered breathing.

Etiology of Insomnia Symptoms in Obstructive Sleep Apnea

Why do some patients with OSA present with insomnia-predominant symptoms while others do not? As discussed above, patients with OSA are typically unaware of the more specific nocturnal respiratory symptoms. If they do not have someone observing their sleep, they may only be aware of more nonspecific symptoms, such as a sense of poor nocturnal sleep or daytime symptoms. Nonetheless, there appears to be a subset of patients whom have insomnia-predominant symptoms and it remains unclear whether these symptoms are due to the OSA alone or whether these patients are otherwise predisposed to insomnia symptoms.

One of the studies demonstrating higher levels of insomnia in women with OSA also showed the insomnia symptoms were more prominent in women despite similar frequencies of snoring and daytime hypersomnolence complaints between both the men and women enrolled in this study [8], contributing further evidence that it is not simply the sleep-disordered breathing causing the insomnia complaints.

Given that insomnia symptoms are a prevalent complaint in psychiatric disorders, it is not surprising that patients with OSA presenting with insomnia-predominant symptoms are more likely to have concomitant psychiatric disorders and/or cognitive-emotional symptoms. What is less clear is whether the insomnia symptoms are related to the OSA only and the mood symptoms are simply a result of chronic, unrecognized sleep-disordered breathing causing poor sleep or whether the population of OSA patients presenting with insomnia-predominant symptoms are also independently at risk for mental illness and/or insomnia.

One study did try to identify different subtypes of insomnia associated with OSA by comparing multiple sleep latency test (MSLT) results between OSA patients with predominant sleep-onset insomnia complaints versus those with predominant sleep-maintenance complaints [4]. This study found that those with predominant sleep initiation symptoms had significantly reduced propensity to fall asleep during the MSLT and reported lower subjective sleepiness scores. The authors postulated that this subset of patients were in a state of hyperarousal, suggesting that their insomnia symptoms were not simply related to the OSA.

It is becoming increasingly clear that insomnia and obstructive sleep apnea have a more complex relationship than previously thought, and in fact, it may be worthwhile to consider their relationship a “two-way street.” Studies done in patients with PTSD and insomnia symptoms have shed some light on this model of a complex sleep disturbance. In these studies, patients with PTSD and insomnia symptoms have demonstrated a higher than expected prevalence of sleep-disordered breathing. In this model, it is speculated that both pathological processes (i.e., the hyperarousal due to PTSD as well as the sleep-disordered breathing) contribute to sleep fragmentation. The sleep fragmentation, in turn may worsen obstructive respiratory events and cause further sleep fragmentation and insomnia symptoms by allowing for more airway instability which is seen in lighter sleep stages and sleep–wake transitions. Additionally, the poor quality of sleep these patients experience

can worsen the insomnia-based symptoms by contributing further to anxiety associated with sleep. Although this model was initially hypothesized in relation to patients with PTSD, it is certainly possible that it could extend to patients with chronic insomnia due to other causes, including psychophysiological insomnia. Thus, insomnia of any etiology may play a role in worsening sleep-disordered breathing by the effect of hyperarousal on upper airway stability. The resulting respiratory events can then aggravate the insomnia symptoms by contributing to the sleep fragmentation.

Another consideration in the relationship between insomnia and sleep-disordered breathing is the effect of sedative-hypnotic medications in exacerbating any underlying breathing disturbance. In particular, the benzodiazepines, not uncommonly prescribed for insomnia, have the potential to cause upper airway instability and lead to obstructed breathing due to their muscle relaxant properties on the upper airway musculature.

OSA Treatment and Insomnia

Just as the relationship between insomnia and sleep-disordered breathing can be considered a two-way street, the same can hold true for the treatment of these disorders [11, 12]. There is evidence that treating the breathing disorder alone may improve the insomnia [13, 14], although these studies also demonstrated that the addition of cognitive behavioral therapy aimed at improving any component of psychophysiologic insomnia provided the greatest degree of improvement of insomnia symptoms. Conversely, patients who are predisposed to insomnia, particularly those with prominent sleep-onset symptoms, may have more difficulty tolerating treatment with continuous positive airway pressure (CPAP) therapy. It may be necessary to also consider at least a trial of hypnotic therapy in these patients to help improve adherence to the CPAP therapy. The nonbenzodiazepine benzodiazepine receptor agonists (BzRA), may be a good choice for this group of patients. This group (zaleplon, zolpidem, and eszopiclone) have the same hypnotic effects of the nonselective BzRA's; however, they too have fewer muscle relaxant properties that can exacerbate sleep-disordered breathing. Isolated studies with each of these medications have not indicated any worsening of OSA [15–17]; however, there has been little research in this area and caution is advised in using any medications that may have muscle relaxant properties. There is very little information available as well regarding the safety of other sedating medications in OSA, although one recent study has demonstrated the safety of ramelteon, a selective melatonin-receptor agonist in patients with mild-to-moderate obstructive sleep apnea [18].

Insomnia Associated with Other Forms of Sleep-Disordered Breathing

Breathing abnormalities other than OSA may be seen during sleep and may also be associated with insomnia symptoms. For example, the central sleep apneas (including Cheyne-Stokes breathing seen most frequently with advanced congestive heart failure) are often associated with complaints of fragmented sleep. There have been no direct studies specifically addressing

whether suppressing the central respiratory events improves sleep quality. Furthermore, one of the largest trials evaluating positive pressure therapy treatment for heart patients with central sleep apnea did not demonstrate any improvements in quality of life in patients treated with CPAP therapy, despite significant declines in the apnea–hypopnea index [19]. Too little work has been done in this area to come to any firm conclusions regarding the etiology of the disturbed sleep and whether treating the breathing disorder improves subjective sleep complaints.

Another major category of sleep-disordered breathing includes the sleep-related hypoventilation/hypoxemia syndromes. As with the central sleep apnea syndromes, there has been very little work looking at associations of these disorders with insomnia. Theoretically, hypoventilation syndromes could contribute to some degree of sleep fragmentation due to arousals related to hypoxemia and/or hypercapnia, although there is not enough information available to determine if this is a clinically significant contributor to insomnia symptoms.

Insomnia Associated with Chronic Obstructive Pulmonary Disease

Although chronic obstructive pulmonary disease (COPD) is not defined as sleep-disordered breathing, per se by the ICSD-2, patients with COPD may have significantly impaired ventilation during sleep as well as a high frequency of insomnia symptoms. As COPD is one the most common underlying lung diseases one would encounter in clinical practice, it is worthwhile to address the interaction of COPD and insomnia in this chapter.

Multiple studies have noted a high frequency of insomnia complaints in patients with COPD [20–25]. In addition to higher frequency of subjective sleep complaints, patients with COPD have been found to have decreased total sleep time, increased arousals and decreased REM sleep, compared with matched controls without COPD [20, 26]. The etiology of the sleep architecture abnormalities and subjective complaints is likely multifactorial: typical daytime symptoms of COPD such as cough, excessive mucus production and breathlessness may also occur during sleep and cause sleep disruption. The alveolar gas exchange abnormalities associated with COPD are accentuated during sleep, during which time the normal ventilatory responses to hypercapnia and hypoxemia are blunted. During REM sleep, the ventilatory responses are blunted even further. Sleep-related hypoxemia has been postulated as a contributing factor to the poor sleep quality, as one study did correlate arterial oxygen desaturation with sleep fragmentation, particularly during REM sleep [20]. It is not clear however, that oxygen supplementation improves objective or subjective sleep abnormalities [20, 27].

Medications used to treat COPD may also contribute to insomnia complaints and poor quality sleep. In particular, theophylline and the inhaled beta agonists have stimulant properties which could affect sleep quality. Alternatively, the inhaled anticholinergic agent, ipratropium bromide has been shown to improve sleep quality in patients with COPD, perhaps related to improved respiratory status [28].

Patients with COPD may also have coexistent sleep apnea (also known as the Overlap Syndrome). The reported incidence of concurrent sleep apnea

in patients with COPD varies: earlier studies estimated the prevalence at approximately 10–15%, which is higher than expected in a normal population of the same age [29–31]. More recently, it has been determined that the prevalence of OSA is not higher in patients with (mild) COPD than in a comparable group of patients without COPD [32]. Therefore, the appearance of COPD and OSAS in one individual (overlap syndrome) may appear by chance without any pathophysiologic linkage. Patients with overlap syndrome had more severe desaturations during sleep and worse sleep quality than patients with only one of these disorders [32]. This too may contribute to sleep disruption in COPD and measures aimed at addressing sleep apnea may also help to improve sleep quality in these patients.

Treatment of Insomnia in COPD

Treating insomnia in patients with COPD is similar to treating insomnia in the general population, although with a few considerations. First, as noted above some of the medications used to treat COPD may contribute to sleep disruption and may present obstacles to treatment. It may be possible to alter the timing of the more stimulating medications so that they are less likely to interfere with sleep. Identifying and treating any concurrent sleep apnea is also an important consideration. CPAP therapy is an appropriate treatment option in patients with overlap syndrome, although in some patients it can lead to increased lung volumes with resultant worsened hyperinflation and ultimately worsening ventilation due to further compromises in respiratory muscle function [33]. In these patients, bilevel positive airway pressure may be a better option, as this therapy can treat the OSA as well as improve ventilation in patients with COPD [34].

Medical treatment of insomnia in patients with COPD is also an option, although again with some special considerations. Benzodiazepines are commonly prescribed for insomnia, although they may pose additional risk in patients with COPD. A large number of studies [35] have reviewed the effects of the benzodiazepines on respiratory function in both normal individuals as well as those with COPD, with variable results. Most though not all studies demonstrated detrimental effects on a variety of respiratory parameters in patients with and without lung disease. Studies have been performed with the nonbenzodiazepine BzRA zolpidem [36–38], suggesting that there is not a significant impairment in respiratory parameters when administered to patients with COPD, although there are overall few studies thus results must be interpreted cautiously. It remains reasonable to recommend that these medications may be used with caution in patients with underlying respiratory abnormalities, although the nonbenzodiazepine BzRA's may be a better choice than standard benzodiazepines in this population. Recent studies have demonstrated the safety of ramelteon in patients with mild-to-moderate as well as severe COPD [39, 40], although there is little information on the use of other designated sedative-hypnotics in this specific group of patients.

Conclusion

Insomnia is not an infrequently presenting symptom in patients with sleep-disordered breathing. It is important to obtain a careful history that may lead one to assess further with polysomnography for sleep-disordered breathing, as

patients presenting with insomnia may not have the classic signs or symptoms of sleep-disordered breathing, In particular, patients with milder forms of sleep-disordered breathing, women, and the elderly are more prone to present with insomnia which may improve with treatment of the underlying respiratory impairment. Patients with insomnia and sleep-disordered breathing may also face other challenges in treating their concurrent disorders, benefiting from other standard approaches to insomnia treatment such as behavioral therapy or medications along with treatment of the sleep-disordered breathing.

Finally, patients with COPD pose a unique group of patients, with a high prevalence of insomnia complaints. Their insomnia is likely multifactorial and may be related to the disease process and medications as well as concurrent sleep apnea. There are some special considerations in this group, particularly with the use of positive pressure therapy for treatment of OSA and with medication choices.

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20

Insomnia as a Presenting Symptom of Sleep-Related Movement Disorders, Hypersomnias and Parasomnias

Keith J. Nagle

Abstract

Insomnia can be considered as a symptom and as a diagnosis. A number of sleep disorders have insomnia as a principle presenting symptom. A careful history is needed to assess for the presence of coexisting sleep disorders in patients complaining of poor sleep quality.

In this chapter, we will explore the clinical features of three common neurologically based sleep disorders that may have insomnia as a presenting feature: restless legs syndrome (RLS), narcolepsy with or without cataplexy, and parasomnias.

Several medications used to treat insomnia may exacerbate the patient's RLS and paradoxically worsen their insomnia. Montplaiser drew attention to the severe sleep disruption in persons with narcolepsy; findings included an increased number of awakenings, increased wake time after sleep onset, and increased time in stage I sleep. These findings have been replicated to varying degrees in a number of other studies.

Finally, the coexistence of several sleep problems is more often the rule than the exception. Patients with multiple components to their impaired sleep quality are common and each may need to be addressed to optimally help these patients.

Keywords: RLS, Narcolepsy, Sleep disturbances, Parasomnias, Antidepressants, Trazodone, Benzodiazepines

Introduction

Insomnia can be considered as a symptom and as a diagnosis. A number of sleep disorders have insomnia as a principle presenting symptom. A careful history is needed to assess for the presence of coexisting sleep disorders in patients complaining of poor sleep quality.

From: *Clinical Handbook of Insomnia,* Current Clinical Neurology
Edited by: H.P. Attarian and C. Schuman, DOI 10.1007/978-1-60327-042-7_20,

In this chapter, we will explore the clinical features of three common neurologically based sleep disorders that may have insomnia as a presenting feature: restless limb syndrome, narcolepsy with or without cataplexy, and parasomnia.

Restless Limb Syndrome

The syndrome of RLS was initially coined by Ekbom in 1945 [1]. The four cardinal features are a desire to move the limbs (akathesia), usually caused by uncomfortable sensations (dysesthesia), with symptoms worse at rest and relieved by movement, and symptoms worse in evening [2] (Table 20.1).

Prior to the media and pharmaceutical company popularization of this condition in the early part of this decade, it was uncommon for a patient to present with symptoms of restless limb syndrome. More commonly a patient would present with insomnia, typically sleep-maintenance insomnia.

Many patients do not bring up their prominent limb dysesthesias for reasons that may include an insidious onset of their RLS symptoms over many years, a lack of understanding of how the seemingly disparate limb dysesthesias might contribute to their sleep complaint, and fear that the leg symptoms were a sign that "they were going crazy."

Support of the above clinical generalizations can be found in the study by Banno et al. [3]. They investigated the delay in diagnosis and presenting symptoms in 218 patients determined to have RLS and referred to their sleep clinic in Manitoba, Canada. Of 218 patients, 39% of men and 46% of women had a chief complaint of insomnia. The duration of this symptom was 11 years. Similar findings were reported by Bjorvatn et al. in their epidemiological study of RLS in Scandinavia [4]. Let us hope that as a medical community we are improving upon these results.

Many patients with RLS will have sleep-onset insomnia related to limb dsyesthesia and akathesia related to the inactivity of bedtime. Another presentation, possibly related to the slowly progressive chronic partial sleep-deprivation elicited by this illness, the patient may have short sleep-onset latency. However, after satisfying their core sleep requirement in the first 3–4 h of sleep, periodic limb movements that had not elicited arousals early in the sleep period begin to produce arousal. These mid-sleep period arousals may be short or can be longer. A characteristic feature is a tendency for the patient to get out of bed, often with trips to the bathroom or kitchen. The patient will not necessarily report RLS symptoms at this time.

Several medications used to treat insomnia may exacerbate the patient's RLS and paradoxically worsen their insomnia. These agents include those with anticholinergic properties (tricyclic antidepressants, diphenhydramine) and serotoninergic agents (SSRIs). Trazodone, one of the leading agents to treat insomnia in the USA, tends to have little efficacy for the insomnia of RLS. Clonazepam and other GABA agonists may partially help RLS-induced insomnia but typically have only a mild effect. In addition, tachyplaxis often develops with benzodiazepines and may necessitate increasing doses of medicine with minimal response and an aggravation of the chronic partial sleep deprivation. In the case of clonazepam, the long half-life could lead to increased somnolence and possibly traffic accidents during peak morning commuting hours. Further complicating the insomnia and RLS would be a compensatory use of caffeinated agents or other stimulants that exacerbate the RLS.

Table 20.1 Diagnostic Criteria for RLS.

Key RLS diagnostic criteria	Supportive features
□ Urge to move the legs – usually accompanied or caused by uncomfortable leg sensations	□ Sleep disturbances Involuntary leg movements
□ Temporary relief with movement – partial or total relief from discomfort by walking or stretching	□ Positive family history for RLS
□ Onset or worsening of symptoms at rest or inactivity, such as when lying or sitting	□ Positive response to dopaminergic therapy
□ Worsening or onset of symptoms in the evening or at night	

One should also consider that leading theories concerning the genesis of chronic insomnia often start with an inciting period of insomnia. RLS can be such an inciting agent and lead to the emergence of a coexisting insomnia in addition to continued RLS symptoms. Treatment with behavioral interventions may be of benefit [5].

Fortunately, the clinician who considers the diagnostic possibility of RLS in patients presenting with insomnia can uncover this diagnosis with targeted questioning. Many reviews on the clinical diagnosis, investigations, and treatment options of RLS have recently been published [6–8]. In brief, the interview and examination confirm the diagnosis of RLS and suggest possible secondary etiologies, such as peripheral neuropathy. Diagnostic testing is largely directed toward excluding common secondary causes of RLS. These conditions include pregnancy, anemia, iron deficiency, hypothyroidism, and diabetes. Common screening laboratory studies include a cell count, ferritin, TSH, and fasting glucose level or glycosylated hemoglobin measurement. The presence of neuropathy, a suggestion of renal insufficiency, or myelopathy would lead to evaluation of these disorders.

The treatment of RLS first addresses sleep hygiene and dietary provoking factors, namely caffeine. A medication review is needed to identify agents that might cause or exacerbate RLS. Currently, selective dopamine agonists are the most commonly used first line agents in treating RLS. Gabapentin, due to its relatively benign side effect profile, particularly at bedtime, is favored by some. A number of other medications have been used with benefit to treat this condition as discussed in several recent reviews [6, 7, 9].

In a seemingly perpetual cycle, RLS may precipitate chronic insomnia in patients so predisposed to this latter condition. Thus, focus on sleep hygiene issues may be important for these patients. In addition, other sleep disorders can cause or exacerbate RLS. If persistent RLS symptoms continue despite treatment or excessive daytime somnolence (EDS) is present, one may need to consider polysomnography to identify coexisting sleep disorders.

Narcolepsy with or Without Cataplexy

The hallmark symptom of narcolepsy is EDS. EDS combined with phenomena related to REM dysregulation – cataplexy, hypnagogic hallucinations,

and sleep paralysis – form the diagnostic tetrad initially proposed by Yoss and Daly in 1957 [10]. The coexistence of cataplexy in a person with EDS is highly supportive of the diagnosis. Confirmation can include a polysomnogram with multiple sleep latency test to exclude coexisting sleep disorders and to document sleep-onset REM periods. The human leukocyte antigen subtype DQB1*0602 is often present and 90% have a low hypocretin level in the cerebrospinal fluid.

It may seem surprising to find this diagnosis discussed in a book on insomnia. However, sleep fragmentation is a frequent finding and many have suggested disturbed nocturnal sleep as the fifth component of the narcolepsy tetrad. Thus, those with narcolepsy are not the sleepy bears seen in cartoons that, when finally able to take rest, hibernate in a deep sleep. Quite the opposite can be the case.

Most of the data concerning nighttime sleep in narcoleptics were obtained over 20 years ago. Montplaiser drew attention to the severe sleep disruption in persons with narcolepsy at the First International Symposium on Narcolepsy [11]. Findings included an increased number of awakenings, increased wake time after sleep onset, and increased time in stage I sleep. These findings have been replicated to varying degrees in a number of other studies.

Zorik et al. [12] found a high number of awakenings from nocturnal sleep (25.4 per night), similar to that of persons with sleep-disturbed breathing (36.4), and far more frequent than those with other causes of daytime sleepiness (10.8). The majority of the awakenings in narcolepsy were over 30 s. Sleep efficiency was also decreased.

Browman et al. [13] compared sleep patterns in 11 persons with narcolepsy compared with 11 controls using polysomnography over two consecutive nights. They found an increased number of arousals >2 min in patients with narcolepsy relative to controls (6.5 vs. 2.7 and 4.7 vs. 1.5 awakenings, respectively).

In a review of baseline PSG in 312 narcolepsy-cataplexy subjects who were HLA DQB1*0602 positive, the percent awake during sleep was 17% and the sleep interruption severity score was elevated. Less prominent abnormalities were present in all narcolepsy patients [14].

More recently the mechanisms underlying light sleep of patients with narcolepsy have been reported by Khatami et al. [15]. In the setting of sleep deprivation, persons with narcolepsy have improved intensity of nonREM sleep during the recovery night and their REM onset latency is longer. At baseline these subjects had decreased sleep intensity and, as is typical of narcolepsy, REM onset periods. These findings suggest that the lower sleep intensity (as measure by delta power of EEG) contributes to the frequent nocturnal awakenings in persons with narcolepsy and contributes to early onset REM periods. Further, their work also shows that patients with narcolepsy have the capacity to increase their sleep intensity.

All of these studies suffer from small numbers and being unblinded and most are largely descriptive.

Regrettably, persons with narcolepsy are symptomatic for several years prior to the correct diagnosis. This delay is in part related to the manifestations of this disorder developing over many years. Further, many patients develop only subtle or incomplete components of the narcolepsy tetrad. Diagnosis entertained prior to narcolepsy includes depression in 17% and over 40% have

symptoms of depression and/or anxiety [16, 17]. In the initial years prior to a correct diagnosis of narcolepsy, a diagnosis of insomnia could mistakenly be entertained. However, my review of studies describing initial misdiagnosis in persons presenting with narcolepsy did not yield a false diagnosis of insomnia. Undoubtedly, a diagnosis of sleep-maintenance insomnia secondary to depression likely occurs in some patients with undiagnosed narcolepsy. A careful sleep history should avoid diagnostic missteps.

A final consideration regarding insomnia and narcolepsy involves the occurrence of insomnia as a complication of stimulant therapy.

Parasomnia

Parasomnias are a group of related sleep disorders that feature a disordered arousal or semi-arousal from sleep. Several types of parasomnia may produce insomnia including sleep walking (somnambulism), night terror (parvor nocturna) nightmare, and REM sleep behavior disorder. The fear, either of self-injury during the events or due to their frightful nature, can lead to sleep avoidance or highly fragmented sleep. Insomnia related to these events can be worse if there is a coexisting history of abuse or panic disorder [18].

In a study by Barry Krakow [19], the significance of nightmares in patients presenting for treatment of a sleep problem was dramatically highlighted. In 718 patients presenting to two sleep treatment facilities in Albuquerque, New Mexico, 186 subjects ranked a nightmare complaint among their sleep problems. Of these, 117 linked their nightmares to disrupted sleep. Insomnia severity was markedly elevated relative to a control group without nightmare.

Summary

Insomnia may be due to or exacerbated by a number of neurologically based sleep disorders. A careful sleep history that includes a review of sleep symptoms should allow identification of these patients. Those with restless limb syndrome often will present with sleep-onset or sleep-maintenance insomnia. Those with parasomnia are typically easily identified once the patient shares the occurrence of these events. The difficulty with sleep fragmentation due to narcolepsy is essential to optimally treating this group of patients. Though unlikely a common presentation, the slowly evolving presentation of persons with narcolepsy may lead to an early misdiagnosis of depression-related insomnia. Finally, the coexistence of several sleep problems is more often the rule than the exception. Patients with multiple components to their impaired sleep quality is common and each may need to be addressed to optimally help these patients.

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21

Insomnia and Pain Disorders

Catherine C. Schuman and Melissa M. Clark

Abstract

During the past decade there has been an increasing interest on the impact and interaction of pain and sleep disturbance. This chapter will present an overview of the growing literature on pain and insomnia, as well as a brief review of cognitive behavioral treatment options. In the United States, 15-20% of the population experiences acute pain and 25-30% experiences chronic pain. Almost a third adults experience at least one symptom a few nights or more per week according to the National Sleep Foundation's 2005 Sleep in America poll

It has been conservatively estimated that 28 million Americans experience sleep complaints in the context of a chronically painful condition.

The pathophysiology of either condition and especially the comorbidity of the two have been poorly studied so have therapeutic interventions.

Given the immense impact of sleep and pain on individual's and society, there is a need to further understand and explore the pathways of sleep disturbance and pain.

Keywords: Pain, Cognitive behavioral therapy, Insomnia, Pain medications

Introduction

Pain and insomnia have become two of the most common symptoms reported by primary care patients. Most patients reporting pain, particularly chronic pain also report some form of sleep disruptions. With up to fifty percent of patients experiencing some form of pain and/or insomnia each year there is now a clinical priority to address and treat these symptoms and their impact on quality of life.

From: *Clinical Handbook of Insomnia,* Current Clinical Neurology
Edited by: H.P. Attarian and C. Schuman, DOI 10.1007/978-1-60327-042-7_21,

Definition

As defined by the International Association for the study of pain, pain is an "unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage [1]." It is a biological signal providing information that allows one to survive and protect against damage. It can be caused by a host of acute and chronic medical conditions including, burns, headaches, arthritis, fibromyalgia, muscle ache, and back pain.

Insomnia is a disruption in sleep that is defined as difficulty initiating and/or maintaining sleep or the complaint of nonrestorative sleep, which causes clinically significant distress, or impairment in functioning [2]. The disruption can be caused by psychiatric disorders, medical disorders, developmental disorders, sleep disorders, environmental factors, and medication reactions.

Epidemiology

In an US annual estimate, 15–20% of the population experiences acute pain and 25–30% experiences chronic pain [3]. Over 4 billion work days are lost and hundreds of billions of dollars are spent on health care per year due to pain. Given the significant impact of pain on patient's and society, it becomes paramount that we understand the factors that lead to and amplify the pain experience. Sleep is one factor that has received a lot of attention recently.

Insomnia is a common and growing complaint in the general population with 33–54% of adults reporting the experience of one symptom a few nights or more per week night according to the National Sleep Foundation's 2005 Sleep in America poll [4]. Despite the prevalence of insomnia in the general population, it is under-recognized in medical settings and the majority of patients remain untreated [5]. Of note, women are 1.5 times more likely than men to experience insomnia when using full diagnostic criteria [6].

Insomnia is not always uniquely identified in the literature and is generally combined into the category of sleep disruption which includes nonrestorative sleep and other primary sleep disorders. There is limited but growing epidemiological information on the prevalence of insomnia and comorbid pain. In clinical samples, sleep disruption has been found to impact 50–88% of patients experiencing a pain condition [7–12]. Pain may be a biological signal, but sleep is a biological essential and given persistent deprivation or disruption, will become nonnegotiable. Microsleep which occurs when sleep becomes nonnegotiable is believed to be responsible for many auto and industrial accidents.

It has been conservatively estimated that 28 million Americans experience sleep complaints in the context of a chronically painful condition [13].

Both pain and sleep disruption have been associated with psychiatric morbidity [14, 15], medical morbidity [16], disability [17, 18], and quality of life [19]. Given the impact of having a pain or sleep condition, it appears that we have only begun to explore the complex relationship of having both and their indirect sequela.

Diagnostic Issues

Because pain and sleep disruption are both complex and clinically challenging symptoms, it is important for us to better understand their pathways in order to develop the most effective treatments. While exploring the literature about sleep and pain it is important to first understand how each is measured. The gold standard for measuring sleep is a polysomnogram which produces objective information about time spent in each stage of sleep, number and length of awakenings, and provides specific information necessary to identify and differentiate sleep disorders. Polysomnography is expensive and important in diagnosing several sleep disorders, but not necessary to measure insomnia and consequently not regularly used when measuring sleep disruption associated with pain in research. Actigraphy is less costly and is considered an objective measure of sleep, which provides information on sleep onset, duration, and number and length of awakenings, but does not differentiate sleep stages and unfortunately has not frequently been used to measure sleep in association with pain. Most studies have relied on a retrospective self-report measure of sleep because they are the least expensive and most easily used method for patients. Typically, a daily sleep log which is kept by the patient, measures time to fall asleep, time sleeping, number and length of awakenings, naps, and daytime sleepiness.

Pain is primally measured using self-report. Unlike sleep, pain is almost always subjectively measured. Pain experience is a subjective experience that is most validly measured using self-report.

Pathophysiology

The pathophysiology of insomnia is not well-understood and there is no current pathophysiological hypothesis that fully explains how sleep impacts pain. There has been mixed evidence from investigations wishing to identify a causal model of how sleep disruption impacts pain experience. Perhaps one of the most identified explanations for how sleep impacts pain was developed by Moldofsky and his colleagues. The early theory postulated that alpha–delta sleep fragmentation explained nonrestorative sleep patterns [20] and was responsible for the musculoskeletal pain experienced by patients with fibrositis, a chronic pain syndrome [21]. This theory dominated the literature with small and uncontrolled samples for many years. These findings have not been replicated in more recent controlled studies [22, 23]. In addition, Mahowald and Mahowald pointed out in their 2000 review, that if sleep fragmentation caused musculoskeletal or fatigue symptoms then one would expect to find a higher incidence of pain symptoms in patients who have obstructive sleep apnea disorder because of its fragmented sleep [24]. This review also highlights the problematic nature of associating restorative or nonrestorative sleep with musculoskeletal pain and or fatigue syndromes because the only organ system of the body known to benefit from sleep is the brain.

Other theories have been postulated, but none have fully explained the complex interactions of the sleep and pain pathways. One such theory is that in the face of acute and chronic pain, there is an over activation of the stress response via the hypothalamic–pituitary–adrenal axis which leads to insomnia

[25, 26]. There are two brief, but interesting introductions to the neurobiology of pain and sleep, the first can be found in the 2000 review of sleep disturbance and nonmalignant chronic pain by Menefee et al., and the second in the 2005 review of the interactions of sleep and pain by Roehrs and Roth [27, 28].

Although no models have been identified to understand the pathways between sleep disruption and pain, there is a consistent literature describing a correlational relationship and an emerging literature on the bidirectional relationship between pain and sleep disturbance. Clinical studies have consistently shown that pain is associated with reduced sleep quality, including longer time to sleep onset, reduced total sleep time, and more frequent and longer awakenings [12, 29–32]. Currently, the literature is spotlighting the impact of sleep disturbance on pain and the bidirectional relationship. Studies can generally be categorized into cross-sectional or longitudinal studies and are either disease specific or general in scope.

If you are seeking information on a specific pain condition, there are two comprehensive reviews regarding sleep and specific pain conditions. The first, by Roehrs and Roth, 2005, discusses the sleep disturbances found in different acute and chronic pain conditions [28] and the second, by Menefee et al., 2000, reviews the literature on a broad range of nonmalignant chronic pain conditions, as well as comorbid primary sleep disorders and mood disturbances. Whether it is from more global assessments of pain or for specific pain conditions, there has been a consistent pattern of research with evidence that sleep disturbance is associated with pain severity [8–10, 12, 33, 35].

Therapeutic Concerns

Recently, there has been a shift to identify sleep as the variable that can be treated or modified in order to decrease the impact of sleep on pain. While attempting to find modifiable risk factors for postoperative pain, Wright et al., 2009, look at disrupted sleep the night before breast surgery [33]. They assessed 24 patients scheduled for routine breast-conserving surgery and found that patients with the lowest sleep efficiency experienced significantly heightened levels of pain over the week following surgery. This is the first study to document significant adverse effects of sleep disruption on subsequent acute pain in a clinical setting. Of note, this study also found no relationship between sleep duration and postoperative pain, which is consistent with the Smith et al., 2007, findings that sleep disruption, may have a more profound effect on pain than sleep deprivation [34].

In another attempt to find modifiable risk factors that lead to or magnify the pain experience, Edward et al., 2008, were the first to do a microlongitudinal study using the general population [36]. They utilized data from a naturalistic, telephone study using a representative national sample of 971 adults. Participants completed daily assessment of hours slept and reported frequency of pain symptoms over a 1-week period. Results indicated that hours of reported sleep on the previous night were highly significant in predicting the next day's pain frequency. Of interest, the results also indicated a curvilinear prospective association of sleep duration with subsequent daily pain reports and those obtaining either less than 6 or more than 9 h of sleep experienced greater next day pain.

There appears to be sufficient support that the impact of sleep and pain is bidirectional. Given the bidirectional nature of pain and sleep, when a patient presents with one symptom it may improve outcome if we assess for the other and administer the appropriate treatments. There is a limited but growing body of literature assessing the best treatments for comorbid sleep disruption and pain. In a world of evidence-based treatment, there are currently no evidence-based guidelines for the treatment of comorbid sleep disruption and pain. There is more evidence for a host of pharmacological and nonpharmacological treatments that have been found useful for managing pain and disrupted sleep independently, and it is likely that a combination of the treatments will be helpful. For a more comprehensive review of the medical and pharmacological treatments of sleep disruption and pain you may find several relatively recent reviews helpful [27, 28, 37]. Pharmacological treatments are often the first line of treatment used when patients present with pain or insomnia. However, for insomnia, cognitive–behavioral treatments have been shown to have comparable effects to medical interventions in the short term and substantially better effects over time [38–40]. For the purposes of this chapter, we will focus on a review of the psychological and cognitive–behavioral approaches of treatment for comorbid sleep disruption and pain.

Cognitive–behavioral treatments can include the use of a myriad of techniques to improve sleep including sleep restriction, stimulus control, sleep hygiene, diaphragmatic breathing and relaxation training, hypnosis, and cognitive therapy. In individualized combinations, these treatments are effective in addressing the complex factors of the 3 P's model; the predispose, precipitate, and perpetuate factors of insomnia [8].

There appear to be only two case studies and two randomized clinical trials that have assessed cognitive behavioral treatments in the context of sleep disruption and pain. The two case reports, by Morin and his colleagues, utilized a multiple baseline design to assess the impact of sleep restriction and stimulus control treatments focused on treating insomnia in patients experiencing pain [41, 42]. Both case reports supported the use of treating insomnia secondary to pain using sleep restriction and stimulus control and one showed long-term gains during a 2 and 6-month follow-up assessment.

The first randomized clinical study by Currie, Wilson, Pontefract, and deLaplante 2000, assessing cognitive–behavioral treatment for insomnia in the context of pain consisted of 60 heterogeneous chronic pain patients with chronic insomnia [43]. Treatment consisted of a 7-week individual treatment program that included stimulus control, sleep restriction, sleep hygiene, and relaxation training to better manage their sleep symptoms. Participants were randomly assigned to either an immediate treatment or a waitlist control condition. Sleep was measured via sleep diaries and actigraphy. After receiving cognitive behavioral treatment for sleep, significant improvements were found for sleep latency, wake after sleep onset sleep efficiency and sleep quality, and for the most part maintained at the 3-month follow-up.

The second and more recent randomized clinical trial assessed the impact of behavioral insomnia therapy for fibromyalgia (FM) patients. Edinger, Wohlgemuth, Krystal and Rice, 2005 compared cognitive–behavioral treatment with an alternate behavioral treatment and usual care for improving sleep and other fibromyalgia symptoms. The sample consisted of 47 FM patients with chronic insomnia complaints and compared CBT, sleep hygiene and

usual FM treatments alone. Sleep was assessed via sleep logs and actigraphy, while questionnaires measured global insomnia symptoms, pain, mood, and quality of life. Participants that received CBT reported a 48% reduction in total wake time, while participants who received sleep hygiene treatment reported a 20% reduction and those who received the other or unusual FM treatments only reported a 3.5% reduction in total wake time. Using their adopted strict improvement criterion for sleep, 57% of the CBT recipients showed improvements, while only 17% for the sleep hygiene recipients and 0% for the other or unusual treatment. In general, the CBT also showed benefits over the other treatments for insomnia symptoms, and for improving subjective mental well-being and mood.

Conclusion

Given the immense impact of sleep and pain on individuals and society, there is a need to further understand and explore the pathways of sleep disturbance and pain. The time has come to expand our use of experimental methods with more rigorous methods, using larger sample sizes to better understand how we can improve treatment options. The literature is promising, but it is important to identify more tailored treatment approaches to specific pain conditions with an emphasis on improving sleep disruption.

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Part V

Treatments

22

Cognitive-Behavioral Therapy for Insomnia

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Abstract

The most common cognitive-behavioral therapies for primary insomnia are: sleep hygiene education, stimulus control, sleep restriction, relaxation training, and cognitive therapy out of which stimulus control therapy is the most well validated and is considered "the gold standard" for the behavioral treatment of insomnia. In practice, most behavioral sleep medicine clinicians adopt a multicomponent approach which usually contains stimulus control, sleep restriction, and sleep hygiene therapy. Adjunctive interventions include phototherapy, relaxation therapy, and cognitive restructuring. CBT can be combined with pharmacological methods, but it has been shown more effective than medication on the long term.

Keywords: Cognitive-behavioral therapy, Cognitive restructuring, Relaxation therapy, Phototherapy, Stimulus control, Sleep hygiene, Sleep restriction consolidation

In the present chapter, we will provide an overview of how primary insomnia is assessed and treated using cognitive-behavioral treatments. In addition, we provide some (1) "upfront" information which reviews the cognitive and behavioral theories regarding the etiology of chronic insomnia and (2) some "follow-up" information of the efficacy of CBT for insomnia. The former is provided so that the reader may appreciate the principles on which CBT is founded. The latter is provided so that the reader may appreciate the extent to which CBT for insomnia has been empirically validated.

Theoretical Perspectives on Insomnia

Behavioral perspective: Since the late 1980s, insomnia has largely been conceptualized from within a behavioral framework. The original model was proposed by Spielman et al. and it continues to be the leading theory for both Sleep Medicine and the subspecialty area of Behavioral Sleep Medicine [1].

From: *Clinical Handbook of Insomnia,* Current Clinical Neurology
Edited by: H.P. Attarian and C. Schuman, DOI 10.1007/978-1-60327-042-7_22,

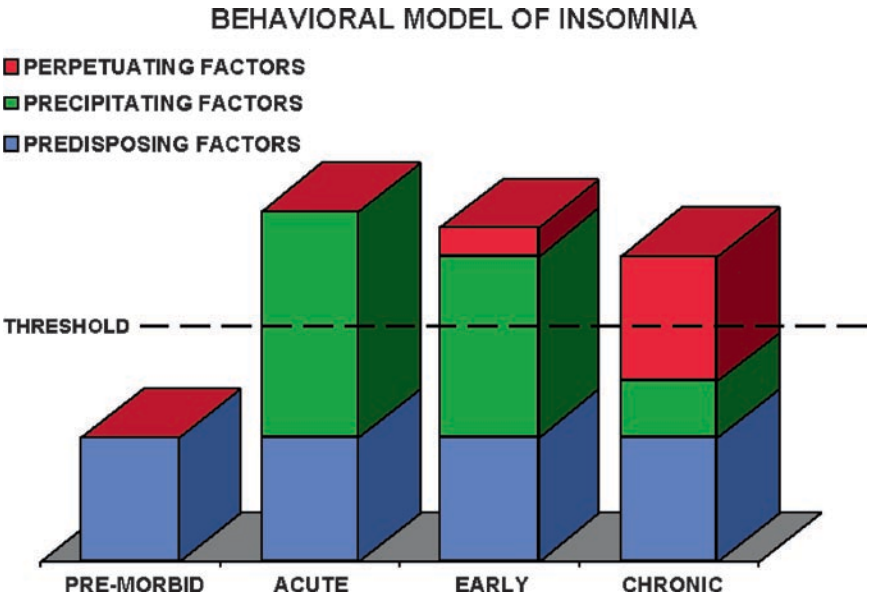

Figure 22.1 A schematic of the differential diagnosis process for the Dx of primary insomnia

As illustrated in Fig. 22.1, the behavioral model posits that insomnia occurs acutely in relation to both predisposing (trait) and precipitating (state) factors and occurs chronically in relation to perpetuating or maintaining factors. Thus, an individual may be prone to insomnia due to trait characteristics, experience acute episodes because of precipitating events, and have chronic insomnia owing to a variety of perpetuating factors.

With respect to trait factors, personality characteristics [2, 3], physiologic arousal [2, 3], and genetic predisposition [4], are each thought to contribute to predispose the individual to acute episodes of insomnia. Typical precipitating events (which represent stressors within the larger stress diathesis model of disease) include situational stress [5], acute injury or pain, bereavement, etc. Perpetuating factors, as the term implies, maintain the chronic form of the disorder even after the precipitating events have either been stabilized or resolved. Perpetuating factors are any of a variety of compensatory strategies in which the patient engages in an attempt to cope with insomnia symptoms. Typical examples of such factors include: excessive daytime napping, extending sleep opportunity, keeping variable sleep–wake schedules, using alcohol as a hypnotic, spending excessive time awake in bed, diminishing daily activity level due to fatigue, etc.

Central to the behavioral model of chronic insomnia is the role of classical conditioning as the primary maintaining factor. It is hypothesized that, over time, insomnia becomes a conditioned response to the bed and bedroom environment. This process presumably occurs via traditional principles of classical conditioning, due to repeated parings of the bed and bedroom (conditioned stimuli) with states of psychophysiologic hyperarousal (unconditioned stimuli) that are thought to interfere with the normal biologic processes of sleep initiation and maintenance.

Cognitive perspective: A number of authors have stressed the importance of cognitive factors in primary insomnia (e.g., [6–8]). Given their emphasis on the role of cognition, they and others have developed interventions, which provide for the cognitive component of the more broad-based cognitive-behavioral approach. Within this perspective, two related types of cognitions are thought to be operational: one set is related to the patient's beliefs about their disorder; the other set is related to cognitive processes like intrusive thoughts and worry.

Morin et al., for example, have found that patients with primary insomnia have a number of maladaptive beliefs about sleep, including unrealistic views about what constitutes adequate sleep and catastrophic beliefs about the consequences of insomnia. Such beliefs presumably contribute to insomnia via (1) increasing sleep-related performance anxiety and (2) by prompting and promoting maladaptive compensatory behaviors. Support for the role of such factors derives from data showing that successful cognitive-behavioral treatment of insomnia is associated with a reduction in negative beliefs and attitudes about sleep [9, 10]. While this is suggestive, more work is needed to demonstrate the "insomnogenic" potential of such cognitions. This is so, because one can easily imagine that successful therapy may change one's thoughts and beliefs, but also that such changes may not be responsible for the treatment gains.

Hall et al. and Harvey and Payne have focused more on cognitive process (vs. content) issues. Central to this area is that patients with insomnia often complain that they are unable to sleep because of intrusive thoughts or excessive worry. These thoughts and images are characterized as being "intrusive" and may occur in isolation or as unwanted perseverative-type problem solving (worry). The content of the "thoughts and worry" may be centered on the kind of dysfunctional attitudes and beliefs described above, but they are often more general in content. The ideation and imagery that occurs as intrusive thoughts is often related to mundane daily activities and/or work or relationship issues. As with dysfunctional attitudes and beliefs, intrusive thoughts and perseverative thinking (from within the radical cognitive perspective) are thought to be responsible for the occurrence and severity of insomnia. The more moderate view is that these phenomena are, along with behavioral and conditioning factors, contributory.

Support for the cognitive perspective comes from a variety of studies which have found that patients with primary insomnia complain of higher levels of presleep rumination compared with normal controls (e.g., [11, 12]). Investigations of presleep thought content have found that the presleep cognitions of patients with primary insomnia tend to be more negatively toned, and that patients report increased general problem solving and thoughts pertaining to environmental stimuli at or around sleep onset (e.g., [13–15]).

Neurocognitive perspective: In sharp contrast to the cognitive model, the neurocognitive perspective all but suggests that dysfunctional beliefs and worry are epiphenomena. It is posited that cognitive factors are likely to mediate the occurrence and severity of insomnia when the disorder is acute. When, however, the disorder is chronic, cognition occurs secondary to conditioned arousal. Put differently, patients with chronic insomnia are not awake because they are given to rumination and worry, but rather ruminate because they are awake.

The neurocognitive perspective [3] is an extension of the traditional behavioral model. As laid out by Spielman et al. [1], the behavioral model allows

for a compelling conceptualization regarding how maladaptive behaviors lead to conditioned arousal and chronic insomnia. The Spielman model does not, however, spell out what the conditioned arousal is, or why and how "arousal" interferes with sleep initiation and/or maintenance and/or the perception of sleep. These latter issues are precisely the province of the neurocognitive model which defines "arousal" as conditioned cortical arousal. This form of arousal may be observed in patients with primary insomnia as high-frequency EEG activity (14–45 Hz) at or around sleep onset and during NREM sleep [16]. High-frequency EEG activity, it is hypothesized, allows for abnormal levels of sensory and information processing and long-term memory formation. Increased sensory processing is thought to interfere with the ability to initiate sleep (as measured by traditional PSG measures). Increased information processing during PSG-defined sleep is thought to interfere with the subject's ability to perceive PSG sleep as "sleep." Increased long-term memory formation (attenuation of the normal mesograde amnesia of sleep) is thought to interfere with the patient's morning judgments about sleep quality and quantity.

Support for the neurocognitive perspective [17] comes from a variety of studies which have found Beta EEG (14–45 Hz) to (1) be elevated in patients with insomnia [16, 18–21], (2) be positively associated with patient perceptions of sleep quality [3, 22], (3) be positively associated with sleep state misperception (the degree of discrepancy between subjective and objective measures of sleep) [16, 23], and (4) vary with successful CBT treatment for insomnia [24]. There is also preliminary evidence that the occurrence of elevated NREM Beta activity is sensitive and specific to primary insomnia (vs. insomnia secondary to major depressive disorder) [16] and data which suggest the long-term memory function at peri-sleep-onset intervals is altered in patients with chronic insomnia [25].

Assessment and Measurement

Self-report assessment: Behavioral Sleep Medicine specialists often utilize a number of retrospective assessment tools to gather more precise diagnostic information. In addition, Behavioral Sleep Medicine specialists utilize daily sleep diaries (e.g. [26]) to prospectively monitor sleep complaints. Prospective assessment is important for (1) evaluating the severity of insomnia complaints on a day-to-day basis, (2) identifying the behaviors that maintain the insomnia, (3) determining to what extent circadian dysrhythmia is present, and (4) gathering the data needed to measure and guide treatment response.

The sleep component of sleep wake diaries is typically completed after waking and obtains information on: time to bed, wake time, sleep latency (SL), frequency of nightly awakenings (FNA), wake time after sleep onset (WASO), total sleep time (TST), early morning awakenings (EMA), medication/substances taken before bed, and subjective assessments of sleep quality. The daytime measures, which are completed prior to going to bed include: nap frequency and duration, fatigue ratings, stimulant consumption, and medication usage.

Objective assessment: In current clinical practice, the diagnosis of primary insomnia does not require an in-laboratory, polysomnographic (PSG) study to substantiate the diagnosis. This is true for three reasons. First, there is enough of a general correspondence between the subjective complaint and objective measures, that PSG assessment is not required to verify the sleep

continuity disturbance. Second, traditional polysomnography does not reveal, or allow for the quantification of, the underlying sleep pathophysiologies that presumably give rise to the patient's complaints. Third, and most pragmatically, third party payers will not reimburse for sleep studies on patients with likely primary insomnia. Sleep studies are, however, indicated if the patient demonstrates symptoms consistent with other intrinsic sleep disorders and/or fails to respond to treatment.

When assessed with polysomnography, patients with primary insomnia reliably exhibit increased SL, increased FNA, increased wake after sleep-onset time, and decreased total sleep relative to good sleeper controls. PSG findings, however, do not correspond in a one-to-one fashion to patient perceptions of sleep continuity. Patients with insomnia routinely report more severe sleep disturbance than is evident on traditional PSG measures [27–29]. Some have argued that this discrepancy might be explained by the findings that patients with primary insomnia show a greater degree of psychopathology, including tendencies to somatize internal conflicts and exaggerate symptoms (e.g., [30–32]). Others have argued that the subjective–objective discrepancy findings reflect a cardinal feature of the disorder, that is, the persistence of sensory and information processing into NREM sleep. The continuance of such processes into PSG-defined sleep is thought to be the basis for patient difficulties distinguishing between wakefulness and sleep [3]. The extent to which one or both of these factors contribute to the discrepancies between subjective and objective measures of sleep in insomnia continues to be a matter of on-going debate. (For additional information on these issues, please see the following section on the cognitive-behavioral perspective on insomnia.)

When polysomnography is not feasible, the use of alternative, less costly objective devices can be particularly helpful when the clinician suspects a high degree of sleep state misperception. Sleep state misperception is a term (as well as disorder) used to describe the common finding among patients with insomnia that there is a discrepancy between a patient's subjective impression of sleep parameters and what is measured via objective recording methods. At the level of self-report, extreme values (gathered retrospectively or prospectively) may suggest that this is a component of the disorder (e.g., sleep latencies of greater than 2 h, wake after sleep onset of greater than 2 h or a TST of equal to or less than 4 h). In the absence of a PSG study, actigraphs may be used to obtain corroborating prospective data. Actigraphs are wristwatch like devices that utilize sophisticated movement detectors to estimate the traditional sleep continuity parameters (e.g., SL, WASO, FNA, and TST). This information may, in turn, be compared with the self-report data to assess the degree to which sleep state misperception is occurring. The extent to which subjective/objective discrepancies can be resolved using actigraphy has not been subjected to empirical validation. In our clinical practice, however, we have found that actigraphy can be used to assess for sleep state misperception.

Cognitive-Behavioral Treatment

The most common cognitive-behavioral therapies for primary insomnia are: sleep hygiene education, stimulus control, sleep restriction, relaxation training, and cognitive therapy. For a detailed explanation of each of these therapies the reader

is referred to a book by Charles Morin entitled, "Insomnia: Psychological Assessment and Management" [6].

Of all the available psychological treatments, stimulus control therapy is the best validated and is considered "the gold standard" for the behavioral treatment of insomnia. In practice, most behavioral sleep medicine clinicians adopt a multicomponent approach which usually contains stimulus control, sleep restriction, and sleep hygiene therapy.

Therapeutic Regimen

The Cognitive-Behavioral Treatment of insomnia generally requires 4–8 weeks time with once a week face-to-face meetings with the clinical provider. Sessions range from 30 to 90 min depending on the stage of treatment and the degree of patient compliance. Intake sessions are usually 60 to 90 min in duration. During this session, the clinical history is obtained and the patient is instructed in the use of sleep diaries. No intervention is provided during the first week. This time frame is used to collect the baseline sleep wake data that will guide treatment for the balance of therapy. The primary interventions (stimulus control and sleep restriction) are deployed over the course of the next one to two, 60-min sessions. Once these treatments are delivered, the patient enters into a phase of treatment where TST is upwardly titrated over the course of the next two to five visits. These follow-up sessions require about 30 min unless additional interventions are being integrated into the treatment program or extra effort is required to gain the patient compliance. Adjunctive treatments include cognitive therapy, relaxation training, and relapse prevention.

First Line Interventions

Stimulus control therapy: Stimulus control therapy (SCT) is recommended for both sleep initiation and maintenance problems. The therapy is generally considered to be the first-line behavioral treatment for chronic primary insomnia because it has the most research support [33]. Stimulus control instructions limit the amount of time patients spend awake in the bed/bedroom, and are designed to decondition presleep arousal and reassociate the bed/bedroom environment with rapid, well consolidated sleep. Typical instructions include: (1) keep a fixed wake time 7 days per week, irrespective of how much sleep you got during the night; (2) avoid any behavior in the bed or bedroom other than sleep or sexual activity; (3) sleep only in the bedroom; (4) leave the bedroom when awake for approximately 15–20 min; (5) return only when sleepy. Some clinicians, in an effort to prevent "clock watching" behavior, encourage patients to leave the bedroom as soon as they feel "clearly awake" or experience annoyance and irritation over the fact that they are awake. The combination of these instructions reestablishes the bed and bedroom as strong cues for sleep and entrains the circadian sleep-wake cycle to the desired phase.

Sleep restriction: Sleep restriction therapy (SRT) is recommended for both sleep initiation and maintenance problems. The therapy requires patients to limit the amount of time they spend in bed to an amount equal to their average TST. To accomplish this, the clinician works with the patient to (1) establish a fixed wake time and (2) decrease sleep opportunity by limiting the subject's time in bed (TIB) to an amount that equals their average TST as ascertained

by baseline sleep diary measures. Once a target amount of TIB is set, the patient's bedtime is delayed to later in the night so that the TIB and average TST are the same. Initially, this intervention results in a reduction in TST, such that the patient gets less total sleep than they are accustomed to. This controlled form of sleep loss usually corresponds to a decrease in SL and wake after sleep-onset time. Thus, during the acute phase of treatment, the patient gets less sleep, but sleeps in a more consolidated fashion (i.e., they fall asleep more quickly and stay asleep for longer periods of time). The increase in consolidated sleep is formally represented as sleep efficiency (TST/TIB).

The patient's sleep efficiency is monitored on a weekly basis. If the patient's average weekly sleep efficiency reaches 85–90% (depending on age), then the patient's sleep opportunity is incrementally increased by 15 min. The increase in sleep opportunity is accomplished by having the patient retire 15 min earlier for the next week of treatment. The upward titration process is usually continued for about 4 weeks, thus allowing for an increase of about 1 h in sleep opportunity. When the patient does not reach the 85–90% bench mark, some clinicians reduce the total sleep opportunity to the previous "set point," others maintain the subject's total sleep opportunity until adequate sleep efficiency is observed, while still others combine these approaches. With respect to the last possibility, the clinician may maintain the subject's total sleep opportunity for 2–3 weeks and then downwardly titrate the TIB when there is clear evidence that the patient cannot sustain their clinical gains.

This therapy is thought to be effective for two reasons. First, it prevents the patient from coping with their insomnia by extending sleep opportunity. This strategy, while increasing the opportunity to get more sleep, produces a form of sleep that is shallow and fragmented. Second, the initial sleep loss that occurs with SRT is thought to increase the "pressure for sleep" which in turn produces quicker sleep latencies, less wake after sleep onset, and more efficient sleep.

Three points merit further comment. First, total TIB is manipulated by phase delaying the patient's sleep period. This, along with keeping a fixed wake time, results in sleep restriction. It is plausible, however, that total TIB could be altered by having the subject wake up at an earlier time. This approach is not adopted for the following reasons: fixing "wake up time" at an early hour:

- Does not capitalize on the fact that extending wakefulness is easier to tolerate than curtailing sleep
- Delays the initial increase in time awake before sleep for 24 h (and thus delays the clinical effect)
- May reinforce the tendency for EMA
- Undermines the opportunity to pair "sleep" with the bed/bedroom

Second, it should be noted that SRT has a couple of paradoxical aspects to it. One paradox is that patients who report being unable to sleep are in essence being told to sleep less. The other paradox occurs over the course of treatment. With therapy, patients find that it is difficult to stay awake until the prescribed hour. This, if not paradoxical, is at least ironic for the patient that initially presents with sleep-onset difficulties. Finally, it should be noted that Sleep Restriction may be contraindicated in patients with histories of mania or seizure disorder, because it may aggravate these conditions.

Adjunctive Interventions

Sleep hygiene education: Sleep hygiene education is recommended, along with SRT and STC, for both sleep initiation and maintenance problems. It may also have some value as a means toward increasing TST. Sleep hygiene education addresses a variety of behaviors that may influence sleep quality and quantity. The intervention most often involves providing the patient with a handout and then reviewing the items and the rationales for them. Table 22.1 contains a

Table 22.1 Sleep hygiene instructions.

1. *Sleep only as much as you need to feel refreshed during the following day*. Restricting your time in bed helps to consolidate and deepen your sleep. Excessively long times in bed lead to fragmented and shallow sleep. Get up at your regular time the next day, no matter how little you slept.
2. *Get up at the same time each day, 7 days a week*. A regular wake time in the morning leads to regular times of sleep onset, and helps to set your "biological clock."
3. *Exercise regularly*. Schedule exercise times so that they do not occur within 3 h of when you intend to go to bed. Exercise makes it easier to initiate sleep and deepen sleep.
4. *Make sure your bedroom is comfortable and free from light and noise*. A comfortable, noise-free sleep environment will reduce the likelihood that you will wake up during the night. Noise that does not awaken you may also disturb the quality of your sleep. Carpeting, insulated curtains, and closing the door may help.
5. *Make sure that your bedroom is at a comfortable temperature during the night*. Excessively warm or cold sleep environments may disturb sleep.
6. *Eat regular meals and do not go to bed hungry*. Hunger may disturb sleep. A light snack at bedtime (especially carbohydrates) may help sleep, but avoid greasy or "heavy" foods.
7. *Avoid excessive liquids in the evening*. Reducing liquid intake will minimize the need for nighttime trips to the bathroom.
8. *Cut down on all caffeine products*. Caffeinated beverages and foods (coffee, tea, cola, chocolate) can cause difficulty falling asleep, awakenings during the night, and shallow sleep. Even caffeine early in the day can disrupt nighttime sleep.
9. *Avoid alcohol, especially in the evening*. Although alcohol helps tense people fall asleep more easily, it causes awakenings later in the night.
10. *Smoking may disturb sleep.* Nicotine is a stimulant. Try not to smoke during the night when you have trouble sleeping.
11. *Do not take your problems to bed.* Plan some time earlier in the evening for working on your problems or planning the next day's activities. Worrying may interfere with initiating sleep and produce shallow sleep.
12. *Train yourself to use the bedroom only for sleeping and sexual activity.* This will help condition your brain to see bed as the place for sleeping. Do *not* read, watch TV, or eat in bed.
13. *Do not try to fall asleep.* This only makes the problem worse. Instead, turn on the light, leave the bedroom, and do something different like reading a book. Do not engage in stimulating activity. Return to bed only when you are sleepy.
14. *Put the clock under the bed or turn it so that you cannot see it.* Clock watching may lead to frustration, anger, and worry, which interfere with sleep.
15. *Avoid naps.* Staying awake during the day helps you to fall asleep at night.

Author's note: The above list includes the usual practices described as "good sleep hygiene," but it also includes some principles subsumed under "Stimulus Control therapy" (#2,12,13), "Sleep Restriction Therapy" (#1,2,15), and "Relaxation" (#11,13)

set of Sleep Hygiene Instructions. It should be noted that in this formulation, several aspects of other therapies are adopted. For example, items 1, 2, 12, 13, and 15 are traditionally considered part of Stimulus Control and/or SRT.

Sleep hygiene education is most helpful when tailored to a behavioral analysis of the patient's sleep wake behaviors. The tailoring process allows the clinician (1) to demonstrate the extent to which they comprehend the patient's individual circumstances (by knowing which items do and do not apply), (2) to show his or her to the rules, which are in many ways too "absolutistic." Let us consider two examples: command of the clinical literature when explaining the various and sundry "imperatives," and (3) the opportunity to suggest modifications:

- The admonishment to avoid caffeinated products may be, in general, too simply construed. Caffeinated beverages may be used to combat daytime fatigue (especially during acute therapy) and, if the withdrawal is timed correctly, may actually enhance the subject's ability to fall asleep.
- The prohibition against napping may not be practical. Elderly subjects or subjects with extreme work performance demands may indeed need to compensate for sleep loss. A more considerate approach to napping may entail taking into account the time of the nap, the duration of the nap, and how nocturnal sleep is handled on days when subjects nap. Napping earlier in the day will allow for more homeostatic pressure for nocturnal sleep. Limiting the duration of the nap will allow for less of a discharge of the homeostat and enhance the subject's sensation of feeling rested from the nap (by avoiding awakening from slow wave sleep). Going to bed later, when one naps during the day, may minimize the effects of the nap on nocturnal sleep.

Finally, it can be argued that the most important aspect of sleep hygiene education derives not so much from the "tips" provided, but from allowing the clinician the opportunity to demonstrate their knowledge. A thoughtful and elaborate review may enhance the patient's confidence in their therapist and in the treatment regimen. Such enhanced confidence may, in turn, lead to greater adherence/compliance with the more difficult aspects of therapy.

Cognitive therapy: Several forms of cognitive therapy for insomnia have been developed. Some have a didactic focus [6], others use paradoxical intention [34], others employ "distraction and imagery" [35], and still others use a form of cognitive restructuring [36]. While the approaches differ in procedure, all are based on the observation that patients with insomnia have negative thoughts and beliefs about their condition and its consequences. Helping patients to challenge the veracity of these beliefs is thought to decrease the anxiety and arousal associated with insomnia. The cognitive restructuring approach, adapted from for the procedure used for panic disorder [37–39], is illustrated below.

Cognitive restructuring focuses upon catastrophic thinking and the belief that poor sleep is likely to have devastating consequences. While psychoeducation may also address these kinds of issues, the more important ingredient of cognitive restructuring lies not in disabusing the patient of erroneous information, but rather in having them discover that their estimates are ridiculously inaccurate (a testament to the tendency to think in less than clear terms in the middle of the night). When undertaking this exercise with a patient, it needs to be introduced in a considerate way, one which avoids any hint that the therapist is being pedantic, patronizing, or condescending.

The following are examples of the catastrophic thinking that occurs when the patient is lying in bed trying to sleep. "If I don't get a good night's sleep,

I'll be in a bad mood tomorrow. If my mood is poor tomorrow, I will – yet again – be short with my wife. If I'm irritable with my wife (again), she may start thinking about not putting up with this anymore. If she thinks about not putting up with this anymore, she'll consider leaving me..." [get divorced].

I won't be able to stay awake or concentrate when I'm driving to work. If I don't stay awake or concentrate when I'm driving, I may get into an accident..." [wreck the car].

I won't be able to function tomorrow at work. If I am not able to function at work, I may get a reprimand. If I get reprimanded... " [get fired].

The first step in the cognitive restructuring process is to have patients discuss and make a list of the kinds of negative things they think can happen when their sleep is poor. Usually, the list is constructed with the patient and placed on the cognitive therapist's ever present in-office chalkboard. Column one is the list of catastrophic events. Please note that the patient may need to be prompted to identify the underlying and most catastrophic thought. For example, he/she may say "I worry about not being able to fall sleep" when what he/she is primarily worried about is the extreme version of this proposition: spending the entire night awake.

Once the list is compiled (5–10 things constitutes a reasonable list), patients are then asked how likely they think each of the events are, given a night of poor sleep. For instance, the therapist may ask "When you are lying in bed imagining being so tired tomorrow that you might perform badly at work, at that moment how certain are you that your work will be 'substandard', how certain are you that you'll be 'reprimanded,'" etc. These data are represented in column two. Next, the patient is asked how frequently their sleep is poor, and for how many years they have been suffering from insomnia. This number is coded as the "number of days with insomnia" and is set to the side of the table (to be coded later in column 3). The final data needed from the patient is an estimate of how frequently each of the catastrophic events has occurred. These are coded into the fourth column. The combination of these four sources of data is then used to show the patient that there is a substantial mismatch between their degree of certainty and the number of times the negative events have actually transpired.

For example, the clinician might observe, "You have suffered from insomnia for five nights a week for the last three years. This means that you have had about 800 really bad nights. You also said that when you're thinking about what might happen if you don't fall asleep, you are 90% certain that on the next day you are going to perform so badly that you'll be reprimanded. If it happened 90% of the time and you've had 800 bad nights, then you should have been reprimanded about 700 – let's say 500 – times." These data are represented in column five. The last column of data is then compared with the list in column four, so that the patient can see the mismatch between the number of instances that should have occurred and the number of instances that actually occurred, in reality. For an example of the chart described above, see Table 22.2.

Number of days with insomnia 800

Relaxation training: Different relaxation techniques target different physiological systems. Progressive muscle relaxation is used to diminish skeletal muscle tension [40–44]. Diaphragmatic breathing is used to make respiration

Table 22.2 Cognitive restructuring.

1	2	3	4	5
Event	Certainty when lying awake and unable to sleep	# days with insomnia	# of event occurrences	# of event occurrences given certainty
Get reprimanded	90%	800	5	620 (500)
Get fired				
Get divorced				
Wreck the car				
Be awake all night				

slower, deeper, and mechanically driven from the abdomen as opposed to the thorax. (It is interesting to note that this form of respiration resembles what occurs naturally at sleep onset.) Autogenic training focuses on increasing peripheral blood flow by having subjects imagine, in a systematic way, that each of their extremities feels warm.

Most practitioners select the optimal relaxation method based upon which technique is easiest for the patient to learn and most consistent with how the patient manifests arousal. Like cognitive techniques, learning to effectively use relaxation training often requires substantial practice. Many clinicians recommend the patient rehearse the skill during the day in addition to practicing prior to sleep. When integrating into stimulus control instructions, if relaxation training causes some initial "performance anxiety," it may be best to have the patient practice in a room other than the bedroom. It also should be borne in mind that some patients, especially those with a history of panic disorder, may experience a paradoxical response to relaxation techniques.

Phototherapy: While many may not consider phototherapy a behavioral intervention, the use of bright light is often important to integrate into the treatment regimen. This is especially true when circadian factors appear to substantially contribute to the insomnia complaint. There is substantial empirical evidence that bright light has sleep-promoting effects.

In the case where the patient's insomnia has a phase delay component (i.e., the patient prefers to go to bed late and wake up late), bright light exposure in the morning for a period of 30 min or more may enable them to "feel sleepy" at an earlier time in the evening. In the case where the patient's insomnia has a phase advance component (i.e., the patient prefers to go to bed early and wake up early), bright light exposure in the late evening/early night may enable them to stay awake until a later hour. Phototherapy is often accomplished via a "light box" which typically generates white light or more selectively blue spectrum light at 5,000–10,000 lux. The dose is adjusted by altering the distance and duration of light exposure. It is generally assumed that phototherapy has no significant side effects, but this is not always the case. Mania may be triggered by bright light, but rarely, if ever, in patients not previously diagnosed with bipolar mood disorder. Other side effects are insomnia, hypomania, agitation, visual blurring, eye strain, and headaches. Light boxes may not be recommended for individuals with certain eye conditions, including retinopathy secondary to diabetes. In some cases, equivalent or better phase shifting

properties may be accomplished by scheduling time outdoors by taking early morning walks, for example.

The sleep-promoting effects of bright light may occur via several mechanisms, including shifting the circadian system, enhancement of the amplitude of the circadian pacemaker, promoting wakefulness during the day and sleep at night, or indirectly, via its antidepressant effects.

Complicating factors: There are a number of potential complicating factors that require continuous monitoring and evaluation throughout the course of treatment, particularly if the patient fails to show expected clinical gains after 2–4 sessions of active treatment. The most common complicating factors are poor treatment compliance, issues related to comorbid psychiatric and medical disorders, and the simultaneous use of sedative hypnotics.

Treatment compliance: The single most important complicating factor is poor treatment compliance. At the beginning of treatment, the clinician should proactively address the fact that the prescriptions may seem counterintuitive and that adhering to the treatment will be difficult. Providing the patient with a complete and thoughtful rationale for each aspect of the treatment, managing the patients expectations, and encouraging an active self-management approach are essential. Providing the rationale for treatment is likely to gain compliance in at least two ways. First, the effort to explain therapy is less imperative, and thereby makes the patient an active partner in the treatment process and less resistant or reactive to the prescriptions. Second, a fluid, interesting, and compelling explanation will support and enhance the patient's perception of the clinician as a competent authority.

With respect to expectation, patients should not anticipate that the results will be immediate. In fact, patients should be cautioned that their sleep problem is likely to briefly "get worse before it gets better." Sometimes an appeal to the research literature, demonstrating that treatment gains are maintained and often continue to improve in the long-term, may help maintain their motivation despite the short-term difficulty adjusting to the procedures.

With respect to "active self management," it is important to remember that the treatment alternative is medication and that this requires very little in the way of life-style change. Thus, the clinician must spend a considerable amount of time working with the patient to "make and stay with the investment."

Comorbity of mental and medical disorders: Many patients with chronic insomnia report mild or subthreshold levels of depressive symptoms. When depressive symptoms become severe, they may interfere with the patient's ability and motivation to successfully follow the recommended protocol. If medical factors become exacerbated, expectations for clinical gains need to be tempered until there is stabilization. Throughout the course of treatment both medical and psychiatric factors should be monitored and consideration given for the need for further evaluation and intervention.

CBT & sedative hypnotics: Not yet addressed is the possibility of using sedative hypnotics acutely, along with cognitive-behavioral treatment for insomnia (i.e., dual or combined therapy). This is a promising and under-investigated area of inquiry. Initial studies were mixed [45–47], but promising work continues [48]. The benefit of combined therapy is a more rapid reduction of symptoms. The risk of combining pharmacotherapy with behavioral treatment, however, is that once patients start using medications, they may be less inclined to adopt or tolerate the behavioral interventions. Work is ongoing

to determine the most effective way to combine these two strategies to capitalize on the immediate reduction in symptoms afforded by sedative hypnotics and the long-term efficacy of cognitive-behavioral treatment [49].

Perhaps more important than the issue of combined therapy to the practice of CBT for insomnia is that many of the patients referred for cognitive-behavioral treatment have been taking sedative hypnotics for years and are very apprehensive about discontinuing treatment. Often the initial phases of treatment involve collaboration with the referring physician to assist the patient in the weaning process. Use of sleep diaries to provide feedback about sleep continuity during the withdrawal process and education about rebound insomnia and the medication itself are important for this kind of intervention. It should be noted that the chronic use of sedative hypnotics often leaves the patient with as poor a sleep continuity profile as if no medications at all were being used (cites). This is difficult for the patient to appreciate because of the rebound insomnia that occurs during the withdrawal period. As noted previously in this chapter, the natural assumption during the withdrawal from medication is "This is how I will sleep without medications from now on." In combination with a careful weaning process, sleep diaries may serve as the "hard data" to demonstrate to the patient that this assumption is not true.

The Efficacy of Cognitive-Behavioral Treatment

There are, however, a variety of studies that attest to the efficacy of behavioral treatments for primary insomnia. These studies have been reviewed in two meta-analyses [50, 51]. Results from the two quantitative reviews are as follows: 32–41% global improvement in sleep following behavioral treatment where SL was reduced by 39.5–43% (effect sizes: 0.87–0.88), number of intermittent awakenings was reduced by 30–73% (effect sizes: 0.53–0.63), duration of intermittent awakenings was reduced by 46% (effect size: 0.65) and TST increased by 8–9.4% (effect size: 0.42). In actual minutes, pre-post measures revealed that patients fell asleep 24–28 min sooner, had 0.5–1.2 fewer awakenings and obtained about 30–32 more minutes of sleep a night. Comparative data showed that SRT or stimulus control yielded the greatest improvement, followed by multicomponent therapies. Treatment gains were maintained or enhanced over follow-up periods ranging from 3 weeks to 3 years. In addition to these data, there is now a study by Morin et al. which suggests that behavior therapy yields, during acute treatment, comparable results to pharmacotherapy for insomnia and that behavior therapy has better long-term efficacy [50]. A study by our group [52] confirms this finding in a comparative meta-analytic study and extends it by demonstrating that during acute treatment behavior therapy yields results comparable with those of pharmacotherapy and may provide superior results for sleep-onset problems.

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23

Pharmacological Treatment of Insomnia

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Abstract

Drugs currently used for the treatment of insomnia include benzodiazepine receptor agonists (BzRAs), a melatonin receptor agonist, sedating antidepressants, several atypical antipsychotics, sedating antihistamines, and unregulated substances such as valerian and melatonin. Among these compounds substantial evidence of efficacy exists only for the BzRAs and ramelteon; moreover, these drugs are among the safest of centrally acting drugs in common clinical use. Sufficient variability in BzRA pharmacokinetics provides clinicians with options to meet the needs of most patients. Efficacy and safety data of other drugs used to treat insomnia are currently inadequate to allow evidence-based treatment decisions. As the view of insomnia changes from a symptom of an underlying disorder to that of an independent, often chronic disorder, commonly comorbid with a variety of medical and psychiatric conditions, there is increased recognition of the need for long-term treatment. Further research on long-term use and use in comorbid illness is needed. Improvement in the management of insomnia will result from systematic research with these drugs, with drugs in development, and with novel therapeutic approached, such as combined therapies.

Keywords: Insomnia, Pharmacotherapy, Benzodiazepine receptor agonists, Melatonin receptor agonists, Antidepressants, Melatonin, Valerian

Introduction

There is abundant scientific evidence regarding efficacy and safety of drugs with an FDA indication for treatment of insomnia but little data regarding other medications commonly used by clinicians to treat insomnia [1]. Despite the absence of research-based data, physicians have commonly turned to off-label use of drugs for treatment of insomnia [2, 3]. A number of factors have likely contributed to the use of nonapproved medications in clinical practice,

From: *Clinical Handbook of Insomnia,* Current Clinical Neurology
Edited by: H.P. Attarian and C. Schuman, DOI 10.1007/978-1-60327-042-7_23,

including (1) scheduling status of hypnotics, (2) labeling that discouraged use of hypnotics for more than a few weeks, (3) minimal data on long-term use of hypnotics, (4) limited data on use of hypnotics in patients with comorbid conditions, and (5) concern about tolerance, dependence, and adverse reactions.

In addition, the conceptualization of insomnia has influenced clinical practice. In 1984, when the NIMH issued its consensus statement regarding treatment of insomnia [4] chronic insomnia was predominantly considered to be a secondary phenomenon – a symptom of primary psychiatric or medical illness, or the outcome of maladaptive behavior. Treatment was first directed toward the primary or underlying condition with the expectation that insomnia would improve as a result. Use of hypnotic medication was considered adjunctive and recommended use was limited to a month or less. Advances in knowledge about insomnia have led sleep researchers and clinicians to reassess this viewpoint and consider independent treatment of insomnia [5–7]. Findings that contradict the symptom model of insomnia include the following (1) many individuals with chronic insomnia do not have a clearly-identifiable underlying medical, psychiatric or behavioral disorder [8, 9] (2) insomnia may not remit with treatment of a comorbid disorder [10] (3) treatment of insomnia itself may improve aspects of a comorbid disorder [11–13] and (4) chronic insomnia is a risk factor for the subsequent development of psychiatric disorders [14, 15].

These findings in part led the NIH to conduct a conference in 2005 to explore the state of scientific knowledge of insomnia and its treatment [1]. In brief, the expert panel concluded that chronic insomnia is a major public health problem and recommended the term "comorbid insomnia" rather than "secondary insomnia" reflecting the limited understanding regarding the association of various illnesses and insomnia. In addition, they concluded that pharmacological treatment of insomnia with benzodiazepine receptor agonists (BzRA's) is safe and efficacious (although additional long-term studies are needed), whereas evidence is lacking to support the use of sedating antidepressants, antihistamines, alcohol, and a variety of other substances to treat insomnia.

This chapter reviews current knowledge about medications used to promote sleep and implementation of pharmacological treatment for insomnia.

Historical Perspective

Drug treatments for insomnia have been sought since ancient times when herbal potions, fermented beverages, and opium were used. In the mid-nineteenth century bromides and chloral hydrate, along with laudanum (a mixture of opium and alcohol) were common. Barbiturates, developed in the early twentieth century, were the most frequently used prescription sleep aid until the 1960s when benzodiazepines were introduced. Barbiturates, while effective, were lethal in doses as low as ten times the therapeutic dose and had other safety concerns including residual sedation, tolerance, dependence, and potentiation of effects by other sedating agents, particularly alcohol. Benzodiazepines were an important breakthrough because of their markedly improved safety profile. Benzodiazepines became the primary pharmacological treatment for insomnia in the 1970s and 1980s. Their use declined in the 1990s along with a dramatic increase in the use of sedating antidepressants [2]. By 2002, drugs with an

Table 23.1 Drugs most commonly used for insomnia from 2005 to 2007.[a]

Drug[b]	FDA indication(s)	Occurrence (in millions)		
		2005	2006	2007[c]
Zolpidem	Insomnia	3.748	3.329	3.620
Trazodone	Depression	3.135	2.361	2.125
Eszopiclone	Insomnia	1.072	1.264	1.362
Quetiapine	Schizophrenia	1.084	0.941	0.852
Ramelteon	Insomnia	0.169	0.726	0.772
Mirtazapine	Depression	0.795	0.587	0.726
Temazepam	Insomnia	0.616	0.540	0.641
Amitriptyline	Depression	0.612	0.365	0.473
Lorazepam	Anxiety and panic disorders	0.447	0.341	0.454
Clonazepam	Seizure and panic disorders	0.520	0.321	0.450
Alprazolam	Anxiety and panic disorders	0.351	0.267	0.268
Cyclobenzaprine	Muscle spasm	0.154	0.172	0.234
Clonidine	Hypertension	0.275	0.154	0.211
Tizanidine	Spasticity	0.015	0.019	0.171
Zaleplon	Insomnia	0.403	0.213	0.167
Carisoprodol	Musculoskeletal pain	0.096	0.133	0.158

[a]Data from the *Physician Drug and Diagnosis Audit* (Verispan: Yardley, PA) on drugs with the desired actions of "hypnotic," "promote sleep," or "sedate night."
[b]Drugs listed in order of rank in 2007.
[c]2007 data projected from 11 months' data.

FDA indication for insomnia were prescribed less frequently than medications used off-label [3]. In 2002, the most-commonly prescribed medication for insomnia was trazodone. Data supplied by Verispan, Inc. [16] for the years 2005 through 2007 (see Table 23.1) suggest that prescribing patterns may be changing slightly. Use of trazodone and amitriptyline has begun to decline while use of BzRA hypnotics and ramelteon has increased. While use of quetiapine decreased slightly from 2005 to 2007, its use for insomnia has doubled since 2002. Self-treatment with alcohol or over-the-counter sleep aids is even more common than use of prescription medication for insomnia [17].

Drugs currently used for insomnia include those with an FDA indication for treatment of insomnia (BzRA's and a melatonin receptor agonist (ramelteon); Table 23.2), other psychotropic medications (e.g., sedating antidepressants, antipsychotics; Table 23.3), over-the-counter sleep aids (primarily containing diphendydramine; Table 23.3), and unregulated substances (dietary supplements, herbal preparations; Table 23.3).

Benzodiazepine Receptor Agonists

BzRA's (which include both benzodiazepines and nonbenzodiazepines) act by modulating the effect of gamma aminobutyric acid (GABA) at the benzodiazepine binding site on the $GABA_A$ receptor complex [18]. GABA is the most

Table 23.2 Characteristics of drugs with an FDA indication for insomnia.

Drug name	Receptor specificity	Dose range (mg)	Elimination half-life (h)	Metabolism (CYP enzymes)
Estazolam	Bz$GABA_A$	1–2	10–24	3A
Flurazepam	Bz$GABA_A$	15–30	48–120[a]	3A4
Temazepam	Bz$GABA_A$	15–30	8–20	None
Triazolam	Bz$GABA_A$	0.125–0.25	2–6	3A4
Quazepam	Bz$GABA_A$	7.5–15	39–73[a]	Not available
Eszopiclone	Bz$GABA_A$	1–3	6	3A4, 2E1
Zaleplon	Bz$GABA_{A,\ alpha\ 1}$	5–20	1	(Minor: 3A4)
Zolpidem	Bz$GABA_{A,\ alpha\ 1}$	5–10	1.5–2.4	3A4, 2C9
Zolpidem extended-release	Bz$GABA_{A,\ alpha\ 1}$	6.25–12.5	1.6–4.5	3A4, 2C9
Ramelteon	MT1 and MT2	8	1–2.6	1A2, (minor: 2C, 3A4)

Bz GABA$_A$ gamma-aminobutyric acid, type A receptor complex ; *MT* melatonin; *CYP* cytochrome P-450 (letters and numbers refer to specific CYP enzymes).
[a]Refers to elimination half-life of active metabolite.

Table 23.3 Characteristics of other drugs used to treat insomnia.

Drug name	Drug type	Usual dose for insomnia (mg)[a]	Usual dose for therapeutic indication (mg)	Elimination half-life (h)	Metabolism (CYP enzymes)
Amitriptyline	Antidepressant, tricyclic	25–50	100–300	12–24	2D6, 2C19 (minor: 1A2, 3A4)
Doxepin	Antidepressant, tricyclic	25–150	100–300	10–30	2D6, 2C19 (minor: 1A2, 3A4)
Trazodone	Antidepressant, phenylpiperazine	50–150	200–600	3–14	3A4, 2D6
Trimipramine	Antidepressant, tricyclic	25–150	100–300	15–40	2D6, 2C19 (minor: 1A2, 3A4)
Nefazodone	Antidepressant, phenylpiperazine	50–150	150–450	6–18	3A4, 2D6, 2C19
Mirtazapine	Antidepressant, tetracyclic, piperazinoazepine	15–30	15–45	13–40	3A4, 2D6, 1A2
Olanzapine	Antipsychotic, thienobenzodiazepine	2.5-20	10–20	20–54	1A2, 2D6
Quetiapine	Antipsychotic, dibenzothiazepine	25–200	300–800	6	3A4
Diphenhydramine	Antihistamine	50–100	25–50 tid or qid	4–8	2D6, 3A4
Doxylamine	Antihistamine	25	25 qid	10	None
Melatonin	Hormone	1–10	Not applicable	0.5–1	1A2
Valerian	Plant extract	400–900	Not applicable	Not established	Uncertain

CYP cytochrome P-450 (letters and numbers refer to specific CYP enzymes).
[a]Therapeutic dose for insomnia not established. Listed doses refer to those cited in literature and used in clinical practice.

common inhibitory neurotransmitter in the central nervous system. The $GABA_A$ receptor complex includes receptors for a variety of drugs including BzRA's, barbiturates, neurosteroids, anesthetics, and alcohol. These drugs enhance the hyperpolarizing effect of GABA when GABA is present. $GABA_A$ receptors are comprised of a central chloride channel surrounded by five protein subunits. Nineteen subunits from seven gene families (alpha 1-6, beta 1-3, gamma 1-3, delta, epsilon, pi, theta, and rho 1-3) have been identified thus far. The function of each $GABA_A$ receptor appears to be influenced by the combination of these subunits. In animal models, for example, alpha 1 subunits appear to be associated with sedation, anticonvulsant actions, and amnesia; alpha 2 and alpha 3 subunits may be involved in anxiolytic and myorelaxant effects; and alpha 5 subunits have been linked to aspects of cognitive function. It is important to remember, however, that $GABA_A$ receptor subtype function has not been established in humans, and that $GABA_A$ receptor ligands described as receptor "selective" have a relative, not absolute, selectivity at therapeutic concentrations.

BzRA hypnotics (Table 23.2) include drugs with a benzodiazepine chemical structure (estazolam, flurazepam, quazepam, temazepam, triazolam), and drugs with different chemical structures (eszopiclone, zaleplon, zolpidem). Benzodiazepines bind with relatively equal affinity to four alpha subunits (alpha 1, 2, 3, and 5) while the nonbenzodiazepines zaleplon and zolpidem bind with relative selectivity to alpha 1 subunits. Eszopiclone is less selective. No clinically relevant differences have been established for drugs with differing binding patterns. BzRA's are relatively rapidly absorbed but differ in elimination half-life (ranging from 1 to 48 h or more) which affects duration of action. Drugs with very short half-lives may be less effective in maintaining sleep. Drugs with longer half-lives may be more effective in sleep maintenance but may cause residual sedation and drug accumulation with repeated nightly doses. Elimination half-life is usually increased in the elderly population.

Other benzodiazepines not approved as hypnotics by the FDA but often used to treat insomnia include lorazepam, clonazepam, and alprazolam. These drugs are indicated for treatment of anxiety or panic disorders; clonazepam is also indicated in treatment of seizures. Their pharmacologic properties are similar to benzodiazepine hypnotics; thus, while efficacy in insomnia has not been as extensively studied with these drugs, they appear to have similar effects on sleep. Their half-lives are relatively long (11–40 h).

Efficacy

The efficacy of BzRA hypnotics, measured by polysomnography as well as subjective report, is well established for treatment of insomnia, at least for studies of a few nights to several weeks, in individuals with primary insomnia [19, 20]. All BzRA's reduce sleep latency and most increase total sleep time, the net result of affecting both sleep onset and sleep maintenance. Specific measures of sleep maintenance (e.g., wake time after sleep onset (WASO), number of awakenings) have not been systematically reported until recently. Zolpidem, while improving total sleep time, does not reliably improve WASO except in the extended-release form. Zaleplon, which has a very short duration of action does not reliably increase total sleep time. However, this short duration of action allows dosing for patients who may have only 4–5 h left before they must rise in the morning with minimal risk of residual sleepiness [21].

Although few in number, longer-duration trials including those with non-nightly dosing support continued efficacy of BzRA's without the development of tolerance. Two 6-month, placebo-controlled studies of nightly use of eszopiclone in primary insomniacs demonstrated persistent reduction in subjective sleep latency, fewer awakenings, reduced WASO, increased total sleep time, and improved daytime function [22] as well as better quality of life and reduced work limitations [23]. Open-label treatment following the double-blind phase in one eszopiclone study suggests sustained efficacy for up to 1 year [24]. Polysomnographic studies of zolpidem and zaleplon revealed evidence of persistent efficacy over 5 weeks of nightly use [25, 26]. Open-label 1-year extension trials of zaleplon revealed continued efficacy in the elderly [27]. Patients receiving zolpidem 10 mg for up to 12 weeks and zolpidem extended-release in a non-nightly regimen for 6 months reported improvements in sleep latency, total sleep time, awakenings, and sleep quality compared to placebo, without evidence of rebound insomnia (worsening of insomnia beyond pretreatment levels) on the nights drug was not taken [28–30].

Although BzRA's have not been extensively studied in insomnia coexistent with other medical or psychiatric conditions, the published data indicate improvements in sleep similar to that seen with primary insomnia. Zolpidem 10 mg increased total sleep time and improved sleep quality in a 4-week placebo-controlled study of depressed patients with persistent insomnia despite adequate control of depressive symptoms with SSRI medication [31]. Preliminary data indicate that zolpidem extended-release coadministered with escitalopram improves subjective measures of sleep in patients with either comorbid depression [32] or anxiety [33]. Eszopiclone co-therapy with fluoxetine was superior to fluoxetine and placebo in improving sleep and reduced ratings of depression [34]. Similarly, eszopiclone cotherapy with escitalopram was superior to escitalopram plus placebo in improving sleep and decreasing symptoms of anxiety [35]. Triazolam improved sleep latency, total sleep time, and number of awakenings in rheumatoid arthritis patients with chronic pain. Moreover, objectively measured daytime sleepiness and duration of morning stiffness decreased [36]. Triazolam also decreased sleep fragmentation as well as daytime sleepiness in patients with periodic limb movements [37]. Further research into the waking state benefits of insomnia treatment is needed.

Safety

The most common side effects of BzRA's are drowsiness/somnolence, dizziness, and headache. Much less common but more serious safety concerns include impaired motor and cognitive function while blood levels are present (either at night or the next day), amnesia for events occurring when the drug is active, the risk of dependence or abuse in susceptible individuals, drug interactions, and toxicity. However, compared to other drug classes, the margin of safety (therapeutic index) is wide; that is, the ratio of effective dose to lethal dose is so large that toxicity is rare.

The risk of residual sedation on the day after using hypnotic medication is determined by the dose and the rate of elimination. Short-acting drugs (e.g., zolpidem, zaleplon, triazolam) typically have no residual sedation. More slowly eliminated medications (i.e., those with intermediate or long half-lives) can exert their effects into the next day for variable periods of time resulting in sleepiness which may impact waking function.

The impact of short or long-term use of BzRA's on daytime cognition is unclear. Changes attributed to hypnotics may be subtle [38] and the clinical significance is not clear [39]. Any meaningful study would have to investigate the impact of insomnia itself on cognition. A number of studies have indicated no impairment in psychomotor or cognitive performance 8 h postdose for most short- to intermediate-acting BzRA's [40–42]. A study of driving showed no next-morning impairment in normals following zaleplon, zolpidem, or temazepam in typical presleep doses. However when given only 4–5 h before driving, zolpidem, but not zaleplon impaired driving [43]. The generalizability of these findings to insomniacs is unknown.

Falls and resultant injury, particularly in the elderly, are a concern for many psychotropic medications. Any sedating medication could potentially increase fall risk, but one large study documented that the only medications which independently predicted falls were narcotics, antidepressants, and anticonvulsants [44]. In addition, insomnia itself appears to be a risk factor for falls. Brassington and colleagues [45] found that reported sleep difficulty, but not use of psychotropic medication, was an independent risk factor for falls in community-dwelling adults over 64 years of age. In another recent study, the risk for falls was statistically significant for insomnia without hypnotic use and insomnia which persisted despite hypnotic use, but not for hypnotics without insomnia [46]. One interpretation of these findings is that if the hypnotic relieves the insomnia, the hypnotic is not a risk factor for falling.

Memory impairment can occur with BzRA's but is not specific to BzRA's. Anterograde amnesia (memory failure for information presented after the drug is ingested) can be seen with all sedatives including alcohol and barbiturates. The extent of amnesia depends on plasma concentration and the proximity of information input relative to peak plasma concentration with higher doses producing a higher prevalence of amnestic events [47–49].

Rebound insomnia refers to a worsening of sleep beyond pretreatment levels when a drug is discontinued abruptly. Rebound is more likely after high doses of short-acting or intermediate-acting drugs. The likelihood and severity of rebound is related to dose but not necessarily the duration of use. When rebound insomnia occurs, it generally lasts only one to two nights and can be minimized or prevented by using the lowest effective dose and then tapering before discontinuation [50]. Studies of non-nightly administration of zolpidem and zolpidem extended-release show no evidence of rebound insomnia on the nights medication was not taken [28–30].

In the absence of a history of chemical dependency or abuse, there is little evidence to warrant concern over drug dependence with BzRA use. Although substance abusers have shown they will self-administer BzRA's during the day and report a degree of "drug liking," there is no compelling data that BzRA hypnotic use per se by patients in the clinical situation leads to dependence [51]. In addition, use of BzRA's for months or years is rarely associated with dose escalation [52] and patients generally do not administer hypnotics for purposes other than to promote sleep [53, 54]. When self-administrated, the rate of hypnotic use depends primarily on the severity of insomnia, in particular the perceived quality of sleep the previous night [55].

While little is known about the frequency with which hypnotic medications are misused, one study indicated that the rate of misuse of all benzodiazepines

occurred at 2 per 10,000 prescriptions [56]. Because this study included patients in whom benzodiazepines were prescribed regardless of indication, the results should be applied cautiously to patients for whom BzRA's are used as hypnotics.

Melatonin Receptor Agonists

Ramelteon, a melatonin receptor agonist, is approved by the FDA for insomnia characterized by sleep-onset difficulty. It is the only non-BzRA drug approved for insomnia and is not a scheduled substance. Ramelteon is rapidly absorbed and eliminated. It is an agonist at both melatonin type 1 and melatonin type 2 receptors [57] which are located in the suprachiasmatic nucleus (among other tissues) and are involved in the regulation of sleep and circadian rhythms. Some evidence indicates that agonists of melatonin type 1 receptors inhibit suprachiasmatic nucleus neurons, possibly resulting in attenuation of wake-promoting activity, thus favoring sleep. Melatonin type 2 receptors may play a role in the biological timing of the sleep/wake cycle.

Efficacy and Safety

Polysomnographic and subjective data indicate that ramelteon 4–32 mg decreases sleep latency in adults with primary insomnia [58] with efficacy maintained for up to 5 weeks [59]. Similar improvements in sleep latency have been reported in elderly primary insomniacs treated with ramelteon [60, 61]. Preliminary data of long-term use (up to 12 months) indicate sustained efficacy for sleep latency [62]. Improvements in total sleep time appear to be the result of effects on sleep latency, with no observable impact on sleep maintenance variables such as wake after sleep onset. Ramelteon appears to have chronobiotic properties, producing a phase advance at doses as low as 4 mg [63], potentially explaining Ramelteon's ability to promote sleep without appreciable subjective sedation. Ramelteon has not been directly compared with other hypnotics nor has it been evaluated in broad clinical populations.

The most common adverse events with ramelteon are headache, somnolence, dizziness, fatigue, and nausea [64]. Clinical trials with doses up to 16 mg have indicated no residual sedation or cognitive impairment as well as no withdrawal symptoms or rebound. Because of low abuse potential [65], ramelteon may have a role in the treatment of insomnia in individuals with a history of chemical dependence; however, there are no published reports with that population.

Sedating Antidepressants

Sedating antidepressants are commonly used "off-label" for treatment of insomnia despite limited efficacy data and potentially significant safety concerns. In fact, trazodone is the second most prescribed drug for insomnia; mirtazapine and amitriptyline are also frequently used [16]. Factors contributing to this pattern include perceptions of increased safety and low potential for dependence compared to BzRA's, as well as FDA scheduling and ability to prescribe them for long-term use. In addition, some physicians may also

believe they are treating insomnia as a manifestation of depression, although antidepressants are typically prescribed for insomnia at doses below the range needed for antidepressant effects.

The sedating effect of antidepressants is likely associated with multiple mechanisms including histamine type 1 and serotonin type 2 receptor antagonism along with alpha-adrenergic receptor antagonism [66–72].

Efficacy

The majority of data regarding effects of antidepressants on sleep comes from data on patients with depression using doses higher than those typically used for insomnia. These data generally indicate that the tricyclic antidepressants such as amitriptyline, doxepin, and trimipramine and the nontricyclic drugs such as trazodone and mirtazapine shorten sleep latency and increase sleep efficiency in depressed patients, although small sample sizes and experimental design weaknesses limit the value of these studies [73, 74]. Efficacy has not been adequately studied in nondepressed individuals or in the lower doses generally prescribed for insomnia.

There have been two studies investigating trazodone in nondepressed insomniacs at a dose typically used for insomnia. In a 2-week placebo-controlled study [75] both trazodone 50 mg and zolpidem 10 mg shortened subjective sleep latency and increased subjective sleep duration, with improvements with zolpidem being somewhat greater than those with trazodone. An earlier study of nine primary insomnia patients taking trazodone 150 mg for 3 weeks showed improvement in reported sleep quality but not in polysomnographic sleep latency or total sleep time [76].

There has been one double-blind placebo-controlled crossover study of trazodone in depressed individuals at a dose typically used for insomnia. In twelve patients on SSRI medications, trazodone 100 mg taken for seven nights improved polysomnographic measures of sleep, but subjective sleep quality improved equally with trazodone and placebo [77].

Among the tricyclics, only trimipramine and doxepin have been studied in primary insomnia. In one study, improved total sleep time was found in a trial of 15 primary insomniacs taking trimipramine (mean 166 mg ± 48 mg); but there was no placebo control, and polysomnographic measures were made before an adequate period of washout from prior medications had occurred [78]. In another study, subjective sleep quality was improved by trimipramine 100 mg when compared to placebo taken nightly for 1 month, but there were insignificant increases in total sleep time [79]. A 4-week study of doxepin 25–50 mg showed increased total sleep time and improved subjective sleep quality [80]. Improvements in polysomnographic and subjective measures of sleep maintenance in both adult and elderly primary insomniacs have been demonstrated with low-dose doxepin (1–6 mg) which is under development as a hypnotic [81, 82].

Despite the frequent use of amitriptyline and mirtazapine in insomnia treatment there are no published studies of their use in primary insomnia. In addition, amitriptyline does not reliably improve sleep in depressed individuals, at least in small-sample studies [83, 84]. In a small study without placebo control mirtazapine 15–30 mg improved polysomnographic measures of sleep continuity in depressed individuals for up to 28 days [85].

Safety

In general, sedating antidepressants have more frequent and potentially significant side effects than BzRA's, at least at antidepressant doses [73, 76]. In fact these side effects are a principal reason why SSRIs are more likely to be used for treatment of depression than tricyclics and other sedating antidepressants [86]. Safety of antidepressants used for treatment of insomnia, like efficacy, has not been properly evaluated at the doses most commonly employed. The half-life of most sedating antidepressants ranges from 9 to 30 h, exclusive of active metabolites, suggesting that accumulation and carryover sedation is likely. Importantly, the lethal-dose/effective-dose margin is much narrower compared to BzRA's. In trials of tricyclics used to treat primary insomnia there have been reports of leucopenia, thrombocytopenia, and increased liver enzymes with doxepin [80] and dizziness, dry mouth, and nausea with trimipramine [78]. Other potentially serious side effects with tricyclic antidepressants include anticholinergic effects, orthostatic hypotension, and potentially serious cardiac effects which are the prime cause of lethality in overdose. Daytime somnolence, dizziness, and weight gain have been reported with mirtazapine [87]. Troublesome side effects with trazodone include orthostatic hypotension, cardiac arrhythmias and conduction abnormalities, and priapism [74, 88, 89]. Carryover sedation is also likely even with doses below 100 mg [75, 90, 91].

Sedating Antipsychotic Drugs

Other prescription drugs used "off label" to treat insomnia include the atypical antipsychotic drugs olanzapine and quetiapine. Although recent data suggests use of quetiapine for insomnia is now decreasing, it was the fourth most-commonly used drug for insomnia for the years 2005–2007 [16]. Unlike older antipsychotic drugs which exert their effects principally via dopamine antagonism, these drugs have multiple mechanisms of action. Their sedating effects are likely mediated via histamine type 1 antagonism as well as serotonin type 2 antagonism. Small studies reporting the effects of these drugs in both primary insomnia [92] and comorbid insomnia [93, 94] lack placebo control. Side effects include hypotension, weight gain, glucose intolerance, effects on cardiac conduction, and residual sedation. Additionally the potential for drug-drug interactions limits their use in individuals without major psychiatric disorders.

Sedating Antihistamines

Most over-the-counter sleep aids contain the histamine type 1 receptor antagonists diphenhydramine or doxylamine. Although sedation is a common side effect of the first-generation antihistamines, evidence for efficacy in treating insomnia is limited. One double-blind placebo-controlled study showed improvement in subjective sleep latency and sleep quality with diphenhydramine 50 mg, although side effects were common [95]. A more recent study in elderly insomniacs showed improvement only in reported number of awakenings with diphenhydramine 50 mg taken for 14 days [96]. Tolerance to the sedating effects develops within 3–4 days, at least when used three times per day [97, 98].

Daytime sedation may be a problem given the relatively long elimination half-life of first generation antihistamines. Cognitive and psychomotor impairment have been demonstrated with diphenhydramine [99]. Other side effects include dizziness, fatigue, tinnitus, blurred vision, urinary retention, and a variety of gastrointestinal problems.

Melatonin

Melatonin is secreted endogenously by the pineal gland, retina, and intestinal tract. In humans it is normally secreted at night and suppressed by light exposure. Melatonin facilitates synchronization of circadian rhythms and may have sleep-promoting effects. These physiological effects appear to be mediated, respectively, by melatonin 2 and melatonin 1 receptors. Melatonin has a short half-life (40–60 min) but melatonin preparations include fast-release and sustained-release forms. Several studies have shown exogenous melatonin to have sleep-promoting properties when administered outside the period of usual exogenous secretion [100, 101] but results from studies of melatonin administration during the "biological night" have been inconsistent [102–104] even in studies of older insomniacs who have reduced melatonin production [105]. Meta-analyses have also produced conflicting data [106, 107]. Discrepancies may be the result of differences in melatonin preparations (including dose and pharmacokinetic properties) as well as numerous methodological issues.

Although serious side effects appear uncommon, the risk of long-term use has not been studied. In addition, melatonin is not regulated by the FDA. The most commonly reported adverse effect is headache. High doses or acute use may increase residual sedation. Daytime use of melatonin has shown deleterious effects on neurobehavioral performance, but there are no studies defining the duration of this effect with night-time administration [108]. Melatonin may affect blood pressure in both normotensive individuals [109] as well as in hypertensive individuals treated with calcium channel blockers [110]. Additionally, low levels of impurities in several commercially available melatonin preparations have been reported [111].

Valerian

Valerian preparations are commonly used as over-the-counter treatment for insomnia [112]. These preparations include more than 400 extracts from the plant *Valeriana officinalis,* a number of which have CNS activity. Classified as a nutritional substance by the FDA, commercial preparations contain combinations of these chemicals in unknown proportions [113]. The mechanism of action of valerian preparations is unknown but may involve inhibition of GABA reuptake, serotonin receptor activity, and adenosine receptor antagonism [114].

There are few well-controlled research studies available regarding hypnotic efficacy of valerian. Some studies found an increase in slow wave sleep and K-complex density, but had conflicting results as to effect on sleep latency, WASO, or REM compared to placebo [115–120]. Side effects are rare and mild, and include headache, weakness, and possibly morning sedation [120].

Indications for Pharmacotherapy of Insomnia

Acute forms of insomnia are perhaps the most straight-forward indication for pharmacological intervention. When daytime impairment is judged to be problematic, treatment is indicated and generally pharmacotherapy is the only viable option. The consensus among sleep medicine specialists for the treatment of transient and short-term insomnia (lasting about 4 weeks or less) is that BzRA's are preferred, administered at the lowest effective doses for the clinically relevant period of time. Use of shorter-acting drugs, such as zolpidem or zaleplon, typically avoids residual sedative effects. Ramelteon may be a viable option for individuals without sleep maintenance difficulty.

A consensus regarding long-term pharmacologic treatment for chronic insomnia has yet to be established. Published studies of eszopiclone, zaleplon, and zolpidem extended-release indicate maintenance of efficacy without tolerance for up to 12 months but additional long-term clinical trials are needed. It is likely that other BzRA's would show sustained clinical benefit as well, but studies have not been conducted. There are few reasons to withhold or discontinue long-term use of BzRA's when such treatment is effective and there is no evidence of dependence or abuse. BzRA hypnotics should be used cautiously, if at all, in individuals with a history of alcoholism or drug abuse.

Patients should be cautioned against the concomitant use of alcohol or other sedating medications to avoid potentiating the sedating effects and narrowing the therapeutic ratio. Hypnotics have the potential to exacerbate untreated obstructive sleep apnea since they interfere with arousal processes. Because the majority of hypnotics undergo hepatic metabolism [121], they should be used in lower doses if they are used at all in patients with significant liver disease. Dose should be reduced in the elderly because of age-related changes in drug metabolism. Use in pregnant women should be avoided as the safety of the BzRA's and ramelteon in pregnancy has not been established. Sexually active females should be counseled and contraceptive methods should be assessed before prescribing these drugs.

Implementing Pharmacotherapy for Insomnia

As is true for many medical interventions hypnotic administration should be complemented by patient education and appropriate behavioral interventions. Sleep hygiene recommendations may include (1) maintaining consistent bedtimes and rise times, (2) avoiding excessive time in bed, (3) avoiding exercise and stressful activities close to bedtime, (4) optimizing the sleep environment (e.g., dark, quiet, cool; and in bed rather than recliners or couches), (5) minimizing use of alcohol and stimulants (e.g., decongestants, caffeine, nicotine), (6) discontinuing behaviors incompatible with sleep in the bedroom (e.g., clock checking, reading, TV, etc.), and (7) avoiding long or frequent naps in susceptible individuals.

Sleep hygiene manipulation alone will infrequently be beneficial for chronic insomnia. More likely it will serve as adjunctive treatment to either pharmacological or structured cognitive-behavioral treatment. In some patients medications may be useful on a short-term basis while attempts to adjust maladaptive behavior are undertaken. Nonetheless, even the most behaviorally compliant patient may require long-term treatment with medication.

Based upon available evidence BzRA's or ramelteon are the hypnotics of choice, unless there is a history of chemical dependence or abuse. Ramelteon might be considered when there are concerns regarding substance abuse, with the caveats that ramelteon seems to be most effective for insomnia at the beginning of the night and has not been specifically evaluated in the substance abuse population. While short-acting hypnotics are preferable to avoid or minimize risk of residual sedation, agents with longer half-lives may be appropriate in patients for whom daytime sedation is not a significant concern, such as the patient already hyperaroused or having generalized anxiety. Short-acting BzRA hypnotics or ramelteon are appropriate for patients having predominantly sleep-onset problems. For those with sleep maintenance difficulty, hypnotics with longer durations of action may be needed to promote sleep throughout the night. Age and concurrent conditions should be closely considered in choosing a hypnotic, and dose and schedule must be clearly delineated by the physician. It is useful to contract with the patient for an explicit treatment regimen, particularly if there is concern about psychological dependence or substance abuse. As with all sedating medications, BzRA hypnotics have the potential to reduce motor and cognitive function when the drug is active. The potential for this impairment should be discussed with individuals who might have duties or obligations in the middle of their sleep period (e.g., parents with small children, medical or public safety professionals with on-call obligations, and individuals with nocturia who need to safely ambulate to the bathroom.)

Because the risk of side effects with BzRA's increases with dose, it is important to establish the lowest effective dose for an individual patient. A low dose will adequately treat a reasonable percentage of patients. If necessary, dose can be titrated upward after a few nights of an inadequate response. Clinical experience suggests that some patients with psychiatric illness respond well only to higher than recommended doses of BzRA hypnotics. Adjustments in dosage and schedule should be made by the physician based not only on global assessments of sleep but on improvement in the specific nighttime and daytime symptoms which led to treatment. Close monitoring is desirable for certain populations who are at higher risk, such as the elderly as well as those who might misuse BzRA's, use other sedating medications or alcohol, or have medical conditions likely to alter response to hypnotics.

Patients should be instructed to take BzRA hypnotics at bedtime, or a few minutes before. Ingestion of a hypnotic too long before getting into bed is likely to increase the risk of adverse reactions. The package insert for ramelteon directs ingestion within 30 min of bedtime.

The schedule of use is generally nightly, but studies examining non-nightly use have not identified any significant problems with rebound phenomenon on nonmedication nights. Among the BzRA's, zaleplon is unique in that it is very short acting and can be taken after the usual bedtime, as long as 5 or more hours remain before rise time. This allows an "as needed" treatment schedule as patients can wait to determine if they will have difficulty with sleep onset on any given night.

Long-term nightly hypnotic use appears to be an option for some chronic insomniacs, although exactly for whom and how long is unclear at this time. Available safety data on BzRA's indicates that nightly use for several months or longer is an acceptable treatment approach, at least for primary insomniacs.

Future studies are needed to determine the pros and cons of various treatment durations in both primary and comorbid chronic insomnia, and to determine if drugs other than BzRA's have a place in long-term management.

Future Pharmacological interventions

As the view of chronic insomnia shifts from that of a symptom of an underlying disorder to that of a chronic illness, long-term treatment studies are needed to allow assessment of rate and duration of treatment response and remission. Such studies would also provide insight regarding the potential benefit of insomnia treatment and required duration of treatment upon comorbid illness.

Advances in the understanding of the neurobiology of sleep–wake neural mechanisms as well as sleep–wake modulating systems (e.g., emotional, circadian) have prompted intense research for novel insomnia treatments. These efforts will likely parallel further progress in basic neuroscience and eventually lead to new, perhaps better, treatment alternatives. Already of note are ongoing investigations of low-dose doxepin, new melatonin receptor agonists, benzodiazepine receptor partial agonists, histamine inverse agonists, orexin antagonists, serotonin-2a/c antagonists, and other candidates. Perhaps future insomnia medications will reduce the physiologic "hyperarousal" during sleep, which has been described in primary insomniacs, via influence on the HPA axis, without necessarily increasing total sleep time, but improving sleep quality.

In addition to the development of new medications, another potentially promising avenue for insomnia treatment research involves cotherapy. Much as psychiatrists routinely prescribe multiple drugs for bipolar disorder, major depression, and other difficult-to-manage conditions, some chronic insomnia patients may benefit from multiple drugs to promote sleep and/or decrease wake. Research is needed to identify the characteristics of such patients and the efficacious and safe combinations of drugs.

Conclusion

Research into the pathophysiology and morbidity of insomnia has resulted in the view that insomnia is an independent disorder deserving of specific treatment. Thus, establishing evidence-based treatment approaches is essential. At the present time evidence is available to support the use of BzRA's and ramelteon for the treatment of insomnia, for either short-term or long-term treatment. Specific needs of an individual patient can be met by selecting the drug based on relative duration of action. Drugs other than BzRA's should be considered when substance abuse is a significant clinical concern, or in the case of treatment failure. Importantly, recent studies have found that some daytime symptoms of insomnia improve with pharmacological treatments, and a small amount of research indicates that comorbid conditions may improve with treatment of insomnia.

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Part VI

Appendix

24

Contents/Directory

From: *Clinical Handbook of Insomnia,* Current Clinical Neurology
Edited by: H.P. Attarian and C. Schuman, DOI 10.1007/978-1-60327-042-7_24,

Outline Plan for a Sleep History Assessment Comprising Content Areas and Suggested Interview Questions

Content Area	Prompt question	Supplementary questions
Presentation of the sleep complaint		
Pattern	Can you describe the pattern of your sleep on a typical night?	Time to fall asleep? Number and duration of wakenings? Time spent asleep? Nights per week like this?
Quality	How do you feel about the quality of your sleep?	Refreshing? Enjoyable? Restless?
Daytime effects	How does your night's sleep affect your day?	Tired? Sleepy? Poor concentration? Irritable? Particular times of day?
Development of the sleep complaint	Do you remember how this spell of poor sleep started?	Events and circumstances? Dates and times? Variation since then? Exacerbating factors? Alleviating factors? Degree of impact/intrusiveness?
Lifetime history of sleep complaints	Did you used to be a good sleeper?	Sleep in childhood? Sleep in adulthood? Nature of pastepisodes? Dates and times? Resolution of past episodes?
General health status and medical history	Have you generally kept in good health?	Illnesses? Chronic problems? Dates and times? Recent changes in health?
Psychopathology and history of psychological functioning	Are you the kind of person who usually copes well?	Psychological problems? Anxiety or depression? Dates and times? Resourceful person? Personality type?
Issues of differential diagnosis Sleep-related breathing disorder (SBD)	Are you a heavy snorer?	Interrupted breathing in sleep? Excessively sleepy in the day?
Periodic limb movements in sleep (PLMS) and restless legs syndrome (RLS)	Do your legs sometimes twitch or cannot keep still?	Excessively sleepy in the day? Trouble sitting still without moving the extremities?
Circadian rhythm sleep disorders	Do you feel you want to sleep at the wrong time?	Too early? Too late?
Parasomnias	Do you sometimes act a bit strangely during your sleep?	Behavioral description? Time during night?
Narcolepsy	Do you sometimes just fall asleep without warning?	Times and places? Collapses triggered by emotion? Poor sleep at night?
Current and previous treatments	Are you taking anything to help you sleep?	Now? In the past? Dates and times? What has worked? What have you tried yourself?

A Sleep Diary

Instructions to Patient

This Sleep Diary is designed to provide a record of your experience of sleep, and your use of medication or alcohol to help you sleep. As you will see, information about seven nights (one week) can be recorded on one form. Please complete one column of the diary each morning, soon after you wake up. Take a few minutes to do this, trying to be as accurate as you can. It is your best estimate that we are looking for, but try not to get into the habit of clockwatching at night.

Further Instructions to Clinician

At the foot of the page, there are five boxes into which you can insert the mean values for the variables sleep-onset latency (SOL: question 3), number of times of wakening from sleep (WAKE: question 4), wake time after sleep-onset (WASO: question 5), total sleep time[1] (TST: question 6), time in bed (TIB: question 2 minus question 1) and sleep efficiency (SE: TST divided by TIB, multiplied by 100)

[1]You may prefer to calculate TST yourself [TIB minus (SOL plus WASO)], rather than asking patients to work this out. In this case you can exclude question 6 from the Sleep Diary.

Name_____

Week Beginning_____

Measuring the Pattern of Your Sleep

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
1. What time did you rise from bed this morning?							
2. At what time did you go to bed last night?							
3. How long did it take you to fall asleep (minutes)?							
4. How many times did you wake up during the night?							
5. How long were you awake *during* the night (in total)?							
6. About how long did you sleep altogether (hours/mins)?							
7. How much alcohol did you take last night?							
8. How many sleeping pills did you take to help you sleep?							

Measuring the Quality of Your Sleep

1. How well do you feel this morning? 0 1 2 3 4 not at all moderately very							
2. How enjoyable was your sleep last night? 0 1 2 3 4 not at all moderately very							

For Office Use Only

SOL	WAKE	WASO	TST	TIB	SE

The Insomnia Severity Index

Name:_____ Date:_____

1. Please rate the current (i.e., last 2 weeks) severity of your insomnia problem(s).

	None	Mild	Moderate	Severe	Very
a. Difficulty falling asleep:	0	1	2	3	4
b. Difficulty staying asleep:	0	1	2	3	4
c. Problem waking up too early:	0	1	2	3	4

2. How satisfied/dissatisfied are you with your current sleep pattern?

Very satisfied	Satisfied	Neutral	Dissatisfied	Very dissatisfied
0	1	2	3	4

3. To what extent do you consider your sleep problem to interfere with your daily functioning (e.g., daytime fatigue, ability to function at work/daily chores, concentration, memory, mood, etc.).

Not at all interfering	A little	Somewhat	Much	Very much interfering
0	1	2	3	4

4. How noticeable to others do you think your sleeping problem is in terms of impairing the quality of your life?

Not at all noticeable	A little	Somewhat	Much	Very much noticeable
0	1	2	3	4

5. How worried/distressed are you about your current sleep problem?

Not at all worried	A little	Somewhat	Much	Very much worried
0	1	2	3	4

Guidelines for Scoring/Interpretation

Add scores for all seven items (1a + 1b + 1c + 2 + 3 + 4 + 5) =

Total score ranges from 0 – 28; if total score falls between:

0–7 = No clinically significant insomnia

8–14 = Subthreshold insomnia

15–21 = Clinical insomnia (moderate severity)

22–28 = Clinical insomnia (severe)

Transcript of a Relaxation Therapy Session (12-Min Duration)

The exercises on this tape are designed to help you relax. Relaxation is a skill, which you can learn. It is just like any other skill, so don't be surprised if you find it takes practice because that is how we learn skills. So do practice. Practice a couple of times a day, especially as you start to learn. Of course, you will want to use the relaxation when you go to bed, to help you relax and go to sleep, but you will find it most useful if you have already learned what to do.

It is best to practice at a time when you know you won't be disturbed. The tape will last between ten and fifteen minutes so you will need at least that length of time set aside. When you do your relaxation exercises in your bed, you will be able to listen to the tape there too. But after a while you will have learned what to do and you will be able to just follow the exercises in your own mind.

The exercises themselves begin now.

Settle yourself down. Lie down with your hands and arms by your sides; have your eyes closed. That's good.

We will start by just thinking about your breathing. Your breathing can help you relax; the more deep and relaxed it is the better you will feel and the more in control you will feel. So begin by taking some slow regular breaths. Do that now. Breathe in fully, fill up your lungs fully; breathe in, hold your breath for a few seconds now, and let go, breathe out … Do that again, another deep breath, filling your lungs fully when you breathe in, hold it … and relax, breathe out. Continue that in your own time, noticing that each time you breathe in the muscles in your chest tighten up, and as you breathe out there is a sense of letting go. You can think the word ‘relax’, each time you breath out. This will remind you that breathing out helps you relax. It will also help you to use this word to tell yourself to relax whenever you need to. You will find that your body will begin to respond. Breathing slowly, comfortably, regularly, and deeply; thinking the word ‘relax’ every time you breath out; enjoying just lying still and having these moments to relax, concentrating on the exercises.

Now I'd like you to turn your attention to your arms and hands. At the moment just lying at your sides. I'd like you to create some tension in your hands and arms by pressing your fingers into the palms of your hands and making fists. Do that with both hands now. Feel the tension in your hands, feel the tension in your fingers and your wrists, feel the tension in your forearms. Notice what it is like. Keep it going … and now relax. Let those hands flop. Let them do whatever they want to do; just let them relax. Breathing slowly and deeply, you will find that your fingers will just straighten out and flop, and your hands and arms will feel more relaxed. Allow them to sink into the couch or into the bed, just allow your arms to be heavy. Breathing slowly and deeply, thinking the word ‘relax’ each time you breathe out, and finding that your hands and arms just relax more and more and more. Your arms and your hands so heavy and rested. It's almost as if you couldn't be bothered moving them. Just because you have let go of the energy and tension that was in the muscles there. Breathing slowly and deeply, both your hands, both your arms, heavy and rested. Let go of the energy and tension that was in the muscles there, breathing slowly and deeply. Both your hands, both your arms, heavy and rested and relaxed.

I'd like you to turn your attention now to your neck and shoulders. Again we're going to get your neck and shoulders into a state of relaxation following some tension we're going to introduce. I'd like you to do that by pulling your shoulders up towards your ears. Now, do that; pull your shoulders up towards your ears. Feel the tension across the back of your neck, across the top of your back and in your shoulders. Feel the tension, keep it going not so much that it's sore, but keep it constant. Feel it, and now let go … relax; go back to breathing slowly and deeply. Let that tension drain away, let it go. Breathe deeply, and as you do so, notice that the tension, almost like a stream, drains away from your neck, across your shoulders, down the upper part of your arms, down the lower part of your arms and out through your fingertips. Draining out and leaving a sense of warmth and relaxation deep in your muscles. Breathing slowly and deeply and allowing that to take place. Just let the tension go. If it doesn't seem to go, don't force it, it will go itself. Be confident about that. Just breathe slowly and deeply and allow yourself to be relaxed; remembering to think the word 'relax', each time you breathe out. Using that word 'relax' to focus on the sense of relaxation that you get, using the word 'relax' to remind you of the success your are having in relaxing your body.

I'd like you to concentrate now on your face, and on your jaw, and on your forehead. I'd like you to create some tension in these parts of your body by doing two things together at the same time. These things are to screw up your eyes really tightly and bite your teeth together. Do these things together now. Bite your teeth together; feel the tension in your jaw. Screw up your eyes; feel the tension all around your eyes, in your forehead, in your cheeks, throughout your face, wherever there is tension. Now keep it going … and relax; breathing in through your nose and out through your mouth, slowly and deeply. Notice how your forehead smoothes out and then your eyelids and your cheeks. Allow your jaw to hang slightly open. Allow your whole head to feel heavy and to sink into the pillow; breathing slowly and deeply. Allow there to be a spread of relaxation across the surface of your face and into all those muscles in your face. Allow your eyelids to feel heavy and comfortable, your jaw and your whole head; breathing slowly and deeply, enjoying the relaxation which you feel in your body. Relax each time you breathe out. Relax just that little bit more each time you breathe out".

Concentrating now on your legs and feet, I want you to create some tension here by doing two things at the same time; and these things are to press the backs of your legs downwards and to pull your toes back towards your head. Do these things together now. Create the tension in your legs, press the backs of your legs downwards and pull your toes back towards your head. Feel the tension in your feet, in your toes, in your ankles, in the muscles in your legs. Feel what it is like. Don't overdo it; just notice what it is like … and relax. Breathing slowly and deeply once more; just allow your feet to flop any old way. Allow the muscles to give up their energy, give up their tension. Let it go, breathing slowly and deeply. Notice how your feet just want to flop to the side. Notice how your legs feel heavy as if you couldn't be bothered moving them. Heavy and comfortable and rested and relaxed. Just that little bit more relaxed each time you breathe out.

Be thinking about your whole body now; supported by the bed, sinking into it, but supported by it. You've let go the tension throughout your body. Your body feels rested, comfortable. Enjoy each deep breath you take. Just use these

few moments now to think about any part of your body that doesn't feel quite so rested and allow the tension to go. It will go. Breathe slowly and deeply; thinking the word ‘relax’ each time you breathe out. Just let any remaining tension drain away; from your hands, your arms, your neck and your back. Heavy and rested, comfortable and relaxed. From your face and your eyes, from your forehead; letting the muscles give up their energy. Like a stream of relaxation flowing over your whole body. Let your legs and feet feel relaxed; sinking into the bed. Breathing slowly and deeply.

In a few moments, this tape will finish; but you can continue to relax. You may wish to repeat some of the exercises yourself and that is fine. You may wish to enjoy just continuing as your are. You may wish to think on your visualization scene or build pictures in your mind that will help you to relax further. It's up to you, but continue to relax.

The tape itself stops now.

The Sleep Behavior Self-Rating Scale

Instructions for Patients

This rating scale helps us to understand what your behavior pattern around bedtime is like. It is fairly self-explanatory. Please take a few minutes to fill it in as accurately as you can. Please indicate how often you do the following things *in your bed before falling asleep* or *while in your bedroom*. Complete the form by considering what you would do in an average week.

Behavior	Never	Rarely	Sometimes	Often	Very often
Read a book or magazine					
Watch TV					
Listen to the radio					
Have a conversation with someone					
Speak on the telephone					
Eat or drink					
Smoke					
Please also answer the following questions:					
I take naps during the day or evening					
I feel sleepy when I go to bed					
I switch the light off as soon as I get into bed					
I spend a lot of time lying awake in bed at night					
If I can't get to sleep within approx. 20 min I get out of bed and move to another room until I feel sleepy again					
I set myself a regular rising time each morning					
If I have a bad night's sleep I still get up at my usual time					

Source: Adapted from Kazarian SS, Howe MG, Csapo KG (1979) Development of the sleep behavior self-rating scale. *Behavior Therapy 10*: 412–417.

Summary of the Sleep Scheduling Treatment Program

Instructions to Clinician

You can reproduce this summary sheet as a handout to give to your patients. Bear in mind the implementation issues described in the text and in Table 5.3.

1. Work out your current average sleep time and plan to spend that amount of time in bed.
2. Decide on a set rising time to get up each morning and put that into practice.
3. Establish a threshold time for going to bed by subtracting sleep time from rising time, and stay out of bed until your threshold time.
4. Lie down intending to go to sleep only when you feel sleepy at or after the threshold time.
5. Follow this program 7 days/nights a week.
6. If you do not sleep within 15 min get up and go into another room. Do something relaxing and go back to bed when you feel sleepy again. Repeat this if you still cannot sleep or if you waken during the night.
7. Adjust the new schedule by a maximum of 15 min per week, dependent upon your sleep efficiency.
8. Do not use your bed for anything except sleep (and sexual activity) and turn the light out when you go to bed.
9. Do not nap during the day or evening.

Calculating Current Sleep Requirement for Sleep Restriction

First, write down in the spaces below the amount of time you think you actually slept on each of the last ten nights, from your Sleep Diary (it may be easier to convert the time to the total number of minutes per night.)

Second, add up the total time you have slept across these nights.

Third, divide the total by 10 to get the average length of your night's sleep.

Night	Amount Slept
1.	
2.	
3.	
4.	
5.	
6.	
7.	
8.	
9.	
10.	

Total amount of time over 10 days = _____

Average sleep time = _____/10 = _____

Self-Monitoring Form of Sleep-Related Thoughts

Situation	Automatic thoughts	Emotions
Watching TV in the evening	"I must get some sleep tonight, I have so much to do tomorrow"	Anxious 80%

Dysfunctional Beliefs and Attitudes about Sleep Scale

Instructions to Patient

Several statements reflecting people's beliefs and attitudes about sleep are listed below. Please indicate to what extent you personally agree or disagree with each statement. There is no right or wrong answer. For each statement, circle the number that corresponds to your own *personal belief*. Please respond to all items even though some may not apply directly to your own situation.

Strongly disagree										**Strongly agree**
0	1	2	3	4	5	6	⑦	8	9	10

1. I need 8 hours of sleep to feel refreshed and function well during the day.

0	1	2	3	4	5	6	7	8	9	10

2. When I don't get proper amount of sleep on a given night, I need to catch up on the next day by napping or on the next night by sleeping longer.

0	1	2	3	4	5	6	7	8	9	10

3. Because I am getting older, I need less sleep.

0	1	2	3	4	5	6	7	8	9	10

4. I am worried that if I go for 1 or 2 nights without sleep, I may have a "nervous breakdown."

0	1	2	3	4	5	6	7	8	9	10

5. I am concerned that chronic insomnia may have serious consequences on my physical health.

0	1	2	3	4	5	6	7	8	9	10

6. By spending more time in bed, I usually get more sleep and feel better the next day.

0	1	2	3	4	5	6	7	8	9	10

7. When I have trouble falling asleep or getting back to sleep after nighttime awakening, I should stay in bed and try harder.

0	1	2	3	4	5	6	7	8	9	10

8. I am worried that I may lose control over my abilities to sleep.

0	1	2	3	4	5	6	7	8	9	10

9. Because I am getting older, I should go to bed earlier in the evening.

0	1	2	3	4	5	6	7	8	9	10

10. After a poor night's sleep, I know that it will interfere with my daily activities on the next day.

0	1	2	3	4	5	6	7	8	9	10

11. In order to be alert and function well during the day, I believe I would be better off taking a sleeping pill rather than having a poor night's sleep.

0	1	2	3	4	5	6	7	8	9	10

12. When I feel irritable, depressed, or anxious during the day, it is mostly because I did not sleep well the night before.

0	1	2	3	4	5	6	7	8	9	10

13. Because my bed partner falls asleep as soon as his/her head hits the pillow and stays asleep through the night, I should be able to do so too.

0	1	2	3	4	5	6	7	8	9	10

14. I feel that insomnia is basically the result of aging and there isn't much that can be done about this problem.

0	1	2	3	4	5	6	7	8	9	10

15. I am sometimes afraid of dying in my sleep.

0	1	2	3	4	5	6	7	8	9	10

16. When I have a good night's sleep, I know that I will have to pay for it on the following night.

0	1	2	3	4	5	6	7	8	9	10

17. When I sleep poorly on one night, I know it will disturb my sleep schedule for the whole week.

0	1	2	3	4	5	6	7	8	9	10

18. Without an adequate night's sleep, I can hardly function the next day.

0	1	2	3	4	5	6	7	8	9	10

19. I can't ever predict whether I'll have a good or poor night's sleep.

0	1	2	3	4	5	6	7	8	9	10

20. I have little ability to manage the negative consequences of disturbed sleep.

0	1	2	3	4	5	6	7	8	9	10

21. When I feel tired, have no energy, or just seem not to function well during the day, it is generally because I did not sleep well the night before.

0	1	2	3	4	5	6	7	8	9	10

22. I get overwhelmed by my thoughts at night and often feel I have no control over this racing mind.

0	1	2	3	4	5	6	7	8	9	10

23. I feel I can still lead a satisfactory life despite sleep difficulties.

0	1	2	3	4	5	6	7	8	9	10

24. I believe insomnia is essentially the result of a chemical imbalance.

0	1	2	3	4	5	6	7	8	9	10

25. I feel insomnia is ruining my ability to enjoy life and prevents me from doing what I want.

0	1	2	3	4	5	6	7	8	9	10

26. A “nightcap” before bedtime is a good solution to sleep problem.

0	1	2	3	4	5	6	7	8	9	10

27. Medication is probably the only solution to sleeplessness.

0	1	2	3	4	5	6	7	8	9	10

28. My sleep is getting worse all the time and I don't believe anyone can help.

0	1	2	3	4	5	6	7	8	9	10

29. It usually shows in my physical appearance when I haven't slept well.

0	1	2	3	4	5	6	7	8	9	10

30. I avoid or cancel obligations (social, family) after a poor night's sleep.

0	1	2	3	4	5	6	7	8	9	10

Scoring and Interpretation Guidelines

The total DBAS score is obtained by adding the score of each item (reverse score for item 23) and dividing by the total number of items. The are no norms available for this scale but a higher score indicates that your patient endorses more intense and more frequent dysfunctional beliefs and attitudes about sleep.

An abbreviated 16-item version is currently under validation.

Example of an Automatic Thought Record Used for Cognitive Therapy

Situation	Automatic thoughts	Emotions	Alternative thoughts	Emotions
Awake in bed in the middle of the night	"I won't be able to function tomorrow"	Anxious 80%	"There is no point in worrying about this now. Sometimes I can still function after a poor night's sleep".	Anxious 25%

The Glasgow Content of Thoughts Inventory

Instructions to Patient

This is a brief measure which should only take you a few minutes to complete. We are interested in the types of thoughts that you have while you are trying to get to sleep. Many people with insomnia complain of a "racing mind" or of thoughts that seem to get in the way of falling asleep. Simply mark one of the boxes for each of the items on the scale as an indication of how often this particular thought has been a problem for you during the past week.

Further Instructions to Clinician

The GITI is scored by adding up responses to give a total score for thought intrusion. "Never" is scored 1, "sometimes" 2, "often" 3 and "always" 4. Our preliminary work suggests that a score of 42 yields a sensitivity of 100% and a specificity of 83% in discriminating between insomniacs and good sleepers (Harvey and Espie 2003). Principal component analysis identified 3 subscales – "cognitive intrusions relating to active problem-solving (items 1, 3, 8, 12, 14, 15, 19, 21 and 23)," "cognitive intrusions relating to sleep and wakefulness" (items 5, 6, 7, 9, 11, 18, 22, 24, and 25), and "cognitive intrusions relating to somatic and sensory engagement" (items 2, 4, 10, 13, 16, 17, and 20). You may find it helpful also to calculate this subscale profile to identify in which area(s) the main intrusions fall.

	Never	Sometimes	Often	Always
1. Things in the future				
2. How tired/sleepy you feel				
3. Things that happened that day				
4. How nervous/anxious you feel				
5. How mentally awake you feel				
6. Checking the time				
7. Trivial things				
8. How you can't stop your mind from racing				
9. How long you've been awake				
10. Your health				
11. Ways you can get to sleep				
12. Things you have to do tomorrow				
13. How hot/cold you feel				
14. Your work/responsibilities				
15. How frustrated/annoyed you feel				
16. How light/dark the room is				
17. Noises you hear				
18. Being awake all night				
19. Pictures in your mind				
20. The effects of not sleeping well				
21. Your personal life				

	Never	Sometimes	Often	Always
22. How thinking too much is the problem				
23. Things in your past				
24. How bad you are at sleeping				
25. Things to do to help you sleep				

The Glasgow Sleep Effort Scale

The following seven statements relate to your night-time sleep pattern *in the past week*. Please indicate by circling *one* response how true each statement is for you.

1. I put too much effort into sleeping at night when it should come naturally
   Very much To some extent Not at all
2. I feel I should be able to control my sleep at night
   Very much To some extent Not at all
3. I put off going to bed at night for fear of not being able to sleep
   Very much To some extent Not at all
4. I worry about not sleeping if I am in bed at night and cannot sleep
   Very much To some extent Not at all
5. I am no good at sleeping at night
   Very much To some extent Not at all
6. I get anxious about sleeping before I go to bed at night
   Very much To some extent Not at all
7. I worry about the long-term consequences of not sleeping at night
   Very much To some extent Not at all

A Medication Withdrawal Schedule Form

Week	Type	Dosage (mg)	Number of nights	Total amount (mg)	% dosage reduction	Self-efficacy (0–100%)
Baseline						
Week 1						
Week 2						
Week 3						
Week 4						
Week 5						
Week 6						
Week 7						
Week 8						
Week 9						
Week 10						

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