Sleep Medicine and Mental Health

A Guide for Psychiatrists and Other Healthcare Professionals

Karim Sedky
Racha Nazir
David Bennett
Editors

Springer

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This book is dedicated to Dr. Divya Khurana, who passed away unexpectedly in a plane crash. Dr. Khurana was a professor of Pediatrics and Neurology at Drexel University College of Medicine. She was a child neurologist with special interests in epilepsy and sleep medicine and worked for more than two decades at St. Christopher's Hospital for Children in Philadelphia. She dedicated her career to her patients and to educating medical students and residents. Her sudden passing has left a void in the hearts of all who knew and loved her. Dyvia's infectious smile and endless energy will be deeply missed by her colleagues and all the families whose lives were forever impacted by her. This book serves as an everlasting memory to her achievements including the two chapters that she wrote in her last few months of her life.

Divya Khurana, MD (1965–2019)

Preface

The field of sleep disorders is relatively new, starting in the early twentieth century. Dr. Allan Rechtshaffen and Dr. Anthony Kales developed the first manualized scoring parameters in 1968 to standardize how clinicians measure sleep stages and respiratory events. While their practice parameters manual has been updated over the years, the basics remain the same. Dr. Kales is one of the first psychiatrists to cultivate interest in this field. Leaders from other disciplines including medicine/pulmonology, neurology, psychology, ear nose and throat physicians, anesthesiologist, and dentistry also emerged. This highlights the role that sleep plays across various domains of human functioning and the importance of a multidisciplinary approach to the assessment and treatment of sleep disorders.

As such, one growing trend in the field is the recognition that a multidisciplinary approach can provide optimal care. While many of the current sleep centers are directed by pulmonology programs, the involvement of mental health professionals is empirically established and increasingly appreciated as part of a multidisciplinary team approach. For example, pulmonary physicians excel in assessing and treating sleep disordered breathing conditions, especially those with lung disease (including chronic obstructive pulmonary disease), and the metabolic derangement related to it. Neurologists, in contrast, excel in assessing and treating comorbid seizures, movement disorders, and other sleep-related comorbidities that are neurologically diagnosed (such as narcolepsy). Similarly, psychiatrists prescribe and treat conditions that can interact significantly with sleep disorders. For example, the use of antipsychotic or antidepressant medications that cause increased weight gain can lead to an increased risk of sleep apnea. Psychiatrists and psychologists can also play an integral role in providing therapies for insomnia, hypersomnia, or other circadian rhythm disorders. Psychiatrists and psychologists can also play a major role in bariatric surgery assessments that help to address both weight loss and sleep-related breathing disorders. Dentists have also played a cornerstone role in creating dental devices and other dental procedures that help to treat sleep apnea. Maxillary facial surgeons similarly have played an integral role in correcting the airway passages of those whose sleep apnea is due to craniofacial abnormalities. In addition, primary care physicians are usually the first line of assessment and referral for many individuals with sleep disorders and play a very important role in identifying sleep problems and facilitating their management. Finally, ear nose and throat physicians have been key in treating children and adolescents who have adenotonsillar

enlargement as well as using endoscopes to diagnose airway obstruction. While assessment and treatment of sleep disorders, especially sleep-related breathing disorders, are fairly straight-forward, the financial cost of positive pressure ventilation (including costs associated with non-compliance) is high. Moreover, the associated long-term medical complications to untreated respiratory events and/or insomnia lead to higher risk of morbidity and mortality. It is thus imperative to have a multidisciplinary team in all sleep centers in the United States with therapists and psychiatrists playing a major role, as currently mental health professionals are playing a growing but still underutilized role in this field.

The introduction of simplified in-home polysomnography in recent years represents a second trend that has increased access to the assessment of sleep disorders as an alternative to the costly, time-consuming, and inconvenient laboratory-based sleep study. These in-home studies are increasing in their reliability and validity compared to earlier equipment, although still not as diagnostically accurate as those studies conducted in the laboratory. While one would imagine that more individuals would be treated with improved outcomes, issues around adherence continue to be a major factor hindering optimal outcomes. Again, our field of mental healthcare professionals can thus play a major role in working with patients to enhance adherence, especially when it comes to medication, behavioral therapy for insomnia, and positive pressure ventilation. The use of substances such as alcohol, nicotine, opioids, and other substances can further complicate sleep-related breathing disorders. Addiction medicine providers can thus also play a major role in managing comorbid addiction, which can improve the patient's overall psychological and sleep conditions.

Despite progress in assessing and developing evidence-based interventions for sleep disorders, healthcare providers' knowledge about sleep disorders remains relatively limited. For example, not all medical schools and residency training programs offer access to sleep medicine (whether through didactics or access to clinics that evaluate sleep disorders). In addition, older trainees have had limited exposure to this field given the recent evolution of this specialty. As such, the aim of this book is to address the need for a third trend, increased education among mental health and other healthcare professionals about the assessment, classification, and treatment of sleep disorders. In doing so, we highlight the strong relationship between psychiatric conditions and sleep disorders. Sleep disorders are very prevalent among individuals with psychiatric conditions. This relationship appears to be a bidirectional one, with an increased risk for non-response and/or relapse of psychiatric conditions if sleep disorders persist; but likewise, psychiatric conditions can lead to insomnia and to other sleep disorders. It is thus imperative for mental health professionals to be able to appropriately assess, refer, and if appropriate treat sleep problems. During our clinical careers, the editors have encountered a significant number of patients who struggled with insomnia, hypersomnia, and/or sleep disordered breathing that was often missed in prior treatment planning. These individuals often did not respond to psychiatric therapy until their comorbid sleep disorders were addressed.

It is important to note the increasing depth and knowledge currently occurring in the field of sleep and its disorders. While this book is an attempt to cover the most

important topics on sleep disorders, it is by no means inclusive of every sleep condition. Its aim, however, is to educate clinicians and trainees on the field of sleep problems and to stimulate their increased reading and practice about the field for the patients they manage. The editors hope that readers will find this book helpful as a first step toward this goal.

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Introduction

How the brain works has long been an unfolding mystery, with psychiatry and psychology representing two of the fields that seek to understand the interaction between brain biology and behavior. Even after decades of major developments, many mysteries remain. Earlier neuropsychiatrists such as Sigmund Freud posited a correlation between sleep and psychological functioning (e.g., suggesting that dreams reflected unconscious wishes). Yet despite progress in both psychiatry and sleep medicine, much is still unknown in both fields. This has sometimes led to rather limited sleep medicine education for psychiatrists and other healthcare professionals, with studies consistently showing minimal sleep education for trainees [1, 2]. While there are no recent studies that assess training in sleep medicine for physicians, a more recent study among psychology trainees found similarly limited training, with only 6% of training programs offering courses in sleep [3]. Efforts to improve sleep training persist, however, as neurology and neuroscience educators recently recommended at least 2–4 hours of sleep medicine education during medical school to enhance students' education [4].

Sleep medicine and psychiatry share significant overlap in both the pathophysiology of disorders and symptom presentation. For example, monoamine neurotransmitters (e.g., serotonin, norepinephrine, and dopamine) play a major role in depression and anxiety as well as in the control of sleep staging. It is thus not surprising to find that serotonin deficiency can lead to both depression and sleep disorders. In addition, serotonin affects airway muscular tone and can lead to increased respiratory events in those with serotonin deficiency. However, psychotropic medications that increase serotonin can also lead to restless leg syndrome, a condition that often leads to the interruption of sleep. Similarly, many psychotropic medications lead to weight gain and obesity, increasing risk for the development of sleep apnea.

Since psychiatric conditions are often diagnosed only after excluding other primary medical conditions, it would make sense to offer enhanced sleep medicine education to psychiatrists. For example, it is important to recognize that thyroid conditions can cause depression, and as such thyroid stimulating hormone (TSH) levels are commonly requested by psychiatrists when evaluating a patient for a mood disorder. In contrast, however, many mental health professionals fail to screen for sleep apnea symptoms, even in high-risk individuals. Given that sleep apnea can elicit a variety of psychiatric symptoms, this represents a missed opportunity to not

only treat the sleep apnea but to also relieve psychiatric symptoms, possibly leading to unnecessary psychiatric interventions. As such, the aim of this book is to increase mental health professionals' awareness of normal sleep, sleep pathologies, and how such pathologies can interact with psychiatric conditions.

While several classifications of sleep disorders exist, we will primarily use the International Classification of Sleep Disorders – Third Edition (ICSD-3). However, when relevant to highlight differences, criteria from the Diagnostic and Statistical Manual of Classification – Fifth Edition (DSM-5) and from the International Classification of Disorders – Tenth Edition (ICD-10) are also presented.

The book includes 17 chapters, with the first chapter providing an overview of normal sleep. The second chapter provides an overview of insomnia, followed by Chapters 3 through 6, which address the treatment of this common sleep problem using: cognitive behavioral therapy for insomnia (CBT-I), yoga and mindfulness based cognitive behavioral therapy for insomnia (Y-MBCTi), Acceptance and Commitment Therapy for insomnia (ABC-I), and pharmacological interventions. Chapters 7 and 8 address sleep disordered breathing (e.g., obstructive sleep apnea) and psychosocial approaches to enhance adherence to positive airway pressure (PAP). Chapters 9, 10, 11, and 12 cover the sleep disorders of hypersomnia, narcolepsy, circadian rhythm disorders, movement disorders, and parasomnias. Next, Chapters 13, 14, 15, and 16 discuss sleep in special populations including children and adolescents, women, older adults, and veterans. The book concludes with a chapter examining the overlap between sleep disorders and psychiatric disorders. We hope that this book will be valuable to clinicians who are interested in furthering their education in sleep medicine and will further enhance clinicians' ability to help their patients with sleep problems.

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Contents

Part I Introduction

1 Introduction to Sleep and Sleep Disorders 3
Racha Nazir

Part II Insomnia

2 Insomnia 25
Guadalupe L. Rivera and Henry J. Orff

3 Cognitive-Behavioral Therapy for Insomnia (CBT-I) 47
David Bennett

4 Yoga and Mindfulness-Based Cognitive-Behavioral Therapy for Insomnia (Y-MBCT$_i$) 67
Basant Pradhan and Sahana Malik

5 The ABCs of Insomnia (ABC-I): An Acceptance Commitment Therapy (ACT)-Based Insomnia Treatment Development Study: Pilot Results and Future Directions 85
Lavinia Fiorentino, Jennifer L. Martin, and Cathy A. Alessi

6 Pharmacotherapy for Insomnia 101
Puneet Narang, Jacob Held, and Steven Lippmann

Part III Sleep Related Respiratory Disorders

7 Sleep-Disordered Breathing 131
Kimberly Kreitinger, Matthew Light, Sagar Patel, and Atul Malhotra

8 Psychosocial Approaches for Addressing Nonadherence to Positive Airway Pressure (PAP) Therapy 151
Gerd R. Naydock

Part IV Other Sleep Disorders

9 Hypersomnia and Narcolepsy 169
Rakesh Bhattacharjee

10 Circadian Rhythm Disorders and Chronotherapy for Mood Disorders 189
Sara Timtim and David K. Welsh

11 Movement Disorders of Sleep 211
Divya S. Khurana and Karen S. Carvalho

12 Parasomnia 235
Divya S. Khurana and Karen S. Carvalho

Part V Sleep Disorders in Special Populations

13 Sleep and Psychiatric Problems in Children and Adolescents 261
Kishan Nallapula and Ron B. Mitchell

14 Sleep Disorders in Women 275
Ashabari Pellechi and Karim Sedky

15 Sleep Disorders in the Geriatric Population 293
Shafagh Heidari and Steve Huege

16 Sleep Disorders in Veterans: Prevalence, Consequences, and Treatment 315
Peter J. Colvonen, Guadalupe L. Rivera, and Jae Park

Part VI Overlap Between Psychiatric Conditions and Sleep Disorders

17 The Overlap Between Sleep Disorders and Psychiatric Disorders . . . 343
Nikhil Rao

Index 375

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Part I

Introduction

Introduction to Sleep and Sleep Disorders

1

Racha Nazir

Introduction

Sleep is a brain state in which there is diminished responsiveness and motor inhibition, with associated recumbence and closed eyes. Sleep represents an important aspect of life, constituting about a third of our life. While the exact function of sleep is unknown, it is thought to be required for energy conservation, resetting of the body, and memory consolidation, with significant complications arising in those with sleep problems [1]. Due to challenges in daily living and the easiness of cutting back on sleep, it is thus not shocking to find 60 million Americans struggling from sleep disorders [2]. Some surveys suggest a continuous decrease in the average duration of sleep: in 1960 Americans slept 8–8.9 hrs on average, while in 1995 this number decreased to 7 hrs, with more than 30% of adults sleeping less than 6 hrs in 2004 [3, 4, 5]. Both direct and indirect economic burden as a consequence of sleep problems was estimated at $924 for young individual and $1,253 per geriatric patient compared to those without insomnia in a 2007 analysis of Americans [6]; a total of $13.9 billion in lost revenue was assessed in 1995, with $1.97 billion spent on hypnotics in the United States [7].

Disruption of sleep and the presence of sleep disorders can lead to and even worsen psychiatric (e.g., depression and anxiety), medical (e.g., diabetes mellitus [DM], strokes), and cognitive conditions (e.g., problems with memory consolidation) [1]. In addition, about 328,000 accidents occur yearly in the United States due to drowsiness and/or fatigue, with up to 21% involving fatalities [8]. Moreover, individuals with sleep problems have a 1.62 times higher risk of being injured than workers without sleep problems, with up to 13% of work injuries can be attributed to sleep problems [9]. To highlight the importance of sleep on cognition, the Accreditation Council for Graduate Medical Education (ACGME) changed their regulations for trainees in 2011 to cap their weekly working hours at 80 after a

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cornerstone study showed a higher number of errors among intensive care unit residents working continuous hours compared to those on a limited schedule [10].

While training of medical students and residents on sleep medicine tend to be minimal, many specialties are offering sub-specialization in the field. The American Board of Medical Specialties (ABMS) has sub-specializations in sleep medicine for residents in internal medicine, family medicine, psychiatry, neurology, and anesthesia. In addition, dentists can also specialize in sleep medicine given their significant role in the evaluation of oral causes of sleep apnea and management of dental devices to treat it. However, residency training in sleep medicine for all of these specialties is inadequate, leaving only a small number of practitioners knowledgeable about this field. Compared to a 1978 survey that found only 46% of surveyed medical schools offered education or training for sleep disorders, a slight increase to 55% was reported in 1995 [11, 12]. Internal medicine trainees had the highest exposure to sleep medicine (27.1%), followed by psychiatry (25.9%) and neurology (19.3%) residents, with only 7.2% of pediatrics residents receiving some training. However, the average duration of teaching for sleep medicine was only 2.1 hrs [13]. Another survey completed by neurology residency program directors conducted in 2010 found 81% of their programs had a formal sleep rotation [14]. In addition, in psychiatry 34% of chief residents reported having elective rotations in sleep available at their institution [15]. While previous studies showed improvement in sleep education among trainees, this later study suggested a possible decline in sleep medicine education among psychiatry residents over time. In addition, an international survey involving 12 countries in 2011 further suggested that the average sleep training is rather limited given the importance of sleep as less than 2.5 hrs of sleep education was provided in medical schools, with 27% not having any [16]. The United States and Australia were the only two countries with an average of more than 3 hrs of education.

In addition to the high prevalence of sleep problems and the often minimal education about them, it is important to note how sleep can affect the outcome of psychiatric conditions. In the past, it was thought that sleep problems would resolve once psychiatric conditions (e.g., depression) were treated. However, recent studies suggest that sleep problems, while often related to psychiatric disorders, are distinct from psychiatric disorders and that not directly addressing sleep problems can lead to relapse of psychiatric disorders or hinder recovery [14]. This was one of the reasons for removing subtypes of insomnia (e.g., insomnia due to psychiatric conditions, and insomnia due to substances) in favor of only acute and chronic insomnia as diagnostic criteria in the *International Classification of Sleep Disorders* – Third Edition (ICSD-3) [17]. While physicians tend to prescribe sedating psychotropic medications (e.g., the antipsychotic quetiapine for individuals with bipolar disorder or schizophrenia, and sedating antidepressants like trazodone or mirtazapine for depressed or anxious persons), studies suggest that these medications might not be sufficient to treat insomnia. Furthermore, some psychotropic medications can cause significant metabolic syndrome (including symptoms of weight gain), increasing the risk of obstructive sleep apnea. Similarly, some of the serotonergic agents might increase the occurrence and severity of restless leg syndrome (RLS) leading to sleep deterioration.

Understanding normal sleep and screening for sleep disorders are an essential first step toward improving general health. The aim of this chapter is to provide knowledge about normal sleep, sleep evaluation, and an introduction to the treatment for sleep problems. Psychiatrists, psychologists, and other behavioral health professionals should incorporate screening of sleep problems in their patient assessments.

Functions of Sleep

While the functions of sleep are still not completely understood, disorders of sleep can lead to significant health consequences. Many of the assumed functions of sleep are derived from studies of the consequences of sleep deprivation.

Memory and Sleep Memory formation is divided into a stabilization stage occurring while awake (i.e., memory encoding) and an enhancement or consolidation stage that largely occurs during sleep [1]. The enhancement stage can help to restore lost memories and/or form new ones. Both slow wave sleep (SWS) and rapid eye movement (REM) sleep stages are essential for memory consolidation, with the former causing reactivation and redistribution of hippocampal memories (and consolidation of declarative memory) and the latter causing an increase in cortical synaptic memory consolidation (and consolidation of procedural and emotional aspects of memory) [18]. While longer durations of sleep (i.e., 8 hrs) showed the greatest positive effects on memory consolidation, short and ultrashort (e.g., 6 mins) sleep durations also showed improvements in memory consolidation compared to those with sleep deprivation. In addition, the closer the sleep onset is to the time of learning (e.g., within 3 hrs), the greater the consolidation effect was observed compared to when sleep onset occurred the next day [19]. Interestingly, some studies suggest that the psychopharmacological inhibition of REM, while expected to worsen memory, actually leads to better procedural memory consolidation in addition to an increase in non-REM (NREM) stage 2 spindle activity [19].

Process of Synapse, Circuit Maintenance, and Sleep Some researchers hypothesize that sleep has a role in achieving neuronal synaptic homeostasis by downscaling synapsis occurring during the day to the most important ones and eliminating unnecessary ones. This focused and preserved synapsis will lead to less energy consumption [20]. This can be understood perhaps more readily using the analogy of storing pictures on the cell phone, and deleting some of these pictures leading to energy conservation in the phone battery consumption. It is important to note that the downscaling of synapsis occurs mainly during SWS due to repeated depolarization–hyperpolarization states and an outcome of decrease in synapsis by 20% [20].

Attention and Working Memory Acute sleep deprivation worsens attention, with errors of omission (e.g., failing to identify a target letter) that are highly erratic (i.e., variable task performance) [21]. While sleep deprivation duration is correlated with the severity of attentional problems, some individuals might be more susceptible to this than others for unknown reasons [21]. Functional imaging has shown a reduction in the dorsolateral prefrontal cortex and intraparietal sulcus activity during sleep deprivation; the latter brain site has been associated with disorders of inattention and impulsivity such as attention deficit hyperactivity disorder and borderline personality disorder [21]. Neuronal network breakdown including the thalamocortical connections and amygdala to dorsolateral prefrontal cortex after sleep deprivation might explain some of these attentional problems [21].

Reward Processing, Dopamine, and Sleep Deprivation Sleep deprivation might lead to hypersensitization in the dopaminergic function of the mesolimbic rewards system, a connection mainly occurring between the ventral tegmental area and the prefrontal cortex. This leads to an incremental impairment of reward discrimination, with individuals sometimes even failing to discriminate between rewards and punishments. Thus, more risky decisions and higher reward sensitivity usually occur among sleep-deprived individuals. In addition, emotionally driven pleasure responses in the amygdala and striatum (including food intake) become impaired in sleep-deprived individuals leading to unhealthy decisions. Normally, during increased prolonged arousal, dopamine increases; however, a decrease in dopamine-2 (D2) and dopamine-3 (D3) receptor internalization occurs during sleep deprivation. An increase in dopamine-1 (D1) stimulation has been linked to increased risk for addictions ranging from overeating to substance abuse [21]. Some researchers have suggested that the presence of insomnia in childhood can lead to increased risk of addiction later in life [22] and increased risk of alcohol relapse following continued insomnia [23].

Brain Energy Conservation, Restoration, and Sleep During NREM, parasympathetic activity is usually increased (with a corresponding decrease in sympathetic activity). This slows heart rate and respiration as well as energy consumption, leading to energy conservation [24, 25]. Removing toxic waste from the brain during sleep has also been proposed as a function of sleep, including the removal of extracellular β-amyloid [25, 26].

Neuroendocrine Modulation, Obesity, Diabetes Mellitus (DM), and Sleep While growth hormone and prolactin increase during sleep, cortisol and thyroid stimulating hormone decrease [27]. Some studies suggest a neuroendocrinal and glucose control modulation function of sleep. In individuals with insufficient sleep duration, ghrelin (a peptide that leads to increased hunger) increases while leptin (a hormone causing satiety) decreases. This leads to dysregulation of appetite causing increased

hunger and increased risk for pathologies related to glucose metabolism and the development of DM [27]. Similarly, hormonal dysregulation (growth hormone, prolactin, and cortisol) has been found following sleep deprivation [27]. Obesity and DM have thus been partially attributed to the lack of insufficient sleep in children, adolescents, and adults [27].

During sleep, noradrenergic tone decreases especially during REM. In cases of insomnia or sleep deprivation, there is lack of this decrease in sympathetic activity. This increase in sympathetic activity can lead to heightened anxiety [21].

Immune Function and Sleep Infections are associated with increased sleep, although it is unclear whether this is due to a response to bacterial products. However, it is known that increased sleep during infection has been linked to lower morbidity and mortality [28, 29], perhaps due to sleep's role in energy conservation.

Normal Sleep and Sleep Architecture

An average adult sleeps 6–8 h, representing a third of our lives. Sleep is divided into two main stages based on findings from electroencephalogram (EEG) waves, eye movements, and chin electromyographic changes detected by polysomnography (PSG): non-rapid eye movement (NREM) and rapid eye movement (REM). NREM is further divided into stages 1 through 3 sleep, with stage 3 (also called slow wave stage [SWS] or delta sleep) historically divided into stages 3 and 4, depending on the percentage of delta waves in each epoch that characterizes this stage. However, this distinction was removed as disorders occurring during stages 3 and 4 are similar. The sleep cycle in adults starts with N1, which highlights the person's drowsiness (sometimes in newborns, sleep can start with the REM stage), followed by N2, and a deeper stage of sleep, N3. REM usually occurs 90–120 min after sleep onset in adults, usually occurring briefly in the first cycle with a gradual increase in its duration as sleep progresses. Conversely, the reverse occurs for NREM sleep (i.e., the ratio of NREM/REM is high initially and decreases later in the night). There are usually four to five NREM/REM cycles during the night.

Non-Rapid Eye Movement Stages (NREM)

Brain waves help detect wakefulness and stages of sleep, with the highest in frequency occurring during wakefulness and slowly decreasing as sleep deepens. NREM sleep is divided into three major stages: a light stage of sleep (stage 1 or N1); a deeper stage (stage 2 or N2); and SWS (also known as stages 3 and 4, N3, or delta wave sleep). The arousal threshold, referring to how readily one is awakened, is lowest during NREM stage 1 and highest in NREM stages 3 and 4. Table 1.1 shows the changes occurring in different wake–sleep stages.

Table 1.1 Sleep characteristics and waves

	Duration	Respiration and HR	Chin activity	Type of waves	Blinking and REM
Wakefulness with eyes open	–	Regular unless controlled voluntarily	High	Beta and alpha	Might have REM due to reading; occasional blinking observed
Wakefulness with eyes closed	–	Regular unless controlled voluntarily	Normal or high	Alpha activity (8–13 Hz) in the posterior head regions	No blinking
N1	1–5%	Regular	Decreased compared to wakefulness	Theta (4–7 Hz)	Blinking and eye movements stop
N2	45–55%	Regular	Decreased compared to wakefulness	K complexes (0.5 s spike) and spindles (12–16 Hz)	No eye movement
N3	5–20%	Regular	Decreased compared to wakefulness	Delta waves (0.5–2 Hz)	No eye movement
REM	20–25%	Irregular and increased	Atonia; penile tumescence	Sew tooth waves (EEG desynchronization)	REM

HR heart rate, *EEG* electroencephalogram, *REM* rapid eye movement

Wakefulness Low-amplitude, high-frequency, desynchronous beta waves characterize brain activities in humans when alert with their eyes open. Synchronized, slower alpha waves (8–13 Hz) in the posterior head region replace beta waves when the person is drowsy and eyes are closed. As eye movements while reading can very easily be confused with the REM stage, it is important to detect the background EEG to confirm this staging. Normal or high chin activity as well as regular breathing is also observed during wakefulness.

Stage 1 (or N1) Stage 1 is the shortest in duration representing 0–5% of total sleep time (TST). It is characterized by theta waves (4–7 Hz), with a subtle slowing in frequency and relaxation of muscular activity (i.e., masseter muscle or chin tone and/or leg muscles) compared to the wake state. Hypnic jerks characterized by sudden muscle contraction, a non-pathological condition, can be observed during this stage and are brief.

Stage 2 (or N2) Stage 2 represents 45–55% of TST and is much more pronounced with the development of sleep spindles (short, rapid, and synchronized bursts of

brain activity with low amplitudes of 7–14 Hz) and K complexes (a brief 0.5 s, but large electric spike). The function of these waves is not clearly understood. No eye movement occurs in this stage.

Stage 3 and 4 (or N3) Stage 3 and 4 represents 20–25% of TST and is characterized by the large amplitude delta waves (large 75 microvolt or 0.5–2 Hz). The only difference between stages 3 and 4 is the percentage of the delta waves (i.e., delta waves span 20–50% of the epoch in stage 3 but more than 50% in stage 4). It is important to note that higher amplitude waves occur during N3 sleep when the person is younger (e.g., a 3-year-old child will have larger and more frequent delta waves than a geriatric individual). Memory consolidation (especially declarative memory) is believed to occur in both N3 stage and the REM stage.

Rapid Eye Movement Stage (REM)

In the REM stage, all muscles except for the ocular, heart, and breathing muscles are in complete atonia. Although dreams occur in all stages of sleep, it is during REM that vivid dreams occur. Individuals who lack atonia during REM and who act on their vivid dreams will sometimes injure their bed partner due to their movements (i.e., REM behavior disorder [RBD]). While most individuals have a lag time of 90–120 min before initiating REM, individuals with a short REM latency (as in narcolepsy) will present with hypnagogic hallucinations (i.e., they initiate dreaming while awake, which the individual may perceive as hallucinations). The classic sleep paralysis in narcoleptics occurs when they wake in the morning but cannot move their muscles due to continued atonia while in the REM stage. Similarly, the sudden loss of muscle tone (i.e., cataplexy) that occurs with emotional stimulation in narcolepsy is due to the rapid onset of REM with its atonic state. It is important to note that REM starts during the first 60–120 min of sleep initiation (depending on the individual's age), with shorter durations of REM occurring in the initial phases and longer durations toward the second half of the night. In addition, REM density, defined as the number of eye movements/time, increases in the second half of the night. Thus, disorders elicited during REM occur more often in the second half of the night (an important question to ask patients or their partner is "when does the disorder occur in the night?"). Vital signs including breathing are usually irregular and variable during the REM stage. Electroencelphalogram (EEG) shows irregular wave amplitude (also known as saw teeth activities) of the brain during this stage. Phasic waves are observed during rapid eye movements occurring in the pons, lateral geniculate thalamus, and occipital cortex [30]. Both penile tumescence in males and vaginal engorgement in females occur during this stage. In addition, brain metabolism increases during this stage. The REM stage duration significantly decreases in individuals prescribed serotonergic agents, stimulant medications, and/or benzodiazepines (BNZs).

Process C and Process S

In the early 1980s, the Swiss sleep researcher Alexander Borbely proposed that sleep depends on two processes: Process C, involving circadian rhythms, and Process S, involving sleep/wake homeostasis [31]. Process S is the propensity to feel sleepy with longer periods of wakefulness. However, after sleeping, the propensity to sleep decreases to its lowest point, slowly increasing as the person stays awake. There is a neurochemical basis for Process S as adenosine increases in the basal forebrain and inhibits A1 receptors, subsequently leading to an inhibition of wakefulness. In addition, A2 receptors induce Fos expression leading to sleepiness. Coffee and caffeinated beverages are adenosine receptor antagonists, thus leading to increased alertness.

Process C involves our internal clock (circadian oscillator), centered in the suprachiasmatic nucleus in the anterior hypothalamus, and stimulates sleep to occur at certain times and wakefulness at others. Although it depends in part on time cues that include light exposure and social cues (e.g., food intake, going to work/school, presence of a clock; these are usually referred to as Zeitgebers), [32] its duration typically exceeds the 24-hour day in the absence of cues (average around 24.9 h). Studies suggest that during sleep deprivation, the frontoparietal area is sensitive to sleep pressure (Process S), while the thalamus and basal ganglia are more affected by circadian rhythms (Process C) [33].

Understanding the effects of photoentrainment and sleep becomes very important. When light stimulates certain retinal cells containing melanopsin, through the retinohypothalamic tract, it leads to stimulation of the suprachiasmatic nucleus of the hypothalamus to inhibit melatonin secretion (which helps to control body temperature, hormones including cortisol, and vital sign variation during sleep). Through the preganglionic sympathetic neurons in the lateral horn of the spinal cord, light/darkness affects the superior cervical ganglia (through norepinephrine), which have their postganglionic neurons in the pineal gland, which secretes melatonin. The pineal gland increases the enzyme *N*-acetyltransferase to form *N*-acteyl-5-methoxytryptamine from tryptophan leading to the increased formation and secretion of melatonin. Thus, with gradual onset of darkness, melatonin is secreted. Dim light melatonin onset (DLMO) refers to the slow increase in melatonin secretion (until a level causing sleepiness is reached) as a response to darkness. DLMO occurs 2 hrs before the onset of sleep time, and when melatonin reaches a certain level, individuals start feeling sleepy. It is thus not surprising to find delayed sleep onset (circadian rhythm phase delay) among people who are exposed to late night light exposure from cell phones, computer screens, TV, or other devices.

Over the counter melatonin, which stimulates melatonin 1 and 2 receptors in the brain, and melatonin agonists (Rozerem) have been used to treat certain forms of insomnia. Three possible mechanisms of melatonin or its agonist exist: it is theorized to work by either causing a shift in circadian rhythm phase, reduction in body temperature, or by directly acting on sleep centers causing sleepiness [34]. In addition, agomelatine has been suggested to regulate circadian rhythm and also act as an antidepressant. Thus, some researchers recommend the use of much lower melatonin

doses (i.e., 0.3–0.5 mg) 3–5 hrs before the target bedtime as a way to stimulate a melatonin surge (or DMLO). Calcification of the pineal gland in the geriatric population can lead to circadian rhythm problems and thus cause deficiency in melatonin production. Due to the overlap between Process C and Process S, the lowest alertness levels occur at 4–6 a.m. and, to a lesser extent, around 2–4 p.m.

Sleep Changes Over Life Stages

Sleep Duration and Age Sleep duration varies significantly depending on the age of the individual, with a gradual decrease as the individual ages. According to the National Sleep Foundation, recommended sleep durations are as follows: newborns (<3 months) are expected to sleep 14–17 hrs a day; infants (3–11 months) 12–15 hrs; toddlers (1–2 years) 11–14 hrs; preschoolers (3–5 years) 10–13 hrs; school-aged children (6–13) 9–11 hrs; teenagers (14–17) 8–10 hrs; younger adults (18–25) 7–9 hrs; adults (26–64) 7–8 hrs; and geriatric population 7–8 hrs [35, 36].

Sleep Architecture and Children In newborns, due to the lack of typical waves that characterize sleep stages (i.e., sleep spindles and K complexes that characterize stage 2 NREM sleep develop at 3 and 6 months after birth, respectively), a different type of sleep staging is observed. Sleep at this age is divided into an active stage (equivalent to REM sleep), "non-active" stage (equivalent to NREM), intermediate stage (having characteristics of both previous stages), and indeterminant stage (cannot be characterized as either of the first three stages). Spindles occur at 2–3 months after birth, K complexes at 4–6 months, and delta waves at 4–5 months [37, 38]. Thus, waves characteristic of sleep stages in older children and adults emerge by 6 months, when sleep is divided into NREM and REM sleep.

In newborns, sleep usually starts with the onset of an active sleep stage (or what is equivalent to REM in adults) and its sleep percentage starts to gradually decrease at 3 months [38]. This is in comparison to older children and adults in which it is pathological if REM occurs within the first 15 min of sleep and might signify insomnia or narcolepsy. In adults, REM latency (time from sleep until the first occurrence of REM sleep) is 90–120 min. However, REM latency and sleep cycles tend to be shorter in infants (45–60 min cycles) and older children (60–90 min cycles). In addition, active sleep (REM equivalent) constitutes 50% of the infant's sleep, 30% at age two, and only 20–25% in older children and adults.

Consolidation of Night Sleep and Napping. In newborns, sleep is usually interrupted every 2–4 hrs due to their frequent need for nutrition. Consolidation of nighttime sleep usually occurs around 6 months, at which time parents can sleep better [38]. Sleep is further consolidated at night as napping gradually becomes less frequent, with most children ceasing to nap by 5 years of age. In some cultures, however, adults usually continue to have an afternoon nap (around 4–5 p.m.). In the

geriatric population, daytime napping can occur at a higher frequency due to daytime fatigue and the interruption in their nighttime sleep.

Sleep Architecture and Geriatrics Compared to younger adults, geriatric individuals have the same sleep latency (SL) and REM duration, but exhibit a decrease in SWS stage duration, total sleep time (TST), and sleep efficacy (SE). In addition, increased waking after sleep onset (WASO) occurs as well as a possible albeit slight increase in stages 1 and 2 sleep. Aging and associated neuropathological processes affecting the suprachiasmatic nucleus, medical issues (e.g., pain, frequent urination, polypharmacy), comorbid sleep problems (e.g., increased prevalence of sleep apnea), and psychiatric problems (e.g., depression and anxiety) can further affect sleep among geriatric individuals.

Circadian Rhythm and Age During the adolescent period, there is a tendency for the development of circadian rhythm delay. This means that adolescents usually go to sleep and wake up at later times than normal, with maintenance of sleep duration if given the opportunity. This often becomes problematic as youth get older and school start time becomes earlier. In addition, exercising relatively late at night might increase the risk of such phase delay. The use of electronics (especially with schoolwork necessitating computer use) can further complicate adolescent sleep. Thus, sleep deprivation and daytime sleepiness is not uncommon in this age group. A growing number of school districts, however, are starting school somewhat later in the morning as research indicates that later starting times are associated with longer sleep durations [39]. Additionally, later start times were associated with less daytime sleepiness [40]. In contrast to adolescents, geriatric individuals often develop circadian rhythm advance (i.e., early sleep onset and early morning awakening) with fragmented sleep [41]. Due to the decrease in delta waves, N3 usually is significantly shorter in this older population compared to their younger counterparts.

Neurobiology and Neuroanatomy of Sleep

While aspects of sleep continue to be a mystery, there has been a significant increase in knowledge about the neurobiology of the sleep–wake cycle. Table 1.2 reviews specific brain areas and neurotransmitters involved in sleep–wake cycles. Wakefulness is promoted by activity in the pons, midbrain, and posterior hypothalamus through the monoamine neurotransmitters including acetylcholine, norepinephrine, dopamine, serotonin, histamine, and orexin. Damage to the posterior hypothalamus causes a coma-like state [42]. NREM sleep, on the other hand, depends on activity in the preoptic area in the anterior hypothalamus and forebrain through gamma-aminobutyric acid (GABA) and galanin neurotransmitters. Thus, damage to these centers will lead to loss of the major inhibitory neurotransmitters leading to insomnia [42]. REM initiation depends on pontine and midbrain

Table 1.2 Brain areas and neurotransmitters involved in the sleep–wake cycle

	Brain centers	Neurotransmitters	Function	Pathology	Medications
Wakefulness	Lateral and posterior hypothalamus stimulate dorsal raphe (orexin A/B), locus coeruleus (orexin A), and tuberomammillary nucleus in posterior hypothalamus (orexin B)	Orexin		Deficiency of orexin leads to narcolepsy	Suvorexant is an orexin antagonist that helps elicit sleep
	Dorsal raphe nucleus (orexin A/B)	Serotonin	Causes wakefulness and decreases REM sleep		Stimulation by SSRIs causes insomnia; however, agomelatine blocks 5-HT2 receptors inducing NREM sleep
	Locus coeruleus (orexin A)	Norepinephrine	Highest in wakeful state, less in NREM, and lowest in REM sleep		Stimulation by SNRIs cause insomnia; alpha-1 antagonist (prazosin) help decrease nightmares/PTSD symptoms, while alpha-2 antagonist (clonidine) causes sleepiness
	Reticular formation (lateral dorsal tegmentum and pedunculopontine tegmentum)	Acetylcholine	Discharge during wakefulness and REM-On (which induces REM onset) and inactive in NREM	Decreased acetylcholine in dementia patients is often associated with excessive sleepiness	
	Substantia nigra and ventral tegmental nucleus	Dopamine	Causes wakefulness	In parkinsonism, damage to SN leads to sleepiness	Stimulants increase dopamine, causing wakefulness; antipsychotic medications cause sedation; ropinirole and pramipexole induce sleepiness by auto-activation of inhibitory D2/D3 receptors

(continued)

Table 1.2 (continued)

	Brain centers	Neurotransmitters	Function	Pathology	Medications
	Tuberomammillary nucleus (orexin B) in posterior hypothalamus	Histamine projections to cerebral cortex, amygdala, substantia nigra	Active in wake, less in NREM, and silent in REM	Lesions of the posterior hypothalamus cause coma-like state [23]	Antihistaminic medications (Benadryl or diphenhydramine) cause sedation
NREM	Ventrolateral preoptic area in anterior thalamus Forebrain	GABA Galanin	Inhibited by monoamines and acetylcholine		Benzodiazepines and gabapentin cause sedation
REM [22]	Subcoeruleus nucleus Dorsal paragigantocellular reticular nucleus Pontine Caudal midbrain	REM-On: – acetylcholine, glutamate, GABA, and glycine REM-Off: – noradrenaline, adrenaline, serotonin, histamine, and GABA.	Monoamines are least active during REM		SSRIs and SNRIs inhibit REM duration; norepinephrine is inactive during cataplexy; thus, venlafaxine has been used to treat cataplexy

REM rapid eye movement, *SSRIs* selective serotonin reuptake inhibitors, *NREM* non-rapid eye movement, *SNRIs* selective norepinephrine reuptake inhibitors, *PTSD* post-traumatic stress disorder, *SN* substantia nigra, *GABA* gamma-aminobutyric acid

structures, with acetylcholine, glutamate, and glycine being important for REM initiation. It is thought that the subcoeruleus nucleus (in the mesopontine junction) is the main REM generating center, with stimulation causing REM atonia (mainly through GABA/glycine in ventromedial medulla) while damage to it causes a reduction in REM sleep [43].

Sleep Disorder Classifications

Three major classification systems exist and are often used to classify sleep disorders: the *Diagnostic and Statistical Manual of Mental Disorders* – Fifth Edition (DSM-5) [44], the *International Classification of Sleep Disorders* – Third Edition (ICSD-3) [17], and the *International Statistical Classification of Diseases and Related Health Problems* – Tenth Edition (ICD-10 [40]; see Table 1.3). Within the

Table 1.3 Classification of sleep disorders according to the *Diagnostic and Statistical Manual of Mental disorders* – Fifth Edition (DSM-5), *International Classification of Sleep Disorders* – Third Edition (ICSD-3), and *International Statistical Classification of Diseases and Related Health Problems* – Tenth Edition (ICD-10)

Classification	Types
DSM-5 (Sleep–wake disorders)	Insomnia Hypersomnia Narcolepsy Breathing-related sleep disorders: obstructive sleep apnea–hypopnea, central sleep apnea, sleep-related hypoventilation Circadian rhythm sleep–wake disorders Parasomnia: Non-rapid eye movement (NREM) sleep arousal disorders, nightmares, REM behavior disorder (RBD) Restless leg syndrome (RLS) Substance- or medication-induced sleep disorders Others: other specific insomnia, unspecified insomnia, other specified hypersomnolence, unspecified hypersomnolence, other specified sleep–wake and unspecified sleep–wake disorders
ICSD-3	Insomnia Sleep-related breathing problems Central disorders of hypersomnolence Circadian rhythm sleep–wake Parasomnias Sleep-related movement disorders (i.e., restless leg syndrome, nocturnal seizures) Other sleep disorders
ICD-10	Insomnia Hypersomnia Circadian rhythm problems Sleep-related breathing problems Sleep-related movement disorders (i.e., restless leg syndrome, nocturnal seizures) Parasomnias Other sleep category and drug-induced sleep disorders

United States, DSM-5 is the primary manual used to diagnose psychiatric disorders, whereas in most other countries ICD-10 is used. Sleep specialists, especially in the United States, usually use ICSD-3.

In DSM-5, sleep disorders were divided into ten major categories: insomnia, hypersomnia, narcolepsy, breathing-related sleep disorders (obstructive sleep apnea, central sleep apnea, sleep-related hypoventilation), circadian rhythm sleep–wake disorders, non-rapid eye movement (NREM) sleep arousal disorders, nightmares, REM behavior disorder (RBD), restless leg syndrome (RLS), and substance- or medication-induced sleep disorders.

In contrast, the ICSD-3 has divided sleep disorders into seven major categories depending on the associated signs and symptoms. If the duration of sleep is affected, this can lead to either insomnia (sleeping less than expected) or hypersomnia (sleeping longer than expected). If the individual's sleep–wake cycle does not match the expected sleep–wake cycle, then circadian rhythm problems occur. One of the most frequently used diagnostic categories is sleep-related breathing problems that include obstructive sleep apnea. In addition, sleep-related movement disorders include neurological issues (i.e., restless leg syndrome, nocturnal seizures). Parasomnias are often encountered in children and include sleep walking and sleep talking. A final sleep category falls under the terminology of "other sleep category" for those problems that do not meet diagnostic criteria elsewhere.

The ICD-10 classification system for sleep disorders is similar to that of ICSD-3, with the addition of drug-induced sleep disorders as a diagnostic category. While the aim of these classification systems is to bring uniformity and consistency in diagnoses, differences in diagnostic criteria exist across systems (see Chap. 2). As such, we will focus on the use of the ICSD-3 classification because it focuses on sleep disorders in a more comprehensive manner, while highlighting differences from the other two classification systems.

Effects of Psychotropic Medications on Sleep

Total Sleep Time and Sleep Efficacy Sedating psychotropic medications that work through histamine and alpha-1 blockage (i.e., trazodone, mirtazapine, doxepin, risperidone, quetiapine, and olanzapine) can lead to increases in TST [45]. Among psychotropic medications (even the sedating ones), low-dose doxepin is the only medication approved by the Food and Drug Administration (FDA) to treat insomnia. Other psychotropic medications have not shown significant efficacy in treating insomnia, with a growing concern that the use of second-generation antipsychotics can increase risk of metabolic syndrome and extrapyramidal side effects [46]. However, benzodiazepines and Z-drugs (i.e., zolpidem, zopiclone, eszopiclone, and zaleplon) increase TST and sleep efficacy while decreasing REM, and thus can be helpful in treating insomnia and REM behavior disorder (RBD). In comparison, monoamine oxidase inhibitors (MAOIs) can lead to insomnia by prolonging sleep latency (SL) and increasing arousals [45].

REM Stage In addition, psychotropic medications can also lead to inhibition of REM duration due to their stimulation of serotonin and norepinephrine (thus masking narcolepsy signs during polysomnography [PSG] and mean sleep latency test [MSLT] results through stimulation of 5-HT1A) and to sleep fragmentation (through 5-HT2 agonist and alpha-2 inhibition effects). It is important to note the presence of eye movements, which can be confused with REM, during NREM sleep in individuals taking selective serotonin reuptake inhibitors (SSRIs), especially fluoxetine. Since the omnipause neurons in the brain stem inhibit saccadic eye movements, the increase in serotonin from SSRIs will lead to inhibition of the "omnipause" neurons causing the occurrence of saccadic eye movements (also known as "prozac eyes"). This latter phenomenon was found in 48.8% of individuals treated with fluoxetine compared to only 5.8% of individuals on tricyclic antidepressants [46].

Movement Disorders Serotonergic agents (i.e., antidepressants and/or atypical antipsychotic medications) have been shown to often increase the occurrences of RLS (with an onset before sleep, but can also lead to an interruption in sleep), periodic leg movements (PLMS), and/or bruxism (teeth grinding). The antidepressant bupropion has the least negative impact on these side effects and might theoretically improve RLS due to its dopaminergic stimulation. Similarly, gabapentin and BNZs have been used off-label to treat RLS.

Obstructive Sleep Apnea Many psychotropic medications, especially antipsychotic drugs, can lead to weight gain and increased risk of OSA. Some studies suggest this increased risk is independent of the antipsychotic medication's weight gain effects, possibly acting through reduction in the hypoglossal nerve activity during inspiration [47, 48].

Interaction Between Sleep Disorders, Psychiatric Complications, and Medical Problems

Although the function of sleep is yet to be fully understood, a direct bidirectional relationship between sleep disorders and both medical and psychiatric disorders are well delineated. For example, in children with obstructive sleep apnea (OSA), attention deficit hyperactivity-like symptoms [49, 50] and depression [51] have been reported. Similarly, a bidirectional relationship is observed in manic individuals with a lack of sleep precipitating the onset of mania and manic episodes leading to a decreased need for sleep. Accordingly, studies suggest that sleep disorders need to be addressed during the treatment of psychiatric disorders to better attain remission to euthymia. Chapter 17 discusses this relationship in more detail.

Similarly, a higher prevalence of diabetes mellitus (DM), cardiovascular complications (i.e., hypertension, strokes, and heart disease), obesity including high (HDL) and low-density lipoprotein (LDL) levels [52], and even cancer have been linked to

untreated OSA. In addition, OSA severity is associated with an increased prevalence of hypertension, leaving some to suggest treatment resistance to such medical and psychiatric complications if OSA is not addressed [53, 54].

Sleep Assessment Measures

The assessment of normal sleep can include clinical interviews, questionnaire-based self-report scales, and the use of equipment (e.g., to conduct polysomnography). Clinical interviews may inquire about one's sleep pattern including naps, work/academic schedule, food intake, and screening for specific sleep disorders including OSA. Self-report questionnaires include sleep logs (recording when the person went to sleep, how often and how long they had arousals, and what time s/he woke up during a 1–2 week period), the 7-item Insomnia Severity Index (ISI) to screen for insomnia, and the 8-item Epworth Sleepiness Scale (ESS) to screen for daytime sleepiness.

Similarly, there are objective measures, some of which are less sensitive compared to polysomnography (PSG), including actigraphy (a sensor worn to measure movement, based on the assumption that the person is asleep if they do not move) and pulse oximetry (measuring oxygen saturation), while others measure autonomic activities that have been correlated to sleep. Nocturnal pulse oximetry has been used to detect any decrease in oxygen during sleep, suggesting the occurrence of respiratory events. Home sleep testing (HST), which measures airflow, chest expansion (or lack of), and nocturnal oximetry, has been increasingly used due to its easy accessibility, especially for individuals with developmental disorders or those with anxiety disorders who might not tolerate polysomnography, and the lower cost (compared to PSG). However, PSG (i.e., a "sleep study") remains the gold standard method for diagnosis of sleep disorders. PSG records brain waves, blood oxygen levels, heart rate, breathing, and eye and leg movements to assist in identifying sleep disorders. Thus, for certain populations (e.g., people with significant metabolic syndrome and/or pulmonary complications), a HST is not preferred because it is less sensitive in detecting respiratory events. PSG is the standard of practice for pediatric populations as well, given the lower scoring cutoff used in this population, and thus any missed events by HST (compared to PSG) might lead to less accurate classification of the respiratory events (see Chap. 7), while many insurance companies require the PSG study to be used initially for diagnosis.

PSG includes EEG leads around the eyes to depict the eye movements (i.e., to diagnose rapid eye movements [REM] stage), around the masseter muscle (to detect teeth grinding and helps in staging of sleep including atonia during REM), and around the bilateral limb to diagnose periodic leg movements (i.e., individuals might move their limbs often during sleep, interrupting it). In individuals suspected of having seizure activity, extra EEG leads are used to better detect abnormal brain activity (i.e., epileptic activity). Airflow sensors include pressure and thermal flow to both the nose and mouth (to diagnose apnea–hypopnea index, which is the number of respiratory events per hour and is critical to the diagnosis of apnea). A snoring microphone is

available to detect snoring. Two chest and abdominal belts are available to assess the extent of breathing and chest/abdominal expansion. Oximetry (and in pediatrics, end tidal carbon dioxide detection) is available to detect oxygen level. In comparison, HST has limited recording capabilities, which include nasal sensor for airflow detection, one abdominal belt, and pulse oxygenation (variable forms of equipment and information leads are available). A newer form of in-home sleep study (WatchPAT) depends on the vascular sympathetic activity and involves attaching fewer leads. Chapter 7 discusses respiratory descriptors in detail.

Conclusion

Sleep is a very complex process that is necessary for living organisms. While its exact function is not completely understood, its abnormalities can lead to significant medical and psychiatric complications. The overlap in neurotransmitters between sleep and psychiatric conditions further highlights the importance of addressing sleep disorders in individuals with psychiatric complications.

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Part II

Insomnia

Insomnia

2

Guadalupe L. Rivera and Henry J. Orff

Introduction

Insomnia is diagnosed in cases where an individual has difficulty falling or staying asleep, or wakes earlier than desired, with associated impairment in daytime functioning (e.g., social, occupational, cognitive, and/or psychological). Chronic, untreated insomnia is known to be associated with increased risk for psychiatric problems, suicidal ideation, and unhealthy lifestyles (e.g., alcohol/drug abuse), and may lead to poorer physical health, disruption in major social and occupational responsibilities, and decreased quality of life. Consequently, insomnia is associated with an increase in societal costs (e.g., absenteeism, health-related costs, risk for dementia, metabolic syndrome). It is therefore important for primary care and behavioral health professionals to screen for insomnia, especially among individuals with comorbid psychiatric conditions.

Prevalence and Chronicity

Definition of Insomnia and Prevalence Insomnia is a common sleep disorder occurring in 35–52% of adults who report problems with sleep (i.e., going to sleep, maintaining sleep, or early morning awakening) [1–3]. A lower prevalence of 9–15% is observed when adding negative daytime consequences as a diagnostic

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factor [4, 5]. This prevalence is lowered further to 6% when excluding other sleep disorders (e.g., sleep apnea), psychiatric factors, and medical- and/or substance-induced insomnia [2]. With the implementation of the *Diagnostic and Statistical Manual of Mental Disorders—Fifth Edition* (DSM-5) and the removal of the primary versus secondary insomnia distinction, up to 31.8% of individuals treated psychiatrically may meet criteria for insomnia [6]. Additionally, there is evidence to suggest that prevalence of insomnia may be culturally dependent as rates of insomnia appears to vary by country (Netherlands, 5.4%; Japan, 10.0%; Australia, 10.5%; the United Kingdom, 11.0%; the United States, 13.4%; Germany, 14.6%; France, 21.7%; South Korea, 23.5%; China, 24.0%; Brazil, 30.5%) [7]. The causes of such variability across countries are unclear.

Gender and Age and Insomnia Prevalence Women and geriatric populations are at particularly high risk for insomnia. Due to hormonal changes during menstruation, pregnancy, and menopause, women are 1.41 times more likely than men to experience insomnia [8]. During menstruation, sleep problems may increase due to symptoms such as cramping, bloating, headaches, and tender breasts, or due to symptoms associated with premenstrual dysphoric disorder (PMDD), or dysmenorrhea [9, 10].

During pregnancy, sleep difficulties (in both quality and quantity of sleep) may result from alterations in progesterone, prolactin, and melatonin (modulation of melatonin by reproductive hormones may cause dysregulation of sleep/wake mechanisms) as well as the physical changes associated with pregnancy [10]. Associated morning sickness, back pain, and frequent urination have often contributed to insomnia during this stage. Additionally, inadequate breathing due to fetal enlargement and compression over the lungs (lowering pulmonary function) causes further sleep interruptions and increased risk of obstructive sleep apnea (OSA). In a retrospective study of 486 pregnant females, insomnia was 2.03 times higher in the third trimester compared to earlier pregnancy stages [11]. Sleep quantity had an inverse relationship to sleep quality, with a gradual decrease in sleep quality as pregnancy progressed [10]. In addition, the presence of depression is associated with a higher insomnia risk among pregnant woman, with an odds ratio (OR) of 2.63 [11]. Similarly, the postpartum period is associated with increased insomnia risk that is partly attributed to newborn's frequent arousals and need for feeding overnight [10, 11].

Menopause may also present challenges for sleep among women with a prevalence reaching 40–60% [12]. It has been theorized that declining estrogen levels are associated with increases in sleep difficulties (e.g., hot flashes and other vasomotor symptoms) [10]. In a study comparing 38 menopausal women with insomnia compared to 34 non-insomniacs, estradiol and follicle stimulating hormone levels were related to increased wake after sleep onset (WASO) and hot flashes when compared to controls [12].

Geriatric populations also tend to experience higher rates of insomnia (OR = 1.3), possibly due to shallower sleep, increased WASO, advanced sleep phase preference, and associated medical comorbidities (i.e., pain, heart problems, urinary complications) [13]. In a review by Kamel and Gammack, one cause of insomnia that may naturally occur in aging is alteration in circadian rhythms (typically advanced sleep phase preference), which can lead to poor sleep quality. Additionally, frequency of napping may increase with aging and retirement, which also may impact sleep by weakening homeostatic pressure for sleep at night [14].

Medical and Psychiatric Conditions and Sleep Individuals with medical comorbidities or psychiatric disorders experience elevated rates of insomnia. For example, 45% of those with major depressive disorder, 33% with anxiety, 25% with schizophrenia spectrum disorders, and 24% with bipolar disorder experience insomnia [6]. The relationship between insomnia with both depression and anxiety appears to be bidirectional [14, 15]. Chronic pain (e.g., fibromyalgia, chronic pain, back pain, headaches) is also associated with an increased prevalence of insomnia, with headaches being associated with an OR of 1.4–1.7 for insomnia [16–19]. Additionally, 68–84% of those who suffer from migraines have comorbid insomnia [20–22]. Some studies have also linked insomnia to reduced pain tolerance and increased central sensitization to pain [21]. Lastly, chronic insomnia is known to lead to increased risk of metabolic syndrome, and subsequently a higher risk of Type II diabetes [17].

Other Factors Stress can also increase one's risk for insomnia. People with financial stressors (e.g., the unemployed and those with lower socioeconomic status [SES]), shift workers [23], and those living in a noisy environment also struggle more with insomnia [24]. In contrast, people who are married or in a relationship had a lower prevalence of insomnia compared to single, widowed, or divorced individuals [25].

Insomnia and Consequences

Insomnia has been associated with an elevated rate of mortality especially among men [26]. Decreased productivity, absenteeism, and even accidents are some of the associated complications. Sleep deprivation, which can result from insomnia, has been linked to substantially poorer mood, cognitive performance, and motor performance [27].

Psychiatric Disorders and Insomnia Since insomnia is thought to be a disorder of hyperarousal (increased arousal and increased physiological activation), it is not surprising that up to 40% of individuals with insomnia also have comorbid psychiatric disorders (especially anxiety, which often involves increased arousal and

depression), compared to 16% of those without insomnia [4]. While in some cases insomnia may precede mood disorders, in others, insomnia develops after the onset of depressive episodes, highlighting the potential bidirectional relationship [28]. In a meta-analysis of 34 prospective studies, individuals with insomnia were more than twice as likely to be depressed [29].

A link between insomnia and suicidality has been suggested, independent of the presence of a mood disorder. In a study involving 14,456 older individuals, the presence of poor sleep predicted a 39% increase in suicide risk attempts at 10-year follow-up compared to those without poor sleep [30, 31]. This finding was replicated in a meta-analysis showing individuals with sleep disturbance (specifically those diagnosed with insomnia and/or nightmares) to have a higher relative risk for suicidal ideation, with attempts and death by suicide ranging from 1.95 to 2.95 [32]. Depression did not appear to mediate the relationship [33]. Similarly, a 3.5-fold increase in suicide attempts has also been observed in individuals with insomnia, with highest prevalence in middle-aged females, independent of comorbid psychiatric conditions [33]. The link between psychosis and insomnia has been less well delineated. However, in a study of 388 individuals with psychotic disorders, the presence of comorbid insomnia predicted a fourfold increase in suicide during the ensuing 8 years [34].

Medical Complications and Insomnia Examining physical consequences, short sleepers have a 12% higher mortality rate [23]. In a meta-analysis of 15 studies, a higher risk of cardiovascular events (including acute myocardial infarction, coronary heart disease, and stroke) was found among those with difficulty initiating sleep (OR 1.27), maintaining sleep (OR 1.11), and experiencing non-restorative sleep (OR 1.18) [35]. Likewise, another meta-analysis found individuals with insomnia to have a 45% increased risk of cardiovascular complications [36], with this risk being more pronounced among females.

A link between short sleepers and metabolic syndrome has also been suggested. In a meta-analysis examining metabolic syndrome (including abdominal obesity, dyslipidemia, and elevated glucose and blood pressure), short sleepers were 1.27 times more likely to develop metabolic syndrome, although long sleepers were also 1.23 times more likely [37]. Similarly, obesity had an OR of 1.89 and 1.55 in both children and adult short sleepers, respectively, compared to controls [38]. A separate meta-analysis linked insomnia to an increased risk of developing hypertension (OR ranging from 1.05 to 1.21) [39]. In addition, individuals with insomnia tend to report a greater loss of function, even compared to patients with congestive heart failure [40].

Several proposed mechanisms for these metabolic side effects have been suggested including an increase in sympathetic activity [41, 42], and hypothalamic pituitary adrenal axis dysregulation leading to an increase in cortisol and subsequent hypertension and tachycardia. An increase in appetite in insomniacs secondary to decreased

leptin and increased ghrelin levels subsequently leads to obesity, impaired glucose tolerance, atherogenesis, and/or increased lipid levels [42]. In addition, studies on sleep curtailment have shown that chronically restricting sleep causes an increase in inflammatory cytokines and change in metabolic activity, leading to further metabolic changes. These findings suggest that chronic sleep loss could increase age-related pathologies (i.e., diabetes and hypertension) [43].

Quality of Life and Insomnia Insomnia may also affect daytime functioning and quality of life. Daytime impairment can include problems such as feeling tired/fatigued during the day, daytime sleepiness, performance issues (poor focus or attentional problems, poor social or academic/vocational problems, errors or accidents), and worry about sleep. Research has shown that among the daytime consequences of insomnia, the increased occurrence of accidents poses the greatest risk as individuals with insomnia are 2.5–4.5 times more likely than normal sleepers to have an accident [44, 45]. Work productivity is also compromised, with higher rates of absenteeism, decreased concentration, and difficulty performing duties, or a general decrease of work performance noted in poor sleepers [46]. Vitality and mental, physical, and social functioning are all negatively affected by insomnia. In general, insomnia negatively impacts quality of life, regardless of how it is measured [47].

Models of Insomnia

There have been several theoretical models proposed to describe insomnia, its origins, and onset. Three models commonly recognized by the scientific community are detailed below: the stimulus control model, the three factor model, and the neurocognitive model.

The Stimulus Control Model

The stimulus control model was applied to insomnia by Bootzin and Nicassio [48]. Based on instrumental conditioning, the model describes how a stimulus may elicit a variety of responses depending on conditioning history. In individuals with insomnia, large amounts of time are spent in the bedroom and the bed, engaging in non-sleep-related activities that might include but are not limited to reading, watching television, engaging in social media on a cell phone or tablet, worrying, and/or thinking. Large amounts of time spent doing non-sleep-related activities in the bedroom can lead to what is called stimulus dyscontrol. Stimulus dyscontrol lowers the probability that sleep-related behaviors will commence when one is sleepy. Conditioning to remain awake at bedtime occurs as the bedroom is repeatedly paired with being awake in bed, making it more difficult for sleep-related cues in the bedroom (the bed, soft pillow, closed drapes/darkness, etc.) to elicit sleep.

The Three Factor (3-P) Model

The 3-P model, also known as the Spielman model or the behavioral model, is named for its emphasis on predisposing, precipitating, and perpetuating factors and was applied to insomnia in 1987 by Spielman, Caruso, and Glovinsky [49]. The Spielman model is based on a diathesis-stress model that delineates how acute insomnia can become chronic. According to this model, insomnia occurs due to both trait (predisposing factors such as gender, age, physiology) and life stressors (precipitating factors). Chronic insomnia can then evolve into maladaptive coping behaviors (perpetuating factors such as sleep extension). The role of sleep extension in maintaining insomnia is critical as individuals with insomnia will often go to bed earlier or get out of bed later (or nap) in an effort to extend their sleep time as compensation for prior sleep loss. The 3-P model highlights how sleep extension may worsen insomnia by leading to a growing discrepancy between sleep opportunity (lots) and sleep ability (poor). Sleep restriction, in which one's amount of time in bed is limited in order to improve sleep drive, is used to counter the drift toward sleep extension.

The Neurocognitive Model

The neurocognitive model proposed by Perlis, Giles, and Mendelson [50] represents an extension of the 3-P model noted above. In this model, neurobiological and neurophysiological factors are integrated to help explain how insomnia leads to conditioned cortical arousal that may result in enhanced sensory processing, memory formation, and conscious awareness at night. The model also predicts that increased cortical activity resulting from insomnia leads to the loss of mesograde amnesia during sleep (greater awareness of wakefulness), which in turn may help to explain phenomena such as the subjective-objective discrepancy between sleep and wakefulness. The latter may be the underlying cause for such conditions as "sleep state misperception" or paradoxical insomnia.

Diagnosis of Insomnia

Diagnostic and Statistical Manual of Mental Disorders—Fifth Edition (DSM-5) [51]

To meet the criteria for diagnosis of insomnia in DSM-5, the individual must present with a complaint of difficulty initiating sleep (with a sleep latency greater than 20–30 min), difficulty maintaining sleep (due to frequent awakenings or problems re-initiating sleep after such awakenings), and/or early morning awakenings with trouble re-initiating sleep (awakening much earlier than one intended to wake up). Additionally, impairment and duration criteria need to be met. Daytime impairment is noted when an individual experiences clinically significant distress socially, academically, or in any area of functioning due to his/her poor sleep. Duration

requirements include the sleep problems occurring at least 3 nights a week for a minimum of 3 months when provided sufficient opportunity for sleep. Exclusions for an insomnia diagnosis include the insomnia not being better explained by another sleep-wake disorder (e.g., narcolepsy, a breathing-related sleep disorder, a circadian rhythm sleep-wake disorder, a parasomnia), or due to the use of a substance (e.g., a drug of abuse and/or a medication). See Table 2.1 for more information about DSM-5 insomnia criteria and that of other diagnostic systems.

The DSM-5 also classifies insomnia as "episodic" (occurring in at least 1 month but less than 3 months), "recurrent" (two episodes in 1 year), and/or "persistent" (lasting for more than 3 months). In addition, DSM-5 codes specify whether the insomnia occurs with mental comorbidity, medical conditions, or with other sleep disorders.

International Classification of Sleep Disorders—Third Edition (ICSD-3) [52]

In *International Classification of Sleep Disorders—Third Edition* (ICSD-3), insomnia is defined as a persistent difficulty with sleep initiation, duration, consolidation, or quality, occurring despite adequate opportunity and circumstances for sleep, and resulting in daytime impairment. The ICSD-3 groups insomnia into four major categories: chronic insomnia disorder, short-term insomnia disorder, other insomnia disorder, and isolated symptoms and normal variant (see Table 2.1).

In chronic insomnia disorder, the individual (or their parent/caregiver) must report symptoms of difficulty initiating sleep, difficulty maintaining sleep, waking up earlier than desired, resistance to going to bed on an appropriate schedule, and/or difficulty sleeping without parent or caregiver intervention. In addition, at least one sign or symptom signifying difficulty with daytime functioning (e.g., fatigue, attention, concentration, or memory impairment; impaired social, family, vocational, or academic performance; mood disturbance/irritability; daytime sleepiness; behavioral problems; reduced motivation; proneness for errors; concerns or dissatisfaction with sleep) must also be present. The reported sleep/wake complaints must not be better explained by inadequate sleep opportunity or inadequate circumstances (e.g., the environment is unsafe, or not dark, quiet, and comfortable). The sleep problems must be present for at least 3 months and not be due to another sleep disorder. For short-term insomnia, all of the above symptoms and criteria must be met, but the sleep symptoms should have occurred for less than 3 months.

Other insomnia disorder is diagnosed when individuals complain of difficulty initiating and maintaining sleep but do not meet the full criteria for chronic or short-term insomnia. In ICSD-3, the isolated symptoms and normal variant category explain two different phenomena; excessive time in bed versus naturally short sleep need. For example, some individuals may spend an excessive amount of time in bed and not perceive that as a problem for sleep. Alternatively, naturally short sleep is considered to not be problematic if the individual routinely obtains less than 6 h of sleep a night but has no complaints or daytime difficulties.

Table 2.1 Criteria for insomnia diagnosis across classification systems

	DSM-5	ICSD-3	ICD-10
Sleep symptoms from either patient or parental observation: Problems initiating sleep Problems maintaining sleep Waking up early	Yes	Yes to symptoms being reported by patients (not by caregiver) In addition: Resistance to bedtime Difficulty sleeping without parents	Yes Other symptoms include: Lying awake for a long time before you fall asleep Sleeping for only short periods Being awake for much of the night Feeling as if you have not slept at all Waking up too early
Associated significant distress	Yes – described as associated social, occupational, academic, and educational impairment	One of the following: Fatigue/malaise Attention or memory problems Impaired social, occupational, or academic problems Mood disturbance Daytime sleepiness Behavioral problems Lack of energy Errors and accidents Concern about sleep	Not required
Exclusion criteria: 1. Cannot be explained by inadequate sleep opportunity or inadequate circumstances 2. Exclusion of other sleep disorders	Yes – in addition to specific exclusion to substance induced	Yes	Yes – and is not etiologically linked to a mental disorder, substance use, or a general medical condition
Duration and frequency	At least 3 nights/week for 3 months	At least 3 nights/week and if less than 3 months, is considered acute; if more than 3 months, is considered chronic insomnia	Not specified

Table 2.1 (continued)

	DSM-5	ICSD-3	ICD-10
Specifiers	Insomnia due to: Comorbid mental disorders Comorbid medical disorders Comorbid sleep disorders Episodic (1–3 months) Persistent (>3 months) Recurrent (two or more episodes per year)	Acute insomnia; chronic insomnia	Primary insomnia Adjustment insomnia Paradoxical insomnia Psychophysiological insomnia Insomnia due to other mental disorder Other insomnia not due to a substance or known physiological condition

International Classification of Disorders—Tenth Edition (ICD-10-CM) [53]

The *International Classification of Disorders—Tenth Edition* (ICD-10-CM) denotes both organic sleep disorders and nonorganic sleep disorders/sleep disorders not due to a substance of known physiological condition. The general characterization of insomnia, whether organic or not, is in line with other diagnostic manuals where difficulty in falling asleep or remaining asleep are the main symptoms, though a timeframe of experiencing the symptoms is not noted (see Table 2.1). Insomnia may occur as a primary disorder or be associated with another medical or psychiatric conditions.

Insomnia Subtypes

Recent versions of diagnostic nosologies have moved away from separating insomnia into primary or secondary distinctions. It has been argued that aside from the difficulty of differentiating whether insomnia was primary or secondary, physicians might forego treating secondary insomnia and focus more on treating the primary disorder, producing a less effective outcome [54]. However, older terminologies still persist in the clinical literature and therefore a brief review is provided to provide familiarity with these terms:

Adjustment Insomnia (Acute)

Adjustment insomnia usually occurs following a stressful life event (e.g., family loss, career problems, or financial hardship). However, acute insomnia can progress

to chronic insomnia, depending on psychiatric predisposition, coping skills, and other life events. This usually occurs within 3 months of a stressful event. Some authors divided adjustment insomnia into acute (less than 2 weeks), transient (2–4 weeks), and sub-chronic (1–3 months) [55].

Prevalence The 1-year prevalence of this disorder among adults ranges between 15% and 20%, with higher rates in females and older adults [56].

Idiopathic Insomnia (Childhood Onset)

This type of insomnia usually starts in infancy or early childhood, without a known cause, as it does not appear to include medical, psychiatric, or substance involvement. However, circadian rhythm dysregulation and sleep-wake abnormalities are suspected. In addition, a genetic predisposition has been suspected because idiopathic insomnia runs in families as a long sleep latency worsens in subsequent generations [57]. It usually has insidious onset with a chronic and lifelong course without any significant periods of remission. A decrease in slow wave sleep (SWS) and rapid eye movement (REM) duration as well as sleep continuity interruption has been found in a recent meta-analysis of individuals with this disorder [58].

Prevalence Studies suggest a prevalence of less than 1% in the adult population [57].

Paradoxical Insomnia (Sleep State Misperception)

Paradoxical insomnia, also called sleep state misperception, occurs when a patient's complaint of insomnia lacks objective measures indicating the presence of insomnia (i.e., normal sleep duration on polysomnography [PSG] or observed sleep duration). Showing patients objective measures of their sleep can help reduce stress related to perceived sleep difficulties.

Prevalence Paradoxical insomnia is believed to occur in less than 5% of people with insomnias [59].

Inadequate Sleep Hygiene

Patients with this type of insomnia usually have either activities that increase arousal or those that are inconsistent with good sleep organization. The former usually includes the use of substances (e.g., caffeine, nicotine, and alcohol), exercise, or excessive physical activity late at night, while the latter include naps during the day, a variable sleep/wake schedule, uncomfortable sleeping environment, and spending time in bed without sleeping (watching TV, studying, etc.).

Prevalence While 1–2% of adolescents and adults may present with poor sleep hygiene practices, up to 5–10% of individuals referred to a sleep clinic exhibit problems in this domain [56].

Behavioral Insomnia of Childhood

As the name indicates, this form of insomnia affects children and has two major subtypes: sleep onset association and limit setting. Sleep onset association insomnia occurs when the child associates sleep with an object (i.e., transitional object as bottled milk or blanket) and in the absence of this object struggles to sleep. This is often an issue with younger children who learn to fall asleep with a bottle in their mouth.

Another common type of behavioral insomnia in children pertains to limit setting: children often do not want to go to sleep and may start making excuses such as being hungry, thirsty, or even engage in behavioral outbursts (screaming and crying) to avoid sleep when bedtime is initiated.

Prevalence Childhood behavioral insomnia has been thought to occur in 10–30% of children [56].

Psychophysiological Insomnia (Conditioned Insomnia)

Psychophysiological insomnia occurs when one's worries about falling asleep actually cause an increase in arousal, leading to further difficulties falling asleep. Psychophysiological insomnia is one of the most common types of insomnia, in part due to the conversion of other types of acute insomnia into this chronic type if not adequately treated. This type of insomnia is often associated with anxiety, especially generalized anxiety.

Prevalence This type of insomnia is probably the most common subtype of insomnia. It has been thought to occur in 1–2% of the general population and is diagnosed in 12–15% among those referred to the sleep clinic [56].

Insomnia Due to Mental Disorder

Insomnia is a frequent complaint associated with a range of psychiatric disorders including anxiety, depressive disorders, and the manic phase of bipolar disorder. Anxious individuals are often overstimulated and report that their "mind is racing" as they worry about various things, including their lack of sleep, while lying in bed. While depression can present with both decreased and excessive sleepiness, many depressed individuals present with prolonged sleep latency and frequent nighttime or early morning awakening. This latter criterion is one of the DSM-5 criteria for

melancholic depression. Similarly, individuals with bipolar disorder typically experience a decreased need for sleep (both shortened duration and lack of tiredness during the day) during a manic state, although they may not experience the decreased sleep to be distressing. While it is common to encounter insomnia secondary to a mental disorder [57], if such insomnia is more than expected for the given psychiatric problem or requires a discrete treatment it can be given a separate DSM-5 diagnosis.

Prevalence The prevalence of insomnia related to other mental disorders is estimated to be between 1 and 3%. However, up to a third of people presenting with insomnia symptoms receive a diagnosis of mental disorder [5].

Insomnia Due to Medical Condition

Insomnia is often associated with one of several medical conditions. Pulmonary diseases such as chronic obstructive pulmonary disease (COPD) and asthma are associated with a high risk for developing insomnia. Pain and musculoskeletal disorders can similarly interrupt sleep. Cancer, with its associated pain and increased risk of depression and anxiety, has also been associated with insomnia. Gastrointestinal (GI) problems such as GI pain, ulcers, and reflux can also lead to insomnia. Other medical disorders such as diabetes mellitus can indirectly cause insomnia through increased urination at night.

Prevalence This type of insomnia will largely depend on the medical condition involved. For example, 20% of individuals with pain disorder report at least one symptom of insomnia, compared to 7.4% of those without pain. Among individuals seen in pain clinics, 65–90% of individuals complain of sleep disturbance [60].

Insomnia Due to Drugs or Substances

The Substance Abuse and Mental Health Services Administration (SAMHSA) has noted a high risk of sleep difficulties among people with a substance use disorder (SUD), with insomnia symptoms very common during withdrawal and recovery [61]. These sleep disturbances vary dependent on substance of choice and can be affected during active use, withdrawal, and abstinence [62]. Neurobiological systems may be disrupted with long-term misuse of substances, creating irregular sleep and wakefulness, which may lead to insomnia [63]. The risk of developing an SUD because of insomnia is independent of other mental health disorders [64], with a majority of patients reporting that their sleep difficulties began prior to the onset of drinking, by more than 10 years [65, 66].

Difficulties falling asleep and staying asleep (or both) are common complaints with chronic use of alcohol, and even abstinence [65, 67], with symptoms lasting weeks to months, or even years, during recovery [61]. Importantly, presence of

insomnia during childhood may increase risk for addiction later in life, being associated with early initiation of alcohol, cannabis, and other illicit drugs, and also shows greater misuse of those substances [68]. Approximately 10% of the population uses alcohol to help with sleep [69], which is particularly detrimental to alcohol-dependent individuals, as it may continue abuse and relapse [65]. Similarly, untreated insomnia may cause some individuals to use alcohol to self-medicate their sleep difficulties [65]. Difficulties falling asleep are commonly seen in individuals withdrawing from cannabis use [70] with symptoms lasting from a few days to weeks [61]. A comprehensive review of the literature found that cannabis use may cause a decrease in slow wave sleep and an increase in stage 2 sleep, with no consistent effects observed in total sleep times [71]. As the endocannabinoid system is critical in the regulation of the circadian rhythm sleep-wake cycle, the authors emphasized the need for further systematic investigations of cannabinoids on sleep.

Stimulants (e.g., cocaine and methamphetamines) are stimulating during intoxication and lead to sedation and hypersomnia during withdrawal. Cocaine use has been shown to increase sleep latency and REM sleep latency and decrease sleep efficiency and REM sleep [72, 73]. During withdrawal, sleep disturbances and unpleasant dreams are reported [73, 74]. Sleep quality is seen to worsen during recovery, with perceived sleep improvement by the individuals [75].

In contrast, while "club drugs" (e.g., GHB and ketamine) and opiates (e.g., heroin, oxycontin) are sedating, rebound insomnia can occur during withdrawal. One study with patients on methadone maintenance showed poor sleep efficiency, with total sleep time as 6 h, or less, a night [76]. Increased nighttime wakefulness and reduced total sleep time, sleep efficiency, and REM sleep was also shown in patients on methadone maintenance [77], with one study showing that sleep had not returned to normal levels up to 1 year following treatment [78]. Likewise, sedative anxiolytic drugs such as benzodiazepines cause sedation and sleepiness, though withdrawal from these medications (especially the short acting ones) can also lead to transient insomnia [75].

Several prescription drugs can lead to insomnia, either during administration or secondary to withdrawal [75]. Theophylline and other sympathomimetic bronchodilators including steroids are commonly used to treat asthma and often lead to insomnia. Adrenal hypersecretion, increased glucocorticoids, and thyroid hormones can also lead to insomnia, as can statins (e.g., atorvastatin). Beta-blockers, such as atenolol, are associated with both insomnia and nightmares. Stimulant medications (through secretion of dopamine and norepinephrine stimulation) and serotonergic, dopaminergic, and norepinephrine stimulating agents can also lead to insomnia. Phenelzine (a monoamine oxidase inhibitor) has been particularly associated with significant insomnia. Caffeine-containing substances (i.e., soda, coffee) may lead to insomnia, since the caffeine can act in the body for at least 2–4 h, which can make sleep onset more difficult, as a result of adenosine receptor antagonism.

Prevalence Observed in 0.2% of an elderly Korean population [79], and 3% in a European population [80]. In patients with alcohol use disorder, the prevalence of insomnia during withdrawal is 30–60% [65, 81], and 60–90% during active use [67, 82, 83], with about 75% of daily cannabis users experiencing sleep difficulties dur-

ing withdrawal [84]. A study of 225 patients on methadone maintenance found that 84% had clinically significant sleep disturbance (scores >6 on the Pittsburgh Sleep Quality Index [PSQI]) [85].

Evaluation and Treatment

Evaluating individuals with insomnia is an important aspect of any history taking or examination. Assessment can include self-report paper-and-pencil subjective measures of sleep disturbance (e.g., Insomnia Severity Index [ISI] [86]—a measure used to assess severity of insomnia; Pittsburgh Sleep Quality Index [PSQI] [87]—a measure used to assess level of general sleep disturbance; or Epworth Sleepiness Scale [ESS] [88]—a measure used to assess severity of daytime sleepiness), and use of a sleep log or diary. In addition, objective measures include the use of actigraphy or an overnight sleep evaluation in a sleep clinic (polysomnography).

Management of insomnia can be complicated. While previously it was thought that addressing associated psychiatric or medical conditions will improve insomnia, more recent studies suggest that treating sleep can actually lead to improvements in so-called "primary" disorders [89, 90]. Although prescription of hypnotic medication for sleep is common, studies have shown that Cognitive-Behavioral Therapy for Insomnia (CBT-I) is equivalent in the short term to medication administration and significantly better over the long term. In a meta-analysis conducted of 21 studies through 2000, both medication and psychotherapy were equally effective in treating insomnia, with moderate to large effect sizes. However, a greater decrease in sleep latency was noted for those receiving behavioral therapy rather than those using medication [91].

CBT-I is accepted as the first-line treatment for adults with chronic insomnia [92]. CBT-I is used to address both the behaviors related to insomnia (sleep drive/timing and stimulus control) as well as the cognitive distortions and anxiety related to sleep [93]. In general, CBT-I is more effective than the use of hypnotics, has fewer and typically short-term side effects, and maintains sleep improvement better for long term. Given the common comorbidity between insomnia and psychiatric conditions, CBT-I has also shown efficacy in improving both conditions. In a recent meta-analysis including 37 randomized studies using CBT-I, 35.6% of individuals achieved remission (compared to only 17.4% in the comparison group), with significant and large effect size improvements in sleep efficiency, subjective sleep quality, sleep latency, and wake after sleep onset (WASO) measures; however, no effects on total sleep time were observed [94]. These effects were maintained up to 12 months post-treatment. Additionally, although CBT-I improved psychiatric conditions with a significant and large effect size, it minimally affected comorbid medical conditions [94]. Chapter 3 discusses the constituents of CBT-I, which include sleep restriction, stimulus control, sleep hygiene instructions, and addressing cognitive dysfunctions related to sleep. As with other types of therapy, psychoeducation constitutes an important aspect of treatment.

Of the four principal components of CBT-I, the most commonly used in clinical settings is sleep hygiene instructions. Although helpful to patients with insomnia, sleep hygiene should not be conceptualized as the root cause of insomnia, nor does addressing sleep hygiene necessarily lead to significant improvement in insomnia. However, generally speaking, good sleep hygiene practices help to create a better foundation for sleep and are a useful adjunct to CBT-I or medication treatment for insomnia. For maximum effectiveness, sleep hygiene should be discussed/reviewed with the patient and not simply disseminated via a printed handout. Common examples of sleep hygiene instructions include:

1. Have a regular sleep schedule, even on the weekends.
2. Go to bed only when you are sleepy.
3. If you are not able to fall asleep in about 20 min, get out of bed and do something relaxing until you feel sleepy. Do not go back to bed until you feel sleepy. Repeat until you can fall asleep quickly in bed.
4. Avoid caffeine, nicotine, and alcohol for at least 4–6 h before going to bed.
5. Use your bed for sleep (and sex) only.
6. Avoid naps during the day.
7. Develop bedtime habits that help condition your body/brain to know when it is time to go to sleep.
8. Taking a hot bath or shower before bed may be helpful.
9. Avoid watching the clock at night.
10. Exercise regularly (but not within 3–4 h of bedtime).
11. Eat regularly (but avoid heavy meals before bedtime). A light snack before bed can sometimes help to prevent hunger in the middle of the night.
12. Make sure your bed and bedroom are a comfortable space for you to sleep.
13. Keep your daytime routine the same, even if you have a bad night's rest.
14. Get as much early sunlight exposure as possible.
15. Keep a sleep diary.

In addition to sleep hygiene and CBT-I strategies noted, multiple prescription and over-the-counter medications are commonly used to treat insomnia. Data compiled from home interviews obtained through the National Health and Nutrition Examination Survey, from 2005 to 2010, determined that 4.1% of US adults over the age of 20 had taken a prescription sleep medication in the past month [95]. The prevalence of sleeping pill use generally increased with age, with the lowest rates for individuals aged 20–39 years (1.8%) and highest among adults of at least 80 years of age (7%). Use of prescription sleep aids was also higher among women (5%) than men (3.1%). In addition, many individuals take over-the-counter remedies for sleep. Although epidemiological data on the use of such medications are limited, the market for sleeping aids has been calculated at upwards of $400 million per year [96].

The Food and Drug Administration (FDA) approved medications for insomnia include benzodiazepines (mainly temazepam and halcion), and the so-called "Z-drugs" (zolpidem and its different formulations: eszopiclone, zaleplon, and

zopiclone). Among the sedating antidepressants, only low-dose doxepin has been approved by the FDA for insomnia. Rozerem (a melatonin receptor agonist), over-the-counter melatonin, and more recently the orexin receptor antagonist suvorexant are also approved for treatment of insomnia. While sedating antidepressants, antipsychotic medications, antihistamines, and some of the anxiolytics (such as gabapentin) have been used to treat insomnia, studies have not necessarily supported their effectiveness. Other herbal remedies including valerian root have shown some promise. Chapter 6 extensively reviews the psychopharmacological options for treating insomnia.

When compared, the risks of long-term hypnotic use fair poorly in comparison to any potential benefits. In a comprehensive report on hypnotic treatment recommendations for the pharmacological management of insomnia, Sateia et al. found weak evidence for the use of most prescribed hypnotic agents [97]. Depending on the medication evaluated, benefits of hypnotic utilization included ease of administration, rapid action, and small improvements in sleep latency, reduction of time spent awake at night, and increased total sleep times (as measured by polysomnography). Risks for hypnotic use however are considerable and include possible dependence, tolerance, and withdrawal. More importantly, work done by Kripke determined that chronic use of hypnotics may be associated with poor sleep, poor health, and reduced survival [98]. The authors concluded that chronic hypnotic use has more risks than benefits. Unfortunately, despite the availability of non-pharmacologic treatments for insomnia such as CBT-I, access to such treatments are limited, with less than 1% of chronic insomnia patients receiving such care. The reality therefore remains that for most individuals, pharmacologic intervention will continue to be the most commonly available treatment for chronic insomnia.

Several other investigational modalities are being explored as possible treatments for insomnia. Acupuncture, for example, has been suggested as a treatment for insomnia. In a meta-analysis of 46 randomized studies, acupuncture was found to be more effective than a sham comparison condition as measured by Pittsburgh Sleep Quality Inventory scores [99]. The combination of acupuncture and herbs or hypnotics showed better efficacy than either alone [99]. Cranial electric stimulation has been increasingly used and approved by the FDA for the treatment of insomnia and other psychiatric conditions. This modality uses micro-electric currents frontally across the head daily for 20 min to an hour for 1–2 weeks with a decrease in frequency afterwards. However, a recent meta-analysis found inconclusive results of its efficacy for insomnia [100]. Mindfulness therapy is a newer intervention for insomnia (see Chap. 4). Mindfulness may be helpful in cases where the individual needs to be more aware of and able to control their thoughts, especially when attempting to sleep at night [101]. Acceptance and Commitment Therapy (see Chap. 5), which includes elements of mindfulness, may help improve sleep by allowing the individual to accept and experience "short-term" discomfort (e.g., restlessness, fatigue) while completing the requirements of sleep therapy (e.g., sleep restriction and stimulus control strategies) [102]. Hypnotherapy may be beneficial as it allows the individual to self-manage their anxiety, practice deep relaxation, and reduce overcrowding of thoughts through relaxation and imagery [103]. Lastly, in a recent

meta-analysis, self-help therapy (e.g., books, booklets, brochures, guidebooks, audiotapes, videos, TV programs, Internet) for insomnia has demonstrated small-to-moderate effect size improvements in sleep efficacy, sleep latency, WASO, and sleep quality [104], although some materials are likely more effective than others.

Conclusion

Insomnia is a common disorder that can occur at any time throughout an individual's lifetime. Predominant symptoms include having trouble falling asleep, waking up in the middle of the night, and/or waking up earlier than intended in the morning with associated daytime complaint. Daytime impairment may include cognitive, psychological, performance, and/or social/vocational difficulties. CBT-I is considered the most empirically supported treatment for insomnia, though hypnotics and other interventions may work for some individuals. Consideration of insomnia in any clinical assessment is essential for optimizing psychiatric treatment outcomes.

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Cognitive-Behavioral Therapy for Insomnia (CBT-I)

3

David Bennett

Introduction

Chronic insomnia is the most common sleep problem, affecting 6–10% of the population and negatively impacting quality of life [1–3]. *Insomnia* is defined as "a predominant complaint of dissatisfaction with sleep quantity or quality" associated with difficulty initiating sleep, maintaining sleep, or early morning awakening with an inability to return to sleep despite having an adequate opportunity for sleep [4]. *Diagnostic and Statistical Manual of Mental Disorders* (*Fifth Edition*) (*DSM-V*) criteria also require that insomnia occurs at least three nights per week, is present for at least 3 months, and causes distress and/or problems at work or with others [4]. While insomnia is very common and might precipitate or perpetuate a variety of medical and psychiatric disorders, research highlights the generally underdiagnosed and undertreated nature of insomnia [5, 6].

Many interventions have been used to treat insomnia. In the 1800s, chloral hydrate and a combination of opium and alcohol (laudanum) were used, but with serious side effects that included dependency [7]. Barbiturates were commonly used until the 1960s, when they too were observed to have safety concerns [7]. While there have been advancements in the availability of newer hypnotic medications with relatively lower side effects than earlier medications, issues of efficacy and side effects, including tolerance, pose challenges and often lead individuals to search for alternatives. In a recent Canadian study, 15% of all adults reported using herbal or dietary products, 11% a sleep medication, 4% over-the-counter (OTC) medications, and 4% alcohol to improve sleep in the past year. Others reported using reading (33%), listening to music (25%), and trying to relax (21%) to address their insomnia [8]. In contrast, only 10% of patients with insomnia attending a

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university medical center in the United States were referred for cognitive-behavioral therapy for insomnia (CBT-I) [9].

CBT-I is based, in part, on the premise that behaviors conducive to good sleep can be learned. CBT-I is recommended as a first-line treatment for insomnia [10–12] and is associated with comparable efficacy relative to medications in the short term and with greater continued therapeutic effects compared to medication in the long term [13, 14]. Moreover, CBT-I is often preferred to medication by patients [15, 16]. This chapter provides an overview of CBT-I and its components, as well as research on its efficacy in different modalities (e.g., individual therapy; group administration; Internet-based administration; bibliotherapy) and with different populations.

Cognitive-Behavioral Therapy for Insomnia (CBT-I): What Is It?

CBT-I, which typically entails 4–10 weekly sessions, involves identifying factors that may hinder one's ability to fall and stay asleep while teaching skills related to stimulus control, sleep restriction, relaxation training, and cognitive therapy.

Given that CBT-I requires significant commitment to be effective and some of its components are counterintuitive (e.g., using sleep restriction to help improve the quantity and quality of sleep), it is important for individuals to understand the rationale for CBT-I. In providing a rationale for stimulus control, the notion that the bed and bedroom have become conditioned to arousal rather than to sleep is highlighted. Conditioned arousal is developed through repeated experiences of frustration, anxiety, or tension when one is unable to sleep. Many individuals with insomnia, for example, report struggling to stay awake on the sofa in the living room yet become wide awake upon going to bed. Stimulus control instructions aim to discontinue or "extinguish" the association between being in bed and alertness, and instead strengthen the bed as a cue for sleep. CBT-I therapists typically begin with an assessment of the individual's sleep patterns, factors causing problematic sleep, comorbid disorders, and any contraindication to CBT-I in the first session. Sleep education and review of the sleep log are usually conducted in the second session. Subsequent sessions include the use of validated CBT-I techniques (i.e., stimulus control, sleep restriction, relaxation, and cognitive restructuring), in addition to methods to improve adherence. The use of Socratic questioning can be utilized to stimulate individuals to think about their cognitive distortions. A final closure session is usually included to review treatment gains and procedures. It is important to note that stimulus control, sleep restriction, and sleep hygiene are considered first-line treatments and cornerstones of this multicomponent therapy. Relaxation and cognitive restructuring are considered second-line treatments that can be incorporated if there is incomplete response or if there are predisposing or precipitating factors that may hinder response to one of these modalities.

Sleep Pattern Assessment

Assessments can be helpful in treatment planning for CBT-I and typically include soliciting the following information:

- The amount of time spent asleep; time spent awake in bed; whether insomnia occurs in initiating sleep, maintaining sleep, and/or early morning awakening; the number of awakenings during the night and time spent returning to sleep; whether one feels rested upon waking; and the regularity of the sleep schedule (including whether weekends differ from weekdays).
- History of insomnia, including any past and current efforts to treat it.
- Identification of potential antecedents, in terms of both acute stressors and factors related to poor sleep hygiene (e.g., watching TV while falling asleep; drinking caffeinated or alcoholic beverages at night). A step-by-step review of the individual's bedtime routine can prove helpful, as can reviewing their daytime routine including work schedule, eating and exercise times, and duration and timing of naps.
- Cognitions and the extent of sleep-related anxiety while trying to fall asleep.
- Psychiatric problems (e.g., anxiety; posttraumatic stress disorder [PTSD]; depression; bipolar disorder) that can interfere with sleep.
- Medical problems (e.g., asthma; chronic obstructive pulmonary disease [COPD]; cardiac conditions; pain and neuropathy; headaches; as well as gastrointestinal, renal, endocrine, and rheumatologic problems).
- Medications (e.g., stimulants; decongestants; antidepressants; corticosteroids; beta-agonists; and beta-antagonists) and other substances (caffeine; alcohol; nicotine) that can interfere with sleep.
- Presence of other sleep problems (e.g., circadian rhythm sleep-wake disorder; restless legs syndrome; sleep apnea; narcolepsy; parasomnias; nightmares) that can interfere with sleep.

There are a number of useful assessment measures to assist in collecting this information. Sleep diaries are important for both initial assessment and monitoring treatment progress (see [17] for an example, the Consensus Sleep Diary). The diary should be completed upon waking to enhance the accuracy of recall of the prior night's sleep. In addition, given that people are often poor estimators of their sleep onset and overall amount of sleep [18], obtaining assessment information from significant others can enhance the accuracy of the sleep information.

Self-report questionnaires to consider using with adults include the following:

- *Insomnia Severity Index* [19], a seven-item measure of insomnia symptoms and their impact on daytime functioning.
- *Insomnia Symptom Questionnaire* [20], a 13-item measure of insomnia.
- *Pittsburgh Sleep Quality Index* [21], a 19-item measure of sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleep medications, and daytime dysfunction.

- *Sleep Disturbance Questionnaire* [22], a 12-item measure that includes four factors: attributions regarding restlessness/agitation, attributions concerning mental overactivity, attributions concerning the consequences of insomnia, and attributions concerning lack of sleep readiness.
- *Sleep Hygiene Index* [23], a 13-item scale of sleep hygiene habits (e.g., "I go to bed at different times from day to day"; "I use alcohol, tobacco, or caffeine within 4 hours of going to bed or after going to bed.").
- *Daytime Insomnia Symptom Response Scale* [24], a 20-item measure of complaints regarding cognitive and motivational problems (e.g., "think about how unmotivated you feel"), negative affect ("think about how irritable you feel"), and fatigue ("think about how tired you feel").
- *Glasgow Content of Thoughts Inventory* [25], a 25-item measure of the content, character, and intrusiveness of cognitions when one is attempting to fall asleep.
- *Dysfunctional Beliefs About Sleep* [26], a 16-items scale assessing the extent to which one has unrealistic beliefs about sleep or their ability to cope with sleep loss (e.g., "I have little ability to manage the negative consequences of disturbed sleep"). Its four subscales are labeled perceived consequences of insomnia, worry/helplessness about insomnia, sleep expectations, and medication.
- *Morningness-Eveningness Questionnaire* [27], a 19-item scale for assessing chronotype, whether one is most active and alert in the morning ("larks") or evening ("owls").
- *Pre-sleep Arousal Scale* [28], a 16-item measure of cognitive and somatic arousal prior to falling asleep.

Scales for assessing sleep among children or adolescents are often completed by parents and include the following:

- *Children's Sleep Habits Questionnaire* (CSHQ) [29], a 38-item parent report of children's sleep behavior during the past week. In addition to a total sleep problem score, the CSHQ contains subscales for bedtime resistance, sleep anxiety, sleep onset delay, parasomnias, night awakenings, sleep-disordered breathing, and daytime sleepiness.
- *Pre-Sleep Arousal Survey for Children* [30], a 16-item child report of cognitive arousal (e.g., "worry about falling asleep") and somatic arousal (e.g., "cold feeling in your hands, feet or your body in general") before falling asleep.

Subjective measures such as self-reports, however, can be biased by an individual's perception of their sleep. Thus, objective data might be more helpful in documenting sleep patterns as actigraphy, polysomnography, and self-reports obtained through diary or retrospective questionnaires often yield different estimates of sleep duration [31]. Actigraphy provides data on rest/activity patterns, with inactivity presumed to indicate sleep. Some actigraphy measures also contain a light sensor to help detect circadian rhythms that often provide unique information when compared to patient-reported sleep logs [32, 33]. Actigraphy, however, has also been found to both under- and overestimate total sleep time, although collecting data for

more than a week can enhance the reliability of sleep time estimates [34]. More recently, smart phone apps have met or exceeded the accuracy of wrist-based actigraphy in identifying sleep-wake cycles among healthy populations, although their performance is less accurate among those with poor sleep efficiency and in clinical populations [35]. The Sleep on Cue app, for example, has been found to estimate sleep-onset latency accurately within 3 minutes among individuals without insomnia [36]. Polysomnography, while not generally used to assess insomnia, can be used to help rule out other sleep problems, including sleep-related breathing disorders and periodic limb movement disorders.

After assessment, it is important to provide individuals with a conceptualization of their insomnia. Spielman's 3P factor model [37] has often been used to do so and includes discussion of predisposing factors (e.g., gender and hormonal changes associated with it; age), precipitating factors (e.g., any acute stress leading to development of acute insomnia), and perpetuating factors changing the acute insomnia to chronic in nature (e.g., continued maladaptive behaviors such as worrying about sleep; looking at the clock; and the presence of contributing medical problems). Similarly, case conceptualization also includes identifying conditioned responses (e.g., bed being associated with alertness rather than sleep), physiological arousal (e.g., bodily tension), emotional arousal (e.g., anxiety and worry), psychosocial influences (e.g., loss of a family member), and cognitive factors (i.e., maladaptive cognitions) that interfere with sleep. These contributing factors are presented in the context of providing a rationale for insomnia onset and maintenance and are addressed in CBT-I's sleep education component.

Sleep Education

After the initial sleep assessment session, CBT-I therapists usually review sleep diary findings and 3P factors with the patient. This is followed by providing sleep education regarding aspects of sleep, including how sleep needs vary from person to person but with 7–8 hours considered as adequate sleep duration for most adults [38], and the importance of good *sleep hygiene*, which includes refraining from napping during the day, exercising (though perhaps not in the late evening), eating a light snack an hour before bedtime, and avoiding beverages at night. Since alcoholic beverages can lead to sleep interruption and caffeine can remain in the system for 4 hours causing diuresis and stimulation leading to insomnia, these beverages should be avoided especially in the evening before bedtime. Similarly, nicotine can lead to stimulation and withdrawal symptoms causing irritation and insomnia and thus should generally be avoided. Using ear plugs or white noise to create a quiet environment has also been beneficial [39]. In addition, replacing old mattresses and pillows, establishing an optimal room temperature (typically somewhat cool), and blocking out light can also create an environment conducive to sleep [39]. Finally, it is important to maintain consistent wake- and bedtimes.

It is important to set expectations when it comes to CBT-I, which includes the possibility of initial worsening of symptoms (e.g., with sleep restriction, there is a

possibility of decreased duration of sleep initially followed by a gradual increase in sleep time). Incremental improvements with realistic expectations should be emphasized so that individuals do not expect a rapid cure and become discouraged when this does not occur.

Stimulus Control Therapy

Another major perpetuating cause of insomnia is the increase in non-sleep-related activities while lying in bed. Stimulus control addresses the common problem in which one begins to associate their bed and bedroom with being alert and staying awake, even when tired [40]. Such conditioned arousal may worsen if the individual worries about being unable to fall sleep or about being exhausted the next morning, further increasing their wakefulness. To address this and to optimize stimulus control, the following guidelines are initiated [41]:

1. Go to bed only when you are sleepy.
2. Use the bed only for sleep or sex. Eliminate TV, phones, computers, reading of exciting or highly engaging material, worrying, and other activities that could interfere with your sleep onset.
3. If you do not fall asleep within 10 minutes (estimating the time, as clock-watching is discouraged), get out of bed, go to another room, and return to try again only when you are sleepy. When in the other room, do something relatively non-stimulating (e.g., reading in dim light; do not eat, smoke, or exercise).
4. If upon returning to bed, you cannot fall asleep within 10 minutes, repeat steps 2 and 3.
5. Set your alarm to wake up at the same time every day, regardless of how much you slept that night.
6. Do not nap during the day as doing so may interfere with sleep onset at night.

While Stimulus Control Therapy (SCT) has proven effective even as a monotherapy, it is important to note that some individuals find stimulus control to be challenging. This includes difficulty finding a nonscreen activity that does not affect sleep, fear of disrupting the bed partner if they must leave bed at night, and ambivalence about following these directions. If the individual is using a positive pressure ventilation device or is at risk for falling, this can further complicate adherence to the plan.

Sleep Restriction Therapy

One of the major perpetuating factors that increase the risk of chronic insomnia is the mismatch between sleep opportunity and sleep ability. Sleep restriction therapy (SRT) aims to improve sleep drive by restricting one's time in bed in an effort to replace intermittent, light sleep with more deep, consolidated sleep [42]. SRT

is recommended if sleep efficiency (i.e., sleep time divided by time in bed) is less than 85% (or less than 80% for older adults). Improving sleep efficiency can be particularly helpful for individuals who tend to lay awake in bed or who wake up multiple times during the night. As sleep efficiency improves, the target amount of time spent in bed is gradually increased. The initial time in bed target is estimated by taking the average of one's current amount of sleep (i.e., not their time in bed, which can be much greater). If, however, an individual is sleeping 5 hours or less a night, then 5 hours is set as the starting point. If individuals are sleeping less than 85% (i.e., sleep efficacy less than 85%), then downward titration of sleep time is indicated, provided the total initial sleep time is more than 5 hours. Time in bed is gradually increased (e.g., by 15–30 minutes a week) until the individual establishes a pattern of well-consolidated sleep. For sleep-deprived individuals who are anxious about aggressively restricting their time in bed, a more gradual decrease can be used (cf. *sleep compression therapy* [43]).

SRT also emphasizes the importance of establishing a consistent wakeup time and bedtime, regardless of how much sleep one has the night before. To do so, the individual counts back from their target wake time. For example, if you need to rise at 6 AM and are in bed (but not necessarily asleep) for 5 hours, then your initial bedtime would be set at 1 AM. As part of establishing a good sleep routine, the individual needs to get out of bed within 5 or 10 minutes of their target wake time and to maintain this schedule throughout the week. Sleeping later on weekends, for example, can make sleep onset more difficult come Sunday night when the individual is not sleepy. While consistent weekday and weekend sleep hours are the ideal, sometimes a maximum 1 hour variance can be acceptable. However, a greater variance is expected to affect one's sleep pattern. As in stimulus control therapy, naps are generally discouraged because they can interfere with having a strong sleep drive at the scheduled bedtime.

While generally an integral part of CBT-I, sleep restriction may be contraindicated in some cases [44]. Because SRT can increase daytime sleepiness at the beginning of treatment, individuals who need to be highly vigilant (e.g., long distance drivers, air traffic controllers, and those who work with heavy machinery) should not engage in SRT. Likewise, SRT is not recommended for individuals with conditions that are exacerbated by sleepiness or deep sleep such as epilepsy, parasomnias, and sleep-disordered breathing. In addition, as with stimulus control, a fear of waking one's bed partner (e.g., when going to bed after one's partner) can be a deterrent to SRT adherence. Problem solving around this issue before implementing SRT can be helpful, as can obtaining buy-in from the partner.

Managing High Arousal and Utilizing Cognitive Restructuring

Creating a Relaxing Environment for Sleep

Ruminating over the day's events, worrying about the following day's schedule, or playing an exciting video game just prior to bedtime can increase arousal and

alertness and thus interfere with sleep onset. Suggestions to help manage high arousal at bedtime include the following [45]: scheduling some relaxing downtime just prior to bedtime; scheduling "worry time" during the day to decrease worrying at bedtime [46]; creating a "to do" list for the next day to help diminish worries about unfinished tasks; and practicing relaxation techniques (e.g., meditation, diaphragmatic breathing, progressive muscle relaxation, guided imagery, autogenic training that focuses on peripheral blood flow or simply listening to relaxing music). To optimize adherence, making a recording of relaxation techniques in session with the patient or using phone apps (e.g., a meditation app) can help to facilitate the practice of relaxation techniques.

Cognitive Restructuring

The cognitive model of insomnia [47, 48] proposes that negative thoughts or cognitions can increase one's arousal and distress. Such "automatic" thoughts (e.g., "I need to fall asleep now or I'll be exhausted in the morning") can lead to increased monitoring and a distorted perception of one's sleep deficit, which can further increase negative thoughts. In addition, daytime thoughts can also create increased arousal and anxiety. ("If only I slept better last night. I probably won't be able to fall asleep tonight either.") To address such sleep hindering thoughts, cognitive restructuring is taught. Cognitive restructuring teaches individuals to identify thoughts that interfere with their sleep, and then to evaluate the evidence for such thoughts (i.e., is the thought accurate? What's the actual likelihood that you won't be able to fall asleep soon?). Gradually, the individual learns to generate more adaptive alternative thoughts (e.g., "I am frustrated, but if I get out of bed for a while, maybe I will become sleepy enough to fall asleep later"). *Thought records* are often used to help individuals record their thoughts, the thoughts' antecedents (i.e., what were they doing when they had the automatic thought), associated feelings (e.g., sadness; hopelessness; anxiety), evidence for and against the accuracy of the thought, and possible alternative thoughts.

Efficacy of CBT-I

A growing body of research supports the efficacy of CBT-I. In a review of five randomized controlled trials, CBT-I was found to be superior to both benzodiazepine and nonbenzodiazepine medications in the long term, although benzodiazepines might be more effective in the short term [49]. Brasure and colleagues similarly found CBT-I to be more effective than inactive control conditions in improving insomnia [50]. Likewise, a meta-analysis of 20 studies found sleep efficiency to improve by a mean of 10%, sleep onset by 19 minutes, and total sleep time by 8 minutes [14]. While the 8-minute improvement in total sleep time is modest, Trauer and colleagues suggest that sleep restriction might initially suppress greater improvements in total sleep time [14]. Importantly, these studies find that improvements in insomnia following CBT-I are generally well maintained and even

continue to improve at 1-year follow-up. While CBT-I can effectively treat insomnia, factors such as the modality by which it is presented, co-occurrence of physical and mental health conditions, and age of participants need to be considered for their possible impact on CBT-I's efficacy.

Modality: Does CBT-I Format Affect Improvements in Sleep?

While CBT-I is typically provided in individual in-person sessions, alternative formats have been used to make CBT-I more accessible. Swift and colleagues, for example, provided a daylong CBT-I psychoeducational workshop in community settings for up to 30 people and found insomnia symptoms to decrease significantly among those randomized to the CBT-I condition, but not for those in the wait list control condition at a 3-month follow-up [51]. In a more traditional, smaller group format with 5–8 participants, CBT-I was found superior to relaxation training in decreasing both insomnia and depressive symptoms [52]. Consistent with this finding, a meta-analysis of eight-group CBT-I studies found medium to large effects for improving sleep onset latency, sleep efficiency, and time awake after sleep onset using group CBT-I [53]. Thus, group CBT-I is an effective treatment for insomnia, although some research has found individually administered CBT-I to be more effective [54].

CBT-I is also delivered via telehealth and the Internet. Telehealth-based CBT-I used along with telehealth-based CBT for depression was found to be more effective than usual care in improving sleep among older adults [55]. In addition, rural participants who received CBT-I via either telehealth or the Internet both reported similar improvements [56]. Session attendance, however, was better in the telehealth condition, whereas homework completion and overall treatment preference were higher in the Internet condition. Similarly, Internet-based trials of CBT-I are superior to non-CBT treatments and to no-treatment comparison conditions in improving sleep efficiency as well as fatigue, mood, and overall daytime functioning [13]. A meta-analysis of 15 Internet-based CBT-I studies found that mean sleep efficiency improved from 72% to 79% while sleep time increased by 20 minutes [57]. Such improvements are well maintained at 18-month follow-up [58]. Of note, while Seyffert and colleagues found no significant differences between Internet-based CBT-I and in-person CBT-I conducted by a trained therapist [57], one recent study did show somewhat greater efficacy for in-person CBT-I [59]. Longer treatment duration and a higher degree of personal clinical support were also associated with greater treatment gains when CBT-I is presented online [60]. Internet-based websites such as Sleepio and RESTore are readily accessible for those who do not otherwise have access to a CBT-I trained professional, although these sites do generally charge a fee.

Phone apps such as CBT-I Coach can also be used to supplement CBT-I. While patients can use the app to record sleep diary information, set daily reminders, and practice relaxation [61], it is not yet clear whether such apps significantly enhance

CBT-I's efficacy. In addition, adherence can be problematic for both technology-based and traditional CBT-I. Horsch and colleagues, for example, reported only 52% adherence for technology-mediated (e.g., app- or Internet-based) insomnia treatments even though individuals believed that they had adhered quite well to the interventions [62].

Finally, there are several books available to help individuals apply CBT-I principles. These include Cognitive-Behavioral Treatment of Insomnia [63], The Insomnia Answer [64], Overcoming Insomnia [65], Quiet Your Mind and Get to Sleep: Solutions to Insomnia for Those with Depression, Anxiety or Chronic Pain [66], and Insomnia Solved [67]. Such self-help CBT-I can be effective. A meta-analysis of 35 studies found moderate improvements in sleep that were comparable to in-person CBT-I, with both bibliotherapy and traditional CBT-I interventions showing greater improvement than sleep medication or minimal treatment comparison conditions [68].

Contraindications to CBT-I

There are few situations in which CBT-I should be avoided or at least used with caution. However, among individuals struggling with excessive daytime sleepiness, both SRT and SCT can initially worsen daytime sleepiness. Thus, for conditions such as narcolepsy or sleepiness secondary to obstructive sleep apnea (OSA), this treatment might be a poor fit. In individuals actively using substances, both intoxication and withdrawal from a substance can hinder CBT-I progress. Similarly, those who are in acute medical or psychiatric crisis are not optimal fits for CBT-I. There are also individuals for whom sleep deprivation might cause damage including in those with seizures (sleep restriction can lead to worsening of seizures), parasomnias (sleep restriction leads to deeper sleep and worsening of sleep walking), and those with a history of mania.

Insomnia, Comorbid Health Conditions, and CBT-I

Physical Health Conditions

Individuals with insomnia often have comorbid physical health conditions, including those that can interfere with sleep onset or maintenance. Chronic pain, for example, is associated with lighter sleep that can increase nighttime waking [69]. Likewise, about 20% of patients presenting in general medical settings have severe and persistent insomnia [70]. The relationship between physical health and insomnia may be bidirectional as insomnia can impact the body's stress system and increase risk for health problems, including hypertension and diabetes [71].

A meta-analysis of 37 CBT-I randomized clinical trials among individuals with both insomnia and a comorbid physical or mental health condition found

medium to large effect sizes for improvements in sleep efficiency, sleep onset latency, and wake after sleep onset, although consistent with other studies, there was only modest improvement in total sleep time [72]. Importantly, the comorbid health conditions also showed small to medium improvements following CBT-I, although these improvements were greater for mental health problems than for physical health problems. Specific to chronic pain, CBT-I is associated with some improvement in pain severity and functioning [73]. CBT-I also has been associated with improvements in biomarkers (e.g., C-reactive protein) that contribute to cardiovascular disease risk, thus possibly helping to prevent the development or worsening of cardiovascular disease through inflammatory, metabolic, autonomic, and circadian pathways [74]. While CBT-I is generally effective for individuals across health conditions, contraindications do exist. For example, sleep restriction can lead to increased seizure activity among individuals with epilepsy and as such should be omitted from CBT-I when treating individuals with epilepsy [75].

Mental Health Conditions

Individuals with insomnia are also at increased risk for many mental health problems, again with a bidirectional relationship possibly existing between insomnia and mental health. Insomnia is often comorbid with depression, and depressed individuals with insomnia tend to have more severe depression and poorer depression outcomes than those without insomnia [76]. CBT-I has been found to be effective in treating insomnia among depressed individuals and can help to alleviate their depressive symptoms as well [77, 78]. Sleep characteristics important to consider among individuals presenting with both insomnia and depression include the following [45]: (a) individuals with depression may go to bed earlier in the evening and rise later in the morning, in part to escape their distress, further increasing their time in bed. Behavioral activation therapy [79] can be used to help counter this pattern, along with encouraging the maintenance of consistent bedtimes and waking times; (b) conversely, other depressed individuals tend to wake earlier than desired, possibly due to having a "morningness" chronotype, i.e., being a "morning person." Establishing an earlier wake time (and, ultimately, earlier bedtime) can be helpful for this pattern; (c) dysfunctional thoughts about sleep (and other aspects of one's life that may help to maintain depression) can lead to hyperarousal at bedtime and to inaccurate sleep-related expectations. Cognitive therapy can help the individual develop more adaptive thoughts; and (d) obstructive sleep apnea is more prevalent among depressed individuals [80, 81]. As such, providers should screen for apnea and, if present, refer for treatment.

Individuals with bipolar disorder also tend to experience sleep problems that often include insomnia [82, 83]. The relationship between mood and insomnia appears to be bidirectional among individuals with bipolar disorder, as nighttime sleep predicts daytime mood and vice versa [84]. When using CBT-I for individuals

with bipolar disorder, sleep restriction should be used with care as it might precipitate manic or hypomanic symptoms associated with sleep deprivation, although a small pilot study suggested that sleep restriction can be used safely and effectively for individuals with bipolar disorder and insomnia [85].

Anxiety disorders (e.g., generalized anxiety) and PTSD are also often comorbid with insomnia [86, 87]. Again, CBT-I is associated with improvements in insomnia for those with anxiety or PTSD as their presence did not reduce CBT-I's efficacy [88, 89], and CBT-I has been associated with a small to moderate improvement in anxiety symptoms [90]. For an excellent resource on using CBT-I with veterans who have insomnia, including those with comorbid PTSD, see the treatment manual available online by Manber and colleagues [45].

Alcohol and other substance use disorders are also common among individuals with insomnia. For example, one study found that 55% of individuals with an alcohol problem reported frequently using alcohol to help fall asleep [91]. In a community sample, 10% of all adults reported using alcohol, 8% prescription medications, and 10% OTC medications in the past year to help with their sleep [92]. Given that the negative effects of substances on sleep cannot be combatted by CBT-I (e.g., alcohol can affect sleep composition and lead to increased nightmare frequency and snoring [93]), treatment for substance use is typically recommended before treating insomnia. CBT-I, though, has been associated with sleep improvements among individuals with both alcoholism and insomnia [94].

While the above mental health problems represent perhaps the most often studied psychiatric diagnoses in relation to insomnia, rates of insomnia are also elevated among many other psychiatric populations, including attention-deficit/hyperactivity disorder (ADHD) and schizophrenia [95, 96]. Again, evaluation of any medications and their possible side effects regarding insomnia needs to be considered (e.g., stimulants used for ADHD can increase insomnia, but changes in the amount and timing of doses may decrease this risk). In addition, while CBT-I has been associated with positive improvements in insomnia in multiple studies of individuals with depression, bipolar disorder, anxiety, PTSD, and substance abuse, more research is needed to document CBT-I's efficacy for other comorbid mental health problems.

Hypnotic Medication Use and CBT-I

The use of an antidepressant for the treatment of comorbid depression is not a contraindication if the medication is at a stable dose before the initiation of CBT-I. However, addition of new medications while implementing CBT-I is not ideal as medication side effects can hinder the patient's perception of progress with their sleep. While many behavioral specialists might prefer patients to be off hypnotics during CBT-I, it is acceptable to have patients on a stable, daily maintenance dose of hypnotics during CBT-I, especially among people who express concern when medication discontinuation is mentioned. As needed hypnotic use should be avoided, however, as variable use of hypnotics can interfere with CBT-I's efficacy and may erode the patient's self-efficacy for making progress. When hypnotics

are discontinued, a gradual taper and close collaboration between the treating provider and therapist is required. However, tapering during CBT-I can lead to withdrawal symptoms from the hypnotic, which without patient education can be misperceived as CBT-I lacking in efficacy and worsening one's sleep.

CBT-I by Age Group

While most studies have examined the efficacy of CBT-I with young to middle-age adults, evidence for its efficacy with both younger and older age groups exists.

Children

Insomnia occurs among roughly one in five school-aged children [97]. Behaviorally oriented interventions that include CBT-I have been found to have small to large effect sizes in improving children's sleep-onset latency, night awakenings, and sleep efficiency, although such gains were not found in children with special needs [98]. Although some studies have used CBT-I with child populations, most have examined either individual components of CBT-I (e.g., sleep education) or alternative interventions (e.g., structured bedtime routine; bedtime pass) with the latter often used with toddler and pre-school-aged children for whom the full components of CBT-I may not be developmentally appropriate.

Adolescents

In contrast to child populations, CBT-I has more frequently demonstrated efficacy among adolescents. A recent meta-analysis of nine studies found CBT-I to be associated with a 16-minute improvement in total sleep time on objective measures and by 29 minutes on adolescent report with a 3–5% increase in sleep efficiency after treatment, with these gains generally maintained over time [99]. Of note, when adolescents were given the choice, most selected Internet administered CBT-I rather than group CBT-I [100]. In addition to considering the optimal mode of administration, the potentially important role of parents in facilitating and supporting adolescents' insomnia treatment needs to be considered.

Older Adults

Older age is associated with an increased risk of insomnia [101]. As with younger age groups, CBT-I also exhibits efficacy among older adults [102]. In addition, CBT-I is associated with improvements in some domains of cognitive functioning among older adults who have both insomnia and mild cognitive impairment [103]. One modification in stimulus control therapy, however, is recommended for older

adults who are fragile and for whom getting out of bed in the middle of the night could be unsafe. Rather than getting out of bed, *countercontrol* can be used instead [104]. In countercontrol, the individual sits up in bed and does something nonstimulating (e.g., reading) rather than getting out of bed.

CBT-I Limitations

While CBT-I has been recommended as a first line of treatment, as noted earlier, some of its methods should be avoided in certain populations (e.g., sleep restriction in individuals diagnosed with seizures). In addition, there is a high dropout rate [3] and patients should not expect rapid improvements. At present, it is also not well established that individuals with intellectual disabilities can benefit as well as others from CBT-I. Finally, CBT-I may be less effective if insomnia is due in part to other sleep disorders, in which case polysomnography should be conducted.

Summary

CBT-I is associated with improvements in sleep across a variety of populations, from adolescents to older adults to individuals with comorbid physical or mental health problems. In addition, individuals generally rate CBT-I's component interventions (e.g., sleep hygiene, stimulus control, cognitive therapy, and relaxation training) favorably, with only sleep restriction receiving a somewhat lower rating [16]. Although CBT-I offers fewer risks with superior long-term efficacy relative to sleep medications, patients are rarely referred to CBT-I, especially in the primary care settings where most insomnia treatment occurs [105]. Challenges associated with CBT-I include the limited accessibility of trained providers, cost (especially if sessions are not adequately covered by insurance), and the time involved (e.g., in comparison to sleep medications). In addition, limited awareness of CBT-I by some healthcare professionals, an erroneous belief that patients would generally prefer the "quick-fix" of a sleeping pill, and the lack of knowledge among patients that CBT-I exists as a treatment option [105, 106], also detract from the broader use of CBT-I. A possible solution to this is the use of a stepped care model in which patients are referred initially to online programs or bibliotherapy, with a later referral made to individual CBT-I therapy if needed. However, it is important to provide patients with access to troubleshooting issues that might arise especially in situations where online, bibliotherapy, or group therapy is used.

To address some of these challenges, innovations in CBT-I have led to potentially greater dissemination via Internet, telehealth, group, and bibliotherapy-based modalities in addition to traditional in-person individual therapy. Improving physician and patient knowledge about, as well as access to, CBT-I will be critical for its further dissemination. The growing implementation of integrated care in the United States and other countries may facilitate increased insomnia screening and referral to CBT-I by primary care physicians and/or the behavioral health specialists with

whom they work. The effective use of CBT-I in a primary care setting, for example, was recently exemplified in a study by Davidson and colleagues [107]. Likewise, the ongoing development and validation of CBT-I using Internet-based programs and phone apps may offer further opportunities for CBT-I dissemination to populations who might not otherwise engage in traditional in-person therapy. In addition, ongoing research is needed to address ways to improve CBT-I adherence and retention, which have included e-mail/phone reminders and increased clinician contact [108], and might also include identification of those individual most at risk for dropout (e.g., individuals with short sleep duration and depressive symptoms [109]) and the use of motivational interviewing. Finally, Acceptance-based Behavioral Therapy (ABT) has recently been used for the treatment of insomnia with positive results for both treatment retention and efficacy [110], offering the possibility that elements of ABT could be integrated into CBT-I to enhance its treatment retention and efficacy.

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4

Yoga and Mindfulness-Based Cognitive-Behavioral Therapy for Insomnia (Y-MBCT$_i$)

Basant Pradhan and Sahana Malik

Introduction

Insomnia is characterized by subjective dissatisfaction with one's quantity or quality of sleep. It is the most frequently reported sleep disorder and may manifest as early morning awakening, or difficulty falling asleep or staying asleep. Approximately 10–15% of the adult population suffers from insomnia, which can have significant negative consequences if left untreated [1]. Prevalence of insomnia increases with age and may be primary or secondary to other conditions. Insomnia costs the US economy 63 billion dollars per year [2]. A study involving more than 10,000 working adults revealed that more than 20% of them had experienced periods of insomnia that lasted over a year [3]. Furthermore, inadequate or nonrestorative sleep is associated with a variety of medical, psychiatric, or cognitive complications in both adolescents and adults [4, 5]. Patients with sleep-related problems often do not verbalize their struggles with insomnia or seek professional help for these problems. For example, the incidence of insomnia in the primary care setting can be as high as 69%, but only one-third of patients discuss their sleep problem with their physician [6]. Hypnotic medications are frequently used to treat insomnia, but some patients prefer nondrug approaches to avoid tolerance and dependence [7].

Mindfulness-based approaches have emerged as novel strategies for stress reduction and emotion regulation, among other health benefits. Although preliminary

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work has been conducted on using meditation-based interventions for individuals suffering from chronic sleep disturbances, data on standardized treatment models using yoga and meditation interventions together in an integrated and evidence-based manner are rather lacking. In this chapter, we provide an overview of the science behind sleep and insomnia and describe how a standardized approach using yoga and mindfulness-based cognitive therapy (Y-MBCT) can address these issues. This model can be used by healthcare professionals in their routine clinical practice to address their patients' sleep-related problems in a targeted, time-limited, and customized way. We discuss the utility of the Yoga and Mindfulness Based Cognitive Therapy for Insomnia ($Y\text{-}MBCT_i$), a proof of concept model backed by preliminary data that can be used alone or in combination with other evidence-based approaches, including medications for insomnia and related conditions such as excessive sleepiness or parasomnias (strange phenomena happening during sleep).

Approach to Assess Insomnia

The diathesis-stress model [8], more commonly known as the "3-P" model (**p**redisposing, **p**recipitating, and **p**erpetuating factors), is quite relevant to assess the factors that contribute to the development and maintenance of insomnia. Of note, the 3-P model applies equally well to a wide variety of psychological-behavioral conditions besides insomnia.

In evaluating insomnia, there are several factors one must take into consideration. A central task is to determine whether the insomnia is a process-C (circadian) condition or process-S (related to homeostasis) condition. These are independent mechanisms and need to be assessed separately in each patient suffering from sleep problems because treating a Process-C-based insomnia as a Process-S-based insomnia can result in treatment failure. In the Process-S, the likelihood of falling into nonrapid eye movement (NREM) sleep is increased by the amount of time previously spent awake and thus promotes sleep. The Process-C tends to offset the Process-S so that we do not go to sleep until we are ready (i.e., it follows a circadian arousal process that promotes alertness). The Horne Ostberg questionnaire can be used to determine whether the sleep complaints are circadian rhythm-based (morningness-eveningness) [9].

Another task is to determine whether it is a rapid eye movement (REM) stage or non-REM (NREM) problem. REM sleep is essentially independent of Process S and Process C. It is important to have a basic understanding of these two types of sleep to help determine the correct diagnosis and, subsequently, implement effective treatment interventions. These have been already explained in Chap. 1 of this book.

The differential diagnosis of insomnia can be systematically assessed by examining six domains as described later:

(a) Is any medical condition(s) causing the insomnia?
(b) Is any psychiatric condition(s) causing the insomnia?
(c) Is any substance abuse causing the insomnia?
(d) Is the insomnia circadian rhythm Process-C based?

(e) Are there associated parasomnias or movement disorders such as restless leg syndrome (RLS) or periodic limb movement disorder (PLMD)?
(f) Finally, if (a) to (e) are negative, then the possibility of primary insomnia should be entertained and referral to a sleep disorder center should be made.

Role of Yoga and Mindfulness Interventions in Insomnia

Insomnia is one of many areas in which a mindfulness-based approach appears to be particularly suitable. Emerging evidence predominantly from the adult population suggests that mindfulness-based interventions (MBIs) can be effective in the treatment of insomnia. In practice, MBIs are often combined with other therapeutic approaches. For example, mindfulness-based stress reduction (MBSR; [10]) is a widely used structured group program to reduce stress and improve self-regulation. Similarly, mindfulness-based cognitive therapy (MBCT) merges mindfulness with cognitive-behavioral therapy (CBT) and thus typically includes mindfulness meditation in addition to sleep restriction, stimulus control, sleep education, and sleep hygiene. A few studies have examined the effects of mindfulness-based stress reduction (MBSR), mindfulness-based therapy for insomnia (MBT-I), and the addition of mindfulness as a component in a multimodal approach [1, 11]. Our group conducted a meta-analysis of the relevant studies [12] with the purpose of assessing the effects of mindfulness interventions (MBIs) on sleep disturbance in the general population. This meta-analysis examined 16 pertinent studies that enrolled a total of 575 individuals from 8 to 87 years of age. In all, 82.1% of participants were female (472 out of 575 participants). The outcome measures of sleep were total sleep time (TST; the number of minutes that the individual actually slept during one night); sleep onset latency (SOL; minutes taken by the individual from the bed time until falling asleep); sleep efficiency (SE; time slept divided by the total time spent in bed); and wake after sleep onset (WASO; the number of minutes spent awake after initially falling asleep). Sleep measurements were evaluated before and after MBIs, using both subjective and objective methods. In the majority of studies, these sleep parameters were calculated on the basis of self-reported sleep logs (i.e., subjective measurements). We found MBIs to be associated with a large increase in sleep efficiency (SE; effect size = 0.88; $p < 0.0001$) and a medium increase in total sleep time (TST; ES = 0.47; $p = 0.003$) as assessed by sleep logs. In addition, wake after sleep onset and sleep onset latency also showed medium to large decreases (WASO: ES = −0.84, $p < 0.0001$; SOL: ES = −0.55, $p < 0.00001$). Changes in sleep when measured by polysomnography and actigraphy, however, were not statistically significant. In this meta-analysis, the sleep improvements as assessed by sleep logs continued 2–6 months following the treatment initiation. Although interpretation is limited by the subjective nature of the assessment tool and the small number of studies on MBIs for insomnia, especially in adolescent populations, these results suggest that mindfulness-based interventions can improve sleep.

It is important to note that yoga and meditation interventions are heterogeneous, involve many different components, and often are not used in a standardized manner

[13]. There are many distorted views surrounding yoga and meditation, with a lack of clarity as to what these terms mean in actual day-to-day practice. In addition, their use is often carried out in nontargeted ways. For example, yoga is largely understood as a physical or postural technique, while meditation is seen as a breathing technique. This kind of dichotomous view and fragmented use of yoga and meditation restrict their scope and their utility. It not only prevents the integration of body and mind, but also poses significant challenges in research when evaluating the comparative efficacy of yoga or meditation interventions across different studies. Yoga and meditation interventions are more effective when used in combined, synergistic, and targeted ways [14]. Such a holistic and integrated approach is in accordance with the ancient Indian scheme of the Eight-limbed Yoga of Patanjali (*Sanskrit*: Astanga yoga) [15], or the Noble Eightfold Path of the Buddha (*Pali*: Atthangika Magga [16]) as they were proposed originally. In fact, literature [17, 18] suggests that the integrated use of the varying aspects of yoga is more effective than the use of specific components in isolation. As discussed earlier, MBIs have shown promising effects for the treatment of insomnia across a limited number of predominantly uncontrolled studies. However, data on standardized treatment models using both yoga and meditation interventions together in an integrated and evidenced manner are rather lacking. The Y-MBCT$_i$ model integrates the cognitive-behavioral treatments for insomnia with the principles and practices of standardized yoga and mindfulness meditation interventions in a customized manner. The translational format of the Y-MBCT$_i$ model is based on the psychobiology of sleep physiology and pathologies. It combines this information with not only standardized and evidence-based meditation protocols, but also yoga interventions and behavioral therapy modules so that the multiple components can be used in an integrated and customized manner.

The Components of the Y-MBCT$_i$ Model

Y-MBCT$_i$ model is targeted, time-limited (8–10 sessions) and translational in nature (3 T's). It is targeted because it targets insomnia from biopsychosocial perspectives using subjective and objective approaches. It is time-limited because over 8–10 sessions it involves administration of a standardized protocol to treat insomnia. It is translational in nature because it integrates the basic science behind sleep physiology and pathology with the five cognitive-behavioral therapy modules as well as with the principles and practices of standardized yoga and meditation interventions in a way tailored to the individual patient.

Goal of Y-MBCT$_i$

The translational format of the Y-MBCT$_i$ model is backed by basic research on the psychobiology of sleep and related pathologies. It combines these insights with evidence-based meditation protocols, both yoga interventions and behavioral

therapy modules, so that these heterogenous approaches can be used in an integrated and personalized manner. The goal of the Y-MBCT$_i$ model is to help the afflicted individuals increase their awareness of the mental and physical states that develop with chronic insomnia and to develop adaptive ways of working with these undesirable states. In this model, meditation exercises are used to help the patient monitor the mental and physical states associated with their chronic insomnia without reacting to them in an overwhelmed way. Discussion takes place between the patient and the treatment provider about how to create this mindful state in a customized way and how to apply it to problematic situations that may arise in one's daily life as a result of insomnia.

The mindful state (described later) is systematically developed in the individual and characterized by alertness, calmness, and a nonreactive stance. In particular, attention is brought to the mental and physical states of sleepiness and fatigue as participants are taught to discern these two states. The cognitive–behavioral therapies (CBT) embedded in the Y-MBCT$_i$ model include a focus on reducing unwanted wakefulness at night, decreasing the ruminations and anticipatory anxiety (catastrophization) related to the impact of insomnia on the individual's life, and effectively managing the emotional reactions to the sleep disturbances and daytime fatigue.

Components of Y-MBCT$_i$

The Y-MBCT$_i$ model involves a broad array of many psychotherapeutic components that can be categorized under two main therapeutic approaches:

(a) Standardized yoga and meditation protocols (discussed later)
(b) Cognitive-behavioral therapies (CBT)

The CBT portions are divided into five main components (detailed later):

(i) Sleep restriction
(ii) Stimulus control
(iii) Behavioral activation
(iv) Behavioral experiments
(v) Mindfulness-based graded exposure therapy (MB-GET, [18, 19])

The yoga and meditation modules consist of an initial sleep assessment followed by the implementation of the standardized Y-MBCT$_i$ protocol. The sleep assessment includes:

(i) Obtaining a thorough history using the 3-P model
(ii) Administration of the assessment scales: the *Insomnia Severity Index* scale (ISI, [4]) and the *Assessment Scale for Mindfulness Interventions* (ASMI, [13, 19, 20])
(iii) Assessment using biological measures (EEG, etc.) at different time intervals as outlined later in Fig. 4.1

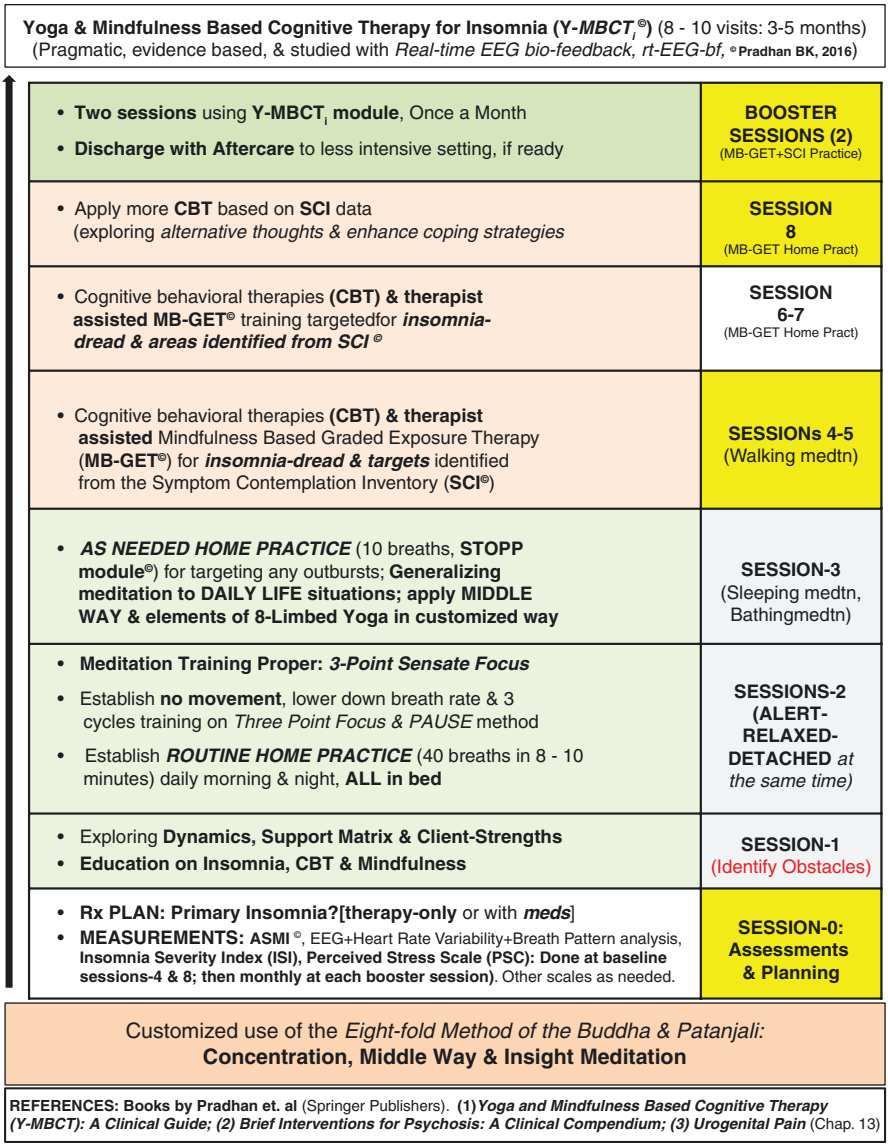

Fig. 4.1 Methodology of the Y-MBCT$_i$ model

The standardized Y-MBCT$_i$ protocol includes the following:

(a) Training on the standardized yoga and meditation protocols: This is the first step in the Y-MBCT$_i$ protocol. This step helps the patient regain a state of mind (the mindful state) necessary to observe life stressors more neutrally or in a less reactive manner rather than being flooded by or habitually repeating them with-

out control. The *mindful state* (which is *simultaneously alert, calm, and detached/nonreactive*), once attained, brings more focus and attentional reorientation. This shift enables the patient to engage in nonjudgmental self-observation of their thoughts, feelings, (unpleasant) memories, sensations, and impulses/behaviors (*Buddha's five factors model* of human experience [13, 20]) instead of habitually indulging in them in a repetitive and emotionally charged manner.

(b) The second step in the Y-MBCT$_i$ protocol involves conducting a behavior analysis (identifying antecedents, behaviors that are problematic, and consequences: the ABC paradigm) and training the patient on five components of CBT. This step is done only after generating the *five-factor inventory* of the insomnia experience which is similar to the *thought records* often used in CBT sessions (e.g., for the treatment of anxiety or depression). However, it is more all-encompassing (detailed in Pradhan et al. [19]). This step enables the provider to formulate a collaborative treatment plan targeted toward handling the sleep problem(s).

The five main components of the CBT intervention in Y-MBCT$_i$ are briefly described later:

1. Sleep restriction [21] is an empirically supported treatment for insomnia that complements the mindfulness principles. It involves regulating sleep by setting a limited time in bed (e.g., 12:00 a.m. to 6:00 a.m.). By restricting the amount of time in bed, the individual avoids compensatory behaviors for sleep loss such as taking naps or staying in bed to catch more sleep. These compensatory behaviors can lead to a reduced homeostatic drive for sleep and thus perpetuate the sleep problem.
2. Stimulus control [22] is another empirically supported treatment for insomnia that can work well in conjunction with the mindfulness techniques. Stimulus control involves associating the bed and bedroom with feeling sleepy. Activities like eating, doing work, or watching TV in bed are discouraged as it weakens this association. Patients should not go to bed until they feel sleepy and they should get out of bed if unable to sleep for a period of time. This concept is designed to help maximize the opportunity of falling asleep more easily.
3. Behavioral activation: This is specifically targeted towards reducing daytime sleepiness, which may be a result of insomnia itself or it may be a by-product of the sleep restriction technique, especially during the early stages of its use.
4. Behavioral experiments: The behavioral experiments are driven by basic data about the patient generated by the five-factor inventory of insomnia and the weekly activity schedule (illustrated below in Fig. 4.2). These experiments are aimed at challenging the dysfunctional thoughts (cognitive distortions) and behaviors related to insomnia and thus serve a crucial role in the Y-MBCT$_i$ protocol.
5. Mindfulness-Based Graded Exposure Therapy (MB-GET [19, 20]). MB-GET is another CBT method used to reduce the significant amount of dread, catastrophizing, and anticipatory anxiety seen in patients with sleep problems, especially insomnia. MB-GET involves *increasing awareness but decreasing reactivity* to

WEEKLY ACTIVITY SCHEDULING: Pleasant-Physical-Social

Name:_____ **Practice week: from date** _____**to date**_____
Please plan **SIX fixed activity each day** to break the cycle of STRESS, DEPRESSION & ANXIETY. **Maximum free time allowed is 2-3 hours a day** (this free time can be reduced by meditation/adding activities).
(1) Sleep and wake up times: _____ respectively; (2) **Time for formal/easy meditation practice** in bed at night & when wake up (15-20 minutes each time):_____. (3) Easy **Physical Exercise time:** _____; (4) **Lunch & Dinner times:**_____; (5) **Time to work on career / job application /Coping skills:** _____**; (6) Informal/Easy meditation practice for uncalm situations** in daily life: 3-4 times a day.

Day of the Week	How satisfied are you on adhering to the Activity Schedule? (0=Not satisfied; 10=Super)	OBSTACLES that come in the way between YOU & YOUR ACTIVITY SCHEDULE	What is the ACTION PLAN to enhance your adherence to the activity schedule?
Friday			
Saturday			
Sunday			
Monday			
Tuesday			
Wednesday			
Thursday			

Happy Practicing, You can do it! **Basant Pradhan, MD**

Fig. 4.2 The weekly activity schedule

both sleep and insomnia-related symptoms and their precursors (antecedents). The act of consciously, purposefully, and calmly focusing on sleep problems, their antecedents, and consequences as done in MB-GET is truly a contemplative and *responsive* approach, rather than reactive. This set of techniques makes or tries to make symptoms more objective targets of reflection and neutral (detached) observation rather than an intolerable source of subjective anxiety, frustration, and dysphoria. The behavioral experiments and the MB-GET interventions often complement each other. As compared to the traditional exposure-based treatments that have been criticized for relative lack of patient engagement, the mindfulness component inherent in the MB-GET model promotes patient engagement with the exposure tasks, in addition to enhancing the efficacy and empowerment [23].

By combining these sleep-related behavioral change interventions with mindfulness meditation, participants are taught to make significant changes in the way they approach both sleeping and waking stress, and they master the ability to bring yoga and mindfulness into their daily lives.

The schematic presentation of the methodology of the Y-MBCT$_i$ model is depicted in Fig. 4.1.

Customizations in the Y-MBCT$_i$

Assessment, treatment planning, and delivery of the interventions in the Y-MBCT$_i$ model are customized on the basis of the client's scores on the following measures:

1. Level of mindfulness: This is measured by the *Assessment Scale for Mindfulness Interventions* (ASMI; Pradhan [13]). This is a clinician-rated 18-item scale and measures the level of mindfulness in seven dimensions, including its practice. Scores range from 0 to 90 with higher scores indicating a higher level of mindfulness.
2. Level of stress: This is measured by the Perceived Stress Scale (PSS) [24]. The PSS is a widely used 10-item self-administered scale that measures the degree to which the various situations in one's life are appraised as stressful. Items were designed to explore how unpredictable, uncontrollable, and overloaded the clients find their lives. The scale also includes a number of direct queries about current levels of experienced stress. Scores range from 0 to 40 with higher scores indicating a higher level of stress. The items are easy to understand, and the response alternatives are simple to grasp.
3. Insomnia Severity Index (ISI, [25]): This clinician-administered scale assesses the severity of both nighttime and daytime components of insomnia. It has seven questions and the total scores range from 0 to 28.

   Interpretation of the total score categories ranges from no clinically significant insomnia (scores from 0 to 7), subthreshold insomnia (8–14), moderately severe clinical insomnia (15–21) to severe clinical insomnia (22–28). A positive "Treatment Response" on this scale is defined as a decrease in the ISI scores by at least 8 points; "Remission" is defined as ISI scores less than 8. In contrast, "Deterioration" is defined as an increase of ≥3 points in ISI scores [26, 27]. The aforementioned measures serve as guides for the implementation of the various components of this multimodal treatment model.
4. The *weekly activity schedule* (see Fig. 4.2): This is a rather simple and easy-to-do behavioral module that serves as a primer of the behavioral structure that is to be used in an incremental manner by combining the desirable behaviors/activities with positive reinforcement strategies. This helps in establishing sleep-promoting behaviors and healthy coping mechanisms.

Achieving the Meditation Skills Before Implementing the CBT Interventions is the Key to Success in this Therapy

After the patient is systematically trained in the standardized yoga and meditation modules as demonstrated in Fig. 4.1, she or he is encouraged to focus more on the practice of meditation to achieve a mindful state, which in turn can be used to carry out the CBT interventions in a less emotionally charged and more organized manner. In the Y-MBCT$_i$ model, emphasis is placed on meditation

skills as well as meditation practice because both are complementary to each other and necessary for applying this multicomponent model effectively. In the Y-MBCT$_i$ model, as the program progresses, participants are taught to use mindfulness principles and behavioral strategies when working through undesirable states. Using mindful awareness as a platform, participants are taught to respond to sleep disturbance with mindfulness skills and contemplation rather than react automatically by increasing their (often unsuccessful) efforts to rest. For example, awareness of internal cues (sleepiness rather than fatigue) along with a recognition of ineffective reactive tendencies (avoid fatigue by going to bed) is used to make changes in both the relationship to sleep and sleep-promoting behaviors.

General Instructions on Meditation for Clients Using the Y-MBCT$_i$ Model

If you are suffering from insomnia, research shows that you will likely benefit greatly from a regular mindfulness practice (at least 15–20 minutes daily) like this one [20]. A little bit each day (even 10 minutes) is better than one longer session once a week [13, 20]. A good habit is to practice meditation in bed upon rising in the morning and again in bed just before falling asleep. This routine helps you begin and end your days with mindfulness and constitutes an important step in cultivating the meditative lifestyle (i.e., the Buddha's *Middle Way*) [24].

Instructions for Meditation

(i) Find a place where you can sit still or stand or lie down undisturbed for 10–20 minutes: it is better to keep the spine erect during this practice. Please reduce any unwanted bodily movements by locking yourself into an easy posture (*Sanskrit*: *asana*). Allow yourself to settle, both mentally and physically.

(ii) This is an attention practice rather than a physical practice: the primary task is to feel comfortable, breathe slowly from the belly with your mouth closed, and OBSERVE your breath. You should bring focus to the physical sensations associated with breathing (such as touch, hot/cold sensations) and the movements in your body while breathing. Take your time to make yourself as comfortable as possible so that your mind is not drawn too much toward bodily discomfort, if any. You can use any cushions, stools, or other props to ensure comfort. You may choose to close your eyes.

(iii) If you're feeling agitated, tense, or stressed, take a moment to tune into your body and notice any parts that may be tense (e.g., shoulders, face, jaw, chest). Use the STOPP module [19] to reduce any agitation. The STOPP module of mindfulness is Pradhan's behavioral adaptation of the Middle Way philosophy of mindfulness traditions, which has been successfully applied in clinical situations within the age range of 6–80 years [19, 20]. STOPP is an acronym for **S**tress, **T**hree (or **T**en or **T**wenty or **T**hirty) meditative breaths, **O**bserve,

Practice and **P**rogress. The STOPP module specifically helps to quickly de-escalate anger or hyperarousal symptoms as they arise spontaneously in daily life in response to triggers.

(iv) Next, you will practice the *"Three Point Sensate Focus" meditation* [20], which is one of the cornerstones of the Y-*MBCT$_i$ model*. As the name suggests, you will use three physical aspects of meditation to keep your attention grounded on the breath and bodily sensations ("*grounding the mind onto the body*"). Examples include touch, sound, hot/cold sensations, beginning-middle and end of each in-breath and out-breath, or breath-associated movements. You can begin by taking the whole focus of your attention to the tip of the nostrils. Note the sensations of breath entering and leaving the body. You may note a slightly cool sensation as you inhale and a warmer sensation upon exhalation. Allow the sensation to completely absorb your attention. Stay with this practice for 3–5 minutes (about 15–20 standardized meditative breaths) during each practice session.

(v) Next, follow the flow of the breath as it moves through the nostrils, down the throat and into the lungs (inhalation). Then back out the lungs through the throat and out the nostrils (exhalation). Allow the mind to follow the passage of the breath as it enters and leaves your body.

(vi) Know that thoughts, feelings, or memories may drift through your mind. That's perfectly normal. There is no need to resist them or try to push them away. No need to be concerned with the nature of any particular thought. Be a gentle, impartial (neutral) observer to any thoughts that may arise and label them as "just distractions." Refocus on your breath and associated sensations or movements.

(vii) Continue your meditation until you achieve the mindful state (concurrent alertness, relaxation, and detachment/nonreactivity to the ongoing stimuli). This may take 5-25 minutes.

(viii) When you are ready to complete the practice, over three slow and deep belly breaths, bring your awareness back to your body by feeling the weight of your body against the chair, by registering any sound from your surroundings, and by recalling the room you're sitting in. Begin to move and stretch your body and open the eyes. Feel free to sit peacefully and readjust to your surroundings before going about your day.

The Five-Step SPASM Method for Honing Meditation Skills

In addition to the instructions given previously, the *SPASM* method is used in the Y-MBCT$_i$ model to hone the meditation skills further in the practitioner. Details of the five steps in the SPASM method are as follows:

S: *Sit Straight* and *Still, Slow* down the breath rate
P: *Pause* momentarily after breathing out
A: Be *Aware* of the distractions but do nothing, just *Accept*/observe them and *Acknowledge* their presence

S: Refocus on the physical *Sensations* (such as breath sensations, sounds, etc.) rather than on the thoughts or other distractions

M: *Middle Way*: To decrease a striving and self-critical/perfectionist attitude during meditation practice, it is important to follow the Buddha's *Middle Way*. This creates mindful awareness (e.g., a state of calmness, alertness, and detached/open monitoring of the objects in one's awareness) that helps cultivate a "being" state of mind rather than a "doing" or "striving" state of mind [13]. Of note, unlike the striving/perfectionist attitude (which is an extreme style), the *Middle Way* is the path of moderation.

General Instructions on Sleep Hygiene for Clients Using the Y-MBCT$_i$ Model

Instructions on *sleep hygiene* include but are not limited to the following:

- Keep the bedroom dark, noiseless and with a comfortable bed.
- Keep the time that you go to bed and wake up fixed, in order to create a daily sleep routine. Use an alarm to do so. Contrary to popular belief, maintaining the same daily wake-up time is more important than maintaining the same bed time because circadian rhythm is more sensitive to the former.
- Start your day with mindfulness practice and end your day with mindfulness practice, all in the bed. This is quite easily done by practicing 40–60 standardized meditative breaths using the "Three Point Sensate Focus" meditation protocol [20].
- Avoid alcoholic drinks and stimulants (i.e., caffeinated beverages) for up to 4–6 hours before going to bed. Avoid heavy physical exercise within a 3-hour window of going to bed.
- Remain in bed and meditate even if you're not able to sleep. This prevents arousal states and also allows for conditioning the meditation to induce a sleepy state.
- Try your best to avoid sleeping when you are not in bed. If you can't help it, restrict the daytime nap to less than 30–45 minutes.

Results of the Y-MBCT$_i$ Model in Four Patients (Tables 4.1 and 4.2)

The methodology of this open label case series was adopted from our meta-analysis published earlier [12]. The outcome measures of sleep were total sleep time (TST; the number of minutes that the individual actually slept during one night); sleep onset latency (SOL; minutes taken by the individual from the bed time until falling asleep); sleep efficiency (SE; time slept divided by total time spent in bed); and wake after sleep onset (WASO; the number of minutes spent awake after initially falling asleep). These sleep outcome measures were calculated on the basis of self-reported sleep logs (subjective measurements).

Table 4.1 Demographics and clinical variables of patients with chronic insomnia ($n = 4$)

	Subject 1	Subject 2	Subject 3	Subject 4
Demographics				
Age (years)	47	52	58	19
Gender	Male	Male	Male	Female
Race	White	White	Hispanic	Hispanic
Occupation	Healthcare provider	Company executive	Retired clerk	High school student
Clinical profile	Mild GAD	MDD (moderate)	Obesity (BMI = 34.2)	Mild GAD
Insomnia type	Delayed onset sleep and intermittent waking up	Delayed onset sleep and early morning awakening	Delayed onset sleep	Delayed onset sleep and intermittent waking up
Insomnia duration	8 years	11 years	8 years	6 years
Medications	None	Zolpidem 2.5 mg/d prn	Zolpidem 5 mg/d prn	Fluoxetine 20 mg/d
No. of Y-MBCT$_i$ sessions needed	8 (done in 12 weeks)	12 (done in 18 weeks)	10 (done in 16 weeks)	8 (done in 10 weeks)

Notes: *GAD* generalized anxiety disorder, *MDD* major depressive disorder, *BMI* body mass index

As shown in Table 4.1, the mean age of participants was 44 years (SD = 17.26 years) and mean duration of insomnia was 8.25 years (SD = 2.06 years). The mean number of Y-MBCT$_i$ sessions was 9.5 (SD = 1.91).

The pre- and posttreatment data on efficacy of Y-MBCT$_i$ in these four patients are shown in Table 4.2. Posttreatment, all four patients improved not only on all sleep parameters (ISI, SE, SOL, TST, and WASO scores) but also in their level of mindfulness (as reflected in their ASMI scale scores).

Conclusion and Future Directions

When examining the neurophysiology and psychobiology of sleep and integrating it with the quintessential pragmatism of cognitive-behavioral therapy and self-empowering methods of yoga and mindfulness, the rationale for and utility of the Y-MBCT$_i$ model becomes more evident. This model can be used as a stand-alone therapy or in combination with sleep-promoting medications. Although the evidence presented here is preliminary, it does suggest that the Y-MBCT$_i$ model is feasible and has the potential to bridge some of the existing treatment gaps within the realm of therapy for sleep-related problems such as insomnia [28]. Moving forward, in our ongoing clinical research, we intend to study the efficacy of the Y-MBCT$_i$ model using a randomized control trial design in a large sample. We will also examine the potential utility of the multisystem real-time biofeedback parameters (consisting of real-time EEG, heart rate variability, and breath pattern analysis) to see if they can serve as biomarkers of treatment response.

Table 4.2 Pre- and Posttreatment data on efficacy of Y-MBCT$_i$ ($n = 4$)

	Subject 1	Subject 2	Subject 3	Subject 4	Mean % change	Paired *t*-test values (pre- vs. post-interventions)
Pre-Rx ISI scores	19	24	23	20	−53.3 (SD = 13.53)	$Mean_1 = 21.50$ (SD = 2.38), $mean_2 = 10$ (SD = 2.94), $t = 6.7337$, $p = 0.007$, df = 3 (95% CI = 6.06–16.94)
Post-Rx ISI scores	7	8	13	12		
Pre-Rx TST in minutes (mean, SD)	434.4 ± 47.2	422.3 ± 46.3	476.8 ± 38.2	364.5 ± 38.4	8.0 (SD = 4)	$Mean_1 = 424.5$ (SD = 46.32), $mean_2 = 460$ (SD = 49.85), $t = 4.19$, $p = 0.025$, df = 3 (95% CI = 62.51 to −8.58)
Post-Rx TST in minutes (mean, SD)	488.3 ± 54.2	468.2 ± 51.4	496.3 ± 37.3	387.4 ± 36.5		
Pre-Rx SOL in minutes (mean, SD)	42.4 ± 18.6	84.2 ± 32.3	57.3 ± 22.4	123.6 ± 27.4	−63.7 (SD =15.0)	$Mean_1 = 76.87$ (SD = 35.63), $mean_2 = 34.7$ (SD 13.9), $t = 3.59$, $p = 0.037$, df = 3 (95% CI = 4.82–79.53)
Post-Rx SOL in minutes (mean, SD)	20.1 ± 11.4	45.4 ± 17.6	25.6 ± 19.2	47.7 ± 16.3		
Pre-Rx SE in % (mean, SD)	73.6 ± 6.4	68.4 ± 7.5	75.4 ± 7.3	64.7 ± 8.2	14.9 (SD = 7.1)	$Mean_1 = 70.52$ (SD = 4.9), $mean_2 = 80.9$ (SD = 5.02), $t = 4.54$, $p = 0.02$, df = 3 (95% CI: −17.64 to −3.11)
Post-Rx SE in % (mean, SD)	87.3 ± 11.5	75.2 ± 7.8	81.5 ± 7.8	79.6 ± 8.8		
Pre-Rx WASO in minutes (mean, SD)	34.3 ± 11.6	48.7 ± 21.8	18.3 ± 6.2	38.4 ± 24.2	−57.64 (SD = 7.18)	$Mean_1 = 34.92$(SD = 12.63), $mean_2 = 14.6$ (SD = 5.78), $t = 5.13$, $p = 0.014$, df = 3 (95% CI: 7.73–32.92)
Post-Rx WASO in minutes (mean, SD)	15.2 ± 7.4	22.3 ± 14.3	8.7 ± 4.3	12.2 ± 8.6		

Pre-Rx ASMI scores (mean, SD)	54	52	43	48	44.65 (SD = 9.23)	$Mean_1 = 49.25$ (SD = 4.86), $mean_2 = 71$ (SD = 4.97), $t = 14.57$, $p = 0.0007$, df = 3 (95% CI: −26.50 to −17.00)
Post-Rx ASMI scores (mean, SD)	77	73	68	66		

Notes: ASMI = Assessment Scale for Mindfulness Interventions (scores range from 0 to 90: higher the scores, higher is the level of mindfulness); ISI = Insomnia Severity Index (scores <8 = no significant insomnia, >22 = severe insomnia); SE = sleep efficiency (in %); SOL = sleep onset latency (in minutes); TST = total sleep time (in minutes); WASO = wake (in minutes) after sleep onset; SD = standard deviation; df = degree of freedom; CI = confidence interval

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5 The ABCs of Insomnia (ABC-I): An Acceptance Commitment Therapy (ACT)-Based Insomnia Treatment Development Study: Pilot Results and Future Directions

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Introduction

Insomnia is characterized by complaints of difficulty initiating or maintaining sleep, or early morning awakening which lasts for at least 3 months and causes clinically significant distress or impairment in social, occupational, or other important areas of functioning [1]. Insomnia is a prevalent disorder, estimated to affect 9–20% of the adult population, and up to 33% of the older adult population [2]. Insomnia is more common when medical or psychiatric co-morbidities are present [3].

Poor quality sleep has a host of debilitating consequences. These include functional impairment and loss of productivity, excess health care utilization, high psychiatric co-morbidity, particularly depression and anxiety, and increased suicide risk [3]. Sleep also affects the physiological stress response and immune system function, with growing evidence suggesting that insomnia is associated with cortisol, a stress-related hormone in the hypothalamic-pituitary axis, and with activation of proinflammatory cytokines (markers of inflammation) [4, 5]. These physiological correlates may explain the observed relationship between insomnia and poor health outcomes.

Currently, the most effective treatment for chronic insomnia is Cognitive Behavioral Therapy for Insomnia (CBT-I), which has been shown to be at least as effective as commonly used hypnotic prescription medications in the short term, and to have longer-lasting benefits compared to medications [6]. Despite being the gold standard treatment for insomnia, CBT-I has some significant limitations [7–9].

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Only about one-third of studies' participants sleep as well as good sleepers who have never experienced clinical insomnia, 50–60% have moderate-range improvements, and 19–26% have no response to treatment. In addition, the effect sizes found in CBT-I studies are lower than the effect sizes compared to CBT for other disorders [10]. A particular drawback of CBT-I is treatment adherence, which tends to be poor. Poor adherence to CBT-I is specifically related to the behavioral recommendations of sleep restriction (i.e., limiting time spent in bed to actual sleep time) and stimulus control (i.e., strengthening the association between bed and sleep, by only sleeping in bed and getting out of bed when not asleep within about 15–30 minutes). These recommendations seem counterintuitive to most insomnia patients who believe they should stay in bed longer to try and sleep and/or rest and who have significant fear related to sleep loss when time in bed is limited by these approaches.

We believe that there is another issue that contributes to the poor adherence in CBT-I. Often times symptoms like fatigue, sleepiness, disturbances in mood, and overall wellbeing get worse during the first few sessions due to sleep restriction techniques, stimulus control, and changes in daytime habits that impact sleep (e.g., avoid caffeine late in the day), before these symptoms get better over time. This contributes to patients' early discouragement and likely lessen adherence to these specific treatment components, or even worse, lead to discontinuation of CBT-I treatment altogether.

Finally, another shortcoming of CBT-I is the potentially arousing nature of the cognitive restructuring component of the treatment. During this technique, the patient is asked to recognize maladaptive thoughts, such as thinking errors related to sleep and insomnia (e.g., overgeneralizing, catastrophizing); to test and assess their accuracy; and to change them to more adaptive, realistic thoughts. This process, which is meant to aid sleep by decreasing anxiety related to sleep, may actually disrupt sleep by engaging the patient in thinking and cognitive arousal pre-sleep, which interfere with the process of cognitive de-activation and relaxation necessary to fall sleep.

Acceptance and Commitment Therapy (ACT) is considered part of the "third wave cognitive behavioral therapies," with the first wave being behaviorism and the second cognitive therapy [11]. Third wave cognitive behavioral therapies incorporate mindfulness (i.e., being in the present moment) as a core principle and technique of psychotherapy. Mindfulness therapeutic techniques have been shown to have positive effects on sleep [12], anxiety [13], and immune system function [14].

ACT has been shown to be effective in treating a variety of anxiety disorders. Unlike other mindfulness-based techniques (e.g., Mindfulness-Based Stress Reduction, Mindfulness-Based Cognitive Therapy), ACT does not always include formal meditation practices. Instead, ACT offers a variety of practical exercises and metaphors aimed at fostering psychological flexibility through mindfulness, acceptance of personal experiences and experiential willingness (i.e., embracing current experience and giving up the need to control or change private experiences), cognitive defusion (i.e., non-identification with thoughts) while making a commitment to "act" in accordance with one's chosen values. An insomnia-related example may be the willingness of a patient to sacrifice a diurnal nap to enhance the probability of a better night's sleep in accordance with the value of living a healthy life.

We believe ACT-based insomnia treatment offers techniques that will promote higher motivation to follow the behavioral prescriptions of insomnia treatment as well as higher acceptance of the discomfort that often comes with compliance with these prescriptions. Higher motivation and acceptance should increase adherence, reduce the likelihood of treatment discontinuation, and therefore improve treatment effectiveness. In developing and providing ACT-based insomnia treatment, we provide the patient with examples of other things in life where things get worse before they get better that are still worth pursuing, in addition to providing tools to help the patients stay with the program during those challenging times (exercises fostering psychological flexibility which entail mindfulness, acceptance, value-based committed action, cognitive defusion, and self as context techniques).

This approach is particularly relevant for those behavioral components of treatment discussed above that are known to pose challenges in adherence, and for those populations who have shown greater difficulty in adhering and benefitting from standard CBT-I (e.g., older adults, people with comorbid conditions). In addition, other advantages of ACT include the willingness to "give up control" over initiating sleep, as well as promote decreased cognitive and physiological arousal, which are important steps toward falling asleep and may even decrease overall stress levels.

Dr. Fiorentino had previously co-authored a case report study on the benefits of incorporating ACT to the treatment of a recurring insomnia patient in a clinical setting [15]. Inspired by that first case study and by the numerous successful clinical experiences we have had incorporating ACT strategies in the treatment of sleep disorders, we created a treatment manual that, in a more standardized and repeatable fashion, could be used by any trained clinician to treat insomnia successfully. We called the treatment ABC-I: Acceptance and the Behavioral Changes to treat Insomnia.

This chapter describes the development of the ABC-I intervention and summarizes the results of two pilot studies designed to test the effectiveness of this novel intervention. Pilot studies were conducted in two populations that are known to have suboptimal adherence to CBT-I due to medical and psychological comorbid conditions (i.e., older veterans with medical comorbid conditions and women veterans with post-traumatic stress syndrome).

Methods

The development of the ABC-I manual and its initial testing were conducted following the National Institute of Health (NIH) guidelines for the development of behavioral treatments [16]. The first part of the study was the development of the treatment (stage 1a), and included developing a manual, identifying the target population, establishing training and monitoring procedures for the administration of the treatment, and selecting appropriate outcome measures. The second part of the study entailed testing of the treatment through pilot studies (stage 1b) and looking at acceptability and feasibility of treatment. In this chapter, we will focus on the manual development and main sleep outcomes of the pilot studies.

Stage 1a—Treatment Manual Development

Traditional ACT-based therapeutic exercises were customized for the treatment of insomnia and other new ACT-inspired exercises for insomnia were created. Materials exemplifying these exercises (metaphors, visualizations, drawings, meditations) were developed and incorporated into routine clinical care of the behavioral insomnia clinic at one Veterans Administration (VA) healthcare system. Patients were invited to provide their impressions and feedback about the understandability, acceptability, and helpfulness of the materials. The materials were then revised in accordance with the feedback received from patients and re-proposed to other insomnia patients in routine clinical care. A patient manual was created incorporating the ACT-based exercises with the sleep education, sleep hygiene, stimulus control, and sleep restriction components of traditional behavioral treatment of insomnia both by revising the components of available behavioral insomnia treatment materials and developing new treatment materials. We purposefully excluded the cognitive restructuring component of traditional CBT-I and instead added the ACT exercises. After several iterations, a manual involving five weekly sessions was developed. The sessions lasted approximately 1 hour each.

ACT-Inspired Metaphors and Exercises in ABC-I

ABC-I is composed of five sessions, each of which has a specific purpose. Table 5.1 highlights the different items discussed and focused on during each session. Metaphors are often utilized during these sessions to increase the individual's insight into the consequences of insomnia and used to motivate the individual to "put effort" to improve or change the outcome.

Session 1

Insomnia and What Is Important to You—Writing Exercise This exercise was created to foster the patient's awareness of what makes their life meaningful (e.g., family, friends, work, health, religion) and the connection between having insomnia and the patient's experience in those areas of life (e.g., "when I sleep poorly I am less able to concentrate at work," "when I can't sleep I am more irritable with my friends and family"). Making the link between the effects of insomnia and important aspects of the patient's life may increase their motivation to implement the behaviors that will improve their sleep even when these behaviors are notoriously challenging (e.g., changing life style habits).

Surfing Metaphor The surf metaphor is designed to convey two important aspects of fostering good sleep. The first aspect is **PREPARATION.** Like a surfer prepares to have a good surfing experience by waking up early to catch the good waves, waxing their board, wearing a wet suit, and stretching, so can the patient prepare for a good night's sleep by adhering to sleep hygiene rules such as avoiding naps, avoiding caffeine, and exercising at the optimal times. The second aspect involves **GIVING UP CONTROL** over sleep by fostering a mindful and accepting attitude toward when sleep will come (like a surfer waits for the wave to arrive).

Table 5.1 Components of each session in the ABC-I treatment

Session number and title	Main goals	Treatment components	Exercises/ homework
1. "Learning How to Surf"	–Enhance motivation to adhere to behavioral prescriptions –Understand the futility of trying to control sleep –Provide sleep education (define insomnia, the sleep stages and the macrostructure of sleep) –Learn lifestyle habits that enhance sleep and ones that hinder sleep –Foster acceptance of experience of discomfort in the name of committed actions that are value driven	–Values –Acceptance –Mindfulness –Committed action –Sleep education –Sleep hygiene –Stimulus control	–Insomnia and what is important to you –Metaphors: Chinese finger trap Surfing –Leaves on a stream exercise –Drawing life with/ out insomnia –Action plan for the week –Sleep diary
2. "Renovating your Home"	–Learn about the homeostatic and circadian sleep processes –Understand the rationale behind sleep restriction	–Values –Acceptance –Mindfulness –Committed action –Sleep restriction	–Metaphors: Pizza dough Silly putty Piggy bank Hiking Renovating your home –Action plan for the week –Sleep diary
3. "Taking Your Mind for a Walk"	–Adjust time in bed –Understand the concept of dirty versus clean discomfort –Experience cognitive defusion	–Values –Acceptance –Mindfulness –Committed action –Cognitive defusion –Self as context	–Physicalizing –Clean versus dirty discomfort –Take your mind for a walk –Two plates scale metaphor –Action plan for the week –Sleep diary
4. "Acceptance & Commitment"	–Adjust time in bed –Review	–Values –Acceptance –Mindfulness –Committed action –Cognitive defusion –Self as context	–Action plan for the week –Sleep diary
5. "If Not Tonight Tomorrow Night"	–Adjust time in bed –Understand relapse prevention techniques	–Values –Acceptance –Mindfulness –Committed action –Cognitive defusion –Self as context	–Action plan for relapse prevention

Chinese Finger Trap Experiential Exercise Each patient is given a Chinese finger trap to put on their bed-stand as a reminder to "stop trying to sleep." Chinese finger traps are woven bamboo tubes where you place an index finger in either end. If you try to pull both fingers, the tube constricts, and your fingers are trapped. On the other hand, if you push your fingers inward, it causes the tube to loosen which frees both fingers. This gadget is used as a metaphor for doing what may be perceived as counterintuitive at times (e.g., stop trying to fall asleep, sleep restriction) in order to promote sleep.

Leaves on a Stream Meditation This is a classic ACT exercise. In this meditation, the patient is first guided in a brief mindfulness exercise that includes breath work and focuses on the physical body and the senses, followed by a visualization exercise depicting the patient's thoughts as flowing downward leaves in a stream. In addition to being pleasantly relaxing for most patients, this exercise is used to explain the concepts of mindfulness (being in the present moment and your experience of being alive with your breath, your sensations, etc.) and cognitive defusion (if you can imagine your thoughts as leaves on a stream, you cannot be your thoughts).

Drawing Your Life with and Without Insomnia – Homework Exercise In this exercise, the patient is asked to depict using the media they like (e.g., pencil, paint, collage) their life with insomnia on one page and their life without insomnia on a different page. This exercise has a dual aim. First, it helps remind the patient of the aspects of their life that are suffering because of insomnia and therefore should increase their motivation to work on the lifestyle changes that promote healthy sleep. Second, the ability to visualize a life without insomnia is the first step to having the willingness to plan and implement the necessary changes to achieve good sleep.

Session 2

Pizza Dough/Silly Putty Metaphor These metaphors are used to better describe the concept of quality of sleep (consolidated sleep as opposed to interrupted) and how in ABC-I we work first on consolidating sleep as if we were making the dough for a pizza, and then on expanding sleep as if we were spreading the dough to make the pizza. Similarly, we describe having a variety of pieces of silly putty and making one consolidated ball of putty which then we can shape into what we want (the length of sleep we want).

Hiking and Renovating Your Home Metaphors In behavioral treatment of insomnia, symptoms (e.g., fatigue, sleepiness, mood) often get worse for patients initially before they get better. These metaphors help patients realize that there are other things in life where things get worse (hiking paths often go temporarily in the oppo-

site direction of the top of the mountain; homes can look in complete disarray while being restored) before they get better (you arrive at the top of the mountain; your house is completely renovated).

Session 3

Physicalizing Visualization Exercise In this visualization exercise, the therapist guides the patient in visualizing (1) their insomnia, and (2) their feelings and thoughts about having insomnia as two different objects in front of them. The benefits of this exercise are twofold: first, imagining insomnia as an object outside of oneself helps the patient realize that there is more to the patient than insomnia (if I am able to see it in front of me, it is not all of me). For anxious patients who feel overwhelmed by their insomnia, this simple exercise can be very helpful in bringing a different perspective ("I have insomnia, but I am not insomnia and there is more to me than insomnia"). Second, this exercise helps the patient better understand the ACT concepts of "clean versus dirty discomfort" explained below.

Clean Versus Dirty Discomfort Metaphor These concepts refer to the difference between experiencing pain while accepting it as it is (clean discomfort, for example, "I cut myself while chopping vegetables while cooking. The cut hurts, my hand is bleeding"), versus applying negative judgment to the experience of pain (dirty discomfort, e.g., "I cannot believe I cut myself, I am so clumsy"). The overall discomfort felt is greater during dirty discomfort versus clean discomfort. Understanding this difference is a step toward being able to recognize negative self-judgment and stop it. Patients are then encouraged to approach their pain with self-compassion instead of criticism (e.g., "I cut my hand, so I'll wash my wound, put a bandage on it, protect it from further harm, and take care of my hand and myself so I can heal").

Take Your Mind for a Walk This is an experiential exercise in which the provider and the patient go for a 5-minute walk. The provider walks slightly behind the patient and talks in the direction of the patient's ear. The provider pretends to be the patient's mind and speaks to them with harshness and criticism to emulate the patient's negative judgments. By this time in treatment, the provider has gotten to know the patient and can reproduce plausible thoughts the patient may have (e.g., "This is such a stupid exercise; I must not be doing this right; I should stop this nonsense now"; "This is never going to help my insomnia") and also neutral statements of perceptions and actions (e.g., "I'm getting hungry," "I want to turn left at that corner"). The patient's role is to listen to "their mind" talking to them and notice their feelings and actions that follow.

The aim of the exercise is for the patient to realize that their mind says a variety of things to them all the time; some may be helpful, while other thoughts are not helpful. What is important is realizing that no matter what their minds tell them, they have a choice on how to respond and which thoughts to give power to by

allowing them to influence their actions. The patient is then encouraged to give power to the thoughts that are value driven and behave in the directions of their values.

Two Plates Scale Metaphor This metaphor is described to the patient to understand the relationships among willingness to experience life as it is, acceptance, and suffering. The specific example with insomnia is that on one side of the scale is a plate with the patient's insomnia, and on the other side of the scale is a plate with the patient's willingness to experience insomnia for what it is (clean discomfort, such as not sleeping well, feeling unrested). If the willingness plate is empty, insomnia is going to be the heaviest plate (because there will be dirty discomfort, such as "I am the worst sleeper in the world, I'll never sleep well"). If the willingness plate is full, the insomnia plate will be balanced or even lighter than the willingness plate.

Session 4

There are no new metaphors/exercises introduced in this session. Session 4 provides opportunities to check-in, review and trouble shoot any challenges. Most patients are sleeping significantly better and feeling better by session 4. Interestingly, one of the most prevalent challenges we encounter at this point in the therapy is the patients' frustration of not being able to fill out the sleep diary with precise times because they have been instructed not to look at the clock at night if they wake up. In these cases, we remind the patient that what is most important is how they feel about their sleep and how they feel and function throughout the day, not calculating the exact amount of sleep they are getting. For most patients, this reminder is enough to dispel frustration. For other patients, the desire to know what time they are waking up at night and be as precise as possible on their sleep diary makes them check the time at night when they wake up even if they have been instructed not to. In these cases, it is helpful to review healthy and unhealthy sleep habits as well as discuss any problematic control strategies that the patient might be engaging in to deal with anxiety. We use metaphors (e.g., Chinese finger traps) and experiential exercises (e.g., leaves on a stream) to create awareness of unhelpful coping strategies and foster helpful ones.

Session 5

The mantra "if not tonight, tomorrow night" is introduced as a potential relaxing mantra to repeat to oneself during the night or day after a patient's poor night of sleep.

Identify Target Population

Our interest was in developing a treatment that would enhance the existing treatment of insomnia by increasing the motivation to engage in the treatment and would benefit those patients that have a harder time adhering to traditional CBT-I (e.g., older adults and patients with comorbid conditions). We, therefore, decided to first pilot test our treatment in older adults with comorbid conditions. Subsequently, we also piloted ABC-I in women veterans. For both pilot studies, we recruited a convenience sample of patients from one VA healthcare system.

Stage 1b—Pilot Studies

Pilot Study 1

Participants This study was approved by the human safety research committees of the VA Greater Los Angeles Healthcare System and the University of California, Los Angeles. A total of 10 individuals were screened for participation in the study. Six of these individuals were not eligible for treatment and were thus excluded (one did not meet criteria for insomnia, three had significant symptoms of untreated sleep apnea, one had significant cognitive impairment and one had poorly controlled psychiatric symptoms involving psychosis). The remaining four individuals began ABC-I; however, one of these individuals discontinued because of an unexpected major surgery shortly after the beginning of treatment. Therefore, three individuals completed the full intervention, all of whom completed the post-treatment and 3-month follow-up assessments. It is important to note that while documentation of the hypnotic medications prescribed for these individuals was not reported, patients were instructed to continue with the same regimen during this study. Each participant who initiated treatment is described below.

Participant 1 was an 81-year-old Caucasian married man living with his spouse. He worked part-time as a psychiatrist. His medical comorbidities included prostate cancer, memory loss, anemia, and impaired hearing. He previously had tried CBT-I but dropped out after the second session because he "couldn't handle it, it was too hard." This patient reported struggling with insomnia for over 20 years and was a chronic user of sedative-hypnotic medications.

Participant 2 was a 60-year-old Caucasian single man (living with his brother). He was unemployed. His medical and psychiatric comorbidities included generalized anxiety disorder, major depressive disorder (MDD), back pain, gastroesophageal reflux disease (GERD), diabetes, and hypertension.

Participant 3 was a 77-year-old Caucasian married man living with his spouse (having marital problems). He was retired. His medical and psychiatric comorbidities included post-traumatic stress syndrome, MDD, legal blindness, diabetes, and fibromyalgia.

Sleep Outcome Measures

Self-Reported Sleep Measures The Insomnia Severity Index (ISI) is a seven-item insomnia severity questionnaire that assesses difficulty falling asleep, nighttime awakenings, early morning awakenings, impairment of daytime functioning, noticeability of impairments, distress and worry about sleep, and current dissatisfaction with sleep. Each item is rated on a Likert scale ranging from 0 (not at all) to 4 (extremely). The ISI total score is obtained by adding the scores on the seven items (range 0–28). Reported ISI internal consistency is high (i.e., 0.78), and any score below 8 is considered not clinically significant insomnia [17]. The Glasgow Sleep Effort Scale (GSES) is a seven-item self-report that measures sleep effort. The GSES uses a 3-point Likert scale (0 = low effort, 2 = high effort) and has been shown to discriminate between insomniacs (high effort) and good sleepers (low effort) [18].

Objective Sleep To objectively quantify sleep in the home sleep environment, we used wrist actigraphy, which has been validated for the estimation of sleep parameters in adults and is recommended when sleep is assessed for multiple nights in the natural sleep environment [19]. Participants wore the actigraph on the dominant arm for 3 days and nights (72 hours) at baseline, post-ABC-I and at 3-month follow-up. We used the Octagonal Sleepwatch-L (Ambulatory Monitoring, Inc., Ardsley, NY), a wrist-mounted actigraph that records activity and illumination exposure each minute with an accelerometer, a light transducer, and a microprocessor. The wrist actigraph is a watch-sized device that has been useful in longitudinal, naturalistic (i.e., not in a sleep laboratory) assessment of sleep patterns. Commercially available software uses validated algorithms to score sleep versus wakefulness for each 1-minute epoch of recording. We estimated the total and percent time asleep at night, and nighttime number of awakenings averaged over the three recording days per phase of study as the main measures of nighttime sleep.

Results

The results of the initial pilot study are summarized in the figures below: Fig. 5.1 showed the average ISI over a seven-night period, Fig. 5.2 shows changes in GSES over a seven-night period, Fig. 5.3 shows actigraphic awakenings, and lastly Fig. 5.4 depicts the percentage of sleep. All three patients reported significant improvements in insomnia severity (ISI) and decreases in the amount of effort (GSES) put into sleeping by the end of the study.

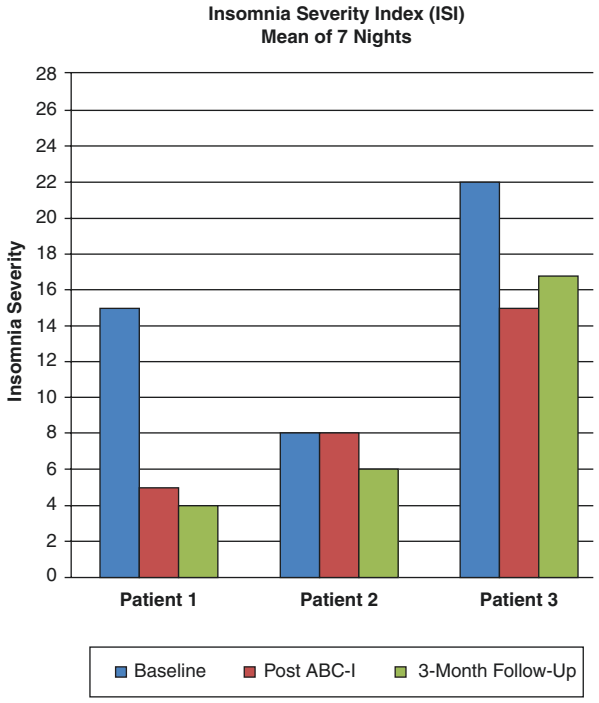

Fig. 5.1 Average ISI over 7 nights for each of the 3 individuals

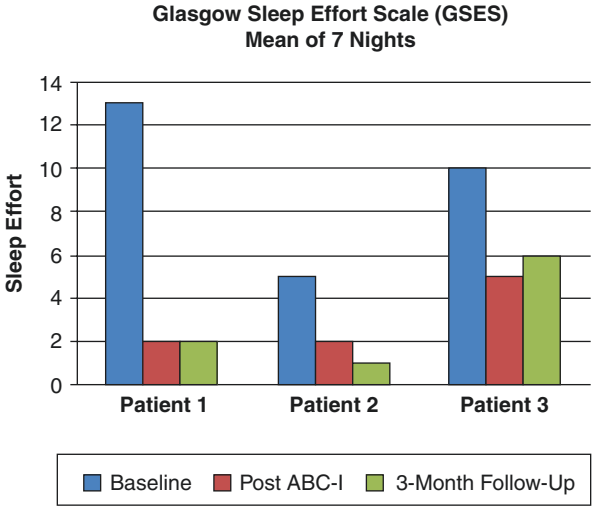

Fig. 5.2 Average GSES over 7 nights for the 3 individuals

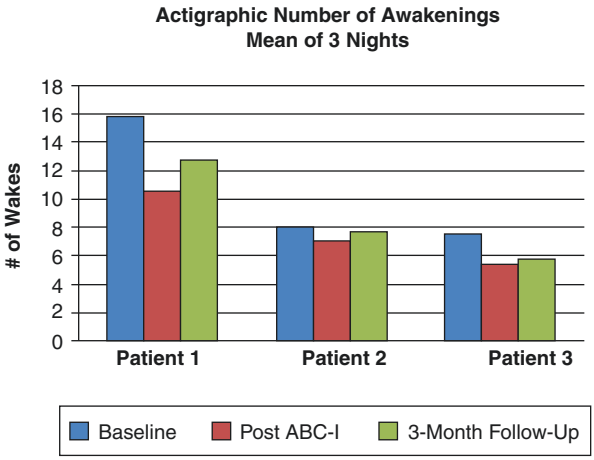

Fig. 5.3 Actigraphic depiction of nighttime awakenings among the 3 enrolled patients averaged over 3 nights

The objective sleep results also show that for all three participants there was improved sleep with fewer awakenings at night and higher (better) nighttime sleep percentage for all three participants post-ABC-I treatment. However, at the 3-month follow-up, some of these benefits in objective sleep were lost.

Pilot Study 2

Participants The second pilot study was also approved by the human safety research committees of the VA Greater Los Angeles Healthcare System and University of California, Los Angeles. A total of 11 women veterans with insomnia (identified as meeting diagnostic criteria for chronic insomnia disorder) participated [20]. The mean age for the 11 individuals was 56.4 (with standard deviation [SD] = 13.3) years. Six women were not eligible for treatment: three due to

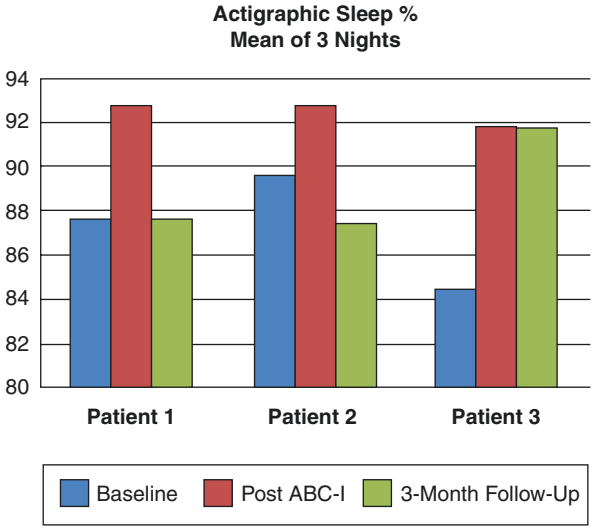

Fig. 5.4 Percentage of sleep depicted by actigraphy over 3 night period for the 3 individuals

moderate-to-severe untreated sleep apnea (based on AHI > 15 using home sleep apnea testing) and three based on unstable medical conditions. However, women who had stable medical or psychiatric comorbidities were not excluded. A total of five women with insomnia disorder completed the treatment (one through teletherapy having moved to a different city before the final session) and the pre- and post-treatment evaluations. While researchers did not document the hypnotic medications prescribed, patients were instructed not to change their medication regimen while enrolled in the study.

Sleep Outcome Measures

Self-Reported Sleep Measures The ISI and GSAS (described above) were utilized to assess subjective sleep quality [17, 18]. In addition, a daily sleep diary to compute weekly nighttime sleep efficiency (i.e., time asleep over time in bed from bedtime to get up time the next morning). This study did not include objective outcomes as the focus was on the clinical improvement in insomnia symptoms, rather than on objective changes in sleep, and to prepare for a larger clinical trial comparing ABC-I to CBT-I.

The Pittsburgh Sleep Quality Index (PSQI) is a 19-item questionnaire that assesses sleep quality and sleep disturbances. The PSQI measures subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. A global sleep quality score derived from the PSQI was used to summarize the overall quality of sleep over the prior 1-week period (modified from the original 1-month duration; the change was made to allow assessment of sleep after completion of the intervention). PSQI global sleep quality scores are continuous (range 0–21), with high scores reflecting poor sleep quality. A PSQI total score below 5 is considered good sleep [21].

Table 5.2 Baseline and post-treatments scores for 5 women who received ABC-I

Measure	Baseline mean (SD)	Post-treat. mean (SD)	*t* (*p*-value)	Effect size (*d*)
Sleep quality (PSQI)	14.8 (3.4)	10.5 (4.9)	2.33 (0.10)	1.26
Insomnia severity (ISI)	18.5 (5.3)	7.2 (7.2)	2.22 (0.11)	2.13
Sleep effort (GSAS)	6.5 (4.5)	2.7 (3.4)	0.97 (0.40)	0.84
Sleep efficiency (diary)	82% (11%)	94% (2%)	−5.14 (0.01)	1.09

Results

The results of the second pilot study are summarized in Table 5.2. Participants experienced clinically meaningful improvements in all outcome measures. They demonstrated reduced self-reported sleep disruption on the PSQI, improved insomnia symptoms on the ISI, and reduced sleep effort on the GSAS. In addition, sleep efficiency based on nightly sleep diaries was improved. All effect sizes were large. One important finding from this study was that all participants completed the intervention (one participant completed the treatment by phone because she moved out of the area during the intervention phase).

Discussion

Good sleep is crucial to health and wellbeing. Unfortunately, insomnia is prevalent in the general population, with even higher rates exhibited in older adults and individuals with medical or psychiatric comorbidities. Insomnia is a disruptive disorder associated with increased utilization of healthcare services and poor quality of life. The most common approach to insomnia management is pharmacological therapy, typically with sedative-hypnotic medications approved by the Food and Drug Administration (FDA) for the treatment of insomnia or with other psychotropic medications that have sedating properties. Common pitfalls of medication management of insomnia are the side effects (e.g., daytime sluggishness, risk of falls in older adults), the palliative but not curative nature of the treatment, the insomnia rebound effects upon medication intake cessation, and the tolerance and addiction potential. Therefore, sleep medications should not be used as a first-line treatment for insomnia.

In 2005, the National Institutes of Health convened an "Insomnia state of the science" panel concluding that cognitive-behavioral treatment of insomnia (CBT-I) produces short-term improvements equivalent to medications and that the long-term outcomes surpass those of pharmacological therapies for insomnia [6]. More recently, the American College of Physicians (ACP) also recommended CBT-I as a first-line therapy for insomnia disorder in adults [22]. Numerous studies have confirmed the efficacy of cognitive-behavioral therapies. However, CBT-I is not a

"patient friendly" treatment—the recommendations given to patients are challenging to adhere to, and often counterintuitive and anxiety provoking. Through our years of clinical and research experience with CBT-I, we noticed that even in the best-case scenarios, patients did not like the treatment and were at times frustrated with it, but eventually grateful because it greatly improved their sleep. In the worst-case scenarios, patients were discouraged and frightened by its methods, refused to adhere to certain recommendations or dropped the treatment completely (actively deciding to "keep their insomnia" or returning begrudgingly to medication management of insomnia).

For these reasons, we felt that CBT-I could be improved, and we developed a novel approach to the behavioral treatment of insomnia, specifically designed to address the likability of and adherence to treatment. In order to do this, we borrowed elements from ACT, which is considered part of the "third wave cognitive behavioral therapies," which incorporate mindfulness (i.e., being in the present moment) as a core principle and technique of psychotherapy.

This chapter outlines the ABC-I manual development and treatment components and our preliminary testing of the ABC-I in three older male veterans with comorbid medical conditions and five middle-age women veterans. In both pilot studies, participants slept better, put less effort into sleeping, and had lower insomnia severity scores at the end of treatment. The first pilot study had objective actigraphy data that showed improvements in the number of awakenings and sleep percentage. This study also had a 3-month follow-up which showed that gains for subjective measures either maintained or improved at follow-up. Follow-up results for the objective measures were less consistent and show room for improvement.

Importantly, except for the individual that had an unexpected major surgery soon after enrollment, all participants finished treatment (one with teletherapy after moving to a different city), including an individual who had previously dropped out of standard CBT-I. In addition, based on anecdotal qualitative data participants reported, they enjoyed the ABC-I exercises, particularly the Chinese finger traps metaphor, life with and without insomnia drawings, leaves on a stream meditation, physicalizing exercise, and take your mind for a walk. Interestingly, as clinicians, we also experienced more pleasant patient-therapist interactions during ABC-I compared to our experience with traditional CBT-I. As one clinician, recently learning ABC-I, insightfully stated: "In ABC-I, I feel like I am side by side with the patient on their journey to better sleep. In CBT-I I feel more like a teacher explaining to the patient what is good for their sleep and what is not."

There are important limitations to this work. The preliminary nature of these findings, the convenience sample methodology, and the small sample size and lack of controls obviously greatly limit the generalizability of the findings. Comparative effectiveness studies are needed to evaluate the efficacy, retention, and adherence outcomes of the ABC-I in comparison to CBT-I in larger groups of insomnia patients. However, our findings show promise for ABC-I as a behavioral treatment of insomnia. This is true especially in the most challenging cases where patients have previously failed CBT-I and/or have numerous medical/psychiatric comorbidities impacting their attitude toward the behavioral sleep treatment

recommendations. In contrast to our clinical and research experience with CBT-I, participants in the ABC-I program were not discouraged by elements of the treatment. On the contrary, they stated that they enjoyed many of the ABC-I exercises and metaphors. Since likability of an activity is directly related to compliance to and sustainability of a health behavior modification, we believe ABC-I may be an important contribution to the field of behavioral insomnia treatment.

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Pharmacotherapy for Insomnia

6

Puneet Narang, Jacob Held, and Steven Lippmann

Introduction

Insomnia is characterized by trouble initiating or maintaining sleep, with early morning awakenings and unpleasant daytime consequences. It is, however, not attributable to environmental circumstances or inadequate opportunity to sleep [1]. Insomnia is categorized by short-term or chronic versions. Those of shorter duration meet symptom criteria and are present for less than 3 months. Chronic insomnias classically have persisted for over 3 months at a frequency of at least three occurrences per week.

Insomnia includes poor sleep quantity and/or quality, with one or more of the following: difficulty getting to and/or staying asleep, too early awakenings, and distress at daytime dysfunction. To meet this definition, sleep problems should not be etiologically related to pharmaceuticals, substance use or abuse, a primary sleep disorder, nor coexisting medical and/or psychiatric conditions. Short-term insomnia affects 30–50% of all people [2]. The prevalence of chronic versions is about 5–10% of inhabitants in industrialized nations [3, 4]. Chronic sleep dysfunction induces impairment in functional status [5], with increase absenteeism [6] and occupational and/or motor vehicle accidents [6, 7]. Persistence is a risk factor for developing psychiatric illnesses, especially mood disorders [8, 9]. Chronicity also imposes substantial economic burdens on society [10, 11].

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Chloral hydrate was prescribed as a soporific drug in the 1800s. Barbiturates and other compounds were utilized to diminish insomnia and anxiety in the first half of the twentieth century. The first benzodiazepine, chlordiazepoxide, was introduced to our market in 1963; flurazepam was the first one approved for prescribing as a hypnotic in 1970. Zolpidem became available in 1992, as the first in a group of non-benzodiazepine receptor agonist hypnotics. In the United States, pharmaceutical approvals of drugs to counter insomnia were additionally granted to a tricyclic drug (doxepin), a melatonin agonist (ramelteon), and recently to an orexin receptor antagonist (suvorexant).

Sleep Assessment

History Besides asking about sleep quantity and quality, inquire about negative daytime consequences (e.g., daytime sleepiness or concentration problems). Question patients about sleep apnea symptoms since apneas are an underappreciated differential, especially among obese individuals, men, and older persons. Other conditions, including abnormal circadian rhythm or movement disorders (i.e., restless leg syndrome), should be considered. Current prescription medications, drugs of abuse, and substances such as alcohol, tobacco, and/or ingestion of stimulant beverages, and/or over-the-counter agents are reviewed for actions which might cause or worsen insomnia.

Examination Before prescribing a sleep-inducing agent, a thorough examination is performed to identify medical ailments, psychiatric illness, emotional distress, and/or environmental issues that may contribute to insomnias.

Subjective/Objective Assessments Sleep questionnaires (e.g., the Insomnia Severity Index or a sleep log) are beneficial to discern sleep patterns and daytime consequence assessments [12]. The Epworth Sleepiness Scale helps to evaluate daytime sleepiness [13]. A polysomnographic sleep study (actigraphy) or home sleep-testing are means of objectively detecting sleep patterns and/or disorders.

Sleep Hygiene

Psychoeducation for better sleep hygiene is helpful for patients being treated for insomnia. Such intervention teaches habits and behaviors to promote better sleep [14]. It starts with encouraging regularized bedtimes and maintaining a quiet, comfortable, and dark atmosphere in the bedroom. Recommendations also include minimizing daytime naps and not exercising or discussing stressful circumstances shortly before bedtime. Some people find a nocturnal glass of milk helpful.

Stress the importance of avoiding caffeinated beverages after midday. Just 400 mg of caffeine can disrupt nighttime sleep in healthy subjects when consumed

up to 6 hours before sleep [15]. Caffeine often creates problems with sleep at latency, total sleep time, efficacy, and quality. Alcohol also negatively affects sleep. While it promotes falling asleep quickly (i.e., short sleep latency), it also often yields more frequent awakenings in the second half of the night (i.e., rebound). Sleep quality subsequently deteriorates along with next-day dysfunction [16]. Ceasing alcohol consumption several hours before bedtime promotes sounder, more sustained sleep. Unfortunately, sleep hygiene techniques are not consistently effective as a single intervention, but they augment response to other modalities.

Psychotherapy

Cognitive behavioral therapy (CBT- I) often helps minimize insomnia [17]. It offers a wide spectrum of effects on sleep mechanisms and is the treatment of choice for chronic insomnias [18]. Sleep restriction, stimulus control, and sleep hygiene are commonly applied simultaneously. Chapter 3 presents CBT-I usage. Other promising psychotherapeutic modalities include mindfulness, described in Chap. 4, and acceptance and commitment therapy in Chap. 5. Pharmaceutical treatments are considered whenever psychotherapies are unavailable, ineffective, or not practical. Prescribing sleep-inducing medicines during early phases of CBT-I augments their effectiveness [19].

Pharmacotherapy

Prescribing After the assessment is completed, underlying conditions are managed. When insomnia persists and/or the patient is not an optimal candidate for non-pharmacologic interventions, then a "sleeping pill" may be indicated (see Table 6.1 for guidelines). When selecting a drug, the risks and benefits are discussed with the patient, in a shared decision-making process.

Efficacy/Choice Hypnotic drugs are prescribed at the lowest effective dose for the shortest time possible. The type of sleep disturbance is considered (e.g., sleep latency vs sleep maintenance) so that a medicine with the most suitable pharmacokinetic properties is selected. Practice guidelines with scientific data guide such choices. The clinical aspects of pharmacotherapy are discussed to provide patients with proper expectations for the risks and benefits. Comparisons between the advantages of different medicines are difficult, since much research is biased and limited. Adverse pharmaceutical effects are more pronounced for elderly patients, especially for those with comorbid medical or mental conditions.

Many sedating antidepressant and antipsychotic drugs are prescribed in off-label indications with the hope of inducing better sleep. These medications have less data supporting their applications during primary insomnias; however, they are an especially appropriate pharmacotherapy for individuals with psychopathology.

Table 6.1 Insomnia treatment guidelines

	American College of Physicians [20]	Am. Academy of Sleep Medicine [21]
First intervention	Adult patients with chronic insomnias should receive CBT-I as the initial treatment (strong evidentiary recommendation)	CBT-I – a standard treatment, with a favorable benefit-to-risk ratio
Secondary recommendations	Apply a shared decision-making approach, including discussion of benefits, harm, and costs, to decide whether to prescribe pharmacotherapy for adults with chronic insomnia, when CBT-I was not successful. (weak recommendation) Prescribing: Doxepin, non-BZRA, suvorexant Elderly: Doxepin, non-BZRA, ramelteon	Sleep maintenance: Doxepin, suvorexant Sleep onset: Ramelteon, triazolam, zaleplon Sleep onset/sleep maintenance: Eszopiclone, temazepam, zolpidem Not recommended: Diphenhydramine, melatonin, trazodone, tiagabine, tryptophan, valerian
Comments	CBT-I reportedly provides better value than pharmacologic interventions Evidence was not sufficient to determine the comparative efficacy and safety of medication management Insufficient data about melatonin Benzodiazepines were not addressed since investigations rarely met guideline inclusion criteria (insufficient evidence) Evidence was not sufficient to evaluate risks or benefits of long-term medication prescribing for people with chronic insomnias	Clinical practice recommendations were not possible for some benzodiazepines due to research inadequate for statistical analysis All recommendations are graded as weak (based on limited evidence; this reflects a lower degree of certainty of outcome and appropriateness, but not an indication of ineffectiveness)

Barbiturates are rarely recommended due to narrow therapeutic indices, drug tolerance or dependency, long half-lives, and/or risk of fatal toxicities. Among benzodiazepines, those with shorter half-lives or fewer active metabolites are most frequently the best choice. Generic formulations are usually less expensive. There are other classes of pharmaceuticals prescribed to promote sleep, including controlled, schedule IV drugs, and substances not within control lists. Over-the-counter agents may be appropriate for some individuals, but efficacy and/or side-effect profiles limit their selection. Non-response to multiple dose adjustments and/or medication trials prompts a clinical re-evaluation (see Tables 6.2 and 6.3 for a full list of psychopharmacological options). Polypharmacy with sleep aids is not advised.

Education Patients are counseled not to combine alcohol, medications, or other substances due to the risk of sedation and/or more side effects. Discuss how they can cause compromised cognition and/or motor skills and about unwanted complex

Table 6.2 Relative efficacies[a]

Class	Generic name	Reduces sleep latency (min)	Increases total sleep (min)	Wake after sleep onset (min)
Benzodiazepines (schedule IV)[b]	Estazolam [22]	–	–	–
	Flurazepam [23]	–	–	–
	Quazepam [24, 25]	–	–	–
	Temazepam [26]	37	99	–
	Triazolam [27, 28]	9	25	–
Non-BZRAs (schedule IV)	Eszopiclone [29]	15–24	23–67	5–37
	Zaleplon [30, 31]	8–15	29	2
	Zolpidem Immediate Release (IR) [32]	12–20	23–29	13–25
	Zolpidem Extended Release (ER) [33]	8–13	23–29	13–25
	Zolpidem (SL; Edluar) [34]	18	23–29	13–25
	Zolpidem Oral Spray [35]	5–12	23–29	13–25
	Zolpidem (SL; Intermezzo) [36, 37]	5–12	23–29	13–25
Tricyclic antidepressant	Doxepin [38, 39]	2–15	12–32	10–23
Melatonin receptor agonist	Ramelteon [40–43]	9	1–13	4–5
Orexin receptor antagonist (schedule IV)	Suvorexant [44, 45]	0.3–22	10–50	5–28

[a]Heterogeneity in research design, medication doses, patient population, methodology of assessment, lack of polysomnography data, publication bias, and number of studies, make comparison between agents and investigations difficult

[b]Objective data not available because some studies utilized subjective scales and questionnaires

sleep behaviors, like sleep-walking or sleep-driving. Impairments at next-day driving competence are particularly dangerous, particularly with longer-duration medicines. Injury due to gait disturbance and falling down are of particular concern for older individuals. For patients taking any sleep aid, instruct them to report abnormal changes in thinking or behaviors, especially including depression or suicidal ideation. Hypnotics are recommended only when necessary, following prescribing guidelines, and for the shortest possible time period. Properly controlling patient use patterns is a long-term issue.

Tmax is the time taken by the drug to reach maximum concentration in plasma. Onset time and onset of action are dependent on Tmax. The area under the curve (AUC) describes the total drug concentration over time. It is an important parameter in evaluating the bioavailability of a drug from its dosage form as it represents the

Table 6.3 Medication summary

	Generic Name	Formulation	Indications	Adult dose	Time to peak (hours)	Half-life (hours)	Active metabolites
Benzodiazepines (schedule IV)	Estazolam [22]	Tab: 1, 2 mg	⇨Sleep latency, ⇨increase sleep maintenance	1–2 mg	2	10–24	–
	Flurazepam [23]	Cap: 15, 30 mg	⇨Sleep latency, ⇨increase sleep maintenance	15–30 mg	~1	2.3–100	+
	Quazepam [24, 25]	Tab: 15 mg	⇨Sleep latency, ⇨increase sleep maintenance	7.5–15 mg	2	39–73	+
	Temazepam [26]	Cap: 15, 30 mg	⇨Sleep latency, ⇨increase sleep maintenance	7.5–30 mg	2	4–18	–
	Triazolam [27, 28]	Tab: 0.125, 0.25 mg	⇨Sleep latency	0.125–0.5 mg	2	2–6	–
Non-BZRAs (schedule IV)	Eszopiclone [29]	Tab: 1, 2, 3 mg	⇨Sleep latency, ⇨increase sleep maintenance	1–3 mg	1	6	–
	Zaleplon [30, 31]	Cap: 5, 10 mg	⇨Sleep latency	5–20 mg	1	1	–
	Zolpidem Immediate Release (IR) [32]	Tab: 5, 10 mg	⇨Sleep latency	Men: 10 mg Women: 5 mg	2	3	–
	Zolpidem Extended Release (ER) [33]	Tab: 6.25, 12.5 mg	⇨Sleep latency, ⇨increase sleep maintenance	Men: 12.5 mg Women: 6.25 mg	2	3	–

	Zolpidem (SL; Edluar) [34]	SL tab: 5, 10 mg	⇨Sleep latency	Men: 5–10 mg Women: 5 mg	1	3	–
	Zolpidem Oral Spray [35]	Bottle: 4.5 mL (4.8 g) with 30 metered actuations or 7.7 mL (8.2 g) with 60 actuations, after 5 initial priming actuations	⇨Sleep latency	Men: 5–10 mg (1–2 sprays) Women: 5 mg (1 spray)	1	3	–
	Zolpidem (SL; Intermezzo) [36, 37]	SL tab: 1.75, 3.5 mg	⇨Sleep latency after middle-of-the-night awakening	Men: 3.5 mg Women: 1.75 mg	~1	3	–
Tricyclic antidepressant	Doxepin [38, 39]	Tab: 3, 6 mg	⇨Increase sleep maintenance	6 mg	4	15	+
Melatonin receptor agonist	Ramelteon [40–43]	Tab: 8 mg	⇨Sleep latency	8 mg	1	1–3	+
Orexin receptor antagonist (schedule IV)	Suvorexant [44, 45]	Tab: 5, 10, 15, 20 mg	⇨Sleep latency, ⇨increase sleep maintenance	10–20 mg	2	12	–

extent of absorption. Half-life of a drug is the time it takes for the plasma concentration or the amount of drug in the body to be reduced by 50%. Half-life determines the length of the drug effect. It also needed to decide the dosing interval.

Benzodiazepine Receptor Agonists (Schedule IV)

Benzodiazepines (BNZs) are a group of medications indicated for insomnia, anxiety, and seizures. They vary in onset of action, duration, and indications. There are five Food and Drug Administration (FDA)-approved BNZs for insomnia treatment and include estazolam, flurazepam, quazepam, temazepam, and triazolam (see Tables 6.2 and 6.3). However, temazepam is the most commonly used medication from this group. Unique pharmaceutical property information follows for each individual one. Benzodiazepines primarily potentiate the effects of gamma-aminobutyric acid (GABA) through modulation of $GABA_A$ receptors [46].

Adversities BNZs often result in somnolence, hypokinesia, dizziness, diminished cognition, and impaired coordination. Daytime somnolence occurs predominantly with the longer-acting versions; women and older people are more susceptible to over-sedation. BNZs can cause respiratory suppression that might worsen breathing in patients with chronic obstructive pulmonary disease and/or a sleep apnea. Sometimes they may induce delirium, overt confusion, and amnesia with altered behavior, or even with the development and/or worsening of dementias. Elderly individuals are especially susceptible to these dangers and also prone to mobility problems, falls, and resultant injuries, like hip fractures. BNZ use sometimes results in misuse, with psychological/physical dependency, withdrawal, and after discontinuance, rebound insomnia. The drugs that exhibit shorter half-lives are favored in prescribing for people with initial insomnia, geriatrics, and/or females, at as low a dose as is effective, and for the shortest duration possible.

Interactions Avoid co-prescribing BNZs with soporific pharmaceuticals that could add to sedation and/or respiratory depression. They should not be utilized together with alcohol. There is a "Black Box Warning" for all BNZs, noting that concomitant use with opioids may result in over-sedation, respiratory depression, coma, and/or death.

Most BNZs, except for temazepam, are primarily metabolized by hepatic cytochrome CYP3A enzymes. Co-administration of agents that are CYP3A inhibitors increases BNZ concentrations and effects; use with enzyme inducers diminishes levels and potency. Discontinuation of jointly used CYP3A inhibitors decreases BNZ concentrations, while stopping enzyme inducers has the opposite effect.

Pregnancy BNZs are generally contraindicated during pregnancy due to risk of fetal harm. Investigations involving animals and/or humans evidence risk for fetal abnormalities.

Lactation These drugs are not advised during lactation due to secretion in breast-milk that can cause sedation of infants and respiratory depression. Temazepam could be one exception, since one study reported 10 breast-fed infants without adverse reactions, despite their mothers being prescribed temazepam [47].

Comorbidities BNZs are rarely prescribed for patients with sleep apneas. Due to misuse potential, they are not indicated for anyone with substance abuse predispositions.

Estazolam (Prosom)

Efficacy Estazolam decreases sleep latency and increases total sleep time [22].

Pharmacokinetics The median time to peak concentration (Tmax) of estazolam occurs 2 hours after administration. It is protein bound and metabolized via CYP3A to inactive products. Excreted in urine, the half-life is 10–24 hours. This medication thus is ideal for individuals with middle insomnia and/or early morning awakening.

Prescribing Start estazolam at 1 mg, before bedtime. Dosage may be increased to 2 mg.

Special Populations For elderly patients, dosing should be initiated at 0.5 mg nightly. Dosage adjustments are not required during renal impairment; yet, they might be needed for individuals with impaired hepatic function.

Flurazepam (Dalmane)

Efficacy Flurazepam decreases sleep latency and increases total sleep time [23].

Pharmacokinetics Tmax occurs about 1 hour after administration. Flurazepam is protein bound and hepatically metabolized via CYP3A. Subsequently, it is excreted in urine within 2 hours, with active metabolites evidencing very long half-lives between 47 and 100 hours. Thus, flurazepam is not an ideal sleep aid.

Prescribing Flurazepam had been recommended at 30 mg, before bedtime. Lower amounts may be effective, but both dosages yield prolonged durations.

Special Populations While 15 mg had been suggested as an initial bedtime dose for older patients and adjustments were not required for those with renal disease, it

was not recommended for people with hepatic disease. This drug is not frequently suggested to be prescribed as a general sleep aid and especially not for older persons due its prolonged effects.

Quazepam (Doral)

Efficacy Quazepam decreases sleep latency and increases total sleep time [24].

Pharmacokinetics Tmax occurs at 2 hours. Quazepam is protein bound and metabolized via CYP3A and somewhat by 2C9 [25]. The parent drug and its active metabolites are excreted in urine and feces with a half-life of 39–73 hours.

Prescribing The starting dose is 7.5 mg, before bedtime. It might be increased to a 15 mg, if well tolerated.

Special Populations No dosing adjustments are expected for elderly patients. However, prescribe it with caution to persons with renal or hepatic impairment.

Temazepam (Restoril)

Efficacy Temazepam inconsistently decreases sleep latency, increases total sleep time, and promotes fewer nocturnal awakenings [26].

Pharmacokinetics Tmax occurs 1–2 hours after administration. Temazepam is protein bound, metabolized through conjugation, and excreted in urine with an average half-life of 9 hours.

Prescribing Start temazepam at 15 mg, before bedtime. The maximum dose is 30 mg, but lower doses may also be effective.

Special Populations The starting dose for older individuals should be 7.5 mg nightly. Extra precaution applies to anyone with renal or hepatic dysfunction.

Triazolam (Halcion)

Efficacy Triazolam decreases sleep latency and lengthens sleep maintenance [27]. However, benefits diminish with continued use.

Pharmacokinetics Tmax occurs at 1–2 hours [28]. Metabolized by CYP3A, metabolites are conjugated and excreted in urine, with a half-life approaching 2 hours.

Adversities Triazolam is associated with increased wakefulness during the final hours of sleep and the drug is unlikely to leave residual sedation in the morning.

Interactions Co-prescribing with strong CYP3A inhibitors is not recommended (e.g., ketoconazole, itraconazole, nefazodone, ritonavir, indinavir, nelfinavir, saquinavir, and lopinavir).

Prescribing Start triazolam at 0.25 mg, at bedtime. Lower quantities can be effective and 0.5 mg is the maximum prescribed.

Special Populations Reduce the dose to 0.125 mg for older patients and 0.25 mg is the maximum recommended. While there are no adjustments anticipated for persons with renal impairment, caution applies to those with impaired liver function.

Nonbenzodiazepine Receptor Agonists (Schedule IV)

This group is composed of zolpidem in its different release formulations, eszopiclone, and zaleplon. In a meta-analysis of effectiveness of these drugs on sleep parameters in adults compared to placebo, a statistically significant, but small, improvement was documented [48]. Z drugs decreased subjective and polysomnography (PSG) sleep latency compared with placebo, especially with larger doses and in younger patients and regardless of type of drug [48].

Comparative studies between the Z drugs have generally evidenced conflicting effectiveness between these medications. In a meta-analysis, zolpidem was suggested to have lower rebound insomnia and shorter sleep latency than zopiclone [49]. Since zaleplon is rapidly absorbed and cleared from the body, studies suggested a shorter sleep latency (SL) and less rebound compared to zolpidem, but having a shorter sleep duration [49] (see Tables 6.2 and 6.3).

Since non-benzodiazepine receptor agonists (non-BZRAs) are approved for the treatment of insomnia, information that applies to them all is listed below to avoid repetition. Unique formulation information follows.

Adversities Non-BZRAs may result in complex sleep behaviors, such as preparing and eating food (i.e., sleep eating), driving (i.e., sleep walking), making phone calls, and engaging in inappropriate sexual (sexsomnia) or other activities. Risk of such events increases at higher doses and/or with concomitant sedative drug use. Other side effects could include dizziness, somnolence, headache, hallucinations, next day sedation, nausea, dyspepsia, vomiting, and dry mouth. Primarily in depressed patients, more affective symptoms and suicidal concerns may emerge. Angioedema and/or anaphylaxis have been rarely reported.

Interactions Non-BZRAs are prescribed cautiously with other sedatives since effects are potentiated. They should not be used together with alcohol or drugs.

Prescribing Non-BZRAs are not recommended to be administered near mealtimes due to delayed absorption, resulting in decreased efficacy and next-day somnolence. Serum concentrations differ in practical terms between genders; prescribing requires caution since women evidence higher serum levels than men.

Pregnancy Non-BZRAs are not recommended in pregnancy. Animal investigations evidence adverse fetal effects; there is limited research in humans. Zolpidem exposure near the dates for delivery can result in neonatal sedation and respiratory depression.

Comorbidities Non-BZRAs are controlled substances; strict precautions are advised for all patients with any substance misuse predispositions.

Eszopiclone (Lunesta)

Mechanism The details are not clear but it is likely through binding or coupling to GABA receptors [29].

Efficacy Eszopiclone decreases sleep latency and increases sleep maintenance.

Pharmacokinetics Tmax occurs approximately 1 hour after administration. Eszopiclone is bound to plasma proteins, metabolized by CYP3A and CYP2E1 enzymes, and excreted in urine. The half-life is near 6 hours; however, with a high-fat meal, the maximum concentration (Cmax) is reduced and Tmax delayed about an hour.

Adversities Unpleasant taste is a documented complaint.

Interactions Co-administration of CYP3A or 2E1enzyme inhibitors increases eszopiclone concentrations and effects, while inducers diminish potency. Discontinuation of concomitant inhibitors decreases its effects, while stopping inducers increases them. As an eszopiclone example, concomitant administration of ketoconazole, a potent CYP3A inhibitor, increased the area under the curve (AUC), Cmax, and Tmax by one to twofold. The maximum suggested dose of eszopiclone is 2 mg for anyone utilizing potent CYP3A inhibitors.

Prescribing The recommended dose of eszopiclone is 1 mg, just before bedtime. It should only be utilized when there are more than 7 hours remaining before a planned awakening. If well tolerated, dosages can be increased up to 3 mg.

Special Populations In elderly people, dosage should not exceed 2 mg nightly. This is due to more pronounced effects in this population and the prolonged half-lives, reaching 6–9 hours in older adults. During lactation, this medication should be prescribed with great caution as its effects on newborns are not well studied. However, data from European racemic zopiclone research indicates that occasional administrations evidenced little risk to older infants [50]. Close infant monitoring applies during breast feeding. While routine dosing is suggested in those with renal impairment, caution should be exercised for individuals with mild-to-moderate hepatic dysfunction. A maximum of 2 mg can be provided to patients with more significant impairment.

Zaleplon (Sonata)

Mechanism The action derives from selectively binding to the omega-1 receptors on the alpha subunit of $GABA_A$ receptors and potentiating t-butyl-bicyclophosphorothionate [30].

Efficacy Zaleplon decreases sleep latency.

Pharmacokinetics Tmax occurs approximately 1 hour after administration. Zaleplon is bound to plasma proteins, metabolized by aldehyde oxidase and by CYP3A enzymes, and excreted in urine, or somewhat in feces. The half-life of zaleplon is an hour, but when taken with a high-fat meal, Cmax is reduced and Tmax delayed.

Interactions Co-administration with inhibitors of aldehyde oxidase or CYP3A increases zaleplon concentrations. Use with inducers diminishes potency. Discontinuing aldehyde oxidase or CYP3A inhibitors decreases zaleplon levels; stopping inducers increases its effects. The initial dose is 5 mg for patients being prescribed an aldehyde oxidase and/or CYP3A inhibitor, like cimetidine.

Prescribing Start zaleplon at 10 mg, just before bedtime. The maximum dose is 20 mg, but lower amounts may also be effective.

Special Populations In elderly persons, a starting dose of 5 mg is recommended, with 10 mg being the maximum. During lactation, adverse effects to

breastfed infants are not anticipated because of a short half-life and the low amount excreted into breastmilk [31]. Nevertheless, breastfed infants should be monitored. While no dosing adjustment is required in individuals with mild-to-moderate renal dysfunction, there are no guidelines about patients with more serious compromise. A maximum dose of 5 mg is recommended for those with mild-to-moderate hepatic dysfunction, but it is not recommended when function is worse.

Zolpidem

Due to the many zolpidem formulations, data that applies to all agents is listed below. Unique formulation information follows.

Mechanism Zolpidem is a $GABA_A$ receptor modulator, binding to the benzodiazepine site of the alpha-1 subunit and potentiates GABA.

Pharmacokinetics Zolpidem is bound to plasma proteins and metabolized by CYP3A and somewhat to CYP1A2, CYPC9, CYP2D6, and CYP2C19 [51]. Following metabolism, the inactive products are excreted in urine.

Interactions Coadministration of inhibitors to the above hepatic enzymes potentiates zolpidem concentrations and actions, while inducers diminish levels and effects. Discontinuation of concomitant inhibitors and/or inducers has the opposite results.

Special Populations Adverse effects to breastfed infants are not anticipated due to a short half-life and low levels excreted in breastmilk [52]. Whenever prescribed during breastfeeding, monitor the infant. No dose adjustment is expected during treatment of individuals with mild-to-moderate renal impairment. However, caution should be exercised in cases with severe dysfunction.

Zolpidem Instant Release (IR)

Efficacy Zolpidem IR decreases sleep latency [32].

Pharmacokinetics Tmax occurs after approximately 2 hours. The half-life of zolpidem IR is nearly 3 hours. When ingested with a high-fat meal, Cmax and AUC are reduced and Tmax prolonged.

Prescribing The recommended initial and maximum dose is 5 mg for women and 5–10 mg for men.

Special Populations The recommended elderly initial and maximum dose is 5 mg. The same applies during with mild-to-moderate hepatic dysfunction, but it is not recommended in persons with severe compromise.

Zolpidem CR (Ambien CR)

Efficacy Zolpidem CR decreases sleep latency and improves sleep maintenance [33].

Pharmacokinetics Tmax occurs at about 2 hours. The mean elimination half-life near 3 hours. When ingested with a high-fat meal, Cmax and AUC are is reduced and Tmax doubles.

Prescribing The recommended initial and maximum dose is 6.25 and 12.5 mg for women and men, respectively. Zolpidem CR should only be taken if at least 7–8 hours remain before anticipated awakening.

Special Populations An initial and maximum dose of 6.25 mg is recommended for geriatric populations. The same dose is recommended for patients with mild-to-moderate hepatic impairment, but it should not be used in more compromised cases.

Zolpidem SL (Edluar)

Efficacy Zolpidem SL decreases sleep latency following nocturnal awakenings [34].

Pharmacokinetics Tmax is 1 hour with half-life nearly 3 hours. When ingested shortly after a high-fat meal, the mean AUC and Cmax decrease and Tmax is prolonged.

Prescribing The initial and maximum dose is 5 mg for women and 5–10 mg for men. This sublingual tablet should not be swallowed or ingested with water; rather, it is placed under the tongue and allowed to disintegrate.

Special Populations An initial and maximum dose of 5 mg is recommended in geriatric populations. The same dose is recommended for patients with mild-to-moderate hepatic impairment, but it should not be used in more compromised cases.

Zolpidem SL (Intermezzo)

Efficacy Zolpidem SL decreases sleep latency after a middle-of-the-night awakening [36].

Pharmacokinetics Tmax occurs at about 1 hour. The half-life is approximately 3 hours. When ingested with a high-fat meal, Cmax and AUC are reduced and Tmax is lengthened.

Prescribing The recommended initial and maximum dose is 1.75 mg for women and 3.5 mg for men. It should be administered only once per night, if needed, when the patient awakens too early and experiences difficulty returning to sleep. This sublingual tablet should not be swallowed or ingested with water; rather it is placed under the tongue and allowed to disintegrate. Utilize it only if there are at least four more hours remaining before a planned awakening.

Special Populations For elderly people and patients with hepatic impairment, the initial and maximum dose is 1.75 mg. For anyone with infection risk, be aware of recent studies on zolpidem, zaleplon, eszopiclone, and ramelteon documenting a higher incidence of infections during zolpidem and eszopiclone prescribing [37].

Zolpidem Spray (Zolpimist)

Efficacy Zolpidem Spray decreases sleep latency [35].

Pharmacokinetics Tmax occurs at 1 hour. The half-life is over 3 hours, but with a high-fat meal, Cmax and AUC are reduced and Tmax is increased.

Prescribing The initial and maximum dose is 5 mg for women and 5–10 mg for men. Zolpidem Spray should only be utilized when 7–8 hours remain before a planned awakening. The usual required dose is either one spray (equivalent to 5 mg) or two. It is important to note that the product must be primed with five sprays before the first application and this must be repeated if not used for about 14 days. For priming, the spray container is held upright with the black spray opening directed into the mouth, fully pressing the pump down to assure a full dose and spray pointed above the tongue.

Special Populations For elderly people and those with mild-to-moderate hepatic dysfunction, the recommended initial and maximum dose is 5 mg. It is not recommended for patients with more severe hepatic impairment.

Tricyclic Antidepressant

Doxepin (Silenor)

Doxepin has long been prescribed to treat people with depression and/or anxiety. It is also approved at 3–6 mg doses (much lower doses compared with depression

dosage ranging from 25 to 200 mg) for decreasing a patient's difficulty with sleep maintenance [38] (see Tables 6.2 and 6.3).

Mechanism Doxepin is a tricyclic antidepressant drug and an antagonist of H1 histamine receptors. Blockade of the wakefulness-promoting effect of histamine explains its efficacy. At these dosages, it exerts relatively little activity at cholinergic, adrenergic, serotonergic, dopaminergic, and muscarinic receptors.

Pharmacokinetics Tmax occurs after nearly 4 hours. With a high-fat meal, Tmax is delayed and AUC is increased. Doxepin is widely distributed and protein bound. It is metabolized primarily by CYP2C19 and CYP2D6 enzymes, and to a lesser extent, by CYP1A2 and CYP2C9. Following oxidation and demethylation, its nordoxepin metabolite remains pharmacologically active. Nordoxepin is then conjugated and excreted in urine. The doxepin half-life is 15 hours and the half-life of nordoxepin approaches 31 hours.

Efficacy Doxepin, at doses between 1 and 6 mg, diminishes awake time and increases total sleep efficiency and duration [39]. Objective and subjective improvements are reported, but sleep latency data is less clear.

Adversities The adverse effects of low-dose doxepin commonly include sedation, headache, and nausea [39]. The usual unwanted reactions (e.g., QT prolongation) associated with tricyclic antidepressant drugs are not likely at low dose quantities. It does not induce dependence or abuse potential. Doxepin is contraindicated during urinary retention, related drug allergies, for patients taking a monoamine oxidase inhibitor (MAOI) in the previous 2 weeks, or in people with closed-angle glaucoma (the latter, a rare condition).

Interactions Doxepin co-administration with sedating pharmaceuticals and/or alcohol potentiates sedation and is not advised. Cytochrome inhibitors and/or inducers affect doxepin levels. For example, co-prescribing with cimetidine may double doxepin levels, thus do not exceed a 3 mg dose.

Prescribing The recommended dose is 6 mg, taken 30 minutes prior to bedtime. However, quantities as low as 1 mg can be effective. Doxepin should not be administered within 3 hours of a meal due to delayed absorption, decreased efficacy, and increased next-morning sedation.

Special Populations A starting dose of 3 mg is recommended for elderly persons. Use is best avoided during pregnancy. Animal research documents adverse effects

on fetuses; there are no adequate human investigations. Prescribe during gestation only if potential benefit justifies risk. During lactation, doxepin is excreted in breast-milk and adverse consequences are reported among nursing infants. This is particularly so when mothers were taking doxepin dosages higher than in insomnia-approved amounts [53].

Kidney dysfunction is unlikely to alter prescribing practice. In those with hepatic impairment, a starting dose of 3 mg is recommended; dosage titration is based on tolerability.

Comorbidities Since doxepin is not associated with dependence or abuse potential, it may have special utility for patients with substance abuse histories.

Melatonin Receptor Agonist

Ramelteon (Rozerem)

Mechanism Ramelteon is a selective agonist with high affinity for melatonin MT1 and MT2 receptors [40]. The therapeutic effects of ramelteon are related to the suprachiasmatic nucleus, decreasing signals to be alert (see Tables 6.2 and 6.3).

Pharmacokinetics Tmax occurs after approximately 1 hour. Though ramelteon is well absorbed, less than 2% of it remains after first-pass metabolism. When administered with food, Tmax is delayed, Cmax lowered, and AUC extended. Ramelteon is distributed throughout the body and is protein bound. Metabolism by CYP1A2, CYP3A4, and CYP2C yields a metabolite excreted in urine. The half-life is nearing 2 hours and its metabolite half-life is up to 5 hours.

Efficacy At 8 mg doses, ramelteon decreases sleep latency [41]. In a meta-analytic study, ramelteon reduced subjective sleep latency and improved sleep quality, without increase in total sleep time; however, objectively it improved sleep efficiency [42]. These effects were clinically small, with somnolence being the main adverse event.

Adversities The adverse effects of ramelteon therapy commonly include somnolence, dizziness, and fatigue. It does not induce dependence or abuse.

Interactions Use caution if co-prescribed with sedating medicines, alcohol, or drugs. Coadministration with inhibitors of CYP1A2, CYP3A4, and CYP2C increases ramelteon concentrations and inducers would diminish them. Concomitant donepezil or doxepin increases the AUC and Cmax. Coadministration of fluvox-

amine, a CYP1A2 inhibitor, is contraindicated due to profoundly dramatic increases in AUC and Cmax.

Prescribing The maximum dose of ramelteon is 8 mg. Administer just before bedtime, but ingestion near meals delays absorption and decreases efficacy.

Special Populations In the elderly and those with renal impairment, routine dosing is usual practice. For pregnant females, it is only prescribed if anticipated benefits outweigh potential risks to a fetus. Animal research evidences adverse effects on fetuses and there are no adequate human studies. No information is available about ramelteon during nursing [43]. Prescribe cautiously to patients with mild-to-moderate hepatic dysfunction and not to people with significant impairment.

Comorbidities Ramelteon is not provided to people with sleep apnea. It does not induce dependence nor abuse potential; thus, it may be an attractive intervention for people who have substance abuse histories.

Orexin Receptor Antagonist (Schedule IV)—Suvorexant (Belsomra)

Mechanism Suvorexant is an orexin receptor OX1R and OX2R antagonist. This binding reduces wakefulness and promotes sleep [44] (see Tables 6.2 and 6.3).

Pharmacokinetics Tmax occurs within 2 hours. When administered with food, Tmax is delayed by over an hour, but with little change to AUC or Cmax. Suvorexant is bound to proteins with high bioavailability. Metabolism is by CYP3A, with some contribution by CYP2C19. Its primary metabolite is not pharmacologically active and is excreted in feces and urine with a half-life of nearly 12 hours.

Efficacy Suvorexant, at 10–20 mg doses, decreases sleep latency and increases sleep maintenance. Suvorexant decreases sleep latency and increases total sleep time, and is maintained at 3 months [45].

Adversities Somnolence is the most likely adverse effect, with frequency and severity dose related. Higher doses are not approved due to excessive somnolence risk. Depression and/or suicidal thinking are documented, as are fatigue and nightmares.

Interactions Suvorexant should only be cautiously prescribed with other sedatives and not in conjunction with alcohol or drugs. Co-administration with inhibitors of CYP3A and CYP2C19 increases concentrations and effects. With inducers, concentrations and effects diminish. Concomitant use with strong CYP3A inhibitors is not recommended; with moderate CYP3A inhibitors the starting dose is 5 mg, and only increased up to 10 mg. Since suvorexant increases digoxin concentrations, digoxin levels should be monitored whenever co-administered.

Prescribing The suggested starting dose is 10 mg, taken 30 minutes prior to bedtime and when at least 7 hours remain before planning to awaken. The maximum dose is 20 mg.

Special Populations In elderly persons, consider lower starting quantities. Suvorexant should not be prescribed during pregnancy. Animal research documents adverse fetal effects and there are no adequate human studies. There is little information available about this drug during nursing. In individuals with renal impairment, utilize routine dosing. However, use caution in mild-to-moderate hepatic dysfunction and not for people with more hepatic impairment.

Contraindications Suvorexant is contraindicated in patients with narcolepsy.

Off-Label and Over-the-Counter (OTC) Insomnia Medications

Melatonin

Melatonin is marketed and sold as a dietary supplement and is thus not federally regulated. Patients should be educated regarding potential variations in product potency and concentrations. Exogenous melatonin significantly decreases sleep latency in primary insomnia subjects [54]. In addition, its effects in treating circadian rhythm phase delay and regulating sleep patterns in blind individuals were also highlighted. Lower doses of melatonin (e.g., <5 mg) may be recommended rather than higher amounts [55]. Melatonin should be administered approximately 2 hours prior to bedtime for optimal benefit and to minimize adverse effects. Various melatonin products are available with different release modalities; yet, these agents have not been approved for treating people with insomnia (see Tables 6.2 and 6.3).

Trazodone

Trazodone exerts its soporific effects by blocking 5-HT2A, histamine H1, and alpha receptors. Target doses for insomnia are 25–100 mg, taken at bedtime, not to exceed 200 mg [56]. Peak effect occurs within about 2 hours. Trazodone is extensively metabolized via the liver, with only a small amount excreted in the urine. The half-life is 9 hours. Trazodone reduces subjective sleep latency, total sleep time, and

early awakenings, but below the threshold for clinical significance [57]. Common side effects are dizziness or lightheadedness, dry mouth, headache, blurred vision, nausea, or vomiting. Of particular concern are postural hypotension and priapism. These side effects occur less often at hypnotic dosages than in antidepressant prescribing. Orthostasis and falling are particularly dangerous; priapism is more commonly associated with other predispositions, like sickle cell disease. Trazodone is metabolized by cytochrome P450 enzymes. Avoid prescribing with recent MAOI medication use. In the elderly, utilize the lowest effective quantity since orthostasis significantly increases the risk for falls and subsequent injuries. There are no well-controlled studies in pregnancy or lactation. There is little information for use in individuals with renal or hepatic impairment (see Tables 6.2 and 6.3).

Mirtazapine

Mirtazapine promotes sleep by antagonizing 5 HT 2A/2C and H-1 receptors. Peak effects occur at approximately 3 hours. After administration, mirtazapine is hepatically metabolized and excreted with a half-life of approximately 24 hours. Enzyme inducers of 1A2 or 3A4 reduce mirtazapine efficacy. Doses of 15–30 mg have demonstrated persistent improvement in sleep quality and quantity, and decreased sleep latency; quantities as low as 7.5 mg can be effective [58]. The most common side effects are somnolence, weight gain, and increased appetite. Agranulocytosis is a rare occurrence. Mirtazapine should be avoided with recent MAOI use. A low dose is recommended in geriatric patients due to reduced clearance. Be cautious when prescribing to patients with hepatic or renal impairment. There appear to be no associations between prenatal mirtazapine exposure and congenital malformations [59]. Little information is known about use during lactation (see Tables 6.2 and 6.3).

Quetiapine

Quetiapine is the most commonly prescribed antipsychotic medicine to treat insomnia [60]. Effectiveness in treating insomnia can be attributed to its high affinity for H1 receptor blockade. Commonly applied doses for treating insomnia are 25–75 mg. After administration, quetiapine is hepatically metabolized with a half-life of approximately 8 hours. Common interaction includes CYP3A inducers and inhibitors; quetiapine dose adjustment may be required. Side effects frequently observed are sedation, constipation, orthostasis, weight gain, and xerostomia. As with other antipsychotic medications, metabolic syndromes (e.g., hypercholesterolemia, weight gain, diabetes), extrapyramidal symptoms, and tardive dyskinesia, although rare at low dosages, are serious adverse events. Overall evidence regarding efficacy is sparse, but improved subjective sleep is documented [60]. Some research results were not statistically significant [61]. Provide alternative agents to treat insomnia in patients who are pregnant or breastfeeding; however, in those with bipolar disorders or schizophrenia, quetiapine is considered. Limited data is available about elderly patient tolerance (see Tables 6.2 and 6.3).

Antihistamines

Sedating antihistamines are available over-the-counter (diphenhydramine and doxylamine) and by prescription (hydroxyzine). These agents are often used off-label to

treat insomnia due to their sedative effects and their relatively low-side-effect profile. They share a common mechanism of action in promoting sleep, but there are subtle differences. Hydroxyzine is a more selective antihistamine at H1 receptors and is reported to have less alpha-1 receptor blockade and anticholinergic side effects [62]. Diphenhydramine has a Tmax of 4 hours and a half-life of about 9 hours. Doxylamine has a Tmax of approximately 2 hours and a 10-hour half-life. Hydroxyzine has a half-life of approximately 20 hours and clinical effects are noted within 15–30 minutes (see Tables 6.2 and 6.3).

Shared side effects among these agents include sedation, sleepiness, dizziness, disturbed coordination, epigastric distress, thickening of bronchial secretions, constipation, urinary retention, worsening of cognitive function, and exacerbation of delirium. Elderly patients may be more susceptible. Hydroxyzine is prescribed with caution in anyone with known electrocardiographic potential to prolong QT intervals especially if using more than 100 mg/day. Diphenhydramine and doxylamine are sometimes combined with analgesics and/or marketed for sleep. Patients should be counseled not to exceed recommended daily maximums of analgesics when using these combination products.

Diphenhydramine doses should rarely exceed 50 mg, as higher doses are likely to increase adverse effects without additional benefit [63]. Doxylamine 15 mg has been compared with zolpidem 10 mg and evidenced comparative efficacy [64]. Doses of up to 25 mg are utilized. Hydroxyzine is commonly administered at 25–50 mg, but evidence supporting effectiveness is sparse [65].

Antihistamines are prescribed cautiously, if at all, to elderly patients due to increased risk of adverse effects. They are generally considered safe in pregnancy. During lactation, large doses or prolonged use has the potential to cause adverse effects in infants and diminish milk supplies. Caution is advised for patients with hepatic or renal dysfunction.

Gabapentin

The exact mechanism of gabapentin action in treating people with insomnia is unknown. It blocks voltage-dependent calcium channels and is structurally related to gamma-aminobutyric acid, but is without no effect on binding, uptake, or metabolism [66]. Following administration, gabapentin is renally excreted without hepatic metabolism, with a half-life of 5–7 hours. Gabapentin may enhance slow-wave sleep, increase sleep efficiency, decrease arousals, and increase sleep duration [67, 68]. Doses of 250–500 mg may be effective [68, 69]. Common side effects included dizziness, ataxia, and somnolence. Gabapentin should be applied cautiously and at lower dosages during renal impairment, including age-related function declines of the elderly (to avoid accumulation). There is little data about gabapentin during pregnancy. Some research suggests that gabapentin doses of up to 2100 mg daily produce low levels in breast milk [70]. Gabapentin is only used with caution in patients taking other sedating agents, especially opioids. Some states have classified gabapentin as a controlled substance due to misuse and abuse issues (see Tables 6.2 and 6.3).

Valerian Root

Valerian is marketed and sold as a herbal product derived from the plan *Valeriana officinalis* and is thus unregulated. Understanding of its mechanism of action and pharmacokinetics is limited. Studies examining its efficacy for treating insomnia evidenced conflicting results [71]. Doses vary between 200 and 1000 mg. Higher-quantity doses may cause dizziness, headaches, pruritus, and/or stomach upset. Because product purity and ingredients are not assured, use during pregnancy and lactation is to be avoided.

Psychopharmacological Choices

The choice of each medicine is individualized to each patient. While established guidelines are considered, factors such as cytochrome activity and gene response can also influence medication selection. In some instances, genetic testing can be an aid to choosing the best drug; however, that remains controversial. Age, gender, and associated medical and psychiatric diagnoses can contribute to the medication choice. In addition, various sleep disorders can also guide selections (e.g., those with circadian rhythm problems may favor melatonin). Insomnias often respond better to the same agent that helps members from the same family. In a recent meta-analysis based on polysomnography parameters, comparison of BNZs, non-BZRAs and sedating antidepressants, BNZs, followed by non-BZRAs, were more effective at reducing sleep latency [72]. Non-BZRAs may be better at maintaining sleep.

Depressive and Anxiety Disorders

The implementation of psychotherapy (such as CBT) can be beneficial in individuals struggling with both disorders and insomnia. Since insomnia is common during depressive disorders (e.g., dysthymia and major depressive disorder), consider both insomnia and mood symptoms. Sedating antidepressants such as doxepin, trazodone, or mirtazapine might be preferred agents in this population as they aid mood and sleep. Similarly, anxiety is often a cause for insomnia and thus sedating antidepressants might be the first choice. While BNZs and non-BZRAs are often preferred as second choice, cognitive behavioral therapy and cognitive restructuring also are effective. Serotonergic agents and other sedating antidepressants can be beneficial, as well. In some patients, restless leg syndrome, induced by serotonergic agents, might cause insomnia. In this population, avoiding serotonergic drugs is preferred.

Bipolar Disorder/Schizophrenia

People with bipolar disorder often present with decreased need for sleep, as part of mania/hypomania, or decreased sleep during a depressive episode. Sedating

antipsychotic drugs can benefit these patients diagnosed with bipolar or psychotic disorders. Quetiapine and olanzapine might be the best choices. Risperidone is usually less sedating. While an extended release quetiapine formulation is available, the short-acting version is better at sedation. While antidepressant medicines (e.g., trazodone) are prescribed during depressive episodes of bipolar illness, be aware about a possible shift into mania. BNZs and non-BZRAs can be considered in insomnia-resistant cases.

Substance Abuse

Extra caution is advised for patients with an active or even a remote history of alcohol or drug misuse. Frequent clinic visits and urine drug screening are suggested. There is an increased risk of alcohol relapse in patients with persistent insomnia; BNZ and non-BZRAs are best avoided. While gabapentin has been linked to misuse, sometimes it helps with alcohol cravings, anxiety, and poor sleep. Pain is often significant in this population and gabapentin may provide some comfort. Anxiety and/or depression is frequent in this population. Thus, sedating antidepressant drugs might be of benefit. Some people are resistant to these medications; then quetiapine is a viable option.

Women of Childbearing Age

Discussion with patients about pregnancy is important. Contraception is stressed especially if BNZs or non-BZRAs are considered. Some data suggests BNZs' teratogenicity to fetuses [73]. Sedating antidepressants are considered for women with compromising degrees of depression or anxiety. For those with circadian rhythm disorders, ramelteon or melatonin might be preferred.

Pregnancy

Medications are usually avoided during gestation. Safety of medication during pregnancy is questionable due to the lack of well-controlled studies that examine effects on a fetus. Insomnia is common during pregnancy due to reduced lung volumes, hormonal changes, urinary frequency, and stress. Snoring and sleep apnea occur in this population especially in the third trimester, and should be specifically addressed. Antihistamines have historical use, but BNZs are avoided.

Elderly Patients

Older persons frequently have comorbid medical conditions and age-related changes to pharmacokinetic and pharmacodynamic properties of medications. Antihistamines, anticholinergic drugs, and/or BNZs can lead to delirium and are less favored. Start with lower initial medication doses and titrate more slowly. Since

circadian rhythm phase advance is common in this population, melatonin or ramelteon might be advantageous. Efficacy and adversities of hypnotic drugs in geriatric subjects confirms significant, but small, improvements in sleep quality, total sleep time, and fewer nighttime awakenings; however, adverse cognitive events were more common [74]. Unpleasant psychomotor aspects were more frequent and daytime fatigue was a problem in people using any sedative. This analysis questions the relative benefit-to-risk ratio for this population.

Other Sleep Disorders

Comorbid sleep disorders should be addressed prior to treating insomnia and/or simultaneously. For example, in people with circadian rhythm disorders, melatonin and light therapy is applied while adjusting sleep patterns. Those with phase shift work can similarly be treated. In persons with obstructive sleep apnea with residual insomnia despite positive pressure ventilation machine or dental devices, the use of BNZs, non-BZRAs, or sedating antidepressant medicines can be considered. Medical or medication causes of restless legs syndrome should be addressed prior to prescribing hypnotic therapy. Treatment strategies for patients with narcolepsy vary greatly from those with primary insomnias.

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Part III

Sleep Related Respiratory Disorders

Sleep-Disordered Breathing

7

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Introduction

Sleep-disordered breathing (SDB) is a group of disorders that includes primary snoring (PS), obstructive sleep apnea (OSA), central sleep apnea (CSA), and hypoventilation syndromes. Primary snoring is snoring without evidence of oxygen desaturation or arousal from sleep. Sleep apnea is cessation or marked reduction of airflow during sleep and is further classified into OSA, CSA, and mixed disease (both OSA and CSA present) based on the presence or absence of respiratory effort. These forms of SDB are accompanied by several physiological perturbations including intermittent hypoxemia, hypercapnia, arousal from sleep, and catecholamine surges, which are thought to mediate downstream consequences of OSA such as cardiovascular disease. Hypoventilation syndromes are exacerbated in the setting of sleep due to reduced ventilatory responsiveness and are included in the classifications of SDB.

In the *International Classification of Sleep Disorders, 3rd Edition* (ICSD-3), SDB has been divided into OSA, CSA, sleep-related hypoventilation disorders, and sleep-related hypoxemia disorders (see Table 7.1) [1]. In contrast, *Diagnostic and Statistical Manual for Mental Disorders, 5th Edition* (DSM-5) has a simpler division of these disorders [2]. In their recent versions, ICSD-3 and DSM-5 removed primary snoring from their diagnostic criteria, whereas the *International Statistical Classification of Disease, 10th Revision, Clinical Modification* (ICD-10-CM) includes snoring as a diagnosis [3]. Snoring can also be important for the bed partner since the noise can disrupt the sleep of others, particularly in people with an underlying predisposition (e.g., bed partners with

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Table 7.1 Classifications of sleep-disordered breathing

	ICSD-3	DSM-5	ICD-10-CM
Primary snoring			Snoring
Obstructive sleep apnea	Obstructive sleep apnea Adult Pediatric	Obstructive sleep apnea Mild Moderate Severe	Obstructive sleep apnea
Central sleep apnea	Cheyne-Stokes breathing Apnea due to medical disorders Apnea due to medications/substances High-altitude periodic breathing Primary central apnea Central apnea of infancy Apnea of prematurity Treatment-emergent central apnea	Idiopathic CSA Cheyne-Stokes breathing CSA comorbid with opioid use	Sleep-related nonobstructive alveolar hypoventilation Obesity hypoventilation syndrome Sleep-related hypoventilation/hypoxemia Primary CSA Cheyne-Stokes breathing pattern CSA/complex sleep apnea
Hypoventilation	Obesity hypoventilation Congenital central alveolar hypoventilation Late onset central hypoventilation with hypothalamic dysfunction Idiopathic central alveolar hypoventilation Hypoventilation related to medication/substances Hypoventilation due to medical disorders	Idiopathic hypoventilation Congenital central alveolar hypoventilation Comorbid sleep-related hypoventilation	Other sleep apnea
Others	Sleep-related hypoxemia disorder		Unspecified dyspnea Other forms of dyspnea Periodic breathing Apnea not elsewhere specified Other sleep apnea Other abnormalities of breathing

insomnia). Patients who sleep poorly as a result of environmental disturbances such as a snoring bed partner are sometimes diagnosed as having "environmental sleep disorder."

Primary Snoring

Snoring occurs due to the vibration of the uvula and soft palate; it can also occur in the setting of upper airway narrowing and collapse. PS, also known as habitual or

simple snoring, is diagnosed when there is snoring without recurrent arousals or oxygen desaturation. It is only diagnosed once OSA has been excluded. PS is quite common and can be problematic, particularly if it bothers the bed partner. Risk factors for PS include nasal congestion, sinusitis, cigarette smoking, pregnancy, and substance use (sedatives and alcohol) [4–6].

Prevalence In a survey-based study of 1011 Australian adults, 20.2% of respondents reported loud snoring at least three times a week; 8.2% of respondents were classified as simple snorers after excluding those with self-reported OSA or symptoms of witnessed apneic episodes [7]. In the questionnaire data from the Wisconsin Sleep Cohort Study, 28% of middle-aged women and 44% of middle-aged men reported habitual snoring with prevalence increasing with age [8].

Psychiatric Disorders and Primary Snoring Limited data exist on primary snoring and psychiatric disorders. One cross-sectional study looked at differences in results of the Minnesota Multiphasic Personality Inventory (MMPI) in individuals with PS and OSA [9]. The MMPI is a tool that measures maladaptive traits and psychiatric symptoms. The PS cohort had a higher MMPI score compared to historical, normative data. The OSA cohort had an even higher MMPI score with more depressive symptoms compared to the PS cohort [9].

Medical Complications and Primary Snoring Most studies on the medical implications of snoring do not exclude those with OSA or, if they do, have not found a connection between PS and medical disease. Limited data do exist on the association of PS and carotid atherosclerosis. Heavy snoring was found to be a risk factor for carotid artery plaque in a study of 110 subjects that underwent polysomnography (PSG) and bilateral carotid arterial ultrasound; analysis of the data was adjusted for apnea hypopnea index (AHI) in addition to body mass index (BMI), smoking, age, sex, and hypertension [10]. The mechanism of this link is thought to be due to endothelial damage from upper airway vibrations.

Management Preventing disturbance to the bed partner is often the main purpose of treating primary snoring. Management is targeted toward the underlying condition if present. For nasal congestion and sinusitis, nasal steroids and decongestants can be helpful. Smoking cessation and elimination of alcohol consumption are likely to be effective based on clinical experience; however, these interventions have not been tested adequately in randomized clinical trials. Another strategy is positional therapy, as sleeping in the lateral position has been shown to reduce snoring in some studies [11, 12]. Correction of nasal septum deviation with rhinoplasty and septoplasty can help with narrowed nasal passages. Less invasive approaches are nasal strips and nasal dilators. A trial of continuous positive airway pressure (CPAP) can be considered on those with severe snoring. Diet and exercise can also be helpful particularly for patients who are overweight or obese since the benefits extend beyond just snoring to overall health and well-being.

Obstructive Sleep Apnea

Evaluation of OSA is the most common indication for obtaining a sleep study. OSA is diagnosed based on the apnea hypopnea index (AHI). An apnea occurs when there is ≥90% decrease in airflow lasting at least 10 seconds (or a duration equivalent to two breaths in children). A hypopnea has variable definitions but is generally defined based on a discernable reduction in airflow (≥50%) with either desaturation (≥3% decrease) or electroencephalogram (EEG) evidence of arousal. AHI is the number of apneas and hypopneas that occur per hour of sleep. The respiratory disturbance index (RDI) can also be used as a tool for diagnosis. The RDI considers both AHI and the number of respiratory event related arousals (RERAs). A RERA occurs when there is a reduction in airflow that does not meet criteria for hypopnea but is followed by an arousal. An AHI or RDI <5/h is in the normal range, while mild adult OSA is diagnosed with an AHI ranging 5–14/h, moderate 15–29/h, and severe ≥30/h.

History-Taking and Physical Examination History is vital in detecting symptoms suggestive of OSA and other SDB. Snoring and its severity, mouth breathing, and awakening with dry mouth suggest the presence of SDB. Snoring is highly sensitive but not specific for OSA [13]. Loud habitual snoring has higher predictive value for OSA as compared to soft intermittent snoring [14]. Tension-type headaches upon wakening and lasting a short duration are sometimes reported [15]. Individuals may report waking up gasping or choking for air. Witnessed apneic episodes by close family members or sleeping partners are a strong indicator of SDB but is a less sensitive predictor in older adults [14]. Cognitive issues, fatigue, and excessive daytime sleepiness are suggestive of frequent arousals. Since insomnia is very common, assessing the sleep pattern is integral. It is worthwhile to inquire about a family history of OSA. Genetic factors contribute to one's propensity for OSA in part due to influences on craniofacial structure and fat distribution. Individuals with parents, siblings, and second-degree relatives with OSA have an increased chance of having it themselves with odd ratios of 2.0, 1.9, and 1.3–1.9, respectively [16]. The use of prescription medications, street drugs, and alcohol can increase the risk for developing of central and obstructive sleep apneas [17, 18].

Physical examination can provide key clues when assessing risk of SDB. Obesity is the strongest risk factor for OSA, with a 10% increase in weight causing a sixfold risk in developing important OSA [19]. Neck circumference, which is a function of body fat, is highly specific for OSA, with values greater than 17″ in men and 16″ in women having good predictive value [20–22]. Other risk factors include male gender, postmenopausal status in women, and older age in men [23, 24]. Upper airway anatomy affects one's predisposition for developing OSA. Enlarged nasal turbinates, nasal septum deviation, and adeno-tonsillar enlargement are associated with OSA and can affect response to therapy [25]. A large tongue (relative to the size of the oropharyngeal cavity) that falls backwards in the supine position can cause airway obstruction and apneas. OSA that resolves by side sleeping is known as

positional sleep apnea. A clue to an enlarged tongue is serrated edges caused by teeth imprinting, which is also known as scalloping [26]. In many cases, fat deposition is the cause of tongue enlargement. The Mallampati score is a tool used to assess the narrowness of the posterior oropharynx. It is graded I–IV based on how much of the posterior oropharynx is visualized when a patient opens the mouth with a protruding tongue. Higher score indicates a narrower space. Grade III (only the base of the uvula visible) and grade IV (uvula not visible) have been linked to OSA [26, 27]. Friedman tongue positioning, that is, a non-protruding and resting tongue position without phonation, appears to have a higher correlation to OSA severity when used in conjunction with the Mallampati scoring system [28]. Bone structure is an important factor in determining upper airway size. Both posterior positioning of the mandible (retrognathia) and an undersized mandible (micrognathia) tend to affect tongue position, diminishing the size of the upper airway and raising the Mallampati score.

Prevalence Several epidemiological studies suggest the prevalence of OSA is substantial. Prevalence estimates vary widely depending on the population studied, the equipment used, and the criteria used to define OSA. A population-based study of 2168 individuals reported up to 50% of men and 23% of women having some clinical evidence of important sleep apnea [29]. Moreover, global prevalence of OSA based on existing data is estimated to be around one billion people [30]. Studies consistently show a higher prevalence of OSA in men compared to women although these differences become less marked following menopause [31]. Some studies suggest a higher prevalence in African Americans [32, 33]. Asian populations have a similar prevalence compared to North American populations but tend to be less obese, suggesting craniofacial structures as an anatomical cause rather than body fat [34, 35]. In individuals undergoing bariatric surgery, 70–80% of individuals have OSA [36, 37]. The Wisconsin Sleep Cohort Study suggested that a 10% or more increase in body weight was associated with a 32% increase in average AHI [19]. The Sleep Heart Health Study also showed an increase in AHI with an increase in weight, with the effects more pronounced in males [38]. Due to the sedentary nature of the job leading to weight gain, occupational drivers have a high risk for OSA [39, 40]. Other groups at risk may be those in the geriatric population and those with psychiatric disease, including depression and post-traumatic stress disorder (PTSD) [41–43].

Several medical conditions increase the risk of OSA. Hypothyroidism can cause tongue and pharyngeal enlargement through deposition of mucoproteins, leading to narrowing of the upper airway; it can also cause a blunted respiratory drive [44]. Adults with polycystic ovary syndrome (PCOS) have an increased prevalence of OSA [45]. This finding could be related to the high rates of obesity and androgen levels in women with PCOS. The hypermobility disorders Marfan syndrome and Ehlers-Danlos syndrome result in collagen abnormalities, hypotonia, and bony structure changes that may explain an increased prevalence of OSA compared to the general population [46, 47]. Prader-Willi syndrome and Down syndrome result in

features that are risk factors for OSA; these include obesity, hypotonia, and craniofacial abnormalities [48, 49]. Cleft palate and other craniofacial abnormalities can also increase the risk of OSA in both adults and children [50].

Psychiatric Disorders and Obstructive Sleep Apnea There is an increased prevalence of OSA in individuals diagnosed with psychiatric disorders, especially depression and PTSD [41, 43, 51]. In addition, there can be overlap in the symptoms associated with OSA and psychiatric disorders. For example, both OSA and depression can present with excessive daytime sleepiness, fatigue, psychomotor retardation, early morning wakening, concentration problems, and weight change [52].

The prevalence of depression in OSA individuals varies from 5% to 63% [52]. US veterans with OSA had a rate of depressive disorders of 21.8% compared to 9.4% in non-OSA controls [53]. While sleep fragmentation might be playing a role in excessive daytime sleepiness and depressive symptoms, hypoxemia is also thought to be a strong contributor [54]. Hypoxemia has been shown to impair noradrenergic and dopamine-rich pathways and lead to neuronal damage in animal studies; this finding suggests a mechanism that may link depression with OSA [55]. Serotonin has been linked to the motor function of the tongue through the hypoglossal nucleus and when deficient, as in depressed individuals, might in theory explain some of the incidental relationship between the two disorders [52]. However, there is no direct evidence of serotonin deficiency in human OSA.

Most of the studies examining OSA in individuals with PTSD have been done in the veteran population. In a meta-analysis, nine out of the ten studies involved veterans with PTSD; overall, 75.7% had an AHI >5/h, and 43.6% had an AHI >10/h [56]. In a study involving 40 civilian females with PTSD, OSA severity was directly correlated to suicidal ideation [57]. Prior to this study, obstructive sleep apnea had been generally linked to suicidal ideation and planning [58, 59].

Data have been limited regarding the associations between OSA and other psychiatric disorders. Some studies suggest an increased risk of anxiety in the OSA population. In a cross-sectional study involving 178 individuals with OSA, anxiety symptoms were present in 54% of subjects [60]. Furthermore, the study showed an association between severity of OSA and presence of anxiety. In an analysis of individuals with bipolar-I disorder, 54% of subjects were found to be at high risk for OSA based on a screening questionnaire [61]. However, data have overall been both conflicting and lacking on this subject. A recent meta-analysis showed high prevalence of OSA in individuals with major depressive disorder and PTSD but was more questionable for those with psychotic disorders, bipolar disorder, and anxiety [41].

While some studies have associated a higher risk of attention deficit hyperactivity disorder (ADHD) in children with OSA compared to those without OSA, studies in adults have not been as compelling [62, 63]. In a study conducted on adults, ADHD was present in 7.4% of those with OSA versus 6.3% in the control group with no statistical difference found [62]. In contrast, a high prevalence of sleep disorders, including OSA, insomnia, and restless leg syndrome, has been reported in adult ADHD although data are somewhat limited [64].

It is important to note that most psychotropic medications, especially antipsychotic medications, are associated with weight gain, possibly causing or worsening OSA [65]. Myles et al. found that men with schizophrenia taking clozapine had a higher prevalence of severe OSA compared with that of population controls; however, when adjusted for age and BMI, this difference was not significant [66]. This finding suggests that the high OSA prevalence is due to increased weight that could be explained by the use of clozapine. Other studies have suggested that atypical antipsychotic medications are an independent risk factor for OSA [67–69].

Medical Complications and Obstructive Sleep Apnea Several medical complications have been associated with OSA, including increased risk of stroke, hypertension, atrial fibrillation, diabetes mellitus, myocardial infarction, hepatic steatosis, and cancer [70–81]. Powerful confounders, particularly obesity, make it difficult to appreciate fully the link between OSA and other medical diseases. Nevertheless, recognition of these associations is important as treatment of OSA can potentially affect the course of these comorbid disorders.

Medications At present, no definitive data have shown a role for pharmacotherapy to treat sleep apnea. For nasal symptoms, improvements can be seen with nasal steroids, leukotriene receptor antagonists, and decongestants. However, while these modalities may be useful in pediatric OSA caused by adeno-tonsillar hypertrophy, they are rarely useful in adult OSA. Nonetheless, maintenance of nasal patency can help with snoring and with CPAP adherence. Other medication approaches include stimulants that can be used adjunctively with CPAP for residual daytime sleepiness. A new, albeit controversial study suggests cannabinoids could improve OSA modestly [82]. However, American Academy of Sleep Medicine has not supported this modality as yet [83].

While antipsychotic medications have been used off-label as a hypnotic agent, studies suggest that these medications can increase AHI [67, 68]. Khazaie et al. found that AHI significantly increased after at least 8 weeks of atypical antipsychotic therapy for insomnia [68]. In the risperidone group, the mean AHI went from 6/h to 36.5/h, with similar findings in the olanzapine and quetiapine groups. Thus, pharmacotherapy must be done cautiously, weighing risks and benefits in this context.

Devices The main treatment of OSA remains positive airway pressure (PAP). Several types of devices exist, the most common being continuous positive airway pressure (CPAP). CPAP provides pressure during both inspiration and expiration at the same pressure setting using a servo controller. Bi-level positive airway pressure is indicated in those requiring more than 20 cmH_2O of pressure, intolerant of CPAP, or with certain pulmonary diseases, for example, hypoventilation disorders or hypercapnic chronic obstructive pulmonary disease. In bi-level PAP, the degree of pressure differs between inspiration and expiration. In general, CPAP adherence

rates have improved over time, with modern studies suggesting excellent adherence in the majority of patients who receive PAP therapy [84]. To improve compliance, device companies have made it possible to send usage data wirelessly to sleep clinicians for monitoring and management. Similarly, individuals can access their compliance data through web applications and directly from the device. Claustrophobia and equipment issues are major challenges. To address anxiety, medication is sometimes indicated; however, exposure therapy is the cornerstone of treatment. In the past, dry mouth was a common problem, but this issue has been addressed in newer models by the addition of humidifiers. Problems with masks include skin allergies and local irritation; thus, newer models use softer material to address the latter issue. There are a variety of options including nasal mask, nasal pillow, and full-face masks to suit individual preferences optimally. Pressure discomfort has been addressed by ramp (a gradual increase in pressure with initiation of the CPAP device) and expiratory pressure relief settings, which are available on most modern devices.

There are several other devices that have been suggested in the treatment of OSA. The least invasive are mechanical dilators; these are objects that are placed outside the nose or inside the nares to widen the nasal passages, thus decreasing airway resistance. An expiratory positive airway pressure device is a simple nasal device with a valve mechanism that attaches to the opening of the nares and exerts resistance with expiration, which, in theory, pressurizes the airway and prevents collapse [85]. However, clinical outcome data and experience have not been very compelling. Nasopharyngeal airway stent is another option, although rigorous outcome data are sparse.

More commonly used are oral appliances, for example, mandibular advancement devices. These devices work by positioning the mandible and tongue forward. This method is usually indicated for mild to moderate OSA cases. Oral appliances can sometimes be used in conjunction with PAP therapy to decrease high-pressure requirements. However, pressure per se is generally not a good predictor of adherence and thus approaches to reduce the pressure requirement are only helpful in a subset of patients with pressure discomfort. Displacement of teeth and temporomandibular joint pain are potential complications of oral appliances, emphasizing the need for well-trained dentists on a multidisciplinary sleep team. Objective sleep apnea testing before and after the use of dental device is indicated to assess efficacy. Some have suggested the use of orthodontic expanders, which are metal devices that help expand the hard and soft palate laterally, resulting in the opening of the nasopharynx. Soft palate implants have also been trialed for mild to moderate OSA, but the response and recurrence rates have limited their use [86–90].

Surgical Treatment There are several surgical options for OSA; these interventions are generally more common and successful in the pediatric population. Adenotonsillectomy is indicated in children with both adeno-tonsillar enlargement and OSA with a meta-analysis by Brietzke et al. showing a success rate of 82.9% [91]. The resolution rate is notably lower in children with co-mobilities, including obe-

sity [92]. Marcus et al. studied neurocognitive outcomes in children with OSA who underwent early adeno-tonsillectomy and found they had greater improvement in behavior and decrease in AHI compared to those who underwent a watchful waiting strategy; however, they did not have improved attention and executive functioning based on neuropsychic assessment [93]. Nasal surgeries, which includes nasal septoplasty, inferior turbinate reduction, and polypectomy, have not been shown to decrease AHI meaningfully, but they can occasionally be performed to facilitate PAP therapy via improving nasal patency [94]. Uvulopalatopharyngoplasty is a common upper airway surgery for OSA that involves the removal of the soft palate, tonsils, and uvula. It does not usually normalize AHI, and relapse is common [95, 96]. A less invasive alternative is the anterior palatoplasty, which can be done as an office-based procedure. The aim of this intervention is to stiffen the palate by inducing fibrosis and scarring. Generally, the surgery entails removing a strip of mucosa in the soft palate and then suturing the area, sometimes using barbed thread [97].

A newer treatment is hypoglossal nerve stimulation. Several devices have been tested, with subtle differences between the various technologies. In general, a generator is implanted under the skin with leads going to the hypoglossal nerve and to respiratory muscles in the chest. Stimulation of the nerve increases pharyngeal muscle tone, preventing upper airway collapse. Problems include difficulty in predicting responders to therapy. In addition, long-term outcome data from randomized trials assessing hard outcomes are lacking.

Other Treatments Weight loss in obese individuals should be recommended as it has been shown to improve OSA, especially when there is a 10% or more decrease in weight [19]. Surgical weight loss can be a powerful tool in attenuating the severity of OSA. In a meta-analysis of 342 patients who had undergone bariatric surgery, AHI dropped from an average of 54.7/h to 15.8/h [98]. Of note, a study of 4667 patients showed OSA to be an independent risk factor for bariatric surgery complications, making some sleep assessment important prior to surgery [99]. In addition, studies have shown that residual OSA and recurrence of OSA is common, making long-term follow-up an important component of overall bariatric surgery management [98, 100, 101].

Studies have suggested the use of double reed instruments and the didgeridoo (a wind instrument native to Australia) improved OSA by strengthening airway tone [102, 103]. However, the role of neuromuscular training for the upper airway remains unclear in OSA. Thus, further study is recommended and ongoing.

Treatment and Psychiatric Disorders Treatment for OSA helps to improve symptoms of daytime fatigue and sleepiness in addition to possibly attenuating the effects of a variety of medical conditions; moreover, it may confer some additional benefit to those with psychiatric conditions. Several studies have shown that CPAP usage improves symptoms of PTSD, including nightmares [104–106]. In one analysis, CPAP therapy halved the mean number of weekly nightmares in a cohort of 69

PTSD-afflicted veterans, from 10.32 to 5.26 nightmares per week [104]. Oral devices have also been shown to improve PTSD symptoms; although they are not as effective in reducing respiratory events compared to CPAP, they are viable option for those who cannot tolerate CPAP therapy [106]. The data for depression and anxiety are less compelling. One meta-analysis found an improvement in symptoms of depression and anxiety with CPAP usage, but this outcome was not significantly different from those using sham PAP [107]. Overall, high-quality data exploring the association between OSA and depression and anxiety are lacking.

Of note, there have been case reports of CPAP therapy precipitating manic episodes, particularly in those with bipolar disorder [108–110]. Given the overall benefit of treating OSA and the paucity of data regarding this link, CPAP therapy with close monitoring is recommended to those who may be susceptible to mania.

Psychiatric conditions are often a barrier to the treatment of OSA, particularly in PTSD and depression. A meta-analysis that pooled data from three separate studies found that those with PTSD and OSA had significantly lower CPAP compliance rates compared to those with OSA alone [56]. This finding stresses the importance of concomitant management and treatment of these comorbid conditions to achieve optimal outcomes.

Central Sleep Apnea

CSA is recurrent cessation in breathing lasting at least 10 seconds (or duration of equivalent to two breaths in children) during sleep, which occur without respiratory effort. The level and response to the partial pressure of carbon dioxide ($PaCO_2$) play a fundamental role in the pathophysiology of CSA. Respiratory drive is largely affected by the level of $PaCO_2$ that is detected by chemoreceptors in the ventral medulla and carotid body [111]. An increase in $PaCO_2$ will lead to stimulation of breathing, while a decrease in $PaCO_2$ will lead to a reduction in the ventilator response and potential cessation in breathing if it drops below a certain level, that is, chemical apnea threshold. The development of and response to central apnea is influenced by a variety of factors, including stage of sleep, chemoreceptor sensitivity, efficiency of CO_2 excretion, and cardiovascular circulation [112, 113]. CSA can be detected in several settings. Healthy individuals exposed to high altitude (>5000 m) can develop central apneas, known as periodic breathing, from alveolar hypoxia that leads to increased ventilation and subsequent hypocapnia below the apnea threshold [114]. Sleep transition apnea can occur in healthy individuals and can be a prominent finding in those with sleep disorders that lead to repetitive arousals; hyperventilation tends to occur after an arousal, resulting in a sleep transition apnea once the $PaCO_2$ falls below the apnea threshold [115]. Complex apnea is an important entity to be familiar with when treating individuals for OSA. Although definitions vary, complex apneas are generally defined as central apneas that emerge with PAP treatment of OSA. The mechanism of complex apneas is not entirely known, but they tend to diminish with continued treatment [113]. Other important

types of CSA include Cheyne-Strokes breathing (CSB) and medication-induced CSA, which will be discussed in more detail in the sections below.

Prevalence Although the prevalence of CSA is overall low, it is common in certain populations, most notably in those with heart failure. In a large cross-sectional analysis, prevalence of CSA was noted to be 0.9% in the general population and 4.1% in those with self-reported heart failure [116]. In other studies, prevalence of CSA in those with congestive heart failure (CHF) ranged from 31% to 55% [117]. Stroke and other neurological disorders have also been commonly associated with CSA, although OSA seems to be the predominate SDB in those with stroke and transient ischemic attacks (TIAs) [70, 118]. In a meta-analysis of 2343 individuals with ischemic or hemorrhagic stroke and TIA, over 70% of those studied had SDB with an AHI >5/h, and 7% of the identified SDB was predominately CSA [70].

Cheyne-Stokes Breathing

Cheyne-Stokes breathing (CSB) is characterized by crescendo-decrescendo breathing followed by central apneas. The presence of this type of breathing often signifies severe cardiac or kidney problems.

Prevalence In those with congestive heart failure (CHF), estimates of CSB are around 30% [119, 120]. The implications of CSB have been controversial, but many practitioners view this breathing pattern as a marker of inadequate medical therapy. The management of CSB beyond addressing the underlying causes is currently unclear as interventional studies have been largely negative.

Medication-Induced Central Sleep Apnea

Several medications have been attributed to causing CSA, with opioids being the most common. Opioids induce respiratory depression by stimulation of the mu opioid receptors on medullary respiratory centers. In addition, opioids attenuate the response of central chemoreceptors to hypercapnia in a dose-dependent manner [121]. These abnormal and blunted ventilatory responses persist with chronic use [84]. SDB is common in individuals with chronic pain on opioid therapy and in methadone maintenance programs. A meta-analysis found the prevalence of SDB in methadone-maintained patients to be 42–70% and in chronic pain patients 71–100% with high rates of CSA and OSA in both groups [17]. In the analysis, older age, male gender, and higher dosage of opioids were predictive of CSA and OSA.

While some studies suggest improved sleep in individuals with pain disorders on opioid medications, others argue that opioids can decrease time spent in slow wave and rapid eye movement (REM) sleep leading to hyperalgesia [17, 122]. We have proposed a theory that is as yet unproven regarding the relationship between opioid use disorder, pain, and sleep. Physical pain clearly can worsen sleep quality, but, in

addition, disrupted sleep has been shown to worsen physical pain [123]. That is, patients with chronic pain disorders report their worst symptoms following a poor night of sleep. Similarly, inducing sleep disruption has been shown to worsen pain thresholds over time, making sleep a potential therapeutic target for people with chronic pain. Because some patients on chronic opioids develop SDB, we have proposed that worsening sleep quality may increase sleep disruption that in turn can worsen physical pain and opioid requirement. In theory, efforts to improve sleep quality could be one strategy to address patients with opioid use disorder.

Treatment and Management Treatment of central sleep apnea depends on the cause. For those with sleep transition apnea, finding and addressing the cause of arousals is key. Reassurance is often all that is needed for those with complex apnea. Treatment of medication-induced CSA would entail discontinuation of the offending agent if possible. In cases when this strategy is not reasonable, oxygen supplementation and PAP therapy can be considered. Treatment of CSA in patients with CHF should be focused on addressing the cardiac etiology with medical management, such as implementation of beta blockers or angiotensin converting enzyme inhibitors. PAP therapy can also be considered in this population. In a randomized trial of 258 subjects, treating CSA with CPAP in individuals with congestive heart failure improved oxygenation and ejection fraction and decreased the sympathetic activity; survival rates were not affected [124]. Adaptive servo-ventilation (ASV) is a newer form of noninvasive ventilator support in which the machine detects the missed breath and provides airway pressure when needed. Of note, a large, randomized study showed that ASV in patients with CHF with reduced ejection fraction and CSA had increased mortality from cardiovascular causes [125]. The medication acetazolamide has been found to decrease the number of events in heart failure patients as well as those with idiopathic and high-altitude-induced CSA [126–129]. It works by inducing a metabolic acidosis, which raises the background $PaCO_2$ and apneic threshold $PaCO_2$ while increasing the difference between the two [130].

Hypoventilation Syndromes

Hypoventilation syndromes are disorders characterized by insufficient ventilation of the alveoli leading to hypercapnia. The etiology can be due to genetically inherited causes, such as in central congenital hypoventilation syndrome. More common causes are morbid obesity and neuromuscular diseases, such as amyotrophic lateral sclerosis. Obesity hypoventilation syndrome (OSH) is defined as the presence of obesity and awake hypoventilation and hypercapnia not attributable to other conditions (e.g., parenchymal lung disease); its prevalence may be rising with the American obesity epidemic. There is a notable overlap with OHS and OSA, with estimates of 10–20% meeting criteria for OHS in obese people with OSA [131]. Hypercapnia can become exacerbated during sleep in hypoventilation syndromes likely due to decreased respiratory drive and upper airway collapse [113]. Bi-level

PAP can be considered in individuals with hypoventilation syndromes to help maintain and even improve $PaCO_2$ while sleeping.

Subjective Diagnostic Tools

While questionnaires are useful screening tools, PSG remains the gold standard for diagnosis of sleep-disordered breathing. In fact, the American Academy of Sleep Medicine discourages the use of questionnaire-based diagnosis [132].

One of the most commonly used screening tools is the STOP-BANG questionnaire, which consists of eight items—snoring, daytime fatigue or sleepiness, observed apneas, treatment for high blood pressure, BMI, age, neck circumference, and gender [133]. Usually the presence of three or more suggests the need to obtain PSG. STOP-BANG has a linear increase in sensitivity and correlation to severity of OSA. Given its low specificity, it should not be used as a diagnostic tool [133].

The Berlin questionnaire is a subjective assessment consisting of 11 questions to stratify the risk of OSA patients [134]. It screens for the presence and quality of snoring, witnessed apneas, daytime fatigue and sleepiness, high blood pressure, and BMI.

The Epworth sleepiness scale (ESS) is a questionnaire that assesses daytime sleepiness by asking about the likelihood of falling asleep in certain situations, such as watching television or being a passenger in a car. In a study involving 212 patients, the STOP-BANG questionnaire had better specificity than ESS or the Berlin questionnaire [135]. Of note, the ESS has some limitations, given that it was developed roughly 30 years ago. Many of the questions are no longer reflective of modern society. In addition, many patients report normal ESS in the setting of substantial caffeine intake making interpretation of the test in the context of the individual patient history important. Moreover, many patients with normal ESS report major improvement in symptoms following therapy despite being reportedly asymptomatic prior to treatment.

Polysomnography and Nomenclature

Two major types of sleep testing exist: PSG and home sleep apnea testing (HSAT). PSG, also known as an in-lab sleep study, is more accurate, but, in adults without medical complications, HSAT is preferred due to lower cost and ease of administration. It should be noted that sleep is not measured directly by EEG during HSAT, resulting in a tendency to underestimate disease severity compared with PSG especially in the setting of comorbid insomnia [136]. Therefore, if there is still a high suspicion for SDB after a negative or inconclusive HSAT, PSG is indicated. In those with important cardiopulmonary disease, neurological or neuromuscular conditions, or suspected hypoventilation syndrome, PSG (with capnometry if available) is recommended [132]. In addition, PSG should be used in children and adolescent suspected of having SDB, since HSAT data are still evolving in these age groups.

There are several types of HSAT. The more traditional models measure airflow, chest wall expansion, and pulse oximetry. There are also models that calculate AHI by measuring surrogates of sympathetic activity, for example, WATCH-PAT.

Several parameters are monitored during a PSG. EEG is used to determine stages of sleep and requires several electrodes that are affixed to the scalp. Extra electrodes or video EEG can be used if nocturnal seizures are suspected. Electrodes placed around the eyes detect REM stage. Nasal and oral probes are used to detect airflow and temperature. Cessation of airflow in these leads helps diagnose apneas and hypopneas. A microphone is usually attached to the neck to capture the intensity and duration of snoring. Chest and abdominal belts are attached to assess inspiration and expiration and are vital in order to distinguish between central and obstructive apneas. Two leg probes help assess periodic leg movements during sleep.

Conclusion

Major overlap occurs between sleep-disordered breathing and psychiatric disorders. For example, in both OSA and depression, individuals will complain of daytime fatigue and sleepiness, insomnia, and feelings of hopelessness. Treatment resistance or decompensation of depression or anxiety can occur if the underlying sleep disorder is not addressed.

Evaluation for SDB entails taking a thorough history and physical that focuses on key risk factors; screening questionnaires can also be implemented to assess risk. Diagnosis relies on polysomnography and home sleep apnea testing. It is worthwhile to pursue the evaluation for OSA and other SDB given the availability of effective treatments, most notably positive pressure ventilation. This approach is even more imperative in patients with psychiatric disorders given the impact that sleep disorders may have on afflicted patients particularly when they go unrecognized.

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8 Psychosocial Approaches for Addressing Nonadherence to Positive Airway Pressure (PAP) Therapy

Gerd R. Naydock

Introduction

Despite the increasing numbers of effective treatments available to ameliorate a large number of chronic medical conditions, the problem of nonadherence to such treatments occurs at alarmingly high frequencies in the general population and these continue to create an excessive economic strain on our health care system and lead to suboptimal treatment outcomes [1]. Individuals who present to their medical providers with somatic complaints do so in the hope of finding a solution that will provide relief from and/or abatement of their physical symptoms and concomitant psychological sequelae. In many cases, an empirically validated and effective solution is offered to the patient, and for any number of reasons is readily dismissed, despite there being no other available alternatives to address the presenting problem [2].

The behavioral pattern reflected in the foregoing is often observed in the treatment of individuals who, after obtaining a formal sleep study with polysomnography, are diagnosed with obstructive sleep apnea (OSA). It is useful to remember that individuals are not necessarily looking for a diagnosis such as OSA, but, rather, are primarily driven to obtain relief from their presenting physical and emotional sufferings [3]. Prevailing estimates suggest that between 48 and 83% of OSA sufferers choose to discontinue what is currently the empirically validated golden standard of treatment, continuous positive airway pressure (CPAP) therapy [4]. A CPAP machine is designed to deliver a constant flow of airway pressure to the throat to ensure that the airway remains unobstructed during sleep. In this manner, it serves as an air splint that eliminates the spontaneous pauses in breath that are associated with sleep apnea. The majority of those who choose to discontinue using their CPAP machines cite physical discomfort and the required lifestyle changes that go along

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with it as primary barriers [3]. This comes as no surprise as people will generally rationalize not engaging in potentially lifestyle-enhancing behaviors (i.e., diet, smoking cessation, exercise) if they find them to be inconvenient, physically or emotionally uncomfortable, burdensome, and/or requiring the individual to sacrifice something that is more psychologically rewarding for them than the treatment that is being offered [5].

As already implied, subjectively human barriers to accepting and committing to CPAP therapy or, for that matter, any other medical treatment are moderated by several biomedical, psychological, and sociological variables that ideally should be addressed in an integrative, multidisciplinary manner. Therefore, unimodal clinical interventions limited to address the biomedical barriers to CPAP therapy are less likely to be effective in optimizing adherence in both the short- and long-term. Over the years, I have seen the results of limiting treatment for OSA to prescribing, titrating CPAP, and occasionally trying on new masks. As is often the case, by the time the patient is seen by a behavioral health professional for an initial assessment, CPAP therapy has already been discontinued and their machines returned to their insurance providers for failing to consistently meet the required 4-hour minimum of nightly usage. It is my belief that many of these problems are unnecessary and could have been prevented by conducting a thorough biopsychosocial assessment of the individual for whom CPAP therapy is being recommended. Conducting such assessments is not dissimilar from other behavioral health assessments for individuals who are seeking bariatric surgery or spinal cord stimulators. Ideally, such an assessment by a trained and skilled behavioral health clinician, preferably with a sleep medicine background, is the first step toward addressing CPAP nonadherence as it will generally identify potential barriers from the patient's point of view. Furthermore, assessing a patient's personal motivations and rationale for accepting and committing to a lifestyle change that may initially be difficult is equally important. Although having the opportunity to conduct a biopsychosocial assessment would be the ideal, more often than not we are likely to begin working with patients who have already been set up at home with CPAP and expressed dissatisfaction with it.

When practicing from a patient-centered and integrative behavioral health perspective, ideally addressing CPAP nonadherence would involve having sleep medicine physicians and behavioral health professionals consult with one another in a timely and effective manner, each taking full responsibility for their area of expertise to help mitigate the subjective complaints and barriers that OSA patients present. Our role as mental health practitioners working with our CPAP nonadherent patients is to help them recognize a potential benefit to themselves and their loved ones for working on developing various cognitive and behavioral strategies to overcome physical and psychosocial barriers that lead to nonadherence. From the point of view of patient self-determinism, it is not within our scope of practice to coerce, shame, frighten, or use other forms of psychological manipulation to gain adherence. I have personally never seen these tactics to be helpful in my own practice and there exists an extensive literature that strongly cautions against the use of such interventions [6]. As I discuss the delivery of specific clinical interventions to

promote adherence within the subsequent sections of this chapter, I will also suggest attitudinal qualities of the practitioner, much of it based on motivational interviewing (MI) techniques. Simply stated, the manner and attitude by which we approach our patients with adherence issues can help determine which outcomes are successful in optimizing adherence.

Empirically Researched Barriers Known to Be Associated with CPAP Nonadherence

With over 20 years of research, we now have a very large knowledge base that has identified the biomedical, demographic, psychological, and social obstacles known to increase risk for CPAP nonadherence [7]. Unfortunately, despite vast improvements over the years to make CPAP more physically tolerable for users, up to half of the individuals with OSA continue to choose to forego this therapy [8]. This is particularly disappointing given that CPAP is 100% effective in ameliorating the physical problems associated with such sleep breathing disorders. This means that nonadherent patients are left with less effective treatment alternatives and as such will continue to lack restorative sleep and excessive daytime sleepiness (EDS), not to mention increased risk of medical comorbidities associated with untreated OSA.

As we work to identify patients' subjective reasons for not continuing with CPAP therapy, it becomes helpful to identify those barriers that are in fact amenable to being modified in treatment. When viewed from a biopsychosocial perspective, the biomedical domain encompasses static variables that are descriptive of the patient's clinical or medical characteristics. Examples of these variables would include degree of daytime sleepiness, greater subjective sleepiness, poorer health, greater body mass index (BMI), and higher apnea/hypopnea index (AHI) [9]. Each of these biomedical variables has been demonstrated to predict CPAP adherence [10]. Additionally, greater BMI is a modifiable condition that can lead to developing a treatment plan that incorporates weight and alcohol reduction as goals [10]. Demographic variables such as age, gender, and marital status have not been consistently associated with nonadherence to CPAP [4]. There are several studies, however, that have found that lower socioeconomic status and identifying as African American conferred a higher probability of nonadherence to CPAP [4].

Behavioral health professionals working with patients with OSA often encounter individuals who are emotionally ambivalent about using their CPAPs. I personally find in my practice that it is a very rare occurrence to meet a patient who is not somewhat motivated to improve their sleep difficulties. Individuals diagnosed with OSA are no exception to this, especially if the untreated symptoms have led to chronic and unremitting insomnia. Many people end up developing generalized anxiety about not having good quality of sleep, and when this is left untreated often develops into depression by the time they are seen for intake for a sleep evaluation. Several practical problems associated with the use of CPAP such as nasal dryness, difficulties adjusting the mask, pressure from the mask, mask leakage, and disturbing noise are well-known reasons for nonadherence [3]. The need to sleep with

one's mouth closed or with the aid of a chin strap as well as traveling with CPAP equipment are also reasons cited for nonadherence. Once again, it is important for the treating behavioral health professional to monitor for such problems when working with their patients on improving adherence. Again, timely and effective collaboration with the CPAP prescriber will be important when such complaints are expressed.

It is noteworthy that biomedical factors appear to explain very little of the variance in the overall use of CPAP [11]. Factors explaining the greatest proportion of CPAP adherence include having higher outcome expectancies for the treatment, greater functional limitations as a result of sleepiness, and a patient perception that lower comorbid medical risks would be achieved [11]. Such findings suggest that patients often hold negative attitudes toward CPAP therapy before treatment is even initiated. As is the case with many individuals who are newly diagnosed with any disorder, there are questions about whether they have received the correct diagnosis from their physician juxtaposed with the failure to recognize and accept that CPAP may be the only effective treatment for them, creating a great deal of uncertainty and emotional vulnerability [3]. Qualitative research also identifies other psychological barriers to adherence including loss of freedom, social stigma, and shame for needing CPAP therapy. These are coupled with the concomitant awareness that significant others know that they are using a medical device, a desire to avoid needing CPAP indefinitely as well as claustrophobic thoughts and anxiety about the CPAP technology itself [3].

Psychological factors contributing to CPAP nonadherence are dynamic and amenable to modification by using evidence-based, psychosocial interventions such as self-management, cognitive-behavioral therapy (CBT), and/or motivational enhancement approaches that target maladaptive coping styles, problem-solving deficits, self-efficacy issues, lack of motivation, and self-defeating health beliefs. OSA sufferers who experience higher levels of claustrophobia in general are the most likely to use CPAP less than 2 hours per night [4]. The employment of CBT and motivational enhancement therapies have been shown to increase use of CPAP for greater than 4 hours per night and is more effective than treatment as usual, which generally encompasses supportive and educational interventions [9]. Interestingly, psychological symptoms such as mood, stress, anger, and social desirability appear to have little to no influence over whether an individual chooses to adhere to CPAP therapy [4].

More importantly, patients who find that CPAP improves their overall daily level of functioning are more likely to remain adherent to this therapy. As previously mentioned, initial beliefs about CPAP will also impact adherence, and I have found in my own practice that addressing these as early as possible in the therapeutic process will yield a greater potential for greater adherence rates. Individuals who present with self-defeating coping styles or have low frustration tolerance are much less likely to persist in their use of CPAP [12]. Those patients with historically poor or inconsistent problem-solving skills tend to have difficulty troubleshooting problems with their CPAP when they occur. Generally, this is attributable to using a passive, maladaptive problem-solving approach, specifically the patient's use of avoidant

behavioral strategies. Alternatively, studies suggest that those CPAP patients who are consistently able to problem-solve related obstacles in an active manner experience the most success with their therapies [4].

Social factors that influence CPAP adherence are varied, and most appear to be associated with the individual's relationships to significant others, particularly bed partners and family members [4]. Patients who self-refer for treatment are more likely to be motivated and adhere to CPAP than those who are referred by a bed partner or someone in their family [10]. An individual whose OSA remains untreated is more likely to be experienced negatively by family members due to their excessive snoring, excessive sleepiness, and hypersomnolence, all of which may interfere with positive social interactions. Conversely, the families of OSA sufferers are in a desirable position to positively influence CPAP adherence when using behavioral strategies, which the patient experiences as supportive and emotionally rewarding.

Initial Session

More often than not, the initial visit will be conducted with individuals who have already been prescribed CPAP therapy and have not been using their equipment for the minimum hours per night as required by most insurance companies. The purpose of this initial visit is to have the patient identify all barriers and obstacles to adherence and this should be done in an empathic, nonjudgmental manner. Ultimately, if we as behavioral health providers respect an individual's right to a self-determined life, whether they ultimately choose to adhere with recommended medical advice will not become the final arbiter of our interventions. It is important to also remember that making a lifestyle change is a process and patients need to see a personal benefit that outweigh their perceived costs of CPAP adherence. Patients can and often do change their minds at a later time. Timing and process need to be considered when patients are approached about making a drastic change in lifestyle as CPAP would require.

Humans are more likely to engage in behavioral tasks that they perceive to be: (1) not too difficult; (2) relatively convenient; and (3) not requiring them to sacrifice something that they find intrinsically valuable or rewarding. The behavioral health clinician will need to assess the patients' views of CPAP on these domains, especially when they are raised as objections for nonadherence. Perceiving a behavioral task as "too difficult" will increase the likelihood that a patient chooses to not take any action at all.

Attempting to convince someone to use CPAP is generally ineffective, particularly considering that this is a novel experience for them. In many cases, by the time you see them, they have yet to experience any therapeutic benefit from CPAP as this may take on average anywhere from two to four sessions. In contrast, there are some patients who report experiencing some therapeutic benefits from CPAP as this may but focus on the inconveniences and personal sacrifices that they feel they must make when adhering to it. In either case, the patient may use several different rationales to justify why they cannot and should not be using CPAP. It is important that

we remain self-aware and refrain from arguing with patients or trying to convince them that their thinking is incorrect.

Approaching nonadherent CPAP patients from the underlying spirit of motivational interviewing (MI) is an extremely effective way to get patients to express their reasons for making changes that they perceive to be difficult, inconvenient, and requiring sacrifices [13]. Rather than immediately attempting to "correct" the patient on any of their objections, we tend to validate their concerns and difficulties through empathic and verbal responses that reflect their difficulties in accepting and making the proposed changes. Again, it can be most helpful and less stressful if we as clinicians begin to take the attitude that it is not our job to "get people to adhere." If we want CPAP adherence for our patients more than they want it for themselves, then we will find ourselves simply wasting their time as well as our own.

As previously mentioned, it is extremely important that we approach our patients' objections to using CPAP in a nonjudgmental manner and avoid using language that could be perceived as condescending or shaming. We as clinicians need to learn to divest ourselves emotionally over whether a patient adheres to treatment or not. Nonadherent patients will often develop their own reasons for adhering to CPAP simply by reminding them that it is ultimately up to them whether to choose any treatment and that we respect their autonomy and ability to make health decisions for themselves. In my own practice, I have found that many of my patients possess a passive communications style and will never question their medical providers about their medical concerns for fear that they will be seen as being a "bad patient." It tends to further strengthen and solidify the therapeutic alliance when we take the time to remind our patients that they *can* and *should* question anything that we recommend if they have personal concerns until they are satisfied.

When it comes to CPAP adherence, our proposed interventions can be tailored around addressing the following questions: (1) how important it is to our patients to appreciate the therapeutic benefits that CPAP therapy could potentially provide to them; (2) what changes would they be willing or not willing to make to obtain the specific benefits that they are seeking; and (3) how likely will they continue to use CPAP for the minimal hours required by their insurance companies if most or all of their perceived barriers and obstacles are removed. Patients can be asked to rate how important it is for them to obtain the therapeutic benefits of CPAP on a scale of 0–10 with "0" indicating "not important" and "10" as "extremely important." In many cases, the use of CPAP may in fact be lifesaving therapy, so it is important to inquire from such patients as to why longevity would be important to them. I have found in my own practice that people will generally tell you that they would like to live well into old age; however, when the question is asked about what they would do with that time, they often do not have any idea whatsoever. I bring this up on account that unless a patient has at least one personally significant and meaningful reason or purpose for making a change from the status quo, it is highly unlikely that they will do so. For example, if a patient tells us that he wants to live to be able to walk his daughter down the aisle on her wedding day, then there is a very strong likelihood that he is willing to make a higher investment in their self-care. Again, our job is not

to tell patients what they *should* do, but, rather, have them tell us what if anything that they want to be able to achieve for themselves.

Earlier in this chapter, I made a brief reference to using MI as a key component of a psychosocial treatment package for improving adherence to CPAP. MI is a multi-theoretical psychotherapeutic approach developed in the early 1980s and focused on guiding patients to resolve their ambivalence when considering making behavioral changes that they may find difficult [6]. The underlying attitude of the practitioner toward the patient is nonauthoritarian, patient-centered, and based on an assumption that patients, not the practitioner, are the experts of their own lives. In other words, approaching patients from an underlying MI spirit necessarily requires the practitioner to become emotionally unattached to the actions taken by their patients. In a very Rogerian sense, practitioners working with resistant patients come to empathically accept and validate patients' reasons for not making behavioral changes even if they do not personally agree with them. This particular way of approaching patient's rationalizations for not making changes is often called "rolling with resistance" [14]. Additionally, the practitioner does not automatically give advice or offer recommendations, but, rather, uses reflective statements, elicits self-ratings of how important it is to an individual to make the proposed change(s), as well as self-efficacy beliefs for making the proposed change. Most importantly, practitioners skillfully ask open-ended questions designed to elicit "change talk" from the patient. In other words, the patient, not the practitioner, comes up with the rationale for making the proposed change. This particular style of approaching patients is likely counterintuitive to those practitioners who are medically trained and will require a major shift in treatment paradigm. Applying an MI approach from day 1 will lead to a fuller understanding of a patient's perceived obstacles and barriers to using CPAP, as well as their reasons for why they might consider using it as well as their readiness to make the change now or at some future time. The following brief vignette illustrates all of the above.

Practitioner: "So I guess that we are here to talk to you about your CPAP machine and ways to get you a better night of sleep."

Patient: "Yeah, I know, I should be using it every night but it's so hard for me to that." "I just can't do it."

Practitioner: "Well I'm definitely not here to lecture you on not using your CPAP." "I don't imagine that it's easy to all of a sudden have to go from sleeping in any manner that you see fit to being hooked up to a machine which is blowing air into your nostrils."

Patient: "That's exactly right." "I just can't seem to get used to that thing." "I don't know what else I can do." "I am always tired during the day at work and my boss is always reminding me that I'm not getting enough done and my wife won't sleep with me because my snoring keeps her up."

Practitioner: "So you would like to be able to please your boss and sleep next to your wife, but not certain whether using your CPAP is worth all the trouble and aggravation."

Patient: "That's about the gist of it doc." "But it sure would be nice not to always be so tired. I even sleep my weekends away and my wife is always complaining that I don't spend enough time with her and our kids."

Practitioner: "It must be tough to be put in the position of having to choose sleep over your family." "So what other treatments have you learned are available for treating your sleep apnea?"

Patient: "Well my doctor told me that there really isn't anything else." "I tried one of those mouth pieces that my dentist made for me and it made no difference in the way I feel." "Surgery is definitely out of the question for me."

Practitioner: "So it must be really disappointing that the dental appliance didn't correct your sleep apnea?" "That sounds like something that you would've been willing to live with to feel better."

Patient: "Yup, that would have made life a whole lot easier for me."

Practitioner: "So knowing that CPAP is the only option available at this time to get you to be able to feel less sleepy and have more energy during the day, how likely on a scale of 0 to 10 with 0 being unlikely and 10 being extremely likely would you be willing to use CPAP for at least 4 hours per night?"

Patient: "Probably a '3'."

Practitioner: "Wow, that's actually more than what I expected you would say." "So you would use CPAP to feel less sleepy and have more energy during the day, but certain things about CPAP would have to be improved if you were to use it." "What improvements would have to be made to CPAP for you to go from a '3' to a '6' in terms of the likelihood that you would use your machine for at least 4 hours per night?"

Patient: "Well, the main thing is that I often feel like I'm being suffocated and then I end up just pulling it off of my face for the rest of the night."

Practitioner: "Well that certainly makes sense." "After all, how could anyone sleep feeling that they are being suffocated." "Now, I can't make any specific promises here, but if it was possible to use your CPAP without acquiring those feelings of suffocation at night, how likely on a scale of 0 to 10 are you likely to use it for at least 4 hours per night?"

Patient: "You mean that's possible?" "Heck I could probably keep it on all night if that were even possible." "You can't imagine how awful it is to have that feeling when you're laying in bed at night."

Practitioner: "Anything is possible, and I've seen many people eventually come to see their CPAP as a good friend rather than something to be avoided." "It won't be easy, but I think there is a good possibility that you will be able to use your CPAP with minimal or no discomfort." "Are you willing to give it a shot here?"

Patient: "You bet!" "When do we start?"

This vignette also brings up the issue of claustrophobia, which can be screened for when meeting a CPAP nonadherent patient for the first time. A 15-item subscale adapted from the Fear and Avoidance Scale will measure claustrophobic tendencies pre-CPAP treatment and can be readministered as necessary once behavioral therapies have been initiated [4]. A cutoff score of 25 indicates that the individual has clinically significant claustrophobic tendencies and graded exposure therapy should be discussed with patients as a possible intervention to desensitize and habituate them to the use of their equipment. There are often times when a change in the individual's mask will resolve this issue. For example, I often meet individuals who were initially started on a full-face mask and simply, by coordinating with the sleep medicine physician, were able to be switched to a nasal or nasal pillow mask that attenuated or completely resolved claustrophobic feelings when using CPAP. In many cases, patients are not aware that other types of CPAP masks are available to them and they are often surprised to learn that there are other options available, shown to them on your PC. It will be necessary to have patients bring their CPAP equipment with them to the session to begin behavioral therapy if that intervention is warranted.

Since the patient is generally looking to ameliorate the effects of excessive daytime sleepiness (EDS), it is recommended that they be screened with the Epworth Sleepiness Scale (ESS), an 8-item self-report scale to assess a patient's likelihood of falling asleep in situations where dozing is undesirable, such as while waiting for a traffic light to change [15]. Generally, a score of 13–15 indicates moderate EDS while 16–24 reflects severe EDS. As CPAP adherence improves, ESS scores should also decrease and as such is a simple way to track treatment progress. Additionally, when patients see these scores decreasing, their motivation levels may increase as well. Again, if ESS scores stay the same or increase from baseline, it is important that we use the spirit of MI to validate the patient's present difficulties in using CPAP and reframe them as an opportunity to try a different approach that might be more effective for them.

The initial visit can also be used to obtain further information about the patients' sleeping partners as well as other positive social supports who might be engaged to help find specific ways to encourage and reward positive behavioral changes at home. It will become very important for the patient's supports to learn to approach the patient's periods of nonadherence in a non-emotionally reactive manner, recognize that nonadherence is a process, and to learn more adaptive ways to communicate their frustrations and disappointments with the nonadherent patient.

If time permits during the initial visit, and the patient seems ready to move forward to improving their CPAP adherence, it can be extremely effective to have them visualize and tell you how their lives will improve when they are less sleepy. In the case of the vignette demonstrating MI, the patient may already begin to see himself enjoying the company of his wife and children and engaging with them in many fun activities. Or perhaps that pay raise at work may not appear to be so elusive now that I am able to be so much more productive there. Such details from your patient in this manner can also deflect focus from their negative to more positive associations with CPAP and making more positive and life-affirming associations with CPAP. For

many people with OSA, just the idea of being less sleepy, irritable, and distractible can create a great deal of intrinsic motivation for them to use CPAP.

Ongoing Sessions

I find in my own practice that humans generally do not desire to experience personal failure, and this particular concern often precludes them from taking risks and committing to life goals that they or others believe might be important. Accordingly, behavioral avoidance and self-defeating thinking tend to create at best a self-fulfilling prophecy, and many of our CPAP patients will use confirmation bias and view setbacks and lack of progress in treatment as just another example of failure in their lives. In these cases, the patient's self-efficacy is severely lacking, and many have already decided that they do not possess the necessary psychological resources to meet their important goals. This is where cognitive-behavioral therapy (CBT) interventions will come to play an important role with self-defeating individuals who often lack in persistence with task completion or frustration tolerance. For many, this may be the first time in their lives that anyone has ever taken the time to teach them how to think critically, rather than simply to react emotionally to internal cognitions that may not have a basis in reality. Again, using the MI spirit, I obtain patients' permission to see if they might want to engage in collaborative empiricism with me to discover the "truth" of their experiences. To date, I have yet to have a patient voluntarily refuse to do this with me.

Using a cognitive-behavioral framework while concurrently continuing to work in the spirit of MI strengthens the therapeutic alliance and is an effective way to intervene with patients who are not adherent to CPAP therapy. As behavioral practitioners, we are always alert and listening actively for anything in the patient's language that would suggest an opinion or assumption that is being made to rationalize the idea that it might be better to simply "give up" or "do nothing at all." Again, we need to resist the temptation to correct the patient in their manner of thinking. Instead, we should respectfully ask them to take the time to personally challenge this thinking to see if it really has validity for them. The application of Socratic questioning tends to work very well with individuals who are nonadherent to treatment. In this manner, we teach the patient to begin to question and challenge their own automatic cognitions or assumptions, find alternative perspectives, understand the behavioral consequences of their automatic cognitions, and, finally, to gain greater understanding about the potential functions the automatic cognitions may have played in their life (e.g., giving them permission to avoid an anxiety-provoking task such as confronting our physician). The following vignette illustrates how using a CBT framework might play out for someone who is having difficulty adhering to CPAP therapy:

Practitioner: "So how did it go over the past week?"

Patient: "Well, I'd like to be able to tell you that I used my CPAP every night, but then I would be lying to you." "I shouldn't have to go through all of this just to feel like I've actually slept through the night."

Practitioner: "Well, it's true that the majority of people in this world don't have to use CPAP to feel like they've actually received restorative sleep so they can function well the next day." "Can you tell me why you personally *shouldn't* have to use CPAP to obtain the same results?"

Patient: "Well, I really don't know the answer to that (chuckling)." "I guess that there isn't really any other way for me, is there?"

Practitioner: "I'm not seeing any alternative at this point." "Using CPAP to get a decent night of sleep could definitely be seen as very unfair since most people don't need to go to such extremes." "So how would you imagine your life to be if you simply said, 'the heck with it,' and just let the insurance have the 'damn thing back.'"

Patient: "That's a pretty fair way of how I look at this." "I hate having to do this every night." "But if I don't use it, nothing will get any better, so I guess I'm going to be stuck with this, right?"

Practitioner: "Maybe, but ultimately it is your decision whether to use CPAP or not." "Perhaps it could be helpful if you tell me about another time in your life that you were inconvenienced or had to give up something which was very important to you in order to gain something that might have been even more important to you?"

Patient: "Well, I did give up drinking about six years ago and have even managed to stay sober."

Practitioner: "That's a fantastic accomplishment and a really great example." "So, what do you imagine would have happened if you continued to choose to drink all of these years?"

Patient: "Oh, I know what would have happened." "I would have lost my family and I probably would be really sick or probably even dead by now as it was taking a toll on my liver."

Practitioner: "Okay, so the thought of losing your family and possibly not living long enough to be able to see your children grow up was more than you could bear, so even though you probably didn't want to give up drinking, you somehow managed to do it anyway and stay sober to boot."

Patient: "Yeah, I'm kind of proud of that (smiling)."

Practitioner: "As you should be." "Can you tell me on a scale of 0 to 10 how unfair you think it is that you no longer permit yourself to drink."

Patient: "That's a really silly question isn't it?" "But I see your point." "In some ways, I'm kind of in the same place as I was six years ago." "My family is not real happy about the fact that I'm not taking care of my health, and the truth is, I can't even enjoy them on account that I'm always needing to take a nap."

Practitioner: "Okay, so if I am understanding you correctly, you might still be willing to make yet another sacrifice and experience some inconvenience as long as you believe that it benefits your family."

Patient: "I guess so." "I never thought about it like that before." "So it sounds like what you're really saying is kind of like giving up a little to get a lot."

Practitioner: "That's actually a very good way to put it." "Besides, can you tell me the name of anyone you personally know who has gotten everything they wanted in this life?"

Patient: "No one that I know of." "I guess that life can be unfair to all of us at times."

Practitioner: "It sure can." "No one seems to get out of here without experiencing some pain and discomfort." "So, what do you think will help you stay the course with CPAP therapy when you have those moments where you would rather just toss it away?"

Patient: "Knowing and accepting the fact that life isn't always fair to everyone really seems to help a lot to endure this." "Also, I've already given up a lot, got through it and in the end, feel better off for doing so."

Practitioner: "So what would you think about typing both of these affirmations into your cell phone and looking at them whenever you feel inclined to give up?" "How do you think that would work for you?"

Patient: "Actually, I already do something similar and look at some of my AA meeting sayings when I'm going through those rough patches." "This could actually help with using my CPAP also."

It is well beyond the scope of this chapter to go into detail here regarding the didactics and practice of CBT and MI with treatment nonadherent patients. The two vignettes offered are simply here to provide you with examples of how behavioral health clinicians and other medical professionals can approach patients, so that in the end it is the patient who ultimately identifies where they are getting stuck emotionally and behaviorally with following through with treatment. Through some thoughtful and strategic questioning by a skilled clinician, most patients will eventually come up with their own unique solution that is also reflective of their own values system. Not all patients will decide to continue using CPAP and it is important that we as clinicians do not personalize this and perceive it to be a failure on our part. Again, just as we have the right to refuse medical advice, they must also be provided with the same consideration. In the end, if a patient decides that they want to discontinue with CPAP therapy, we can still feel positive about having provided them with an opportunity to learn some important coping skills such as critical thinking, problem-solving, and decision-making. Furthermore, if we have treated them in a respectful, patient-centered way, it is possible that at some point they may change their mind about CPAP and wish to seek you out for further assistance.

Finally, I will turn your attention to treatment interventions with patients who use their CPAP less than 2 hours per night on account that they have claustrophobic tendencies and experience high levels of anxiety and panic. It is important to recognize that approximately 30% of OSA patients complain of feeling closed in or claustrophobic when using CPAP [16]. Such patient would also include those who have experienced a past traumatic event that may have involved obstruction and not being able to breath voluntarily. Examples of this may include being suffocated, breathing in noxious fumes, having asthma attacks, wearing a gas mask during military service, or near drowning. This list is not exhaustive. It is not terribly difficult

to conceive how someone who has a mask strapped to their face blowing pressurized air into their nostrils might have traumatic memories of associated events triggered. It might be helpful to take a brief trauma history at the initial session to find out whether your patient has ever been in a life-threatening situation where their natural ability to breath may have been involuntarily restricted. This can be followed up with the modified Fear and Avoidance Scale previously referred to in this chapter that will allow us to rule in claustrophobia as the barrier preventing an individual from using their CPAP.

CPAP-related claustrophobia has been successfully treated with graded exposure therapy since the early part of the 1990s [17]. To date, another behavioral therapy, systematic desensitization, has not been studied for its effectiveness in treating CPAP-related claustrophobia. Some studies do suggest that certain features of desensitization therapy, such as relaxation techniques, can be helpful to these patients [16]. Our primary goal in using graded exposure therapy is to assist our patients to unlearn the past negative associations that are triggered by breathing in pressurized air through the CPAP mask and get to the point that they are eventually habituated to using the equipment without feeling a need to avoid or escape it.

The graded exposure hierarchy for CPAP-related claustrophobia should be kept as simple and as uncomplicated as possible, as this will facilitate practice exposures at home. Fortunately, initial exposures are conducted in the behavioral health practitioner's office in vivo and will naturally require your patient to bring their CPAP equipment into the office with them. The following steps can serve as a guideline for the exposure hierarchy [16].

Step 1: Have your patient sit in a comfortable chair in your office and turn on the CPAP. Without using the straps, have them simply hold the mask over their nose and practice breathing regularly. Have them do this initially for short periods of time (typically 1–5 minutes) and have them gradually build this up for longer periods. They should be encouraged to practice this at home once they seem to show no distress in doing this in the office. It will also be important for you to remind them to not use CPAP at bedtime until such time that they are comfortable using it when they are awake.

Step 2: Again, have your patient sit in a comfortable chair in your office and turn on the CPAP. This time, they will wear the mask with straps rather than just holding it over their nose as was done in Step 1. Again, they are asked to practice breathing regularly until such time that they are able to tolerate wearing the mask for a continuous period of 15 to 20 minutes in your office.

Step 3: This step requires that the patient prepares for taking a nap, wearing full headgear as in Step 2. They will lie down on their bed, recliner, etc. and turn their CPAP on. As in Step 2, they will practice breathing regularly and gradually build up times until they are able to comfortably wear it for 15 to 20 minutes in duration. Whether the patient falls asleep or not is not important here as the primary goal is to have them rest comfortably in bed with their equipment.

Step 4: After completing the third step, the patient will now decide whether or not they are ready to try CPAP at bedtime. If they indicate having reservations about

using CPAP at bedtime, again, in a nonjudgmental manner, listen to their objections and barriers using MI and CBT interventions as previously discussed to help them problem-solve and take the needed risk. Family members can also assist in finding helpful ways to encourage the patient and provide emotional support if needed.

As previously indicated, do not hesitate to ask your patients what they have successfully tried in the past to help them feel more relaxed and prepared for sleep. After all, they are the experts of their own lives. Your patients will tell you variety of different strategies and routines that they have used to prepare themselves for sleep. Some of these methods are not always in accordance with recommended sleep hygiene practices; for example, I have had patients who have become accustomed to falling asleep to the sound of a sports broadcaster on the TV, or specific types of music. Again, our patients often possess their own unique solutions to their own problems, and it is sometimes more helpful to our patients if we take a more pragmatic approach to their problem-solving, provided that it does not lead to their own harm.

Conclusion

For over 30 years, research has shown time after time that CPAP therapy is the gold standard treatment for OSA. Despite its clinical effectiveness, adherence has been quite low due to psychosocial barriers that patients come to express. It is our contention that many if not all of these barriers can be removed using the empirically based therapeutic techniques exemplified in this chapter. Toward achieving greater CPAP adherence rates, there is no substitution for a collaboratively strong working alliance between the health care practitioner and the patient. In addition, practicing from an MI perspective fosters a relationship built on mutual respect and understanding and, not to mention, empowers the patient to begin taking greater responsibility for their own health care choices. Although the psychosocial strategies reviewed in this chapter are not exhaustive, they do have research to back up their effectiveness for patients on CPAP. It is hoped that the reader will take time to explore the use of creative applications of CBT and MI, which can enhance adherence to medical treatments such as CPAP and which can reduce further medical risks, ultimately leading to improved quality of life for our patients.

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Part IV

Other Sleep Disorders

Hypersomnia and Narcolepsy

9

Rakesh Bhattacharjee

Introduction

Hypersomnolence, in simple terms, is synonymous with excessive daytime sleepiness (EDS), where prolonged duration of sleep is often required compared to the age-appropriate norms. While most hypersomnolence is likely due to cumulative inadequate sleep duration or sleep deprivation/insufficient sleep, there are several sleep disorders that cause hypersomnolence in the absence of sleep deprivation or maligned circadian rhythms (Table 9.1). Hypersomnolence may lead to numerous disruptions in daytime functioning. For example, EDS may result in poor school or work performance, mood disturbances, and an increase in the likelihood of work-related injuries or motor vehicular accidents.

EDS is experienced by patients as the inability to stay alert or awake during the day or when wakefulness is expected. Some patients with hypersomnolence endorse a constant irrepressible desire to sleep resulting in frequent inadvertent naps during the day or in some cases "sleep attacks." Sleep attacks are described as inadvertent sleep periods occurring unexpectedly with little or no prodromal symptoms. Most patients experience sleepiness when there is diminished stimulation, such as activities that are dull or boring and monotonous and result in sedentary behavior. Daytime drowsiness or daytime sleep periods can therefore have variable presentations in which patients may experience frequent unexpected sleep attacks or be aware of increasing daytime drowsiness. Furthermore, patients may experience different benefits from daytime naps as some disorders of hypersomnolence result in patients perceiving a temporary benefit in daytime alertness following a nap whereas in other hypersomnolence disorders, patients experience no benefit following a nap. For example, in patients with narcolepsy, individuals often benefit from brief 2 naps

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Table 9.1 Hypersomnolence disorders

Insufficient sleep
Hypersomnolence due to psychiatric disorder 1. Depression 2. Bipolar II 3. Seasonal affective disorder
Hypersomnolence due to medical disorders 1. Hypothyroidism 2. Hepatic disease renal disease 3. Encephalitis 4. Encephalopathy 5. Brain tumors 6. Sarcoidosis 7. Metabolic disease 8. Prader-Willi syndrome
Hypersomnolence due to medications/medication withdrawal Antipsychotics Opioids Anticonvulsants Stimulant withdrawal
Hypersomnolence related to substances/illicit drugs Alcohol Marijuana Opioids
Hypersomnolence due to sleep disorder 1. Obstructive sleep apnea 2. Insomnia 3. Circadian sleep disorder
Hypersomnolence due to hypersomnolence sleep disorder Narcolepsy Idiopathic hypersomnia Klein-Levin syndrome

1–2 times a day whereas in patients with idiopathic hypersomnolence, individuals may, in fact, feel more tired even if they nap for hours at a time.

The presentation of hypersomnolence in children is less straightforward. In some children, particularly young children, the return of daytime napping after the age of 5 may reflect a disorder of hypersomnolence. However, daytime sleepiness is not ubiquitous among children with hypersomnolence disorders, as some children, particularly young children, may instead present with symptoms that mimic attention-deficit/hyperactivity disorder (ADHD) with inattentiveness and hyperactivity at schools coupled with emotional lability.

In this chapter, sleep disorders of hypersomnolence are carefully reviewed, including how to diagnose and treat these disorders. It is important to acknowledge that while these disorders lead to a common presentation of EDS, unique characteristics differentiate these disorders resulting in variable clinical presentations. These differences will be highlighted with the purpose that they will assist the clinician in identifying a diagnosis.

Diagnosis of Hypersomnolence Sleep Disorders

Before discussing different sleep disorders of hypersomnolence, it is important to acknowledge the challenges of diagnostic testing. The ease of questionnaires allows for this method to be commonly used. However, subjective sleep self-reports have limited sensitivity and specificity. As a result, a sleep testing center in which polysomnography (PSG) and multiple sleep latency testing (MSLT) are performed is often required to establish a diagnosis of these disorders (see later for further discussion).

Subjective Inquires

Subjective Questioning

Subjective inquiries about sleep patterns and duration are important to elicit EDS and sleep duration. In addition to inquiries about sleep hygiene, identification of prescribed or over-the-counter medications, substance misuse or illicit drug use, and finally associated medical and psychiatric complications should be excluded as a cause. Longitudinal sleep pattern in association with menstruation in females and cycle hypersomnia should also be elicited. While adults can often verbalize their struggles with EDS, in younger children and older adults, information provided by caregivers (i.e., parents, guardians, and teachers) should be obtained to better characterize their presentation.

Sleep Diaries

In the context of sleep diaries, individuals are encouraged to complete a sleep diary for at least a 2-week duration. The diary can also be used to identify associations between sleep and menstrual periods or other triggers that can impact sleep. Sleep diaries allow patients to prospectively evaluate their sleep and wake times at home.

Sleep Questionnaires

Subjective scales of sleepiness are most frequently used to assess EDS given their ease of administration. Questionnaires vary by evaluating sleepiness in specific moments versus over a specified time period. Momentary assessment offers the ability to measure EDS in different times of the day or following ingestion of a medication or drug. It is important to emphasize, however, that the data collected from questionnaires are self-reported and at risk of subjective bias.

The *Epworth Sleepiness Scale* is most widely used for clinical and research assessment for EDS. It is an eight-item scale assessing a person's propensity for dozing in different situations [1]. Greater scores indicate greater daytime sleepiness, with scores greater than 10 considered abnormal and scores greater than 12 consistent with moderate to severe EDS.

The *Stanford Sleepiness Scale* assesses EDS by asking patients to characterize their self-assessed current state of sleepiness [2]. This is a momentary assessment 7-item scale that is brief and easy to administer, and assesses EDS at different

periods during the day. Similar to the Epworth Sleepiness Scale, higher scores indicate greater EDS.

The *Karolinska Sleepiness Scale* similarly evaluates the momentary self-assessment of daytime alertness or EDS [3]. It is often used in research settings including drug trials and to assess alertness in various occupations.

Objective Measures

Polysomnography and Multiple Sleep Latency Testing The MSLT is the mostly frequently used diagnostic test to assess daytime sleepiness. Testing involves a series of 4–6 nap opportunities during the day spaced 2 hours apart [4]. The first nap opportunity begins in the morning, 2 hours following morning awakening. PSG performed the night before is often prerequisite to MSLT to ensure that the patient slept well the night before (i.e., sleeping at least 6 hours before MSLT) and is used to rule out the presence of sleep disorders such as sleep apnea that may promote EDS. In addition, drug screening is frequently performed to rule out the use of medications or illicit drugs that induce sleepiness or wakefulness.

During the MSLT, patients are informed to attempt to fall asleep with each nap opportunity. Testing is conducted in the dark and in quiet environments to ensure that there is no interference to sleep onset or sleep maintenance. Testing consists of electroencephalogram (EEG), electromyogram (EMG), and electrooculogram (EOG) to verify and identify sleep stages including rapid eye movement (REM) sleep. Each nap opportunity consists of 20 minutes. Pertinent information gathered for each nap trial is whether there was sleep onset, how soon sleep occurred or sleep onset latency, and whether REM sleep occurred during the naps signifying a sleep onset REM period (SOREMP) within 20 minutes. Sleep latency in all nap opportunities is then averaged to determine the mean sleep onset latency. A mean sleep onset latency of less than 5 minutes is considered pathologic [5], and sleep onset latencies >10 minutes may be considered normal [4]. The presence of two or more SOREMPs signifies a diagnosis of narcolepsy.

Multiple Wakefulness Testing The Multiple Wakefulness Testing (MWT) mimics the testing conditions of the MSLT but is used instead to assess the patient's ability to stay awake by resisting sleep during the "nap" period [4]. Therefore, the MWT assesses the potential threat for involuntary sleep and may be used to assess the patient's safety in certain conditions such as driving, working, or other conditions in which sleep should not occur. Similarly, tests of vigilance, including the psychomotor vigilance test [6] and driving simulators, are often used to assess safety in patients with EDS. However, the findings from MSLT and MWT do not correlate well in patients with EDS [7]. Therefore, instead of diagnostic usage, the MWT is used typically to assess treatment outcomes in patients with already diagnosed hypersomnolence disorders.

Wrist Actigraphy Actigraphs are devices worn on the wrist that record three-dimensional movements. In doing so, given the quiescence of sleep, reduced motion is typically detected as a sleep period whereas increased motion denotes wakefulness. While initially intended for research purposes, wrist actigraphy has adopted a larger clinical role and is routinely used in the evaluation of circadian rhythm disorders and insomnia [8, 9]. Given prolonged sleep periods of certain disorders of hypersomnolence, actigraphy may also be used to evaluate total sleep time with the notion that greater than average sleep duration over a 24-hour period may suggest hypersomnolence such as seen in idiopathic hypersomnolence [10, 11].

Sleep Disorders of Hypersomnolence

Narcolepsy

Narcolepsy was first described in 1880 by the French physician Jean-Baptiste-Edouard Gélineau [12]. Narcolepsy is a chronic disabling disease estimated to affect 25–50/100,000 people [13]. With advances in awareness and improvements in access to sleep clinics and diagnostic testing facilities, it is assumed that the prevalence may increase.

The clinical features of narcolepsy consist of the classic narcoleptic tetrad: EDS, hypnagogic hallucinations, sleep onset paralysis, and cataplexy. In addition, sleep fragmentation is considered a clinical feature and comprises the narcolepsy "pentad" [14]. The most common symptom is EDS found in 100% of subjects with narcolepsy often with the presence of recurrent sleep attacks [15, 16].

Cataplexy, involving the paroxysmal loss of muscle tone, is considered most pathognomonic [17]. Cataplexy is best described as more than one episode of brief (<2 minutes), usually bilaterally symmetrical, sudden loss of muscle tone with retained consciousness [16]. In children, cataplexy may mirror a complex movement disorder with bouts of hypotonia and prominent buccofacial muscle involvement including jaw drop, tongue thrusting, eyelid drooping, and/or head rolling [18, 19]. The subtle signs of cataplexy in children may often be missed by parents and clinicians. Common triggers to cataplectic episodes include events that cause intense emotion such as laughing, being frightened, being tickled, being surprised, or feeling stressed, angry, or embarrassed. Finally, cataplexy is often confused for the presence of epilepsy and/or cardiogenic events such as presyncope or syncope and should be considered in the workup of these disorders.

Types of Narcolepsy

The International Classification of Sleep Disorders Third Edition (ICSD-3) has now separated narcolepsy with and without cataplexy into type 1 and type 2 narcolepsy [16]. The cardinal feature differentiating both types of narcolepsy is contingent on reduced or absent levels of hypocretin-1 in the cerebrospinal fluid [20, 21].

Prevalence The prevalence of narcolepsy type 1 (NT-1) ranges from 0.02% to 0.18% in US and European populations to a higher prevalence in Japanese populations (0.16–0.18%) [13, 16, 22]. The prevalence of narcolepsy type 2 (NT-2) is less certain given the greater challenges involved in establishing a diagnosis of NT-2, but one report estimates a prevalence of 20.5/10,000 [16, 23].

Narcolepsy Type 1 (NT-1)

NT-1 is best defined by EDS and REM-sleep dissociation including cataplexy. NT-1 is caused by deficient hypocretin signaling by the hypothalamus. Accordingly, the ICSD-3 criteria for NT-1 are based on the presence of EDS for at least 3 months and either cerebrospinal fluid (CSF) hypocretin-1 concentrations measuring ≤110 pg/mL or one-third of mean values obtained in normal subjects using the same standardized assay *or* the presence of cataplexy and a mean sleep latency of ≤8 minutes and two or more SOREMPS on an MSLT [16]. Of note, a SOREMP identified during the nocturnal polysomnogram is now acceptable to replace one SOREMP during an MSLT [16].

Clinical Features All patients with NT-1 have EDS [15]. Sleepiness is considered debilitating, having an irrepressible need to sleep throughout the day, or frequent lapses into sleep and sleep attacks. Physical activity may reduce the likelihood of sleep, but monotonous activities, such as sitting in a car or even driving a car, will increase the likelihood. EDS will typically manifest in poor work or school performance and can hinder normal social function.

The presence of cataplexy is pathognomonic for NT-1. However, identification of cataplexy remains challenging, particularly for young children [18]. Cataplexy frequency can vary significantly in patients with NT-1 ranging from once or twice a month to more than 20 episodes a day. In addition, the degree of hypotonia varies widely between patients [24], ranging from sporadic partial muscle loss to total body collapse. Also, in addition to the loss of muscle tone, episodes with positive motor phenomena have been described, including muscle twitches, tics, and jerks often involving the muscles of the face. For this reason, cataplexy is often confused with tic disorder or partial motor epilepsy or other complex motor disorders [25, 26].

Hypnagogic and/or hypnopompic hallucinations and vivid dream-like experiences occurring during sleep onset or waking are common affecting 33–80% of patients [16]. The hallucinations may include visual, auditory, and tactile phenomena. While some studies have suggested an increased prevalence of schizophrenia in narcoleptic patients, differentiating psychosis occurring in each disorder is important [27]. For example, other symptoms such as cataplexy and sleep paralysis will occur in narcolepsy unlike schizophrenia. Auditory hallucinations occur in 81% of schizophrenic individuals versus 45% of narcoleptic patients and 9% of controls [27]. However, visual hallucinations are more common in narcoleptic patients (83%) versus in only 29% schizophrenic individuals and in 19% controls.

Sleep paralysis or sleep onset paralysis is the temporary inability to move voluntary muscles usually during sleep onset or during the transition from wake to sleep.

Events can last for several minutes causing significant distress for patients, as patients are unable to move their limbs or even open their eyelids.

The phenomenon of cataplexy, sleep paralysis, and hypnagogic or hypnopompic hallucinations is likely related to REM sleep intrusions. Given that vivid dreams mainly occur during REM sleep, hallucinations may reflect dream-like states permeating into wakefulness. REM sleep is also associated with atonia and the loss of skeletal muscle tone characteristic of cataplexy likely reflects a REM sleep intrusion during wakefulness.

While most patients do not report problems falling asleep at bedtime, many report an inability to maintain sleep consistent with sleep fragmentation [14, 28]. The presence of sleep fragmentation completes the narcolepsy pentad, a sign that is often distinctive compared to continuous sleep in those with primary hypersomnia.

Etiology Loss of hypocretin secreting neurons is considered central to the pathogenesis of NT-1. As stated, hypocretin levels in CSF are low (<110 pg/mL) or undetectable [20, 29]. The etiology is thought to be related to autoimmune or paraneoplastic disorders associated with anti-Ma2 or antiaquaporin 4 antibodies, head trauma, or lesions/tumors of the hypothalamus. An autoimmune etiology is thought to be related to triggers, including viral illness, beta-hemolytic streptococcus infection (thus elevated antistreptolysin O [ASO] has sometimes been elevated in this population), and possible association with vaccinations, including H1N1 influenzae. Therapeutic responses to intravenous immunoglobulin in some patients with narcolepsy [30] also suggest an autoimmune etiology. Variations in onset related to seasonal patterns have also suggested an environmental trigger [31, 32].

NT-1 onset may also follow familial inheritance. There is an association of NT-1 with human leukocyte antigen (HLA) subtypes HLA DQB1∗0602 and DR2 or DRB1∗1501 [33–35]. Nearly all narcoleptic patients with cataplexy are positive for DQB1∗0602, compared to 12–38% of the general population with this HLA subtype. Although the prevalence of familial cases is only 1–2% of first-degree relatives of patients with NT-1, compared to the risk of NT-1 in the general population, this reflects a 10- to 40-fold increase in risk.

Clinical Presentation The age of onset of symptoms typically follows a bimodal distribution with the first peak occurring at adolescence and the second peak around the 35 years of age [36]. Notwithstanding, narcolepsy symptoms can emerge as early as age 5. The challenges to identifying symptoms of narcolepsy, including cataplexy in children, often result in a delayed diagnosis and an inaccurately inflated age of onset.

In addition, symptoms in young children may not equate uniformly to EDS. In young children, sleepiness may present paradoxically with increased hyperactive behaviors, inattentiveness, behavioral disturbances, or decreased school performance. Sleepiness in children may present as the reemergence of daytime napping or greater duration of nocturnal sleep. The onset of hallucinations with behavioral

changes may often lead to misdiagnosis of psychiatric disorders, including anxiety, depression, or schizophrenia. Both obesity and precocious puberty are also commonly associated in children with NT-1.

Most typically EDS is the first manifesting symptom as symptoms of cataplexy typically present later. In rare cases, however, cataplexy may precede EDS. Most often, NT-1 signs and symptoms develop gradually over several years. It is anticipated that with improved awareness, better recognition of these symptoms will lead to the increased diagnosis of NT-1 cases.

Diagnosis Most often, NT-1 is diagnosed on the basis of a constellation of symptoms combined with the findings from PSG and MSLT. The findings from MSLT should confirm a mean sleep latency of less than 8 minutes and often less than 5 minutes. A meta-analysis revealed mean sleep latency of 3.1 ± 2.9 minutes in NT-1 patients [4]. In addition, MSLT must identify two or more SOREMPs or an SOREMP within 15 minutes from the nocturnal PSG coupled with at least one SOREMP during the MSLT [16].

Assessing CSF levels of hypocretin-1 is not routinely done because of limited availability of this testing. Nonetheless, hypocretin-1 levels are both highly sensitive and specific for a diagnosis of NT-1. Of note, however, 10% or narcoleptic patients with cataplexy may have normal hypocretin-1 levels in CSF implying that CSF levels do not perfectly reflect hypocretin signaling or there may be other causes of cataplexy independent on hypocretin [21].

Human Leukocyte Antigen (HLA) subtyping to assess for HLA DR2/DRB1∗1501 and DQB1∗0602 is often performed but is not considered diagnostic for NT-1. Currently, this testing would be considered adjunctive in the workup for NT-1.

Narcolepsy Type 2 (NT-2)

NT-2 is specifically defined as narcolepsy without cataplexy. Should cataplexy develop later during the course of the disease, the disease becomes reclassified as NT-1.

The ICSD-3 criteria share many features of NT-1 but with the absence of cataplexy. Specifically, the ICSD-3 defines NT-2 as EDS lasting for at least 3 months, a mean sleep latency of ≤8 minutes and two or more SOREMPs found on MSLT (again an SOREMP on the preceding nocturnal PSG may substitute an SOREMP on the MSLT), absence of cataplexy, either CSF hypocretin-1 concentrations has not been measured or is >110 pg/mL or >1/3 of mean values in normal subjects using the same assay, and finally the hypersomnolence and/or MSLT findings are not explained by insufficient sleep, other sleep disorders or related to substances or medications [16]. Of note, should CSF hypocretin-1 levels be retested and determined to be undetectable or ≤110 pg/mL or <1/3 of the mean values in normal subjects using the same assay, the disease again becomes reclassified as NT-1.

While cases of narcolepsy without cataplexy represent up to 25% of the clinical narcolepsy population, the precise prevalence of NT-2 is not well defined.

Clinical Features NT-2 is best summarized as persistent irrepressible daytime sleepiness with REM intrusions seen on MSLT and/or nocturnal PSG. Again, essential to the diagnosis is the absence of cataplexy. Characteristic to NT-2, patients find daytime naps as refreshing. Similar to NT-1, NT-2 is also characterized by sleep onset paralysis, hypnagogic hallucinations, and sleep fragmentation.

Etiology NT-2 is often related to an accompanying medical disorder. For example, tumors or lesions, including sarcoidosis of the hypothalamus, autoimmune or paraneoplastic disorders, multiple sclerosis, myotonic dystrophy, Prader-Willi syndrome, Parkinson disease, Niemann-Pick disease type C, and head trauma, may all result in NT-2 [16]. Often in medical conditions resulting in an NT-2 phenotype, one must consider additional etiologies related to the underlying disease to cause symptoms of hypersomnolence. For example, Prader-Willi syndrome or myotonic dystrophy may lead to sleep-disordered breathing and subsequent sleep fragmentation that itself can result in hypersomnolence. Underlying genetic and environmental risk factors, however, are unknown. Unlike NT-1, familial patterns of NT-2 are not well established.

Clinical Presentation The onset of NT-2 typically occurs during adolescence [16]. Similar to NT-1, symptoms of NT-2 are disabling and often socially isolating. There are marked reductions in school or work performance, and significant safety issues regarding driving a motor vehicle or operating machinery. NT-2 is also associated with significant mood disturbances including depression. Finally, NT-2 is also associated with weight gain and obesity.

Similar to NT-1, the identification of symptoms of cataplexy is difficult, and while many children may be diagnosed with NT-2, until cataplexy is well established, a diagnosis of NT-1 may be deferred.

Diagnosis The standard of care to diagnose NT-2 remains combining clinical findings with nocturnal PSG with MSLT. As stated, the MSLT should demonstrate a mean sleep latency that is less than 8 minutes, more commonly less than 5 minutes, accompanied with two or more SOREMPs. (The presence of a SOREMP during the overnight PSG may substitute for one SOREMP during the MSLT portion of diagnostic testing.)

Approximately 24% of narcoleptic patients without cataplexy may have reduced CSF hypocretin-1 levels and another 8% have intermediate levels [37]. Many of these patients may have narcolepsy that evolves to include cataplexy, but remain diagnosed as having NT-2.

About 45% of NT-2 patients are HLA DQB1∗0602 positive (compared to 12–38% of control patients) [16]. However, HLA subtyping is insufficient to

establish a diagnosis of NT-2 and remains an adjunctive test to better establish a diagnosis of narcolepsy.

Narcolepsy and Psychiatric Disorders

Narcolepsy is also associated with mood disturbances, including depression [28, 38] and anxiety [38], and in children may result in hyperactivity, aggression, and inattention presentations [39]. In a small cross-sectional study of 31 Swedish children with narcolepsy during the H1N1 infection epidemic, the presence of psychiatric conditions was seen in 43% of children (29% ADHD, 20% major depression, 10% generalized anxiety, 7% oppositional defiant disorder, 3% autism, and 3% for an eating disorder) [40]. In another recent study that included 320 individuals with narcolepsy, the odds ratio for major depression was 2.67 and was 2.43 for social anxiety compared to controls, highlighting the elevated rates of internalizing problems among those with narcolepsy [41].

Orexin has been thought to stimulate dorsal raphe serotonergic neurons in vitro, thus increasing serotonin bioavailability. It is thus not unexpected the association between reduced CSF orexin in suicidal patients with major depression [42].Some studies suggest a role for orexin in modulating the brain's reward system and brain sensitization causing an overlap with addiction.

Narcolepsy and Medical Conditions

Narcolepsy is commonly associated with obesity, with 74% of adolescents with narcolepsy either overweight or obese, including among patients with an onset of narcolepsy during childhood [43]. Furthermore, weight loss has been described following treatment of narcolepsy [44, 45]. As stated, narcolepsy is also associated with precocious puberty in children, with a prevalence of 17% compared to only 1.9% in controls, which may be related to dysfunction of the hypothalamus [46–48].

In a recent study of 320 individuals with narcolepsy compared to 1464 controls, digestive system issues were 3.27 times more common, upper respiratory tract infections 2.52 times more common, heart disease 2.07 times more common, hypercholesteremia 1.51 times more common, and hypertension 1.32 times more common compared with controls [41]. The reasons for the presence of these higher comorbidities are not well understood; however, it is thought to be related to an increased sedentary lifestyle and increased food intake secondary to sleep fragmentation.

Idiopathic Hypersomnia

Idiopathic hypersomnia (IH) is best characterized as a disorder of hypersomnolence that is inconsistent with narcolepsy; that is, there is a lack of REM sleep intrusions and cataplexy and is not explained by another disorder. Patients with IH are thought to have persistent sleep "drunkenness" or prolonged sleep inertia with persistent difficulty waking up, even with alarm clocks. In addition, patients do not feel refreshed following long naps.

The ICSD-3 defines IH as having irrepressible EDS for at least 3 months, an absence of cataplexy, and MSLT reveals fewer than two SOREMPs or no SOREMP on the previous nocturnal PSG, and the presence of at least one of the following: mean sleep latency ≤8 minutes on MSLT, total 24-hour sleep time is ≥660 minutes on 24-hour polysomnogram or by wrist actigraphy, and finally insufficient sleep syndrome is ruled out and hypersomnolence and/or MSLT findings are not better explained by another sleep disorder, medical disorder, psychiatric disorder, or the use of drugs or medicines [16].

Prevalence The defined incidence and prevalence of IH are unknown. However, some studies suggest a prevalence of 1–5 for every 10,000 in the general population [49].

Clinical Features IH has two subtypes: IH with long sleep time and IH without long sleep time [50]. Patients are subclassified on the basis of total nocturnal sleep with long sleep time being consistent with ≥10–11 hours of nocturnal sleep. Patients with long sleep time tend to be younger and have decreased energy in the morning and a marginally higher sleep efficiency. Notwithstanding, given the heterogeneous nature of IH [51], subclassifying patients on the basis of nocturnal sleep time may be arbitrary and lack validity, as these patients have similar levels of EDS, similar findings from MSLT, similar symptoms of sleep drunkenness, and unrefreshing naps [52, 53].

In addition to symptoms of EDS, some patients may suffer from autonomic nervous system symptoms, including perceived temperature dysregulation, peripheral vascular complaints, orthostatic disturbances, and headaches [53]. Similar to narcolepsy, sleep paralysis and hypnogogic hallucinations may be reported.

Etiology True to its name, the cause of IH is unknown. CSF levels of hypocretin-1 are normal. There is no association with HLA subtypes. A precipitating trigger has not been identified and there is no known genetic inheritance for IH but there may exist familial patterns [50].

Clinical Presentation The typical age of onset for IH is adolescence to young adulthood. Most typically, symptoms remain stable and remain lifelong.

As IH often develops in adolescence, in addition to excluding other sleep disorders such as sleep apnea, clinicians should be cognizant of delayed sleep phase syndrome and insufficient sleep in this age group as this is highly prevalent [54].

Psychiatric, Medical Comorbidities, and Idiopathic Hypersomnia Similar to other disorders of hypersomnolence, IH can also result in poor school and/or work performance, increased risk of motor vehicle accidents, work-related injuries, and risk of mood disturbances.

Diagnosis The nocturnal PSG is indicated to rule out other sleep disorders, including sleep apnea. Generally, findings on nocturnal PSG show increased sleep efficiency. The findings from MSLT as stated should *not* show two or more SOREMPs and a reduced sleep latency (≤8 minutes) [52]. Should CSF be collected, CSF hypocretin-1 levels should be normal (>110 pg/mL).

Kleine–Levin Syndrome

Kleine–Levin syndrome (KLS) is a condition that results in relapsing episodes of EDS associated with psychiatric, behavioral, and cognitive disturbances. Typical episodes last a median of 10 days (range, 2.5–80 days) and usually involve sleeping 18–20 hours in duration (whether interrupted or continuous) [55, 56].

The ICSD-3 provides criteria for diagnosis specifically stating that in KLS, at least two recurrent episodes of EDS must occur and persist for 2 days to 5 weeks, episodes recur more than once a year at least every 18 months, and in between episodes patients have normal energy and alertness, normal behavior, and cognitive function and mood. In addition, the patient must demonstrate at least one of the following during an episode: cognitive dysfunction, altered perception, eating disorder (anorexia or hyperphagia), or disinhibited behavior (such as hypersexuality), and finally the EDS and symptoms are not explained by another sleep or medical disorder or related to drugs or medications [16].

Triggers to episodes of KLS may be related to viral infections (38.2%) or alcohol intake (5.4%) and/or head trauma (9%) [57]. During an exacerbation, patients may sleep almost the entire day, up to 20 hours per day. While diagnostic criteria require these episodes to recur within 12–18 months, they may occur as often as monthly. Typically, KLS resolves after a median of 14 years with the exception of cases in which onset is during adulthood, in which case the course is even more prolonged [16].

Prevalence KLS is an exceptionally rare syndrome, with an estimated 1–2 cases per million. Typically, the disease presents in adolescents or young adults and affects males twice as often as females. In a systematic review of 56 manuscripts, the median onset of KLS was 15 years of age [56], lasting a median of 8 years, during which 7 episodes of 10 days recurred every 3.5 months (median). Although it was more common in males, females had longer episodes than their counterparts.

Clinical Features During an exacerbation, KLS patients are persistently exhausted with EDS (100%), cognitive changes with slowing of speech (96%), apathy, changes in behavior including confusion, hypersexuality (43%), and compulsions (29%) and individuals may suffer from anterograde amnesia [57].

Psychiatric, Medical, and KLS Comorbidity Behavioral changes may be extreme and include hyperphagia, hypersexuality, and engaging in risk-taking behaviors

such as gambling and vandalism. Patients may experience depression (48%) and/or anxiety, with some experiencing delusions or hallucinations [56]. Physical examination is typically normal apart from psychomotor slowing. Related to EDS, patients are severely impaired, with school and/or work dysfunction as many patients may, in fact, be bedridden. Further social impairment may occur as well. The occurrence of EDS with cognitive, behavioral, or mood changes may not always be concurrent. In some episodes, EDS may be the sole presenting feature [56, 57].

In rare instances, menstrual-related KLS (also called menstrual-related hypersomnia) has been described in which episodes are associated with menstruation [58, 59].

Etiology Risk factors for KLS include Jewish heritage and a history of developmental problems. Viral illnesses typically proceed the first episode of KLS. Other triggers include head trauma, travel, alcohol consumption, or exposure to anesthesia [12, 46, 47, 52]. There are familial cases of KLS reported in up to 5% of patients suggesting a possible genetic risk.

Clinical Presentation Typically, adolescents present with recurrent episodes of EDS with normal alertness and functioning in between episodes. Over time, episodes become less severe, with episodes lasting shorter in duration and typically resolving altogether over a median course of 14 years. Male sex, younger age of onset, and hypersexuality typically predict a longer duration of disease. Given the degree of impairment, KLS results in significant school or occupational impairment as well as impact in mood and social relationships [55, 56, 57].

Diagnosis Electroencephalograms during KLS exacerbations will show a general slowing of EEG activity and often paroxysmal bursts of bisynchronous, generalized, moderate- to high-voltage waves [60]. Nocturnal PSG may vary considerably and depend on the timing of when these are done [57, 61]. Total sleep time is typically increased. Should CSF hypocretin-1 levels be measured, these are typically in the normal range. Finding from head imaging such as computed tomography and magnetic resonance imaging is typically normal. However, finding from brain functional imaging is typically abnormal, with hypoperfusion of the left or right frontal and temporal lobes and the diencephalon [62].

Additional Disorders Associated with Hypersomnolence

In addition to the aforementioned disorders of hypersomnolence, it is important to recognize that hypersomnolence may occur with other conditions. Many psychiatric disorders may lead to hypersomnolence. Mood disorders such as bipolar II

disorder or atypical depression may typically present with EDS and often major depressive disorder should be ruled out before considering the aforementioned diagnoses [63–66]. In addition, conversion disorder or somatization should also be considered [67].

Several medical disorders have been associated with hypersomnolence. Conditions causing encephalopathy can lead to persistent daytime somnolence. Conditions such as metabolic disease, hepatic disease, and renal disease can lead to encephalopathy that leads to daytime sleepiness. In addition, hypothyroidism should be considered as a cause for daytime sleepiness. Infectious encephalitis also may lead to hypersomnolence. Brain tumors can lead to hypersomnolence and present like NT-2, as can disorders such as sarcoidosis. Certain congenital disorders also have symptoms of hypersomnolence including Niemann Pick type C disease, Prader-Willi, myotonic dystrophy, Smith-Magenis syndrome, Moebius syndrome, and fragile X syndrome [16].

Several medications can also lead to persistent daytime sleepiness, including several antipsychotic medications, analgesics including opiates, anticonvulsants including benzodiazepines, barbiturates, anticholinergics, and antihistamines [16]. Usage of recreational drugs such as alcohol, marijuana, and opiates can also lead to hypersomnolence [68–70]. It should also be noted that withdrawal of drugs, including psychostimulants, can lead to EDS [71, 72].

Finally, obstructive sleep apnea is commonly associated with EDS. While in many individuals treatment of sleep apnea may lead to improvement in symptoms, there are many who may have residual hypersomnolence despite adequately treating their obstructive sleep apnea [73, 74].

Management

For many conditions causing hypersomnolence, including NT-1, NT-2, IH, and KLS, there is no known cure. Subsequently, the goal of therapy is often guided to improve symptoms. Therapy then becomes primarily focused on restoring one's quality of life.

Before discussing medications, it is important to acknowledge that improving quality of life should involve many nonpharmacologic approaches. For example, modifications in school or work to allow for daytime napping should always be considered. Career counselling should also be considered in patients with hypersomnolence disorders. As symptoms can be debilitating, clinicians need to be aware of the repercussions of disease on both physical health and mental health. For example, as obesity is often comorbid, strategies to help lose weight or control weight are often indicated. As these conditions can impact mental health, ensuring that patients are monitored and connected to mental health, counselling, including that from psychiatrists, is paramount. Furthermore, connecting patients to patient support groups can be helpful.

In narcoleptic children, individualized educational plans (IEPs) should be initiated. Such accommodations should include scheduled naps for 20–30 minutes 2–3 times a day. In addition, extended examination time and makeup sessions for missed

days should be considered. Similarly, those with KLS and IH might be excused for missed days.

Finally, when clinicians are prescribing medications to treat these conditions, it is important to emphasize that these medications have several adverse effects, including possible impact on normal hepatorenal clearance that can provoke drug-drug interactions. Furthermore, several medications can lead to tolerance and addiction, or can be used illicitly and patients must be closely monitored.

Daytime Stimulants

Indications These medications are indicated for management of EDS in those with hypersomnia. In KLS, it is sometimes used episodically to decrease duration of EDS. However, in individuals with narcolepsy or those with IH, they are often used daily.

Methylphenidate and Amphetamines Amphetamines and other central nervous system (CNS) stimulants consist of some of the oldest CNS stimulants used to treat EDS including inpatients with narcolepsy. Examples include methylphenidate, dexmethylphenidate, mixed amphetamine salts, and dextroamphetamine. They are often considered second-line treatment for EDS in narcolepsy, although sometimes they are used first given their lower cost. These work principally by increasing the release of norepinephrine, dopamine and serotonin and inhibiting the uptake of amines by the dopamine transporter. These agents, in addition to decreasing EDS, can enhance performance of motor and cognitive tasks and mental and physical alertness, and improve strength and endurance [75]. This class of stimulants, however, can carry high abuse potential, development of tolerance, should be administered at the lowest therapeutic doses possible, and thus should be closely monitored. Classically these agents were taken more than once a day; however, newer preparations offer the option of a delayed or extended release pill that allows once-a-day dosing.

Modafinil and Armodafinil Modafinil is another class of daytime stimulant whose wake promoting actions are not well known. Modafinil is often considered a first-line therapy for EDS in narcoleptic patients [76]. It is thought to work through dopamine signaling with activation of wake-generating neurons in the hypothalamus [77–79]. In a study assessing efficacy of modafinil, more than 80% of individuals with EDS improved with a significant decrease in the epworth sleepiness scale from 16.5 to 12.4 [80]. Headaches, at 13%, and nervousness, at 8%, were the most significant side effects. Unlike the amphetamine class of stimulants, modafinil has a low potential for abuse and far fewer side effects. Recently, armodafinil (the R-enantiomer of modafinil) was approved [81] and used to treat EDS. Given its longer half-life compared to modafinil, it is attractive to some patients because of its once-a-day dosing schedule. Armodafinil has shown efficacy in up to 71% of individuals with narcolepsy compared to only 33% in controls [82].

Sodium Oxybate (Gamma Hydroxybutyrate)

Indication This medication is used only in patients with NT-1 as it is often indicated to treat both cataplexy and EDS.

Specifics The metabolite of sodium oxalate is gamma-hydroxybutyrate (GHB), a CNS neurotransmitter found in high concentrations in the hypothalamus. GHB is a sedative that acts to consolidate sleep [83]. In doing so, it not only stabilizes sleep, treats sleep fragmentation, and improves EDS but also reduces REM-associated intrusion phenomena such as cataplexy [84–87]. It is thought to stimulate gamma-aminobutyric acid (GABA) B receptors and is thought to modulate the actions of GABA, but also dopamine, serotonin, and endogenous opioids. Given its actions to normalize sleep architecture in narcoleptic patients, the medication is given at bedtime prior to sleep onset. Sodium oxybate does carry the risk of adverse events and does carry the risk of illicit usage. Prescription and dispensing of this medication are carefully controlled in patients with narcolepsy.

Other Medications to Treat Cataplexy

Selegiline In addition to sodium oxybate, selegiline, an irreversible monoamine oxidase-B inhibitor and atomoxetine, a specific noradrenergic reuptake inhibitor has used to treat EDS and cataplexy in patients with narcolepsy [88, 89].

Antidepressant Medications Several medications that aim to disrupt REM-induced atonia have also been used to treat the cataplexy associated with narcolepsy. These include tricyclic antidepressants [90, 91] with their inhibition of monoamines reuptake and inhibition of cholinergic, histamine, and alpha-adrenergic transmission. In addition, selective serotonin reuptake inhibitors (SSRIs) [92] and norepinephrine and serotonin uptake inhibitors (SNRIs) can also help to treat cataplexy, sleep paralysis, and hypnogogic hallucinations.

Medications for Treatment of Kleine–Levin Syndrome

While no specific medications are approved for treatment of KLS, a few medications have been suggested. In a systematic review, both stimulants and lithium were effective in 40 and 41% of individuals, respectively [56].

Conclusion

The presence of hypersomnolence as a presenting feature in psychiatric patients is not uncommon given that hypersomnolence may be a cardinal feature of several

specific psychiatric disorders or may be related to an adverse effect of the patient's prescribed medications. In addition, many recreational drugs, some legal and some illegal, may too result in hypersomnolence for the patient. Notwithstanding the high likelihood of encountering a patient with hypersomnolence, psychiatrists should be aware that hypersomnolence may also be a symptom of a medical or sleep disorder. Furthermore, several hypersomnolence sleep disorders (e.g., narcolepsy) may provoke a mood disorder or anxiety. Accordingly, it is suggested that the psychiatrist or other mental health clinician be familiar with these disorders, given the likelihood that many patients presenting with a psychiatric disorder may indeed be suffering from an undiagnosed sleep disorder.

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Circadian Rhythm Disorders and Chronotherapy for Mood Disorders

10

Sara Timtim and David K. Welsh

Background on Circadian Rhythms

Circadian rhythms are widely recognized as pervasive, but their adaptive function may not be immediately obvious. One thing circadian clocks can do is anticipate changes in the light-dark environment. For example, circadian clocks allow a plant to start preparing the enzymes and substrates for photosynthesis just prior to sunrise, allowing it to both maximize sunlight hours and save energy overnight. Circadian clocks also enable time-separation of opposing or incompatible processes in the body, for example, anabolism versus catabolism, rest versus activity, and storing sugars versus taking them out of storage. Separation in time allows conflicting processes to build up to physiologically meaningful levels at different times, rather than canceling each other out.

Oscillations in basic physiological functions including body temperature, heart rate, and hormones such as melatonin and cortisol have long been observed across many species. Gradually, we have begun to understand how clocks enable coordination of more complex cycles as well, including not only the sleep-wake cycle, but also fasting-feeding, general activity-rest, and (in humans) even alertness and mood [1].

Circadian (ca. 24 hr) rhythmic functions exist at a cellular level, in most cells of the body, if not all. Robust rhythmicity has been seen even in individual fibroblasts cultured in vitro, isolated for weeks from any central signaling. In order for the individual rhythms of these cells to align with neighboring cells in a coherent tissue, some kind of pacemaker signal is required. Sources of such signals are found both locally and centrally [2, 3]. The primary central circadian pacemaker in mammals is

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the suprachiasmatic nucleus (SCN), a region of the hypothalamus that responds to light input from the retina. It integrates signals from the retina and other sources and orchestrates other oscillators throughout the body. The specifics of how this signaling occurs are complicated, involving multiple redundant signaling mechanisms (see references). For our purposes, the key point is that inputs from the SCN synchronize local rhythms by modulating the rhythmic transcription of clock genes (the genetic basis for time-based functions), in cells throughout the body [4]. Hence, circadian oscillators synchronize both (a) a whole organism with external environmental conditions like day-night and changing seasons and (b) tissues and cells in the body among themselves.

Bright Light Is the Most Important Zeitgeber

An organism's circadian clock is entrained to the outside world by environmental cues, sometimes referred to as *zeitgebers*, literally "time keepers." Signaling responses to zeitgebers keep an organism's rhythm synchronized with the 24-hour day and with seasonal changes over a year. For humans, the most important zeitgeber by far is bright light (like sunlight). Several special physiological effects of bright light in mammals are mediated entirely through the eyes [5]. In animal studies, rodents lacking eyes never synchronize their circadian rhythms to a light/dark cycle. Similarly, many blind people suffer from a circadian sleep/wake disorder, failing to synchronize to the 24-hour day. Also, in sighted depressed patients, extraocular administration of bright light does not have an antidepressant effect [6].

Interestingly, however, there is a subset of totally blind patients who are able to maintain a normal circadian rhythm despite lack of a measurable retinal light response by electroretinogram. These patients suggested the existence of a special nonimage-forming system of photoreceptors, distinct from rods and cones, which enabled light detection for circadian signaling. Remarkably, mice genetically modified to lack rods and cones were found to still be able to detect light for purposes of synchronizing circadian rhythms, but lost this ability after removal of the eyes [7].

This mystery was solved with the discovery of intrinsically photosensitive retinal ganglion cells (ipRGCs) [8]. These ipRGCs constitute a small subset of all retinal ganglion cells (whose axons form the optic nerve and transmit light information from the eye to the brain). The ipRGCs not only receive input from rods and cones, as other retinal ganglion cells do, but also express a light-sensitive pigment called melanopsin, with peak sensitivity in the blue range (~480 nm), that allows them to detect light and facilitate circadian entrainment via efferent connections to the SCN [9].

Circadian Rhythm Disorders

Circadian rhythm disorders (CRDs) are a group of conditions that are characterized by dysregulation of circadian timing. They typically come to clinical

attention when patients complain of disrupted timing of sleep, and can be quite common in psychiatric patients. For instance, in a study of euthymic bipolar individuals, 32.4% had an associated CRD [10]. This contrasts with epidemiological studies suggesting a much lower prevalence in the general population [11, 12]. It is thus very important for mental health professionals to understand and evaluate any associated CRD.

Types of Circadian Rhythm Disorders

Circadian rhythm disorders are more common for certain age groups and work schedules. The main circadian rhythm disorders are phase advance (commonly seen in the geriatric population), phase delay (commonly seen in adolescents), irregular (characterized by fragmented sleep), and "free running" (usually occurring in people who are blind or otherwise isolated from bright light).

A. Advanced Sleep-Wake Phase Disorder (ASWPD) Sleep timing is several hours early compared to a conventional schedule, with evening sleep onset (18:00–21:00) and spontaneous early morning awakening (02:00–05:00). Melatonin and core temperature rhythms are typically early as well (though these are not routinely measured clinically). In the absence of social constraints, sleep duration is normal for age, but if patients try to delay sleep to a conventional time, they will still wake up early and be sleep-deprived.

Prevalence ASWPD is thought to be extremely rare except in the elderly, when defined strictly. In a study of 322 people diagnosed with a circadian rhythm disorder, only 1.2% were classified as ASWPD. However, the prevalence of advanced phase is likely far higher because patients tend not to complain about it; unlike delayed phase, which prevents people from getting to work on time, early schedules bring fewer negative social consequences.

ASWPD and Psychiatric Disorders The most important conditions to rule out are depression and bipolar disorder, which can commonly present with early-morning awakening.

B. Delayed Sleep-Wake Phase Disorder (DSWPD) Preferred sleep and wake times are delayed by several hours compared to conventional timing, but in the absence of social constraints sleep is otherwise normal in duration and quality. Patients often present with difficulty falling asleep and subsequent daytime sleepiness, with habitual bedtimes 02:00–06:00 or later. Perhaps 10% of patients who present with insomnia are ultimately found to have delayed sleep phase [13]. DSWPD is treated with melatonin and early-morning bright light exposure.

Prevalence This is the most common of the circadian rhythm disorders, particularly in adolescents, with prevalence as high as 7% of American teens [14]. In a survey-based study, 83.5% of individuals with CRD had DSWPD [15]. DSWPD does not result simply from volitional or social late bedtime preference. DSWPD has been related to polymorphisms in several circadian clock genes, (Clock, CKIε, Per3) [16], and twin studies have indicated a heritability approaching 50% for "morningness-eveningness" preference (of which DSWPD and ASWPD are pathologic extremes) [17]. Some DSWPD patients have decreased homeostatic sleep drive early in the night [18], and wake up even later than their delayed circadian clock phase would imply [19, 20], suggesting an abnormality in homeostatic rather than circadian sleep regulation. Some DSWPD patients also seem to be hypersensitive to the phase-delaying effects of evening light [21].

Comorbidity There is a strong comorbidity between delayed sleep phase and depression, both bipolar and unipolar. In a study of 90 individuals with DSWPD, 64% of them also had moderate-to-severe depression [22]. Similarly, in a case control study involving more than 300 individuals in each group, DSWPD had an odds ratio (OR) of 3.4 for seasonal affective disorder (SAD) compared to controls [23]. In another review, 10% of bipolar individuals had DSWPD, and were more likely to be younger, more obese, and prescribed more mood stabilizers and antidepressants [24]. DSWPD patients are also commonly found to have learning disorders and personality disorders [15, 25]. There is also some evidence of patients developing DSWPD after traumatic brain injury, which can also result in insomnia or irregular sleep-wake rhythm (ISWR) [26].

C. Non-24-Hour Sleep-Wake Rhythm Disorder (Free Running or Non-Entraining) Under constant conditions, humans' endogenous circadian rhythm typically free-runs with a period slightly longer than 24 hours, but normally it is continually realigned to the 24-hour day by corrective effects of daylight. When such adjustment does not occur, patients drift a little each day, such that their sleep-wake cycle moves in and out of phase with the environment every few weeks, making it difficult to maintain any stable schedule.

Prevalence Free running is relatively common in the blind, with prevalence ranging 18–55% [27, 28], but very rare in sighted people. Possible etiologies include decreased sensitivity or exposure to light, or an extremely long circadian period. One sighted individual with the disorder had decreased hypothalamic sensitivity to light (measured by melatonin suppression) [29].

Comorbidity Some free-running patients have schizoid personality disorder [30] or social phobia [29], which could reduce exposure to synchronizers. A bidirectional

relationship between free-running non-24-hour CRD and psychiatric conditions is suggested: in a study involving 57 individuals, 72% had no psychiatric conditions prior to development of free-running, but afterwards MDD developed in 34% of those with no previous diagnoses [31].

Free-Running and Medical Conditions A few sporadic cases have linked traumatic brain injury to the development of non-24-hour CRD [32].

D. Irregular Sleep-Wake Rhythm (ISWR) Sleep is very fragmented throughout the day, without any clear pattern, though total duration may be normal. In healthy individuals, sleep is consolidated through a homeostatic process of sleep drive increasing with accumulated time spent awake (as circadian drive for wakefulness declines) and decreasing with time spent asleep (as circadian drive for wakefulness increases), so defects in either circadian or homeostatic regulation could cause this disorder.

Prevalence ISWR occurs mostly in children with developmental disabilities and adults with dementia and other neurological disorders. These individuals often have degeneration of the central circadian clock or its output pathways, and are institutionalized. However, a form of ISWR can be induced to some extent even in normal patients, by placing them in an environment such as bedrest in a nursing home, where they receive minimal light or cognitive stimulation [33].

Comorbidity Sleep fragmentation is an early symptom of neurodegenerative disorders, including Alzheimer's disease [34]. Children with Angelman syndrome also tend to show an irregular sleep pattern, as well as decreased amplitude of melatonin cycling [35].

E. Shift Work: Shift work and jet lag are "extrinsic" disorders in the sense that endogenous regulation of the sleep-wake cycle is intact but out of sync with the external environment or societal demands. After an abrupt shift in the environmental light/dark cycle, the brain's central circadian clock in the suprachiasmatic nucleus (SCN) adjusts rapidly, but other brain regions [36] and peripheral tissues [37] may take many days to resynchronize fully. Individuals on atypical work schedules (outside of conventional working hours 8 AM–6 PM) can struggle with persistent insomnia and daytime sleepiness.

Prevalence At least 20% of the US workforce is employed in shift work, and of those, an estimated 5–10% develop a shift work sleep disorder [38].

Comorbidity Shift work sleep disorder is associated with psychological symptoms of depression (odds ratio = 2.57, 95% confidence interval [CI] = 2.01–3.27) and anxiety. In general, shift workers are more likely to experience numerous medical comorbidities, including obesity, cardiometabolic disorders, gastrointestinal (GI) distress, and some cancers [39]. Individuals who met criteria for shift work sleep disorder had higher rates of ulcers compared to shift workers who did not meet criteria [38].

F. Jet Lag Individuals traveling across time zones suffer similar sleep disruption, particularly when many time zones are crossed, and particularly when traveling west to east.

Prevalence Given the sporadic nature of air travel, the overall prevalence of jet lag is difficult to estimate systematically.

Comorbidity Mood is commonly disrupted by jetlag or working night shifts. Indeed, for vulnerable patients, particularly those with seasonal affective disorder (SAD) or bipolar disorder, travel across time zones or even irregular social schedules may precipitate clinically significant mood episodes. This effect is commonly attributed to simple sleep disruption, but is perhaps better conceptualized more broadly as a disruption of circadian rhythm, of which the sleep-wake cycle is only the most visible manifestation.

Chronotherapy

Chronotherapy—treatment targeting the circadian timing system—offers some practical methods for treating mood disorders. Its most widely known form is bright light therapy (BLT) for seasonal affective disorder. However, over the past decade, clinical evidence and its basic science foundation have both grown significantly in support of light therapy and other chronotherapeutic approaches for nonseasonal depression as well. For some applications, efficacy is comparable to that for standard medications, whereas side effect profiles are comparatively very mild. As an adjunct to medications, chronotherapy improves remission rates, and can hasten response by at least a week or more. As monotherapy, it offers an option for patients who refuse or cannot tolerate medications. Given these advantages, circadian techniques seem to be underutilized; they are typically mentioned only as brief asides in residency training, and there remains a sense of their being outside the mainstream of clinical practice. Perhaps this is due in part to aggressive competitive advertising for medications by pharmaceutical companies, and in part because the mechanisms plausibly linking circadian processes to mood are not widely discussed. The aim of this chapter is to address this gap for psychiatrists and provide an overview on how to use these techniques clinically.

A Direct Pathway for Light's Effects on Mood

It has long been questioned whether mood changes resulting from aberrant light schedules were mediated by sleep disturbance, by circadian phase shift, or by some other mechanism. In an experiment to investigate this, mice were exposed to an aberrant light cycle that induced depression-like behaviors, but had neither changed the amount and architecture of sleep nor caused changes in circadian timing. This result suggested that light impacts mood-related behaviors in mice at least partly through some pathway independent of sleep structure or circadian phase [40]. A recent follow-up study by the same group found that this appears to occur through a newly discovered direct pathway from ipRGCs to the perihabenular nucleus (PHb) in the thalamus, independent of the SCN, as highlighted in Fig. 10.1 [41].

However, this is probably not the only pathway by which light input to ipRGCs can affect mood. Direct, selective manipulations of the SCN circadian clock in mice can induce a depression-like state [42], and lighting manipulations (long vs. short days) can affect depression-like behavior through effects on neurotransmitter expression in the periventricular hypothalamus [43].

Light can also directly impact alertness, decreasing sleepiness and improving psychomotor vigilance performance [44, 45]. These findings on improved alertness have been borne out using functional neuroimaging, which showed that after light exposure, a large-scale occipito-parietal attention network, including the right intraparietal sulcus, was more active in proportion to the duration of light exposures preceding the scans [46].

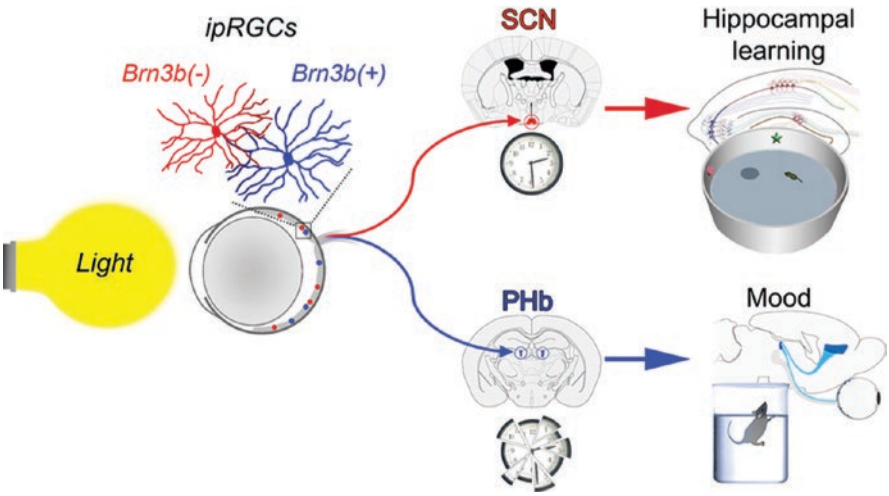

Fig. 10.1 A distinct ipRGC subpopulation independent of the SCN, through the ipRGC-PHb pathway, drives light-mediated mood alterations. These were demonstrated in mice with tests of mood-related behavior including forced swim test. (Used with permission from Fernandez et al. [41])

The Classic Two-Process Model of Sleep Regulation in Relation to Mood

Two overarching physiological processes are thought to influence sleep timing. One, "process S" (sleep propensity), is a homeostatic process resulting in a progressive build-up of propensity for sleep over the course of the day that resets during sleep. The other, "process C" (circadian pacemaker), refers to the rhythmic influence of the SCN, as entrained to the day-night cycle of the outside world by light input from the retina [47]. In human subjects, process S is tracked by electroencephalogram (EEG), using delta power (slow wave activity in the 1–4 Hz range), which is used as an indicator of sleep need, as it varies as a function of time spent awake, and rebounds rapidly during recovery sleep [48, 49]. Process C can be tracked by circadian rhythms of core body temperature or melatonin secretion.

Mood appears to track along with each of these processes over the course of a day. A milestone study on the connection between mood and circadian rhythms used a "forced desynchrony" protocol manipulating subjects' sleep and wake times to days longer/shorter than 24 hours, in which the effect of the two processes could be distinguished because subjects slept at all phases of their circadian cycle over the course of the experiment. Mood was found to change based on the duration of prior wakefulness (process S), but whether this change was improvement, decline, or neutral with increased awake-time depended on circadian phase (process C) [50].

In later studies, mood was worst of all when the minima of the two processes coincided. It is hypothesized that under healthy conditions, the two processes are synchronized, avoiding this extreme low, and keep mood relatively stable. They interact in a complex and nonadditive way that is not yet understood, other than that there seems to be some optimal alignment between these two cycles for affective stability [51].

What Is Circadian Time?

Each individual has an internal circadian cycle that can be tracked over the course of the day through objective physiological metrics. Normally, this internal rhythm is synchronized with environmental day-night, but in pathological states can be substantially phase-shifted or even entirely decoupled.

Even among healthy controls, natural circadian tendency to be early or late ("chronotype") varies widely—evening melatonin onset can vary between individuals by as much as 6 hours. Despite society's moral judgments of industrious morning larks versus dissolute night owls, chronotype is largely biologically determined, and at least partially genetic. It also tends to change fairly predictably with age: early timing in childhood that delays progressively throughout adolescence, until reaching maximum "lateness" around age 20, and then advancing again progressively with age. This

age-based pattern is so consistent that some have proposed the inflection point around age 20 as a marker of the end of adolescence [52].

Circadian phase is clinically important to guide optimal timing of interventions. Studies of "morning" light, for instance, are often based on a clock time, but when light exposure is instead timed according to personal circadian phase, response rates are substantially better [53, 54]. In a research setting, circadian time is most accurately determined by serial evening measurements of serum or salivary melatonin level. These are used to determine dim light melatonin onset (DLMO), which is when melatonin concentration begins to rise above baseline daytime levels under dim light conditions [55]. The measurement is done under dim light because bright light can directly suppress melatonin, masking the evening circadian upswing. DLMO is expected to occur 2–3 hours prior to sleep onset [56]. Alternatively, minimum core body temperature can also be used as a circadian phase marker, and is expected 1–3 hours before wake time in normal patients [57]. In an outpatient setting where these methods are impractical, self-report scales including the Horne-Ostberg Morningness-Eveningness Questionnaire or the Munich ChronoType Questionnaire offer an acceptable rough proxy that significantly correlate with DLMO [58, 59].

Using such methods, it is possible, for example, to quantify the phase-shifting effects of a light pulse (e.g., a 1-hour phase advance means that rhythmic physiologic events regulated by the SCN occurring at 11PM would subsequently occur at 10PM). The magnitude and direction of a phase-shift response depend upon the circadian time of light administration—broadly, morning light leads to phase advance, and evening light leads to phase delay.

Circadian Abnormalities Seen in Depression

Genetic associations have been found between individual clock gene polymorphisms and mood disorders in several targeted genotyping studies, with increased risk of bipolar disorder associated with polymorphisms in clock genes ARNTL and PER2 [60], and increased risk for SAD associated with polymorphisms in clock genes PER2, ARNTL, and NPAS2. Some physiologic circadian abnormalities, including sleep disruption, have also been observed in depressed patients. In patients with unipolar depression, more severe depressive symptoms have been associated with aberrant circadian phase [61]. Weak circadian cycling has been linked to increased susceptibility to mood disorders. In a large study ($n = 91{,}105$) tracking general physical activity using wearable accelerometers, low relative amplitude of these circadian rest-activity cycles was associated with increased lifetime risk of major depressive disorder and bipolar disorder, as well as with greater mood instability, neuroticism, and subjective loneliness [62]. And finally, standard treatments for mood disorders alleviate circadian rhythm abnormalities, suggesting a bidirectional relationship between disturbances in mood and in circadian rhythms [63].

Interpersonal and Social Rhythm Therapy (IPSRT)

Based on early evidence for circadian disruption in bipolar disorder, Frank et al. pioneered a type of behavior therapy aiming to regularize the daily social, sleep, and meal schedules of patients [64]. Interpersonal and Social Rhythm Therapy (IPSRT) has been shown to be an effective treatment for bipolar disorder.

Light Therapy for Nonseasonal Unipolar Depression

Light therapy has been shown to be therapeutic for nonseasonal depression, both as monotherapy and as an adjunct to standard medications. A 2005 American Psychiatric Association (APA) meta-analysis found bright light therapy for seasonal and nonseasonal depression to be efficacious with moderate effect sizes (overall 0.53) equivalent to those in antidepressant trials [65]. More recent studies show adjunctive efficacy as well [66]: light therapy may reduce the latency to antidepressant medication response from the usual 2–4+ weeks to less than a week [67].

In one recent study comparing light, fluoxetine, and the combination of the two [66], light plus fluoxetine had the most consistent effect, with number-needed-to-treat of 3.5. Remission was defined as Montgomery-Asberg Depression Scale (MADRS) score less than or equal to 10 at the 8-week end point, which constitutes the low end of "mild depression." Remission was achieved in about 60% of patients with the combination of light and fluoxetine (20 mg daily), and 40% of patients with light monotherapy, both significantly differing from placebo (30%) and fluoxetine alone (20%). To discriminate the mood effect of bright light from mere sleep improvement/regulation, there was an initial screening week during which patients were instructed to regulate their sleep schedules as much as possible (sleeping only from 2200 to 0800), during which any spontaneous responders were screened out. Light therapy may hence provide a viable alternative for patients who refuse or cannot tolerate medications [66]. Light therapy has been shown to benefit even patients with chronic depression of 2 years or more. In these treatment resistant cases, the advantage of light therapy over placebo was even stronger [68].

Further research is needed. Most studies have been small, and as a whole they are heterogenous enough to make formal meta-analysis difficult. Nevertheless, results have been promising, and several national-level health organizations (including both APA and NIMH) have issued statements advocating the use of light therapy for nonseasonal depression [69, 70].

Light Therapy for Seasonal Affective Disorder

Light therapy is an accepted first-line treatment for SAD. A direct comparison between bright light therapy (BLT) and cognitive behavioral therapy (CBT; 90 min, 2×/week, × 6 weeks), with no placebo group, found the two therapies similarly effective, with remission rates around 50% after 6 weeks [71].

A typical course of light therapy for seasonal affective disorder lasts 1–2 weeks, though 1 week is generally as effective as 2 weeks [72]. Efficacy may be best when treatment is started early. An episode of SAD usually takes 2–6 weeks to reach maximum severity. In a study of patients with a known history of SAD, if treatment was started early at the first sign of symptoms (though not before symptoms actually began), as little as 5 days of bright light treatment was enough to prevent full-blown relapse for the rest of the winter [73].

Seasonal changes of photoperiod or night shift work can induce SAD [74], and it is hypothesized that BLT works in SAD by correcting aberrant internal circadian rhythm phase relationships. The antidepressant effect of light in SAD is potentiated by administration in the early morning (based on circadian time); midday or evening light is less effective for most people. Overall remission rate in major studies was about 55% from morning light, vs. 30% with evening light, vs. 15% for placebo. In the overall population, morning light produced a superior response, with no advantage to adding on evening light. However, there was a small subset of patients that appeared to benefit preferentially from evening light instead. Given that morning light therapy administration tends to produce phase advance, whereas evening light induces phase delays, it has been proposed that some SAD patients could be phase-advanced at baseline and hence benefit more from evening light [54, 75, 76]. Indeed, in one study [77], the closer patients came to a theoretical ideal phase angle after light therapy, the greater the antidepressant effect. However, correcting a circadian phase advance/delay may not account for the entire antidepressant effect, given that nearly half of the depressed patients in this study had started out close to ideal phase to begin with (within 30 minutes).

Typical Outpatient Light Therapy Protocols

A typical protocol for light therapy is 10,000 lux of white light "as soon as possible after waking," for 30 minutes [78]. Light therapy is optimized along four parameters: intensity, spectrum, timing, and duration. Parameters originally established for SAD were used in nonseasonal depression trials and found to be efficacious. Given this baseline efficacy, dosing formally optimized for nonseasonal depression in particular has not yet been established.

Intensity

General clinical recommendations are to use 10,000 lux light (daylight intensity). Over a wide range of intensities, brighter light is more efficacious both for mood effect and circadian phase shift. In general, dimmer lights can also work when used for longer periods of time. The response to bright light therapy using a 2500 lux white light for 2 hours/day was equivalent to using 10,000 lux for 30 minutes/day, and both treatments were efficacious [79]. Hence, at the risk of over-simplifying, some suggest a minimum efficacious dose as 5000 lux-hours daily [80].

The patient must be positioned at the distance from the box specified by manufacturer. Sitting appropriately close to the light box device is important for full effect because light intensity falls off rapidly with distance (inversely proportional to the square of distance). Patients do not have to and should not stare directly into the light.

Spectrum

The general practice is to use full-spectrum white light. The discovery of retinal cells containing the photopigment melanopsin, with peak sensitivity in the blue range, was certainly exciting, and has generated considerable media buzz that blue may be the critical color component for mood applications. However, melanopsin is not exclusively sensitive to blue light, and ipRGCs receive input from the classical image-forming rod and cone photoreceptors. Accordingly, trials comparing blue light to white light in SAD have not generally found a clear difference in efficacy [81]. One study compared blue light to "blue-free" light in the orange range, and detected no difference in SAD efficacy after 6 weeks. In another study, blue-enriched light was efficacious for SAD at a dimmer level than white light. Thus, white light of sufficient intensity is generally thought to be efficacious without any particular blue enrichment.

Timing and Duration

The typical protocol used in research studies is 30 minutes of light box exposure, as soon as possible after awakening, ideally 7–8 AM [66]. Duration of light therapy of 2–5 weeks as monotherapy was efficacious for nonseasonal depression in a recent meta-analysis [82]. For seasonal affective disorder, a typical course is 1–2 weeks, though 1 week was as effective as 2 weeks in a recent study [72]. Some suggest simply continuing to use the light box until spring when symptoms would remit naturally. There may be some advantage in using light as a preventive strategy as well [83]. See Tables 10.1 and 10.2 for recommendations.

Table 10.1 BLT guidelines adapted from Pail 2011

Spectrum	"Full spectrum visible light"
Intensity	5000–10,000 lux (at the patient's eyes)
Duration per session (starting dose)	*30 min at 10K lux;* 2 h. at 2500 lux; 5000 lux-hours
Distance from light source	60–80 cm. Staring into the light is not necessary
Time of day	As early as possible after awakening
Duration of daily treatment	2–5 weeks

Table 10.2 Expected outcomes in nonseasonal depression

Onset of therapeutic effect	3–7 days
Maintenance of therapeutic effect	Unknown

A typical protocol for escalating light box therapy intensity is to start with 30 minutes of morning light per session daily, and if response is insufficient after 1–2 weeks, to add on 15 minutes per session at a time at 1–2-week intervals up to a maximum of an hour each morning. At that point, adding evening light may be attempted, to account for the small subset of patients for whom this is more effective than morning light.

Natural Substitute for Light Box in Nonseasonal Depression

In favorable climates, patients can also substitute walking outdoors without sunglasses for an hour in the morning, as early as possible after waking [84]. Natural sunlight typically greatly exceeds normal indoor lighting, by one or two orders of magnitude (lighting in a typical office is ~500 lux). Insolation from full daylight (not in direct sun) ranges from 10,000 to 25,000 lux, and direct sunlight can be as bright as ~100,000 lux. However, this does not work as well on cloudy or rainy days; dawn on a dark overcast day can be as dim as 100 lux.

Special Populations: Geriatric Patients

Two 2018 meta-analyses focused on nonseasonal depression in older patients of ages ~65–80 years both concluded that using light therapy was effective. One calculated a moderate effect size of 0.422 for a pooled sample of 395 patients [85, 86]. Adverse effects did not differ from placebo. Patients with any history of mania or relevant retinal disease were excluded from the study [87].

Special Populations: Postpartum/Antepartum

Light therapy is an attractive treatment option for depression during pregnancy, due to lack of medication interactions or known risks to the fetus. A recent randomized controlled trial (RCT) of 27 pregnant women did show superiority of 7000 lux white light for 1 hour each morning upon waking for 5 weeks, compared to dim red light placebo. Remission rate was 68.6% (n = 16) vs. 36.4% for placebo (n = 11) [88]. However, at a meta-analysis level, data remain inconclusive on using BLT for peripartum depression [82].

Melatonin Therapy for Insomnia

Melatonin is a hormone that produces circadian phase advances when given in late afternoon or early evening. Melatonin is widely used to treat insomnia in depressed patients, but it is important to emphasize that it can be used in two distinct ways: for circadian phase shift (chronotherapy) and as a direct sedative. To induce a circadian phase advance (facilitating sleep onset at an earlier hour), the melatonin is administered 6 hours in advance of bedtime, at physiologic doses, which are quite small. A

dose of 0.3–0.6 mg facilitated more robust phase shifting than the much larger doses typical of drugstore preparations, on the order of 3–10 mg, because it provides a more discrete time signal, confining the phase-shifting effect to just the right time to produce an advance, and avoiding carryover effects to morning hours, when melatonin can produce delays. However, it is currently more common to use melatonin at relatively high doses at bedtime, for its direct sedative effect. Sometimes high doses can cause sleepiness about 30 minutes after administration, but this typically works in only about 1/3 of patients [89].

Blind patients experience circadian desynchrony in cases where the SCN does not receive light input. In these patients, daily exogenous melatonin (or melatonin agonist) administration has been used successfully as a substitute zeitgeber, though the details of optimal dose and timing are not well-established [90]. Small studies suggest that tiny physiologic doses (up to 300 μg of melatonin) may be enough to successfully entrain blind individuals, who would otherwise have experienced free-running circadian rhythms and drifted later and later each day [91].

Melatonin has not been shown to treat mood disorders, but it is worth mentioning that agomelatine, a melatonin agonist, is an approved antidepressant in Europe [83].

Dawn Simulation for SAD

An alternative to standard bright light, called "dawn simulation," is under study for milder cases of SAD. In dawn simulation, a dim light (gradually increasing to a maximum of ~300 lux) is used during the last 30–60 minutes of sleep before the patient's alarm goes off (through eyelids, which are somewhat translucent), and then for perhaps 15 minutes more after opening eyes. This kind of protocol has a much smaller evidence base, mostly from a single research center, but what evidence there is suggests it might be comparable to bright light for mild to moderate symptoms (but inferior for severe symptoms). This naturalistic light protocol may have better patient compliance since it saves some time, and the dimmer light may be more comfortable [92].

Light Therapy for Bipolar Depression

Naturalistic observations of light exposure hint at a role for BLT in bipolar depression. In a study of 187 patients hospitalized for bipolar depression, those in rooms with east-facing windows (which exposed them to early-morning bright light) had an average length of stay almost 4 days shorter than those with west-facing windows [93]. A few RCTs have been performed in the past few years, building evidence that light therapy is efficacious as an adjunct to standard medications for the depressive phase of bipolar disorder, and that hypomania/mania history is not a contraindication [68]. A 2017 trial examined light therapy adjunctive to standard medications in depressed bipolar patients. In this study, among 63 individuals, with 33 patients undergoing BLT, and response rate was 78.2% vs. 43.3% for control

($p < 0.01$). Patients were exposed to bright light for 1 hour daily between 6:30 AM and 9 AM, 100 cm away from a 5000 lux BLT device vs. a control of 100 lux dim red light [94].

A second RCT in 2018, using 7000 lux (vs. 50 lux dim red control), $n = 23$ for each group, also found a significantly higher remission rate (68.2% vs. 22.2%; adjusted odds ratio = 12.6) at weeks 4–6 and significantly lower depression scores [95].

Dark Therapy for Bipolar Mania

Dark therapy for mania/hypomania is still in the exploratory stage. There is a small base of evidence that mania remission might be significantly hastened using controlled periods of darkness, with the patient strictly cut off from all artificial light overnight. One study in hospitalized manic patients used a protocol of 14 hours of dark therapy for three consecutive nights, added on to pharmacological therapy as usual [96]. Patients were stable for discharge an average of 9 days earlier than in the control group, at least when treatment was initiated early in a manic episode (within the first 2 weeks). This was a small study ($n = 16$ with 16 matched controls) that could not be double-blinded, but with remission so much faster than with standard therapy, initial results were intriguing. In a case study, darkness also stabilized depressive episodes in rapid cyclers [97].

While these experiments were promising, staying in total darkness for 14 hours/night can be uncomfortable for anyone, let alone for a manic patient. So, in recent years, some have experimented with a less-restrictive strategy of using amber-colored glasses in the evening (to preferentially block circadian-sensitive blue light), and had similar results. While studies have been too small so far to draw conclusions, early results have been intriguing, with marked improvement in sleep regularity and overall mania symptoms. One randomized controlled trial that involved manic patients on standard pharmacological therapy wearing blue-blocking goggles from 6 PM to 8 AM for 7 days reduced severity scores on the Young Mania Rating Scale with the substantial effect size of 1.86. Based on power analysis, the study is too small ($n = 12$ treatment, 11 controls) to claim a significant difference, but these initial results were promising [98].

Wake Therapy for Depression

For decades, it has been observed that severe depression can improve rapidly, albeit temporarily, after one night spent awake. Sleep deprivation, or (marketed more appealingly) "wake therapy," has been used to treat thousands of depressed patients in more than 60 studies, and consistently produces rapid (within 24–48 hours) reversal of depressive symptoms in approximately 40–60% of depressed patients [99, 100]. The caveat is that this effect lasts only until the next night's sleep. There is evidence that combining it with light therapy can maintain the effect for up to a week, suggesting potential use as a bridging intervention until medications can take

effect [101]. The exact mechanism is unknown, but some circadian component is suggested by the finding that only sleep deprivation in the second half of the night alleviates depression, whereas sleep deprivation in the first half of the night is depressogenic. While wake therapy is not widely used in the USA, it is more common in Europe, and bears mention in support of the theoretical basis of using circadian interventions for mood disorders.

Combination Therapies

In one study exploring a combinatorial approach, good results were obtained by augmenting antidepressant medication with several chronotherapeutic strategies (sleep deprivation, bright light, and sleep phase advance). Another chronotherapeutic intervention combining bright light, wake therapy, and sleep time stabilization in patients taking duloxetine had positive results after 9 weeks, outperforming a standard cardiovascular exercise program with established mood benefit [102].

Limitations and Conclusions

Potential Adverse Effects from Light Box Use

A safety study of light therapy reported potential adverse effects from full-spectrum fluorescent light boxes including "nervousness," nausea, vomiting, dizziness, and headache [103, 104]. An observational study reported adverse effects of headache, eyestrain, and feeling "wired" [105]. More recently, fluorescent lights are being superseded by light-emitting diodes (LEDs), which produce a more stable intensity and wavelength of illumination (including reduced flickering) and hence may have fewer adverse effects [106]. Any light box setup must have ultraviolet (UV) shielding to prevent potential retinal damage. In a direct comparison with fluoxetine monotherapy, combination fluoxetine + BLT actually had fewer treatment-emergent adverse effects [66]. In general, the side effect profile of BLT is highly favorable compared with antidepressant medications.

In patients with bipolar disorder, light therapy, like other antidepressants, carries some concern for inducing switch to mania. However, this appears to be very rare, and the concern is based on case reports. Two recent dedicated studies in bipolar patients, with a total of 56 depressed patients with known mania history undergoing BLT for a 2- or 6-week course, reported no switches to mania/hypomania [94, 107].

Intrinsic Challenges in BLT Research

Randomized controlled trials of chronotherapeutic interventions can be difficult to conduct because they are intrinsically difficult to blind. For BLT, selecting a placebo can be difficult given widespread public knowledge that bright as opposed to dim

light is expected to improve mood, particularly white or blue-colored light. Furthermore, no threshold intensity, that is, the level of light dim enough to have no effect, has been established. A solution used in some studies was a sham negative ion generator as placebo, because of public perception stemming from advertising and other venues that negative ions may have a salutary effect on mood. Studies that include a priori expectation ratings showing that patients had no bias against the placebo condition are therefore more persuasive.

Advantages of Chronotherapy over Pharmacotherapy

Medications currently dominate the treatment of mood disorders, but established medications have substantial limitations. Except for the newly introduced ketamine and esketamine [83], lag time to therapeutic effect is long. A depressed patient may have to endure several medication trials, each lasting several months, before finding one that is effective (if an effective one is found at all). There is an impetus to find solutions that bridge that time gap and offer other options. Bright light therapy is an effective alternative treatment for nonseasonal depression that is similarly effective to standard medications, and better-tolerated. Chronotherapeutics (including Interpersonal Social Rhythm Therapy, bright light, wake therapy, and dark therapy) are also affordable. Indeed, the fact that they are somewhat difficult to monetize may contribute to their being underutilized, as they lack any particular commercial champion for expanded research or advertising. As the evidence base continues to build, chronotherapeutic interventions are increasingly attractive options in a comprehensive treatment plan for mood disorders.

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Movement Disorders of Sleep

11

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Introduction

Sleep is a complex biological process that involves cyclic changes of brain activity and is a very sensitive biomarker of brain functioning. Sleep is also important for overall physical and mental health and a sense of well-being. Several psychiatric disorders can lead to sleep disturbance and are associated with various sleep-related disorders. Conversely, sleep disorders can lead to a variety of behavioral and psychiatric symptoms. Disrupted sleep has long been linked to mental health issues. A specific subset of sleep disorders characterized by abnormal movements related to sleep can be precipitated by psychiatric disorders and medications commonly used to treat psychiatric symptoms. Mental health problems may also lead to significant sleep disruption and therefore can augment psychiatric symptoms. It is very important for mental health specialists to be familiar with the diagnosis and management of these conditions, which will be our primary focus in this chapter. We will review six different movement disorders associated with sleep, including clinical presentation, relationship to a variety of psychiatric conditions, and current treatment options.

Restless Leg Syndrome (RLS) and Periodic Limb Movement Disorder (PLMD)

RLS is a common subjective sensorimotor condition, occurring while sedentary at night, characterized by predominantly nocturnal dysesthesias (an unpleasant sense of touch often perceived as pain) and relieved by limb movement. It was initially

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described in the mid-twentieth century [1]. In contrast, periodic limb movement disorder (PLMD) is an objective disease diagnosed with polysomnography (PSG) that can lead to frequent arousals at night. Both disorders are frequently comorbid.

Definitions and Diagnostic Criteria RLS is a sensorimotor disorder characterized by an irresistible urge to move the limbs, predominantly in the evening or at night. This is usually accompanied by a peculiar discomfort in the lower extremities often alluded to as a "creepy" or "crawly" feeling. RLS can result in sleep disturbance including insomnia and daytime fatigue. The four cardinal diagnostic features of RLS include: An uncontrollable urge to move the legs that is usually associated with paresthesias or dysesthesias; with symptoms that start or become worse with rest; at least partial relief of symptoms occurs with physical activity; and worsening of symptoms in the evening or at night [2].

PLMD is characterized by periodic episodes of repetitive limb movements during sleep, which most often occur in the lower extremities, including the toes, ankles, knees, and hips, and occasionally in the upper extremities. These movements may be associated with an arousal and, if so, the resultant sleep disruption can cause excessive daytime sleepiness (EDS). PLM-associated microarousals last between 3 and 10 seconds. Standard criterion for diagnosing PLMD has been established at ≥5 leg movements per hour during sleep; however, others have used 15 as the cutoff [2, 3]. Unlike RLS, PLMD is not usually associated with motor abnormalities or complaints during the waking state and is thus only diagnosed by PSG, with occasional complaints from bed partners.

PLMs may or may not be associated with restless legs syndrome (RLS), although most patients with RLS also have periodic limb movements (PLMs) [4]. Earlier, there was significant controversy in the medical literature about PLMD as a separate entity, particularly since initial diagnostic criteria did not include clinical symptoms as a necessary part of the definition, but only the presence of PLMs ≥5 per hour. In addition, there is no differentiation of PLMs due to sleep apnea, medication effect, or in association with some other disorder (e.g., narcolepsy or REM sleep behavior disorder) from PLMs without another specific cause, found as incidental finding in PSGs 5% to 6% in younger adults, and 25% to 58% among elderly people [5].

Prevalence The prevalence of RLS by community survey studies is estimated to vary between 1% and 29% [6–10]. RLS prevalence increases with age, in pregnancy, and among those with kidney failure. The prevalence of PLMD from small population-based studies is estimated to range from 4% to 11% in adults and up to 34% in older people [11–14]. Such repetitive leg movements are often associated with excessive sleep fragmentation, sleep disruption, and impaired daytime functioning [15].

Overlap Between RLS and PLMD Restless legs syndrome (RLS) and periodic limb movement disorder (PLMD) are distinguishable but overlapping disorders.

Both conditions are characterized by nocturnal involuntary limb movements (periodic limb movements or PLMs), but each has distinct clinical features. PLMD requires the presence of periodic limb movements in sleep (PLMS) on polysomnography as well as an associated sleep complaint whereas the diagnosis of RLS is made by meeting established clinical criteria. Approximately 80% of patients with RLS exhibit PLMs during sleep, and the presence of PLMs supports the diagnosis of RLS [16].

RLS, PLMD, and Other Sleep Disorders

RLS, PLMD, and Parasomnias A third of children with PMLD have a history of frequent parasomnias, which include sleepwalking, sleep terrors, and nightmares [17].

RLS, PLMS, and Obstructive Sleep Apnea (OSA) The association between RLS and OSA has been proposed by several authors [18–21]. Moro et al. found that 30% of patients who did not endorse any OSA symptoms, but did endorse insomnia or restless legs symptoms, were found to have OSA in PSG [18]. Passi et al., in a prospective study, found the prevalence of clinically significant restless legs syndrome (RLS) to be 8.3% in 60 sequentially polysomnographically studied patients with clinically significant OSA [19]. Patients with RLS who have comorbid OSA also are at increased risk of reporting insomnia, daytime sleepiness, nocturnal sweating, snoring, and gastroesophageal reflux. In a retrospective study of patients with OSA and RLS, the treatment of OSA significantly improved RLS symptoms in 71.4% of the patients [22]. In patients with clinically significant RLS, treatment of concomitant OSA significantly improved RLS symptoms, enabling drug therapy reduction in more than half of the patients.

RLS, PLMS, and Narcolepsy RLS and/or PLMS have also been found in association with narcolepsy, rapid eye movement behavior disorder (RBD) and insomnia [23–26]. In a study by Plazzi et al., narcolepsy patients had a significantly higher prevalence of RLS (14.7%) compared with normal controls (3.0%) [27]. The directional nature of this relationship is not clear. Modification in dopaminergic pathways has been implicated in both conditions [28, 29]. RLS must be considered in the evaluation and management of nocturnal sleep disruption in patients with narcolepsy given its high prevalence among those presenting with narcolepsy symptoms.

RLS, PLMD, and Psychiatric Disorders Difficulty falling asleep or maintaining sleep, poor sleep quality, nightmares, and EDS symptoms often seen in RLS are some of the key clinical symptoms of sleep disturbances observed in people with major depression, generalized anxiety disorder (GAD), bipolar disorder, and

posttraumatic stress disorder (PTSD) [30–34]. The symptoms of RLS are associated with reductions in patients' quality of life (QoL) and mental health. Research has established a relationship between the symptoms of RLS and mood symptoms, but causality is unclear. Sometimes symptoms of RLS precede those of depression or anxiety, and others relate the severity of mood symptoms to the severity of RLS symptoms [35].

A – Major Depression and Other Depressive Syndromes A two- to fourfold risk of depressive disorder in patients with RLS compared with healthy controls was reported in epidemiological studies [36]. Lee et al. in a large study demonstrated the interrelation between RLS, PLMD, and depression and found that compared with nondepressed people, depressed patients had a higher prevalence of RLS and PLMD [37]. Similarly, Chao et al. also found depressive symptoms to be more prevalent in the RLS group than in the non-RLS group [38]. They demonstrated that difficulty falling asleep, interrupted sleep, early morning awakening, and EDS were significantly more frequent among individuals with severe depression in the RLS group. Interestingly, red blood cell count was significantly lower in individuals with both severe depression and RLS [38]. The reason for these findings was not however clear to the authors questioning its clinical significance.

B – Anxiety Disorders Winkelmann et al., studying 130 patients with RLS, found a markedly greater prevalence of anxiety disorders among patients with RLS relative to a community comparison group RLS patients revealed an increased risk of having 12-month anxiety and depressive disorders with particularly strong associations with panic disorder (OR = 4.7; 95% CI = 2.1–10.1), generalized anxiety disorder (OR = 3.5; 95% CI = 1.7–7.1), and major depression (OR = 2.6; 95% CI = 1.5–4.4) [39]. Importantly, medications commonly used to treat anxiety disorders may play a role in precipitating RLS.

C – Schizophrenia Kang et al. studied 182 hospitalized people with schizophrenia for presence of RLS. The study was controlled with "normal" (free of psychiatric symptoms or psychiatric medications use) subjects recruited from a local community. They observed that 39 patients (21.4%) were found to have RLS and 87 patients (47.8%) met at least one of the RLS diagnostic criteria. The prevalence of RLS was significantly higher in the schizophrenia group than in the control group ($p = 0.009$), as were the RLS scores ($p < 0.001$) [40]. The presence of RLS predicted more severe psychotic symptoms. The cumulative dose of antipsychotic medication was not associated with the presence of RLS, suggesting that dosing is not the primary factor responsible for inducing RLS [40].

D – Other Psychiatric Disorders The prevalence of RLS in functional (psychogenic) movement disorders (FMD) is unknown. Serranovà et al. found FMD to be

associated with a twofold higher prevalence of RLS compared with those in the general population, consistent with prior research [41, 42]. Interestingly only 21% of patients with FMD had both RLS and clinically relevant PLM detected by actigraphy, suggesting false-positive cases either due to suggestibility or due to functional symptoms mimicking RLS [41]. Organic neurological and/or somatic comorbidities, medication use, and gender did not appear to affect RLS expression in patients with FMD, and FMD duration was not a risk factor for RLS development [41].

Psychotropic Medications and RLS Medications commonly used to treat psychiatric disorders have been found to either exacerbate or alleviate RLS symptoms. Selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) are frequently used as first-line agents in the treatment of depression and anxiety disorders and have been associated with an increased incidence of RLS [43, 44]. Second-generation antipsychotics and antihistamines are strongly associated with RLS [39]. In contrast Bupropion, a unique dopamine-norepinephrine reuptake inhibitor with efficacy to treat major depression, does not seem to worsen RLS and may actually be beneficial [45]. Similarly, mirtazapine, which is an atypical antidepressant medication, has been shown not to exacerbate RLS.

RLS, PLMD, and Systemic Diseases

A – Kidney Disease RLS and PLMD have been found to be associated with a variety of systemic diseases. Rijsman et al. found RLS and PLMD in 58.3% and 70.8% of the patients with uremia undergoing dialysis [46]. Nearly all RLS patients had severe PLMD, and the combination was associated with poor sleep quality, insomnia complaints, depression, and emotional distress. Sleep fragmentation and sleep deprivation caused by RLS may contribute to the cardiovascular complications and infections, factors that add significant morbidity and mortality in dialysis patients [47]. Castillo-Torres et al. found a much lower incidence of RLS in Mexican dialysis patients (18%) but a strong association of RLS with iron deficiency anemia and uremic pruritus [48]. Wali et al. also found a lower prevalence of RLS in Saudi patients (19.4%) but demonstrated that most patients had moderate to severe RLS disease and a significant association with OSA and EDS [49]. Lee et al. reported greater prevalence of RLS among patients with non-dialysis-dependent chronic kidney disease (CKD), suggesting that end stage renal disease and not the dialysis procedure itself may be the culprit for RLS [50].

B – Cardiovascular Disease (CVD) Sleep is an important modulator of cardiovascular functioning that contributes to morbidity and mortality and has been linked to prevalent types of CVD, including hypertension, coronary artery disease, atherosclerosis, myocardial infarctions, coronary artery bypass surgery, congestive heart

failure, and stroke [51]. Autonomic arousals, characterized by heart rate variability, produce changes in the sympathetic and parasympathetic activity and contribute to the development of CVD [51]. A prospective study in the United Kingdom found an association between RLS and incidence of stroke, but not between RLS and ischemic heart disease [52]. Li et al. identified a significant association between long-term RLS and coronary disease showing that women with RLS lasting more than 3 years were at increased risk of coronary heart disease, independent of the main risk factors for coronary disease [53].

C – Pain Disorder RLS, pain, and sleep disorders are highly interrelated. Several studies have reported a high (31–64%) prevalence of comorbid RLS in patients with fibromyalgia [54]. The prevalence of RLS increased progressively with pain severity, and even more sharply with the degree of pain spreading with higher prevalence in multisite pain [55]. In fact, clinical management of RLS in patients with multisite pain may significantly improve sleep quality as an independent risk factor [56]. It has been suggested that the immune system plays a role in RLS development. Support for this hypothesis comes from the finding that RLS has been found in two-thirds of patient with psoriatic arthritis (PSA), which occurs when one's immune system attacks healthy cells and tissue, causing inflammation in joints and an overproduction of skin cells [57].

RLS, PLMD, and Neurological Diseases

A – Parkinson's Disease (PD) RLS and PD are conditions known for impaired dopaminergic transmission in the central nervous system and often co-occur. Silva et al. found that patients with PD and RLS have a higher prevalence of dyslipidemia than patients without RLS, suggesting a correlation between restless legs and hyperlipidemia, and leading to increased risk of cardiovascular risk in the patient population [58, 59]. According to a study by Fereshtehnejad et al., PD patients with RLS suffer from more anxiety, worse nutritional status, and worse quality of life than those without RLS [60]. Rana et al. also found an association of psychiatric problems and RLS in PD patients as they found the presence of RLS in PD patients to increase the occurrence of both anxiety and depression [61].

B – Headaches A meta-analysis of 11 case-control studies indicates a 2.65-fold higher RLS prevalence in individuals with migraine than in controls [62]. How RLS might be associated with migraine is unclear but both conditions are thought to involve the A11 dopaminergic nucleus of the dorsal-posterior hypothalamus [63, 64]. A11 nucleus is located in the periventricular, posterior region of the hypothalamus. Hypothalamic A11 nucleus receives innervation from midbrain and brainstem nuclei involved in pain modulation, particularly in the affective and emotional aspects of pain and the behavioral responses to aversive or threatening stimuli [65].

Furthermore, hypothalamic A11 nucleus is the major source of dopamine in spinal cord and is thought to have an important role in pathophysiological pathways in RLS [63]. Treatment of patients with concomitant RLS and migraine with immediate-release pramipexole has been found to improve both headache frequency and RLS symptoms [66]. The prevalence of RLS is also higher among individuals with tension headaches [67].

RLS and PLMD in Children

RLS, PMLS, Attention Deficit Hyperactivity Disorder (ADHD), and Other Psychiatric Disorders As in adults, RLS may lead to significant morbidity in children and adolescents because of the associated sleep disturbance that impacts attention, working memory and other higher-level cognitive functions, academic achievement, mood, behavior, quality of life, and family well-being [68]. Recent literature has documented the occurrence of RLS in children and adolescents, with a large population-based study finding a prevalence of 1.9% for ages 8–11 years and 2.0% for ages 12–17 years [17]. A survey of age of onset among 107 adult patients with RLS indicated that 19.6% reported an age of onset between 0 and 10 years, while 24.3% had an age of onset between 11 and 20 years [69]. Other studies have found that 38–45% of adult RLS subjects have onset of symptoms before age 20 years [69–71].

A significant association between ADHD symptoms and RLS symptoms has being reported [68, 72]. The first study on the comorbidity between ADHD and RLS, conducted with 69 children with ADHD by Picchietti et al. in 1998, showed that 11.5% of the patients with ADHD had RLS according to the pediatric version of the diagnostic criteria for RLS [71]. A study of Konofal et al. for 43 children with ADHD reported that 44% of the study subjects met RLS diagnostic criteria [73]. Kwon et al. assessed the rates of RLS in a sample of 56 Korean children with ADHD. About 42.9% of the participants presented with RLS symptoms, and 7.1% of these were diagnosed with probable or definite RLS [74].

The relationship between iron deficiency (iron is a cofactor for tyrosine hydroxylase, the rate-limiting enzyme for dopamine synthesis) and the hypodopaminergic theories for RLS is interesting, taking in consideration patients with ADHD. Children with ADHD are more likely to have iron deficiency and treatment with supplemental iron has been reported to improve sleep quality and subsequently decrease ADHD symptoms. Dopaminergic agents have been suggested as an option for both ADHD and RLS symptoms in children with ADHD not responsive to first line ADHD pharmacological treatment (i.e., psychostimulants) [73, 75, 76].

Genetics There has been emerging literature in support of PLMS being a marker or endophenotype for a specific common RLS genotype. In a study by Picchietti et al., a positive parental history of RLS was found in 53% of pediatric RLS cases and in 52% of pediatric PLMD cases [71]. Kotagal et al. found occurrence of RLS in 72% of biological parents of children with RLS, further supporting the familial predispo-

sition of childhood RLS noted earlier by Picchietti et al., and interpreted this finding to be consistent with an autosomal dominant pattern of transmission [77]. Interestingly, mothers were almost three times more likely to be the affected parent than fathers. A genome-wide association study by Stefansson et al. found a variant of BTBD9 on chromosome 6p to be implicated in RLS with PLMS (>5 per hour), but not RLS without PLMS [78].

RLS and Low Ferritin Levels Sun et al. found that serum ferritin levels below 50 μg/L in adults were associated with increased severity of RLS [79]. The same has been demonstrated in children [73, 77]. Adolescents may be at a greater risk of such exacerbation of RLS than adults because of the lower iron stores in this age group [77]. Oral iron therapy has resulted in subjective improvement in sleep-wake function among children with low serum ferritin levels [80].

Assessment of RLS Multiple subjective rating scales have been developed to assess RLS severity, sleep quality, and quality of life. The most commonly used are the International RLS study group (IRLSSG) rating scale (IRLS), and the Clinical Global Impression (CGI) scale [81]. Objective measurements are sleep-related parameters by polysomnography (PSG) (Periodic Limb Movements in Sleep; PLMS), PLM index (PLMI), PLMs arousal index (PLMS-AI), and sleep efficiency) or actigraphy [16].

Management of RLS and PLMD There is no specific treatment for PLMD. Treatment of PLMD is centered on pharmacological agents used in the treatment of RLS. The gold standard treatments are the dopamine receptor agonists, specifically pramipexole and ropinirole. Pharmacotherapy includes dopaminergic medications (levodopa or L-dopa, non-ergot derived dopamine agonist such as pramipexole, ropinirole), opioid medications, anticonvulsant medications (gabapentin, pregabalin, carbamazepine), and alpha-adrenergic agents (clonidine). Non-pharmacotherapies included cognitive-behavioral therapy (CBT) or exercise therapy.

Dopaminergic medications are the most used medications for RLS. Like patients with Parkinson Disease (PD), patients with RLS may develop dopamine dysregulation syndrome as well as addictive pattern of dopamine replacement therapy use and/or behavioral disturbances and impulse control disorders (pathologic gambling, compulsive shopping, compulsive eating, and hypersexuality) [16]. Pramipexole and Ropinirole are effective in the treatment of moderate-to-severe RLS. They are both well tolerated and their side effects are self-limited with cessation of therapy. The dopamine agonist pergolide is effective in the treatment of RLS but has been withdrawn in the United States because of the risk of cardiac valvulopathy. L-dopa is effective in the treatment of RLS, but often leads to augmentation phenomena. Hogl et al. reported during a 6-month multicenter, open-label trial with flexible dosing of L-dopa, augmentation occurred in 60% of the patients [82]. RLS with PLMD

is more likely to respond to dopaminergic agents than if not associated with PLMD [83].

Opioid medications are effective in the treatment of RLS, especially for patients with RLS that do not respond to other treatments. A retrospective review of 113 patients on long-term opioid therapy by Walters et al. demonstrated that opioids seem to have long-term effectiveness in the treatment of RLS and PLMD [84]. Long-term opioid therapy should be monitored clinically and/or by polysomnography monitored periodically for the development of sleep apnea.

Effective opioid doses are considerably lower in refractory RLS compared to those prescribed for chronic pain; nonetheless, our current opioid epidemic has also made opioid therapy for RLS less favorable. Other avenues of treatment should be considered before initiating treatment with opioids, including addressing low iron stores and combination therapy with nonopioid agents. In addition, before patients are started on opioids, they should be assessed for opioid use disorder and monitored closely once started.

Clonidine also has been shown to be associated with RLS symptom improvement in two small double-blind placebo-controlled studies. Side effects were frequent but mild, consisting of mostly dry mouth, impaired cognition, lightheadedness, sleepiness post dose, constipation, decreased libido, and headache [85, 86].

Gabapentin is effective in the treatment of mild-to-moderate RLS [16]. Sleep studies also showed a significantly reduced PLMS index and improved sleep architecture following use of Gabapentin [87]. Patients whose symptoms included pain benefited most from gabapentin. Potential side effects include sedation, dizziness, vision changes, and suicidal behavior and ideation. Two studies have shown the efficacy of pregabalin to treat moderate-to-severe RLS [88, 89]. Unsteady gait and daytime sedation were the most common side effects. One single large but short-term (5 weeks) double-blind study with placebo control showed carbamazepine to be significantly more effective than placebo [90]. There is insufficient evidence of efficacy of valproic acid or benzodiazepines on the treatment of RLS [91].

Iron supplementation has not been shown to be effective in the treatment of RLS, except perhaps in patients with proven iron deficiency [16]. Improvement in selected refractory cases has been reported [92, 93].

Accommodative strategies include sleep hygiene, behavioral and stimulation therapies (stimulating feet and toes with vibrations or electrical impulses), compression devices, exercise, and nutritional considerations have been tried in the treatment of RLS with insufficient data to assess its long-term efficacy [16]. A single open trial reported significant improvement with 8 weekly 90-min sessions in group therapy consisting of mindfulness-based exercises, stress-reduction strategies, diary-based analysis, and medical education [94].

Nocturnal Leg Cramps (NLC)

Nocturnal Leg Cramps (NLC) is a musculoskeletal disorder characterized by suddenly occurring, episodic, persistently painful, involuntary contractions of the calf, hamstrings, or foot muscles at night [95, 96]. It can occur in a third of

the population over age 50, with its prevalence increasing with advancing age. Some of these patients also experience cramps while resting during daytime. Living a sedentary life style as well as certain medical conditions such as chronic liver and renal failure, vascular diseases, magnesium or calcium deficiency, dehydration, and varicose veins have been identified as risk factors [96–98].

Definition and Diagnostic Criteria NLC can easily be confused with RLS and PLMD and may in fact coexist. Hallegraeff et al. identified seven criteria, derived from consensus, which can be used to differentiate NLC from RLS or PLMD [96]. These criteria include intense pain that lasts from seconds to a maximum of 10 minutes, localized to calf or foot but seldom in the thigh. It causes significant sleep disruption and distress [96].

Prevalence A large, representative study reported NLC occurring >5 per month in about 6% of the adult US population [99]. Many factors are associated with a greater risk of NLC including: older age, pregnancy, lower education, unemployment, other sleep problems (shorter sleep duration; nocturnal "leg jerks," snoring, snorting/gasping, difficulty falling asleep, difficulty maintaining sleep, nonrestorative sleep, sleepiness, use of sleep medications), higher BMI, smoking and alcohol use, hypertension, heart failure, angina, stroke, arthritis, respiratory disease, cancer, and depression [99].

NLC and Psychiatric Disorders NLC can cause significant emotional distress. It has been linked to depression, but the cause-effect relationship of these two conditions is not clear [99].

Iatrogenic NCL Certain medications are associated with increased risk for NLC including clonazepam, citalopram, celecoxib, gabapentin, diuretics, and zolpidem [100].

Management of NLC Managing the symptoms of patients with NLC can be a challenge and should include lifestyle interventions (increase fluid intake, avoid caffeine and alcohol, brief light exercise prior to bed and passive stretching/deep tissue massage), physical therapy, pain management, and treatment of underlying risk factors. Quinine, the only treatment proven to be (modestly) effective, may result in serious side effects and is no longer recommended for routine use [101]. Magnesium has a favorable side-effect profile, but appears to be no more effective than placebo [102]. Botulinum toxin (BTX) injection into the gastrocnemius muscles has shown to be effective in patients with NCL associated with lumbar spinal stenosis (LSS) [103].

Sleep-Related Rhythmic Movement Disorder (RMD)

Definitions and Diagnostic Criteria RMD consists of repetitive stereotypic movements, such as head banging or body rocking, that recur every second or so and may last from a few minutes to hours, usually prior to sleep onset [104]. RMD is common in very young children but can persist beyond childhood. RMD mostly comprises headbanging (HB), headrolling (HR), bodyrocking, and bodyrolling. It is classified as a sleep-wake transition disorder. However, it can be seen in all stages of sleep including rapid-eye-movement (REM) sleep during which muscle activity is completely absent [105].

The four cardinal diagnostic features of RMD include: (1) Patient displays repetitive, stereotyped, and rhythmic movements involving large muscle groups; (2) Movements are predominately related to sleep; (3) The repetitive movements result in a significant complaint by the patient or bed partner (this may involve at least one of the following: normal sleep interference, significant impairment of daytime functioning, actual or potential self-inflicted body injury); and (4) The movements are not explained by epilepsy or another movement disorder.

RMD is often a benign self-limited condition; however, injury, sleep disturbance, and daytime impairment are concerns of parents. Local trauma is more commonly seen as more severe injuries are rare. Cervical myelopathy, for example, has been associated with neck flexions in a child with RMD [106]. Moreover, there are social consequences of RMD as children may feel embarrassed by their behavior, leading to avoidance of social situations such as sleepovers and overnight camps [104].

Prevalence Parental reports indicate prevalence rates in children less than 3 years of age to be between 5.5% and 67% [107, 108]; however, the unusual wide prevalence is likely due to varied reporting. Gogo et al. demonstrated that the prevalence of RMD in infants and toddlers with objective home videosomnography was much lower at 2.8% [109].

Etiology and Pathogenesis The pathophysiology of RMD is poorly understood. The high reported prevalence of RMD in early childhood suggests a normal developmental variant. One plausible theory is that rhythmic movements are a learned behavior that soothes the child at sleep onset and following night awakenings [110]. This theory, however, does not explain more violent behaviors such as head-banging, nor does it explain movements during other stages of sleep.

RMD and Sleep Disorders Most isolated case reports have suggested the presence of comorbid sleep-related disorders in patients with RMD. Patients with RMD often have sleep-onset insomnia. It is unclear if sleep onset difficulties are induced by the movements or simply accompany them. The association with OSA and RMD has been reported in children and adults [111, 112].

RMD and Psychiatric Disorders An association between ADHD and RMD was suggested by Simonds et al. [113]. Whether sleep disruption from RMD leads to ADHD symptoms or whether the two problems share a common pathway is unclear [113]. Persistence of RMD beyond early childhood appears to be more common in association with neurodevelopmental disabilities. Kohyama et al. identified seven cases of coexisting psychiatric disorders or intellectual disability (ID) among 27 patients with RMD older than 10 years old [114]. ID, pervasive developmental disorder (PDD), and other psychiatric disorders must be ruled out in older children and adults with sleep-related RMD [115].

Management Etzioni et al. reported success in controlling RBD with tried sleep restriction and hypnotic medication [116]. The resolution of RMD with primarily sleep deprivation supports the hypothesis that it can be classified as a type of voluntary movement that serves as a self-soothing behavior in the process of falling asleep, rather than as an involuntary movement disorder [116]. Insomnia, if present, may need to be independently managed. Protective head gear or padding of cribs may prevent injuries from violent head movements.

There are no randomized controlled trials of pharmacological treatments for RMD and current knowledge is based on limited case studies. Benzodiazepines such as clonazepam have shown improvement in anecdotal literature [117–119]. Tricyclic antidepressants and dopamine agonist have showed some improvement in single case reports [120, 121]. More recently, a single case report showed a patient with repetitive head punching improving with dopaminergic antagonists [121].

Other concomitant sleep disorders should be excluded and properly treated. CPAP therapy, for example, has also been found to reduce the frequency of RMD in cases with comorbid sleep apnea [122]. Although usually a self-limiting disorder, RMD should be properly diagnosed and treated in order to prevent secondary social/psychological consequences, physical damage, and persistence into adulthood [116].

Bruxism

Bruxism is a condition in which you grind, gnash, or clench your teeth. If you have bruxism, you may unconsciously clench your teeth when you are awake (awake bruxism), or clench or grind them during sleep (sleep bruxism). Sleep bruxism is characterized by involuntary, unconscious movement during sleep. People with sleep bruxism may not know they're grinding their teeth, and the behavior can continue for years with significant health consequences. If untreated, sleep bruxism can break, loosen, or wear down teeth and lead to headaches, jaw pain, and temporomandibular joint (TMJ) disorder.

Prevalence A 2013 systematic review of the literature identified several large survey studies that reported a bruxism prevalence in adults of 8.0–31.4% [123].

Prevalence of sleep bruxism in children ranges from 5.9% to 49.6% [124]. Bruxism is often associated with neurodevelopmental disabilities and certain genetic conditions such as autism spectrum disorders, ADHD, Down syndrome, and Rett syndrome [125, 126].

Definition and Diagnostic Criteria Sleep bruxism is characterized by rhythmic masticatory muscle activity (RMMA) usually concomitant with microarousals that last about 3–15 seconds in duration [127, 128]. Sleep bruxism can occur during all stages of sleep, but is more common in non-REM stages 1 and 2, most frequently found within the ascending period of the sleep cycle. This period, when sleep patterns shift from NREM to REM, is associated with increased sympathetic tone and arousal activity.

Etiology and Pathogenesis Multiple etiologies have been proposed for Bruxism. The structural etiologic model argues that dental mal-occlusion is the root cause but there is lack of evidence. Adjusting dental occlusion may control the impact of sleep bruxism, but it has not been shown to lead to its resolution [127]. The functional etiologic model suggests that a combination of stress and specific personality traits such as a predisposition to anxiety plays a role. People with bruxism tend to be more introverted and anxious than people without bruxism [129]. Epidemiologic studies have demonstrated that bruxism can also be associated with emotional symptoms, peer problems, and higher total scores on a strength and difficulties questionnaire [130]. Bruxism often becomes more pronounced during stressful periods, like during school examinations, job difficulties, or marital strife [131, 132]. However, some evidence indicates negative correlations exist between psychological stress/disorders and sleep bruxism [133]. In addition, some studies have found stress to lead to awake bruxism but not sleep bruxism [134, 135].

Both awake and sleep bruxism are subclassified into either primary, not related to any other medical condition, or secondary, associated to neurological disorders or considered an adverse effect of drugs. Etiologies commonly associated to bruxism include encephalopathies, hyperthyroidism, gastrointestinal disturbances, and nutritional deficiencies [129]. Sleep bruxism has also been associated with obstructive sleep apnea, snoring, as well as daytime bruxism in children and adults [136]. Additional risk factors for bruxism include smoking or nicotine dependence [137]. Gastroesophageal reflux, movement disorders, and alcohol consumption have also been implicated [138]. Certain medications can also increase risk for bruxism, including serotonin reuptake inhibitors (SSRIs), amphetamines and L-dopa [139, 140]. These symptoms may improve once the underlying emotional stressor is treated or resolved.

Evaluation, Diagnosis, and Management As patients are usually not aware of their symptoms, making the diagnosis can be challenging. Bed partners or family members

may complain of the noise or tooth friction. Some patients present because of tooth wear or damage to previous dental work; others present due to headaches, clicking or pain in the temporomandibular joints. While bruxism has been implicated in myofascial temporomandibular disorder, a study looking at PSG of adult women with and without temporomandibular disorder did not show greater sleep bruxism in either group [141]. Extreme forms of bruxism involve forceful rhythmic grinding or clenching of the teeth with audible tooth contacts in about 20% of the patients. Excessive tooth wear and morning jaw pain seem to be the major factors in diagnosis.

Diagnosis of sleep bruxism is often based on clinical history, in addition to presence of abnormal tooth wear. Patients suspected of having bruxism should be evaluated with a PSG to rule out sleep disordered breathing. PSG with masseter muscle activity recording and audio-video recordings is important to rule out non-bruxism orofacial movements. EEG may be indicated if seizures are suspected.

Management strategies include the use of oral appliances, pharmacotherapy, and behavioral therapies. Montgomery et al. reported on the short-term use of diazepam reducing bruxism in 11 patients [142]. In two randomized, double-blind studies, administrating 1 mg single dose of clonazepam before sleep significantly reduced the bruxism index [143, 144]. Beneficial effects have also been reported with medications such as propranolol, L-dopa, pergolide, gabapentin, tiagabine, and atypical antipsychotics such as clozapine [145–147]. However, this latter medication is rarely used. A recent review concluded that bite splints are the treatment of choice, with clonidine and mandibular advancement devices demonstrating some utility [148]. In refractory patients, there is limited evidence that botulinum toxin (Botox) injections may show some benefit [140, 149].

Medication-induced bruxism improves once the implicated agent is discontinued. For patients with SSRI-induced bruxism, buspirone appears to have relieved the bruxism symptoms in a small series of cases [150]. Aripiprazole, a partial serotonin/dopamine agonist, has also been shown to effectively treat SSRI-induced awake bruxism [146].

Prevention focuses on identifying and treating risk factors associated with bruxism. Patients should be followed by a dentist to monitor dental wear and intervene if needed. For stress-related bruxism, psychological or psychiatric counseling may be helpful if underlying psychiatric disorder or emotional stress is identified.

Nocturnal Seizures/Frontal Lobe Epilepsy (FLE)

Frontal lobe seizures tend to be brief and nocturnal, with sometimes bizarre manifestations and preserved consciousness; thus, they can often be mistaken for parasomnias or psychiatric disorders.

Prevalence The frontal lobe contains 40% of the cerebral cortex, and frontal lobe seizures are the second most common type of seizures seen at presurgical centers for medical evaluation of drug resistant epilepsy [151].

Diagnostic Criteria The average age of onset is usually late childhood or early adolescence, with men and women equally affected. Frontal lobe seizures are often shorter in duration than seizures of temporal lobe origin, with a nighttime preponderance and association with the sleep-wake cycle. They can occur in nightly clusters of up to 70 seizures, and both convulsive and nonconvulsive status epilepticus are frequent [152].

Specific seizure types include focal clonic motor seizures, asymmetric tonic seizures with preserved consciousness, and hyperkinetic seizures, with the later more often occurring during sleep. Hyperkinetic seizures begin suddenly with complex behavioral automatisms. Patients may jump around, thrash, and rock to and fro. They may jump out of bed and run around in circles. Bicycling and stepping movements are often described [153, 154]. More subtle seizures can consist of awakening and moving around in bed. Motor manifestations can be accompanied by vocalization in the form of yelling, grunting, or laughing. Automatisms with sexual content are also reported in the form of pelvic thrusting and genital manipulation. Consciousness is often preserved and the patient returns to baseline quickly after the seizure. Ictal electrographic seizures may not be seen making diagnosis difficult, as they are often mistaken for psychogenic or nonepileptic events. Seizures typically occur in NREM sleep as opposed to REM behavior disorder. Seizures also tend to be very stereotypic in semiology which also helps in distinguishing epileptic events from parasomnias [154].

Etiology and Pathogenesis Frontal lobe epilepsy has multiple etiologies. Frontal lobe seizures can be due to cortical dysplasias and other malformations of cortical development, tumors, vascular malformations, or post-traumatic encephalomalacia [155]. Not infrequently, no identifiable lesion is found on brain imaging studies. Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) is a channelopathy of the nicotinic acetylcholine receptor widely distributed in the frontal cortex. This usually manifests in childhood with clusters of brief, nocturnal seizures with bizarre hyperactive seizures or asymmetric tonic seizures without loss of consciousness [156]. Missense mutations of the gene for the neuronal nicotinic acetylcholine receptor alpha 4 subunit (CHRNA4) have been found to be the primary cause for ADNFLE [157]. More recently other gene mutations (GATOR1 complex gene, NPRL3, potassium channel KCNT1 and DEPDC5) have also been found in patients with ADNFLE [157–159].

FLE and Psychiatric Disorders FLE can often be mistaken for a psychiatric disorder, be misdiagnosed in lieu of a true psychiatric disorder, or may be comorbid with psychiatric illness. In a systematic review of patients with FLE by Gold et al., 27% of patients had a prior psychiatric history with a wide range of diagnoses, most commonly substance use and mood disorders [158]. Due to their seizure presentation, 15% of patients were misdiagnosed with psychiatric conditions such as antisocial personality disorder, dissociative disorder, ADHD, Tourette syndrome, bipolar disorder, and obsessive-compulsive disorder. Psychiatric manifestations were primarily

ictal in 74.2% of cases, postictal in 4.5%, or a combination in 21% [160]. In a psychiatric assessment of 59 children with FLE, about one-third of patients had intellectual disability and more than two-thirds had a psychiatric disorder. The most frequent psychiatric diagnosis was depressive disorder (35% of patients) followed by disruptive behaviors (23.5%), anxiety (20.6%), and bipolar or psychotic disorders (20.6%). Intellectual disability was associated with an earlier onset of psychiatric disorders and more frequent disruptive behavior disorders and aggressiveness [161].

Evaluation and Management An accurate and complete history and a neurologic exam are essential. Interictal EEG is often normal. If interictal spikes are observed, they can help to establish the diagnosis of epilepsy; however, this is often not the case. Prolonged overnight video EEG monitoring is often required for a definitive diagnosis. Not infrequently, ictal scalp EEG may not show definite epileptiform features and the diagnosis has to rely on clinical description and seizure semiology. Neuropsychological testing may show impairment of executive function, response inhibition, and social cognition [162]. Brain imaging studies are recommended to rule out structural intracerebral lesions.

Frontal lobe seizures can be challenging to treat. Several antiepileptic drugs have been used to treat frontal lobe seizures, including levetiracetam, lamotrigine, carbamazepine, oxcarbazepine, valproic acid, and zonisamide. Newer antiepileptic drugs (AEDs) such as lacosamide, perampanel, brivaracetam, and eslicarbazepine have shown to be effective in some cases [163–165]. Surgery is an option for medically refractory cases and should be considered for patients who have failed trials of two or more antiepileptic drugs. Resective surgery has better efficacy if a structural lesion is identified. In a longitudinal study of 70 frontal lobe epilepsy patients treated with resective surgery, 56% of patients were seizure-free at 1 year; however, only 45% were seizure-free at 3 years and 30% at 5 years confirming that long-term post-surgical seizure remission is not the norm [166]. The ideal surgical candidates are those who have MRI and electrophysiological evidence of epileptogenicity that is restricted to the frontal lobe, and in whom a complete resection of the epileptogenic zone is possible. Some authors have suggested the benefit of corpus callosotomy to prevent secondary generalization or of vagus nerve stimulation for medically refractory cases when other surgical procedures are not indicated [167, 168].

Conclusion

In conclusion, sleep-related movement disorders are common and can disrupt sleep. While some are benign and require reassurance with no further intervention, others may lead to significant daytime impairment, cognitive and emotional disturbances, and even more serious medical and psychiatric problems requiring further workup and pharmacological therapy. Several sleep-related movement disorders overlap with psychiatric conditions. It is therefore important for clinicians to be aware of

these disorders and to be knowledgeable about their etiology, comorbid conditions, diagnostic tools, and proper management.

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Parasomnia

12

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Introduction

Parasomnias are a group of sleep disorders characterized by abnormal, unpleasant motor verbal, or behavioral events that occur during sleep or wake to sleep transitions [1]. They are more commonly seen in children but can persist throughout life. Studies suggest that up to 88% of children will have at least one parasomnia [2]. Waters et al. found significantly elevated rates of parasomnias in psychiatric disorders (average prevalence of nightmares was 38.9%, sleep paralysis (SP) 22.3%, sleep-related eating disorder (SRED) 9.9%, sleepwalking 8.5%, and rapid eye movement (REM) behavior disorder (RBD) 3.8%) [3]. Medication usage was found to be a risk factor as well as other sleep disorders, medical comorbidities, and substance abuse [3].

Description and Classifications In the sleep–wake spectrum, at least three different consciousness levels typically occur: wakefulness, rapid eye movement (REM) sleep, and nonrapid eye movement (NREM) sleep. Parasomnias can occur during nonrapid eye movement (NREM) and rapid eye movement (REM) stages of sleep (Table 12.1)

Sleepwalking

Sleepwalking or somnambulism is an arousal disorder during which individuals are disoriented with eyes open, and the events may range from ambulating aimlessly, playing a musical instrument, performing inappropriate behavior like urinating in

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Table 12.1 Parasomnias

NREM sleep	REM sleep
Sleep walking	REM behavior disorder
Confusional arousal (CA)	Nightmare disorder
Sleep terror	Status dissociatus (SD)
Sleep – related eating disorder	Catathrenia
Sexual act during sleep/sexsomnia	Isolated sleep paralysis (ISP)

the closet, driving or moving out of the house, or resulting in self-injurious action like walking off the balcony [4].

Prevalence Somnambulism is more common in childhood than in adulthood with peak prevalence around age 10 years. The prevalence of somnambulism is around 3% in toddlers (age 2.5–4 years), and steadily increases to 13.5% at 10 years of age [2]. Most children outgrow the disorder during adolescence, it can persist into adulthood in as much as 25% of cases [5]. Roughly 80% of sleepwalkers have at least one affected family member. First-degree relatives of sleepwalkers have a ten-fold increased likelihood of somnambulism compared with the general population [6]. In an adult British population interviewed by phone, sleepwalking was found in 2% of the population of 4972 interviewed individuals [7].

Sleepwalking and Other Sleep Disorders Sleepwalking can occur in patients with a variety of other sleep disorders such as restless leg syndrome (RLS), narcolepsy, and sleep apnea [8]. In a Norwegian study, severity of obstructive sleep apnea (OSA) was associated with sleepwalking, with an odds ratio (OD) of 2.0 [9].

Sleepwalking and Neurological Disorders No evidence suggests that chronic somnambulism during adulthood is associated with the subsequent development of neuropathological disorders on the contrary to REM behavior disorder (RBD). Triggers of sleepwalking in the adult population include sleep disorders (restless leg syndrome and sleep apnea), head injury, encephalitis, febrile illness, vitiligo, migraines, stroke, and chronic pain syndrome [10].

Sleepwalking and Psychiatric Disorders Epidemiological data suggest that roughly 25% of adult sleepwalkers self-report concurrent anxiety or mood disorders [7]. Lam et al. reported an increased risk for sleepwalking, SRED, and RBD in outpatients with major depression, with an estimated prevalence of the lifetime diagnoses of sleepwalking, SRED, sleep-related injury (SRI), sleep violence, and REM sleep behavior disorder (RSBD) of 8.5%, 4.0%, 21.0%, 3.6%, and 5.8%, respectively [11].

Some studies suggest the link between serotonin or serotonin precursors and increased motoric excitability and tonic motor activity [12]. Since studies have shown that during deeper sleep stages, serotonin neuronal activity gradually decreases (i.e., during slow-wave sleep [SWS] and REM) with subsequent decrease in muscle tone, serotonergic medications might increase sleepwalking episodes [13].

Iatrogenic Sleepwalking In a systematic review by Stallman et al., 29 drugs, primarily in four classes – benzodiazepine receptor agonists and other gamma aminobutyric acid (GABA) modulators, antidepressants and other serotonergic agents, antipsychotics, and β-blockers – were identified as possible triggers for sleepwalking [14]. However, the strongest evidence for medication-induced sleepwalking was for zolpidem and sodium oxybate [14].

Management While there is generally no treatment for sleepwalking, risk of trauma, violence, and uncontrolled behavior while asleep render management of this disorder important. While ensuring sufficient sleep duration and discontinuing any offending agents (e.g., medication) or associated sleep disorders might help decrease prevalence, ensuring safety is the most important step. This latter includes locking the main doors to ensure the child not leaving the house at night, removing any obstacles from the floor to avoid tripping, etc. Some medications have intermittently been used with some success in cases reports including melatonin administration. While some researchers studied the use of benzodiazepines (clonazepam, triazolam, and flurazepam), others failed to show its efficacy and the frequent drop of individuals treated with this modality [8, 15–19]. Some studies suggested the use of tricycle antidepressant medications or serotonin-selective reuptake inhibitors (SSRIs) [20–23]. However, those who had successful treatment of the associated OSA with either continuous pressure ventilation (positive airway pressure (PAP)) or surgery showed improvement of sleepwalking [24].

Confusional Arousals

Confusional arousals are characterized by episodes of confusion, disorientation, grogginess, and agitation upon awakening. Patient may present agitation, crying or moaning, disorientation, and particularly slow mentation on arousal from sleep. When occurring in young children, during these episodes, children may even resist soothing and become more agitated with caregivers' attempts to comfort them causing significant distress for child and caregiver. Episodes are brief, last a few minutes, and are seen most commonly in infants, toddlers, and children younger than age 5 years.

Prevalence While confusional arousal is more common in children, it declines with age. A British study suggested a prevalence of this disorder in 4.2% of phone-

based survey [7]. Ohayon et al. studied confusion arousals in general population and found them to be strongly associated with the presence of a mental disorder with odds ratios ranging from 2.4 to 13.5. Bipolar and anxiety disorders were the most frequently associated mental disorders [25].

Confusional Arousal and Psychiatric Conditions In a study assessing associated psychiatric conditions in children with confusional arousal, an odds ratio (OR) of 6.1 was associated with anxious mood (40.9% of CA patients had anxiety compared to only 15.3% in those without CA) and an OR of 7.5 was associated with depression (51.3%in CA group had anxiety versus 17.0% in the other group) [25].

Management The initial first step management for this disorder is parental reassurance as it tends to decrease with age [26]. Sleep deprivation and central nervous system depressants can worsen this disorder [7]. Thus, parental and child education about avoiding sleep deprivation is essential. Behavioral treatments have sometimes been suggested including scheduled awakenings (i.e., a 15–20 minutes before the usual event time) of the child before the expected event time [27]. Since restraining the child might lead to increased violence, observation is usually needed [15]. Since comorbid sleep disorders such as OSA might be common, treating these associated disorders will improve confusional arousal events.

Sleep Terrors (Pavor Nocturnus)

Sleep terror or night terror is characterized by episodes of sudden arousal with increased screaming and crying in fright, along with motor activity and autonomic hyperactivity (tachypnea, tachycardia, mydriasis, and diaphoresis) [1]. The patients usually appear terrified and inconsolable and are amnestic or may have a vague recollection of the event [10]. Such episodes can be distressful for the parents or bed partner and may disturb their quality of sleep due to disrupted sleep and consequent daytime hypersomnolence, cognitive, and behavioral changes.

Prevalence It is more common among pre-school children (up to 34% of children <7 years. A prevalence of 2.2% among British adult individuals was found during a phone-based survey [7].

Sleep Terrors and Other Sleep Disorders A study investigated the psychiatric comorbidity, personality traits, and family history of adolescents with sleep terrors and/or sleepwalking found that adolescents with sleep terrors and sleepwalking have an increased prevalence of other sleep disorders, neurotic traits, and psychiatric disorders and problems [28]. Ohayon et al. demonstrated that sleep terrors like other arousal parasomnias such as confusional arousals and sleepwalking may be

indicators of underlying mental disorders [7]. This relationship in younger children is less clear.

Management The most common recommended treatment for night terrors is assurance of parents; in most of the cases children outgrow it. Similar to confusional arousals, sleep deprivation and central nervous system (CNS) depressants will precipitate the disorder [7]. Avoiding episode interruption is essential, as any attempt to arouse the child might lead to aggressive behavior; however, child monitoring is essential during these episodes. Other treatments include scheduled arousals few minutes before the expected episode occurrence [29]. Other used modalities include psychotherapy, relaxation therapy, and hypnosis [30–32].

Sleep-Related Eating Disorders (SREDs)

SREDs are defined as recurrent episodes of involuntary binge eating after partial awakening from the sleep. It is important to differentiate SRED from nocturnal eating syndrome (NES) and compulsive binge eating as a result of impulse control disorders [33]. SRED involves recurrent episodes of eating or drinking peculiar food combination or even the ingestion of toxic substances in a relatively unconscious state during the sleep period, whereas NES is considered a delayed circadian consumption of food where the patient wakes up at night and consciously binges on food, resulting in anorexia and sleep fragmentation [34] next morning. Compulsive binge eating is an impulsive behavior resulting in the conscious consumption of large amounts of normal food [35].

Prevalence Onset of SRED is thought to occur between age 22 and 27 years of age, with 65% of individuals being females [36, 37].

SREDs and Other Sleep Disorders SRED may be associated with sleepwalking, periodic limb movements (PLMS), OSA, or restless leg syndrome (RLS) [38, 39].

SRED and Other Medical Conditions Medical conditions that may trigger the SREDs include encephalitis, autoimmune hepatitis, narcolepsy, smoking cessation, and substance abuse. SREDs, like other parasomnias, have been reported in patients with Parkinsonism [33].

SREDs and Psychiatric Disorders Palmese et al. reported elevated incidence of SRED in a sample of overweight and obese people with schizophrenia and schizoaffective disorder (17% of patients reported potential SRED when completing the self-report) [40].

Iatrogenic SREDs Certain drugs that may precipitate SREDs include zolpidem, mirtazapine, aripripazole, quetiapine, lithium, anticholinergic medications, antidepressants, olanzapine, risperidone, lithium, and triazolam [41–45].

Management of SRED SRED can have serious consequences and lead to excessive weight gain, injuries (mishandling the food), dental caries, and metabolic derangements (diabetes and dyslipidemia) [46]. Since SRED has been associated with some medications (i.e., zolpidem), discontinuation of the offending agent has been suggested to improve SRED.

The preferred drugs used for treatment of SRED are dopamine agonists, benzodiazepines, topiramate, and SSRI [36, 47–50]. Topiramate has shown the most success. Santin et al. studied 20 patients with SRED treated with topiramate, 17 of whom showed cessation or a clear reduction in night-eating episodes. Side effects leading to discontinuation of drug were seen in six patients (30%) with dizziness, visual problems, and worsening of preexisting depressive symptoms. This study illustrates the importance of close follow-up on patients with SREDs treated with topiramate [51].

Sexual Act During Sleep/Sexsomnia

Sexsomnia or sleep sex is characterized by unusual sexual behaviors during sleep. These events may range from sexual intercourse, sexual assault, masturbation, sexual vocalizations, or fondling the bed partners. Sexsomnia occurs during partial arousals in slow-wave sleep. Interpersonal relationship or medicolegal problems can arise.

Prevalence The prevalence of sexsomnia is estimated to be around 7% of the population (80% of whom are men) [24]. The etiology of sexsomnia is not fully understood. Several precipitating factors have been reported including physical contact with another person in the bed, stress, fatigue, alcohol use, and drug abuse [52, 53].

Sexsomnia and Other Sleep Disorders It may coexist with other sleep disorders such as sleep bruxism and OSA [54].

Sexsomnia and Psychiatric Disease Bejot et al. described two cases of sexsomnia in adult women whose personal history was remarkable for traumatic sexual psychological stress during childhood [52].

Serotonin reuptake inhibitors (SSRIs) may act as a trigger for sexsomnia [55]. Sexsomnia has also been described in patients with Parkinson's disease with impulse control disorder and temporal lobe epilepsies [56].

Management There are limited data on the management of sexsomnia. In patients with daytime somnolence and other behavioral problems, pharmacological intervention may be needed.

Clonazepam may be efficacious in cases requiring pharmacological treatment [57]. The use of antidepressant medications such as serotonin reuptake inhibitor GABAergic agents (valproic acid and lamotrigine) has been also suggested [52, 58, 59]. Favorable outcome has been seen with stress management programs or psychotherapy in the case of associated anxiety or depression [60]. In patients with comorbid OSA, continuous positive airway pressure (CPAP) therapy may improve symptoms and improve daytime dysfunction. Sexomnia can have significant legal implications and has been used in court in rape trials [61].

Rapid Eye Movement Behavior Disorder (RBD)

REM sleep is characterized by an activated brain state in combination with skeletal muscle paralysis. This paradox, wake-like brain activity combined with flaccid motor function, prevents the enactment of dream activity. In RBD, REM sleep atonia is lost and patients act out their dreams.

Definitions and Diagnostic Criteria REM sleep behavior disorder criteria, according to the International Classification of Sleep Disorders – third edition (ICSD-3), include repeated episodes of sleep-related vocalization and/or complex motor behaviors. These behaviors are documented by polysomnography to occur during REM sleep or based on clinical history of dream enactment, are presumed to occur during REM sleep. Polysomnographic recording demonstrates REM sleep without atonia (RSWA). The disturbance is not better explained by another sleep disorder, mental disorder, medication, or substance use.

The spectrum of dream enactment behavior ranges from minor movements to leaping out of bed with the frequency of episodes ranging from once every few months to multiple nightly episodes. Unlike NREM parasomnias, the duration of behaviors in RBD is brief, and on awakening from an episode, there is usually a rapid return to alertness and orientation. The reported motor activity usually correlates with remembered dream mentation, leading to the patient's (or patient's bed-partner) complaint of "acting out dreams." Importantly, RBD patients do not have more violent dreams than normal individuals; instead, they merely act them out. Furthermore, during the daytime, they are not more aggressive, nor do they suffer from personality disturbances [62]. RBD vocalizations should be differentiated from sleep talking, which is common (during both NREM and REM), more typical of daytime conversation, and does not, in itself, represent pathology.

Due to its association with REM sleep, RBD tends to manifest in the latter part of the night and only rarely during daytime naps. In the absence of injury, most RBD patients attribute only minimal daytime consequences, if any, to their

nocturnal behaviors. One study noted that 70% of patients reported good sleep quality. However, this is in contrast to the patient's bed partners; 44% of patients were unaware of dream enactment until their bed partners told them. Sleep-related injuries may result due to behaviors such as punching, kicking, or leaping out of bed. Examples of sleep-related injuries may include fractures, dislocations, and lacerations. RBD may have forensic implications as bed partners are frequently the target of violent dream enactment [63].

Prevalence Clinical prevalence of RBD is approximately 0.5% [64]. The first polysomnogram (PSG) population-based study in RBD found that 1.06% of individuals met PSG criteria for RBD [65]. RBD is more common among the elderly and patients with comorbid neurodegenerative disorders. A general elderly population study utilizing PSG identified RBD in 2% and REM sleep without atonia in the absence of the RBD clinical syndrome in 5% [66]. Among Parkinson's disease patients, approximately one-third to one-half has RBD [34, 67, 68]. RBD will progress, in most cases, to an overt synucleinopathy; either Parkinson's disease (PD), dementia with Lewy bodies (DLB), or rarely multiple system atrophy (MSA). The frequency of RBD is as high as 50–80% in dementia with Lewy bodies and 80–95% in multiple system atrophy [69–72]. Multiple genetic variants have been implicated in PD, DLB, and MSA, but the potential role of most of them in RBD is still unknown. Among younger adults (younger than 40 years old), RBD is more likely due to antidepressant medications or narcolepsy [71, 73].

Etiology and Pathogenesis RBD represents the final common pathway of several diverse pathologies, all of which result in a failure to inhibit central motor pattern generators and spinal motor neurons [71]. The majority of patients with spontaneously occurring RBD will eventually demonstrate signs and symptoms of neurodegenerative disorders, most commonly one of the synucleinopathies (Parkinson disease, multiple system atrophy, or dementia with Lewy bodies), often after a prolonged interval lasting decades [63]. Typically 50% of patients will manifest with a neurodegenerative process within 10 years of onset of RBD. Ultimately, 81–91% of otherwise idiopathic cases convert to a neurologic disorder [74, 75].

RBD has been associated with other neurodegenerative pathologies that involve pontine nuclei, which control REM sleep including cases of tauopathy-related parkinsonian syndromes (progressive supranuclear palsy, Guadaloupean parkinsonism), TDP-43-opathies (frontotemporal dementia, amyotrophic lateral sclerosis), and amyloidopathies (Alzheimer's disease). RBD has also been noted in some trinucleotide and tetranucleotide repeat disorders, including spinal cerebellar ataxias, Huntington disease, and myotonic dystrophy type 2 as well as in cases of Wilson disease [76–79]. Occasionally lesions affecting the pons, medulla, or limbic system, such as malignancies, aneurysms, or white matter disease, will cause RBD, and these cases do not appear to progress to neurodegeneration [80].

RBD and Narcolepsy In both RBD and narcolepsy, the brain fails to separate features of REM sleep and wakefulness. In narcolepsy, the persistence of REM sleep atonia into wakefulness manifests as sleep paralysis and cataplexy. In RBD, wakeful muscle tone intrudes on REM sleep and dream enactment behavior emerges. About 50% of patients with narcolepsy also have RBD symptoms, with the strongest association in patients with cataplexy or narcolepsy type I [73, 81–83]. The mechanism of RBD in narcolepsy is thought to be related to the failure of orexin to stabilize REM sleep. In RBD patients with narcolepsy, the dream enactment tends to present earlier, be composed of more simple movements, and is less violent.

Iatrogenic RBD Psychoactive medications can precipitate or worsen RBD. Medication classes include tricyclic and tetracyclic antidepressants, monoamine oxidase (MAO) inhibitors, serotonin-specific reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), and an acetylcholinesterase inhibitor [84–87]. On PSG, drug-induced RBD has more REM sleep-related motor activity in the lower extremities than nondrug-induced RBD. One hundred and thirty-two medication-induced RBD may, in fact, be the most prevalent form of RBD, especially among the young [35, 85].

It is postulated that antidepressants do not represent a de novo induction of RBD, as these patients would have otherwise developed RBD, and ultimately a parkinsonian syndrome later. One study demonstrated that patients with antidepressant-associated RBD have other prodromal markers of alpha-synuclein neurodegeneration, such as hyposmia, constipation, as well as visual and subtle motor impairments [88]. In another study, patients with medication-associated RBD had reduced striatal dopamine dysfunction as measured by 18F-DOPA PET imaging [89]. These findings imply that antidepressants are not causing RBD in isolation but instead are unmasking individuals at risk of a neurodegenerative syndrome.

Differential Diagnosis of RBD This includes NREM parasomnias such as sleepwalking, confusional arousals, and night terrors. In contrast to RBD, NREM parasomnias tend to occur in the first half of the night. In addition, patients with RBD are more likely to act out and report dream mentation when awakened from an episode, with dream mentation being more aggressive in RBD, and violent punching and kicking occurring more commonly. Behaviors that may mimic RBD can occur during the REM sleep fragmentation associated with obstructive sleep apnea or sleep-related gastroesophageal reflux [63, 71]. Furthermore, patients with severe periodic PLMD may also report unpleasant dreams and simulate RBD-like behavior, requiring video polysomnography to distinguish between the two conditions [90].

Less often, conditions such as sleep-related dissociative disorder or nocturnal epilepsy can be confused with RBD. The behavior in sleep-related dissociative disorder is often prolonged, and polysomnography demonstrates wakefulness

throughout the episode. Nocturnal epilepsy is characterized by stereotyped, recurrent, and abnormal behaviors, and the EEG may demonstrate epileptic activity [91]. Parasomnia overlap disorder, a combination of both an NREM parasomnia and RBD, can occur and should be considered as well [92]. In a report of 93 patients with RBD, 10 patients also had a history of sleepwalking or nocturnal wandering behavior [93].

Evaluation, Diagnosis, and Management Diagnosing RBD requires a thorough clinical evaluation, with a detailed review of the sleep–wake complaints followed by a neuropsychiatric history and examination. A report from a bed partner is particularly helpful as many patients are unable to properly recall the sleep-related events by the time they are discussed with a clinician. PSG is important for definitive diagnosis. Even when abnormal behavior does not occur during a single night PSG, REM sleep without atonia (RSWA) is often present, which in combination with clinical history of dream enactment behavior, can establish a diagnosis [94]. PSG is also helpful in ruling out conditions such as sleep-disordered breathing, periodic limb movement disorder, and nocturnal epilepsy as a cause of the nocturnal behaviors.

Initial focus of treatment should be on patient and bed partner safety, by modifying the sleeping environment. Subsequently, the clinician should eliminate aggravating agents, as well as identify and treat comorbid sleep disorders. Most cases of toxic RBD are self-limited following discontinuation of offending medication, and dream enactment behavior typically resolves if underlying obstructive sleep apnea is treated. When violent nocturnal behaviors persist despite these interventions or in situations with a high probability of injury, pharmacotherapy is appropriate.

Clonazepam has been the most widely prescribed agent for RBD, and approximately 90% of patients initially respond well to low doses (0.5–1.0 mg) [93, 95]. While clonazepam's therapeutic mechanism in RBD is not fully understood, it is thought that clonazepam may decrease the frequency of unpleasant nightmares, thus, decreasing dream enactment behaviors [96]. Long-term studies of clonazepam range from sustained benefit without dose escalation to others with a high incidence of dose escalation and treatment failure.

Several studies have suggested that melatonin may be an effective and safe first-line treatment for RBD. Melatonin is an endogenous hormone normally secreted by the pineal gland in response to evening darkness and helps entrain circadian rhythms. Exogenous melatonin in high doses at bedtime (6–15 mg) augments REM sleep atonia and improves RBD symptoms [63]. Although the exact mechanism of melatonin in RBD is unknown, it may be realigning the circadian rhythmicity of REM sleep. Melatonin has been shown to be effective either in combination with clonazepam or as sole therapy [97]. Importantly, a direct comparison study noted that melatonin was equal to clonazepam in treatment efficacy and superior in side effect profile [98].

Cholinergic agents may be useful in RBD among patients who have failed conventional therapy. Two placebo-controlled crossover trials noted that the cholinesterase

inhibitor, rivastigmine, reduced the number of dream enactment behavior episodes among patients who already had mild cognitive impairment [99, 100].

Pramipexole may be effective in mild cases of RBD, in particular, those associated with frequent PLMS. One investigation noted that compared to clonazepam-responsive patients, pramipexole-responsive patients had more mild disease at baseline as measured by REM sleep atonia [101]. Similar to treating obstructive sleep apnea in RBD, pramipexole may decrease nocturnal behaviors by reversing a sleep fragmenting condition, periodic limb movements. Another pramipexole study in RBD patients reported a decrease in distressing nocturnal behaviors along with a decrease in periodic limb movements, but no effect on REM sleep atonia [102].

Other agents with some reported efficacy include imipramine, carbamazepine, rotigotine, levodopa, donepezil, sodium oxybate, triazolam, zopiclone, quetiapine, clozapine, and cannabidiol [103, 104]. Medication refractory RBD is potentially life-threatening condition and may result in severe traumatic injuries [105]. A study of patients with medication refractory RBD and sleep-related injury demonstrated the utility of a customized bed alarm that delivered a calming message at the onset of dream enactment behavior [104].

Patient counseling about the risk for neurodegenerative diseases is recommended. Although circumstances surrounding each individual patient should be taken into account when deciding to disclose the risk for future neurodegenerative disease, general consensus is to inform patients of this risk, in particular, if patients develop RBD after age 60, are not taking antidepressants, and already have nonmotor features of synucleinopathy.

Nightmare Syndrome

Nightmares occur during REM sleep secondary to the vivid dreams. Associated arousal and autonomic hyperactivity (i.e., tachycardia and sweating) occur when the individual get aroused and usually becomes alert. Thus, these individuals are consolable during these episodes and often remember the episodes the following day. This is in comparison to night terrors, which occur in NREM and associated with uncontrollable symptoms that are nonconsolable, with no recollection occurring the next day of the episode.

Prevalence Some studies suggest a high prevalence of nightmares in children reaching 75% [106]. In pre-adolescent children, the range is from 1.8% to 6% and up to 4% in adults [107, 108].

Nightmares and Psychiatric Disorders Frequent nightmares (≥3 times/week) have been reported in 37.3% of inpatients and 24.2% of outpatients with major depression [109, 110]. Nightmares were strongly associated with anxiety, suicidal ideation, and insomnia [110–112]. Frequent (weekly) nightmares were reported in 9–55% of inpatients and outpatients with schizophrenia [112–114].

Iatrogenic Nightmares Nightmares may be induced with the use of medications like beta-blockers, levodopa, acetylcholinesterase inhibitors, and the sudden discontinuation of REM suppressant medications [115].

Management of Nightmare Syndrome Some studies suggest the use of therapy. This includes imagery rehearsal therapy in which the individual is asked to rehearse the dream and change the unpleasant or the ending of the dream to more pleasurable one. Exposure therapy has also been used in which the individual is exposed gradually to the negative aspect of the dream while awake. Other types of therapy include exposure, relaxation, and rescripting therapy, which include progressive muscle relaxation and rescripting the nightmares into a more pleasurable one [116]. A preliminary data suggested the possible use of hypnosis as a treatment modality for this disorder [117]. Eye movement desensitization and reprocessing therapy (EMDR) has also been used, especially in those with associated posttraumatic stress disorder (PTSD) symptoms [118].

Prazosin, a centrally acting selective α1-adrenergic antagonist, has been considered efficacious in the treatment of nightmares, especially posttraumatic nightmares [119]. It is well tolerated and long-term use is often needed, as recurrence rate upon drug discontinuation is high. Tetrahydrocannabinol was reported to result in the reduction of nightmare recurrence and intensity in patients with nightmare syndrome and PTSD [120, 121].

Status Dissociatus (SD)

The states of being are conventionally defined by the simultaneous occurrence of behavioral, neurophysiological, and autonomic descriptors. State dissociation disorders are due to the intrusion of features typical of a different state into an ongoing state [122]. Status dissociates is an extreme form of state dissociation and is characterized by complete dissociation between the transition from wakefulness to NREM and REM stages of sleep. During these episodes, most of the patients will have violent behavior ranging from screaming, crying, running, kicking, or punching and may last for a few minutes to hours. In the severe form of SD, the brain is not able to orchestrate the behavioral, neurophysiological, and autonomic patterns typical of any state of being [122].

The most severe form of SD has been labeled as agrypnia excitata, and has been described in patients with fatal familial insomnia (FFI), alcohol withdrawal syndrome, and Morvan's syndrome [123]. This condition is characterized by a confusoneiric state (dreaming behaviors due to complex hallucinations/dreams), together with motor hyperactivity, autonomic hyperactivity (with tachycardia, tachypnea, hypertension, fever, hyperhidrosis, etc.), and increased blood cortisol and plasma catecholamines [122]. Both the cyclic structure of sleep and the circadian

rhythmicity are lost. Motor activity is increased throughout the 24 hour without any circadian pattern [124].

Pathophysiology SD has been linked to a thalamo-limbic GABAergic dysfunction that releases the hypothalamus and brainstem from the cortico-limbic control [125].

SD and Neurological Disorders SD has been associated with several neurodegenerative disorders (synucleinopathies, tauopathies, and prion proteinopathies), anoxic brain injuries, and strokes [126–128].

SD and Other Sleep Disorders Dissociated sleep was previously reported as a polysomnographic trait in tricyclic-medicated narcoleptic patients [126]. Patients with narcolepsy type 1 experience a number of state dissociation disorders, ranging from wakefulness dissociation (cataplexy, sleep paralysis, hallucinations, and automatic behaviors) to REM sleep dissociation (lucid dreaming, RBD), but patients are still able to orchestrate the proper states of being, even if the system is so unstable that dissociation occurs very frequently [122].

SD and Other Psychiatric Symptoms SD are often seen in association with psychiatric symptom such as hallucination, delusion, delirium, and psychosis [115]. However, state dissociations should not be confused with dissociative disorders, psychiatric disorders characterized by disruption, and/or discontinuation of the normal integration between consciousness, memory, awareness of identity, emotions, perception, body representation, motor control, and behavior [129]. Patients with severe SD eventually reach the final state of akinetic mutism, as often seen in FFI. There is no treatment for SD, but benzodiazepines have been shown to be effective [126].

Catathrenia

Catathrenia or sleep-related groanings are recurrent episodes of groaning during sleep without any underlying otolaryngologic or vocal cord abnormalities, typically occurring during the expiration phase in the REM stage of sleep [10, 130]. Catathrenia is differentiated from central sleep apnea by the presence of vocalization; from sleep-related seizures by electroencephalography; from sleep-related laryngospasm by the differing clinical symptoms; and from expiratory snoring by the peculiar quality and duration of sound [131]. There has been a long discussion if Catathrenia is a sleep disorder or a respiratory disorder. Catathrenia is currently considered to be a parasomnia, in spite of the lack of association with any abnormal behavior, motor activity, or sleep talking [132].

Prevalence The actual demographics are unknown. Although it was thought to be a rare phenomenon, with prevalence being even lower than 0.5% in a sleep disorders clinic [132], catathrenia has been reported in patient with neurodevelopmental disabilities and genetic disorders [131]. There may be different causes for expiratory groaning in sleep, some of which may be related to lung diseases (e.g., chronic obstructive pulmonary disease) or some undisclosed type of sleep-disordered breathing [133].

Catathrenia and Systemic Disease Comorbid disease include tobacco use, obesity, gastroesophageal reflux, hypothyroidism, and asthma [134].

Catathrenia and Psychiatric Disease Alonso et al. found anxiety and depression present in almost half of patients with reported catathrenia [134].

Management of Catathrenia Catathrenia can lead to daytime sleepiness and headaches [135]. No pharmacological treatments are available for treatment of Catathrenia but some authors have reported good results with CPAP in patient with sleep-disordered breathing [136].

Isolated Sleep Paralysis (ISP)

Sleep paralysis (SP) occurs when rapid eye movement (REM)-based atonia perseverates into wakefulness. During episodes of sleep paralysis, the sufferer awakens to rapid eye movement sleep-based atonia combined with conscious awareness. This is usually a frightening event often accompanied by vivid, waking dreams (i.e., hallucinations) [137]. Sleep paralysis is often seen in patients with narcolepsy. SP not associated with narcolepsy is called isolated sleep paralysis (ISP).

Prevalence of SP The prevalence rates of sleep paralysis in the general population are estimated to be approximately 8%, though individual study estimates greatly vary from 2% to 60% [138]. Risk for sleep paralysis may, in part, be genetic; however, the role of genetic influences on sleep paralysis is unknown. Familial sleep paralysis has been reported [139, 140].

Sleep Paralysis and Other Sleep Disorders Sleep paralysis is a common symptom of narcolepsy. Narcolepsy is a sleep disorder characterized by excessive daytime sleepiness, cataplexy (sudden, brief, bilateral loss of muscle tone in response to strong emotions such as laughter or anger), sleep transition hallucinations, sleep paralysis, and disturbed nocturnal sleeping patterns. SP is more commonly seen in patients with narcolepsy that are hypocretin-deficient and have cataplexy [141].

Ohayon et al. found that the prevalence of insomnia disorder in individuals with SP was 4.3% compared with 1.7% of the general population [141]. One study by Vernet et al. reported increased sleep paralysis in obstructive sleep apnea (OSA) patients compared to controls (20% vs 5%) [142]. The presence of poor sleep and/or sleep disruption is associated with SP, making a common symptom in shift workers [143].

Sleep Paralysis and Psychiatric Diseases Several studies have shown that poorer general mental health is significantly associated with frequency of sleep paralysis [144]. Higher scores on self-report measures of depressed mood have been associated with sleep paralysis frequency [145, 146]. Anxiety-related symptoms appear to be associated with sleep paralysis [147]. Patients with a diagnosis of posttraumatic stress disorder (PTSD) and panic attacks showed higher prevalence of sleep paralysis (between 65% and 100%) compared to healthy controls (20–25%) in several studies [145, 148, 149].

Diagnosis and Treatment of Sleep Paralysis Diagnosis of ISP is based upon clinical interviews and/or questionnaires [145, 150]. PSG may be useful to rule out sleep-disordered breathing and narcolepsy. Recurrent isolated sleep paralysis (RISP) consists of multiple episodes of isolated SP that are associated with clinically significant distress (e.g., anxiety and/or fear related to the bedroom/sleep) [151]. Thus, it is recommended that any assessment of SP be made within the context of other psychiatric conditions.

Treatment of SP is often not warranted, as the majority of patients do not experience clinically significant distress and/or impairment. Psychopharmacological options have been utilized to treat SP usually in the context of narcolepsy. The most commonly used agents are tricyclic antidepressants and selective serotonin reuptake inhibitors. Their hypothesized mechanism of action is the suppression of REM sleep [151–153]. Sodium oxybate (gamma-hydroxybutyric acid [GHB]) may lead to reduction in SP episodes, but studies have been inconsistent [154, 155]. Cognitive behavioral therapy and improving sleep hygiene may be useful.

Exploding Head Syndrome (EHS)

Exploding head syndrome (EHS) is characterized by the perception of a sudden loud noise in the head as the patient is falling asleep or awakening from sleep. The frequency is highly variable, from single episodes to clusters of episodes [156]. A variety of other symptoms have been reported to occur, the most common being tachycardia, brief muscle jerks/twitches, and visual phenomena, often described as a flash of light [157]. About 5% of patients have a sensation of momentary respiratory arrest and require a deliberate effort to breathe again [156].

Prevalence of EHS Prevalence is unknown as it is often underreported by patients to the medical providers. A recent study of 211 undergraduates found a lifetime prevalence of 18% and a recurrent prevalence of 16.6% [158]. It appears to be slightly more common in women and patient with psychiatric diseases [159]. Emotional stress and anxiety may lead to disrupted sleep which in turn may trigger EHS symptoms in some people [159].

Management of EHS Treatment is often not needed aside from providing education and assurance [160]. Given the association with stress, relaxation techniques and cognitive-behavioral therapy (CBT) may be an effective treatment option [159]. Benzodiazepines, tricyclic antidepressants, nifedipine, and topiramate have been reportedly effective [159, 161–163].

Diagnosis and Management of Parasomnias

Diagnosis of parasomnias relies on clinical description and is made by obtaining a clinical history from both the patient and the bed partner. Home videos are very important for proper definition of the events. An overnight video-PSG is also required for a diagnosis of REM sleep behavior disorder (to confirm REM sleep without atonia) but not for NREM parasomnias except for the purpose of excluding other sleep or neurological problems (e.g., sleep apnea, periodic limb movement disorder, and epilepsy).

Parasomnias are often exacerbated by sleep deprivation or sleep fragmentation, stress, and anxiety. Treatment of underlying psychiatric disorder (anxiety, depression, PTSD) may decrease the frequency of events.

Patient education and behavioral management represent the first treatment approaches to the patient with parasomnias. Education, reassurance, and a safe environment are important parts of treatment. Maintaining a consistent and regular sleep schedule is very important to avoid acute and chronic sleep deprivation. Environmental precipitants such as insufficient sleep, stress, caffeine, and certain medications should be avoided.

A pharmacologic treatment of parasomnias may be needed in special cases. The main indications for a pharmacologic treatment in patients with disorders of arousals (DOA) encompass the following: (1) Persistence of frequent episodes despite resolution and removal of all potential predisposing and precipitating factors. (2) High risk of injury for the patient or the family. (3) Significant functional impairment (such as insomnia, daytime sleepiness, and weight gain from nocturnal eating). (4) Potential legal consequences related to sexual or violent behavior [47].

Intermediate and long-acting BNZ agents are the most frequently used. They are GABA-A receptors enhancers leading to a hypnotic–sedative effect. The exact mechanism of BZD on parasomnias is unknown. They may have a combined effect on sedation/ sleep induction, arousals suppression, and decreasing slow-wave sleep

[47, 164, 165]. Among the BZD class, clonazepam at 0.5–2 mg is the most common medication used [47].

Antidepressant drugs have been shown to be effective in some parasomnias [166]. Anecdotal data reported efficacy of tricyclic antidepressant (imipramine or clomipramine) and trazodone [21]. Selective serotonin reuptake inhibitors (SSRI) particularly, paroxetine, have shown efficacy in sleepwalking and night terrors [167]. Single case reports have shown the efficacy of other pharmacologic treatments, such as melatonin, hydroxytryptophan, and ramelteon [47, 168–170]. Buspirone can be considered an effective alternate treatment option for NREM parasomnias when other medications are not preferred or cannot be prescribed [171].

Conclusion

In conclusion, parasomnias are common in the general population, especially among children. They consist of complex behaviors during sleep due to inappropriate activation of physiological systems controlling motor activity and/or the autonomic nervous system. Some parasomnias are usually benign such as night terrors; however, others such as REM behavior disorder can result in injuries not only to the patient but also to the bed partner. It is thus necessary for clinicians to recognize, evaluate, and manage these sleep disorders.

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Part V

Sleep Disorders in Special Populations

Sleep and Psychiatric Problems in Children and Adolescents

13

Kishan Nallapula and Ron B. Mitchell

Introduction

Sleep represents a third to two-thirds of the child and newborn's day–night schedule. However, lack of sufficient sleep duration can hinder children's cognitive and psychological growth. While acute sleep deficiency might be reversible, untreated and persistent sleep problems might lead to a more chronic, persistent psychopathology. Thus, awareness of and screening for sleep disorders in young children is very important. There are six major sleep disorders: insomnia, hypersomnia, circadian rhythm problems, sleep-related breathing problems, movement disorders, and parasomnias. For the purposes of this chapter, we define children as anyone below the age of 12 and adolescents as 12–18.

Normal sleep patterns change by age; for example, newborns have a polyphasic sleep pattern lasting 2–3 hours at a time and interrupted by arousal to eat. This is in contrast to the biphasic sleep in children, who have a solid nighttime sleep with one or two naps during the day, usually until age 5 years. In those 5 years old and older, monophasic nighttime sleep is expected. Similarly, duration of sleep varies by age (Table 13.1) [1]. Estimating the prevalence of sleep disorders in children and adolescents is, thus, difficult and generally ranges from 4% to 50% [2]. The definition of insomnia varies by study, with some measuring poor sleep duration as the only diagnostic criteria, while others include daytime consequences. Thus, the prevalence of insomnia in children depends on the diagnostic criteria used and varies considerably.

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Table 13.1 Normal sleep parameters in children

Age	Total sleep time	Naps (on average)
0–2 months	16–18 hours	3.5 per day at 1 month of age
2–12 months	12–16 hours	2 per day at 12 months of age Most children 6–9 months of age sleep through the night
1–3 years	10–16 hours	1 per day at 18 months of age
3–5 years	11–15 hours	50% of 3-year-olds do not nap
5–14 years	9–13 hours	5% of whites and 39% of blacks nap at 8 years of age
14–18 years	7–10 hours	Napping in this age group suggests insufficient sleep or a possible sleep disorder

Development of Sleep Patterns in Infants and Toddlers

Newborns sleep most of their life, up to 18–22 hours daily, while waking up every 1–3 hours for feeding. At 6–9 months, infants are able to consolidate their nighttime sleep to 10–12 hours at night, with one or two naps during the day [3]. This consolidation is related to the infants' improved ability to retain calories as they require fewer meals overnight, leading to less interrupted nighttime sleep. At the same time, infants' biological rhythms mature, which further helps to consolidate sleep. By 6 months, most infants can sleep through the night for 8 hours without feeding.

There are several physiologic arousals that occur during nighttime between sleep cycles. Infants who learn to self soothe are more likely to fall back asleep into the next sleep cycle and are able to further consolidate their sleep. Acquisition of new milestones during the first year may also impact consolidated sleep. Infants who can sit or stand up during the night when they awaken may sustain increased arousals, leading to less consolidated sleep. Physiological separation anxiety (i.e., when infants are unable to self-soothe), typically occurring between 6 and 18 months of age, may also disrupt sleep.

Development of Biological Rhythms

Melatonin and cortisol are the key hormones that regulate the sleep cycle. Changes in body temperature, ambient temperature, light exposure, hunger, and hormonal production help in establishing a biological rhythm for the infant (see Chap. 1). Melatonin production does not rise to detectable levels until 6 weeks of age. By about 6 months, melatonin becomes an integral part of the sleep–wake cycle. Exposure to morning daylight facilitates melatonin suppression during the day, while darkness at night stimulates a melatonin surge that helps to induce sleep. In addition, cortisol, prolactin, and growth hormone levels change during the sleep–wake cycle. Cortisol secretion, for example, peaks in the early morning and is at its lowest levels at 4 am. This morning cortisol rise increases blood glucose, and glucose metabolism facilitates daytime activity [4]. The role of prolactin and growth hormones over daytime function is less understood.

Development of Ultradian Rhythms

Newborns' sleep stages are described as "active," "indeterminate," or "nonactive"; this distinction is used as many of the specific waves characterizing sleep stages develop later in life (i.e., delta waves develop at 4 months). Active sleep is similar to rapid eye movement (REM) sleep, while nonactive sleep is similar to nonrapid eye movement (NREM) sleep. Electroencephalogram (EEG) patterns during active sleep consist of continuous moderate activity similar to that seen during wakefulness. Newborns enter the sleep cycle through an active stage of sleep and then transition to nonactive sleep for the first 3–6 months of life. Newborns, in contrast to older children, appear to be restless during sleep because of the lack of inhibition of muscle movement during active/REM sleep. In addition, the onset of sleep in newborns is characterized by the occurrence of active sleep (equivalent to REM) and is normal, whereas if this was to occur in older children, it might signify narcolepsy. EEG shows bursts of slow waves, intermixed with sharp waves and periods of relative quiet, reflecting very low-amplitude activity in nonactive sleep during the first 3–4 weeks of age. At about 4–8 weeks, sleep spindles (waves that occur mainly in stage 2 NREM) are seen. By about 6 months, high-amplitude slow-wave spikes or K-complexes (also occurring during stage 2 NREM) can be seen [5].

Ultradian rhythm cycles (i.e., cycles repeated in less than 24 hours) are shorter in children and get progressively longer with age. Infant active/nonactive sleep-phase cycles occur approximately every 45–60 minutes. Active/REM sleep is about 50% of total sleep time at birth, 40% at 3–5 months, and about 25–30% by about 1 year of age.

Sleep Disorders

The classification of sleep disorders in children and adults is similar and is addressed elsewhere in this book. However, there are some sleep disorders that are more prevalent or have some developmental characteristics that are specific to children and will be the focus of this chapter. The six main sleep disorders to be highlighted are insomnia, hypersomnia, circadian rhythm issues, sleep-related breathing disorders, movement disorders, and parasomnias.

Insomnia

Insomnia is a common disorder in children and adolescents. Insomnia is diagnosed when a child sleeps less than his/her same-age peers and experiences daytime impairment. While all types of insomnia can occur, two specific types of behavioral insomnia are common in children. This includes "sleep-onset association insomnia," in which the child associates his/her sleep with certain objects (e.g., a blanket) and cannot sleep without it, and "limit-setting insomnia," which occurs when the child stalls to avoid bedtime and sleep (e.g., by asking for food or other activities that prevent sleep onset).

Prevalence The prevalence of insomnia ranges from 10% to 30% in children and adolescents. In a cross-sectional study involving 700 preadolescent children, the prevalence of insomnia was 19.3% [5]. Studies conducted in the United States suggest a prevalence rate of insomnia in 11%. While there was no gender difference in the prepubertal period, a 2.75-fold increase prevalence in girls was reported postmenstrually [5].

Management The most common interventions are forms of behavioral therapy [6]. These include sleep hygiene, parental education, and use of consistent bedtime routines. Parents must be educated regarding the adequate hours of sleep needed for the children based on their age. Regarding sleep hygiene, the sleeping environment should be calm without electronic devices, have minimal light, and be free from unnecessary sounds. Encouraging children to sleep in their own bed is very important, so the children are conditioned to fall asleep on their own. Price et al. (2012) reported that behavioral sleep interventions in infants can decrease both sleep problems and maternal depression in the short to medium term [7]. However, in a recent meta-analysis, a moderate effect was found in behavioral interventions in young children with insomnia and an insignificant effect in older children/adolescents and those with special needs [6]. However, the authors partially attributed this to the small sample sizes.

There are no pharmacological agents approved by the FDA for pediatric insomnia or other types of pediatric sleep disorders. It is important to diagnose primary medical and/or psychiatric conditions in children with sleep-related complaints as treatment of the primary condition might resolve the sleep disorder. However, in some cases, additional agents may be necessary to promote sleep. In such cases, informed consent and assent (from the child if appropriate) must be obtained with the understanding that such agents are used off-label.

Melatonin Receptor Agonists These include melatonin and ramelteon to decrease sleep-onset latency. Melatonin is a very common sleep supplement, available over the counter in different formulations for children. It is available in liquid, gummy, tablet, and soft gel forms. Melatonin has minimal side effects and is very safe even in overdose. However, there is a lack of regulatory oversight (thus variability of melatonin content) that poses a significant concern. While in clinical practice a higher dose of melatonin is often administered an hour before bedtime (i.e., 3–10 mg), studies report that a much lower dose (i.e., 0.5 mg) given 3–5 hours before bedtime to stimulate melatonin surge may be more appropriate [8]. Agomelatine is a melatonin receptor (MT) agonist at the MT1 and MT2 receptors and also a serotonin (5HT2C) antagonist that may help both insomnia and depression [9]. It is currently available in Europe and Australia, but not in the United States. Ramelteon, on the other hand, is a prescription drug that acts as a melatonin receptor agonist. There are limited published data on ramelteon in children, but it is

well tolerated. Ramelteon has a longer half-life and is more effective than melatonin in treating chronic insomnia [10, 11].

Antihistamine Agents These agents block histamine receptors and include diphenhydramine, dicyclomine, and hydroxyzine. Their use in children as sleep aids is widespread but unsupported by quality studies. It is important to note that there is a recent European Medicines Agency's warning about hydroxyzine causing cardiac complications, especially at higher doses.

Sedating psychotropic medications such as mirtazapine, quetiapine, and olanzapine have a similar mechanism of action and cause sedation. However, mirtazapine is only recommended if there are associated depressive symptoms. Antipsychotic medications have a significant side effect profile (including extrapyramidal symptoms and tardive dyskinesia) and are generally reserved for use with bipolar or psychotic disorders.

Alpha-2 Agonists Clonidine has an antihistaminic effect in addition to its primary alpha-2 agonism. These agents decrease sleep-onset latency. Anticholinergic load must always be considered while using these agents. Side effects such as dry mouth, constipation, and tachycardia are common. Overdose with these medications requires urgent medical attention. While guanfacine is also an alpha-2 agonist, it lacks the sedating effects of clonidine.

Benzodiazepine receptor agonists include lorazepam, midazolam, and clonazepam, as well as newer agonists like zolpidem and eszopiclone, and decrease sleep-onset latency. Concerns include abuse potential, sleep-related behaviors like sleepwalking and automatisms, and retrograde amnesia. Benzodiazepines are not the drugs of choice for sleep disorders in children, especially due to their potential cognitive consequences (e.g., memory disturbance).

Others Trazodone is a sedating antidepressant that has sometimes been used for sleep disorders. However, especially in males, priapism is a concern. Doxepin is a tricyclic antidepressant with sedating properties. However, due to a significant side effect profile including anticholinergic and cardiac effects, cautious use is advisable.

Hypersomnia

Hypersomnia is diagnosed when children sleep prolonged hours compared to age-expected duration (Table 13.1). Narcolepsy (with or without cataplexy), idiopathic hypersomnia, Kleine–Levin and hypersomnia due to medication, substance abuse, and psychiatric and/or medical conditions constitute this group of disorders (see Chap. 9).

Narcolepsy with or without Cataplexy This uncommon disorder occurs in 2–7 per 10,000 of the population [12]. Hypersomnia and nighttime interrupted sleep, cata-

plexy (with type 1), hypnogogic and/or hypnopompic hallucinations, and sleep paralysis are the cornerstone presentations to this disorder. However, when this disorder occurs in children, it is not until years later that other typical symptoms develop. Thus, confusing narcolepsy with neurological (i.e., cataplexy as seizures) or even cardiac conditions is common. Obesity and precocious puberty have also been reported. This disorder has been associated with infection, with some studies reporting higher prevalence after the H1N1 epidemic [12].

Idiopathic Hypersomnia This uncommon disorder affects 1% of individuals presenting to the neurology sleep clinic and usually is characterized by prolonged sleep time and excessive daytime sleepiness (EDS) [13]. Onset of this disorder usually occurs during the adolescent or early adulthood phase. Idiopathic hypersomnia has been divided into those with prolonged sleep (requiring more than 10 hours) versus those without prolonged sleep. This can sometimes be confused with narcolepsy, given the similarity of EDS. However, in contrast to narcolepsy where they would have interrupted nighttime sleep, idiopathic hypersomnia individuals usually sleep much longer and uninterrupted hours. In addition, unrefreshing naps (narcoleptic individuals get refreshed after a 10- to 20-minute nap), family history of hypersomnia, and longer sleep latency on a multiple sleep latency test add to the distinction of this disorder from narcolepsy [14]. In contrast to episodic disorders (such as Kleine–Levin), EDS is persistent with hypersomnia. It has a familial tendency with autosomal dominant transmission (20–50%) [15–17].

Kleine–Levin Syndrome This rare disorder occurring in 1.5 cases per million mainly affects adolescents, with a relapsing and remitting episodes of hypersomnia, hyperphagia, and hypersexuality [18]. It affects boys more often than girls (60–90% are males), with episodes usually triggered by infection. It usually lasts about 14 years. Associated psychiatric disorders can occur in 30% of individuals with this disorder and include depression, anxiety, and delusions and/or hallucinations. Various psychopharmacological treatments have been used, including lithium, selective serotonin reuptake inhibitors, mood stabilizers, and even stimulants.

Circadian Rhythm Sleep – Wake Disorders

The superchiasmatic nucleus is the main circadian clock which is affected by both zeitgebers (social cues) and light from the eyes. Circadian rhythm sleep disorder occurs when the body's circadian clock is "out of sync" with daylight or with the individual's needs like work or school. In adolescents, there is a physiological sleep-phase delay. However, this usually conflicts with the need for an early rise time for school and can lead to significant sleep deprivation.

Prevalence Circadian rhythm sleep disorders are common in adolescents, especially phase delay, reaching a prevalence of over 3% [19]. Some studies suggested

even a higher prevalence reaching 16% [20]. A higher prevalence in girls than in boys has been reported (4% versus 3%, respectively) [19].

Circadian Rhythm Problems and Psychiatric Comorbidities Adolescents with circadian rhythm phase delay and an associated decrease in the number of hours of sleep will often present with daytime sleepiness, poor concentration, and irritability/poor emotional self-regulation and family conflicts [21]. Inadequate sleep in adolescents is also associated with high-risk behaviors through disruption of reward-related brain function, leading to recreational drug use, impulsivity, high-risk sexual behavior, and self-injurious behaviors [19, 21, 22].

Circadian Rhythm Problems and Medical Comorbidities Some studies highlighted the possible contribution of circadian rhythm problems in the development of obesity [23].

Management Treatment includes sleep hygiene, bright light therapy, and blue light therapy that focus on promoting earlier sleep onset. Chronotherapy is a modality that gradually delays sleep onset over 2 weeks until the desired time is reached, which can then be maintained. Melatonin given about 1 hour before anticipated bedtime is a safe over the counter option for children and adolescents struggling with a circadian rhythm sleep disorder.

Pediatric Sleep-Disordered Breathing

Primary Snoring (PS) and Obstructive Sleep Apnea (OSA)

Primary snoring (PS) occurs when there is snoring during sleeping without decreased or cessation of airflow with oxygen desaturations. In contrast, obstructive sleep apnea (OSA) is associated with respiratory events, which can range from complete cessation of airway flow (despite brain stem stimulation of a breath; also known as apnea) to oxygen desaturation and airflow restriction (also known as hypopnea). These respiratory events are calculated per hour (i.e., index). In children younger than 18 years, most researchers consider levels below 1 per hour as normal, mild OSA as from 1 to 5 per hour, moderate OSA as from 5 to 10 per hour, and severe OSA as more than 10 per hour. However, others argue that greater than 5 per hour in children is the level at which you would treat OSA unless there are significant comorbidities, such as attention-deficit hyperactivity disorder (ADHD), irritability, cognitive dysfunction, insomnia, or daytime fatigue [24]. It is more controversial with adolescents, however, as some suggest continuing to use the children's cutoff numbers, while others suggest using adult criteria. For adults, less than 5 respiratory events per hour is normal, with 5–15 considered mild, 15–30 as moderate, and more than 30 as severe OSA. Those with mild cases are only treated if they experience associated comorbidities (e.g., daytime sleepiness, insomnia, and headaches).

In children, mouth breathing and dry mouth in the morning, snoring, and early morning headaches can signify OSA. In addition, bed-wetting can signify airway obstruction, resulting in increased secretion of atrial natriuretic factor (ANF). Airway obstruction induces compensatory chest wall expansion, causing enlargements of atria that stimulates ANF secretion. This might also be related to the pressure exerted by the diaphragm on the bladder to bypass obstruction causing diuresis.

Prevalence The prevalence of OSA in children is 1–3%, with primary snoring occurring in 10% of the pediatric population. However, this rate can increase to 80% in children with Prader–Willi syndrome [25] or Down's syndrome and 60% in Marfan syndrome [26].

Psychiatric Disorders and OSA ADHD is a common neuropsychiatric disorder occurring in 3–16% of children. In a study of 45 children with ADHD and 29 controls, 32% of those with hyperactive/impulsive or combined subtypes of ADHD had chronic snoring, compared to 11% with the inattentive subtype of ADHD and 11% of controls. However, the small sample size, the use of a questionnaire to assess primary snoring (Pediatric Sleep Questionnaire), and failure to rule out OSA limit the study's generalizability [27]. In a larger cross-sectional study of 866 children, habitual snoring was associated with elevated hyperactivity symptoms, as assessed by the Conners' Parent Rating Scale, in 22% of children versus 12% of nonsnorers (odds ratio = 2.2) and hyperactivity was more pronounced in boys than in girls with an odds ratio of 4.3 [28]. Several studies report a higher prevalence of ADHD symptoms in children diagnosed with OSA [29]. Both inattention and hyperactivity/impulsivity symptoms are associated with OSA and improve after adenotonsillectomy (AT), the first-line treatment for the sleep disorder. In another large study of children, habitual snorers had an OR of 2.4 for hyperactivity, 4.0 for inattention, and 9.7 for peer problems [30]. This increased OR was independent of hypoxemia, and both inattention and hyperactivity, but not academic performance, improved with snoring cessation after treatment with continuous positive airway pressure (CPAP).

Children with primary snoring have been reported to have lower IQs [31] and reduced language and verbal abilities [32] compared to controls. A review in 2018, however, showed that OSA was not correlated with lower IQ [33]. There were conflicting findings and heterogeneity regarding the measures used and cognitive abilities assessed, highlighting the need for further research in this field. In addition, an overlap between psychiatric disorders and OSA exists. In a meta-analysis, a moderate relationship was found between children's ADHD symptoms assessed by rating scales and OSA [33]. However, contrary to expectation, a high severity of OSA was inversely associated with ADHD symptoms, but AT was found to have a moderate effect in improving both OSA and ADHD symptoms.

A moderate relationship was also found between depressive symptoms as assessed by rating scales and OSA, which also improved in a subset of children after AT [34]. The overlap in diagnostic criteria between depression and OSA including

insomnia, fatigue, and tiredness during the day and even increased suicidal thoughts make it challenging. In a meta-analysis, a higher prevalence of depressive symptoms, as assessed by rating scales, was reported in the children and adolescents with OSA than in controls [34]. AT leads to mild-to-moderate improvements of these symptoms.

A high prevalence of children with behavioral issues present to sleep clinics with their parents hoping to find an underlying sleep disorder as a cause. Subsequent parental symptom inflation is expected, and makes data interpretation difficult. In addition, usually the control group is recruited from the community with a lower likelihood of behavioral issues, representing a potential selection bias [35]. In addition, many studies have relied on a single subjective rating scale to assess OSA, without the use of objective data from polysomnography.

Medical Complications and OSA in Children Studies suggest that hypoxia and OSA are associated with more severe hepatic fibrosis [36]. Oxygen nadir severity is also associated with the stage of hepatic fibrosis and increases in liver function tests (LFT). These are interesting findings that are also reported in the adult OSA literature.

Management of PS and OSA Treatment of OSA will depend on etiology: in the younger population, adenotonsillar hyperplasia is the most common etiology. In these cases, AT is the first-line surgical therapy [37]. However, in a recent multicentered prospective double-blind study (Childhood Adenotonsillectomy Trial; CHAT study), mild cases of pediatric OSA responded to medications/observation as well as to AT [38]. In addition, while the OSA cure rate of AT reached 85% in mild cases of OSA, a high percentage of children with baseline moderate–severe OSA and/or obese children had residual OSA. Thus, the need to use positive airway pressure (PAP) treatments or other surgical methods may be required. For example, in children with craniofacial abnormalities (i.e., cleft palate and Crouzon syndrome), surgeries to increase the retropharyngeal space are required (i.e., maxillary expansion which includes the outward placement of both maxillary [i.e., maxillary expansion] and mandibular bones [i.e., mandibular advancement]). Repair of the cleft palate and lip might lead in some situations to a worsening of snoring. However, adenoidectomy might lead to increased risk of nasal regurgitation.

Apnea of Prematurity

Apnea of prematurity is a common condition in newborns who are born prematurely caused by central apneas due to underdevelopment of the respiratory center, decreased chemoreceptor sensitivity, and carotid body activity. Apnea of prematurity is diagnosed when there is a respiratory pause of more than 20 seconds of breathings or less if it is associated with oxygen desaturation, bradycardia (heart rate < 100/minute), cyanosis, or pallor [39].

Prevalence This will vary depending on gestational age, with an inverse relationship between gestational age and frequency. It occurs in almost all newborns under

29 weeks' gestation and decreases from 85% of infants born at 30 weeks' gestation to 20% of those born at 34 weeks' gestation [40]. Resolution of these apneic events occurs in 92% by 37 weeks' gestation and 98% at 40 weeks.

Management Apnea, cardiac, and oxygen monitoring are usually indicated for several days to a week in premature infants. Treatments with methylxanthines (i.e., theophylline and caffeine citrate) lead to increase in ventilation and carbon dioxide sensitivity and decrease in apneic events. However, tachycardia and emesis might emerge. PAP ventilation through the nasal route has shown to help by maintaining airway patency [41].

Hypoventilation Syndrome

Congenital alveolar hypoventilation syndrome (previously known as Ondine's curse) is a rare autosomal dominant disorder associated with autonomic dysfunction. It has been attributed to the mutation of PHOX2B gene on chromosome 4P12. It is attributed to low chemoreceptor sensitivity to hypoxia and hypercapnia. Ventilatory assistance either during the night or both day and night is often required.

Other uncommon types of hypoventilation syndrome include late-onset central hypoventilation with hypothalamic dysfunction (ROHHAD), hypoventilation secondary to neuromuscular disorders (i.e., Duchenne muscular dystrophy), and sleep-related hypoxia secondary to parenchymal disease.

Parasomnias

Parasomnias are undesirable behavioral events that are associated with sleep. This group of disorders is common in children, with a genetic predisposition to the disorder. It can be divided into those occurring during NREM or those in REM. Sleepwalking, confusional arousal, sleep terror, sleep-related eating disorder, and sexsomnia usually occur during NREM. REM behavioral disorder, nightmares, status dissociates, catathrenia, and isolated sleep paralysis all occur during REM. Chap. 12 discusses parasomnia in detail.

Movement Disorders

Movement disorders include restless leg syndrome, periodic leg movements, nocturnal leg cramps, and nocturnal seizures (i.e., frontal lobe epilepsy). These disorders can all occur in children and, thus, should be screened for. Readers are referred to Chap. 11 for more information about these disorders.

Sleep Problems in Children with Psychiatric Disorders

Sleep problems often coexist with psychiatric disorders. Psychopathology alters sleep patterns and architecture. Sleep disturbances, like sleep deprivation and caregiver shift work, induce transient mood changes even in individuals without a history of psychiatric disorders. It is of utmost importance to address sleep concerns at

every encounter with children and adolescents so as to minimize sleep-related confounding factors in the treatment of psychiatric disorders. Below are some specific sleep-related concerns in children with psychiatric disorders.

Attention-Deficit Hyperactivity Disorder (ADHD)

Children with ADHD have difficulties with sleep initiation, difficulty with bedtime routine, frequent awakenings, restless sleep, and a reduced total amount of sleep [42]. It is important to rule out OSA and other breathing-related sleep disorders that can overlap with ADHD. In addition, stimulants used to treat ADHD can sometimes cause delayed sleep onset especially if prescribed late in the day. Melatonin supplementation and clonidine can be used to treat sleep-onset delay [29].

Mood Disorders

Children with depressive disorders mainly have problems with sleep initiation and maintenance. Just as in adults with depression, a significant portion of children also have early morning awakenings with difficulty returning back to sleep [43]. Surveys of adolescents have also found an association between sleep disturbances and suicidality [21].

Autism Spectrum Disorders

About half to two-thirds of children with autism spectrum disorder (ASD) have associated sleep difficulties [44]. The most common problems are difficulty with sleep initiation and maintenance, nocturnal awakenings, parasomnias, and irregular sleep cycle. Sleep disorders in ASD are also associated with disruptive behavior during the day that is worsened by poor sleep at night [45]. The presence of digital media screens, like a television, tends to disrupt sleep more in children with ASD compared to those with ADHD [46]. Effective behavioral treatment and melatonin may be used to regulate sleep in children with ASD.

Anxiety Disorders

Children with generalized anxiety and obsessive–compulsive disorders have problems with sleep onset and decreased total sleep time [47]. Children exposed to trauma and abuse can also have persistent sleep problems frequently associated with nightmares. Systematic desensitization to fears and cognitive behavioral therapy has shown to improve sleep outcomes in children and adolescents with anxiety [48].

Evaluation

A sleep history from the child (if possible) and the caregiver is essential. A sleep history contains all the components of the child's day and nighttime routines. Emphasis must be given to onset of sleep, duration, total duration of sleep, quality of sleep, nighttime awakenings, sleeping milieu, dreams, and nighttime incontinence (enuresis).

A sleep log will be beneficial to record sleep issues. A sleep log ideally contains all the information above tracked over time. This could be done in a traditional pen

and paper method or using mobile device apps or wearables/smartwatches. However, the reliability and sensitivity of data provided by wearable devices are not yet well reported or validated [49].

There are well-validated scales and questionnaires that may also be used to obtain more specific data. These include the Pediatric Sleep Questionnaire (PSQ) [50], the Children's Sleep Habits Questionnaire (CSHQ) [51], and the Sleep Disorders Inventory for Students [52]. To assess the daytime sleepiness problems, the modified Epworth Sleepiness Scale (ESS) is often used [53].

There are several objective sleep measures that can be used to more accurately assess sleep: actigraphy, nocturnal polysomnography, the Multiple Sleep Latency Test (MSLT), and the Maintenance of Wakefulness Test are laboratory methods to obtain sleep data.

Conclusion

Sleep disorders in children and adolescents are highly prevalent in our society. Given the unpredictable and fast-paced lifestyle, biological rhythms are forcibly altered through artificial lighting, travel through time zones, and, perhaps most common among children and adolescents, electronic device usage. When social activities take precedence over biological needs, especially in the formative years of childhood and adolescence, sleep disorders frequently occur. The association between sleep and psychiatric disorders is well known. Establishing mandatory sleep screening questions at routine primary care visits during infancy and throughout childhood will help identify and treat children proactively. Routine education of sleep hygiene should be disseminated to students and parents through schools. Future epidemiological research through self-report surveys at schools in this population will provide valuable data to assess the burden of sleep disorders and implement appropriate strategies.

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Sleep Disorders in Women

14

Ashabari Pellechi and Karim Sedky

Introduction

Women transition through three major developmental stages during their lifespan: the prepubertal stage, puberty and childbearing stage, and postmenopausal period. While there are subtle physiological differences between genders during the prepubertal stage, it is not until the hormonal changes brought on by the onset of menarche that gender differences in sleep and mood dysregulation emerge. Recurrent variation in the steroidal hormones that control the menstrual cycle, specifically ovulation, menses, and also pregnancy, can have major impacts on both sleep and mood.

Sleep in women differs in a variety of ways, both objectively and subjectively, from men. Women tend to have subjective complaints of nonrefreshing sleep and also require greater need for sleep than men [1]. While women have longer sleep times, shorter sleep latency, and better sleep efficiency, women are more likely to report and experience sleep disturbances such as insomnia (47% greater) than men [2]. In fact, insomnia is estimated to be 1.41 (confidence interval [CI] = 1.28–1.55) times more prevalent in females compared to males [3]. Insomnia, restless leg syndrome (RLS), and obstructive sleep apnea (OSA) are the three most common sleep disorders documented in women (the first two being more common in females compared to males), with associated symptoms, such as fatigue, irritability, and headache [4]. Furthermore, hormonal shifts and mood symptoms present in the 10 days prior to menses, as well as those of pregnancy and menopause, are seen to increase the risk of sleep disorders among women. Psychosocial stressors may further

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precipitate the likelihood of developing these disorders from childhood through postmenopause.

Newborn to Childhood Period

Gender differences in sleep parameters are very subtle among newborns and children. In newborns, sleep is divided into active (equivalent to rapid eye movement, REM), quiet (nonrapid eye movement, NREM), intermediate (transition between NREM and REM), and indeterminate (difficult to score as NREM or REM) stages. Studies have been inconsistent in determining gender-specific results. Some suggest boys sleep less, with more active sleep and wakefulness after sleep onset, compared to girls [5]. However, given the gradual decline in REM duration with increasing age in early childhood, some attribute this gender difference to the relative delay in central nervous system (CNS) maturation occurring in males compared to females [6]. Overall, both genders reach the adult level of total sleep time (TST), 20–25%, by the age of 5 years.

Prevalence of Sleep Disorders in Childhood Insomnia is thought to occur up to 2.8 times more often in children with psychiatric and neurodevelopmental disorders (e.g., attention-deficit hyperactivity disorder [ADHD] and autism spectrum disorders) [7]. Sleep-disordered breathing (SDB) can reach a prevalence of 10% in children, while obstructive sleep apnea (OSA) ranges from 1% to 3%. Contrary to adult studies, gender does not increase the risk of SDB until children reach puberty, where the anatomy of the upper airway is more well defined [6].

Psychiatric Conditions and Childhood During the early childhood period, girls have low levels of sex hormones. Also at this time, gender differences in sleep duration or quality are not present, as girls and boys have an equivalent risk of sleep disorders [8]. Likewise, the prevalence of internalizing psychiatric disorders (i.e., depression and anxiety) is similar for girls and boys at this age. In a cohort of 653 preadolescents, a lower prevalence of depression was found in girls at age 11 (0.31% versus 1.79% in boys), with an equivalent prevalence at age 13 (2.19% versus 2.09%) [9]. In addition, during adolescence, depressed girls have been found to report more problems with sleep (either an increase or decrease) than depressed boys [10].

Medical Complications, Sleep, and Childhood Children who are short sleepers (sleep less than 5 hrs) have been seen to have an association with childhood obesity. In a study involving 126 only girls, short sleepers had increased carbohydrate intake [11]. Adiponectin and resistin were directly proportionate to the sleep duration and inversely related to weight in adolescent girls (i.e., adiponectin was higher in slim girls and increased with the increase in sleep duration) [11]. In contrast, ghrelin showed an inverse relationship with sleep duration in this population.

Menarche and the Reproductive Period

The onset of menarche in females primarily occurs between 11 and 13 years old, where the average age in the United States is 12.5 years [12]. During menarche, ovarian function increases, resulting in a gradual release of sex hormones, estradiol and progesterone, into the bloodstream in a cyclical fashion. The sex hormones are believed to regulate homeostasis of numerous organ systems, as well as the sleep–wake cycle [6]. These hormones are also thought to be protective factors for the development of SDB as highlighted by an unchanged prevalence in females before and after menarche, as compared to a significant increase in males after the onset of puberty [13]. However, significant reduction in slow-wave sleep (SWS) and greater daytime sleepiness in girls have been associated with later Tanner stages (i.e., stage 3 through 5) [14].

The menstrual cycle is divided into three stages based on the ovarian cycle (follicular phase, ovulation, and luteal phase), as well as the uterine cycle (menstruation, proliferative phase, and secretory phase) [15]. These stages are primarily controlled by ovarian sex steroids, estradiol and progesterone, and mediated by cyclic variations in gonadotropins [16]. Through neurofeedback, the hypothalamus releases gonadotropin-releasing hormone (GnRH), which subsequently stimulates the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary.

The *follicular phase* is characterized by a gradual rise in FSH, which both aids the development and maturation of ovarian follicles, and stimulates follicular granulosa cells to produce estrogen (mainly estradiol). During follicular maturation, estradiol rises. At first, its presence suppresses LH. However, during the *ovulation phase*, it results in GnRH stimulation, which causes a sudden rise in LH. This LH surge is responsible for the follicular release of an egg (i.e., ovulation) [17]. High estrogen levels during this part of the menstrual cycle are associated with vocal cord edema that can cause increased upper airway resistance. In addition, a decrease in genioglossal muscle activity during this stage can further compromise airflow, causing a stage-dependent increase in risk for OSA development (i.e., conducting a sleep study during follicular phase can yield a higher prevalence of OSA compared to other phases). Estrogen has also been associated with increases in durations of both REM and SWS, with a decrease in arousal index during sleep [18].

During the *luteal phase*, there is an increase in both progesterone and estrogen released by the corpus luteum. Progesterone causes increased secretions and higher viscosity and leads to an increase in the uterine thickness and lining to prepare for potential embryo implantation. The corresponding lower estrogen levels have been associated with laryngeal muscle size decrease and stiffer and thicker vocal cords, possibly causing a transient decrease in airway size. However, a decrease in airway resistance is expected due to the increase in genioglossal muscle activity. In addition, progesterone has been associated with anti-inflammatory effects. It is postulated that hyperarousal occurs during this stage. Some studies suggest increased daytime sleepiness (but no difference during evenings and nights) during the luteal phase, with an increase in SWS [19]. At the end of this phase, a sharp drop in

progesterone and estrogen occurs if implantation does not occur leading to menses. This can last from 2 to 5 days.

Some studies suggest an increased subjective sleep duration of 1 hr (although most of the night sleep is interrupted) 5 days premenstruation (i.e., during the luteal phase), with sleep duration shortest during ovulation in nondepressed women [20]. Others have not found a significant difference in either sleep structure or duration based on either subjective or objective measures [21]. While female sex hormones have homeostatic effects on the sleep–wake cycle, as well as cardiovascular and metabolic functions, they also appear to have protective effect on the airway, thus decreasing OSA risk.

Hormones, Temperature, and Other Contributors of Sleep Disorders

Body Temperature In males, temperature changes occur during the 24-hour circadian rhythm (see Chap. 1), with the lowest temperature seen 2 hrs before awakening. While a similar pattern occurs among females, it is important to know that body temperature also fluctuates during the separate phases of the menstrual cycle due to changes in sex hormones. During the *follicular phase*, a temperature pattern similar to males is observed. However, an increase of about 0.4 degrees Celsius occurs during the *luteal phase* due to progesterone secretion, with a corresponding decrease in temperature amplitude variability [22]. While some studies suggest a circadian rhythm phase delay in the *luteal phase* and increased nocturnal melatonin secretion, most studies have found comparable levels of melatonin in both luteal and follicular phases [22]. Since body temperature variation and melatonin play an integral factor in sleep pattern and duration, it is not surprising to see sleep duration variability secondary to these changes.

Progesterone Progesterone can improve sleep duration and quality through its sedating effects by stimulating gamma-aminobutyric acid (GABA) receptors, thus increasing SWS [6, 23]. In addition, GABA receptor stimulation enhances the hormone's antianxiety effects [24]. Progesterone is also noted to stimulate ventilatory drive and dilation of the airway through stimulation of the genioglossus muscle [6].

Estrogen Estrogen is thought to have a protective effect against the development of SDB, with decreased risk found among postmenopausal women who have been treated with estrogen (vs untreated) [25]. In addition, estrogen is thought to decrease the oxidative stress induced by chronic hypoxemia (since hypoxemia is common in individuals with OSA, mood disorders might be higher in this population secondary to brain damage) [26]. Estrogen's effect might decrease these hypoxic consequences over the brain and, thus, protect it. While animal studies suggest that estrogen decreases the amount and duration of REM sleep, in humans, it may actually increase REM cycles [27]. Since low estrogen levels can lead to a catecholamine surge, which can result in hot flashes, some studies recommend the use of exogenous estrogen during menopause to improve this common symptom. In addition,

due to high estrogen levels during the follicular phase, estrogen's thermoregulatory effects cause deeper and, thus, better sleep during this phase.

Cortisol Usually, cortisol level is lowest around midnight, followed by a slow increase 2–3 hrs after sleep onset that peaks around 9 am, after which it slowly declines again [28]. However, in stressful situations, levels of norepinephrine, corticotrophin-releasing hormone (CRH), and, in turn, cortisol increase. This rise in cortisol can result in increased electroencephalography (EEG) frequency, interruptions in nighttime sleep, and decreased SWS. Some have suggested that the administration of nutrients, such as vitamin B6, vitamin B5, vitamin C, L-tyrosine, and L-theanine, may help support HPA function via the adrenal glands. Of note, estrogen regulates the morning increase in cortisol that leads to the consolidation of nighttime sleep.

Melatonin Melatonin levels appear to be stable and not affected by hormonal changes in women. However, among depressed women, decreased melatonin amplitude and earlier secretion of melatonin during the *luteal phase* have been observed [20]. In addition, melatonin may decrease fertility in high doses through its disruption of the LH surge [27]. In addition, melatonin can cause decrease in testicular tissue in males [27]. Melatonin usually decreases with age in women especially after menopause.

Testosterone Testosterone levels usually decrease by the end of the day, followed by a slow increase with sleep onset that peaks during the first REM sleep cycle [29]. Research has demonstrated 10–15% decrease in testosterone levels in individuals whose sleep is restricted to 5 hrs per night for eight consecutive nights. In males, low testosterone has also been associated with obesity and OSA [30]. However, most of these studies suggest that obesity independently has a stronger negative correlation with poor sleep than low testosterone alone. For example, treating OSA with continuous pressure ventilation (CPAP) did not change testosterone levels much, in contrast to a decrease in weight, which in turn led to an increase in testosterone [31]. In fact, guidelines warn of potential worsening of OSA in individuals with deficient testosterone levels [32]. Testosterone has also been correlated with reduced sleep efficiency, decreased SWS, and frequent arousals [33].

Thyroid-Stimulating Hormone (TSH) and Prolactin Less is known about the effect of TSH and prolactin and their variability during menstrual cycles in females. Increased response of TSH to thyrotropin-releasing hormone (TRH) has been found in the premenstrual period, possibly mediated by estrogen [34]. Prolactin has been shown to increase dramatically during SWS stages and to decrease during REM stage. Studies suggest limited changes in this hormone during different menstrual

stages as well, with one small study suggesting a second prolactin peak occurring between 2 and 8 pm [35].

Prevalence of Sleep Disorders The prevalence of OSA among morbidly obese adolescent females is about 14.3%, a much higher prevalence than the 1–3% prevalence in the general pediatric population [36]. Furthermore, females with polycystic ovarian syndrome (PCOS) have a much higher prevalence of OSA, reaching 57% [36]. Insulin dependence, metabolic syndrome, and hyperandrogenism are also thought to increase the risk of OSA in this population.

Psychiatric Conditions and Reproductive Periods Although some authors have attributed an increased prevalence of depressive symptoms in females (female-to-male ratio of 2:1) to the cyclic changes of female sex hormones, others have more heavily weighed the roles of psychosocial and cognitive factors, which has ultimately led to multifactorial theories that explain such gender differences [37]. In an epidemiological study conducted in New Zealand, a cohort of 653 preadolescents were followed up for 10 years beginning at age 11 [9]. Interestingly, the study demonstrated a higher prevalence of depression in adolescent females relative to the age-matched males in the study. However, 11-year-old girls had a lower prevalence (0.31% versus 1.79% in males), and 13-year-old girls had an equal prevalence (2.19% versus 2.09%). Overall, the research demonstrated significant gender differences (females greater than males) at 15, 18, and 21 years of age (4.38% versus 1.19%, 23.19% versus 10.78%, and 25.08% versus 11.08%, respectively). While both genders had a significant increase in depression by age 18, females had more than double the prevalence of their male counterparts. Due to estrogen causing an increase in serotonin receptors, synaptic serotonin, and postsynaptic responsivity, it is thought to have antidepressant effects [27]. In addition, estrogen affects pain transmission and other somatic symptoms (such as headaches) and can, thus, indirectly precipitate depression [27, 38].

Premenstrual Syndrome (PMS) and Premenstrual Dysphoric Disorder (PMDD) Two to three weeks before menstruation, up to 80% of females complain of feeling tired, with associated insomnia or hypersomnia, and irritability with gastrointestinal symptoms (i.e., bloating). While symptoms of PMS are usually mild, the severity of symptoms of PMDD causes functional impairment in multiple aspects of women's lives, such as in employment or relationships. Furthermore, one study found that severity of PMS symptoms could be correlated with duration and percentage of REM sleep in the premenstrual period [48].

Sleep Disorders and Reproductive Periods Although circadian rhythm disorders are equally prevalent between genders, insomnia is more common in females.

However, studies suggest up to 28% greater prevalence of insomnia in females compared to males. This might also be confounded by additional factors, like societal expectations of women (i.e., doing childcare and working at the same time), as well as lower socioeconomic status (i.e., females tend to receive lower pay) [39]. It is important to note, however, that in addition to psychosocial factors, some women experience increased sleep disturbances in the premenstrual period, while others experience it mid-cycle [40]. Psychophysiological insomnia, which is a learned form of insomnia, characterized by excessive ruminative worry or hyperactive stress reactivity and arousal that impedes quality sleep, might be more common in females as well, partly due to the increased prevalence of mood symptoms [41].

Conversely, due to the protective nature of female sex hormones, the prevalence of OSA is found to be much lower among females. For example, in a small study of nine healthy females, polysomnography (PSG) showed that sleep-onset latency, wakefulness after sleep onset, and sleep efficacy were stable across different menstrual phases; however, an increase in stage 2 NREM and a decrease in REM were observed in the *luteal phase* compared to the *follicular phase* [42]. These changes during the *luteal phase* might lead to lower OSA levels compared to *follicular phase*, as respiratory events are usually more severe during REM compared to NREM. The literature also suggests that menopause may also increase the risk of developing OSA. In a sample of 133 obese women, 67% of postmenopausal women compared to 31% of premenopausal women met diagnostic criteria for OSA, using a cutoff of 10 per hr [43]. While aging independently increases the risk of OSA in both genders, the significant decrease in female sex hormones is thought to cause a synergistic increased risk in postmenopausal women, who were more often seen to have poor prognostic indicators, like greater neck circumference and waist-to-hip circumference. The importance of sex hormones in the development of OSA is also highlighted by a recent analysis of the Nurse's Health Study in which the early-onset menopausal group and surgically induced menopause group, that is, hysterectomy/oophorectomy, both showed a higher prevalence of OSA compared to the nonsurgical, age-normative menopausal group (hazardous ratio of 1.21) [44]. Of note, the sudden decline in sex hormones in the surgically induced menopausal population might explain their observed higher prevalence.

Menstrual-Related Hypersomnia This rare disorder involves hypersomnia in the temporal context of menses, especially in the last days of menses when sex hormone levels are low [45]. There is an additional overlap of this condition with psychiatric disorders in which increased sleep, weight gain, and depression are shared factors. It is thus not surprising to find that up to 35% of women with menstrual-related hypersomnia are present with symptoms of depression [45, 46]. Of note, hormone replacement therapy has been seen to most effectively treat this condition.

Medical complications Associated with Delayed Phase Sleep Disorder This sleep disorder is primarily thought to be the result of a conditioned temporal delay in an

individual's melatonin secretion, which is thought to have an integral role in sleep onset, maintenance, and awakening. Delayed phase sleep disorder is often seen in individuals who perform shift work, which has also been reported to affect menstrual cycle duration and to increase menstrual pain and bleeding [17]. For example, among the 8% of women who did shift work in the Nurses' Health Study II, 10% reported greater than 7-day variability in their periods. Those working shift work more than 20 months were more likely to have irregular cycles (relative ratio [RR] = 1.23) and to have cycles less than 21 days (RR = 1.27) or more than 40 days (RR = 1.49) [47]. Shift workers also have a higher prevalence of abortions, premature deliveries, and low-birth-weight babies [48]. Similarly, research has linked circadian rhythm dysregulation to breast cancer [17] and infertility in 34% of infertile women [49]. Proposed theories behind this relationship include the presence of a common pathway between stress, infertility, and sleep dysregulation through hypothalamic–pituitary–adrenal activation dysfunction. In addition, stress might cause acute persistent melatonin secretion, which has been linked to amenorrhea. Reduced innervation to reproductive organs and decreased uterine receptivity has also been proposed [50].

Pregnancy

Hormonal changes vary during the three trimesters of pregnancy, with a gradual increase in estrogen and progesterone. In general, estrogen has been associated with nasopharyngeal mucosal edema and rhinitis, leading to narrowing of the upper airway and increasing the risk of OSA [51]. However, when this is coupled by the increase in progesterone during pregnancy, it has been associated with respiratory stimulation by decreasing sensitivity to CO_2 leading to hyperventilation, lowering OSA risk. Altered sleep is common during pregnancy: during the first trimester, several contributing factors include nausea and vomiting, increased urinary frequency, backaches, and general discomfort. By the third trimester, sleep disorders occur secondary to fetal movements, acid reflux, RLS, and shortness of breath from the fetus causing pressure over the lungs [52]. In addition, the risk of OSA increases due to weight gain and hypervolemia, both of which are common in pregnancy. The upward displacement of the diaphragm that occurs as pregnancy progresses leads to decreasing functional residual capacity (i.e., the amount of air left at the end of passive expiration), causing less traction in the upper airway and increased collapsibility. To overcome these risks, females in the third trimester can sleep in a lateral posture, leading to tongue displacement to one side and further opening upper the airway. Some argue that the decreased REM duration that tends to occur during the later stages of pregnancy actually decreases OSA risk, given the higher risk/severity of OSA during REM compared to NREM. For example, cortisol increases by double the normal level from 25 weeks' gestation to the third trimester and up to 4.7 times during labor. Increased cortisol is thought to decrease REM and to increase SWS.

Prevalence Altered sleep (i.e., disrupted sleep and/or SDB) during the first trimester ranges from 13% to 80% and gradually increases to 66–96% in the third trimester.

The risk of snoring increases gradually during pregnancy, with prevalence rising from 7.9% in the first trimester to 21.2% in third trimester. Pregnancy is also associated with an increased prevalence (20%) of RLS, which usually resolves after delivery. However, a fourfold increase in chronic RLS does occur in those with transient RLS during pregnancy. Given the association between RLS and low ferritin levels, it is important to note the lower normal range of ferritin levels in females during reproductive age compared to males (35–40 mcg/l versus 150–200 mcg/l, respectively).

Psychiatric Conditions, Sleep, and Pregnancy The prevalence of depression ranges from 10% to 25% during pregnancy [53]. In a study of 273 pregnant females, decreased sleep quality early in pregnancy was associated with higher depressive symptoms later in pregnancy and during the postpartum period [53]. In contrast, baseline depression prior to pregnancy did not affect sleep, suggesting an important etiological role for sleep on depressive symptoms during pregnancy [53]. Other studies have found increased depressive symptoms in the second [54, 55] and third trimesters [56]. Additionally, in a recent meta-analysis, seven out of ten studies found a relationship between subjective sleep disruptions in the third trimester and development of postpartum depression [57]. However, most of the studies using objective measures of sleep (e.g., actigraphy) failed to find this link, though one randomized controlled trial reported an increased risk of postpartum depression among women who were treated for insomnia (using trazodone or diphenhydramine) [57, 58]. There was no relationship, however, between insomnia during the third trimester and postpartum anxiety or postpartum psychosis [57].

Medical Complications, Sleep, and Pregnancy Females sleeping less than 6 hours in the third trimester have longer labors and a 4.5-fold increase in Cesarean deliveries [59]. Pregnant females with SDB (i.e., either habitual snoring or OSA) have increased rates of both maternal and fetal medical problems, likely due to hypercapnia and hypertension. These include increased rates of gestational diabetes, hypertension (14% versus 6%), and preeclampsia (10% versus 4%) for mothers and fetal heart abnormality, growth retardation (7.1% versus 2.6%), and even death for the fetus [60]. In the 2003 Health Care Cost and Utilization Project involving almost four million deliveries, gestational diabetes was twice as likely, and there was also a fourfold increase in gestational hypertension among women who had SDB [61]. This latter finding may be due to intermittent hypoxia, leading to placental ischemia and increased oxidative stress.

Management of Poor Sleep in Pregnancy For sleep improvement, treatment of associated symptoms is important. For example, reducing spicy food and caffeine, elevating the head while asleep, and use of antacids can help with acid reflux. In addition, reducing ingestion of caffeinated beverages during the day and fluid intake prior to sleep can decrease nocturia. Side-sleeping, especially during the third tri-

mester, can help to enhance breathing. Psychotherapy and possibly medication can be considered for stress-related conditions and associated mood disorders. Since RLS occurs more frequently in pregnant females and studies suggest a higher prevalence of RLS in those not taking folate compared to those taking folate (80% vs 9%, respectively), folate and iron supplements are recommended in this population [52]. Other conservative measures include avoiding alcoholic beverages and smoking, treating anemia, massage, and calf stretches. While dopaminergic agents have been used in nonpregnant females, its teratogenicity is unknown (although these medications are class C drugs, and as such, not believed to be particularly unsafe). PSG should be performed if SDB is suspected, for example, among women with excessive daytime sleepiness, those with snoring, and those who develop gestational diabetes or hypertension. Positional sleep (elevation of bed position and use of a lateral posture) might help decrease the risk of SDB. CPAP continues to be the main treatment for SDB, and less frequently dental devices are utilized. Sometimes supplemental oxygen has been used, but risks of central apnea should be monitored. Surgeries are rarely used due to the risks versus benefits and the possible reversibility of SDB after pregnancy. Several studies suggest that OSA resolves within 3–6 months postpartum. This occurs due to the rapid weight loss (usually 10–15% weight loss), decreased abdominal size, and the return of hormone homeostasis following delivery. Breast-feeding has not been found to affect SDB prevalence in the postpartum period [62].

Postpartum Period

Sleep irregularity and mood disorders are common among new mothers in early postpartum. This might be partly due to the irregularity in sleep occurring in newborns, waking mothers up throughout the night. Newborns' sleep are characterized by a lack of diurnal rhythm, with total sleep ranging from 16 to 20 hrs, frequent arousals, and need for feeding, which often leads to disruptive sleep patterns for mothers. In addition, postpartum blues are very common, especially in those with their first child, with increased worry about adequately mothering [63]. Similarly, postpartum nonpsychotic depression is estimated to occur among 10% of newly delivered mothers, with rates reaching 13.5% (at 32 weeks of pregnancy) and 9.1% (at 2 months postdelivery) [64, 65]. Some mothers also might struggle with physical changes and medical complications postdelivery, including surgical healing, postprocedural complications, or infections.

Prevalence Sleep disorders are very common in the postpartum period, occurring in up to 16.5% of the female population, with insomnia occurring more often in this stage than during pregnancy or other periods of a woman's life [66].

Psychiatric Complications and Sleep Disorders Postdelivery In a recent systematic review, several studies have linked subjectively reported insomnia in the post-

partum period to the development of co-occurring depressive symptoms, with one such study demonstrating a significant reduction of depressive symptoms after treatment of insomnia [57, 67]. Another study following 124 primiparous women from their last trimester to 3 months postdelivery found that first-time mothers had higher prevalence of sleep disruption in the last trimester and depressive symptoms 3 months postdelivery. Excessive sleep can also be problematic, as increased sleep duration, later wake-up time, and frequent naps during the third trimester were each associated with increased risk of screening positive for depression at 2–4 weeks postpartum in a study of 38 primiparous women [68]. Moreover, in a cross-sectional study of 4,191 recently delivering mothers, prevalence of sleep disorders was demonstrated to be 57.7% as assessed by the Pittsburgh Sleep Quality Index, while 16.5% of the women screened positive for depression, as assessed by the Edinburgh Postnatal Depression Scale [65]. Associated depressive symptoms, a prior history of sleep struggles, and primiparity were each associated with poor sleep quality. In addition, having previous sleep problems was associated with a 3.4-fold increase in women's screening positive for depression. Similarly, in another prospective study of 46 women who had their sleep monitored via actigraphy for up to 6 months postpartum, mothers with postpartum depression also experienced worsened sleep quality. Sleep latency, wake after sleep onset, and sleep efficiency also predicted the severity of postpartum depression [69]. While the postpartum period is associated with hormonal dysregulation and an increase in inflammatory cytokines, a study of 56 women found poor sleep quality to be more strongly associated with the recurrence of postpartum depression than with these other factors [70]. However, while some studies suggest a possible relationship between anxiety and psychosis with sleep in the postpartum period, a recent meta-analysis did not find such a relationship to be correlated [71].

Medical Complications and Sleep in Postpartum Period In a study examining 940 first-time mothers, weight retention in the postpartum period was associated with insomnia, with an odds ratio of 3.13 for those sleeping no more than 5 hrs per night compared to those who slept longer [68]. This association might be related to insomnia, which can lead to an increase in ghrelin and a decrease in leptin, collectively causing hunger.

Menopause

Menopause usually occurs between 45 and 55 years of age and can be divided into perimenopause (early phase) and menopause (late phase), with the former associated with irregular bleeding and the latter characterized by amenorrhea lasting 60 days or more, and also FSH levels above 25 IU/L. The perimenopausal period can last from 2 to 8 years. During menopause, estrogen levels decrease, while FSH levels increase.

Estrogen has been noted to stabilize nighttime sleep and to regulate morning cortisol levels. Thus, with decreasing estrogen, nocturnal cortisol rises in menopausal women who experience mild stress. An increase in awakenings occurs in both the perimenopausal and menopausal periods (39–47% and 35–60%, respectively) [72]. Worse insomnia later in life has been associated with insomnia at a younger age, rapid drop in estradiol, and rapid rise of FSH. Hormonal fluctuations are associated with vasomotor symptoms leading to hot flushes and can also lead to increased arousals [73]. Hot flashes occur among 12.5% of premenopausal, 79.0% of perimenopausal, and 39.3% of postmenopausal women [73]. This, in turn, can lead to worsening insomnia, with insomnia occurring among 80% of those having hot flashes. While studies suggest worsening subjective sleep quality in perimenopausal and menopausal women, compared to those at childbearing age, some studies fail to find any sleep differences across these life stages, as assessed by PSG [74]. In addition, circadian rhythm disorders increase at the time of menopause. This might be related to decreases in estrogen, which lead to shifts in the temperature nadir to an earlier time of night, which can result in circadian rhythm phase advancement.

A gradual increase in the risk of OSA has also been found, with prevalence occurring among 71.6% of women in the postmenopausal period compared to 35.1% in the premenopausal period (when using an AHI cutoff of 5 per hour) [75].

Prevalence Insomnia, with its subtypes, occurs at a rate ranging from 28% to 63%, with an odds ratio of 1.5 in perimenopausal women and 3.4 in postmenopausal women compared to those of childbearing age [76]. Similarly, in a cohort study, an odds ratio of 2.0 and 2.2 for sleep dissatisfaction was found in women in perimenopause and postmenopause versus premenopause [74]. Chronic insomnia, in contrast, has been estimated to occur at a rate of 56.6% and 50.7% in peri- and postmenopausal women, respectively; this higher prevalence might be related to the worsening of hot flashes during peri-menopause [74]. This includes lower sleep efficacy, long sleep latency, and difficulty maintaining sleep, with frequent arousals [77]. In a study comparing objective sleep parameters, however, there was no difference between early versus late menopause [77]. However, in late menopause (more than 5 years after menopause), women more often reported complaints of excessive daytime sleepiness.

Psychiatric disorders and Menopause Women experience a higher prevalence of depression and anxiety during menopause. This increase might be related to hormonal changes, although the physiologic symptoms of menopause, such as hot flashes, struggles with adolescent children, empty nest syndrome, or spousal illness, can independently lead to functional impairment [78]. In a Massachusetts Women's Health longitudinal study of 2565 women, a history of depression prior to menopause and increased duration of menopause were both associated with a higher prevalence of postmenopausal depression [79]. However, most of the studies sug-

gest that the increased risk of depression occurs only during the transition to the menopausal stage and actually decreases in the postmenopausal period [80]. Interestingly, a rapid increase in FSH and decrease in estradiol levels during this time were associated with a lower risk of depression [81].

Management Insomnia is a common disorder among women transitioning through menopause. Depending on the type of insomnia, management should be similar to that for the general adult population. However, hormonal replacement therapy should be considered, as it might have an antidepressant effect, as well as direct sleep effects [27]. In a cross-sectional study, women treated with either transdermal or oral hormonal replacement therapy (HRT; i.e., estrogen with or without progesterone) reported less frequent sleep interruption and shorter sleep latency [80]. However, others have failed to find improvements [74]. As such, risk versus benefit should be considered, especially given the potential for associated risk with cancer and thromboembolic events while on hormonal replacement therapy [27]. Thus, some have recommended using a low dose of hormone replacement therapy for less than 5 years, especially to treat hot flashes. Herbal remedies have been used, with black cohosh having moderate effects on hot flashes [82]. Antidepressants (i.e., fluoxetine and venlafaxine) also significantly decrease hot flashes during menopause [83]. Clonidine and gabapentin have infrequently been used, with gabapentin sometimes preferred due to its effects in decreasing RLS symptoms [84].

Other Gender-Specific Factors

Some studies suggest that females are more sensitive to concussion [85]. Sleep disturbance after a single concussion is seen to be more severe in females compared to males. However, this gender difference becomes insignificant with repeated trauma. In addition, there is greater comorbidity of mood, headache, and cognitive changes following concussion in females compared to males [86].

Of note, women have been noted to have less complaints about excessive daytime sleepiness but a higher report of insomnia compared to men. Thus, differences unique to each gender should be taken into consideration during evaluation of sleep disorders. In addition, the medications can have a significant effect on sleep. Therefore, it is important to take a thorough history of all medications and to be vigilant of potential side effects. For example, tamoxifen has frequently been used to treat females diagnosed with breast cancer and might be associated with insomnia secondary to its effect of lowering melatonin levels.

Females diagnosed with PCOS have a particularly higher prevalence of excessive daytime sleepiness (80.4% versus 27% in controls). In PCOS, chronic increase in testosterone, as well as decreases in progesterone and estrogen, can lead to associated medical problems (i.e., diabetes, cardiovascular disease, obesity, and hyperlipidemia) that can also indirectly increase the risk of developing SDB [87].

Conclusion

Women often report sleep disorders as well as internalizing psychiatric conditions. While overlap of symptoms between the two conditions occurs, studies suggest the need to manage both disorders separately. Sleep disorders tend to be multifactorial in their cause, with hormonal changes, cyclic changes associated with menstrual periods, and social stress playing a major role in their etiology. Understanding the unique impact hormonal variations have on female patients during each development stage in their lives, that is, during premenarche, menarche, reproductive cycle, peri-menopause, and postmenopause, will ultimately aid clinicians in their ability to anticipate and appropriately tailor their management and treatment modalities, including hormonal regulation and/or supplementation.

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Sleep Disorders in the Geriatric Population

15

Shafagh Heidari and Steve Huege

Introduction

The quality and architecture of sleep changes over the course of the lifespan. Even in the absence of specific sleep disorder pathology, older adults experience alterations in their sleep patterns that can lead them to present with sleep complaints. Risk factors for primary and secondary sleep disorders increase with age. Complications from other medical disorders can also adversely affect patients' sleep, leading them to seek treatment for sleep complaints, some of which can create additional morbidity for older adults. The diagnosis and treatment of sleep complaints in seniors require a thorough understanding of both the normal and pathological changes that can occur as people age.

Changes in Physiology and Sleep Architecture with Normal Aging

Sleep structure, cyclic hormonal variability, and circadian rhythm entrainment all exhibit changes with age and can increase the risk of sleep disorders. Understanding these changes will help tailor management of sleep disorders in the elderly population and will be discussed below.

Sleep Structure Changes with Age

For individuals over the age of 65, sleep becomes more fragmented and less efficient. Older adults tend to have prolonged sleep latency (SL; the time it takes to transition from wakefulness to sleep), frequent nighttime arousals and awakenings

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[or wake after sleep onset (WASO)], and decreased total sleep time (TST). Sleep becomes less restful as well, with a decrease in deeper stages of sleep (i.e., slow wave sleep [SWS] and rapid eye movement stage [REM]) and a subsequent increase in stage 1 (N1) and stage 2 (N2) sleep due to more frequent spontaneous arousals. Some researchers associated the decrease in SWS to a decrease in growth hormone and prolactin as well as a lack of inhibition (i.e., increase) of ACTH and cortisol. Additionally, since parasympathetic activity increases in SWS, the associated decrease resulting from less SWS might lead to higher levels of cortisol, an increase in sympathetic activity, and utilization of brain glucose consumption (due to lack of parasympathetic activity) leading to medical complications [1]. To compensate for this decrease in SWS, many older adults will take daytime naps to increase their overall amount of sleep time [2–10].

With age comes an increasing prevalence of medical and psychiatric comorbidities, many of which can lead to sleep impairments. Some studies have shown that when controlling for comorbidities such as chronic pain, depression, and heart disease, the rates of insomnia in the aging population is considerably reduced [11, 12]. One study, which went a step further and controlled for social satisfaction and activity status, showed no association between aging and insomnia [13].

Melatonin

At night, the retina is stimulated by the dimming light which leads to the release of melatonin from the pineal gland. The initial rise of melatonin is called dim light melatonin onset (DLMO) and when melatonin levels reach a certain level, it promotes sleep. However, melatonin progressively decreases with age, eventually reaching daytime levels after the age of 65 [2, 10, 14, 15]. Thus, it is often an effective first line agent for older patients with sleep complaints as it can counter the effects of aging on endogenous melatonin levels [15]. Additionally, as individuals age, DLMO occurs earlier in the evening which can lead to sleep phase advancement in the elderly.

Cyclic Hormonal Changes with Sleep and Changes with Age

Aside from the changes occurring to melatonin secretion with age, other hormones such as prolactin, cortisol, and growth hormone also change with age. These hormones both decrease in amplitude and their onset occurs at an earlier phase in the evening, which in turn contributes to sleep phase advancement in older adults. Similarly, bodily temperature tend to increase in the afternoon and decrease to its nadir 2 hours before wake time. However, in older adults, there is a general decrease in the temperature amplitude difference and also a general decline in temperature [15]. Vasopressin secretion decreases with age as well which can contribute to nocturia and sleep disruption since it functions to reabsorb water from the kidneys and decrease urine output.

Zeitgebers and Changes with Age

The average duration of unstimulated sleep–wake cycle is approximately 24.5 hours. However, there are a number of external cues called zeitgebers that help entrain our

circadian rhythm to follow a 24-hour cycle. These cues include daytime activity, physical exercise, meal times, and most importantly, variations between light and dark [16, 17]. Darkness promotes the synthesis and release of melatonin by the pineal gland that then acts on the suprachiasmatic nucleus (SCN) to promote sleepiness. The SCN, housed within the hypothalamus, ultimately controls our circadian rhythm and the sleep–wake cycle [18–20].

In older adults, zeitgebers have less of an effect on circadian rhythm compared to their younger cohorts, thus, the possibility of a mismatch between the circadian rhythm and the needed sleep–wake cycle might be enhanced in the geriatric population [21, 22]. These changes and their effects on the sleep cycle of older adults can be further exacerbated by a number of factors including loss of daily structure (or typical work routines), increased daytime napping, or inconsistent exposure to light, such as in nursing homes where day and night blend together. This often leads to sleep phase advancement, a circadian shift in the sleep–wake cycle where older adults feel tired earlier and earlier each evening and then wake up earlier and earlier each morning. These changes in sleep architecture can result in less total sleep, decreased sleep efficiency (SE, the amount of time spent sleeping compared to the total time in bed), and early morning awakenings [6].

Pathological Sleep Changes in Medical and Psychiatric Disorders in Older Adults

I - Insomnia

The Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-5) identifies insomnia as difficulty falling asleep, staying asleep, or early morning awakenings that results in dissatisfaction with the quantity or quality of sleep. These sleep disturbances lead to impairment in social, occupational, educational, academic, behavioral, or other important areas of functioning, as well as cause significant distress. In addition, for a diagnosis of insomnia, the sleep disturbance must occur for at least three nights per week for at least 3 months and cannot be explained by the presence of another sleep disorder, psychiatric illness, or underlying medical condition [23].

Prevalence of Insomnia In a study involving 13,057 adult subjects from 3 countries, more than a third of the geriatric population complained about insomnia [24]. However, after controlling for activity level and social life satisfaction, there was no increased risk in geriatric for insomnia compared to the younger population. Insomnia in older adults often co-occurs with other disorders, whether psychiatric or medical, and the risk increases with the number of comorbidities. The prevalence of insomnia is over 60% in older adults with multiple comorbidities and is more common in women than in men [7, 9, 15, 25].

Medical Complications of Insomnia Insomnia is often underdiagnosed and can result in deleterious consequences such as chronic fatigue, impaired focus and con-

centration, cognitive decline, an increased risk of falls, worsening psychiatric and medical symptoms, increased risk of nursing home placement, and increased morbidity and mortality [7, 9, 25–30]. Potential medical complications include an increased risk of diabetes mellitus, which is thought to be due to impaired glucose control with subsequent insulin resistance and changes in the levels of leptin (decreased) and ghrelin (increased), which lead to increased food intake and weight gain. Additionally, alterations of the hypothalamic–hypophyseal axis lead to increased cortisol and sympathetic activities, with a resulting increase in inflammatory enzymes. These alterations increase the risk of hypertension, heart disease, and stroke [1].

Psychiatric Complications of Insomnia in Geriatric Individuals In a longitudinal study of middle-aged individuals over a 12-year period, insomnia in women predicted subsequent depression with an odds ratio (OR) of 4.1, but was not associated with increased mortality. In men, insomnia predicted mortality (OR 1.7) and had a higher rate of death at 1.9 times compared to nondepressed individuals. Similarly, in a Chinese geriatric community sample, mental illness was correlated with insomnia in males (OR 8.6) and depression in females (OR 2.2) [31]. Finally, in a study of 110 older individuals, 90% of participants with generalized anxiety disorder reported dissatisfaction with sleep, with a majority having significant sleep problems [32].

Insomnia and Dementia Insomnia is a common complaint in patients with dementia with up to 25–35% of patients with Alzheimer's disease reporting a sleep disturbance. Consequences of insomnia in this population include alterations in mood, significant caregiver burden, and even early nursing home placement [33–38]. Recent studies have shown that patients with dementia tend to have prolonged SL, decreased SE, decreased TST, and an increase in WASO or nighttime awakenings [11, 20, 34, 39, 40]. In individuals with Alzheimer's, there is also a decrease in REM sleep which is likely due to the deterioration of cholinergic neurons specific to this disease process since REM sleep is generated and maintained by cholinergic neurons. However, the most common sleep disorders in patients with dementia are excessive daytime sleepiness (EDS), nighttime wandering, and sundowning (agitation in the late afternoon/early evening) [10, 20, 41–48]. It has been postulated that the accompanying sleep disturbance may be due to a progressive degeneration of neurons in the SCN which regulates our circadian rhythm and sleep–wake cycle [20, 49]. Other common causes of sleep impairment in patients with dementia include poor sleep hygiene, medications or medication side effects, sleep apnea, restless legs syndrome, REM behavior sleep disorder, and/or circadian rhythm sleep disorders [26, 50]. Associated medical conditions such as chronic pain, psychiatric disorders such as depression and anxiety, and environmental factors can further increase this risk. Insomnia can worsen cognitive impairment in individuals with dementia; thus, it is important to com-

plete a thorough history and physical examination to diagnose and treat the underlying etiology [3, 4].

Evaluation Once you have confirmed that a patient has insomnia, further evaluation should be pursued to identify the type of sleep disturbance, risk factors for insomnia such as physical and psychiatric comorbidities and a discussion regarding their sleep hygiene to identify potential contributors to sleep disturbance. A thorough evaluation should include identifying the type of insomnia (difficulty falling asleep, nighttime awakenings, or early morning awakenings), asking about any family history of sleep disorders, identifying any distress or impairment in social, occupational, or educational functioning that has resulted from the sleep disturbance, identifying potential causes or factors contributing to insomnia (i.e., primary sleep disorders, acute or chronic medical causes, pain, psychiatric causes, poor sleep hygiene habits), assessing environmental factors that may contribute to insomnia, evaluating the patient's list of medications, and identifying any substance use (including alcohol, caffeine, and nicotine).

Discussion regarding good sleep hygiene is also crucial since behaviors such as napping during the day, using the bed for activities other than sleep or intimacy, lack of activity or exercise during the day, going to bed too early, and hospitalization-induced insomnia are common. Additionally, environmental factors such as limited sun exposure during the daytime (such as in nursing homes), noise, light, and cold/hot temperatures can precipitate or accentuate the risk of insomnia.

Other sleep disorders include circadian rhythm sleep–wake disorders (i.e., circadian rhythm phase advance), sleep disordered breathing (such as obstructive sleep apnea), and sleep related movement disorders (such as restless leg syndrome) should be excluded. Similarly, psychiatric causes (such as depression, anxiety, and adjustment disorder following the loss of a loved one) can also increase the risk of insomnia. Medical conditions contributing to insomnia should be excluded as well, whether acute or chronic in nature. These include pain (such as from arthritis or musculoskeletal pain), cardiovascular (heart failure), pulmonary (chronic obstructive pulmonary disease, pneumonia), gastrointestinal (constipation, acid reflux), urinary (incontinence, nocturia), and/or neurologic (Parkinson disease [PD], Alzheimer's disease [AD]) problems. Medications or substances such as antidepressants, psychostimulants, antihypertensives (hydrochlorothiazide, beta-blockers), parkinsonian medications (levodopa, selegeline), steroids, antihistamines, anticholinergics, alcohol, caffeine, and nicotine can also cause insomnia or excessive daytime sleepiness with subsequent sleep dysregulation [3, 7, 15, 51].

Physical Examination, Blood Work, and Therapeutic Interventions Further work-up should include a complete physical examination as well as appropriate lab work. Treatment will depend on the identified etiology of the insomnia and treating any underlying medical or psychiatric conditions, educating the patient on

appropriate sleep hygiene, implementing nonpharmacologic interventions (such as cognitive behavioral therapy for insomnia [CBT-I], which includes relaxation therapy and sleep restriction therapy), and sleep assistive medications [15, 25, 26, 51]. However, medications should be used for insomnia in the elderly only if other interventions have failed. A lower starting and maintenance doses of hypnotic medications are required, typically half the normal dose, to reduce the risk of adverse effects given the decrease in organ function (i.e., renal and hepatic clearance), and decrease in water content and increase in fat among older individuals [6]. Generally, there are four classes of medications used in the treatment of insomnia: [1] benzodiazepines (such as lorazepam, alprazolam, clonazepam, temazepam, halcion); [2] non-benzodiazepines or Z-Drugs (which includes zolpidem, zopiclone, eszopiclone, zaleplon); [3] sedating antidepressants (which includes trazodone and tri- and tetra-cyclics [TCA], although low-dose doxepine [silenor] is the only medication approved by the Food and Drug Administration [FDA] for this use), and [4] melatonin or melatonin agonists (ramelteon). Benzodiazepines tend to be the most frequently prescribed class among older adults, however, they carry considerable risk including daytime sedation, increased confusion, increased risk of falls, potential drug–drug interactions, and risk of tolerance, and dependence. Benzodiazepines should be used with caution, if at all, and at the smallest effective dose for the shortest duration possible (3–4 weeks). In addition, benzodiazepines with shorter half-lives are preferable since the risk of daytime sedation is lower [6, 15, 25]. Medications with anticholinergic properties, such as Diphenhydramine, should be avoided in older adults due to increased risk of confusion and delirium.

Insomnia Management in Residential Patients Some of the older adults, especially those with dementia, will reside in residential communities. One of the most common reports from staff members within these communities are sleep impairment and insomnia. When managing these cases, it is important to keep in mind that not all variations in sleep are necessarily pathologic. Residential communities have rigid sleep–wake times that may not coincide with every individual's natural circadian rhythm or accustomed sleep cycle. Additionally, as many of these individuals may be sedentary and napping throughout the day with limited daytime light exposure, it is not surprising that their nighttime sleep may be disrupted [16, 21, 49, 52–56]. Thus, educating caregivers and healthcare providers on proper sleep hygiene may prevent the addition of unnecessary pharmacologic interventions. Appropriate sleep hygiene recommendations include: [1] Physical activity during the day: although comorbid conditions, including dementia, may limit the amount of activity that can be tolerated, even light exercise such as walking can help improve sleep [2]. Light exposure during the day: patients in residential communities may not go outside as frequently compared to noninstitutionalized individuals and this may disrupt their circadian rhythm cycle and lead to sleep impairments. Making sure to go outside every day can help provide necessary external cues to maintain a normal circadian rhythm. Alternately, artificial light therapy can serve as a substitute for those who cannot venture out daily. In one major study, NITE-AD, exposure to bright

light was associated with a 32% reduction in WASO time [57]. A dose between 1000 and 10,000 lux for 30–90 minutes daily, 3 hours before bedtime has been shown to be effective [3]. Consistent sleep schedule: adapting to a consistent structured sleep time can help maintain an individual's circadian rhythm and should be encouraged [4]. Avoid napping during the daytime, [5] Avoid alcohol, tobacco, and caffeine, and [6] Create a comfortable sleeping environment: set a comfortable temperature and bedding, reduce noise, and light. In addition, [7] Avoid heavy meals prior to bedtime, [8] Limit fluid intake in the evenings, and [9] Use the bed only for sleep and intimacy [6, 20, 26, 53, 58–60]. Given the prevalence of poly-pharmacy and medication-related side effects in older individuals, it is worthwhile to educate patients and their caregivers on appropriate sleep hygiene before considering the addition of medications [3, 6].

II - Hypersomnia

Hypersomnia is characterized by excessive daytime sleepiness (EDS) despite adequate and uninterrupted sleep overnight. Symptoms include either recurrent episodes of sleep during the day or prolonged periods (>9 hours) of sleep overnight. Causes of primary hypersomnia include narcolepsy, idiopathic hypersomnia, and more rare etiologies such as Kleine–Levin Syndrome. Secondary causes of hypersomnia are more common and include OSA, RLS, and medication side effects.

Hypersomnia is not uncommon in the geriatric population; however, it can be difficult to distinguish from insomnia and napping (which can be normal in older adults). Evaluation should include both subjective and objective measures with sleep history obtained from the patient and their caregiver as well as the use of scales such as the Stanford Sleepiness Scale or the Epworth Sleepiness Scale [61].

Prevalence In patients diagnosed with PD, EDS ranged from 15.5% to 74%. While the exact mechanism is poorly understood, it has been postulated that the disorder arises from a neurodegenerative process occurring within the SCN. Hypersomnia has also been reported among up to 32% of individuals with Huntington's disease [62].

Assessment and Management As with insomnia, a thorough sleep history obtained from patients and caregivers can assist in identifying the underlying etiology of EDS (i.e., medication induced). If other sleep disorders are suspected, objective measures such as actigraphy and polysomnography (PSG) can be used for diagnostic exclusion, however, elderly individuals with dementia may not be able to tolerate these assessment procedures. Management of EDS should include treating any primary sleep, medical, or psychiatric disorder, and discontinuing any medications that may be precipitating or worsening the sedation. Medications that have been associated with EDS include anti-convulsants, antidepressants, antiemetics, antihistamines, neuroleptics, antihistamines, opiates, and skeletal muscle relaxants [61]. While stimulants are occasionally used, it is important to consider the risk of hypertension and cardiac effects that are associated with this class of medications.

III - Circadian Rhythm Sleep Disorders

In humans, there are a number of external cues that help entrain our circadian rhythm to follow a 24-hour cycle. These cues include daytime activity, physical exercise, arrival of a set meal time, and most importantly, variations between light and dark. Darkness promotes the synthesis and release of melatonin by the pineal gland that then acts on the SCN to promote sleepiness. The SCN, housed within the hypothalamus, ultimately controls our circadian rhythm and sleep–wake cycle [18–20]. However, melatonin progressively decreases with age, eventually reaching daytime levels after the age of 65 [2, 10, 14, 15]. Thus, it is often an effective first line agent for older patients with sleep complaints as it can counter the effects of aging on endogenous melatonin levels [15]. Other ways in which the circadian rhythm can be affected with age are described below.

Advanced Sleep Phase Disorder (ASPD)

ASPD is a circadian rhythm sleep disorder that is characterized by earlier sleep times (typically 6–9 PM) and earlier wake times (2–6 AM) [10, 63]. ASPD is thought to have a prevalence of only 1%, however, this may be a low estimate as many people with ASPD do not experience impairment in social or occupational functioning and may thus underreport symptoms. Because of early waking times, individuals do not struggle to show up to work on time or participate in daytime activities. However, due to earlier sleep times, some individuals may feel hindered in their ability to engage in social activities in the evening [4, 64–68].

Unless there is a co-occurring sleep or psychiatric disorder such as sleep apnea or depression, individuals with ASPD generally report normal sleep duration with good sleep quality and do not experience excessive daytime sleepiness.

Prevalence of ASPD Although the true prevalence of ASPD is unknown, it appears to increase with age and has a strong genetic link, with 40–50% of patients reporting a positive family history. Recent studies of patients with familial ASPD suggest an autosomal dominant transmission with a polymorphism identified in one of the key circadian rhythm genes (hPer3) [64]. In a study assessing sleep disorder in Huntington disease patients, 40% were diagnosed with ASPD [62]. ASPD is thought to be due to an advancement of melatonin cycles since melatonin normally increases in the evening to signal sleep onset. However, in geriatric individuals, melatonin levels increase earlier in the day leading to earlier onset of sleepiness.

Most people with ASPD will not be negatively impacted if their social and work schedules are aligned with their sleep schedules. However, for some individuals, it may not be possible to maintain early sleep times due to conflicting family or work schedules. Because they will still rise early, this may lead to subsequent sleep deprivation.

Management The American Academy of Sleep Medicine recommends chronotherapy and bright light exposure as the first line of treatment for ASPD. Chronotherapy is a behavioral technique that consists of delaying one's bedtime by small increments every night (e.g., 30 minutes to 1 hour) until their desired sleep schedule is achieved.

Light therapy consists of bright light exposure in the evening (7–9 PM) to mimic daytime exposure and delay sleepiness in conjunction with minimizing morning light exposure [10, 15, 66–70]. However, poor patient adherence with these techniques often hinders effective treatment.

Delayed Sleep Phase Disorder

Typically referred to as a "night owl" sleep pattern, delayed sleep phase disorder (DSPD) is characterized by sleep times that are delayed by two or more hours compared to conventional times [71]. Although this disorder is more common in adolescents, it can present dramatically in older adults if their sleep is delayed until the early morning hours. This sleep pattern may have worked well for an individual when they were younger, employed and had greater regularity to their sleep schedule. However, with retirement, there is typically less structure to their day and the external cues that regulate ones circadian rhythm weaken, which can lead to delayed sleep times. In the older population, this can lead to sleep–wake reversal with patients sleeping during the day and remaining awake in the evening [4].

Prevalence The estimated prevalence of DSPD in adults is 0.2–1.7% with both genders being equally affected. Additionally, there is often a positive family history in affected individuals [72]. Prevalence of DSPD in geriatric population is unknown.

Management of DSPD Treatments include behavioral changes (minimize caffeine, alcohol, and nicotine; avoid daytime napping; avoid stimulating activity 2 hours prior to bed; taking melatonin 3–5 mg 1.5 hours before bed (morning light exposure, avoid nighttime light exposure, hypnotics) [20, 71, 73].

Jet Lag

Jet lag occurs as a result of rapid travel across two or more time zones and is due to the body's internal clock becoming misaligned with the external light/dark cycle. The severity of symptoms worsens with increasing number of time zones crossed. Jet lag can affect all age groups; however, older adults tend to experience more pronounced symptoms and require longer periods of time to adjust (sometimes up to weeks or months) [9, 74]. Westward travel (delaying the sleep cycle) is more tolerable and causes less symptoms than eastward travel (advancing the sleep cycle) since it is usually easier to delay sleep onset than to fall asleep earlier [67, 75].

Symptoms usually begin 1–2 days after arrival to the destination and can include excessive daytime sleepiness, headache, cognitive complaints, and insomnia. For longer trips, one option to prevent jet lag would be to prepare for the time zone change by adjusting one's sleep schedule prior to travel. Shifting one's sleep schedule by ~1 hour per night 3–4 days prior to travel may alleviate or prevent jet lag symptoms. Another treatment option is timed light exposure to allow your circadian cycle to adjust to the new time zone. For example, if traveling eastward, which would require falling asleep earlier, one should maximize light exposure in the

morning and early afternoon while avoiding it in the late afternoon and evening [67, 75].

Although not approved by the FDA, melatonin is the treatment that has been recommended by the American Academy of Sleep Medicine for treating jetlag. The general recommendations are 2–5 mg of melatonin nightly, however, studies have shown that 5 mg of melatonin leads to overall better sleep [67, 68, 70, 76]. Benzodiazepines can be used as well and have shown to be efficacious in the treatment of jet lag. However, caution should be used in prescribing benzodiazepines in older adults given increased risk of falls, cognitive impairment, and delirium.

IV - Sleep Disordered Breathing

Sleep disordered breathing (SDB) is a broad term that encompasses obstructive sleep apnea (OSA) and central sleep apnea (CA). The prevalence of SDB generally increases with older age.

Obstructive Sleep Apnea (OSA)

OSA has become an increasingly common diagnosis among the middle-aged population in the United States, affecting 2% of women and 4% of men. Along with weight, age is an important risk factor – the prevalence of OSA increases with age and is associated with higher mortality in older adults [2, 3, 77]. Evidence suggests that the increasing prevalence of OSA with age is independent of other risk factors, including obesity [7, 78].

OSA is characterized by complete (apnea) or partial (hypopnea) airflow cessation during sleep, mostly due to airway collapse. This obstruction leads to an increasing amount of respiratory effort until the airways reopen and breathing is restored (see Chap. 7 for full details about sleep related respiratory disorders). Associated symptoms include snoring, morning headache, EDS, irritability, decreased focus and concentration, and, notably, memory impairment.

Prevalence OSA affects 25–35% of people over the age of 60, with rates highest among individuals in residential settings, affecting up to 49% of dementia patients [6, 7, 10, 79]. In a prospective study of 1394 individuals aged 50 or over who were followed for 14 years, obese individuals developed Alzheimer's disease an average of 6.7 months earlier compared to nonobese individuals [19]. While authors suggested OSA as moderator since increased risk of OSA is found in obese individuals, a major limitation was that OSA was not assessed. In another study, treatment of OSA with CPAP slowed dementia progression as assessed by mini-mental status exam scores during a 3-year period, decreasing by a score of −0.7 versus −2.2 in the non-CPAP group ($p = 0.01$) [80].

OSA and Dementia in Geriatrics While there are limited studies in this population, a small study of five individuals with mild to moderate dementia showed the use of positive airway pressure ventilation (PAP) treatment slowed memory deterioration and stabilized associated mood problems [81].

OSA and Medical Conditions OSA is now increasingly recognized as a potentially reversible risk factor for dementia [10]. Notably, SDB has a higher prevalence in individuals with Alzheimer's than in nondemented older adults and its severity is correlated with the degree of cognitive impairment [2, 10, 46, 77].

The transient episodes of apnea throughout the night result in repetitive periods of hypoxia and surges of sympathetic activity. Not surprisingly, OSA has also been increasingly recognized as an important risk factor for hypertension, metabolic disorders such as diabetes, myocardial infarction, CHF, and stroke, making it that much more important to recognize and treat early [2, 3, 7, 15, 47, 78].

Evaluation and Management OSA is diagnosed by clinical assessment and PSG, however, PSG can sometimes be difficult to conduct, especially in individuals with moderate to severe dementia. Treatment usually consists of using PAP nightly, although oral appliances or surgery can be utilized for those who cannot tolerate a CPAP machine. More conservative measures include weight loss, restriction of alcohol intake, avoiding respiratory depressants such as benzodiazepines, and elevating the head during sleep [3, 10].

Central Sleep Apnea (CSA)

Central sleep apnea is much less common than OSA and is usually associated with congestive heart failure or brain injury such as from a medullary stroke [82]. CSA is characterized by apneic episodes resulting from reduced or absent ventilatory effort. The absence of airflow in OSA is due to an anatomical defect, whereas CSA is due to a central deficit in respiratory effort or drive to breath. A single central apnea episode consists of a >10 second pause in ventilation with 5 or more episodes per hour. In patients with congestive heart failure, CSA can be characterized by the Cheyne–Stokes respirations – a pattern of breathing that consists of an initial increase in ventilation followed by decreased ventilation (crescendo–decrescendo breathing pattern) [1, 19]. The first line of therapy should be to optimize treatment of the patient's heart failure. Other treatment options include PAP therapy, nocturnal oxygen therapy, and Adaptive Servo-Ventilation (ASV) [83]. This latter machine usually has a sensor that would pressure air into the individual's airway when there is a sensed missed breath.

Prevalence CSA is less common than OSA, with an estimated prevalence of 0.9%. While prevalence of CSA will be very variable in geriatric populations due to variability in comorbidity, it is more commonly seen in patients with heart failure and has a higher prevalence in men than women (1.8% and 0.2%, respectively) [83].

V - Sleep-Related Movement Disorders Including RBD, RLS, and PLMD

Restless Leg Syndrome

Restless Leg Syndrome (RLS) is primarily a clinical diagnosis and is characterized by the following: [1] A painful or uncomfortable sensation, sometimes described as

a burning or aching, that is accompanied by an urge to move one's limbs; [2] The sensations and urge to move occur or worsen during periods of rest and primarily at night. Typically, symptoms arise at night when lying in bed [3]. In addition, the sensations are relieved with movement such as walking or stretching.

Prevalence RLS affects about 10% of adults. A positive family history, co-occurring Periodic Limb Movement Disorder (PLMD), lack of excessive daytime sleepiness, and response to dopaminergic medications provide further support for a diagnosis of RLS [3, 84–87]. The prevalence of RLS increases with age, is more common in females, and has a genetic predisposition with mutations found on chromosome 6.

RLS, Psychiatric Conditions, and Sleep Conditions RLS can be very frustrating and, understandably, leads to difficulty falling asleep (prolonged sleep latency) and can also lead to EDS, anxiety, depression, and decreased quality of life. RLS has been linked to decreased D2 binding activity, and as such, may be induced or worsened by selective serotonin reuptake inhibitors (SSRIs), selective serotonin norepinephrine reuptake inhibitors (SNRIs), TCAs, antipsychotics, and antiemetics.

RLS and Medical Conditions RLS can present as a primary condition or may be secondary to iron deficiency, pregnancy, peripheral neuropathy, spinal cord injury, renal failure, and/or certain medications [84, 86]. There have been some studies to suggest that RLS has a higher prevalence in patients with PD, however, the data to support this association has been inconsistent thus far [84].

Since symptoms of RLS share certain features with other conditions, it is important to consider the differential diagnosis and rule out akathisia, peripheral neuropathy, nocturnal leg cramps, and peripheral vascular disease [84].

Evaluation and Management of RLS In patients with RLS, evaluation of iron stores (especially obtaining and maintaining serum ferritin levels above 50 ng/mL) and correcting iron stores is essential. Evaluation of the patient's medication regimen and possibly reducing the dose or discontinuing any medications that may be causing or worsening RLS symptoms (aside from mirtazapine, bupropion, buspirone, and BNZs) can also be helpful as most of the psychotropic medications will worsen RLS.

Treatment of RLS depends on the frequency and severity of symptoms and whether it is of primary or secondary origin. Not every patient with RLS will require treatment or medications. However, regardless of cause or severity, recommended nonpharmacologic interventions include limiting caffeine, tobacco, and alcohol intake which can lessen symptoms in some individuals [84].

For patients with moderate to severe primary RLS (symptoms >15 days per month), there are several medication classes that have been shown to improve symptoms. Dopamine agonists, namely pramipexole and ropinirole, have been well studied and are considered first-line agents in the treatment of RLS. Alternative medications include gabapentin, carbidopa/levodopa (sinemet), ergotamine dopamine agonists (cabergoline and pergolide), opioids, and benzodiazepines [4, 84–86, 88]. However, the risk profile of opioid and benzodiazepine use in older individuals makes these classes of medications less favorable [89]. Some patients may require medications from multiple different classes. For refractory cases, consider referral to a sleep clinic.

For individuals with secondary RLS, treatment of the underlying etiology may relieve symptoms considerably. For patients with an iron deficiency, treatment with iron replacement therapy will often lead to symptom reduction and remission. If any medications have been identified as potential offenders, then consider discontinuing the medication. If RLS is secondary to ischemia or polyneuropathy, gabapentin or pregabalin may be the most effective and appropriate treatment [3, 88].

With regard to prognosis, symptoms of RLS follow a variable course and tend to progress with age. Some individuals may experience complete resolution of symptoms, especially if an underlying cause is identified and treated; however, recurrence of symptoms is typical for most [84].

Periodic Limb Movement Disorder

PLMD, previously called Nocturnal Myoclonus, is characterized by repetitive movements of the extremities, usually the legs, while an individual is asleep. The movements usually occur only in the first half of the night, arise in the first and second stages of NREM sleep, become progressively less frequent in the third stage of NREM, and remit at the onset of REM (since REM is characterized by atonia). The movements usually consist of twitching, jerking, kicking, flailing, or upward flexion of the legs. They typically occur for between 0.5 and 5 seconds at intervals of 4–90 seconds. Formal diagnosis of PLMD requires PSG showing at least 5 periodic limb movements per hour.

Prevalence of PLMD PLMD increases with age with typical onset in middle age and older individuals. PLMD as a distinct diagnosis is relatively rare – periodic limb movements during sleep (PLMS) are usually associated with RLS, narcolepsy, REM sleep behavior disorder, and OSA and are distinct from PLMD. However, more than 80% of patients with RLS will have co-occurring PLMD, although the reverse is not true [7]. Possible causes of PLMD include medications (such as antidepressants, benzodiazepines, and antipsychotics), iron deficiency, diabetes mellitus, neurodegenerative disorders (such as PD, Multiple System Atrophy, and Multiple Sclerosis), renal and/or hepatic failure.

Evaluation and Management The disorder is usually brought to the attention of a physician by the individuals' bed partner since patients with PLMD are usually

unaware of the movements or the subsequent brief arousals that follow. PLMD can present in patients as nighttime awakenings, poor sleep, daytime fatigue, or EDS. Treatment for PMLD is essentially the same as treatment for RLS and consists primarily of dopamine agonists including pramipexole, ropinorole, and rotigotine, as well as gabapentin, gabapentin enacarbil, and pregabalin [4, 88, 90].

REM Sleep Behavior Disorder (RBD)

RBD is categorized as a parasomnia and is characterized by abnormal or disruptive behaviors during REM sleep that can potentially cause injury. Examples of reported behaviors include vocalizations, punching, kicking, grabbing, and flailing. Subjects with RBD may complain of sleep disruption or vivid dreams [7]. Occurrence of these events is variable and may occur rarely or up to several times per night. Diagnostic criteria for RBD include reported symptoms from the patient or their bed partner of potentially injurious disruptive behavior during sleep and polysomnography showing absence of atonia and/or abnormal behaviors during REM sleep.

Prevalence of RBD RBD occurs in 0.5–1% in the general population and 2% in older adults, with men more frequently affected than women. It usually presents in individuals over the age of 50, with average age of diagnosis between 60 and 70, and is significant for its high association with alpha-synucleinopathies [3, 7, 20, 91–93].

RBD and Dementia In patients with RBD followed longitudinally, 38% developed a synucleinopathy at 10 years and 65% at 29 years following RBD symptom onset. RBD has been identified in 33–50% of patients with PD, 80–95% of individuals with Multiple System Atrophy (MSA), and 80% of patients with Lewy body Dementia (LBD). RBD has also been associated with narcolepsy and medication use or withdrawal, but this is typically seen in individuals 40 years or younger.

RBD and Psychiatric Conditions Individuals with confirmed or possible RBD are more likely to report moderate to heavy alcohol use and have a concurrent mental illness, with a higher prevalence of depression and anxiety [94].

RBD and Non-dementing Medical Conditions RBD is also associated with narcolepsy (with up to 50% prevalence), pontine lesions, medications, and withdrawal from substances including alcohol, benzodiazepines, and barbiturates. Medications that have been implicated in precipitating RBD include SSRIs, SNRIs, TCAs, monoamine oxidase inhibitors (MAOIs), mirtazapine, and, less frequently, beta-blockers, and cholinesterase inhibitors [94].

Management of RBD Management of RBD should, first and foremost, center on establishing a safe sleeping environment. Pharmacologically, clonazepam, and melatonin have both been shown to be effective interventions [4]. However, given that RBD primarily affects older individuals, melatonin is the preferred agent due to its safer side effect profile [3].

VI - Other Medical Conditions that Significantly Affect Sleep

Chronic Pain

Chronic medical conditions have been shown to increase an individuals' risk of insomnia and other sleep disorders; however, the highest risk is associated with pain-related conditions such as arthritis, fibromyalgia, and rheumatic conditions [29, 95–98]. Chronic pain increases the risk of insomnia across all ages and increased pain severity is associated with an increased risk for insomnia [96, 97]. The mechanism by which pain leads to insomnia is multifactorial and one factor seems to be due to the behavioral changes made by older adults living with chronic pain. Often, they will limit their physical activity due to pain or fear of injury and this inactivity, in turn, contributes to sleep impairment and the resultant fatigue further reduces physical activity [99]. Additionally, chronic pain in itself has been shown to disrupt sleep by reducing SE, decreasing SWS, and increasing WASO [95, 97]. However, the relationship between sleep and pain is complicated and likely bidirectional as studies have shown that sleep deprivation can lead to hyperalgesia, likely through decreased REM sleep [29, 30, 100, 101].

Medications and Substances

Assessing insomnia in the elderly should always include a thorough review of their medications. Many older adults, especially those with multiple comorbid physical and psychiatric conditions, are likely to be on several medications which puts them at increased risk for adverse effects from polypharmacy. This is because elderly individuals have a larger volume of distribution (due to decreased muscle mass and increased fat deposition) and decreased drug clearance (due to impaired renal and hepatic function) [6]. Thus, clinicians should attempt to reduce medications to the lowest effective dose and discontinue unnecessary medications when possible. Additionally, the timing of medication administration should be clarified as well so that activating medications are taken in the morning and sedating medications are taken at night [6]. Medication classes that have been linked to sleep disturbance include: sedating medications (including anti-histamines, anticholinergics, anticonvulsants and/or opiates) and activating medications (such as psychostimulants, antidepressants as buproprion, duloxetine, beta-agonists, Parkinson's medications (levodopa, selegiline) and steroids) [7, 102]. Other medications may worsen primary sleep disorders or medical conditions which, in turn, contribute to insomnia. For example, certain antidepressants can exacerbate RLS and PLMD, benzodiazepines and opiates can worsen sleep apnea, and beta-agonists decrease melatonin secretion and increase WASO [7].

Aside from medications, there are a number of substances that many older adults frequently use that are often overlooked but have been shown to impair sleep. These substances include caffeine, nicotine, and alcohol which may have a greater impact on the elderly, compared to their younger counterparts, due to reduced clearance. Caffeine's stimulating effect can last from 8 to 14 hours in older adults and can increase sleep latency and nighttime arousals [6, 7, 103]. Nicotine's stimulant effect is thought to be due to its actions on acetylcholine transmission. Aside from its stimulating effects, nicotine is thought to contribute to sleep impairment via nighttime withdrawal symptoms and a higher prevalence of sleep disordered breathing in smokers [7, 103]. Alcohol, a depressant, may decrease SL when consumed acutely; however, it can increase arousals and lead to an overall decreased quality of sleep [6, 7].

Conclusion

Certain sleep disorders are common in the older population and gradually increase with age. Moreover, a bidirectional relationship is increasingly appreciated between the occurrence of sleep disorders and dementia. It is thus very important to evaluate and treat any sleep duration problems (i.e., sleeping too much or too little), respiratory events, and movement disorders. Biophysiological changes (e.g., brain degeneration) occurring in the geriatric population can create further complications and hinder optimal sleep. In addition, associated medical conditions and polypharmacy pose a significant risk for both sleep and psychiatric complications. Thorough assessment and management of sleep conditions, especially in individuals with psychiatric and/or medical conditions, is thus essential to optimize sleep and health in general among older adults.

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Sleep Disorders in Veterans: Prevalence, Consequences, and Treatment

16

Peter J. Colvonen, Guadalupe L. Rivera, and Jae Park

Sleep and Deployment

To better understand the disrupted sleep in the veteran population, it is important to take a moment and examine the chaotic sleep schedule, increased stress, and higher likelihood of physical and psychological injury in the active duty of military personnel. Poor sleep can start even at pre-deployment when an individual is maximizing their time with friends and loved ones [1]. Initial deployment is associated with flying across multiple time zones, sleeping in transient quarters, and the start of the "in-theater" deployment. In a survey done with active duty deployed personnel, it was found that 32% were concerned with insufficient sleep, as they averaged 5.6 hours of sleep [2]. Another study found that 74% reported poor sleep quality while on deployment, and that 40% had sleep efficiency below 85% [3].

Deployment to a combat zone is associated with mortar attacks at all hours of the day, ambushes by enemy combatants, and improvised explosive devices on roadsides. Using the 3-P (i.e., **p**redisposing, **p**recipitating, and **p**erpetuating factors) model of insomnia [4], these experiences, combined with irregular work-hours, make for a perfect storm for the development of sleep disorders. In a study of military personnel referred to a sleep clinic, 51% had OSA and 24.7% had insomnia [5].

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They found that older age, being male, anxiety, and higher body mass index (BMI) were associated with OSA. In contrast, they found that PTSD, pain, being female, and lower BMI were associated with insomnia.

Sleep disorders also influence mental health disorder onset. For example, it was shown that having insomnia during deployment or attaining less than 6 hours of sleep predicted greater PTSD risk [6, 7], adding to the cycle of sleep disorders when the individual is stateside. Another study found that short sleep duration was associated with increased risk of mental health problems, suicide attempts, depression, PTSD, panic disorder, and substance abuse [8]. Taken together, active duty experiences increase the risk for the onset and maintenance of sleep disorders even long after deployment is over.

Difficulty with Prevalence Rates of Sleep Disorders in Veterans

Several studies have suggested that sleep disorders are significantly underrepresented in the military population [9, 10]. This research suggests that although those with sleep apnea are often referred for treatment by a sleep medicine specialist, they are often neglected by other specialty clinics (e.g., PTSD, Substance Use (SU), and Traumatic Brain Injury (TBI)). Sleep disorders, such as insomnia, are neglected for the perceived "primary" disorder (e.g., PTSD or substance use disorder), leading to frequent misidentification and underreporting of sleep disorders. For example, only slightly more than half of VA providers (53%) indicated routinely documenting insomnia and fewer than half (39%) routinely included it in the problem list [9]. As such, the use of medical records to examine prevalence rates of sleep disorders can lead to significant underreporting.

Another shortcoming of accurately addressing prevalence rates in some studies and clinical work is the use of an inadequate screen for sleep problems. There are several studies that use a single item from other measures (i.e., non-sleep specific measures) that ask about sleep. For example, "Trouble falling or staying sleep" is often used to capture insomnia, but is not by itself a validated insomnia measure. A single item misses the relationship between sleep and dissatisfaction, interference with daily life, and cognitive shift or anxiety involved with insomnia [11]. A more comprehensive sleep screen (e.g., Insomnia Severity Index [ISI]) should be used.

Common screening measures, such as the STOP-BANG [12] and Berlin [13], are the most common self-report assessment tools to screen for high-risk of OSA. However, they have not been validated against polysomnography (PSG) in co-occurring mental health (MH) populations, such as in individuals with PTSD, and may not be useful screening tools in co-occurring MH disorders [14]. PSG is the gold standard method for the evaluation of sleep apnea and sleep architecture (e.g., stages of sleep, sleep spindles). PSG has traditionally been conducted in the hospital setting, but this might not be advantageous when assessing patients with PTSD where environmental factors may alter symptom severity [15]. Ambulatory Type 3 devices (e.g., Watchpat, Apnea Airlink, and Nox-T3) may offer a better option for veterans to measure their sleep in their home environment. There is

increasing use of validated portable devices for the detection of sleep apnea that are increasingly affordable and easy to use. While these devices cannot report stages of sleep or sleep architecture, they accurately track apneas/hypopneas for OSA diagnosis. Unfortunately, screening for OSA is not a part of the clinical practice in VA Mental Health clinics [11] and, as such, prevalence rates are difficult to ascertain.

Finally, the role of co-occurring disorders (e.g., PTSD, substance use, depression, and TBI) that have many overlapping symptoms makes isolating sleep disorders difficult. Approximately 25–57.6% of Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) veterans who were seen at a VA healthcare facility had a mental health disorder with a majority of those diagnosed having two or more mental health diagnoses [16–18].

Prevalence, Consequences, and Treatment of Sleep Disorders Among Veterans

Insomnia and Veterans

Prevalence Despite military personnel being particularly vulnerable to insomnia disorder [19], with estimates double and even triple of civilian populations [20], there are no accurate prevalence rates for insomnia disorder in a veteran population. Rates of insomnia diagnosis depend on a range of factors that include the definition of insomnia (e.g., the use of one question such as "trouble sleeping," *Diagnostic and Statistical Manual* – fifth edition [*DSM-5*] criteria), sample characteristics (e.g., treatment seeking versus general population), subjective versus objective measurement (e.g., self-report questionnaire, actigraphy), instrument (e.g., general sleep questions versus better validated sleep questionnaire), co-occurring disorders (e.g., depression, OSA, TBI), gender, and age. It has been shown that the rate of insomnia diagnosis cases in military personnel has increased 19-fold from 2000 to 2009 due to returning veterans of OEF/OIF [5]. In perhaps the best estimate of insomnia among veterans, 57.6% of all incoming veterans to the San Diego VA Hospital ($N = 6820$) screened positive (ISI ≥ 11) [14]. This is parallel to rates from two of the most generalizable prevalence studies that use independent measures of insomnia with a non-sleep-specific sample. In 375 OEF/OIF veterans, 59.1% reported insomnia based on the Pittsburgh Sleep Quality Index (PSQI > 4) [21]. Although no differences in sleep were found based on ethnicity or branch of the military, greater sleep problems were noted in women, service members from lower ranks, those with lower education, and in individuals with higher levels of combat exposure. The ISI was also used to examine the prevalence of insomnia in 917 post-9/11 veterans enrolling in VHA care with and without a history of military sexual trauma (MST); 53.1% of veterans without MST and 60.8% of veterans with MST had clinically significant insomnia symptoms [22]. As many post-9/11 troops retire from military service and begin accessing VHA healthcare in the coming years, the prevalence of insomnia among VHA users is expected to continue to rise [23]. Given the high

overlap of insomnia with co-occurring disorders among veterans, we will review the literature based on the most common clinical combinations: Insomnia with each of PTSD, TBI, suicidality, and depression.

Non-Pharmacological Treatments of Insomnia Non-pharmacological treatments may be more effective than pharmacological treatments for veterans. Cognitive behavioral therapy for insomnia (CBT-I; see Chap. 3 for details regarding CBT-I) is considered to be the frontline treatment for insomnia by the American College of Physicians [24]. Similar to civilian treatment recommendations, CBT-I is the gold standard of treatment for veterans [25]. CBT-I is equal to or better than pharmacological treatments for insomnia and the positive outcomes last longer [26]. In a meta-analysis, CBT-I was shown to be effective in decreasing co-occurring PTSD, substance abuse disorders, anxiety, and depression [6]. It is suggested that CBT-I in veterans should be a part of routine clinical care and prioritized over pharmacologic treatments [27]. Specific studies examining CBT-I for co-occurring disorders are reviewed below.

Pharmacological Treatments of Insomnia Due to the high overlap of insomnia and MH disorders, we will review our recommendations in the context of co-occurring disorders. Selective serotonin reuptake inhibitors (SSRI) and serotonin-norepinephrine reuptake inhibitors (SNRI) are recommended as first-line treatments for PTSD and depression in veterans [25]. However, the effects of SSRI/SNRI on sleep are typically modest or even adverse. Accordingly, adjunctive medication is often used for the treatment of insomnia.

Benzodiazepines (GABA Receptor Agonists) are commonly used for PTSD, anxiety disorders, and insomnia, but are not recommended by the VA [25]. A recent meta-analysis revealed that although short-acting benzodiazepines have modest beneficial effects on sleep in PTSD, their use is not recommended due to the emergence of tolerance, and their association with depression, aggression, and worse psychotherapy outcomes [28]. In a review of benzodiazepines and OSA, results suggest that benzodiazepine use was associated with reduced upper airway muscle tone, decreased ventilatory response to hypoxia, increased AHI and oxygen desaturations, and prolonged apneas [29]. It is suggested that benzodiazepines should be avoided in patients with OSA [30], and probably not used as a first-line treatment for PTSD, depression, or insomnia [25].

The non-benzodiazepine hypnotics carry fewer risks, but need further evaluation with veterans with co-occurring disorders. In a civilian meta-analysis, non-benzodiazepine hypnotics were found to have only slight improvements in sleep over placebo [31]. For example, in a study of 24 subjects with PTSD, eszopiclone was shown to have greater beneficial effects than placebo on sleep quality, duration, and latency, while reducing waking and improving daytime function [32]. Among patients with OSA, non-benzodiazepine hypnotics were shown to improve objective sleep quality without worsening AHI in a meta-analysis [33]; however, this has not been examined in a PTSD sample or veterans.

Two 5-HT2A antagonists, nefazodone and trazodone, cause sedation and promote sleep. In small unblinded studies, trazodone has been shown to promote sleep and reduce nightmares in patients with PTSD and depression [34, 35]. Trazodone may be particularly helpful for patients with alcohol use disorders [36] and OSA [37], where GABA receptor agonists are contraindicated. However, the use of trazodone is limited by common side effects including cognitive and motor impairment [38] and tolerance [35].

Many atypical antipsychotic drugs are sedating and show evidence of efficacy in PTSD-related insomnia and nightmares. In a placebo-controlled trial, adjunctive olanzapine was reported to have beneficial effects on sleep over 12 weeks in subjects who had failed to respond fully to SSRIs [39]. Similar effects were shown for risperidone. In a large, 24-week study of 267 veterans, risperidone significantly improved scores on the PSQI and reduced nightmares [40]. In a 12-week, placebo-controlled study of quetiapine monotherapy, however, there were only modest and transient effects on insomnia, even as there was an overall improvement in PTSD symptoms [41]. In addition, antipsychotic drugs are commonly associated with high rates of adverse events including extrapyramidal symptoms [42]. Moreover, antipsychotic are associated with weight gain that may also increase risk of OSA [43]. Therefore, patient selection may be especially important with antipsychotics to identify those with favorable clinical profiles.

Adrenergic drugs such as prazosin are alpha-1 receptor antagonists and are the best-supported drug treatment for insomnia in PTSD. Including case series, more than 10 trials have reported favorable effects of prazosin in PTSD on sleep, improving insomnia, and reducing nightmares across a range of civilian, military, and veteran groups [44, 45]. In a meta-analysis of 6 randomized trials encompassing 240 subjects, prazosin had significant effects on promoting sleep quality and reducing nightmares [46]. However, a recent multicenter study of prazosin in veterans found no effects on sleep or any other PTSD symptom cluster [47]. This large, well-powered study found relatively strong placebo effects that could have limited the ability to detect prazosin effects. Moreover, as prazosin was already commonly used in veterans with PTSD during the study, treatment-naïve patients may have been difficult to recruit, perhaps leading to selection bias. However, the work indicates that additional studies are needed to identify the circumstances and patients for whom prazosin treatment should be selected. For OSA, there are currently no studies examining the effects of prazosin for decreasing AHI. However, it is possible that prazosin, as a REM suppressor, may decrease nighttime arousals and thus, AHI [48].

Diphenhydramine, gabapentin, hydroxyzine, and tiagabine are commonly used in the general insomnia population, but are not well supported by evidence [49]. For example, the only study examining hydroxyzine in a PTSD sample found that hydroxyzine decreased nightmares and improved sleep better than placebo, although prazosin outperformed both [50]. Melatonin agonists (e.g., ramelteon), orexin antagonists (e.g., suvorexant), and low-dose doxepin are approved treatments for insomnia in the general population. These agents have not yet been systematically evaluated for individuals with co-occurring MH disorders or with veterans.

PTSD and Insomnia

Prevalence Insomnia was the most commonly reported symptom by service members on the PTSD Checklist, a measure of PTSD symptoms [51]. Similarly, 70–91% of individuals with PTSD have co-occurring insomnia [52]. While nightmares and difficulties with falling or staying asleep are among the DSM-5 criteria for PTSD [53], insomnia is best considered a co-occurring and independent disorder [11, 54, 55]. First, insomnia may precede the trauma and predict the development of PTSD [56–60]. Second, when insomnia initially occurs as a symptom of PTSD, it can become an independent disorder when the behavioral and cognitive responses to acute insomnia lead to perpetuating factors (e.g., napping, sleeping pills) and conditioned arousal [61]. Third, nightmares and hyperarousal symptoms may lead to the pairing of the bed with wakefulness (i.e., conditioned arousal). Thus, perpetuating factors and conditioned arousal are often responsible for the maintenance of insomnia even in the absence of PTSD [62]. Finally, even when PTSD is treated using evidence-based treatments, insomnia may still remain [11]. This suggests that insomnia may need to be assessed and treated separately from, or in conjunction with, PTSD.

Consequences Individuals suffering from both PTSD and insomnia experience worsened daytime symptoms of PTSD [63]. In veterans with PTSD, insomnia has negative health consequences over and above the effects of PTSD. Those who reported insomnia complaints had significantly higher overall scores for PTSD severity at 3-month follow-up than service members without insomnia complaints [51]. Clum and colleagues [64] found that insomnia accounted for a significant portion of the variance in physical health complaints even after controlling for other PTSD symptoms and depression. Overall, insomnia is associated with greater severity of PTSD symptoms and poorer quality of life and daily functioning [52, 65].

Treatment While insomnia tends to improve over the course of evidence-based PTSD treatment, it often remains disturbed posttreatment. For example, two studies comparing prolonged exposure therapy (PE) and cognitive processing therapy (CPT) [66, 67] and one study examining cognitive behavioral therapy (CBT) for PTSD [68] found that while sleep improved over the course of treatment, sleep disturbance remained above the clinical cut-off. Further, some of the sleep improvements deteriorated by the 6-month posttreatment assessment [68]. More recently, in a study of active duty military personnel randomized to group CPT or group Present Centered Therapy (PCT) [69], sleep disturbance was the most frequently reported symptom of PTSD both before and after treatment. Of 108 participants, 92% reported sleep disturbance pretreatment and 74–80% (CPT and PCT, respectively) reported sleep disturbances posttreatment. Among participants who no longer met criteria for PTSD posttreatment, 57% still reported sleep disturbances. This suggests that insomnia requires direct intervention.

Several studies have shown that CBT-I improves insomnia symptoms in PTSD patients; recent meta-analyses show large effect sizes for CBT-I in reducing insomnia symptoms in PTSD [70], and medium effect sizes for reducing PTSD symptoms [71].

Other studies support the use of CBT-I in veterans with PTSD as a part of routine clinical care [27]. Taken together, these studies support the use of CBT-I in patients with PTSD.

There is initial evidence that treating the insomnia before PTSD may increase the effectiveness of PTSD treatment in veterans [72]. Unlike treating sleep or PTSD alone, the preliminary findings of integrated CBT-I and prolonged exposure showed positive outcomes on insomnia symptoms, PTSD symptoms, and quality of life. Targeting insomnia prior to PTSD treatment may offer a unique and underutilized opportunity to advance clinical care and research in veterans.

TBI and Insomnia

Prevalence TBI is common among veteran populations. Approximately 20% of veterans who have served in the military since 2001 have reported a probable TBI [73]. These veterans often display behavioral health concerns including insomnia [74–78]. Insomnia is one of the most common yet least studied of the post-TBI sequelae. Recent research suggests that 30–70% of general population patients experience sleep problems following TBI and that these sleep disturbances often exacerbate other symptoms and impede the rehabilitation process and the ability to return to work [79]. Interestingly, it has been shown that even with mild TBI, insomnia is one of the most frequent symptoms [75]. In a study of 2,525 United States Army Infantry personnel 3–4 months after a yearlong combat deployment in Iraq, 53.8% of the individuals who experienced TBI with loss of consciousness reported disturbed sleep [80].

Consequences Insomnia presents functional impairments such as decreased quality of life, decreased cognitive functioning, greater work absenteeism, and increased healthcare need and usage among veterans with varying levels of TBI during rehabilitation periods [81–83]. In a review of the literature on TBI and sleep, Orff and colleagues [84] suggest that TBI interferes with circadian rhythms and sleep efficiency, and is associated with more awakenings, and a higher percentage of non-rapid eye movement and lower percentage of rapid eye movement (REM) sleep than controls. While these were in civilian samples, similar findings are likely in veterans. Some research, however, has failed to find a relationship between sleep impairments and mild TBI [85].

Treatment Treating insomnia in the context of TBI has been shown to improve sleep and TBI symptoms. Ruff and colleagues [86] found that 9 weeks of sleep hygiene and prazosin improved sleep, headaches, and cognitive performance; these results were maintained at 6-month follow-up. In a civilian sample, Castriotta and colleagues [87] found that treating sleep did help normalize the insomnia, but the TBI outcomes (functional outcomes, psychomotor vigilant test) did not get better. There are currently no studies examining CBT-I for veterans with TBI. There is enormous room to examine treating sleep with evidence-based interventions in a much-needed population: veterans.

Suicidality and Insomnia

Prevalence and Consequences Veterans are at a 41–61% higher risk of suicide than civilians [88]. While veterans constitute 8% of the total population, they comprise approximately 20% of suicide death in the United States, and insomnia has been shown to impact suicidal ideation and suicidal behavior among military personnel [89, 90]. Sleep disorders, even when controlling for PTSD symptoms, psychiatric symptoms, and drug and alcohol use, can exacerbate suicidal risk and suicide death [91, 92]. In a large population-based study, sleep disturbance – insomnia specifically – was shown to be a risk factor for suicide death among veterans [93]. In addition, adolescents who completed suicide were found to exhibit greater insomnia prior to the week of the suicide than controls, highlighting insomnia as a potential risk factor for suicidal behaviors [94].

Treatment CBT-I has been shown to be effective in reducing insomnia symptoms, but also has been shown to decrease suicidality in veterans [95]. Trockel and colleagues found that at baseline, 32% of veterans in the study expressed suicidal ideation, while this rate dropped to 21% at the final assessment after CBT-I. Once demographic variables and baseline insomnia severity were adjusted for, each 7-point decrease in their ISI score during CBT-I treatment was affiliated with a 65% decrease in suicidal ideation among the veterans. Treating insomnia through CBT-I can significantly lower the severity of suicidal ideation, which in turn may reduce the prevalence of suicide completion among veterans. Similar results were found in a civilian sample in which insomnia symptoms were associated with greater suicide ideation, even after controlling for nightmares [91].

Depression and Insomnia

Prevalence and Consequences Depression is five times higher among veterans than among nonveterans [88]. Sleep disturbances are a strong predictor of psychological symptoms – including depression – starting from an early time point [96]. For example, a study showed that higher insomnia 4 months postdeployment predicted depression among Iraq War veterans. This may be due to the mediating role that sleep disturbances play between combat stressors and psychological symptoms [96]. Similarly, Wright and colleagues found that among US combat veterans who experienced traumatic situations such as danger of being killed or injured, insomnia severity was a strong predictor of depression [60].

Treatment Other studies in clinical settings have found that treating sleep problems comorbid with depression can be effective even without treating depression separately due to the bidirectional relationship between these two disorders [97–99]. Due to this relationship, antidepressants are often prescribed in efforts to lessen symptoms and impairments in daily life but, as a consequence, may negatively affect sleep. Individuals struggling with insomnia were 2.2 times more likely to receive anxiolytic/hypnotic prescriptions and 1.2 times more likely to receive antidepressant prescriptions [100]. In addition to pharmaceutical approaches to treating insomnia and depression, CBT-I is used within the civilian

population to treat these two disorders. Manber and colleagues found that CBT-I was helpful in improving well-being outcomes such as insomnia symptoms, perceived energy, productivity, and self-esteem in both low and high depressive symptom groups [101]. There is only one study that examined a 4-week CBT-I protocol (usually 6–7 sessions) to sleep hygiene in veterans; contrary to civilian studies, they found both CBT-I and sleep hygiene groups showed equal decreases in depression and insomnia symptoms [102]. More attention is needed to identify how CBT-I can be utilized to decrease depressive symptom severity among veteran populations.

Substance Use and Insomnia

Prevalence and Consequences Insomnia co-occurs in 25–72% of individuals with substance use disorder (SUD) [103]. The relationship between substance use and insomnia differs depending on the type of substance used, chronic versus acute use, and whether the individual is actively using or in withdrawal [104–105]. Insomnia has been shown to negatively affect substance use outcomes. For example, insomnia severity is positively associated with relapse for SUDs [106, 107], as insomnia and SUD have a bidirectional relationship [105]. Impaired sleep may cause lowered inhibition and poor emotional regulation which can increase the risk of substance use [108]. Substances are often used as a means to cope with problems like pain, anxiety, insomnia related to PTSD, and other sleep difficulties [58, 109, 110]. For example, while alcohol reduces sleep onset early in a use cycle, over a number of days of consistent alcohol use (AU) near bedtime, the initial sleep onset effects tend to diminish, but the sleep disruption later in the night persists [111]. Further, insomnia severity is not only related to increased drinking [111, 112], but also to alcohol use disorder severity [113] and higher probability of relapse [104, 114]. While not studied specifically in a veteran population, similar findings are seen in opioid abuse [115, 116], stimulants, and cannabis use [117–120].

Treatment While CBT-I is the recommended treatment for insomnia, its effectiveness is severely diminished with active substance use. As such, decreasing substance use or detoxing is a necessary precursor to initiating CBT-I. Given that residual sleep problems following SUD treatment is linked to higher rates of relapse, insomnia is a clinically relevant factor for clinical intervention [121, 6]. CBT-I may best be considered as a clinical intervention to be used in conjunction with substance use treatment.

OSA and Veterans

Prevalence and Consequences General population studies of OSA in veterans (i.e., not sleep disorder referrals) suggest prevalence rates between 27% and 44% [122, 123]. Prevalence depends on the age of cohort, cohort type (e.g., sleep referral vs. general population), assessment used (Berlin Questionnaire vs.

polysomnography [PSG]), and presence of co-occurring disorders. Consistent with the civilian population, as age increases, so too does the probability of having OSA [124]. In these studies of individuals with OSA, only 4.25% were below 34 years of age.

Similar to civilian outcomes, OSA in veterans is associated with neurocognitive decline, hypertension, increased cardiovascular mortality, stroke, heart attacks, and financial burden on the healthcare system [125–127]. However, in a veteran sample, co-occurring disorders need to be considered. For example, in veterans, OSA is associated with more depression, anxiety, PTSD, alcohol dependence, psychosis, bipolar disorders, and dementia compared to veterans without OSA [128]. There is substantial evidence that OSA is increasing in younger veterans with co-occurring mental health disorders and that OSA symptoms do not have classic risk factors (e.g., older age, higher BMI) among this group; as such, OSA can often go undiagnosed [129].

Treatment of OSA OSA treatment for veterans follows the same recommendations as for civilians reviewed by Malhotra (Chap. 7). Continuous positive airway pressure (CPAP) is the gold-standard treatment for OSA, with meta-analytic reports showing improvement in daytime sleepiness and health-related quality of life [130]. The standard prescription is to use CPAP whenever asleep, including during daytime naps. However, despite CPAP being the most efficacious treatment available to OSA patients, adherence is substandard (3–5 hours per night), thereby significantly limiting its effectiveness [131]. One difference from civilian studies is that veteran samples show even lower adherence rates to CPAP, especially as the severity of the co-occurring disorder increases.

American Academy of Sleep Medicine (AASM) Clinical Guidelines for the treatment of snoring and OSA with oral appliances state that they are indicated for the treatment of mild-to-moderate OSA in patients who: (a) prefer oral appliances to CPAP, (b) do not respond to CPAP, or (c) are not otherwise suitable for treatment with CPAP [132]. A review of the literature suggests that 65% of patients experience a 50% reduction in AHI and that 35–40% of patients experience a normalization of the AHI (i.e., AHI < 5) [133]. When compared directly to CPAP in crossover trials, CPAP consistently shows greater improvements in AHI, but mandibular repositioning devices (MRDs) show higher adherence [134, 135]. MRDs may offer a viable alternative for veterans with OSA who are non-adherent to CPAP.

Weight gain is a risk factor for OSA, with one study showing a dose–response relationship such that a 10% weight gain is associated with a sixfold increase in the odds of moderate-to-severe OSA and a 32% increase in the AHI [136]. A meta-analysis found that while CPAP was the most efficacious intervention in decreasing AHI, exercise training and dietary weight loss also were associated with decreases in AHI [137]. While, this was not examined in a co-occurring PTSD sample, it may be reasonable to assume that these findings could carry over especially as PTSD is associated weight gain and low CPAP adherence [138].

PTSD and OSA

Most of the studies examining OSA in individuals with PTSD have been conducted in a veteran population. In a meta-analysis, nine of the ten studies involved veterans with PTSD; overall, 75.7% had an AHI > 5/h, and 43.6% had an AHI > 10/h – higher than both civilian populations and general veteran populations [139]. In a PSG study comparing veterans with OSA with and without PTSD, individuals with PTSD had significantly higher AHI, arousals, and percent of time with oxygen saturation less than 88% [140]. While no definitive conclusions can currently be drawn about the temporal relationship between OSA and PTSD, there may be a bidirectional relationship through which PTSD/chronic arousal affects OSA onset and severity, and a pathway through which OSA negatively affects PTSD and chronic arousal [141]. Jaoude et al. [142] suggest several possible shared pathways between OSA and PTSD including HPA Axis dysfunction [143, 144] and reduced fear extinction [145]. Additionally, there is evidence that OSA or nighttime fragmentation, when paired with trauma, may decrease processing, resiliency, and coping capacity and lead to a higher likelihood of stress symptoms [146, 147].

As noted above, there is increasing evidence that the classic predictors of OSA, such as BMI and age, may not apply to younger veterans with PTSD. Two recent studies found 67.3–69.2% of younger veterans (mean age = 33.40–35.1 years) were at high risk of OSA and that these veterans had lower BMIs (BMI = 19.08–28.9) than historically seen [129, 146]. Similarly, in a recent PSG study comparing Iranian veterans with and without PTSD, AHI was higher and BMI lower in the PTSD group compared to the non-PTSD group, as AHI was unrelated to BMI [140]. This makes screening particularly difficult, in that the self-report measures (Berlin and STOP-BANG) rely heavily on BMI. In fact, there is initial evidence that the STOP-BANG does not predict high risk of OSA in younger veterans with PTSD [148].

CPAP is still the recommended treatment for OSA in veterans with PTSD. Greater use of CPAP is associated with a lower nightmare frequency [138, 149, 150]. Additionally, one study found that CPAP use decreased nightmare frequency, which was associated with greater CPAP adherence [48]. More recent studies directly examined the effect of CPAP therapy on PTSD symptom reduction. Three studies of CPAP therapy found small but consistent decreases in PTSD severity at 12 weeks [151] and 6 months [152, 153]. A major issue with veterans with PTSD and OSA, however, is lower adherence to CPAP; one hypothesis is that individuals with PTSD often feel claustrophobic with the mask. For example, a recent meta-analysis found that CPAP adherence was lower in patients with both OSA and PTSD than OSA alone [139]. One study found that less use of CPAP was associated with greater baseline nightmare severity as well as greater daytime sleepiness [154]. Due to the dose response of CPAP with positive outcomes, increasing adherence to CPAP with desensitization to the mask requires further review [155].

While OSA treatment only moderately decreases PTSD severity, untreated OSA seems to interfere with successful PTSD treatment. A retrospective study of veterans who had completed CPT at a VA facility found that those with OSA (n = 69)

showed less PTSD symptom improvement than those without OSA ($n = 276$) [156]. However, those with OSA who were treated with CPAP showed more improvement than those who were not engaging in OSA treatment. Reist and colleagues [157] found similar finding in a smaller sample ($N = 18$) undergoing PE, as PCL scores were reduced by 28.25 points in those without OSA, but only by 7.17 points in the OSA group. Collectively, these findings suggest that OSA screening may need to be a first-line protocol for individuals with PTSD.

PTSD, OSA, and Insomnia

Despite high co-occurrence among PTSD, OSA, and insomnia [140, 158–160], diagnosis of each disorder is often underreported due to their symptom overlap [142] and absence of differential diagnostic criteria [161]. One study compared PSG patterns of OSA in veterans and found that those with PTSD were more likely to also have insomnia compared to those without PTSD [140]. Further, recent studies suggest that having all three of PTSD, OSA, and insomnia is associated with a more severe clinical profile than PTSD/OSA or PTSD/insomnia combinations. A nationally representative sample found that individuals with OSA and insomnia had more severe hypertension and cerebrovascular disease than those with OSA alone [162]. In a sample with PTSD, it was found that veterans with PTSD, insomnia, and OSA had worse quality of life, sleep, and depression than veterans with just PTSD/OSA [163].

TBI and OSA

In civilian samples, rates of OSA are higher in individuals with TBI than without [164–166]. In an active duty sample that just returned from deployment to Iraq or Afghanistan and who were referred to a sleep clinic to be assessed for sleep-disorder breathing, approximately 31.9% of those diagnosed with OSA also had a TBI [167]. However, those with TBI did not show higher rates of OSA than those without TBI. The authors' analyses showed that PTSD was more prevalent than TBI and suggest that PTSD and OSA may be more mechanistically linked than either to TBI. In a meta-analysis of TBI studies and sleep disturbances, 25% of individuals with TBI also had OSA [74].

The added consequence of OSA in TBI patients is markedly severe. In a civilian cohort, Wilde and colleagues [165] found that individuals with TBI plus OSA performed significantly worse on measures of sustained attention and memory. It is likely that these findings extend to veteran samples, making OSA an early treatment goal for veterans with TBI. Examining the effects of sleep treatment on TBI outcomes found that CPAP was effective in decreasing AHI, anger, and levels of tension. A third of the sample consisted of veterans, increasing the likelihood that these findings are generalizable to a veteran population.

Together, untreated OSA in TBI has the potential to seriously undermine patient rehabilitation, recovery, and outcomes, making it important to routinely screen for such problems in order to assess both treatment needs and their potential impact on recovery and outcome.

Suicidality and OSA

While there are no studies examining both suicidality and OSA specifically in veterans, there is ample evidence that OSA is related to higher rates of suicide, suicidal ideation, and planning [168, 169]. While it is unclear how OSA contributes to higher rates of suicide and ideation, it is hypothesized that greater fatigue, greater distress, neurophysiologic changes, and decreased emotional coping play a role. Given the importance of decreasing suicidality among veterans, screening and treating OSA should be a primary intervention for all providers treating veterans.

Substance Use and OSA

In individuals with any SUDs, 53.3% screened as being high risk for OSA [170], and in individuals taking opioids or in opioid maintenance, 70–85% had sleep disordered breathing [171, 172]. Alcohol ingestion was reported to worsen snoring and exacerbate OSA due to a weakening of pharyngeal dilator muscle tone and subsequent increase in upper airway resistance [173, 174]. Chronic opioid use increases central apneas and OSA, which goes largely unnoticed due to acute effects of opioids, heightening the likelihood of morbidity and mortality [116, 172].This increased risk for OSA includes chronic use of partial μ agonists such as methadone and buprenorphine, used in the maintenance treatment of opioid use disorder [172]. Despite high levels of co-occurrence between SUDs and OSA, clinical diagnosis of OSA is often overlooked due to similarity of nighttime and daytime symptoms to PTSD and SUDs (e.g., daytime fatigue) [11]. Among veterans, however, one study found no difference in SUD diagnosis rates between those with and without OSA [128], suggesting a need to increase the study of OSA and acute/chronic drugs use and the effects of OSA treatment on long-term SU outcomes. Unfortunately, OSA screening and treatment are not a part of SUD treatment protocols. This is particularly concerning, given that OSA may interfere with co-occurring MH treatment [156, 157], quality of life [163], suicidal ideation [175], and perhaps SUD treatment. Future studies are needed to further evaluate the prevalence of RLS in the veteran population.

Restless Legs Syndrome and Veterans

Prevalence Restless Leg Syndrome (RLS) is a common disorder that has a higher prevalence rate in the veteran population compared to that in the general population [176]. Subjective reports find a prevalence range of 6.6–19.7% between study sites with one outlier of 48.2% [177], 4% of women veterans [178], and 56% of obese veterans [179]. RLS is characterized by an urge to move the legs that is often hard to resist, and is usually, associated with disagreeable leg sensations. These symptoms occur during times of inactivity and may cause interference in sleep as the sensations become stronger in the evening and night, but with significant relief in the morning. RLS symptoms are also alleviated by movement and standing [177].

Consequences Veterans suffering from RLS have an 88% higher risk of mortality and four times higher risk for coronary heart disease and stroke [176]. Mustafa and colleagues [177] found that peripheral artery disease, chronic lung disease, presence of OSA, and presence of periodic limb movement syndrome (PLMS) were associated with a higher risk of incident RLS in a veteran sample.

Common Co-occurring Disorders In the general population, insomnia, depressive, anxiety, and pain disorders are all comorbid conditions with RLS [180]. In veterans, the presence of depression had an odds ratio of 1.70 (with 95% CIs of 1.57, 1.85) among those with RLS [176]. In the general population, one study found the onset of depression to occur after the onset of RLS for the majority of individuals (77%) [181], and RLS was found to coincide with the worsening of the depressive disorder [182]. The cause of RLS is often seen as multidirectional, with no direct cause [183]. Although RLS is commonly reported among individuals with TBI and PTSD, the comorbidity rates are not often reported. More commonly reported are the rates of PLMS, which should not be mistaken for RLS. Sleep disturbance, in the general population, has been shown to co-occur with substance use and possibly higher risk of suicidality, but there have not been reports showing how they may co-occur with RLS [184]. There is still speculation regarding the cause of the enhanced impulsivity seen with RLS, whether it be the syndrome itself or the drugs used to treat it, but the literature on this topic is still limited [184, 185].

Effects on Outcomes There are currently no studies examining the effects of RLS on treatment, health, or quality-of-life outcomes in veterans. It is possible that RLS is not a priority for the veteran faced with co-occurring disorders (e.g., PTSD, SUD, and OSA) and therefore is not a primary clinical or research focus. In the general population, RLS is seen to be a significant negative predictor of health-related quality of life (HRQoL) [186, 187]. Berger [188] found the risk of RLS to be higher for women with children, increasing with one child (odds ratio, 1.98; 95% confidence interval, 1.25–3.13), two children (odds ratio, 3.04; 95% confidence interval, 2.11–4.40), and three or more children (odds ratio, 3.57; 95% confidence interval, 2.30–5.55).

Treatment Current treatments for RLS include dopamine agonists, pregabalin opiates [189], bupropion [190], benzodiazepines, levo-dopa, and rotigotine [191]. When other treatments have failed, gabapentin enacarbil is a viable option [192]. Other non-medication treatments that have been shown to be beneficial include the practice of yoga [193], acupuncture, and exercise [194]. An overview of treatments for RLS also included neutraceuticals (i.e., vitamins, valerian, and Chinese herbs), pneumatic compression devices (PCDs), light therapy, and cognitive-behavioral therapy [194]. In addition, the National Institute of Neurological Disorders and Stroke released treatment options for RLS that include decreasing the consumption of caffeine, alcohol, and tobacco [195].

Treatment for RLS has shown to positively affect health outcomes in the general population, with 24% showing improving in depression [196], 9% in their quality of sleep, 18% in health status assessed by the SF-36 [197], 25% in QoL, 50% in sleep quality, 50% in exercise capacity [198], 59% improvement in sleep quality on the PSQI, 75% reductions in prevalence of insomnia, 78% reductions in depression [199], 26% improvement in function/sleep quality/emotional well-being on the RLS-QLI, 42% in sleepiness on the ESS, and 47% in fatigue [200]. However, data are limited in showing a reduction of RLS symptoms with the treatment of other disorders (PTSD, Depression). Theoretically, it can be suggested that treatment of other disorders will also positively affect RLS, given that the cause is seen as multidirectional [183].

Nightmare Disorder and Veterans

Prevalence Prevalence of nightmares is common in conjunction with PTSD. For example, prevalence estimates range from 50% to 96% [201, 202] with PTSD, but only 4–8% without PTSD [201, 203]. Nightmare frequency was estimated at more than five per week in a sample of sexual assault survivors with PTSD [204], while increased combat exposure in Vietnam veterans was related to increased nightmare frequency [201]. In a retrospective review of 500 active military personnel, Creamer et al. [205] found that 31.2% had nightmares weekly, but only 3.9% reported nightmares as a reason for seeking treatment. Rates of nightmares may depend upon criteria, assessment, and methodology [206].

Consequences The presence of nightmares has been linked to higher suicide rates [207] and increased insomnia, poor sleep quality, and upper airway resistance [208]. However, there is no evidence that nightmares interfere with OSA or PTSD treatment. In fact, nightmares were very responsive to both PTSD and OSA treatment [209, 210]. Finally, a study of PE compared to client-centered treatment found that nightmares significantly decreased with only 20% of participants endorsing nightmares following treatment [211].

Treatment Several non-pharmacological interventions show promise for treating nightmares related to PTSD. Imagery Rehearsal Therapy (IRT) has been the most researched. IRT involves rescripting selected nightmares, that is, writing out the nightmare and changing the storyline, ending or any part of the dream to be more positive and rehearsing these scripts during the day. Several studies have suggested that IRT improves subjective sleep quality and reduces nightmares in PTSD patients, with large effects in several studies [212, 213]. Notably, most studies included in these meta-analyses lacked controls, not all were conducted in PTSD samples, and several versions of IRT were used. Some research suggests that IRT may be more beneficial for patients with a primary nightmare disorder than for patients with PTSD

and nightmares [11, 214]. One of the few studies with an active control condition only showed small effects of IRT and no differences between groups on nightmare frequency [215]. A randomzied control trial (RCT) comparing IRT to prazosin suggested that both treatments outperformed placebo in reducing insomnia and PTSD symptoms, but did not find differences between the two active treatments [216].

Several studies in veterans with PTSD used CBT-I and Imagery Rehearsal Therapy (IRT, described below) together, which improved insomnia and PTSD symptoms compared to treatment as usual [217]. An RCT conducted in veterans with PTSD used combined CBT-I and IRT and showed improvements in insomnia, PTSD, and depressive symptoms compared to the waitlist [218]. Due to the responsiveness of nightmares to CBT-I, it is unlikely that combined treatment is more effective than CBT-I alone. It is suggested to prioritize treatments addressing OSA, insomnia, and PTSD over nightmare treatment alone [11].

Conclusion

Veterans are a unique sample who show higher rates of insomnia and OSA than nonveterans. Veterans are a vulnerable population for sleep disorders due to the irregularity of their deployment sleep/wake schedules, harsh living conditions, the stress of combat, elevated rates of physical and psychological injury, and issues associated with postdeployment psychosocial reintegration. Sleep disorders in veterans are often neglected for the "primary" disorder (e.g., PTSD or substance use disorder), and it is concluded that sleep disorders are frequently misidentified or undereported. This is troublesome because OSA can interfere with co-occurring symptom severity and treatment (e.g., for PTSD). While insomnia does not seem to interfere with co-occurring treatment, it does increase symptom severity and increase odds of suicidality. Left undiagnosed and untreated, sleep disorders may unnecessarily undermine patient rehabilitation and recovery.

Together, treating veterans for sleep disorders is a unique and underutilized way to maximize quality-of-life outcomes, especially among veterans with co-occurring psychiatric disorders such as traumatic brain injury (TBI) and PTSD. Increasing awareness of screening and treatment options should be an increased focus for any clinician working with veterans. Given the high need for evidence-based interventions and the VA's commitment to advancing care, research and clinical guidelines for veterans can help inform clinical care for everyone.

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Part VI

Overlap Between Psychiatric Conditions and Sleep Disorders

The Overlap Between Sleep Disorders and Psychiatric Disorders

17

Nikhil Rao

Introduction

Sleep and neuropsychiatric functioning are intrinsically linked; both are ultimately the products of brain physiology. This is demonstrated quite clearly by a simple perusal of the diagnostic manuals for each: The International Classification of Sleep Disorders (ICSD-3) and the Diagnostic and Statistical Manual of Psychiatric Disorders (DSM-5). Symptoms of sleep disruption are core diagnostic criteria for many of the most common psychiatric disorders, including depression, anxiety, and neurodevelopmental disorders [1]. Likewise, fatigue, restlessness, cognitive difficulties, and changes in mood, arousal, and anxiety are hallmarks of several sleep disorders [2]. Current evidence emphasizes the bidirectional nature of these relationships, with certain sleep disorders consistently linked to certain psychiatric outcomes, while specific psychiatric disorders lead to signature changes in sleep physiology [3, 4, 5]. Both types of disorders also have major effects on quality of life in the short term as fatigue/energy and executive functioning/cognition are negatively affected, and in the long term as risk of cardiovascular and metabolic disease are heightened [6, 7].

Overlap and comorbidity are common as patients with psychiatric disorders often present with sleep issues as a primary complaint, while mood, energy, and cognition changes are often the presenting symptom for individuals with sleep disorders. Distinction between and adequate treatment of both is important for remission of illness, especially in the case of sleep-related psychiatric dysfunction, which usually will not resolve with purely psychiatric medications [7]. Complicating things further is the fact that several psychiatric medications may worsen or cause sleep dysfunction [3].

This chapter provides an overview of the relationship between sleep medicine and psychiatry and is divided into three sections:

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(1) A brief overview of sleep science and diagnostic studies
(2) A review of sleep dysfunction in common psychiatric disorders
(3) A review of commonly used medications and their anticipated effects on sleep

Sleep–Wake Regulation

I review three basic principles controlling sleep in this chapter (but readers are encouraged to review chapter 1 of this book for a more thorough treatment): The light/darkness cycle and its effect on melatonin secretion, process C and process S that control the sleep/wake cycle, and central nervous system neurotransmitters and receptors controlling the sleep/wake cycle.

Process C and Process S

The current understanding of sleep and wake cycles is encapsulated in the Two-Factor Model of sleep regulation [8]. This model proposes a Process C (circadian drive), which drives wakefulness, and a Process S, which drives sleep. Process S describes the buildup of sleep-inducing substances during extended periods of wakefulness (i.e., during the day), slowly accumulating and peaking at bedtime, leading to an increase in sleep pressure. It then fades as the individual sleeps throughout the night. Under this model, Process S is organized and made more regular by Process C, itself governed by the circadian rhythm as arousal/wakefulness peaks during the day and decreases at night—the interaction between the two processes is what creates the sleep/wake cycle [9]. Process C is stimulated by the circadian waking drive (or the internal clock) and is regulated by light and activity (or zeitgebers), which helps keep sleep/wake cycling linked to night and day. When Process C is interfered with, total sleep time remains about the same, but is distributed randomly in naps throughout the day and less organized nighttime sleep. For Process S, direct response to circadian and light signaling is thought to be secondary to the indirect effects through Process C [10].

Sleep Centers and Neurotransmitters

Sleep-generation neurons in the ventrolateral preoptic area of the hypothalamus are responsible for turning off the arousal system during sleep through inhibitory neurotransmitters. Another important cluster of neurons in the pons plays a role in the transition from non-REM to REM sleep by inducing the paralysis and "paradoxical" conscious state characteristic of REM [11].

Wake-cycle regulation is considerably more complex and starts in the upper pons. One pathway involves cholinergic neurons with projections to the thalamus, promoting transmission of sensory information to the cortex. Another major pathway involves the various monoamine origin nuclei (Raphe nucleus, Locus coeruleus) projecting to the hypothalamus. There, inputs from nuclei involved in orexin and hypocretin signaling modified the activity as the monoamine-producing neurons continue their pathways into the cerebral cortex, inducing conscious activity [11].

Suprachiasmatic Nucleus and Melatonin Secretion

The suprachiasmatic nucleus (SCN), lying just above the point at which the optic nerves merge and bifurcate again to become the optic tracts, receives direct input from specialized brightness-detecting receptors in the eyes. In turn, it interacts with the dorsal median nucleus of the hypothalamus to drive not only day/night cycling, but also cycles relating to feeding, physical activity, and steroid and sex hormones [11]. The SCN is also responsible for inducing melatonin production, although melatonin's effects are more indirect than commonly thought on sleep. Rather than acting as a direct inducer of sleep, melatonin seems to be key to signaling the onset of darkness and reinforcing the various circadian rhythms. It is thus better thought of as a facilitator of sleep than an inducer.

The Restorative Role of Slow Wave Sleep (SWS) and REM Sleep Stage

Sleep deprivation as a contributor to mental and physical health problems is well established, including negative effects on metabolic, immunologic, and cognitive functions [12, 13]. Among the most striking endocrine findings are that sleep deprivation leads to pro-inflammatory states and less HPA-axis sensitivity, findings also commonly demonstrated in depression, anxiety, and PTSD [12, 14, 15].

SWS (or N3) and REM sleep are unique in that both demonstrate "rebound," a quality in which we transition quicker to these stages than would otherwise be normal after periods of reduced sleep [13, 16]. This is often taken as evidence that each of these stages of sleep provide important restorative benefits, distinct from each other, to the body and brain [12, 18].

Slow Wave Sleep Function

SWS is thought to be the most "restorative" of sleep periods to the body. It has been demonstrated that deficits in SWS result in less release of the growth hormone, an important mediator of recovery from stress in adults as well as in maintenance of tissue health [12, 17]. SWS deprivation as a mediator of physical illness and overall morbidity is well established, and generally analogous to the findings from broader sleep deprivation research. Emerging, albeit inconsistent, evidence also points to the possibility that SWS is a period of brain renewal and recovery [17]. Among positive evidence, recent studies suggest that neuronal protein synthesis is highest during stage N3 (slow wave) sleep [13, 19]. Impairments in SWS may cause alterations in mood and in the formation of declarative memory [20]. On the other hand, SWS-specific deprivation studies have been inconsistent regarding effects on attention, procedural and emotional memory, and anxiety [17, 21].

REM Function

The importance of REM sleep for health is also well established. Perhaps the most salient finding is that while total sleep deprivation in laboratory animal studies will lead to mortality within 2–3 weeks, REM sleep deprivation with preserved total

sleep will still lead to death within 4–6 weeks. However, in humans the absence of REM sleep has been noted for weeks or months without fatality [3]. REM sleep deprivation, however, has been associated with increases in anxiety, irritability, aggression, and, interestingly, task-based learning [3, 13, 22]. There is also increasing evidence that REM sleep may alter NMDA (n-methyl D-aspartate) receptor sensitivities in a positive manner [13, 19]. These receptors play a key role in synaptic plasticity, and thus in memory and persistent mood states. Overactivity at these receptors can lead to excitotoxicity and may play a role in neurodegenerative diseases including the negative changes seen to hippocampal, amygdalar, and frontal function in depression. Underactivity, on the other hand, may lead to poor memory formation and impaired learning

Neuropsychiatric Considerations in Sleep Disorders

As previously discussed, sleep plays an important restorative role to multiple physiologic systems connected to the nervous system as well as for the brain itself. Most sleep disorders impact total sleep time, quality of sleep, sleep efficiency, and quantity of deep sleep and REM sleep (the latter two of which are most associated with the restorative functions of sleep) [24]. Thus, there is considerable overlap between sleep disorders and neuropsychiatric sequelae and comorbidity; nonetheless, there are some key differences that will be noted throughout [7, 23].

Changes in Sleep Physiology Associated with Psychiatric Illnesses

Sleep dysfunction as a symptom and consequence of psychiatric disorder has been described since antiquity [25]. Indeed, sleep-related symptoms are part of the DSM-V criteria for numerous disorders including major depressive disorder (MDD), bipolar disorder, and post-traumatic stress disorder (PTSD) [1]. Insomnia is a common associated contributor to morbidity, quality of life, and functioning, across almost all psychiatric illnesses, from attention deficit hyperactivity disorder (ADHD) to schizophrenia [3, 26]. Sleep physiology and architecture differences among people with psychiatric disorders are well documented and will be explored further in this section. In addition, occult co-occurring sleep disorders may be present, which, unless addressed, may prevent improvements in both psychiatric and sleep function [3].

Major Depressive Disorder (MDD)

Overlap Between MDD and Sleep Several core diagnostic criteria for major depressive disorder are related to sleep quality. Insomnia (or more rarely hypersomnia) is one of these, with up to 90% of patients with depression also having clinically significant sleep issues [1, 3]. Other sleep-related core symptoms include fatigue and concentration deficits. Several longitudinal studies have identified that

preexisting insomnia is a risk factor for depression with an odds ratio (OR) of up to 6.2 [27, 28, 29]. In one of those studies, patients with depression but without insomnia had an OR of 6.7 for the later development of insomnia [29].

Because of the frequency of insomnia in depression, sedating antidepressants such as amitriptyline, doxepin, trazodone, and mirtazapine may be considered. However, tri- and tetracyclic antidepressants (TCAs) may be a poor choice given their propensity for side effects, not to mention lethality in overdose. Two commonly used antidepressants may improve sleep through modulation of serotonin (5-HT2) receptors in sleep-generating regions of the brain: mirtazapine has shown efficacy in improving sleep continuity and SWS in addition to its benefits in mild to moderate depression, albeit sometimes at the expense of increased appetite and problematic weight gain [30]. Trazodone is effective and well tolerated for sleep at lower doses, but unfortunately often causes side effects at the higher antidepressant doses. It is thus often used in conjunction with other antidepressants because it may ameliorate some of the negative effects of SSRIs on sleep [30]. Agomelatine, a novel agent that acts as an agonist at melatonin receptors and an antagonist at 5-HT2 receptors, has shown some promise in treating both conditions as well [31, 32].

Polysomnogram (PSG) Changes with MDD Clinically, significant changes in polysomnogram recordings occur in 40–80% of individuals with depression, with increasing depression severity being linked to greater likelihood of abnormal findings. Commonly, PSGs in depressed patients show decreased efficiency (i.e., longer sleep latency, more frequent arousals, and early morning awakening), as well as decreased SWS. In addition, they often show decreased REM latency (the time from sleep onset to the first REM onset) and increased REM density (the frequency of eye movements during REM sleep) [33]. Notably, some of these changes, including reduced SWS (N3) sleep and reduced REM latency may persist after the resolution of depressive symptoms. Despite excessive daytime sleepiness being a common finding in depression, Multiple Sleep Latency Test (MSLT) results tend to show no differences between depressed individuals and healthy controls [34]. This later investigation consists of four to five 20-minute naps during the day, following a nighttime PSG. It measures both the average sleep onset and the average REM occurrence.

MDD and Restless Leg Syndrome (RLS)/Periodic Limb Movements (PLMs) Depression occurs more frequently in those with a more severe degree of RLS and PLMs. However, it is not clear whether mood presages PLMs or vice versa [35, 36]. It should be noted that many common antidepressants and neuroleptic medications are known to exacerbate RLS and PLMs [37, 38, 39]. Recent cross-sectional studies from large epidemiological databases by Lee et al. in the United States and Winkelmann et al. in Germany reveal high rates of comorbidity with depression (OR 2.6–4.7) [40, 41]. While some studies suggested symptom overlap between the two disorders (i.e., insomnia, fatigue, and decreased concentration), others have questioned this association [40].

MDD and Obstructive Sleep Apnea (OSA) Respiratory events associated with OSA as well as the abnormal arousals associated with OSA can prevent progression into SWS and REM sleep, both of which are thought to be necessary for the restorative processes of the brain. SWS and REM deprivation may in turn result in neuropsychiatric consequences including depression, possibly secondary to the hypoxemia, sleep disruption, and/or increase in inflammatory hormones (i.e., interleukin 1 and 6) [42, 43]. Some symptoms respond quickly to positive pressure ventilation (PAP) therapy, including depressive symptoms which often show marked improvement within 1 month [44, 45]. Executive functioning including vigilance and attention also quickly improve along with restoration of sleep architecture and reductions in daytime sleepiness [46]. Other problems such as decrements in cognition may show significantly more residual effects, indicating the possibility of chronic damage as a result of hypoxemia [45, 47, 48].

MDD might worsen OSA through several mechanisms, one of which may be due to the increased REM density seen in this population [7, 49]. Since respiratory events are more common during REM stage, OSA severity in turn increases. There is also some limited evidence that MDD may result in decreases in upper airway dilatory tone in non-REM sleep, although the degree to which this is clinically significant remains debated [50]. Peppard et al. reported on a prospective longitudinal sample of individuals diagnosed with OSA showing an increased risk of developing depression over time, positively correlated with disease severity [4]. Comparatively, there is a larger corpus regarding the improvements in cognitive, mood, anxiety, and behavioral symptoms following initiation of CPAP therapy in individuals with sleep apnea [47, 48, 49].

MDD and Narcolepsy Psychiatric symptoms and morbidity in this population is high and may be in part due to the sedentary lifestyle, weight gain, and cognitive dysfunction (especially executive function and decision-making capacity as well as working memory) causing academic/employment challenges [51]. A plurality of studies have found elevated rates of depression and anxiety disorders in this population with a point prevalence of 57% for depression [52, 53]. The Burden of Narcolepsy Disease (BOND) study, a large longitudinal study of more than 9,000 individuals with narcolepsy, reported odds ratios of 3.9 for depressive disorders compared to healthy controls [54]. While there is an overlap in symptoms between narcolepsy and depression (hypersomnia, tiredness, etc.), studies that excluded these presentations continued to show significant correlation between the two disorders [208]. It should also be noted that while most suspect the chronic and debilitating effects of narcolepsy as the cause of depression, others have suggested that depression may occur in these individuals before the onset of narcolepsy symptoms [209]. Additionally, hypocretin deficiency—the primary neuronal pathology causing the physical manifestations of narcolepsy—can lead to an imbalance of monoamine neurotransmitters such as serotonin and norepinephrine leading to imbalance of the monoamines such as serotonin and norepinephrine (e.g., emotional dysregulation mediated through the deficiency of hypocretin leading to decreased serotonin

through its effects over the amygdala) [210]. It is not clear if the interruption of nighttime sleep due to narcolepsy might mediate this relationship.

Anxiety Disorders

Anxiety Disorders and Sleep Duration Insomnia tends to occur in concert or as a consequence of anxiety disorders, reflected in its presence as a diagnostic criterion for generalized anxiety disorder (GAD) [1]. Up to 70% of individuals with GAD report difficulties with insomnia, supporting its inclusion as a core criterion of GAD. This may be influenced by the common symptom clusters involving motor issues (tension, restlessness, fatigue) and arousal (restlessness, concentration deficits, and irritability) [57]. In one study, anxiety disorders occurred in 24–42% of people with insomnia and/or hypersomnia [55, 56]. Insomnia and anxiety in particular typify the bidirectional nature of the relationship between sleep disorders and psychiatric disorders, with longitudinal studies showing that approximately 40–70% of individuals with both problems developed insomnia before an anxiety disorder, while another 40% developed anxiety first [55]. The odds ratios of concomitant anxiety disorder and insomnia/hypersomnia are highest for GAD, obsessive compulsive disorder (OCD), and panic disorder [57]. Nocturnal panic attacks, however, are rarely the primary presentation in panic disorder. Notably, when panic attacks do occur at night, they tend to be during the transition from light sleep to SWS (N2 to N3) and are distinguishable from night terrors (N3 to REM) and nightmares (within REM) [58].

Staner provides an excellent review of the literature on subjective and PSG findings of GAD and insomnia. A recent review of the literature shows that in individuals with GAD, overall changes in PSG are mixed, although the literature shows consistent findings of middle and late insomnia, and a trend toward significance in sleep onset difficulties [59].

In contrast, common subjective reports of sleep difficulty in panic disorder center around middle and early morning difficulties in sustaining sleep. PSG findings in panic disorder are also mixed, with some finding changes in light versus deep sleep and others finding little if any change [57]. Consistently, however, increases in sleep intensity and awakenings after onset of sleep (leading to decreased sleep efficiency) are shown. Interestingly, relative to other anxiety disorders and depressive disorders, there are no changes seen in total REM duration and efficiency [57].

Overactivation of the hypothalamic-pituitary axis (HPA) in both anxiety disorders and insomnia (as evidenced by high plasma cortisol and adrenocorticotropic hormone) might explain the correlation between insomnia and anxiety disorders [211]. As with depression, serotonin abnormalities have been suspected to mediate the relationship between anxiety and insomnia. In a study involving individuals with insomnia, a greater frequency of the short allele variant of the serotonin transporter gene (5HTTLPR) was found [212]. Short allele

variants of the 5HTTLPR gene have been suggested to affect extinction behavior of negative affects, thus increasing the risk of conditioned response, which in turn may explain some of the negative affective experiences (such as catastrophization and misperception of sleep) of insomnia in the absence of psychiatric illness [213, 214].

Anxiety Disorders and OSA Anxiety disorders are commonly seen in the OSA population, with several studies finding rates of clinically significant anxiety in more than 20% of individuals with OSA seen in sleep clinics [9]. The same mechanisms suspected to contribute to the comorbidity of depression with other sleep disorders are the same here and include increase in inflammatory enzymes leading to brain damage, increase in HPA activity (and increase in stress related hormones such as cortisol stimulating glucocorticoid receptors that can induce neurotoxicity) and monoamine neurotransmitter abnormalities (i.e., serotonin and norepinephrine). Hypoxia associated with OSA can cause direct neuronal damage (cells, axons, and glia) and trigger endothelial damage [215, 216]. These pathologic changes have been shown in a study comparing brain areas involved in emotional regulation (hippocampus, medial prefrontal and dorsal prefrontal cortex) between anxious individuals with and without OSA [217].

Anxiety Disorders and RLS/PLMs Recent cross-sectional studies from large epidemiological databases indicate that the comorbidity between panic disorder and RLS (OR 4.7–9.4) is much greater than for generalized anxiety disorder (OR 3.7) or for depression (OR 2.6) [40, 41]. As in depression and ADHD, the dopaminergic system has been proposed to moderate this association [40, 75]

Anxiety Disorders and Narcolepsy A plurality of studies have found elevated rates of depression and anxiety disorders among individuals with narcolepsy with a point prevalence of up to 53% for anxiety disorders [52, 53]. The Burden of Narcolepsy Disease (BOND) study, for example, found an odds ratio of 2.5 for anxiety disorders compared to healthy controls, somewhat lower than the OR for depression [54]. In addition, high rates of social anxiety were found, ostensibly due to the impact of excessive daytime sleepiness (EDS) and cataplexy on social perception and fears of rejection [52].

Posttraumatic Stress Disorder

PTSD is considered a disorder of hyperarousal, with inappropriate daytime and nighttime events, as evidenced by up to 70% of patients with PTSD experiencing regular nightmares that often wake them from sleep [1]. This inappropriate arousal manifests in a range of ways from sleep quality to movement disorders [64]. Additionally, given REM sleep's role in memory and learning, there is some

evidence that REM fragmentation prevents fear extinction and perpetuates maladaptive behaviors in this population [218].

PTSD and Insomnia Pillar et al. document a strikingly poor subjective quality of sleep for individuals with PTSD as they reported latencies of longer than 2 hours and subjective sleep efficiencies of less than 50%. This contrasts to their review of PSG findings, which while variable regarding sleep latency and time awake after onset of sleep, generally showed no impairment of SWS or percentage of REM sleep. On the other hand, consistent findings across studies of increased REM density (frequency of eye movements during REM) may be consistent with the intensity of nightmares perhaps being greater for individuals with PTSD than in normal dreaming [60]. The sleep fragmentation and insomnia associated with PTSD may be due to hyperactivity of the amygdala with concordant impairment of activity in the medial prefrontal cortex leading to poor modulation of REM and NREM periods [219]. Some studies suggest that insomnia in the early post-trauma period can lead to chronic PTSD [219].

PTSD and OSA A consistent and intriguing finding is that PTSD is associated with more severe symptoms of OSA, and at typically lower body mass index (BMI) than in other populations, with lower relative complaints of snoring (especially during REM sleep, which may be a reflection of the high REM density) [61]. As previously mentioned, during REM sleep, the upper airway muscle dilatory tone is often lower, leading to greater rates of airway collapse [62]. Another way in which PTSD may contribute to worsening OSA is through increased sleep fragmentation, which has been suggested to increase airway collapsibility and thus apnea severity and frequency [220].

Just as the sleep disturbance caused by PTSD can sustain or exacerbate both disorders, OSA itself can worsen PTSD through its own effects on sleep fragmentation and interrupted REM sleep [221]. Last, as in anxiety and depression symptoms, the HPA axis changes associated with OSA may be linked to worsening PTSD [222].

PTSD and RLS/PLMs PTSD is also associated with a higher incidence of RLS and PLMD [63]. This may fit with the hyperarousal symptoms noted globally in individuals with PTSD [64].

Attention-Deficit Hyperactivity Disorder

ADHD is classically associated with a range of sleep disorders, including delayed onset of circadian rhythm, fragmentary sleep, and RLS/PLMD during both sleeping and waking [65, 66]. OSA and insomnia are also common in ADHD and tend to exacerbate concentration and executive function performance [68, 69]. These findings have been consistently replicated in children especially with regard to RLS and PLMD [65, 67].

ADHD and Insomnia Common cognitive impairments associated with insomnia with or without comorbid psychiatric disorder include clinically significant impairments in executive functioning, which includes attention, decision-making, and frustration tolerance [70]. Among individuals with ADHD, insomnia occurs in up to 75% of individuals at some point in their life, potentially exacerbating underlying ADHD symptoms. This exacerbation may be mediated by an increase in inflammatory markers and derangements in HPA axis activity leading to neuronal damage, similar to what is seen in other psychiatric disorders [223]. Insomnia may be related to hyperactivity symptoms (increased motoric activity in individuals with ADHD [206]. Others have suggested that inattention symptoms such as lack of organization and distractibility may play a role [224]. Yet other evidence points to undiagnosed RLS as the mediator of the relationship between ADHD and insomnia [225]. Despite this, evidence that insomnia treatment improves ADHD remains sparse [71].

ADHD and OSA Pediatric OSA is also prevalent, and most commonly linked to ADHD and learning disorders, with over 50% of children with OSA having clinically significant ADHD symptoms, learning disorders, or intellectual disability [68, 69]. This fact is of clinical note as therapeutic tonsil- and adenoidectomy can reduce symptoms of ADHD in addition to sleep-disordered breathing. However, to what degree this reduces the need for, or dosages of, medication remains unclear [72–74].

OSA-associated neurocognitive and psychiatric dysfunction is important to recognize and diagnose separately from comorbid primary psychiatric illness, as conventional psychiatric therapies will not result in resolution of symptoms. Additionally, as will be discussed later, psychiatric medications cause changes to sleep architecture that may either exacerbate or improve underlying sleep dysfunction [3, 7, 44, 46].

ADHD and RLS/PLMs RLS and PLMS are reported in up to 44% of individuals with ADHD [75]. Both RLS/PLM and ADHD are marked by restlessness and disordered arousal. The possibility of a shared pathophysiology must be considered given that both disorders respond well to pro-dopaminergic therapies (possibly related to dopamine receptor polymorphisms or dopamine transporter system abnormalities) [75]. Indeed, despite the known class effect of insomnia, there is some evidence to indicate that routine diurnal stimulant therapy in individuals with ADHD may reduce symptoms of sleep dysfunction, especially in the case of long-acting agents [65]. This is important as sleep disruption due to RLS (and other sources) may lead to daytime cognitive issues [66]. As Konofal et al. discuss, both ADHD and RLS/PLMS are marked by "paradoxical overactivity" and both respond with reduced restlessness to dopaminergic stimulation. Thus, potential benefit to RLS symptoms thus may outweigh the potential risk of insomnia from stimulants in some individuals with ADHD [75].

ADHD and Narcolepsy Cognitively, many patients with narcolepsy report feeling mentally foggy. Under scrutiny, this goes beyond the expected deficits in vigilance, or sustained concentration as it also affects executive control of concentration, such as task-switching and error detection [76]. Among individuals with narcolepsy, the rate of ADHD symptoms is 5 to 10 times more common than in the general population [77, 78].

Bipolar Disorder

Bipolar Disorder, Insomnia, and Circadian Rhythm Bipolar disorder is marked and even defined by disturbances in circadian rhythm [1]. Decreased length and need for sleep is a requirement for the diagnosis of mania and hypomania, while hypersomnia (as seen in atypical depression) is seen more frequently in bipolar depressive episodes than in unipolar depression [79]. Insomnia is the most common herald symptom of mania, and may actually precipitate it [80, 81]. Because of the importance of sleep in this disorder, sedating antidepressants such as TCAs have been used historically, but antidepressant use in individuals with bipolar disorder may actually increase the risk of relapse and mood instability compared to sedative hypnotics [82]. Sedating antipsychotics have instead become the preferred choice in this population, providing both sleep-inducing and mood-stabilizing benefits [83].

Comparisons of individuals with bipolar disorder during inter-episode periods of remission to healthy controls reveal few major differences except for increased REM density among those with bipolar disorder; however, the degree to which this may have been influenced by psychotropics is unclear [79, 84]. There is some evidence that REM density may herald future risk of a depressive episode while duration of N2 sleep may be correlated with future risk of a manic episode; however, small sample sizes limit the reliability of this conclusion [84].

PSG Changes PSG differences from control in patients with bipolar disorder during both manic and depressive episodes, despite drastically different sleep latencies (higher in manic phases and lower in depressed phases), as well as total sleep time, share commonalities in reduced REM latency and increased REM density [79, 84].

Schizophrenia

Sleep problems occur among 30–80% of individuals with schizophrenia and run the gamut from PLMD to insomnia to obstructive sleep apnea, all of which are considerably overrepresented compared to controls [85].

Schizophrenia and PSG While there are relatively few PSG studies in schizophrenia, findings of increased sleep latency, decreased periodicity, and substantially decreased slow wave and REM sleep are noted in several meta-analyses [86, 87]. Some studies also raise questions about loss of sleep spindles as a schizophrenia biological endophenotype, although evidence for this is more mixed [87].

Schizophrenia, Circadian Rhythm Problems, and Insomnia A low melatonin level has been suggested to occur in this population. In one study, 2 mg of long-acting melatonin improved sleep efficacy in 19 schizophrenic patients [88]. Treatment with most antipsychotics also tends to improve sleep parameters in this population [89]. Other studies suggest an added benefit on sleep parameters when shifting from the older generation antipsychotics to the newer ones during the acute phase of psychosis, which may be due to the effects of 5HT2 blockade [90].

The negative symptoms of schizophrenia often lead to a more sedentary, solitary life with less employment and other goal directed activity, resulting in an often significant circadian rhythm phase delay. Polypharmacy often causes daytime sleepiness and increased naps, leading to struggles with nighttime sleep. In treating insomnia in this population, the use of the Z drugs (e.g., zolpidem) might be more advantageous than benzodiazepines [91, 92].

Schizophrenia and OSA Individuals with schizophrenia have multiple risk factors for weight gain including the metabolic effects of second-generation antipsychotics, and also generally have low activity levels. This in turn substantially increases their risk for OSA [100].

Schizophrenia and Narcolepsy Individuals with narcolepsy frequently experience vivid hypnagogic hallucinations in part due to their paroxysmal descent into REM sleep, which are often highly detailed and multisensory experiences [93]. This can often be confused with psychosis related to schizophrenia. Talih presents two case reports of individuals initially diagnosed with schizophrenia who were later recognized to have narcolepsy instead [94]. Canellas et al. present a case series of individuals diagnosed with both narcolepsy and psychotic disorders [95] and found that among narcoleptic individuals initially misdiagnosed with schizophrenia, their hallucinations were almost always visual and hypnagogic in nature. Talih also noted that the nature of some individuals' cataplexy presentation (i.e., slack jaw, blank stare, absence of full paralysis) could be misinterpreted as thought-blocking and/or disorganized behavior. Canellas et al. noted that the presence of auditory hallucinations and paranoia can help to differentiate schizophrenia from narcolepsy.

Management of Sleep Disorders and Their Effects on Psychiatric Functioning

Positive Pressure Ventilation (PPV; Continuous Positive Pressure Ventilation and Bi-Level Ventilation) for OSA

While medications are more commonly used for sleep disorders and will be discussed below, PPV is the gold standard treatment for OSA and has remained so for

decades. While alternatives such as appliances and surgery exist, they generally provide poorer results or only benefit a small subset of the population suffering from OSA [96].

PPV in Non-Psychiatric Patients Improvements in neuropsychiatric functioning in patients with OSA who lack psychiatric comorbidity are well established, with benefits seen across a broad swath of cognitive domains including attention, memory, and executive functioning as well as in mood and anxiety [45–48].

PPV and Individuals with MDD and/or Anxiety Disorders The importance of OSA treatment when comorbid psychiatric disorders are present cannot be understated. Benefits in mood have been seen in patients with comorbid depression, generalized anxiety, and panic disorder [7, 49, 50, 61]. In many cases, it may be impossible to achieve clinical response or remission of psychiatric disorder without concomitant treatment of OSA. Improvements in comorbid depression and OSA with PPV treatment include improved mood as well as energy and concentration. Similarly, among individuals with panic disorder, decreases are seen in the frequency of panic attacks [97].

Additionally, in patients with PTSD and OSA, a decrease in the frequency of nightmares is observed [98]. In individuals with ADHD and OSA, there are no studies on PPV, but surgical intervention (e.g., adenoidectomy) has been shown to benefit patients and may substantially decrease ADHD symptoms [72–74, 207].

PPV, Bipolar Disorder, and Schizophrenia There is less research on PPV among individuals with bipolar disorder and schizophrenia. There is one report of a patient switching to mania with CPAP treatment [99]. Regarding schizophrenia, OSA may be underdiagnosed given the common perception that daytime sleepiness may be a result of negative symptoms or from the sedating nature of antipsychotics. Nevertheless, a few small trials indicate improvements in negative symptoms following PPV in this population as well [100–102].

Benzodiazepines and Z-Drugs

Benzodiazepines remain commonly prescribed for anxiety and sleep despite mounting evidence of significant morbidity with their use. In addition to addiction risk, there are other neuropsychiatric risks associated with their use including depression, memory impairment, executive dysfunction, and equilibrium difficulties [103]. When used for sleep, benzodiazepines notably increase total sleep time, albeit with a substantial decrease in both REM sleep and N3 (slow wave) sleep [103, 104]. However, this effect is prone to tolerance, and the consequences of decreased deep sleep remain concerning and may be related to the above-noted neuropsychiatric decline with chronic use [105].

Non-benzodiazepine receptor agonists (also called Z-drugs) may promote increased SWS sleep and typically have little effect on REM sleep [106]. They also have far less of a muscle relaxing effect on the upper airway and thus provoke less

worsening of OSA symptoms than benzodiazepines [107, 108], although they are associated with a known risk of parasomnias, including the potentially dangerous phenomenon of "sleep driving" [109].

In short-term studies, the memory, executive functioning, and vigilance deficits associated with benzodiazepines start to appear as soon as the day after the first night's dose. In contrast, nonbenzodiazepine receptor agonists show little evidence of these neuropsychiatric deficits [110]. However, there is evidence that they may impair neuroplasticity, the clinical magnitude of which is not yet known [111]. Despite these mixed findings, non-benzodiazepine receptor agonists are generally preferred to benzodiazepines for use in insomnia.

Anticholinergics/Antihistaminergics

First-generation antihistamines (with associated strong anticholinergic activity) are commonly used as PRN anxiety medications as well as on a scheduled or PRN basis for Extra-Pyramidal Symptoms associated with the use of antipsychotics [112, 113]. These medications are often taken at bedtime for these symptoms or simply used as sleep aids. Their utility in large-scale trials has been clinically negligible, however, and they are recommended against by the Academy of Sleep Medicine except for brief periods [114]. Antihistamines carry significant risks in long-term use including daytime sleepiness, executive dysfunction problems, and possible risk of dementia [115]. They are associated with declines in memory and in mood when used chronically and as such are also recommended against by the American Geriatric Society's Beers Criteria [116, 117]. Minimization of anticholinergic burden is thus recommended.

Dopamine Agonists

Pramipexole and ropinirole are dopamine-3 receptor agonists used in the treatment of Parkinson's disease as well as in Restless Leg Syndrome and other PLMS [118]. Notably, they have also been of interest in psychiatry where pramipexole in particular has shown some efficacy in treatment-resistant unipolar and bipolar depression [119, 120]. Both medications, however, have shown a small but consistent risk of increasing compulsive and aggressive behaviors regardless of baseline psychiatric or Parkinson diagnosis, with psychosis and mania also being reported [121].

The Effect of Psychiatric Medications on Sleep Physiology and Pathology

A fact that may be a surprise to many is that psychiatric medications are among the most commonly prescribed classes of pharmacotherapy in the general population [122]. At any given time, up to 30 percent of adults in the United States are on a selective serotonin reuptake inhibitors (SSRIs), by far the most commonly prescribed class of psychotropic [123]. Many if not most psychiatric medications have effects on sleep, and not all of them are beneficial [3]. Additionally, certain classes

of medications used for psychiatric symptoms (such as sedative hypnotics) may have deleterious effects on sleep when used chronically that outweigh their putative benefits [103, 115].

Psychotropics encompass a broad range of therapeutic targets and secondary receptor activities, and thus will be discussed on a class-by-class basis. Nevertheless, there are some commonalities among such varied groups and the subclasses within them of anti-manics, antidepressants, and antipsychotics, with perhaps the most striking commonality being the suppression of REM sleep [3]. More positively, many psychotropics including antipsychotics and antimanic agents may improve sleep latency, decrease wake time, and improve sleep quality, although others such as SSRIs may worsen PLMs or even cause insomnia [3, 104, 124].

As a caveat in interpreting the data on psychotropics and their effects on sleep, it should be noted that most of these studies include individuals being actively treated for a psychiatric disorder—which as noted previously in this chapter means that they likely had differences in sleep physiology from those without psychiatric illness. Thus, the findings from these studies regarding the effects of psychotropics may not necessarily apply to those without an underlying psychiatric disorder.

Antidepressants

Antidepressants are a heterologous grouping including SSRIs, serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and several atypical agents. All of these antidepressants are ultimately united by mechanisms involving activity on monoamine receptors within the brain [125–127].

Serotonin plays several notable roles in the sleep cycle as a whole. Of particular clinical interest is the fact that higher levels of serotonin may lead to more fragmentary sleep. Serotonin also plays a key role in suppressing REM sleep, especially via 5-HT2 receptors [128]. Lastly, excess activity at 5-HT3 receptors, especially within the hypothalamus, may exacerbate central sleep apnea [129]. Norepinephrine is also important as it plays a key role in arousal, with higher levels of norepinephrine associated with greater levels of wakefulness that may lead to increased sleep onset latency, disturbances of arousal after sleep onset, and nightmares [130]. In addition, while many of the antidepressants can cause daytime sleepiness through acetylcholine or histamine receptor effects, tricyclic antidepressants have the most sedative effects [126].

Selective Serotonin Reuptake Inhibitors (SSRIs)

As noted above, SSRIs along with the closely related SNRIs are by far the most commonly prescribed antidepressants. SSRIs tend to be relatively "clean" medications as a class with little biologically relevant activity at cholinergic, histaminergic, or other receptors [131]. Thus, their effects on sleep are what one might expect: namely REM suppression (i.e., prolonging REM latency and decreasing overall REM), increasing NREM stage 1, and an increase in sleep fragmentation [125–127]. REM suppression might occur secondary to the serotonin increase at

5-HT1A receptors located in the brainstem, an area responsible for initiating REM [128, 129]. While changes in sleep parameters are significant during initiation of medication, the effects on REM duration might decrease with medication maintenance [125]. Sleep disruptions may be problematic given that depression itself is often associated with poor sleep initiation and maintenance as well as complaints of low daytime energy; however, some studies suggest that these disruptions diminish by the third to fourth week of administration. Subjective reports from multiple trials corroborate this relatively limited duration of sleep disruption in addition to reports of daytime somnolence, which may be related to the reduced sleep time and efficiency that may result from SSRI treatment [132]. While most of the SSRIs are comparable in their effect over sleep stages, fluoxetine tends to have less effect on REM suppression and NREM stage 1 increase but more pronounced arousal effects. REM rebound (i.e., decreased sleep latency and increased total sleep time) occurs for 3–5 days after discontinuing the serotonergic agents (10 days for fluoxetine due to its longer half-life). Thus, it is necessary to discontinue the medication at least 10 days or more prior to a MSLT (multiple sleep latency test) [133].

Counterintuitively, REM suppression in SSRIs may benefit certain aspects of sleep function that are often worse during REM (such as sleep apnea severity) or psychiatric functioning by decreasing intensity of nightmares. They may also contribute improvements in upper airway dilatory tone during non-REM sleep [134, 135]. Additionally, there is a subpopulation of individuals with OSA who experience a dramatic increase in their apnea–hypopnea index (AHI) during REM sleep, which would be suppressed [124]. Improvements in non-REM AHI, however, have been demonstrated in several trials [136, 137]. Although there is a general trend toward improvement in AHI with serotonergic medications, these results have not typically met clinical significance [138].

Last, SSRIs are notable for increasing the risk of developing or worsening PLM symptoms, which lead to arousals, decrease in sleep quality, and decreases in sleep efficiency [139–141]. Relatedly, there is a significant risk especially in children of SSRIs causing or exacerbating bruxism [142].

Selective Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)

SNRIs include duloxetine, venlafaxine, and desvenlafaxine. In addition to their effects on serotonin, they also increase levels of norepinephrine. Thus, they also cause REM suppression, increased stage 1 NREM sleep, and sleep interruption. However, duloxetine tends to have lesser effects over REM suppression and sleep discontinuity compared to the other serotonergic agents [143]. In addition to putatively greater potency in treating depression, they may also be effective in treating pain, especially in the case of duloxetine [144]. On the other hand, they may also have more side effects due to the noradrenergic involvement including increases in blood pressure and anxiety, the latter often comorbid with depression [145]. In general, SNRIs are broadly similar to SSRIs in terms of REM suppression, sleep latency and fragmentation, and risk of PLMs.

Tricyclic Antidepressants (TCAs)

Tricyclic antidepressants (TCAs) being among the first effective antidepressants are party to a rich literature on physiology across multiple domains. Although their use as a primary psychiatric treatment has waned with the advent of SSRIs and later medications due to tolerability and toxicity concerns, they remain clinically useful for a variety of conditions and are frequently encountered in clinical practice. These indications include neuropathic pain, chronic abdominal pain, migraine, and even sleep [126, 146–148]. Notably, the dosages in these uses are much lower than was commonly prescribed for psychiatric disorders. TCAs have a wide spectrum of clinically relevant activity across multiple neurotransmitter pathways including serotonin, norepinephrine, acetylcholine, histamine, and the alpha-2 system, which may underlie their simultaneously broad therapeutic and toxic potentials [149].

TCA receptor activity profiles vary between agents, and thus so too do their effects on sleep. In addition to the effects on sleep noted above via modulation of serotonergic and noradrenergic pathway, individual TCAs exert effects on sleep via anticholinergic activity (leading to a decrease in sleep onset latency), H1 histamine antagonism (leading to lower arousal both while awake and sleeping), and alpha 2 agonism (promoting deeper sleep and decreasing sleep latency) [3, 126, 149].

In terms of individual agent variability, while clomipramine, desipramine, and imipramine disrupted sleep initially in both healthy nondepressed volunteers and depressed individuals, this side effect dissipated only in the depressed population [125]. The likelihood of insomnia is predictable based on the relative magnitude of serotonergic versus cholinergic activity [125]. Amitriptyline and doxepin are often used for their soporific effects. Amitriptyline at lower than 50mg doses is primarily an antihistaminic, thus improving sleep especially in nondepressed individuals. However, its persistent effect has been questioned. Low-dose doxepin formulation has been approved by the Food and Drug Administration (FDA) specifically for sleep. Such TCAs tend to have higher serotonin than norepinephrine activity, as well as substantial H1 activity [125, 149]. Others such as desipramine and protriptyline are highly noradrenergic and are notable for potential benefit in patients who complain of low energy or daytime sleepiness, albeit at the potential expense of worsening sleep onset latency.

Monoamine Oxidase Inhibitors (MAOIs)

This group of medications has rarely been used in the recent years due to their significant dietary restriction and their side effect profile. REM suppression is most pronounced when using MAOIs [150]. Phenelzine and tranylcypromine has also been associated with decreased TST and sleep fragmentation [151]. REM rebound occurs within 2–3 weeks after MAOIs discontinuation.

Atypical Antidepressants

Commonly used atypical antidepressants include bupropion, trazodone, and mirtazapine. These agents have varying chemical structures (although the latter two are chemically related to TCAs) and modes of activity.

Bupropion is unique among antidepressants in that it has negligible activity at serotonin receptors, instead working as a presynaptic reuptake inhibitor of norepinephrine and dopamine [152]. For these reasons, it may be helpful for those patients who complain of lethargy, daytime sleepiness, or concentration and memory difficulties. Bupropion is often associated with increased sleep onset latency likely due to increases in norepinephrine and dopamine; however, rates of insomnia are not any higher for bupropion than for the SSRIs [153]. Interestingly, given the propensity of other antidepressants to worsen sleep limb movement disorders, bupropion may actually alleviate symptoms of RLS/PLMs putatively due to its effects on dopamine [154, 155]. This contrasts favorably to the dopamine agonists pramipexole and ropinirole, given bupropion's lower rate of neuropsychiatric side effects [121, 153].

Trazodone is notable for 5-HT2A antagonism but relatively weak serotonin reuptake inhibition as well as some H1 blockade [156]. As noted previously, inhibition of 5-HT2 leads to a decrease in sleep latency onset and an increase in SWS, which has been demonstrated in both depressed and healthy individuals receiving trazodone [157, 158]. The latter is of interest as SWS is when many of the body's regenerative processes including memory formation and growth hormone release are at their most efficient [20, 21]. Additionally, likely due to its relatively weak serotonin reuptake inhibition, trazodone has little effect on REM sleep [156].

Mirtazapine also has a unique method of action with notable 5-HT2 and 5-HT3 serotonergic blockade, alpha-2 norepinephrine blockade, and H1 histaminergic blockade [159, 160]. H1 and 5-HT2 blockade both likely contribute to the medication's demonstrated tendency to improve sleep onset latency, while the 5-HT2 and alpha-2 antagonism likely contributes to its effects on sleep maintenance and total sleep time. Effects on REM sleep are mixed; mirtazapine is generally believed to exert no effect on REM [161, 162]. Some small-scale studies also indicate that 5-HT3 antagonism in the hypothalamus may improve symptoms of central sleep apnea in rat models, making it one of the few agents available with potential therapeutic benefit for this sleep disorder [163]. Notable downsides to mirtazapine include daytime sleepiness (likely due to H1 blockade) as well as weight gain (from H1 and 5-HT3 blockade), although both are considered to be minimal or self-limited problems in long-term and appropriate dose (>15 mg/day) treatment [164]. Mirtazapine also may be the worst antidepressant in eliciting RLS/PLMs with up to 28% of treated patients developing symptoms [37, 38, 141].

While mirtazapine is used as monotherapy for depression, trazodone is not. Nevertheless, both offer augmentation options for patients with a therapeutic response to SSRI experiencing associated insomnia, especially given that their method of action in 5-HT2 blockade directly counteracts the source of the sleep disruption. They can thus be used as effective adjuncts alongside SSRIs, or even as monotherapy in the case of mirtazapine.

One last antidepressant deserving mention is agomelatine, a melatonin agonist medication with concomitant 5-HT2 antagonism. It has shown promising antidepressant effects as well as improving subjective sleep in depressed individuals. However, its objective effects on sleep architecture are questionable [165].

Antianxiety Medications

Benzodiazepines stimulate GABA-A receptors, causing inhibition throughout higher and lower brain centers including those involved in cognition, respiration, postural and fine motor control, and sedation [166]. Polysomnograms show a decrease in sleep onset latency and sleep fragmentation as well as an increase in total sleep time. However, they also show an increase in beta activity and sleep spindles (consistent with greater time spent in N1 and N2 sleep) at the expense of less time in N3 and REM sleep (the most restorative periods of sleep) [105, 167]. In addition, their muscle relaxant effect may also worsen obstructive sleep apnea and even induce central sleep apneas [168].

Gabapentin and pregabalin, despite their names, primarily exert their effects through the α2δ-1 subunit of the voltage-gated calcium channel, and possibly by mediating glutamate signaling [169]. Both have been shown to improve sleep onset latency, sleep efficiency, and duration of slow wave sleep [170–172]. In regard to their importance in sleep medicine, both have been found to be efficacious in RLS, with pregabalin showing greater tolerability than pramipexole [173, 174].

Buspirone, a 5-HT1A partial agonist primarily used in the treatment of anxiety (but also for depression augmentation), is similar to SSRIs in that it increases REM latency and REM suppression [175]. Buspirone has also been used successfully to treat SSRI-induced bruxism [176].

Mood Stabilizers and Antiepileptic Medications (Anti-Manic Agents)

There is relatively little literature on true anti-manic agents and sleep, although there is much more on antipsychotics—especially second-generation antipsychotics—which are commonly used in the treatment of manic and depressive phases of Bipolar Disorder and which will be examined separately. The most commonly used anti-manic agents in clinical practice are valproic acid (VPA) and lithium carbonate, with carbamazepine also used.

There is a paucity of data on antiepileptic drugs and sleep, although at least one pilot study failed to find any changes in sleep architecture among patients treated with carbamazepine [177]. That same study showed that VPA tends to increase N1 sleep at the expense of SWS. Another interesting study in those with epilepsy reveals that those on VPA for long but not short periods of time had changes in sleep architecture including decreased SWS and REM sleep and higher arousal indices. Those sleep EEG changes mirror the changes seen in obstructive sleep apnea. Given the propensity of VPA to cause weight gain over time, this may imply a correlation with increased risk of OSA [178].

Subjectively, patients taking lithium report a soporific effect. Despite lithium's efficacy in bipolar disorder, its mechanism of action remains poorly understood. However, it is known to assert antagonistic effects on dopamine and glutamate (both involved in wakefulness and arousal) and agonistic effects at GABA receptors [179]. Lithium is associated with preservation of or increases in SWS, with suppression of REM sleep [180, 181]. There is also evidence that lithium may cause an increase in PLMs and RLS, consistent with its dopaminergic influence [36, 37, 182].

Antipsychotic Medications

Second-generation antipsychotics (SGAs) have largely replaced first-generation antipsychotics for long-term use. These agents all share in common the blockade of dopamine at the D2 receptor as well as antagonism of the 5-HT2a receptor, with the importance of the latter in treatment somewhat controversial [183]. In addition, SGAs have varying degrees of activity in the alpha-adrenergic, histaminergic, and cholinergic systems, all of which may be relevant in sleep [184].

Monti and Monti showed in a comprehensive review that, overall, among SGAs and their effect on sleep there is a trend toward decreased sleep latency, fewer arousals and awakenings, variable effect on SWS, and decreased REM sleep [185]. Additionally, due to their antidopaminergic activity, there is a class-level risk of PLMs and RLS [37, 39]. Typical antipsychotics, in contrast, tend to reduce both SWS and REM sleep, further exacerbating the derangements observed in sleep architecture in schizophrenia. Of note, decreases in SWS are associated with worsening negative symptoms in schizophrenia. Olanzapine, however, consistently increased sleep efficiency and slow wave sleep [185]. Risperidone also increases sleep efficiency, as well as decreases sleep latency, but with mixed evidence as to improvements in SWS [186]. Ziprasidone has also shown evidence of improvements in sleep quality and SWS and REM suppression in both healthy controls and individuals with mental illness [187, 188].

Quetiapine is the most commonly used off-label antipsychotic, particularly for sleep [189, 190]. Alongside its use in bipolar disorder maintenance and schizophrenia, it is also an important pharmacologic tool in managing unipolar depression, bipolar depression, and psychosis in Parkinson's and Lewy Body Dementia [191]. Although doses used for these indications are usually lower (<100mg), weight gain and daytime somnolence remain prominent concerns, and PLMs were seen in some studies even at these lower doses [190, 192]. In terms of effects on sleep architecture, quetiapine increases total sleep time, decreases sleep latency, with mixed effects on SWS, and may suppress REM [196.197].

Finally, it is worth considering the high rate of weight gain associated with SGAs that may predispose patients receiving these medications chronically to OSA. While weight gain, dyslipidemia, and diabetes as consequences of antipsychotics are well documented, OSA risk is less so [193]. Nevertheless, the circular interplay between second-generation antipsychotics, OSA, and weight gain is highly concerning.

Alpha-Adrenergic Agents

Clonidine, a presynaptic alpha-2 agonist, and prazosin, an alpha-1 antagonist are commonly used for ADHD, anxiety, and PTSD-related issues in pediatric and adult patients. Both have the ultimate effect of decreasing adrenergic tone. Clonidine, along with melatonin, is one of the few recommended pharmacologic interventions for pediatric insomnia [194]. It is also used in ADHD treatment for both hyperactivity and insomnia (stimulant-induced or otherwise) [195]. Clonidine has also been used for decreasing nightmares associated with PTSD [196]. Prazosin has seen increasing use in adult PTSD specifically for nightmares. Most prazosin trials for

nightmares do show efficacy in decreasing nightmares and arousals and improving subjective sleep quality, despite a recent exception [197].

There is more literature on clonidine's effects on sleep physiology, which indicate a decreased sleep onset latency, decreased sleep fragmentation, decreased REM sleep, and a trend toward an increase in deep sleep [198]. Clonidine also appears to help with ADHD-associated initiation insomnia whether intrinsic or a result of a medication effect [199]. Clonidine has been shown to decrease episodes of apnea/hypopnea associated with REM but not non-REM sleep, an effect only partially explained by REM suppression [200]. Clonidine shows some benefit in the treatment of RLS and PLMs as well [201].

Stimulants

Stimulants remain the first-line therapy for ADHD [202]. They have also been a mainstay of treatment for narcolepsy and individuals with persistent daytime sleepiness after treatment of OSA [203]. This group of medications increases dopamine release and/or decrease reuptake as well as decreasing norepinephrine reuptake, although caffeine increases wakefulness mainly through its anti-adenosine effects [202]. The potential of stimulants to cause insomnia is well established and can be a major reason for discontinuation [204]. However, there are also emerging data that children and adults with ADHD who are on appropriate doses of stimulants have fewer problems with sleep than those whose ADHD is unmedicated. Symptomatic improvements in restlessness before bed, PLMs, and sleep fragmentation have all been reported [204–206]. Although this is somewhat counterintuitive, the findings appear relatively robust, and may make sense from the standpoint of self-regulation and that ADHD is a hypodopaminergic disorder.

Conclusion

Throughout this chapter, we have surveyed the links between sleep disorders, psychiatric disorders, and sleep physiology. Due to the extensive crossover, careful assessment of the patient for both sleep and psychiatric issues is necessary to ensure that you are accurately targeting the underlying pathology. Medications, both those used for sleep and for psychiatric purposes, have effects across all three domains. Some medications that offer putative solutions to problems (such as hypnotics in OSA and anxiety) may actually exacerbate cognitive and mood deficits by negatively affecting sleep efficiency and deep sleep. Other medications, though not thought of as sleep medications in their own right, might offer solutions to common sleep problems that the patient may also be experiencing (such as the use of clonidine for RLS). Through nuanced and careful selection of medication treatments for sleep or psychiatric disease, one can often successfully treat disturbance in the other domain in a parsimonious fashion. Barring that, we as clinicians can ensure that in our quest to improve one aspect of functioning, we do not exacerbate or create new problems in another domain

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Index

A
Acceptance and commitment therapy (ACT), 86
  ABC-I, 88
    Chinese finger trap, 90
    clean *vs*. dirty discomfort, 91
    components, 89
    hiking and renovating metaphors, 90
    intervention, 87
    life with and without insomnia, 90
    patient's awareness, 88
    pizza dough/silly putty metaphor, 90
    plate scale mataphor, 92
    poor night of sleep, 92
    review and trouble shoot challenges, 92
    stream meditation, 90
    surf metaphor, 88
    take mind for walk, 91
    VA healthcare system, 92, 93
    visualization exercise, 91
  anxiety disorders, 86
  behavioral components, 87
  cognitive defusion, 86
  development of ABC-I, 87
  insomnia treatment, 87
  manual development, 88
Advanced sleep-wake phase disorder (ASWPD), 191
Attention-Deficit Hyperactivity Disorder (ADHD), 271

B
Benzodiazepine receptor agonists, 108, 360
  estazolam, 109
  flurazepam, 109
  quazepam, 110
  temazepam, 110
  triazolam, 110
Bruxism, 222
  awake and sleep, 223
  definition and diagnosis, 223
  diagnosis, 223
  etiology and pathogenesis, 223
  management strategies, 224
  medication, 224
  prevalence, 222

C
Cataplexy, 173
Cheyne-Stokes breathing, 141
Children and adolescents
  biological rhythm, 262
  circadian rhythm sleep, 266
  development of sleep patterns, 262
  evaluation, 271–272
  movement disorders, 270
  parasomnias, 270
  pediatric sleep disordered breathing (*see* Pediatric sleep disordered breathing)
  psychiatric disorders, 270
    ADHD, 271
    anxiety disorders, 271
    autism spectrum disorders, 271
    mood disorders, 271
  sleep disorders, 263
    hypersomnia, 265
    insomnia, 263
  sleep parameters, 262
  sleep pattern by age, 261
  ultradian rhythms, 263
Chronic insomnia, 79
Chronotherapy treatment, 194
  advantages, 205
  bright light therapy, 194, 204
  circadian abnormalities, 197
  circadian techniques, 194

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Chronotherapy treatment (*cont.*)
circadian time, 196–197
combinatorial approach, 204
dark therapy, 203
IPSRT, 198
light's effects on mood, 195
light therapy
bipolar depression, 202
BLT guidelines, 200
dawn simulation, 202
intensity, 199
non-seasonal depression, 200, 201
non-seasonal unipolar depression, 198
during pregnancy, 201
seasonal affective disorder, 198–199
spectrum, 200
timing and duration, 200–201
typical protocol, 199
potential adverse effects, 204
sleep regulation to mood, 196
wake therapy, 203–204
Circadian rhythm disorders (CRDs), 189, 190
ASWPD, 191
circadian timing, 190
DSWPD, 191
electroretinogram, 190
ipRGCs, 190
ISWR, 193
jet lag, 194
medical and psychiatric disorders, older adults, 300
ASPD, 300
DSPD, 301
jet lag, 301
non-24-hour sleep-wake rhythm disorder, 192
shift work, 193
Circadian time, 196–197
Cognitive-behavioral therapy for insomnia (CBT-I), 38, 39, 48
age groups
adolescents, 59
children, 59
older adults, 59
closure session, 48
cognitive restructuring, 54
contraindication, 56
description, 48–54
efficacy of, 54
hypnotic medication, 58
limitations, 60
mental health conditions, 57
alcohol, 58
anxiety disorders, 58
bipolar disorder, 57
psychiatric diagnoses, 58
substance use disorders, 58
modality, 55
physical health conditions, 56, 57
relaxing environment, 53–54
sleep education, 51, 52
sleep pattern assessment, 49–51
with adults, 49
children/adolescents, 50
Spielman's 3P factor model, 51
subjective measures, 50
treatment planning, 49
sleep restriction therapy, 52, 53
stimulus control therapy, 52
subsequent sessions, 48
Continuous positive airway pressure (CPAP) therapy, 151
behavioral tasks, 155
biomedical barriers, 152
biomedical factors, 154
biopsychosocial assessment, 152
claustrophobia, 163
cognitive-behavioral framework, 160
ESS scores, 159
graded exposure hierarchy, 163
issue of claustrophobia, 159
MI approach, 153, 157
motivational interviewing, 156
nonadherent patients, 152
nonjudgmental manner, 156
OSA, 153
patients' subjective reasons, 153
proposed interventions, 156
psychological factors, 154
social factors, 155
treatment interventions, 162

D

Delayed sleep phase disorder (DSPD), 301
Delayed sleep-wake phase disorder (DSWPD), 191
Dim light melatonin onset (DLMO), 10, 197
Doxepin, 116

E

Epworth sleepiness scale (ESS), 143, 159
Excessive daytime sleepiness (EDS), 159
amphetamines, 183
antidepressant Medications, 184
armodafinil, 183
in children, 170
daytime drowsiness/sleepiness, 169, 182
daytime stimulants, 183

diagnostic testing, 171
Epworth Sleepiness Scale, 171
Karolinska Sleepiness Scale, 172
MSLT, 172
MWT, 172
sleep diaries, 171
sleep patterns and duration, 171
sleep questionnaires, 171
Stanford Sleepiness Scale, 171
wrist actigraphy, 173
encephalopathy, 182
idiopathic hypersomnia, 178–180
clinical presentation, 179
etiology, 179
ICSD-3, 179
prevalence, 179
Kleine–Levin syndrome
behavioral changes, 180
clinical presentation, 180, 181
diagnosis, 181
ICSD-3, 180
menstrual-related hypersomnia, 181
prevalence, 180
risk factors, 181
modafinil, 183
narcolepsy (*see* Narcolepsy)
selegiline, 184
sodium oxybate, 184
Exploding head syndrome (EHS), 249

F
Frontal lobe seizures, 224
antiepileptic drugs, 226
diagnostic criteria, 225
etiology, 225
interictal EEG, 226
prevalence, 224
psychiatric disorder, 225

H
Home sleep environment, 94
Home sleep testing, 18
Hypersomnolence, *see* Excessive daytime sleepiness (EDS)

I
Insomnia, 25
adjustment insomnia, 33
behavioral in children, 35
CBT-I, 38, 39
chloral hydrate, 102
cognitive behavioral therapy, 103
common complaints, 36
diagnosis
classification systems, 32–33
DSM-5, 30–31
ICSD-3, 31
ICD-10-CM, 33
diathesis-stress model, 68
differential diagnosis, 68
drugs, 37
due to medical conditions, 36
FDA medications, 39
geriatric populations, 27
idiopathic insomnia, 34
inadequate sleep hygiene, 34–35
medical and psychiatric disorders, older adults, 27, 295
medical complications, 28
melatonin therapy, 201–202
menopause, 26
during menstruation, 26
mental disorder, 35–36
neurocognitive model, 30
pharmacotherapy, 103
poor sleep quantity, 101
during pregnancy, 26
prevalence, 25
process-C, 68
process-S, 68
PSQI, 38
psychiatric disorders, 27
psychophysiological, 35
psychotherapy, 103
quality of life, 29
rapid eye movement, 68
shift workers, 27
sleep assessment, 102
sleep hygiene, 102
stimulants, 37
stimulus control model, 29
stress, 27
substance use disorder, 36
3-P model, 30
treatments, 40, 104
veteran population, 317
adrenergic drugs, 319
antipsychotic drugs, 319
benzodiazepines, 318
depression, 322
non-pharmacological treatments, 318
pharmacological treatments, 318
PTSD Checklist, 320
substance use, 323
suicidality, 322
TBI, 321
Insomnia Severity Index, 75, 93
Interpersonal and Social Rhythm Therapy (IPSRT), 198

Intrinsically-photosensitive retinal ganglion cells (ipRGCs), 190
Irregular Sleep-Wake Rhythm (ISWR), 193
Isolated Sleep Paralysis (ISP), 248–249

L
Light therapy, 198–199

M
Major depressive disorder (MDD), 346
  narcolepsy, 348
  OSA, 348
  polysomnogram changes, 347
  RLS and PLMs, 347
Medical and psychiatric disorders, older adults, 295–308
  affect sleep
    chronic pain, 307
    medications, 307
    substances, 308
  circadian rhythm disorders
    ASPD, 300
    DSPD, 301
    jet lag, 301
  hypersomnia, 299
  insomnia, 295
  movement disorders, 303–307
    PLMD, 305
    RBD, 306
    RLS, 303
  SDB
    CSA, 303
    OSA, 302
Mindfulness-Based Graded Exposure Therapy (MB-GET), 73
Mindfulness-based interventions (MBIs), 69
Mindfulness-based stress reduction (MBSR), 69
Monoamine Oxidase Inhibitors (MAOIs), 359
Multiple Sleep Latency Testing, 172
Multiple Wakefulness Testing, 172

N
Narcolepsy
  clinical features, 173
  medical conditions, 178
  psychiatric disoder, 178
  type 1 (NT-1)
    cataplexy, 174
    clinical presentation, 174, 175
    diagnosis, 176
    hypnagogic and/or hypnopompic hallucinations, 174
    loss of hypocretin, 175
    sleep paralysis, 174
  type 2 (NT-2), 176
    clinical presentation, 177
    diagnosis, 177
    etiology, 177
Nocturnal Leg Cramps (NLC), 219
  definition, 220
  Iatrogenic, 220
  management, 220
  prevalence, 220
Nonbenzodiazepine receptor agonists (non-BZRAs), 111
  eszopiclone, 112
  zaleplon, 113
  zolpidem, 114
    zolpidem CR, 115
    zolpidem IR, 114
    zolpidem SL, 115
    zolpidem spray, 116
Non-rapid eye movement stages (NREM), 7–9
  stage 1, 8
  stage 2, 8
  stage 3, 9
  wakefulness, 8
Normal aging changes in sleep, 293
  cyclic hormonal changes, 294
  melatonin, 294
  structure changes with age, 293
  zeitgebers, 294

O
Obstructive sleep apnea (OSA), 151, 267
Off-label and over-the-counter (OTC), 120–123
  antihistamines, 121
  diphenhydramine, 122
  gabapentin, 122
  melatonin, 120
  mirtazapine, 121
  quetiapine, 121
  trazodone, 120
  valerian, 123

P
Parasomnias
  antidepressant drugs, 251
  catathrenia, 247
  confusional arousals, 237
  diagnosis, 250

exploding head syndrome, 249
isolated sleep paralysis, 248–249
nightmare syndrome, 245–246
pharmacologic treatment, 250
REM sleep, 241
sexsomnia, 240
sleep terror, 238
sleepwalking, 235
SREDs, 239
status dissociates, 246
Pediatric sleep disordered breathing
apnea of prematurity, 269
hypoventilation syndrome, 270
PS and OSA, 267
Periodic limb movement disorder (PLMD), 212
Pittsburgh Sleep Quality Index (PSQI), 38, 96
Polysomnography (PSG), 18
Premenstrual dysphoric disorder (PMDD), 280
Premenstrual syndrome (PMS), 280
Primary snoring (PS), 267
Psychiatric disorder
management and effects
anticholinergics/antihistaminergics, 356
benzodiazepines, 355
dopamine agonists, 356
positive pressure ventilation, 354–355
Z-drugs, 355
sleep dysfunction, 346
ADHD, 351
anxiety disorders, 349
bipolar disorder, 353
major depressive disorder, 346
PTSD, 350
schizophrenia, 353–354
Psychiatric medications effect, 356
alpha-adrenergic agents, 362–363
anti-anxiety medications, 360–361
buspirone, 361
gabapentin and pregabalin, 361
anti-manic agents, 361
antipsychotic mediactions, 361
atypical antidepressants, 359
agomelatine, 360
bupropion, 359
mirtazapine, 360
trazodone, 360
MAOIs, 359
SNRIs, 358
SSRIs, 357
stimulants, 363
tricyclic antidepressants, 358
Psychopharmacological choices, 123–125
bipolar disorder, 123
depressive and anxiety disorders, 123
substance abuse, 124
women of childbearing age, 124
elder patients, 124
pregnancy, 124
sleep disorders, 125
Psychotropic medications, 215

R
Ramelteon, 118
Rapid Eye Movement Stage (REM), 9, 345–346
Rhythmic movement disorder (RMD), 221–222
definitions, 221
diagnostic features, 221
etiology and pathogenesis, 221
management, 222
prevalence, 221
psychiatric disorders, 222
sleep related disorders, 221
Restless leg syndrome (RLS) and PLMD, 211–219
anxiety disorders, 214
assessment, 218
cardiovascular disease, 215
characterization, 212
in children, 217–219
depressive syndromes, 214
genetics, 217
headaches, 216
kidney disease, 215
low ferritin levels, 218
management, 218
clonidine, 219
dopaminergic medications, 218
gabapentin, 219
iron supplementation, 219
opioid medications, 219
narcolepsy, 213
obstructive sleep apnea, 213
overlapping disorders, 212
pain disorder, 216
parasomnias, 213
parkinson's disease, 216
prevalence, 212
psychiatric disorders, 213, 214
schizophrenia, 214

S
Selective Serotonin Reuptake Inhibitors (SSRIs), 357–358

Sleep
architecture and children, 11
architecture and geriatrics, 12
assessment measures
airflow sensors, 18
home sleep testing, 18
polysomnography, 18
snoring microphone, 18
brain areas and neurotransmitters, 13–14
characteristics and waves, 8
circadian rhythm and age, 12
disruption of sleep, 3
DLMO, 10
duration and age, 11
effects of photoentrainment, 10
functions of, 5
attention and working memory, 6
immune function, 7
memory formation, 5
neuroendocrinal and glucose control, 6
process of synapsis, 5
remove toxic waste, 6
sleep deprivation, 6
melatonin 1 and 2 receptors, 10
neurobiology and neuroanatomy, 12
in newborns, 11
night sleep and napping, 11
non-rapid eye movement stages, 7–9
NREM, 6
obstructive sleep apnea, 17
overview, 3
process C, 10
process S, 10
psychiatric conditions, 4
psychotropic medication
effects, 16
movement disorders, 17
obstructive sleep apnea, 17
REM stage, 17
time and efficacy, 16
rapid eye movement, 7, 9
restless leg syndrome, 4
sleep disorders
classification of, 15
in DSM-5, 16
ICD-10 classification system, 16
ICSD-3, 16
Sleep disordered breathing (SDB), 131, 302
central sleep anea, 140, 303
Cheyne-Stokes breathing, 141
hypoventilation syndromes, 142
medications, 141
prevalence, 141
treatment and management, 142
classifications of, 132
history, 134
home sleep apnea testing, 143, 144
obstructive sleep apnea, 134, 302
ADHD, 136
CPAP, 137
medical complications, 137
medications, 137
oral appliances, 138
physical examination, 134
prevalence, 135
psychiatric disorders, 136, 140
PTSD, 136
surgical options, 138
treatment, 139
weight loss in obese, 139
screening tools
Berlin questionnaire, 143
ESS questionnaire, 143
STOP-BANG questionnaire, 143
snoring, 132, 133
Sleep-related Eating Disorders (SREDs), 239–240
Sleep restriction therapy, 52–53
Sleep-wake cycle, 13–14
Sleep-wake regulation, 344–345
melatonin secretion, 345
process C, 344
process S, 344
sleep-generation neurons, 344
suprachiasmatic nucleus, 345
Slow wave sleep function, 345
Status dissociatus (SD), 246–247
Stimulus control therapy, 52
Suvorexant, 119

T
Tricyclic antidepressants (TCAs), 358–359

V
Veteran population
co-occurring disorders, 317
depression, 322
disrupted sleep, 315
insomnia, 317
adrenergic drugs, 319
antipsychotic drugs, 319
benzodiazepines, 318
non-pharmacological treatments, 318
pharmacological treatments, 318
PTSD Checklist, 320
substance use, 323

suicidality, 322
TBI, 321
nightmares, 329
consequences, 329
prevalence, 329
treatment, 329
OSA, 323
CPAP, 325
PSG patterns, 326
PTSD, 325
substance use, 327
suicidality, 327
TBI, 326
prevalence rates, 316
RLS, 327
consequences, 328
co-occurring disorders, 328
effects, 328
prevalence, 327
treatment, 328, 329
screening measures, 316

Y
Y-MBCTi model, 70
CBT intervention
behavioral activation, 73
behavioral experiments, 73
MB-GET, 73
sleep restriction, 73
stimulus control, 73
CBT portions, 71
insomnia severity index, 75
level of mindfulness, 75
level of stress, 75
meditation instructions, 76–78
methodology, 72
mindful state, 71
pre- and posttreatment data, 80–81
protocol, 72
sleep assessment, 71
sleep hygiene, 78
SPASM method, 77
STOPP module, 77
translational format, 70
weekly activity schedule, 74
Yoga and meditation interventions, 69

Z
Women, sleep disorders, 275
differences uniques
to gender, 287
hormonal shifts, 275
insomnia, 275
menarche and reproductive
period, 277
body temperature, 278
cortisol level, 279
estrogen, 278
follicular phase, 277
increased sleep duration, 278
luteal phase, 277
medical complications, 281
melatonin levels, 279
menstrual cycle, 277
menstrual-related hypersomnia, 281
PMDD symptoms, 280
PMS symptoms, 280
polycystic ovarian syndrome, 280
polysomnography, 281
progesterone, 278
psychosocial and cognitive
factors, 280
reproductive periods, 280
testosterone levels, 279
TSH and prolactin, 279
menopause, 285
estrogen, 286
management, 287
prevalence, 286
psychiatric disorders, 286
mood symptoms, 275
newborn to childhood, 276
postpartum period, 284, 285
pregnancy, 282
baseline depression, 283
increased depressive
symptoms, 283
management of poor sleep, 283
medical complications, 283
prevalence, 283

Z
Zeitgebers, 190