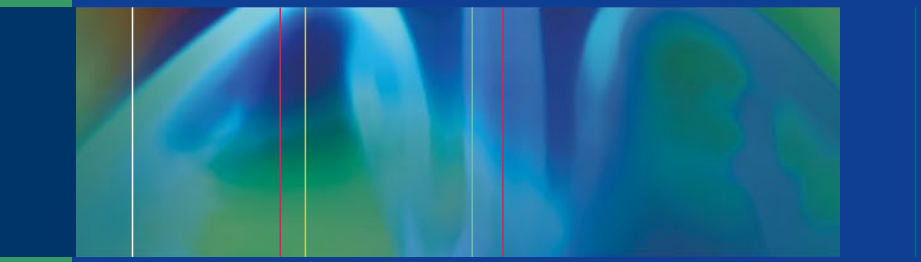
Imran S. Khawaja
Thomas D. Hurwitz *Editors*



Comorbid Sleep and Psychiatric Disorders

A Clinical Casebook

Springer

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Editors
Imran S. Khawaja
Center for Sleep Medicine
VA North Texas Health
Care System, Department of
Psychiatry and Neurology
and Neurotherapeutics UT
Southwestern Medical Center
Dallas, TX
USA

Thomas D. Hurwitz
Minneapolis VAHCS
Hennepin County Medical
Center, and University of
Minnesota Medical School
Minneapolis, MN
USA

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Preface

Sleep problems and psychiatric illness go hand in hand. There is no psychiatric disorder during which sleep is not disturbed, and there has been an increasing emphasis on recognizing and treating sleep disorders in patients with comorbid psychiatric disorders. In fact, evidence supports a bidirectional relationship between the two domains.

Because of this bidirectional relationship, increasing clinical sensitivity to sleep disturbance enhances monitoring of severity, natural history, progress of therapy, and risk of relapse of psychiatric disorders. Clinicians must become increasingly cognizant of this. For instance, we now recognize insomnia as both a symptom of mood disorder and a predictor of its occurrence and severity. We are learning that sleep-disordered breathing is frequently comorbid with depression.

In many academic medical centers, there is little education about sleep medicine available for medical students and residents. Indeed, physicians may even contribute to worsening sleep for their patients by prescribing medications. For example, many psychiatrists do not recognize that selective serotonin reuptake blockers and other antidepressant drugs may precipitate REM sleep behavior disorder. Primary care providers who are often the first to treat mental health and sleep problems come to realize that their residency training did not provide adequate training about sleep and mental health. Though there are now a number of textbooks on sleep disorders for psychiatrists, we provide here a practically oriented casebook on the topic, which can provide trainees and clinicians with some concrete examples that may complement their practice.

In this casebook, we present cases the reader can recognize as relevant to their own patients, perhaps seen very recently. Most of these cases represent reasonably common occurrences, though some may seem unusual for a non-sleep-trained psychiatrist. It is our hope that these may stimulate further study and increasing familiarity.

We have made an effort to keep these chapters brief and easily digestible. The book focuses on major categories of sleep disorders such as insomnia, hypersomnias, sleep-disordered breathing, parasomnias, circadian rhythm disorders, and restless legs syndrome with emphasis on comorbid psychiatric disorders. Authors have introduced their cases with a compelling title, followed by clinical history, relevant examination, and relevant laboratory and polysomnographic data. Questions are posed to stimulate the reader, followed by discussion of the diagnosis, treatment, and useful take-home points.

We hope that this book of 23 chapters/cases will inform and stimulate clinicians from various backgrounds including psychiatry, general medicine, pediatrics, and psychology. We are confident that readers will find these cases helpful and applicable in their clinical practice.

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Dallas, TX, USA Imran S. Khawaja, MBBS, FAASM
Minneapolis, MN, USA Thomas D. Hurwitz, MD, FAASM, DLFAPA

Contents

Contributors

Susamma Abraham, DNP, APRN, FNP-C Center for Sleep Medicine, Department of Neurology, Sleep, VA North Texas Health Care System, Dallas, TX, USA

Hrayr P. Attarian, MD, FACCP, FAASM Department of Neurology, Northwestern Medicine, Chicago, IL, USA

Noelle E. Balliett, PhD Outpatient Mental Health, VA Puget Sound Healthcare System, American Lake Division, Tacoma, WA, USA

Elisa Basora, MD Department of Pediatrics – Respiratory Medicine, UT Southwestern Medical Center, Dallas, TX, USA

Philip M. Becker, MD Sleep Medicine Associates of Texas, PA, Dallas, TX, USA

Austin W. Blum Department of Psychiatry and Behavioral Neuroscience, University of Chicago, Chicago, IL, USA

Matthew S. Brock, MD Department of Sleep Medicine, Wilford Hall Ambulatory Surgical Center, JBSA Lackland USAFB, San Antonio, TX, USA

Gregory S. Carter, MD, PhD Department of Neurology and Neurotherapeutics, The University of Texas Southwestern Medical Center at Dallas, Dallas, TX, USA

Sandra Cooper, RPSGT Center for Sleep Medicine, VA North Texas Health Care System, Dallas, TX, USA

Nilam Danish, MBBS Department of Neurology (Sleep Lab), Veterans Affairs North Texas Health Care System, Dallas, TX, USA

Joanne L. Davis, PhD Department of Psychology, The University of Tulsa, Tulsa, OK, USA

Patricia Dickmann, MD Addiction Recovery Service, Department of Psychiatry, Minneapolis Veterans Affairs Medical Center, Minneapolis, MN, USA

Department of Psychiatry, University of Minnesota Medical School, Minneapolis, MN, USA

Ayesha Ebrahim MD TruCare PA, Grapevine, TX, USA

Department of Medicine, VA Medical Center, Dallas, TX, USA

Vijayabharathi Ekambaram, MD, PhD Department of Psychiatry and Behavioral Sciences, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA

Joshua N. Friedlander, Psy.D Behavioral Health Directorate, Walter Reed National Military Medical Center, Bethesda, MD, USA

Jon E. Grant, JD, MD, MPH Department of Psychiatry and Behavioral Neuroscience, University of Chicago, Chicago, IL, USA

Madeleine Marie Grigg-Damberger, MD Department of Neurology, Clinical Neurophysiology, and Sleep Medicine, University of New Mexico School of Medicine and Medical Center, Albuquerque, NM, USA

Hisham Hamdan, MD Department of Neurology and Neurotherapeutics, The University of Texas Southwestern Medical Center at Dallas, Dallas, TX, USA

Ali M. Hashmi Department of Psychiatry and Behavioral Sciences, King Edward Medical University, Lahore, Pakistan

Thomas D. Hurwitz, MD, FAASM, DLFAPA Minneapolis VAHCS, Hennepin County Medical Center, and University of Minnesota Medical School, Minneapolis, MN, USA

Nireman Iqbal, MBBS King Edward Medical University, Lahore, Pakistan

Muna Irfan, MBBS Department of Sleep/Pulmonary, VA Minneapolis, Minneapolis, MN, USA

Department of Neurology, University of Minnesota, Minneapolis, MN, USA

Abhisek Chandan Khandai, MD, MS Department of Psychiatry, Northwestern McGaw Medical Center, Chicago, IL, USA

Imran S. Khawaja, MBBS, FAASM Center for Sleep Medicine, VA North Texas Health Care System, Department of Psychiatry and Neurology and Neurotherapeutics UT Southwestern Medical Center, Dallas, TX, USA

Khurshid A. Khurshid, MD Department of Psychiatry, University of Massachusetts Medical School, Worcester, MA, USA

Bhanu Prakash Kolla, MD, MRCPsych Department of Psychiatry and Psychology, Mayo Clinic, Rochester, MN, USA

Elliott Kyung Lee, MD, FRCP Department of Psychiatry, Royal Ottawa Mental Health Center Sleep Disorders Clinic, Ottawa, ON, Canada

Guo Lulu, MD Hennepin Healthcar, Minneapolis, MN, USA

Meghna P. Mansukhani Center for Sleep Medicine, Mayo Clinic, Rochester, MN, USA

Candace Meinen Center for Sleep Medicine, Mayo Clinic, Rochester, MN, USA

Katherine E. Miller, PhD National Center for PTSD, Dissemination and Training Division, VA Palo Alto Healthcare System, Menlo Park, CA, USA

Vincent Mysliwiec, MD Department of Sleep Medicine, Wilford Hall Ambulatory Surgical Center, JBSA Lackland USAFB, San Antonio, TX, USA

Aneeqah Naeem The Warren Alpert Medical School, Brown University, Providence, RI, USA

S. Kamal Naqvi, MD Department of Pediatrics – Respiratory Medicine, UT Southwestern Medical Center, Dallas, TX, USA

Britta Klara Ostermeyer, MD, MBA, FAPA Department of Psychiatry and Behavioral Sciences, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA

Ahmed Qureshi Department of Psychiatry, VA Medical Center, Orlando, FL, USA

LaDonna Saxon, PhD Department of Mental Health, Veterans Affairs Medical Center, Dallas, TX, USA

Carlos H. Schenck Minnesota Regional Sleep Disorders Center, Minneapolis, MN, USA

Department of Psychiatry, University of Minnesota, Minneapolis, MN, USA

Wolfgang Schmidt-Nowara, MD Department of Neurology and Sleep Disorders, Dallas VA Medical Center, Dallas, TX, USA

Sean Shirley, MD Department of Sleep Medicine, Wilford Hall Ambulatory Surgical Center, JBSA Lackland USAFB, San Antonio, TX, USA

Elizabeth E. Sita, MD Department of Psychiatry, Northwestern Medicine, Chicago, IL, USA

Heather Swanson, MD Addiction Recovery Service, Department of Psychiatry, Minneapolis Veterans Affairs Medical Center, Minneapolis, MN, USA

Department of Psychiatry, University of Minnesota Medical School, Minneapolis, MN, USA

Ranji Varghese, MD Department of Neurology, Hennepin County Medical Center, Minneapolis, MN, USA

Anna Wani, MD Department of Pediatrics and Family Community Medicine, UT Southwestern Medical Center, Dallas, TX, USA

Joseph Westermeyer, MD, MPH, PhD Addiction Recovery Service, Department of Psychiatry, Minneapolis Veterans Affairs Medical Center, Minneapolis, MN, USA

Department of Psychiatry, University of Minnesota Medical School, Minneapolis, MN, USA

Chapter 1
Is It OSA or Depression or Both?

Ali M. Hashmi, Imran S. Khawaja, and Wolfgang Schmidt-Nowara

Clinical History/Case

A 51-year-old married white man with a medical history of obesity, diabetes, and hypertension presented to an outpatient psychiatry clinic with depressed mood nearly every day for more than 2 months. He also had associated symptoms of depression including diminished interest in activities, low energy, memory problems, and significant weight gain in recent years. His family had noticed that he was less active. The patient endorsed sleep maintenance insomnia as well as fatigue and sleepiness during the daytime. He also reported difficulty with memory and concentration. He reported some hopelessness but denied suicidal ideation either now or in the past. He had no history of psychotic symptoms. He had no previous psychiatric care.

A. M. Hashmi
Department of Psychiatry and Behavioral Sciences, King Edward Medical University, Lahore, Pakistan

I. S. Khawaja
Center for Sleep Medicine, VA North Texas Health Care System, Department of Psychiatry and Neurology and Neurotherapeutics, UT Southwestern Medical Center, Dallas, TX, USA

W. Schmidt-Nowara (✉)
Department of Neurology and Sleep Disorders, Dallas VA Medical Center, Dallas, TX, USA
e-mail: wolfgang.schmidt-nowara@va.gov

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Examination/Mental Status Exam

The patient was a slightly disheveled, overweight man who appeared to have not taken much care in his appearance. He seemed to be tired and "hungover" with deep bags under his eyes which looked bloodshot. When the treating clinician went to fetch him in the waiting area, he was asleep sitting in the waiting room chair, snoring slightly. On physical exam, the patient had a BMI of 38 and neck circumference of 21 inches. His mood was depressed with affect being appropriate to his mood. He was cooperative but appeared weary and listless. He denied any psychotic symptoms and mental state examination did not reveal any evidence of paranoia or any other psychotic symptoms.

Patient health questionnaire-9 (PHQ-9) score was 23 (scores of 10 and above indicate depression) at first visit. The presumptive initial diagnosis was major depressive disorder without psychotic features. He was started on sertraline 25 mg daily to gradually titrate up to 100 mg a day over two weeks as tolerated. He was counseled about weight loss and exercise and asked to maintain proper control over his diabetes and hypertension.

At the first follow-up visit 6 weeks later, the patient reported some improvement in his mood but continued to complain of poor concentration and excessive daytime sleepiness. He indicated that he had recently been involved in a motor vehicle accident when he had fallen asleep at the wheel while standing at a traffic light (fortunately, no one was injured). His wife was present at the session, and upon questioning, she reported a several year history of loud snoring to the extent that she had moved into another room a while back. When asked about his sleep, his wife reported that when they slept in the same room, he snored loudly and often stopped breathing and then gasped for air.

Special Studies

Due to concern for obstructive sleep apnea (OSA), an attended polysomnogram (PSG) was performed. It showed severe OSA with an apnea-hypopnea index (AHI) of 84 events per hour

(normal is <5) and an arousal index of 50 per hour. Oxygen saturation nadir was 70%. A trial of continuous positive airway pressure (CPAP) was initiated during the PSG, and at a pressure of 10 cm H_2O, most of the sleep-disordered breathing events were eliminated. Oxygen saturation was normalized.

Results

At the first visit after CPAP initiation, the patient reported a remarkable improvement in mood and a significant increase in energy level. The patient requested to be tapered off his antidepressant medication which was accomplished by a gradual taper over the next few weeks. He was able to maintain improvement in mood and alertness despite no longer taking sertraline.

Question

In a case like this, how would you differentiate between OSA and depression keeping in mind that the two conditions can be comorbid? How would you rule out one or the other and would there be any therapeutic implications?

Diagnosis, Differential Diagnosis, and Discussion

Chronic sleep loss and sleep disorders impose a large public health burden. Awareness among the general public and healthcare professionals is increasing, but many patients remain undiagnosed and without treatment. It is estimated that 50 to 70 million Americans suffer from a chronic disorder of sleep and wakefulness, adversely affecting daily functioning and health. Insomnia is the most common sleep disorder, followed by sleep apnea and restless legs syndrome (RLS) [1].

Mental disturbance is extremely common among those who suffer from sleep disorders. Most psychiatric patients have sleep complaints, and a primary sleep disorder frequently

includes neuropsychiatric features. Up to 2/3 of patients who present to a sleep disorders center report an episode of depression within the previous 5 years, and one quarter described themselves as depressed at presentation [2].

Obstructive sleep apnea (OSA) is by far the most common form of sleep-disordered breathing. The essential elements are diminished or stopped breathing during sleep and a break in sleep continuity, or arousal, to correct the problem. OSA results from an obstruction of the upper airway that occurs because of reduced motor tone of the tongue and/or airway dilator muscles [2] during sleep. Impaired breathing in the form of apneas, i.e., stopped breathing, or hypopneas, i.e., diminished breathing, can cause harmful reductions in the level of oxygen in the blood. The prevalence of OSA in the general population is approximately 20%, defined by an apnea-hypopnea index (AHI) of 5 or more events per hour. OSA is more commonly seen in obese patients. Patients with OSA are at increased risk of developing excessive daytime sleepiness (EDS), poor neurocognitive performance, and multi-organ dysfunction [3].

Up to 63% of patients with OSA can also have comorbid depression [4]. The exact mechanisms underlying the association between OSA and depressive symptoms are not known. Poor sleep quality and frequent arousals may adversely affect mood. In addition, intermittent hypoxemia secondary to repeated hypopnea/apnea can also influence mood [5]. As a chronic condition, OSA is associated with the release of several pro-inflammatory cytokines such as IL-6 and tumor necrosis factor [6]. A similar immune response involving pro-inflammatory cytokines such as IL-1, IL-6, and interferons was noted among patients with depression [7]. Several inhibitory and excitatory neurotransmitters, such as serotonin, norepinephrine, and γ-aminobutyric acid (GABA), are involved in both the sleep/wake cycle and mood regulation. Distinguishing between depression and OSA can be difficult since they share many common clinical features (Table 1.1).

Table 1.1 Overlapping symptoms of OSA and depression

Obstructive sleep apnea	Overlapping symptoms	Depression
Snoring	Fatigue/daytime sleepiness	Sadness
Witnessed apneas	Non-refreshing sleep (despite adequate sleep times)	Guilt
Snorting arousals	Insomnia	Agitation
Gasping for breath	Irritability	Anhedonia
	Weight gain	Suicidal ideation
	Psychomotor retardation	Weight loss

Adapted from International Classification of Sleep Disorders, third Edition and Diagnostic and Statistical Manual of Mental Disorders, fifth edition

Other confounding factors include the comorbid existence of diabetes, obesity, and cardiovascular disease which have been independently associated with both OSA and depression [8, 9]. Most standardized depression rating scales such as the Beck Depression Inventory and others have not been validated in OSA patients.

When assessing a patient suspected to having both OSA and depression, a general rule of thumb is to evaluate OSA fully and, if found, assume that the mood disorder is secondary to OSA until shown otherwise. As shown in the table, patients with OSA generally do not exhibit symptoms such as suicidal ideation, persistent sadness (fatigue and listlessness is more common), or ruminative guilt. If the patient presents with these symptoms, a major depressive disorder is much more likely and will need corresponding treatment.

The patient or bed partner may report the presence of snoring, episodes of choking or gasping for air, or witnessed apnea indicating sleep-related breathing disorders. Additional signs of sleep apnea include awakening with a dry mouth, nasal congestion, nighttime cough, nocturnal enuresis, and morning headaches. It is helpful to have a bed partner present to identify variations in the quality of snoring, because apnea may present as episodes of loud snoring that alternate with

quiet episodes of pauses in breathing. The presence of a bed partner can also be helpful in identifying the deleterious effects of snoring on interpersonal relationships, a possibility that is often a key motivating factor in seeking out a sleep evaluation. Obesity is an established risk factor for sleep apnea. The weight and height of each patient should be documented, as well as any weight changes over the past few years or attempts at weight loss. Menopause, independent of age and body mass index, is also a risk factor for sleep apnea. Determining if a woman is premenopausal or postmenopausal can help determine if she is at risk for sleep apnea. A recent meta-analysis [10] reported a high prevalence of sleep-disordered breathing (SDB) (including OSA) in pregnant women and showed that its prevalence increases as the pregnancy progresses with rates in the third trimester as high as 47%. SDB during pregnancy is associated with adverse maternal and fetal outcomes including gestational hypertension (GHT)/preeclampsia, gestational diabetes (GDM), and low infant birth-weight. Early screening for OSA in pregnancy may help in reducing these adverse outcomes.

Treatment of comorbid insomnia and anxiety with a benzodiazepine and hypnotic may worsen OSA. These medications may decrease muscle tone in the already functionally impaired upper airway dilator muscles, blunt the arousal response to hypoxia, and increase the arousal threshold for apnea event, therefore increasing the number and duration of apneas [11].

Depression is known to have an effect on adherence to treatment of chronic medical conditions like cardiovascular disease, and treatment of depression tends to improve acceptance and compliance. Depressed patients might have poor adherence to CPAP use, suggesting that depression should be treated aggressively in patients with comorbid OSA [12]. Continuous positive airway pressure (CPAP) treatment improves daytime sleepiness in patients with OSA. In clinical studies, improvement in daytime sleepiness often translates into improvement in the depressive and anxiety symptoms as most mood and anxiety scales have sleep-related questions. Studies have reported discrepant results of CPAP treatment

on comorbid depression. Most authors suggest that treatment of OSA has an overall beneficial effect on quality of life and mood. The improvement in "depression" may imply that CPAP is having an effect on epiphenomena such as fatigue, sleepiness, and motivation rather than depression. Thus, anything but the mildest depressive symptoms associated with OSA should be treated aggressively with antidepressant medication and psychotherapy to ensure optimal outcomes. OSA patients undergoing CPAP treatment should be regularly screened for persistent depressive symptoms which should be treated concomitantly for best outcomes.

Conclusion

OSA and depression are common in the general population and often coexist although a conclusive causal link has not been found. Treatment of OSA often results in improvement in some symptoms of depression (fatigue, excessive daytime sleepiness, memory/concentration issues) but others may persist [13]. Multiple pathophysiological mechanisms have been proposed for this association which can predispose patients with OSA to develop depression including poor sleep quality and frequent "micro-arousals," intermittent hypoxemia, raised levels of multiple inflammatory cytokines such as tumor necrosis factor and interleukin-6, and other comorbid medical conditions that predispose to depression such as obesity, diabetes, and cardiovascular disease.

Pearls/Take-Home Points

- OSA and depression are common and frequently comorbid. Both can coexist with, and contribute to, chronic medical conditions such as obesity, diabetes, coronary artery disease, hypertension, and other metabolic illness.

- Differentiating between depressive and OSA symptoms can be difficult. A thorough history including from a spouse or bed partner can be essential in making an accurate diagnosis.
- Untreated OSA and depression symptoms can result in significant medical and social morbidity including in pregnant women.
- Optimal outcomes are achieved when both OSA and depression are treated aggressively to remission.

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Chapter 2
Case Study: Post-traumatic Stress Disorder "I Am Having Nightmares on My Back"

Susamma Abraham, Sandra Cooper, and Imran S. Khawaja

Clinical History/Case

Mr. J is a 58-year-old white male and an Air Force veteran with a past medical history of gout, diabetes, hypothyroidism, and hypogonadism. His psychiatric history included PTSD, depression, generalized anxiety disorder, and bipolar disorder. Medications included clonazepam and Divalproex ER (Depakote ER) for mood. His primary care provider referred the patient because of complaints of loud snoring,

S. Abraham (✉)
Center for Sleep Medicine, Department of Neurology, Sleep, VA North Texas Health Care System, Dallas, TX, USA
e-mail: susamma.abraham@va.gov

S. Cooper
Center for Sleep Medicine, VA North Texas Health Care System, Dallas, TX, USA

I. S. Khawaja
Center for Sleep Medicine, VA North Texas Health Care System, Department of Psychiatry and Neurology and Neurotherapeutics, UT Southwestern Medical Center, Dallas, TX, USA

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fatigue, mood swings, and loss of libido. His endocrinologist recommended a sleep study before testosterone replacement. During the initial clinical visit, he complained of excessive daytime sleepiness (EDS) and fatigue for the last 3 years. There was a history of loud snoring and witnessed apneas with gasp arousals. He described his sleep as fragmented and reported having nightmares nightly. The PTSD was associated with nightmares that caused him to wake up multiple times with delayed return to sleep. Awakenings from nightmares were more frequent when sleeping in supine position as compared to non-supine sleep. Nightmares were frequent, occurring nightly and often multiple times per night. STOP-BANG score was 7/8. Epworth sleepiness scale (ESS) was 18/24.

He did not smoke and drank a beer/week and occasional wine. He consumed 3–5 cups of coffee a day.

His sleep schedule was as follows: time to bed 11 p.m.–2 a.m., sleep onset 60 minutes to several hours, wake time 9–11 a.m., estimated sleep hours 8–10 hours. Nap once during the day for 45 minutes to an hour.

Examination/Mental Status Exam

He was alert and oriented to person, place, and time. Height is 76 inches, and weight was 255 lb. with a BMI of 31. Neck circumference was 18 inches, and the oral cavity exam revealed with a Mallampati of 3/4.

Special Studies

Polysomnography. One-night diagnostic polysomnography (PSG) was performed. (Please refer to Fig. 2.1 for 5 minutes epoch of PSG showing REM sleep with severe obstructive sleep apnea events in supine position.)

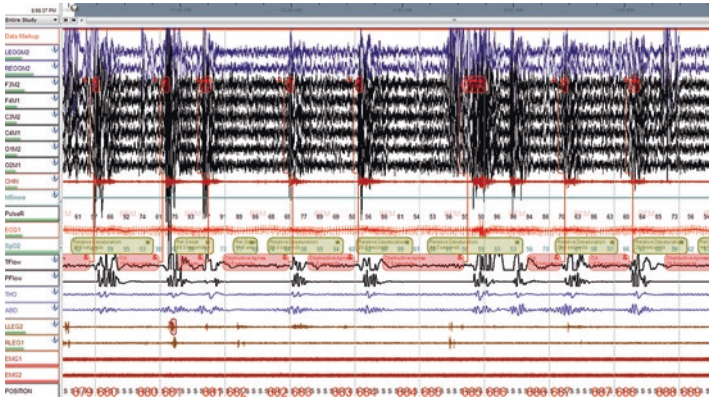

FIGURE 2.1 PSG 5 minute epoch of REM sleep with severe obstructive sleep apnea events in supine position

Results

The PSG showed severe obstructive sleep apnea (OSA) with apnea-hypopnea index (AHI) 81.1 with minimum oxygen saturation of 77%. Most of the sleep-disordered breathing events were in REM and supine sleep.

Time in bed (TIB) 452 minutes, total sleep time (TST) 392 minutes, sleep efficiency of 89%. Sleep latency was 5.2 minutes. Wake after sleep onset (WASO) was 43.5 minutes. Stage N1 was 5.2 minutes (14% of total sleep time), stage N2 was 283 minutes (72% of TST), and no stage N3 sleep. Rapid eye movement (REM) sleep was 54.5 minutes (14% of TST).

The patient was treated with auto CPAP at 5–20 CWP. During the first follow-up visit, the patient reported that there was a dramatic improvement in his PTSD symptoms, nightmares frequency, and intensity. He reported that the nightmares are reduced "to almost none." He

reported feeling better, less sleepy, and more energetic during the day.

Question

Why did nightmares get better with the use of the CPAP machine?

Differential Diagnosis and Diagnosis

PTSD, nightmares, and OSA, worsening of nightmares secondary to REM-related OSA.

General Remarks

A defining symptom of PTSD is frequent nightmares related to the traumatic event. These nightmares tend to occur mainly in REM sleep. Obstructive sleep-disordered breathing events are often prominent in REM sleep, either by frequency or duration and degree of O2 desaturation—the reason being decreased muscle tone of the airway during REM sleep more likely causing the partial or complete airway obstruction. When patients wake from REM sleep, there is a high probability of dream recall [1]. In patients with PTSD, these dreams are distressing and affect the overall perception of PTSD [2]. We hypothesize that CPAP helped our patient by reducing the number of awakenings from REM sleep.

It is known that awakenings from stage REM sleep facilitate registration of the dream memories and if there are no awakenings in stage REM, subjects might not remember their dreams. Another study reported that REM AHI and interrupted sleep at night were independent factors of nightmares in OSA patients, and there is a significant improvement in

nightmare occurrence with the CPAP treatment. These fewer disruptions of REM sleep might have contributed to the decreased perception of the nightmares even though the REM sleep percentage remains the same or increases after CPAP therapy. Ross et al. have suggested that rapid eye movement (REM) sleep mechanisms are dysfunctional in patients with PTSD which causes interruptions in normal sleep architecture and can lead to excessive daytime sleepiness [3]. Literature suggests that untreated OSA increases the sleep-related symptoms of PTSD, especially the number and intensity of nightmares, frequent awakenings, difficulty falling back to sleep, and increase in daytime sleepiness and tiredness. CPAP therapy may reduce the frequency of nightmares among veterans with OSA and PTSD, and improved CPAP compliance may be associated with increased symptom improvement.

A study reviewed by Tamanna et al. [4] showed that there is a positive correlation of REM sleep percentage with the number of nightmares which supported the hypothesis of having a dysfunctional REM sleep mechanism in the pathogenesis of PTSD**.** Studies suggested that individuals who are awakened during REM sleep can recall dreams at a high rate. The frequent disruptions of REM sleep caused by sleep-related breathing events might have led to an increased recall of dreams occurring in REM sleep. CPAP can potentially help by reducing the awakening from stage REM sleep, thus reducing the chances of dream recall.

Pearls/Take-Home Points

Frequent awakenings secondary to sleep apnea can worsen subjective nightmare perception in PTSD patients. CPAP treatment may help by reducing these awakenings from REM sleep.

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Chapter 3
I Need My Methadone, but I Cannot Breathe at Night

Patricia Dickmann, Heather Swanson, and Joseph Westermeyer

Clinical History/Case

A 58-year-old man presented to clinic after he was found to be overusing his methadone, which had been prescribed by his primary care physician for lower back pain. His prescribed daily dose was 60 mg, but he was frequently running out early. To cope with the withdrawal symptoms, he turned to heroin use via insufflation. In addition, he was concurrently using other substances (primarily cocaine and alcohol). Due to ongoing alcohol and drug use, the primary care physician referred the veteran to a methadone maintenance

P. Dickmann (✉) · H. Swanson · J. Westermeyer
Addiction Recovery Service, Department of Psychiatry, Minneapolis Veterans Affairs Medical Center, Minneapolis, MN, USA

Department of Psychiatry, University of Minnesota Medical School, Minneapolis, MN, USA
e-mail: patricia.dickmann@va.gov

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clinic. Several weeks after starting methadone maintenance therapy, he was referred to the Sleep Medicine clinic due to his reports of frequent nighttime awakenings with startled reactions.

Past Medical History: His past psychiatric history was significant for military-related PTSD and major depressive disorder. There was no history of psychiatric hospitalizations, suicide attempts, or self-injury. Medical history was significant for chronic musculoskeletal pain, COPD, and hepatitis C. There was no heart disease aside from hypertension.

Substance use history was significant for drug and alcohol use since his return to the United States from Vietnam, which he utilized in an effort to self-medicate PTSD symptoms. Drug use included alcohol, marijuana, stimulants (both cocaine and amphetamines), as well as the aforementioned opioids. He was a one pack per day smoker with chronic respiratory sequelae. He consumed three to four cups of coffee per day. Substance use led to legal issues, including prison time. The patient had no history of substance use treatment.

Medications: Chlorthalidone 25 mg daily, flunisolide nasal spray, fluoxetine 40 mg daily, formoterol inhaler, lisinopril 40 mg daily, metoprolol 25 mg twice daily, and vardenafil 20 mg as needed. After transitioning from primary care to the methadone maintenance program, his methadone dose was gradually titrated to a dose of 80 mg daily. Due to his ongoing alcohol use, he was started concurrently on disulfiram 500 mg three times per week.

Family History: There was no family history of substance use or mental health issues. In addition, there was no family history for obstructive sleep apnea (OSA), narcolepsy, restless legs syndrome (RLS), or other sleep disorders. Social history was notable for unemployment, supported by VA pension. The patient was twice divorced with four children.

Review of Systems: On initial evaluation, he reported the following symptoms: excessive daytime sleepiness with frequent dozing; observed snoring and "snort arousals"; frequently waking up with a dry mouth and headaches; and restless legs. He denied symptoms consistent with cataplexy, hypnagogic or hypnopompic hallucinations, or sleep paralysis. The onset of all the aforementioned symptoms was shortly after starting methadone.

Examination/Mental Status Exam

Physical examination revealed a BMI of 22.68. Oropharyngeal Mallampati score was class 4. Neck circumference was 15.5 inches. He had no other pertinent physical findings.

Differential Diagnoses

- Obstructive sleep apnea (OSA)
- Central sleep apnea (CSA)
- Hypoxemia secondary to COPD
- PTSD-related insomnia

Special Studies

Ferritin, methadone peak and trough, polysomnography (PSG), electrocardiogram (EKG).

Results

Ferritin level was within normal limits. Methadone peak and trough levels were within normal range. PSG demonstrated poor sleep efficiency. The study was notable for the presence

of ataxic breathing and mixed apneas with desaturations of oxyhemoglobin reaching a nadir of 86%. Apnea/hypopnea index was 55/hour with most events being central. He had an abnormal EKG with prolonged Q-T interval and ventricular hypertrophy. As per the sleep technicians, the sleep apnea did not improve on CPAP but did improve with adaptive servo-ventilation (ASV).

Final Diagnosis

Central sleep apnea.

Follow-Up

The patient's sleep quality and efficiency significantly improved with the use of adaptive servo-ventilation (ASV). Methadone maintenance was continued and the patient attended a residential treatment program, ultimately leading to complete cessation of recreational drug use.

Question

Why does methadone put this patient at increased risk for central sleep apnea?

Discussion

The clinical history, in combination with the overnight sleep study which included several treatment techniques in an effort to improve the sleep apnea, clarified the diagnosis. The patient was determined to have central sleep apnea caused by methadone maintenance therapy.

The two main types of sleep apnea are obstructive and central. Obstructive sleep apnea (OSA) is by far the most

common and is characterized by recurrent episodes of upper airway collapse during sleep. During apneic periods, there is evidence of respiratory effort on the polysomnogram. In central sleep apnea (CSA), however, respiratory effort is diminished or absent during periods of diminished or absent air flow [1]. Often CSA is associated with OSA or secondary to other causes. Various other causes include Cheyne-Stokes breathing-central sleep apnea, due to congenital heart failure, high-altitude sleep-breathing disturbance, primary central apnea, opioids, or other CNS depressants [2]. Primary central apnea is uncommon and is seen in less than 10% of patients presenting for PSG. Though difficult to determine in the general population, rates of central sleep apnea in patients prescribed methadone maintenance therapy are significantly higher. A review suggests that the mean prevalence of CSA in the context of opioid therapy is approximately 24%, though a range of 14.1–60% is noted in the literature [3].

Prescription opioid use has increased dramatically over the past few decades, thanks in part to pain becoming conceptualized as "the fifth vital sign" and providers in the 1990s and 2000s being encouraged to aggressively treat pain with opioid analgesia [4]. Though the addictive nature of these substances was initially downplayed, it has become abundantly clear that the opposite is true [5]. Methadone and buprenorphine are two of the medication options commonly used in the treatment of opioid use disorder.

Whether prescribed, replacement, or illicit, opioids are associated with a wide variety of sleep problems. Though they have sedative properties, opioids have been found to be disruptive to sleep architecture. Some of the changes include reductions in total sleep time, stage N3 sleep, and REM sleep, as well as increased number of arousals, more frequent shifting between stages, and increased N2 sleep [6]. Methadone maintenance treatment patients have a high prevalence of central sleep apnea related to damage to central respiratory rhythm control [7, 8]. A study by Peles et al. found that reductions in total sleep time, REM sleep, and slow wave sleep had

not recovered to baseline levels up to 1 year following treatment [9]. Long-term opioid use is associated with daytime sleepiness and fatigue. In addition, opioids decrease central respiratory drive leading to decreases in tidal volume, respiratory rate, and minute ventilation. Opioids also may increase upper airway resistance and lead to rigidity of accessory respiratory muscles [10].

Pearls

- Central sleep apnea is significantly less common than obstructive sleep apnea, but is not uncommon in patients utilizing opioids including methadone maintenance therapy.
- Sleep may take over 1 year to normalize following cessation of long-term opioid use.

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Chapter 4
Alcohol Is the Only Thing that Helps Me Sleep, or Does It?

Elliott Kyung Lee

Clinical History/Case

Mr. J. Daniels is a 55-year-old human resources manager. He comes in complaining of a 10-year history of increasing problems with initiating and maintaining sleep on most nights and subsequent fatigue during the day. Problems began when he started working a new position. This involved working under a new supervisor that he calls a "nightmare." He feels she is constantly overseeing his work and being overly critical. Initially, when problems developed, he began taking some wine at night for his anxious state of mind and found this was helpful for him falling asleep. However, over the course of several years, sleeping problems became worse despite him using more alcohol to help with his sleep. His wife has always complained about his snoring, but recently, even his children have begun to complain about his snoring at night. Recently, his wife told him that he had some kind of conversation with her in the middle of the night, but he has no recollection of this.

E. K. Lee (✉)
Department of Psychiatry, Royal Ottawa Mental Health Center Sleep Disorders Clinic, Ottawa, ON, Canada
e-mail: Elliott.lee@theroyal.ca

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Because of his fatigue and ongoing insomnia and stress, he has visited his family doctor several times for assistance with coping. He has been prescribed trazodone, and although it helped a bit with falling asleep, it made him quite groggy in the day. He tried some over-the-counter drugs (Benadryl, melatonin) but again found if anything some modest benefit, but they made him groggy during the day. His wife has had some concerns about his drinking at night time, but on several occasions when he has tried to stop his alcohol, his insomnia has become unbearable. On several occasions, he has even gone a week without any alcohol but only found that insomnia was worse so went back to having some alcohol to at least get some modest relief for insomnia. Currently, he is now requiring four or five drinks a night to get himself to sleep by his report and continues to consume this, even though he is aware that this is probably not good for his health. Sometimes he has had some mild anxiety in the mornings and so will occasionally sneak a quick drink to calm himself for the day if he doesn't have to go into work too early or on weekends.

His medical history is significant for hypertension, borderline diabetes and kidney stones. His current medications include only perindopril for hypertension.

His psychiatric history is significant for some heavy alcohol use as a university student, with some depression at the time. He tried one or two antidepressants through his family doctor, but had no significant benefit. He did not have any previous suicidal ideation or attempts or contact with a psychiatrist.

His family history is significant for a maternal grandfather that had problems with alcohol.

Examination

Height: 5′9″. Weight: 225 lbs. Neck circumference: 17 inches. Blood Pressure 134/78.

HEENT: Nasal passages show some mild obstruction with a slightly deviated nasal septum to the right. Oropharynx shows a low hanging soft palate (Mallampati III) with an elongated uvula that is swollen and erythematous. Tongue base is enlarged with some dental impres-

sions (i.e. scalloping). There is a moderate overbite with a mild overjet.

Lungs: Lungs clear to auscultation bilaterally.

Cardiac: Normal S1 and S2 with no rubs, murmurs or gallops.

Mental Status Exam: On exam, he is generally calm and cooperative, with a dress shirt and slacks. He is flushed looking, is moderately overweight and makes intermittent eye contact during the interview. His speech is generally regular rate, rhythm and tone, but he sounds sullen and fatigued. Thought form is generally linear and goal directed, but sometimes he loses his train of thought and asks you to repeat your questions. He has a mildly constricted affect and endorses a depressive mood, frequently saying "if only I could get some sleep, I think I would feel better during the day". No perceptual disturbances are noted. Insight seems to be good and judgement is intact. He denies any suicidal or homicidal ideation and is presumed to be reliable.

Special Studies

Polysomnography study revealed an Apnea Hypopnea Index (AHI) of 19/hour with oxygen saturation dropping to a minimum of 77%, worse in supine sleep and REM sleep. Total sleep time captured was 5 hours and 23 minutes. Periodic limb movement arousal index was elevated at 12/hour. The sleep was very fragmented with frequent arousals, and almost no slow wave sleep was seen. The patient reported consuming three alcoholic beverages in the evening prior to the study.

Questions

1. What is your differential diagnosis for this patient?
2. How might alcohol contribute to the presentation of his symptoms?
3. What treatment suggestions would you offer this gentleman?

Differential Diagnosis and Diagnosis

Mr. Daniels has developed an alcohol use disorder, as illustrated by DSM-5 criteria, including his pattern of consumption of alcohol, with failed efforts to cut down, continued consumption of alcohol despite knowledge of consequences and evidence of tolerance and withdrawal occurring [1]. Additionally, the sleep study results and his symptoms of sleep disturbance are compatible with a breathing-related sleep disorder, obstructive sleep apnoea/hypopnoea. Although a diagnosis of insomnia disorder can be considered, the findings of sleep-disordered breathing, together with the known history of high alcohol consumption, may better explain his insomnia symptoms. The interaction of alcohol together with his sleep problems, however, can be complex. It is unclear in his case as to whether or how much alcohol consumption may contribute to, exacerbate or even cause insomnia symptoms and sleep-disordered breathing. To explore these potential interactions, it will be helpful to consider the acute effects of alcohol on sleep, and then examine chronic effects of alcohol on sleep and withdrawal from alcohol, and then inspect how alcohol may interact with several sleep disorders, most notably breathing-related sleep disorders.

Acute Alcohol Use on Sleep

The acute effects of alcohol on sleep have been extensively studied. Although there have been differences in methodologies and sample characteristics, several consistent patterns have emerged. Acute alcohol administration acts as a sedative, shortening sleep latency and increasing deep sleep in the first half of the night but suppressing REM sleep. These characteristics make alcohol appealing as a hypnotic. As alcohol is metabolized, increased sleep fragmentation is accompanied by an increase in REM sleep and stage N1 and wake time in the second half of the night [2–4]. These findings of increased fragmentation of sleep and decreased sleep efficiency with

acute alcohol use may be more pronounced in women [5]. These changes in sleep architecture can even be seen 6 hours after the consumption of the last alcoholic drink (e.g. the "happy hour" consumption of alcohol), long after such consumption could be detected with a blood alcohol level [6]. Tolerance to these initial effects may develop after 3–10 nights of continuous nocturnal alcohol consumption [7]. This pattern of decreased sleep latency and increased deep sleep in the first part of the night, followed by a more fragmented sleep in the latter part of the night, can sometimes lead patients to conclude that alcohol was helpful for the first part of the night but was of an insufficient quantity to maintain benefits for the second half of the night. As a result, these experiences may lead patients to erroneously conclude that increasing alcohol consumption would offer further benefit for sleep. More than one in ten patients may consider using alcohol as a hypnotic to treat perceived insomnia symptoms [8].

Chronic Alcohol Use on Sleep

With chronic alcohol use, data are more sparse and less consistent, owing again to definitions of chronicity and differences in sample patients and methodologies. Some general findings have included increased sleep latency, decreased sleep efficiency and decreased slow wave sleep [2, 3], but others dispute such findings in reviews [4]. More consistent alcohol use has also been associated with worsening of several sleep disorders including obstructive sleep apnoea (OSA), restless legs syndrome and periodic limb movement disorder and parasomnias [9].

Alcohol Withdrawal on Sleep

Insomnia following cessation of alcohol is common. One third to one half of patients in alcohol withdrawal identify insomnia symptoms [10]. Overall sleep architecture during

the withdrawal period shows increased arousals, profound decreases in slow wave sleep and increases in REM sleep [11]. Significant disruptions in circadian rhythm may be seen in the alcohol withdrawal period [2]. Not surprisingly as a result, many patients describe chronic insomnia and disturbing dreams during abstinence [2]. These disturbances may persist after even 2 years of abstinence [9]. Sleep disturbances in the abstinence period are a strong predictive factor for subsequent relapse [12].

Alcohol and Snoring/OSA

Obstructive sleep apnoea (OSA) is a common sleep disorder characterized by repeated obstructions during sleep in the upper airway leading to sleep fragmentation, hypoxemia and subsequent daytime sleepiness. Population estimates suggest 4–30% of people may be affected by this problem, with differences in the definition of OSA accounting for differences in the prevalence [13]. The severity of sleep-disordered breathing is often measured by the frequency of sleep-disordered breathing events measured, as well as by the degree of hypoxemia seen for a patient. The apnoea hypopnoea index (AHI) is a common measure used to quantify the severity of OSA. AHI is defined as the total number of apnoeas plus hypopnoeas in the night divided by the number of hours of sleep. A generally agreed-upon definition of the severity of sleep-disordered breathing is an AHI between 5 and less than 15 events per hour is considered mild obstructive sleep apnoea, while between 15 and 30 events per hour is considered moderate-severity OSA, and greater than 30 events per hour is severe OSA [1, 14]. Common symptoms of untreated OSA include excessive daytime fatigue or sleepiness, insomnia, morning headaches and dry mouth, poor

concentration and attention and even depression [1]. Several treatments can be helpful including weight loss, positional therapy, oral appliances and even surgical options. However, the most common treatment offered for this is continuous positive airway pressure (CPAP therapy), which consists of a mask that is worn over the nose to pump air into the airway to splint it open.

Some large studies have found epidemiological associations with OSA and alcohol consumption [15, 16], but others have not [17–19]. Acute alcohol use can cause normal people to have snoring and OSA [8, 20–23]. This may occur as a result of increasing nasal and pharyngeal resistance [19, 24], vasodilation of nasal mucosa, the depressant effect of alcohol on hypoglossal nerve activity, as well as the blunting effect on response to ventilatory hypoxaemia or hypercapnia [25, 26]. The resultant consequences of this may include increasing the frequency, duration and severity of sleep-disordered breathing events. These effects have been shown to be more pronounced in males, heavier drinkers and leaner people [25, 26]. It is possible progesterone may modulate the effects of alcohol on upper airway tone and chemoreceptor sensitivity, which may partially explain the mitigation of effects of alcohol on women compared to men [25]. Effects of moderate alcohol consumption on AHI have varied. Four standard drinks of alcohol (10 g) will raise the blood alcohol level in an 80 kg male to approximately a 0.5 g per kg body weight [27]. See Table 4.1 and Fig. 4.1 for doses of ethanol and breath ethanol concentration [9] and comparable dose equivalents of alcohol. A 0.5 g per kg body weight can bring the average AHI from 10 to 20 events per hour in one study by Collop et al. of 14 male subjects [25], though other studies with similar dosages of alcohol have not found comparable changes in AHI [28, 29].

Table 4.1 Ethanol dose and approximate breath ethanol concentration (BrEC)

Blood ethanol level	BrEC	No. of 12 oz. US beers
0.2 g/kg	0.02	1–2
0.4 g/kg	0.03	2–3
0.6 g/kg	0.05	3–4
0.8 g/kg	0.07	4–5
1.0 g/kg	0.09	5–6

This table from Roehrs and Roth [9] outlines the approximate alcohol concentration in fasting men, consumed over 30 minutes, measured 30 minutes after last consumption. In the USA, legal intoxication is typically defined as a BrEC of 0.08 although depending on the state, this could range from 0.05 to 0.10.

Figure 4.1 Dose equivalents of alcoholic beverages. (With permission from National Institute on Alcohol Abuse and Alcoholism https://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/what-standard-drink)

Pearl
Consequently, alcohol's effects on sleep-disordered breathing may differ depending on the subject's size, gender, baseline breathing difficulties as well as dose, type and timing of alcohol and chronicity of use.

Alcohol and Insomnia

36–91% of patients with alcohol use issues report insomnia [30–32], with the wide heterogeneity occurring as a result of differences in sample characteristics (e.g. population characteristics, drinking severity, duration of drinking, etc.) as well as differences in the definition of insomnia. While half of patients in acute alcohol withdrawal have reported insomnia symptoms, in about half of these patients, insomnia symptoms may persist for weeks to months in a protracted alcohol withdrawal syndrome [31]. Several mechanisms may play a role, including the presence of genetic polymorphisms associated with insomnia and alcohol dependence, disturbances in sleep architecture and homeostatic drive, induced depression, disruptions in circadian rhythm and the presence of comorbid sleep disorders (sleep apnoea, PLMS) [31]. Persistent sleep architectural changes may persist for 21–27 months of abstinence [31]. Initial insomnia in particular has been identified as the most consistent marker for predicted future relapse [33], but other sleep architecture findings that have also been associated with increased relapse risk include alterations in REM sleep parameters as well as increased periodic limb movements [31].

Despite these findings, neither psychologic treatment of insomnia symptoms with CBT-I nor pharmacologic treatment with a hypnotic, such as quetiapine, has been shown to have impact on subsequent relapse to drinking behavior [34, 35].

Other agents including ramelteon (a melatonin agonist), acamprosate and trazodone have also been investigated in patients with insomnia and alcohol use disorders, and while these medications have demonstrated improvements in sleep parameters in these patients, relapse risk potential and other measures of alcohol use issues have not changed substantially [31]. On the other hand, studies evaluating gabapentin (900–1800 mg a day in divided doses) for insomnia and drinking outcomes in alcohol-dependent patients have thus far generally shown positive results in terms of drinking outcomes, with mixed results on sleep changes, with some studies showing benefits and others showing no changes [31, 36, 37]. Similarly, limited studies evaluating topiramate (300 mg daily) on insomnia and alcohol outcomes in these patients have also shown some benefits for both sleep problems and reduction of alcohol relapse [38, 39].

Pearl
In patients with insomnia and a history of alcohol use disorder, who are currently abstinent, gabapentin or topiramate may be useful agents to consider for assisting with sleep measures and reducing potential for adverse drinking outcomes. Trazodone, ramelteon and acamprosate have been shown to be helpful for sleep in patients with alcohol use disorder and sleep complaints, but have not been shown to affect drinking outcomes in these patients. Studies of all these agents are limited, and further work is needed.

Consequently, in the case of Mr. Daniels, regarding treatment options, it would be prudent to have him go to an intensive outpatient program to treat his alcohol use disorder. In the acute withdrawal phase, insomnia may be an anticipated symptom, for which he could be prescribed either gabapentin or topiramate at night. Since he has a history of kidney stones,

gabapentin may be a better choice for him at night to assist with insomnia than topiramate (which can be associated with kidney stones), and gabapentin may also be helpful for anxiety symptoms and periodic limb movements. Additionally, since significant sleep-disordered breathing is identified on his sleep study, he should be counselled on treatment options. Due to the severity of sleep-disordered breathing, CPAP therapy should be recommended to improve the continuity of his sleep. Frequent alcohol consumption has been shown to adversely affect CPAP compliance, though cultural factors may also play a role [40]. Gabapentin in his case may also be helpful for initiating and maintaining sleep with CPAP therapy. Ongoing supportive therapy should be provided to reduce anxiety and encourage adherence to treatment.

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Chapter 5
Doctor, My Child Snores and Has ADHD. Is There a Relationship?

Madeleine Marie Grigg-Damberger

Clinical History/Case

A 12-year-old boy with attention deficit hyperactivity disorder (ADHD) was referred to our pediatric sleep clinic by his pediatrician for snoring, being late to school, more behavior problems, and failing grades. His parents complained their son has snored since he was age 5, but it had gotten much worse in the last year since he had strep throat twice. His snoring was so loud it could be heard on the other side of their trailer home. They did see him stop breathing when sleeping but sometimes heard him gasp or snort. He sweated excessively when sleeping. He had started wetting the bed again, previously dry since age 7. His mother had heard snoring and sleep apnea could cause ADHD and want him tested.

He also had trouble falling asleep. He was usually sent to bed on school nights by 9 p.m., but he could not fall asleep until 10:30 or 11 p.m. because he "was thinking about pleasant

M. M. Grigg-Damberger (✉)
Department of Neurology, Clinical Neurophysiology, and Sleep Medicine, University of New Mexico School of Medicine and Medical Center, Albuquerque, NM, USA
e-mail: mgriggd@salud.unm.edu

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things." Sometimes while trying to fall asleep, he would play video games on his tablet. His parents had taken it away, but he said without it, he still could not fall asleep, so they gave it back to him. They then needed to "drag him" from his bed by 6:30 a.m. to get him ready for school. His teachers complained he was falling asleep in school. His grades had been Bs and Cs and were now Ds and Fs. He had trouble finishing his homework. On weekends, he would stay up until midnight or later and then slept till 10 a.m. or so.

His teachers complained he stares into space, can't sit still, has outbursts of anger, and falls asleep in class. He has had two visits to the emergency room for scalp lacerations for "acting stupid." His tonsils had gotten big and he sometimes has trouble swallowing. On the Epworth Sleepiness Scale, for Children and Adolescents (ESS-CHAD), he was rated 13/24 consistent with moderate excessive daytime sleepiness (EDS).

In the past, his pediatrician had prescribed clonidine (0.1–0.2 mg half hour before bed) to help him sleep, but it no longer helped, and they stopped it. Melatonin 3 mg at 8 p.m. didn't help at all.

Past Medical History: He was born full term without complication. He walked at 10 months but talked late at 3 years, not sure why. He suffers year-round from chronic nasal congestion and allergies worse in the fall and spring. He is allergic to kiwi, dust, and dogs. He has never been hospitalized or had surgeries. Child does not drink caffeine and has no exposure to tobacco. They have dogs at home but they stay outside. His immunizations are up-to-date.

Medications: Methylphenidate extended release 54 mg; cetirizine 10 mg every morning, and fluticasone propionate one spray in each nostril every morning.

Family History: Father had ADHD but "outgrew it." Father snores. Mother and two older brothers are night owls. Paternal grandfather sleeps with continuous positive airway pressure (CPAP).

Review of Systems: In the last 2 weeks is positive for nasal congestion, growing pains, shortness of breath, staring spells, angry a lot, anxiety, cries easily, depression fidgety, difficulty completing tasks, and easily distracted and frustrated.

Examination/Mental Status Exam

He looked sleepy and sluggish. He was normocephalic without dysmorphic features. On exam, his heart rate was 71 beats per minute, respiratory rate 18 breaths per minute, blood pressure 100/60 mm Hg, oxyhemoglobin saturation breathing room air 94%, weight 41.1 kilograms (90 pounds), height 149 centimeters (58 inches), and body mass index 18.5 mg/kg^2. His neck was 13 inches in circumference. He had mild maxillary overbite, a narrow high arched palate, long narrow tongue, Friedman class 3 airway, and 3+ tonsillar hypertrophy. His nasal mucosa was pale and boggy, 50% narrowed consistent with moderate inferior turbinate hypertrophy. He had allergic shiners and was a mouth breather. His chin was normal in size and location. The remainder of his physical exam was normal.

Differential Diagnoses

- Allergic rhinitis due to pollen, dog hair [J30.1 and J30.81].
- Attention deficit hyperactivity disorder, combined type [F90.2].
- Chronic insomnia disorder [F51.01].
- Delayed sleep-wake phase disorder [G47.21].
- Hypertrophy of tonsils and adenoids [J35.3].
- Inferior turbinate hypertrophy [J34.3].
- Insufficient sleep syndrome [F51.12].
- Obstructive sleep apnea syndrome [G47.33].

Special Studies: We ordered a comprehensive in-laboratory attended overnight polysomnogram with end-tidal and transcutaneous CO2 monitoring.

Results: His overnight polysomnogram (Table 5.1) showed severe pediatric obstructive sleep apnea with a mean of 13.8 obstructive apneas and hypopneas per hour of sleep. Respiratory events were typically obstructive hypopneas which were much more common when sleeping supine (Fig. 5.1). He exhibited almost continuous moderate to loud snoring across the entire night. His respiratory disturbance index (RDI) supine was 33

Table 5.1 Results of his overnight polysomnogram

Polysomnographic measure	Results
Study start time	8:59 p.m.
Study end time	5:08 a.m. (at father's request)
Total recording time	478 minutes
Total sleep time	426 minutes
Sleep efficiency	89%
Sleep maintenance	97%
Sleep latency	24 minutes
REM latency	67 minutes
Sleep stages	24% NREM 1, 45% NREM 2, 16% NREM 3, 15% REM sleep
Wake after sleep onset	14 minutes
Arousal index	35 arousals per hour of sleep, 15 arousals per hour due to respiratory events, 0.4 arousals per hour due to periodic limb movements
Awakening index	0.1 awakening per hour of sleep
Pediatric obstructive apnea hypopnea index	13.8 per hour of sleep

Table 5.1 (continued)

Polysomnographic measure	Results
Respiratory disturbance index	15 per hour of sleep
Apnea index	0.0 obstructive apneas, 1.7 central apneas, and 0.0 mixed apneas per hour of sleep
Hypopnea index	13.8 per hour of sleep
Effect of body position and sleep stage on respiration	RDI NREM sleep 12 per hour, REM sleep 16 per hour; RDI supine 33 per hour, 4 per hour lateral; RDI REM supine, 33 per hour
Oxygen saturation and CO2	Average SpO2 awake and asleep was 97%. 0% of TST with EtCO2 50 torr or more
Heart rate	Sinus rhythm with mean heart rate awake: 80 beats per minute, 67 during NREM and 66 during REM sleep
Periodic limb movements	A mean of 2.4 periodic limb movements per hour of sleep noted. A mean of 0.4 periodic limb movements per hour of sleep caused arousal

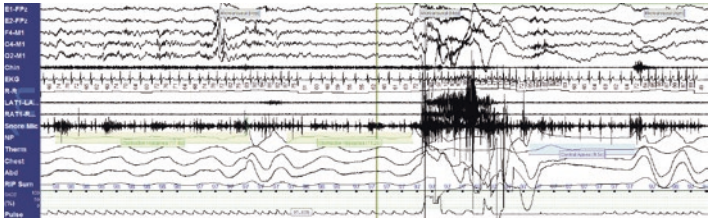

Figure 5.1 Run of obstructive hypopneas causing arousals

per hour, lateral 4 per hour. Respiratory events were not more common in REM sleep (RDI NREM 12 per hour, REM 16 per hour), but RDI in REM sleep supine was 33 per hour.

Final Diagnoses

- Allergic rhinitis due to pollen, dog hair [J30.1 and J30.81].
- Attention deficit hyperactivity disorder, combined type [F90.2].
- Delayed sleep-wake phase disorder [G47.21].
- Hypertrophy of tonsils and adenoids [J35.3].
- Inferior turbinate hypertrophy [J34.3].
- Obstructive sleep apnea syndrome [G47.33].

Question 5.1: Based on the history and findings, what interventions would you recommend for this patient?

Follow-Up

We asked the patient to return in follow-up with his parents and advised them of the results of the sleep study showing severe pediatric obstructive sleep apnea. We recommended referral to pediatric otolaryngology to consider upper airway surgery to treat sleep apnea. The patient also exhibited symptoms suggestive of delayed sleep-wake phase disorder (DSWPD) with difficulty falling asleep before 11 p.m. to midnight, preferring to sleep until 10 a.m. or later on weekends, forced to get up by 6 to 6:30 a.m. on school days.

The child also had delayed sleep-wake phase disorder (DSWPD), not uncommon in children, adolescents, and adults with ADHD. We discussed cognitive and behavioral interventions to improve his sleep (Table 5.2) [1]. Many patients with DSWPD also have comorbid insomnia and poor sleep hygiene. For his DSWPD we provided education about it and recommended bright light therapy (BLT) summarized in Table 5.3 [2]. We also emphasized the importance

Table 5.2 Cognitive and behavioral treatment strategies to treat insomnia in children with attention deficit hyperactivity disorder [1]

1. Create a quality sleeping environment
Dark, quiet, non-stimulating, and perceived as safe (dim nightlight if needed)
Eliminate visual and auditory stimuli (turn off electronics)
Adjust ambient temperature if necessary (cool better than warm)
Develop a successful bedtime routine which is consistently followed and tailored for the developmental age and abilities of the child
Promote self-soothing skills that allow the child to fall and return to sleep on his own
2. If child has difficulty falling asleep
Temporarily delay child's bedtimes by calculating the average sleep onset time during baseline and then adding 30 minutes (e.g., average sleep onset 9: 30 p.m. during baseline, initial bedtime 10 p.m.)
Once child falls asleep within 15–20 minutes, gradually move the bedtime earlier in 30-minutes increments as long as the child continues to fall asleep quickly until reaching a parent-determined goal bedtime (e.g., 8: 30 p.m.)
Do not allow the child to make up for lost sleep by going to bed earlier or sleeping later
3. Parent-child interactions
Parents avoid responding to the child's disruptive bedtime behaviors (crying, tantrums, calling out, or leaving the bedroom)
Parents who have difficulty ignoring the child can use the excuse me drill
Parents periodically check on the child but only when the child is showing desired behaviors (calm, quiet, and in bed). This is not repeated for nighttime awakenings
A bedroom pass (allowing for only one bedroom exit a night) is often useful

Table 5.3 Bright light therapy (BLT) for treating delayed sleep-wake phase disorder in children and adolescents

Patient should sit outdoors in natural light, near a bright-lit window, or 12 to 18 inches from 10,000 lux light box or wear the light visor for approximately 30 minutes upon awakening each day
Light should be present just above eye level to have the greatest impact on the retina. If not using a light visor, place the light box on a counter with the patient sitting in front of it
Patients should engage in other activities while in front of the light, occasionally glancing at it without looking directly at the light (to avoid causing significant eye strain and/or headaches).
During light therapy, patients can do homework, eat breakfast, read, watch TV, or play video games
To motivate older children and adolescents to wake up early and spend 30 minutes in front of bright light, discuss that many patients report feeling more alert and attentive during day when using BLT even before moving the bedtimes earlier and increasing nighttime sleep duration
Timing of bright light therapy
Start BLT at time they are currently awakening, and then gradually move the wake time and BLT application time 15 to 30 minutes earlier every other day
As wake-up time is moved earlier, the bedtime should also be moved earlier
Potential pitfalls of bright light therapy
If light therapy is delayed too long after awakening, it may further delay their circadian rhythm. If patient awakens more than 30 minutes later than planned, avoid using the BLT that day
Avoid looking directly at bright light for long periods to avoid eye strain and/or headache; just glance at the light briefly
Some patients may experience hypomania or mania using a light box; if this occurs, they should immediately discontinue using it

of minimizing exposure to evening bright light by wearing either glasses which filter blue light or amber-tinted lenses.

We supplemented this with 0.5 mg of oral melatonin dosed nightly at 8 p.m. We explained to the child and his parents that small daily doses of melatonin were being used to act as a time cue, not as a hypnotic. For the greatest magnitude of a phase advance to occur, 0.5 mg of melatonin should be taken 10–12 hours before the mean midpoint of sleep on free days (or 6–8 hours prior to the mean sleep onset time on free days) [3]. We encouraged the patient and family to set an alarm to remind them to take the melatonin at consistent time in order to produce a 90± 30 minute phase advance. We also advised that relapses in treatment and decompensation are common, requiring resuming the whole sequence of advancing the bedtimes and timing of bright light exposure. Because the family was more focused on OSA as the cause of his problems, we delayed adjusting his bedtimes until after adenotonsillectomy.

He underwent adenotonsillectomy with inferior turbinectomy. He tolerated surgery well only requiring supplemental oxygen via nasal cannula the first postoperative night. Because he had severe pediatric obstructive sleep apnea before surgery, we repeated his overnight sleep study 3 months after surgery. The repeat PSG showed no snoring or significant sleep apnea. His pediatric obstructive apnea hypopnea index was now only 0.9 per hour of sleep. He was doing better in school. His grades were Bs and Cs, and he was not falling asleep in school. His ADHD had “not gone away” but he was more attentive and less hyperactive in school. He was usually asleep by 9:30 on school nights and 10:30 to 11 p.m. on weekends. His parents confiscate his tablet at 8:30 p.m. He was up by 6 a.m. on school days, 8 a.m. on the weekends.

Discussion

ADHD is a neurodevelopmental condition characterized by inattention, hyperactivity, and impulsivity and a prevalence of 11% in children ages 4–17 years [4]. The most recent diagnostic criteria for ADHD adapted from the DSM-5 are summarized in Table 5.4 [5]. Comorbid sleep disorders are at

Table 5.4 Diagnostic criteria for attention deficit/hyperactivity disorder in children adapted from DSM-V [5]

Symptoms of inattention	Symptoms of hyperactivity and impulsivity
Makes mistakes or fails to attend to detail(s)	Squirms in seat, fidgets, taps hands and feet
Difficulty sustaining attention when performing tasks or activities	Leaves seat in situations or settings when expected to remain in it
Does not seem to listen when spoken to directly	Runs and climbs in inappropriate situations
Does not follow through on instructions or fails to finish schoolwork or other duties	Unable to play or engage in leisure activities quietly
Difficulty organizing tasks or activities	"On the go" acting as if "driven by a motor"
Avoids, dislikes, or is reluctant to engage in tasks which require sustained mental effort	Talks excessively
Easily distracted by external stimuli	Difficulty waiting their turn
Forgetful in daily activities	Intrudes on or interrupts others
Loses things necessary for tasks or activities	Blurts out answers before question has been completed

The three core features of ADHD are inattention, hyperactivity, and impulsivity. The three subtypes of ADHD are combined, predominantly inattentive, and predominantly hyperactive/impulsive
All three core symptoms are present in the combined type and ADHD diagnosed when ≥6 symptoms of hyperactivity/impulsivity and ≥ 6 symptoms of inattention have been observed often in the past 6 months. Inattentive subtype diagnosed if ≥6 symptoms of inattention (but <6 symptoms of hyperactivity/impulsivity) have persisted for ≥6 months. Hyperactive/impulsive presentation – diagnosed if ≥6 symptoms of hyperactivity/impulsivity (but <6 symptoms of inattention) have been present for ≥6 months

least twice as common in children with ADHD compared with typically developing (TD) children. A recent study confirmed 64% of children with ADHD had sleep problems compared with 25% in typically developing (TD) children using parental questionnaires [6]. Subjective sleep-wake complaints most often reported by parents of children with ADHD are bedtime resistance, longer sleep latencies, more nighttime awakenings, and daytime sleepiness [7]. However, there is a paucity of indisputable objective evidence that ADHD *alone* disrupts sleep [8]. The most consistent objective finding is that children with ADHD more often have longer mean sleep latencies than TD children (50 vs. 30 minutes, respectively) [9, 10].

While ADHD alone does not disrupt sleep, comorbid anxiety disorders, internalizing behaviors, and/or depression in children with ADHD do. Recent studies find problematic sleep behaviors (such as trouble sleeping, sleeping less than other children, overtiredness, and nightmares) are far more likely to be found in children with ADHD who have anxiety, internalizing behaviors, and/or depression [6, 11, 12]. An evening preference (night owls) when present in children with ADHD may predispose them to difficulty falling asleep and contribute to their bedtime resistance [6]. Comorbid sleep disorders in children with ADHD appears to worsen many of their ADHD symptoms [10]. Concomitant internalizing and/or externalizing comorbidities in 392 children with ADHD increased their risk for moderate-severe sleep problems and problematic sleep 2.4-fold [13]. A recent population-based cohort study of 605 children found snoring or other symptoms of OSA were associated with a two-fold increased risk for a diagnosis or symptoms of ADHD and a three- to four-fold increased risk for behavior problems or a conduct disorder [14].

Even Habitual Snoring in Children Increases Their Risk for Attention and Behavior Problems

Any severity of OSA including habitual snoring in typically developing children significantly increases their risk for problems with attention, executive function, behavior and emotional regulation, and poorer scholastic performance [15–19].

Children with OSA of any severity are at increased risk for significantly lower intelligence quotient (IQ) scores, albeit in the low normal or borderline range [20–22]. A study recorded overnight PSG and performed formal neurocognitive testing on 31 Caucasian middle-class children with OSA (mean age 9, mean AHI 10/h, mean nadir SpO_2 91%, mean desaturation index 2/h), 13 with primary snoring (mean age 8.6 years), and 60 controls [23]. Mean total, verbal, and performance IQs were significantly lower (98, 96, and 101, respectively) in those with OSA and the primary snorers (95, 91, and 100.5) compared to controls (116, 118, and 110). Another study found habitually snoring children had IQ scores a mean of 10 points lower compared with non-snoring controls [15]. Worse yet, the IQ scores of the snoring children did not improve when retested 6 months following AT. A third study found 163 children (ages 10 to 17 years) with OSA did not perform particularly worse on formal neurocognitive tests than controls but still had lower school grades and greater attention deficits [24]. Another recent study of a community-based cohort of 1115 children who underwent overnight PSG and neurocognitive and behavioral phenotyping [25]. They found SDB primarily affects behavior in children, not cognition.

Treatment of Obstructive Sleep Apnea Has Favorable Effects on Symptoms of Attention Deficit Hyperactivity Disorder

A 2014 meta-analysis found a moderate relationship between ADHD and SDB symptoms and a moderate lessening of ADHD symptoms 2–13 months after adenotonsillectomy [26]. A recent prospective cohort study found ADHD symptoms lessened in 86% of 59 children with ADHD 3 months after adenotonsillectomy [27]. Another study of 53 children (ages 3–12) found a significant decrease in ADHD symptoms (inattention, hyperactivity, cognitive disorders, and/or oppositional behavior) at 3 and 6 months following surgery [26]. The childhood adenotonsillectomy (CHAT) study found

improved parent- and teacher-rated behavior and attention following surgical treatment for OSA, despite normal results on neurocognitive tests. Poor school performance because of attention and behavior problems may be a more sensitive "real-world" biomarker of neurocognitive impairment in children.

Insufficient Sleep Affects Typically Developing and ADHD Children in Different Ways

Studies have shown insufficient or poor sleep in children with ADHD has been associated with increased distractibility [28], a higher prevalence of hyperactivity, restlessness and conduct problems [29], and deficits of overnight consolidation of declarative and emotional memories [30, 31]. A recent study compared 18 children diagnosed with ADHD with 20 age-matched TD controls [10]. Poor sleep negatively affected children with ADHD and TD but in different ways. Sleep problems in TD children were predictive of increased ADHD behaviors but not impaired attention. Whereas, poor sleep in the children with ADHD was predictive of reduced attention (especially for tasks requiring sustained attention) but did not particularly worsen their already present other ADHD behaviors.

Behavioral Interventions to Improve Sleep Problems in Children with ADHD

Management of sleep problems in children with ADHD includes sleep hygiene and behavioral interventions which include establishing a consistent bedtime ritual, limit setting, a behavioral reward system, relaxation strategies, and setting times for returning to check on the child during the night. A randomized controlled trial assessed the effect of a behavioral intervention on daytime functioning, behavior, and working memory in 244 children with ADHD (ages 5–12) [32].

Compared with control children, intervention children had fewer moderate-severe sleep problems at 3 months (56% vs 30%) and 6 months (46% vs 34%). At 3 months this equated to a reduction in absolute risk of 26% and an estimated number needed to treat of 3.9. At 6 months the number needed to treat was 7.8. Approximately a half to one third of the beneficial effect of the intervention on ADHD symptoms was mediated through improved sleep, at 3 and 6 months, respectively. Teachers reported improved behavior of the children at 3 and 6 months. Working memory (backward digit recall) was higher in the intervention children compared with control children at 6 months. A cluster-randomized translational trial is further studying this issue [33].

Another recent study in 361 children (ages 5–13) with ADHD and parent-reported moderate-to-severe sleep problems found sleep hygiene and parenting were modifiable factors independently associated with sleep problems in children with ADHD. More consistent parenting was associated with decreased bedtime resistance and sleep anxiety [34]. Poorer sleep hygiene was associated with increased bedtime resistance, sleep duration problems, and daytime sleepiness. These factors should be considered when managing sleep problems in children with ADHD.

Pearls/Take-Home Points

- Comorbid sleep disorders are at least twice as common in children with attention deficit hyperactivity disorder (ADHD) as compared with typically developing (TD) children.
- Subjective sleep-wake complaints most often reported by parents of children with ADHD are bedtime resistance, longer sleep latencies, more nighttime awakenings, and daytime sleepiness.
- The most consistent objective finding is that children with ADHD more often have longer mean sleep latencies than TD children.

- Management of sleep problems in children with ADHD includes sleep hygiene and behavioral interventions which include establishing a consistent bedtime ritual, limit setting, a behavioral reward system, relaxation strategies, and setting times for returning to check on the child during the night.
- Parent-reported moderate-to-severe sleep problems found sleep hygiene and parenting were modifiable factors independently associated with sleep problems in children with ADHD.
- More consistent parenting was associated with decreased bedtime resistance and sleep anxiety.
- Poorer sleep hygiene was associated with increased bedtime resistance, sleep duration problems, and daytime sleepiness.

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Chapter 6
Is It Narcolepsy or Depression Making My Patient Sleepy?

Philip M. Becker

Sleeping well is a joy and sleeping too much a bane when one wants to be awake, alert, and fully functional. When a patient presents with depressed mood, weight gain, fatigue, sleeping long hours, or problems of intrusive daytime sleepiness, the depressive disorder is considered to be atypical [1, 2]. When depressive symptoms are severe, it is significantly more likely that a mood disorder would be the principal diagnosis and that therapeutic intervention with antidepressant therapy may offer improvement. The challenge for a psychiatrist arises when the patient's primary complaint is "being so tired I can't function." It is the atypical patient who raises the question of a disorder of hypersomnia such as narcolepsy or its variants [3].

The Case of Thomas

- *History of present illness*: Thomas is a 20-year-old college student who arrives with his mother on the recommendation of his college health service. Thomas was considered

P. M. Becker (✉)
Sleep Medicine Associates of Texas, PA, Dallas, TX, USA
e-mail: pbecker@sleepmed.com

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to be depressed by the service's nurse practitioner. Academic performance had fallen over the academic year. Thomas left his original major of engineering to begin study in anthropology "because it would be easier and the classes are later so I can sleep in." He is struggling in all classes after receiving escitalopram 10 mg and then 20 mg p.o. a.m. "All I want to do is sleep." He reports that he has been having increasing difficulty getting up to attend classes and he falls asleep when reading for more than 10 minutes. He feels discouraged and disappointed by his poor performance, and mother reports him to be more irritable and angry. Although he gained 15 pounds during his first year at college, weight has remained stable with no changes in appetite. He still socializes with his friends, although he admits there are times he would prefer to sleep rather than go out. He denies hopelessness or suicidal thoughts. He reports that he is sleepy behind the wheel when making the 3-hour trip between home and school, reporting increasing sleepiness approximately 1 hour into his trip. He has had no automobile accidents, but he does report that he will close his eyes at stoplights. He averages three cups of coffee and a caffeinated energy drink daily to help his alertness. He drinks alcohol during parties on the weekend, consuming 2–4 alcoholic beverages on Friday and/or Saturday night with higher quantities of alcohol adding to his sleepiness. He denies the usage of recreational agents, specifically amphetamines or cocaine. He has experimented with marijuana but it makes him sleepier than normal.

- *Past history*: Thomas is in good health without other medical problems or medications. He has never been hospitalized. He had normal development. There is no history of head trauma or CNS infection. At home he resides with his father, an attorney; mother who is a homemaker; younger sister; and brother. No one else in the family has similar sleep complaints. Mother is currently receiving treatment with escitalopram, and father had previous history of antidepressant therapy during situational stress.

- *Sleep history*: Mother reports that he was a normal sleeper until age 14 when he began staying up past 11:00 p.m. It became more difficult to awaken him to attend school. Around age 15 Thomas began to have increasing difficulty staying awake in morning and afternoon lecture classes. He otherwise performed well in advanced placement throughout high school. Around age 10 the family and teachers became concerned that Thomas was inattentive with mild hyperactivity, leading to the prescription by his pediatrician of amphetamine salts. The amphetamine salts were discontinued at age 14 when sleep onset difficulties presented and Thomas did not wish to continue taking medication. To the best recollection of mother and the patient, there was no associated infection at the time of development of the symptoms of sleepiness.

His current sleep routine at college is to retire between midnight and 1:00 a.m., falling asleep immediately. He averages 0–1 brief awakenings during the night with no difficulties returning to sleep. Nocturia is denied. Depending upon his class schedule, he wakes from an alarm feeling groggy between 9:00 a.m. and 11:00 a.m. A few times per week, he will nap for 60–90 minutes, awakening a bit groggy but then feeling better for 2–3 hours.

Sleep disorders review: His self-rating on the Epworth Sleepiness Scale was 16 on the 24-point measurement, indicating rather severe daytime sleepiness. There is no history of cataplexy with vigorous laughter or anger, denying even momentary eyelid closure, head nod, facial droop, or articulation difficulties. He recalls one episode of awakening from sleep being paralyzed when in high school, but it has not recurred. There have been no hypnagogic or hypnopompic hallucinations. Dreams at sleep onset are denied, and he has had no abnormal increase in dreaming or nightmares. There is no automatic behavior during the daytime. To the best of his or mother's knowledge, there is no snoring, pauses in breathing, abnormal leg activity, leg restlessness, sleep walking, sleep terrors, or bruxism.

Examination

Thomas is a well-developed, well-nourished young man who appears his stated age. He is dressed casually in jeans and a T-shirt. He is able to provide appropriate responses to questions without delay. Affect and mood is full range and appropriate to content without evidence of cognitive disturbance. There is no presentation of sleepiness, eye closure/staring, or change of facial muscle tone during his 60-minute visit. Vital signs show a blood pressure of 110/72 mm HG with a pulse of 68/minute, regular, and weight of 78.1 kg on a 181 cm frame. Physical examinations of HEENT, posterior airway, lungs, cardiac auscultation, abdomen, and extremities are within normal limits. Neurologic examination shows cranial nerves II–XII to be intact. Strength is normal for abduction and adduction in the upper and lower extremities. Deep tendon reflexes are equal and symmetric of the extensors and flexors in the arms and legs. Sensory examination shows no deficits. He has normal gait and station with good performance of alternating hand movements, finger to nose, and tandem walking.

Special Studies

At the college health service, Thomas had testing that showed normal thyroid functions, complete blood count, chemistries, and negative Epstein-Barr titers. No further blood analysis was considered necessary.

Thomas received a provisional diagnosis of idiopathic hypersomnia, although narcolepsy, type II without cataplexy, or the lesser possibility of hypersomnia associated with a psychiatric disorder could not be ruled out by history [3, 4]. The lack of therapeutic benefit and increasing sleepiness on escitalopram resulted in the recommendation to taper escitalopram 20 mg over the next 14 days. 8 After being drug-free for an additional 10 days, Thomas attended an overnight diagnostic polysomnogram and a multiple sleep latency

test to assess the potential for nocturnal sleep pathology or abnormal REM sleep regulation. During the 10-day drug-free period, he kept a sleep log that showed that he was averaging 8.2 hours of nightly sleep from approximately 12:30 a.m. until 9:00 a.m. He took four naps but followed the request to avoid naps and caffeine in the 48 hours prior to polysomnographic testing. The discontinuation of escitalopram resulted in only modest reduction of his sleepiness and no change in mood.

Thomas reported for polysomnographic testing at 8:00 p.m. He was pleasant and cooperative according to the technologist, completing pretest paperwork and hookup of his polysomnographic testing (PSG) according to the American Academy of Sleep Medicine (AASM) monitoring criteria [3] (10–20 system montage of EEG at bilateral frontal, central, and occipital regions referenced to the contralateral mastoid; chin-cheek EMG; EOG; nasal/oral airflow thermistor and pressure transducer + snoring; modified lead II ECG; chest and abdominal piezoelectric effort bands; pulse oximeter; bilateral anterior tibialis EMG; position sensor; video recording). He remained awake until lights were turned off at 11:55 p.m. Scoring was completed according to AASM criteria and demonstrated a normal night of sleep. Thomas had a total sleep time of 475 minutes after a sleep onset latency of 16 minutes, sleep efficiency of 93%, REM sleep latency after sleep onset of 68 minutes, normal distribution of sleep stages with 8% in stage NI, 48% in stage N2, 19% in stage N3, 25% in stage REM sleep during four individual epochs, an apnea/hypopnea index of 3.4/hour, respiratory disturbance index of 5.1/hour, nadir of oxyhemoglobin saturation to 91%, minimal to mild snoring, no periodic leg movements of sleep, spontaneous arousals of 4.4/hour, and no other abnormalities of ECG, EEG, or behavior. He reported that he slept fairly well although he considered the testing “a little weird.” He completed a urine drug screen in the morning that was positive for marijuana (the patient reported he had been at a party about 1 week earlier and shared a joint. He again denied regular use of recreational drugs).

Two hours after arising, he proceeded to the AASM protocol for the four-nap multiple sleep latency test (MSLT). He was instructed to allow himself to fall asleep naturally while lying in bed with the lights off at 2-hour intervals. He was not to nap between trials. He fell asleep during each nap opportunity at 2.0 minutes, 4.0 minutes, 6.0 minutes, 3.5 minutes, and 9 minutes, respectively. The mean sleep latency was 4.9 minutes. In nap trial #1 and #3, he entered REM sleep at an average of 8 minutes.

Results/Conclusion

After a normal nocturnal polysomnogram, the MSLT findings of excessive daytime sleepiness (mean sleep latency <8 minutes in four or five nap trials) and two REM sleep onsets were considered diagnostic for narcolepsy, type II (without cataplexy). It was considered unlikely that his isolated use of marijuana would contribute to the results (repeat urine drug screen 4 weeks later was negative for marijuana or other drugs of abuse). Depression was considered an unlikely contributor [5, 6].

Therapeutic Intervention/Course

Thomas and his mother returned to review the results and to initiate treatment. The nature of narcolepsy without cataplexy was discussed, and the importance of adequate sleep, scheduled naps, and safety was reviewed. He was begun on armodafinil 150 mg as a 2-day test dose of one-half tablet and thereafter one tablet p.o. upon arising. He had understood that it would take approximately 1 hour to experience therapeutic benefit. At follow-up in 4 weeks, he reported continued problems awakening in the morning but improvement of his alertness in the morning and early afternoon. After 3:00 p.m. he had return of sleepiness until 7:00–8:00 p.m. His self-rating on the Epworth Sleepiness

Scale fell to 12/24, moderate severity. There were no side effects of headache, nervousness, GI upset, anxiety, or mood disturbance. As he felt he could perform better, he reported his mood to be better. To enhance therapeutic response, the patient was instructed to use a "double alarm." At the early alarm 90 minutes before his planned arising, he would take an increase dose of armodafinil 250 mg. The second alarm allowed him to awaken more alert and ready to start his day. He reported further improvement of alertness in class through the later afternoon and tolerated the 250 mg dosage well. The improvement was reflected in the Epworth Sleepiness Scale score of 11/24. "I feel good." He was now able to drive between college and home without needing to stop because of sleepiness.

Question: What to do in a patient with mood complaint and sleepiness?

Assessing Differential Diagnoses

Patients with mood disorders often report feeling tired but not necessarily sleepy [1, 2, 4, 5, 7, 8]. Assessment begins by *understanding the difference among tiredness, fatigue, and sleepiness*. Tiredness is a cognitive complaint. A tired person often reports problems of motivation and inertia. In contrast, fatigue is a physical manifestation with lower energy and a lethargy that worsens when effort is applied (think of metal fatigue like in airplane wings). People who are sleepy often report being tired and fatigued, but the sleepy patient will report themselves nodding off in sedentary situations that lack stimulation (viewing television and movies, passively listening or reading). The sleepy patient has sleep disorder or sedation. Positive answers to questions about the muscular weakness of cataplexy during emotional situations, sleep paralysis, or sleep-related hallucination will increase the likelihood that narcolepsy is present.

A *24-hour sleep log* may prove helpful to identify lifestyle issues. *Insufficient sleep* is common [9, 10]. It is estimated that a third of adults receive less sleep than is their requirement to assure daytime alertness, leaving them sleepier at the end of the workweek. If there is *circadian misalignment* from the "normal" bedtime related to a delayed sleep phase, sleepiness would be present in the morning with improving alertness later in the evening. Thomas reported his best alertness late into the evening that is common for young adults, including many with narcolepsy. Although caffeine will improve alertness for 2.5–4 hours, *tolerance* to short-term alertness develops within a matter of days, and rebound sleepiness can result.

Assess sleep disorders: Reports from an observer are helpful in identifying potential sleep-related signs such as the snoring of obstructive sleep apnea, restless leg syndrome, periodic leg movements of sleep, or abnormal behaviors such as sleepwalking, sleep talking, or dream enactment. Although endocrinologic abnormality or CNS injury can result in hypersomnia, there should be sufficient other symptoms to identify such an origin for the hypersomnia.

Clinical evaluation alone may not be sufficient to identify the etiology of hypersomnia. Mild to moderate sleepiness may be a feature of major depressive disorder, particularly in young adults and bipolar depression [6, 10]. It may be appropriate to encourage 14 continuous days of maximizing sleep time (adding 1 additional hour to nightly sleep) to *assure that insufficient sleep is not an explanation* for the clinical complaint. It is strongly recommended that *polysomnography with multiple sleep latency testing be considered when sleepiness is identified as intrusive into normal function*.

Medications with sedative properties often complicate the picture [7, 11–13]. Agents such as benzodiazepines, opioids, neuroleptics, or sedating antidepressants/antihistamines need to be assessed for potential sedative side effects. SSRIs and SNRIs are curious in that approximately 10–15% of patients experience hypersomnia (or the reverse, insomnia). If clinical course allows dosage reduction, the contribution

of the pharmacologic agent to hypersomnia can be assessed. Downtitration should lessen the sedative side effect. If depression is severe, uptitration could be considered to determine if a higher dose worsens the hypersomnia. When discontinuation is not an option, lowering the sedating antidepressant and the addition of bupropion may result in improvement in alertness.

Pearls

The International Classification of Sleep Disorders, third edition (ICSD 3), reports that narcolepsy is rare at an incidence of 0.02% to 0.18% of the US and Western European population [3]. A majority of patients with hypersomnia do not have narcolepsy. A patient presenting with intrusive excessive daytime sleepiness is best described as experiencing hypersomnia until testing confirms the diagnosis.

- Assure that a patient is receiving adequate hours of sleep. Ideally, sleep time should be above 8 hours per night for 10 or more days.
- Narcolepsy represents a disorder of REM sleep regulation [11]. Narcolepsy type I is the classic patient who has cataplexy, going weak with laughter or anger, and experiences sleep paralysis at offset or onset of sleep, as well as auditory or visual hallucinations as they drift into sleep or come out. Type I patients show deficiency of orexin/hypocretin on spinal fluid analysis.
- Narcolepsy type II patient reports no cataplexy and little or no sleep paralysis or hallucination and demonstrates on multiple sleep latency testing an average sleep latency of $\leq$8 minutes and abnormal REM sleep onsets in at least two of the nap trials [3].
- Idiopathic hypersomnia with or without long sleep is the clinical challenge when the MSLT identifies

hypersomnia (or does not do so) with no REM sleep onsets [1]. At times it is necessary to repeat the MSLT on an additional one or two occasions to clarify the diagnosis. Sleep specialist continue to gain understanding of idiopathic hypersomnia, and such patients may or may not respond adequately to wake-promoting agents or psychostimulants.

- When the MSLT shows the patient to be normally alert (>10 minutes on mean sleep latency), the clinical complaint of intrusive sleepiness may result from insufficient sleep, patients who require >8 hours of sleep per night, significant anxiety that results in a heightened arousal system preventing sleep onset under laboratory conditions, or atypical depression.
- If the depressed patient is currently treated with an antidepressant, the recommendation is to taper and discontinue therapy before testing. If a patient's depression is severe, particularly with prior suicidal ideation, it may be necessary to see the response of an increase in the medication. If the patient is less sleepy with a decrease or sleepier with the increase, the antidepressant agent may be a contributor to the hypersomnia.

Recommended Reading

1. American Academy of Sleep Medicine. International classification of sleep disorders, third edition. Darien, IL: American Academy of Sleep Medicine, 2014.

   (a) *Hypersomnia associated with a psychiatric disorder (ICD-10-CM code: F51.13)* requires three criteria for the diagnosis:

(i) (1) Daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least 3 months; (2) daytime sleepiness occurs in association with a concurrent psychiatric disorder; (3) symptoms are not better explained by another untreated sleep disorder, a medical or neurologic disorder, or the effects of medication or drugs.

(ii) Patients often report poor quality and nonrestorative sleep and focus primarily on the hypersomnia and only later does it become clear that there are psychiatric symptoms.

(iii) Associated psychiatric disorders include mood disorders, conversion or undifferentiated somatoform disorder, and less frequently other mental disorders such as schizoaffective disorder, adjustment disorder, or personality disorders.

(iv) ICSD 3 reports that 5–7% of hypersomnolence is related to a psychiatric disorder with women showing a higher prevalence, age of presentation around 20–50 years, and a wide range of 5–50% of patients with major depressive disorder experiencing hypersomnolence (estimated 50% in seasonal affective disorder).

(v) Additional features: There has not been adequate definition of the predisposing or precipitating factors, onset, course, complication, or pathophysiology. Hypersomnia may linger after improvement of depression. In children and adolescents, it is common to see other biologic symptoms of weight loss and anhedonia.

(vi) Unresolved issues and future directions: The section authors recognized the discordance between objective sleepiness and subjective complaints. The potential for decreased energy and lack of interest may keep a depressed patient in bed for long hours. The Nosology Committee recommended a more

effective definition of hypersomnolence in this population and better methods to measure the complaint.

(b) *Narcolepsy type I (ICD-10-CM code: G 47.411)* has alternate names of hypocretin deficiency syndrome, narcolepsy-cataplexy, and narcolepsy with cataplexy.

(i) Daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least 3 months.

(ii) Presence of one or both of the following:

1. Cataplexy (one or more episodes of <2 minutes of bilaterally symmetrical sudden loss of muscle tone with retained consciousness) *and* a mean sleep latency of ≤8 minutes on an MSLT +2 or more sleep onset REM periods during the nap trials. If there was REM sleep onset during the nocturnal polysomnogram (<15 minutes), this would qualify as one of the REM sleep onsets.
2. CSF measurement of the hypocretin-1 concentration, measured by immunoreactivity, is either <110 pg/mL or < 1/3 of mean values obtained in normal subjects within the standardized assay. Note: Hypocretin-1 assay of CSF is not readily available and generally limited to active research centers.

(iii) ICSD 3 provides an excellent description of cataplexy symptoms. Presentation is quite variable and often specific to the emotional reaction of a particular patient. It is more common for it to be subtle than dramatic. An examiner is unlikely to see significant cataplexy during consultation, although subtle signs of slight facial relaxation, momentary eye closure/twitching, or slight head drop may be noted if a patient is anxious, laughs, or becomes

surprised during the interview. Cataplexy typically is short-lived with uncommon episodes lasting 2 minutes, unless a patient has had abrupt discontinuation of therapeutic agents. It is estimated that 33% to 80% of narcolepsy patients have the REM sleep abnormalities of hypnagogic/hypnopompic hallucinations and/or sleep paralysis. Sleep disturbance can be common.

(iv) Associated features: There are higher rates of obesity in narcolepsy patients. Although there is an increased prevalence of depressive symptoms in patients with narcolepsy, there have been conflicting reports of how often these symptoms qualify as major depressive disorder. Narcolepsy type I patients who report significant depressive symptoms should be considered to be good candidates for the treatment of depression and cataplexy with antidepressant medication. Narcolepsy patients may have higher levels of anxiety disorders than the general population, particularly panic disorder.

(c) *Narcolepsy type II (ICD-10-CM code: G 47.419)* is also called narcolepsy without cataplexy.

(i) The diagnostic criteria requires all of the following to be met:

1. Daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least 3 months.
2. MSLT findings of mean sleep latency of ≤8 minutes with two or more sleep onset REM periods (REM sleep onset less than 15 minutes during overnight polysomnography can be used as one of the REM sleep onsets).
3. Cataplexy is absent (if cataplexy presents later, diagnosis changes to type I).

4. CSF hypocretin-1 concentration need not be measured, but if done it needs to be >110 pg/mL or one-third of mean values of normal.
5. Hypersomnolence and/or MSLT findings are not better explained by other causes such as insufficient sleep, obstructive sleep apnea disrupting REM sleep, circadian rhythm disorder, medication effect, substance misuse, or pharmacologic withdrawal.

(ii) Associated features: Sleep paralysis, hypnagogic hallucinations, automatic behavior, memory lapses, ptosis, blurred vision, and/or diplopia may be present. Narcolepsy patients have a higher incidence of REM sleep behavior disorder or nonrapid eye movement parasomnias. There are cases of patients who presented with insomnia and were subsequently found to have narcolepsy type II.

(iii) Medical disorders associated with secondary narcolepsy type II: Tumors or sarcoidosis of the hypothalamus, autoimmune or perineoplastic disorders with anti-Ma-2 or anti-aquaporin-4 antibodies, multiple sclerosis, myotonic dystrophy, Prader-Willi syndrome, Parkinson's disease, and head trauma. As some of these disorders show a higher incidence of sleep apnea, apnea needs to be treated, and repeat MSLT needs to confirm continued abnormal REM sleep onsets. Exploration continues on the potential relationship of infections or immunizations and narcolepsy.

(iv) Demographics: The exact prevalence is unknown, although ICSD 3 reports that narcolepsy type II is <25% of the clinical population compared to type I. Population-based studies suggest a point prevalence of 20.5/100,000. It has been reported that during MSLT two (2) or more sleep onset REM periods occurred in 4–9.5% of non-complaining

community subjects, although the studies did not control for shift work, sleep deprivation, or sleep apnea. As is true for type I, age of onset peaks between 10 and 25 with a smaller increased presentation around age 35.

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Chapter 7
A Case of Narcolepsy Misdiagnosed as Schizophrenia

Nireman Iqbal, Nilam Danish, Ayesha Ebrahim, Aneeqah Naeem, and Imran S. Khawaja

Clinical History

Ms. X, a 23-year-old African American female who was diagnosed with schizophrenia, was referred to the sleep clinic for persistent daytime sleepiness. Patient's mother insisted that

N. Iqbal
King Edward Medical University, Lahore, Pakistan

N. Danish
Department of Neurology (Sleep Lab), Veterans Affairs North Texas Health Care System, Dallas, TX, USA

A. Ebrahim
Department of Medicine, VA Medical Center, Dallas, TX, USA

MD TruCare PA, Grapevine, TX, USA

A. Naeem
The Warren Alpert Medical School, Brown University, Providence, RI, USA

I. S. Khawaja (✉)
Center for Sleep Medicine, VA North Texas Health Care System, Department of Psychiatry and Neurology and Neurotherapeutics UT Southwestern Medical Center, Dallas, TX, USA
e-mail: Imran.khawaja2@va.gov

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the patient had a problem besides schizophrenia, as she was always falling asleep. The mother was concerned as the patient consistently missed school and when she was able to attend, she often dozed off in class.

Ms. X had always been sleepy since her teenage years and was labeled as "lazy" by her teachers because she had trouble completing her assignments on time. Her grades suffered because of her inability to complete her homework. Teachers would reprimand her for falling asleep in class and classmates made fun of her. Classmates nicknamed her as "sleepy head."

The patient acknowledged that she had been sleepy for many years, taking 1–2 naps daily for approximately an hour each. Her Epworth sleepiness scale (ESS) was 14 (normal range is less than 10). She also mentioned that her nighttime sleep was fragmented.

Four months ago, her primary care doctor had referred her to a psychiatrist because of complains of seeing images and hearing sounds when falling asleep. She felt the presence of "someone" in the room. She felt that the faces looked like the Devil. Her psychiatrist diagnosed her with schizophrenia based on these symptoms. In addition, she often felt someone sitting on her chest making it difficult to breath which often caused her to have a "panic attack." These symptoms mostly occured around the time of sleep or waking up. She denied any paranoid feelings and did not have any disorganized behavior auditory hallucinations.

Her psychiatrist prescribed her Risperidone 1 mg twice a day. She was on the medication for 4 months with no improvement in her hallucinations. When the hallucinations did not improve, her psychiatrist increased the dose of Risperidone to 2 mg twice a day, which further worsened her drowsiness. She stopped driving because of excessive daytime sleepiness.

Additionally, she experienced occasional sudden loss of muscle tone. She described the episodes as "buckling of her knees" when she would laugh too hard. The psychiatrist thought these were "conversion reactions," or orthorstatic hypotension from the medications. It was later discovered that these episodes were triggered by strong emotions.

She also experienced an inability to move her body in the morning, feeling as if someone was sitting on her chest.

This inability to move initially frightened her, but she soon became accustomed to it, knowing that the impairment would improve in a few minutes. She acknowledged that she previously drank energy drinks to help her stay awake but then discontinued them as they would make her more anxious and cause palpitations.

Clinical Examination

The patient was a young, well-groomed, slightly overweight female, with a BMI of 30. No abnormalities of speech were noted. The neurological, cardiovascular, respiratory, and abdominal examinations were unremarkable. She denied any paranoid thinking or delusions.

Diagnostic Studies

The patient was advised to keep a sleep diary for 2 weeks. Given her excessive daytime sleepiness and episodes of transient muscle weakness, the sleep doctor recommended a full "hypersomnia workup" which includes a nocturnal polysomnography (PSG) followed by a multiple sleep latency test (MSLT) the next day.

Results of Studies

The polysomnography (PSG) results showed a total sleep duration of 7 hours and 10 minutes, with a sleep onset latency of 6 minutes, and 75% sleep efficiency. The patient entered the REM sleep within 12 minutes of falling asleep. The sleep was fragmented with an arousal index of 15 per hour and multiple awakenings that required 5–10 minutes to return to sleep. The apnea-hypopnea index (AHI) was 0.5. No snoring or periodic leg movements were detected.

The multiple sleep latency test (MSLT) showed a mean sleep latency (MSL) of 3 minutes 35 seconds and SOREM (sleep onset REM Period) in 3 out of 5 naps.

Further Investigations

No further workup was needed as the MSLT was positive for narcolepsy with cataplexy.

Diagnosis

The clinical history, polysomnography (PSG), and mean sleep latency test (MSLT) confirmed the diagnosis of narcolepsy with cataplexy, or type 1 narcolepsy. The sleep doctor prescribed modafinil 200 mg daily for excessive daytime sleepiness and added venlafaxine 75 mg to treat cataplexy. Cataplexy refers to the sudden loss of muscle tone which is triggered by emotions. The sleep doctor suggested discontinuation of risperidone. General behavior modifications were advised such as getting a good night sleep, taking one to two naps during the day, and avoiding sleep deprivation. In the next 2 weeks, the patient noticed a significant improvement in the excessive daytime sleepiness; her ESS dropped from 14 to 8, and her performance at school improved.

Discussion

The overlapping clinical symptoms of schizophrenia and narcolepsy often make it challenging to differentiate the two conditions in patients with EDS. Narcolepsy is a chronic neurological disease with five domains of symptoms including excessive daytime sleepiness (EDS), cataplexy, hypnagogic/hypnopompic hallucinations, sleep paralysis, and sleep fragmentation. Though cataplexy is pathagnomic, daytime sleepiness, hypnagogic hallucinations and sleep paralysis can be seen in normal individuals as well. Schizophrenia symptoms can be classified as positive (auditory/visual hallucinations, delusions), negative, (lack of motivation, poverty of speech, flattening of affect etc) or cognitive (working memory problems, excecutive functions). Sleep paralysis, hypnagogic/hypnopomic hallucinations can miminc positive symptoms of schizophrenia leading to a misdiagnosis of

psychosis. Therefore it is important to get a detailed history of these symptoms.

Many patients with narcolepsy get used to feeling sleepy not realizing that they have a sleep disorder. In the USA alone, the occurrence is about 1 in 20,000. Though narcolepsy may run in some families, most cases are not genetic. The disorder usually manifests itself in adolescence or the 20's. The unpredictable sleep attacks may not only affect one's quality of life, but they can be harmful to one's self and others too, especially when a person is driving, walking, or at work.

Pathophysiology

Narcolepsy results from the loss of the neuropeptides, orexin-A, and orexin-B (also known as hypocretin-1 and hypocretin-2). These neurotransmitters are a product of the prepro-orexin gene and are made by neurons in the lateral hypothalamus. Orexin-A and orexin-B have excitatory effects when they bind the Ox1 and Ox2 receptors on postsynaptic neurons.

Pathogenesis involves the destruction of hypocretin-producing cells of the ventral thalamus (via either autoimmune processes or infections, i.e., influenza, streptococcus, and H1N1 vaccination) in genetically susceptible individuals that are carriers of one or more alleles of human leukocyte antigen (HLA) DQB1*0602, with 98% of patients testing positive for it.

Cataplexy

Narcolepsy may occur with or without cataplexy, a condition in which patients suddenly lose muscle tone with retained consciousness. Cataplexy is triggered by strong emotions, like laughter, embarrassment, surprise, or anger. It can cause the head to drop, one's face to droop, the jaw to weaken, or make the knees give way. These attacks can also affect the patient's entire body and may cause one to fall. It is important to note that not everyone with narcolepsy has cataplexy, but cataplexy could be a sign of narcolepsy.

Excessive Daytime Sleepiness

All individuals with narcolepsy experience excessive daytime sleepiness (EDS), during which one feels an irresistible urge to sleep during the day. While it is normal to feel tired by the end of the day, a person suffering from EDS associated with narcolepsy feels as if he or she is tired all the time. The sleepiness makes it difficult to stay alert during the daytime. Many patients describe their condition as if they are fatigued all the time or at times irritable. They have a hard time concentrating, and the condition may be accompanied by poor memory retention and mood swings. A common misconception is that a narcoleptic person may sleep more than an average person. The assumption is usually false. In fact, narcoleptics do not sleep more hours than others, but their sleep is scattered all over the day in small intervals.

Hypnagogic/Hypnopompic Hallucinations

Patients often describe hallucinations as nightmares or experiences that seem real while falling asleep or waking up. Patients may experience hearing sounds or complete sentences when going to sleep and, in some situations, have unwanted visuals such as seeing faces and people standing at the bedside. Some also report a sense of being touched and presence of someone in the room. Sleep paralysis often accompanies these hallucinations. Hypnagogic hallucinations often lead to a diagnosis of psychosis if narcolepsy is not in the differential diagnosis.

Sleep Paralysis

Sleep paralysis is the inability to move or speak for a short time when one is falling asleep or when one is waking up. One may feel as if it is hard to breathe. For some patients, this can be a suffocating or frightening experience.

Misdiagnosis of Narcolepsy

As illustrated from the case, narcolepsy is often missed or diagnosed only years after symptoms first appear. Early diagnosis and treatment play a vital role in disease management and preventing psychosocial issues related to the disorder. Excessive daytime sleepiness is common in patients with depression and other mental health disorders whereas cataplexy can offen be confused with syncope or orthostatic hypotension from medications.

Conversion Disorder

Physicians should be mindful that cataplexy can look like a conversion reaction. A patient with conversion disorder and excessive daytime sleepiness, cataplexy, sleep paralysis, or hypnagogic hallucinations may suffer from narcolepsy. Narcolepsy is estimated to occur in 0.03–0.16% of the general population. Cataplexy with excessive daytime sleepiness is pathagnomic for narcolepsy. Providers often misdiagnose cataplexy as conversion disorder, malingering, or syncope if narcolepsy is not in their differential diagnosis. A referral to a sleep specialist for a polysomnogram and multiple sleep latency tests to evaluate narcolepsy is recommended if daytime sleepiness is present.

Narcolepsy Often Misdiagnosed as Schizophrenia

A study compared the psychotic features of both disorders and found that more narcolepsy patients present with visual hallucinations while schizophrenic patients present with auditory hallucinations. The delusional component found in schizophrenia is absent in narcolepsy psychosis. It is therefore vital that the treating physician consider narcolepsy in the differential of unusual or refractory schizophrenia. Narcolepsy can be confirmed by safe and noninvasive testing, mainly the MSLT. The co-occurrence of narcolepsy and schizophrenia in the same patient is unlikely, but possible.

The presence of psychotic symptoms in narcolepsy type 1 (NT1) is responsible for delayed diagnosis due to the misdiagnosis as schizophrenia. A study published in Journal of Clinical Sleep Medicine found that out of 1451 narcolepic patients 82% of the respondents received a diagnosis of narcolepsy one year or more after the onset of symptoms. More research is needed to identify shared and distinctive clinical characteristics between NT1 and schizophrenia to help avoid such a significant delay in diagnosis. Furthermore, in order for treatment for either condition to be successful, it is crucial that narcolepsy symptoms are not mistaken for those of schizophrenia.

In cases where a psychotic illness is diagnosed instead of narcolespy, there is an increased burden of medication side effects as seen in our patient. Once patients with psychotic disorders are on antipsychotic medications, it is difficult to discontinue them for MSLT testing, making it more important to get a detailed history of these symptoms.

Pearls

1. Narcolepsy should be considered a differential diagnosis in patients presenting with hallucinations and psychosis.
2. Although a patient taking antipsychotic medications may attribute sleepiness to psychotropic drugs, workup for narcolepsy can prevent misdiagnosing narcolepsy as schizophrenia, schizophreniform disorder, or conversion disorder.

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Chapter 8
Mood Disorder or a Case of Sleeping Beauty Syndrome?

Ranji Varghese and Guo Lulu

Clinical History/Case

A 23-year-old Caucasian female who self-referred to our sleep clinic for recurrent hypersomnolence episodes was accompanied by her mother who provided collateral information. The patient worked as a chemical dependency counselor and had no significant past medical history, traumatic history, neurodevelopmental history, or incidences during birth.

The patient's first hypersomnolence episode occurred at age 18. She was attending a local business conference and when she did not appear for any conference activities, the patient's colleagues became concerned. She was eventually found by her mother in the hotel room asleep and difficult to awaken. The patient was estimated to have been sleeping for more than 15 hours. The patient was brought home where she

R. Varghese (✉)
Department of Neurology, Hennepin County Medical Center, Minneapolis, MN, USA
e-mail: ranji.varghese@hcmed.org

G. Lulu (✉)
Hennepin Healthcare, Minneapolis, MN, USA
e-mail: lulu.guo@hcmed.org

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had continuous sleep and would only be awakened by her parents' insistence to eat or to use the bathroom. The patient herself did not report hunger during these episodes of awakening. According to her mother, she would be emotionally volatile if awakened during these sleepiness episodes and would have a "numb, blank stare." The patient recalled that she would "not be in touch with reality" during momentary awakenings.

Hypersomnolence occurred for approximately 3 weeks, with profound unarousable sleepiness lasting for 15–20 hours in a day. After the third week of this pattern, she began to report feeling "kind of normal" again, with improved cognition, continued but with decreased hypersomnolence and improved appetite. These improvements continued steadily for 2 weeks until week 5 at which point she returned to baseline and resumed normal activities without any ongoing cognitive, sleep, or mood deficits.

She was not medically evaluated during the first incident. She and her family believed she was struggling with a flu-like virus. She was not using any medications prior to this event and denied any history of using illicit drugs or alcohol. There was no medical history including head trauma that precipitated this.

Her second episode occurred in the fall of the following year. She denied any prodromal symptoms but acknowledged that 1–2 hours before the onset she felt an urge to sleep that was outside of her normal nocturnal sleep schedule. That evening she began sleeping and did not awaken again until the next afternoon, a period estimated to be 15–18 hours. This pattern of profound hypersomnolence lasting 15–20 hours per day continued for 3 weeks. Associated symptoms consisted of anorexia, decreased need to void, and disinhibited behaviors including irritability if awakened. The patient again reported having feelings of derealization, as "if my reality was fake." The episode lasted almost 3 weeks, at which point she gradually began to improve until returning to baseline at week 4.

After returning to baseline, the patient reported new onset depressive features and anxiety. She stated that her anxiety was primarily driven by worries of a future hypersomnolence attack. In addition to psychological distress, these sleepiness

attacks resulted in significant social and occupational problems including losing her job due to inability to work.

Shortly after her second episode, she was evaluated by a local psychiatrist. Due to presumed depression leading to sleepiness and concerns for anxiety, the patient was started on citalopram 10 mg daily and titrated to 20 mg daily. The patient reported that mood and anxiety improved with citalopram.

Her third episode started the following year when she was working in Alaska. She again had some prodromal sleepiness before the onset of hypersomnolence episodes. During this time she would remember having partial conversations and brief suicidal thoughts without any suicidal plans. Her mother noted a blunted affect and slower and slurred speech upon awakenings. The main hypersomnolence event lasted 2–3 weeks again with gradual return to baseline 5 weeks from the start. There was no history of alcohol or drug use that precipitated this. She again lost her job. At this point her anticipatory anxiety of experiencing another event worsened, and she began to have panic symptoms. Citalopram was eventually increased to 40 mg daily but eventually discontinued as it was no longer addressing the anxiety.

The patient was transitioned to venlafaxine and began supportive psychotherapy which she thought was helpful. However anticipatory anxiety of having another episode and worries about her health continued.

Three years after the initial episode, she had a fourth hypersomnolence event which lasted a total of 5 weeks. She reported anxiety but not significant depression prior to the event. If awakened during the event, she also recalled panic-like feelings and visual hallucinations “like as if I was in a dream.”

During this last episode, the patient was brought in by her family to the local emergency room. Notable workup included MRI head and metabolic panel and chemistry and urine toxicology. All lab values were normal. The on-call psychiatrist diagnosed the patient with a psychogenic dissociative episode vs. a hypersomnolence syndrome. He recommended increasing venlafaxine to a total dose of 112.5 mg

and increasing therapy sessions and referred to a regional sleep center for further evaluation of hypersomnolence.

The patient was seen in the sleep clinic 2 months after her last episode. A thorough physical, neurological, and mental status examination was performed. She was noted to be slightly anxious but not clinically depressed. The patient's mother verified that her symptoms were similar in each of the four episodes and felt that her comorbid anxiety were precipitated and worsened by these events. The patient's mother also did not feel that there was any secondary gain from these events, as she noted that her daughter enjoyed her work and was very distraught by how her life was disrupted by these experiences. There was never any history of illicit drug use or any alcohol use.

Given the convincing personal and corroborative history provided by her mother and verified by outside medical records, it was felt that sleep diagnostic testing would be unnecessary. She was given the diagnosis of a recurrent central hypersomnolence syndrome.

Past Medical History: Apart from anxiety that developed from her sleepiness syndrome, the patient denied any pertinent medical history, particularly head injuries, past hospitalizations, or surgeries. She has no allergies to medications.

Medications: Venlafaxine.

Family History: There is no one in the family that has a sleep disorder. The patient's mother has mild anxiety.

Review of Systems: The patient has had increasing anxiety for the last few weeks with regard to future sleeping spells. The patient reports that she snores mildly, no witnessed apnea, dry mouth upon awakening, or snort arousals.

Examination/Mental Status Exam

Physical Exam

The patient looked comfortable, was alert and oriented, and did not appear tired or sleepy. On exam, her heart rate was 79 bpm, respiratory rate was 18 breaths per minute, and blood

pressure was 130/81 mm Hg. Her weight was 73.5 kg (162 pounds), height 172 cm (68 inches), and body mass index 24.6 mg/kg^2.

Her neck circumference was 38.1 cm (14 inches). Oropharyngeal examination revealed a Friedman tongue position 3. Thyroid was not enlarged.

There were no neurologic abnormalities.

Physical examination was otherwise normal.

Mental Status Examination

The patient did not exhibit any deficits in memory, attention span, or speech.

Her mood was euthymic, not depressed; her affect seemed mildly anxious but was congruent with her internal mood.

The language expression and fund of knowledge were within normal limits.

Thought process was logical, with normal rate and content.

There were no abnormal psychotic thoughts or hallucinations.

Her level of insight, judgment, and motivation was assessed to be good.

There was no preoccupation or verbalization of suicidality or passive death wishes.

Differential Diagnosis

- Narcolepsy without cataplexy [G47.419]
- Idiopathic hypersomnolence without long sleep time [G47.11]
- Multiple sclerosis [G35]
- Insufficient sleep syndrome [F51.12]
- Bipolar 2 disorder, depressed episode with mixed features [F31.81]
- Kleine-Levin syndrome [G47.13]

Special Studies

- Head MRI: normal.
- Thyroid studies.

Results

- TSH – 1.75
- Free T4–1.0
- T3, total – 157

Final Diagnosis

The patient's symptoms correlate with recurrent primary hypersomnia, highly suspicious for Kleine-Levin syndrome (KLS). KLS appears as recurrent sleepiness that lasts for weeks with complete return to baseline between episodes. The prevalence is estimated to be 1–2 per million with a predisposition for males to females in a ratio of 2:1. While the syndrome usually appears in the second decade, onset has been described in patients younger than 12 years and older than 20 years.

Other primary hypersomnias that may be considered include narcolepsy. While daytime sleepiness affects both, narcolepsy is not characterized by a return to normal levels of daytime wakefulness as compared to the KLS. Lesions in areas of the brain responsible for promoting wakefulness like multiple sclerosis or tumors that obstruct CSF flow in the third ventricle have also been observed with new onset sleepiness. These are readily distinguished by head imaging, and in our patient's case, head MRI was obtained and normal. Chronic sleep deprivation is not an uncommon reason for patients complaining of daytime sleepiness. In these cases, obtaining adequate sleep rapidly reverses hypersomnia symptoms. Encephalitic syndromes was also considered, but in the absence of other systemic symptoms and multiple hypersomnia episodes over several years, this was highly unlikely.

Symptoms of KLS may overlap with that of bipolar depression; however, this was unlikely as there was no history of hypomania or mania episodes in our patient. The irritability and occasional disinhibited behaviors that can appear similar to hypomania/mania or mixed episodes occurred exclusively in the hypersomnolence episodes, which when present in bipolar disorder occurs during fully wake states. Her depression occurred weeks after her first episode and worsened in the setting of hypersomnolence events. The depression during these events may be a consequence of the Kleine-Levin syndrome and due to losses that occurred because of the debilitating nature of the illness.

The patient also developed anticipatory anxiety due to worries that future events would cause major life disruptions and embarrassment from disinhibited behaviors.

In summary, this young female has symptoms highly suggestive of Kleine-Levin syndrome. Based on the onset of her events, the characterization of the events includes anorexia, irritability, and reduced long-term working memory following the episode. Moreover, return to baseline between the episodes is one of the hallmarks of this case.

General Remarks

The symptoms of Kleine-Levin syndrome (KLS) are characterized by their intermittent and periodic nature. Because KLS is rare, other conditions with similar symptoms are usually considered first, and the condition is usually a diagnosis of exclusion. When given the diagnosis, reassurance that the condition is real and manageable provides relief to the patient. In this case, we began pharmacotherapy with lithium based on existing literature that suggests its efficacy in reducing future events. We also recommended that she wear a medical identity bracelet that identifies her as having KLS and to notify her mother in the case she is found to be an altered mental state. Since having started lithium, the patient had one mild episode

lasting 2 days. She has been episode free for almost 2 years since starting treatment.

KLS usually occurs as a 2:1 ratio in males as compared to females. Episodes progress fairly rapidly from time of onset and reach their symptomatic period within 24 hours. The episodes themselves usually last between 1 and 3 weeks. The classic triad of hyperphagia, hypersomnolence, and hypersexuality is not always present. In a case series, only 45% of KLS patients had this triad. In our case, patient had anorexia and had no reported symptoms of hypersexuality. Although depression is not a core feature of KLS, some patients can become extremely upset during episodes, and it is important to monitor mood.

Treatment for KLS is limited to maintaining safety for the patient and supportive cares. A few studies support the use of lithium as preventative therapy demonstrating a decrease in both the duration and intensity of symptoms. However, it should be noted that none of the trials using lithium have been double-blinded or placebo controlled. A Cochrane review could not come to a conclusion for pharmacological recommendation because there was no study qualified for the inclusion criteria. Other mood stabilizers and antiepileptics studied have included valproic acid, carbamazepine, phenytoin, gabapentin, and lamotrigine. None of these have consistently demonstrated significant benefit. Antidepressants including tricyclics, selective serotonin reuptake inhibitors, and serotonin-norepinephrine reuptake inhibitors have not been shown to have any prophylactic effect. Stimulant medications including modafinil and methylphenidate are rarely helpful.

Pearls/Take-Home Points

Kleine-Levin syndrome (KLS) is often under-recognized and also misdiagnosed. When suspicion for KLS is raised, a thorough clinical evaluation should be performed, including detailed history from family members and a neurologic and psychiatric examination.

Additional studies may include PSG, EEG, drug screen, neuroimaging, as well as serological and CSF studies to rule out alternative diagnoses as clinically indicated.

Although controversial, lithium is used as therapy for prevention. However, in spite of the progress made in neuroscience, the search for the cause, genetic factors, pathophysiology, and drug treatment of KLS is still ongoing. There has been no definite conclusion for pharmacological treatments for KLS, and studies are difficult due to the rarity and complexity of the disease.

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Chapter 9
My Son Is a Night Owl. Can You Help?

Anna Wani, Elisa Basora, and S. Kamal Naqvi

Chapter Outline

- Identify key presenting symptoms of delayed sleep phase syndrome
- Understand how to delineate delayed sleep phase from other overlapping disorders
- Review treatment strategies for delayed sleep phase

Clinical History

A 14-year-old obese male was sent for evaluation for excessive daytime sleepiness. He was accompanied by his mother, who was concerned that her previously academically successful son was now falling asleep in all of his classes and

A. Wani
Department of Family and Community Medicine, UT Southwestern Medical Center, Dallas, TX, USA

E. Basora · S. K. Naqvi (✉)
Department of Pediatrics – Respiratory Medicine, UT Southwestern Medical Center, Dallas, TX, USA
e-mail: kamal.naqvi@utsouthwestern.edu

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unable to function at the level he was functioning prior. Symptoms started about 1 year ago, when she noted that he was sleeping a lot more than usual. On weekdays, she would send him to his room to sleep at about 9 p.m. – she would hear him up and moving about as late as 1 a.m. He was very difficult to arouse in the mornings for school, often running late. His teachers had also started to complain about him falling asleep in his classes – and his grades were declining rapidly. Apart from this, she reported that after school he was also taking naps and seemed only active in the night-time hours. Mom reported weekends were much better in terms of his functioning, as he could revert to his night owl pattern. As long as he could work at nighttime, his assignments and homework were being completed on time. The patient referred to himself as a "vampire." Mom reported that after teacher conference with one of his teachers, she noted that she had had her son as a student both in the morning and in the last period of the day. This patient's grades were significantly better when she had them in the last period of the day rather than the morning when he was mostly sleeping.

Examination/Mental Status Exam

Physical exam revealed a drowsy, obese young male with slow mentation, otherwise intact neurologic status. Pulse was 80 beats/minute, respiratory rate was 14 breaths/minute, and blood pressure was 100/60 mmHg. No increase work of breathing. The remainder of the cardiovascular exam was normal. His oropharynx was Mallampati grade I, tonsil size 1+.

Interview of the patient reveals a well-adjusted adolescent with a good social support network. He expresses his frustration about his poor performance at school and inability to stay awake at school. He wishes that the timing of school could be different so that he could perform as well as he knows he can.

Tests

- Sleep study
- Sleep log with actigraphy

Results

Sleep study shows oAHI 0/hour No clinically significant sleep apnea. Reduced sleep efficiency due to prolonged sleep latency. Abnormal sleep architecture due to lack of REM sleep on the study (Figs. 9.1, 9.2, and 9.3).

Sleep log	
Sunday	Thursday
In bed 10 p.m.	In bed 11 p.m.
Sleep 1 a.m.	Sleep 1 a.m.
Wake 6:45 a.m.	Wake 7:30 a.m.
Monday	Friday
In bed 9:30 p.m.	In bed 3 a.m.
Sleep 2 a.m.	Sleep 4 a.m.
Wake 6:50 a.m.	Wake 1 p.m.
Tuesday	Saturday
In bed 11 p.m. (nap from 4:30 p.m. to 8 p.m.)	In bed 5 a.m.
Sleep 3 a.m.	Sleep 5 a.m.
Wake 8:30 a.m.	Wake 1:30 p.m.
Wednesday	Sunday
In bed midnight	In bed 10 p.m.
Sleep 2 a.m.	Sleep 1 a.m.
Wake 6:30 a.m.	Wake 6:30 a.m.

Sleep log
Monday
In bed 11 p.m.
Sleep 2 a.m.
Wake 8 a.m.

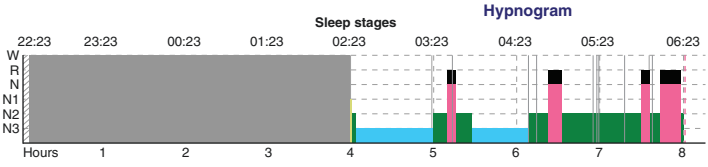

FIGURE 9.1 This is a hypnogram from the patient's sleep study. The figure highlights the prolonged sleep latency and decreased REM sleep noted on the recording. Of note, once the patient is finally able to sleep, he sleeps with minimal disturbances

Question

How would you treat this disorder?

D/D and Diagnosis

History and physical is important to delineate this disorder: delayed sleep phase syndrome. Treatment for this disorder includes low-dose melatonin in the evening, in addition to emphasizing consistent schedules on the weekdays and weekends. The use of bright light is more helpful in advance sleep phase; however, it can be tried for delayed sleep phase in the mornings for 30 minutes to 1 hour at desired wake time. It is important to know the patient's baseline sleep schedule so that bright light can be used after body temperature nadir.

Because this is a disorder that commonly presents in adolescence (16%), nighttime sleep patterns are not clear as

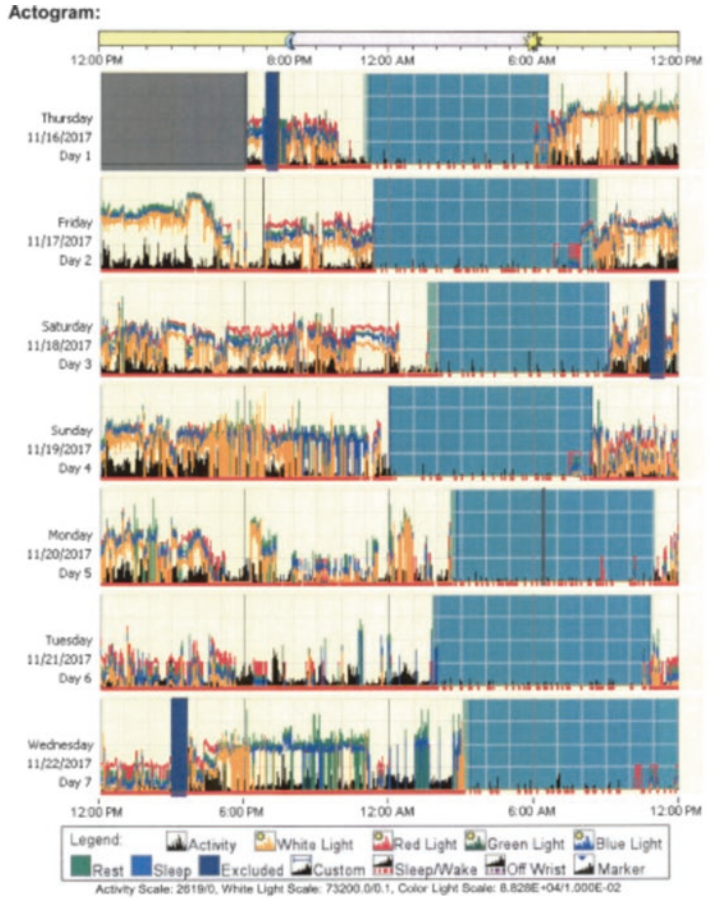

FIGURE 9.2 This is the first week of a 2-week actigraphy recording. Delayed sleep phase is very obvious, with average bedtime being well after midnight and wake typically not earlier than 10 a.m. in the earliest

parents are not as involved in sleep routines as younger children.

The differential diagnosis for delayed sleep phase is broad as it presents with excessive daytime sleepiness, perceived decreased attention, decreased functioning, and lack of motivation.

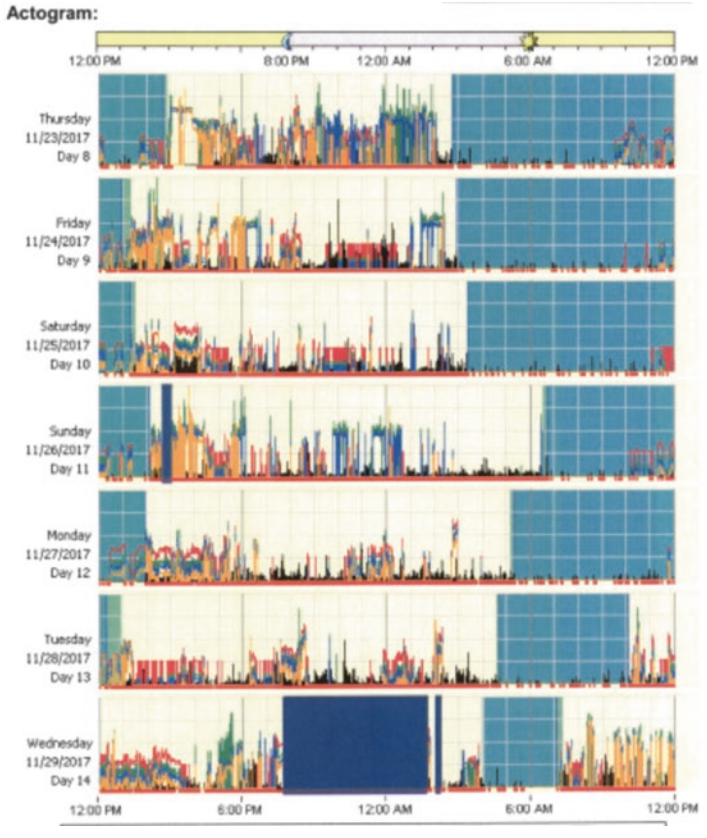

FIGURE 9.3 Second week of actigraphy recording. Highlights the persistent and consistent delayed sleep phase in this patient. The last 2 days of the recording seem to be when the patient attended school. He slept for an average of 3 hours each school night

Sleep-disordered breathing: Overlapping symptoms are excessive daytime sleepiness and decreased functioning. Parents are often not sure if their adolescent child snores. At times, a sleep study can be helpful to rule out sleep-disordered breathing as a contributing factor.

Hypersomnolence: Disorders of central hypersomnolence can also present as excessive daytime sleepiness during the day and perceived lack of motivation. The use of sleep logs actigraphy can be helpful to measure objective sleep times. It is important to know about delayed sleep phase prior to ordering an MSLT, as there can be SOREMs noted on an MSLT, in the first two naps as this is the normal time of REM onset and delayed sleep phase.

Atypical depression: Depression in adolescence is increasingly common. Atypical depression is characterized by excessive sleep, lack of motivation, and sometimes weight gain. A thorough mental status exam in addition to sleep logs, actigraphy, and depression inventory scales can be helpful to rule out depression.

Discussion

Given the prevalence of delayed sleep phase in the adolescent population, consideration must be given to altering what is the "normal" scheduled for this age group. A push for delayed school start times and alternate methods of education such as night classes, online school must be considered.

As medical practitioners, the question arises whether it is our responsibility to advocate for this already at risk population. Obtaining more sleep or adequate sleep is important for development, learning, and avoidance of mood disorders in adolescence.

A subtype of delayed sleep phase is motivated delayed sleep phase. This refers to the patient who is motivated to skate stays on the schedule to avoid coming to a "normal" schedule; this is usually related to secondary gain in terms of lack of accountability for school and other goals. In such cases, special consideration of alternate work and school schedules must be considered.

Pearls

- Delayed sleep phase is a prevalent problem in the adolescent population.
- A thorough history and physical as well as gathering of objective data is important prior to making the diagnosis and ruling out other overlapping diagnoses.
- Primary treatment of delayed sleep phase involves counseling about consistent sleep schedule and low-dose melatonin.
- As a medical community, we must consider petitioning for the adolescent population to push for adjusted school times given the pervasive nature of delayed sleep phase in the adolescent population.

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Chapter 10
Wandering in the Nursing Home

Candace Meinen, Bhanu Prakash Kolla, and Meghna P. Mansukhani

Clinical History/Case

An 82-year-old white man with a past medical history significant for hypertension, hyperlipidemia, coronary artery disease status post three-vessel coronary artery bypass grafting, and Alzheimer's disease (AD) residing in an assisted living facility presents with a chief complaint of nighttime wandering. He is accompanied by his daughter, who provides much of the history due to the patient's memory issues. She reports that his assisted living facility has stated that he will likely need to transition to a memory care unit if his nightly wandering does not resolve. He has left the care facility a couple of times in the last 6 months and has been found wandering into other residents' rooms at night. There seems to be no clear antecedents to this behavior with multiple days going by without these

C. Meinen · M. P. Mansukhani
Center for Sleep Medicine, Mayo Clinic, Rochester, MN, USA

B. P. Kolla (✉)
Department of Psychiatry and Psychology, Mayo Clinic, Rochester, MN, USA
e-mail: kolla.bhanuprakas@mayo.edu

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events occurring. Per his daughter, daytime sleepiness is also noted, with naps scattered throughout the day at any given time. Although the patient's daughter is uncertain as to the clear time frame of the onset of these symptoms, she thinks that they have been progressively worsening over the last year. The staff has not noticed any snoring or witnessed apneas when the patient is asleep. The patient is unable to provide a history regarding symptoms of restless legs syndrome or sleep-related breathing disorder. When asked about sleep-wake times, his daughter states that the assisted living staff was unable to report any consistent bedtime or wake times for the patient. Per staff, they try to maintain a bedtime around 9 p.m.; however, the patient seems to have difficulty sleeping at night and will nap in the daytime, sometimes up to four different times each day, for a variable duration of time. He is currently taking simvastatin 80 mg nightly, omeprazole 20 mg daily, carvedilol 6.25 mg twice daily, lisinopril 10 mg daily, tamsulosin 0.4 mg nightly, and donepezil 10 mg daily.

Examination/Mental Status Exam

Physical examination shows a blood pressure of 124/68 mmHg with a regular heart rate at 74 beats per minute. Body mass index (BMI) is 23 kg/m^2 and neck circumference is 37 cm. Examination of the oropharynx shows normal lateral and anteroposterior diameters without significant tonsillar hypertrophy. Friedman palatal position is class II. There is mild overbite and a 1 mm overjet noted. Cardiac examination is significant for a 3/6 crescendo decrescendo systolic murmur heard best at the right upper sternal border. Lungs are clear to auscultation. Mini-Mental Status Examination shows a score of 12/30.

Special Studies and Results

Patient Health Questionnaire 2 (PHQ2) was completed and was negative. A 2-week period of actigraphy was recommended given the unclear history, which showed concern for an absent circadian rhythm (see Fig. 10.1). Overnight

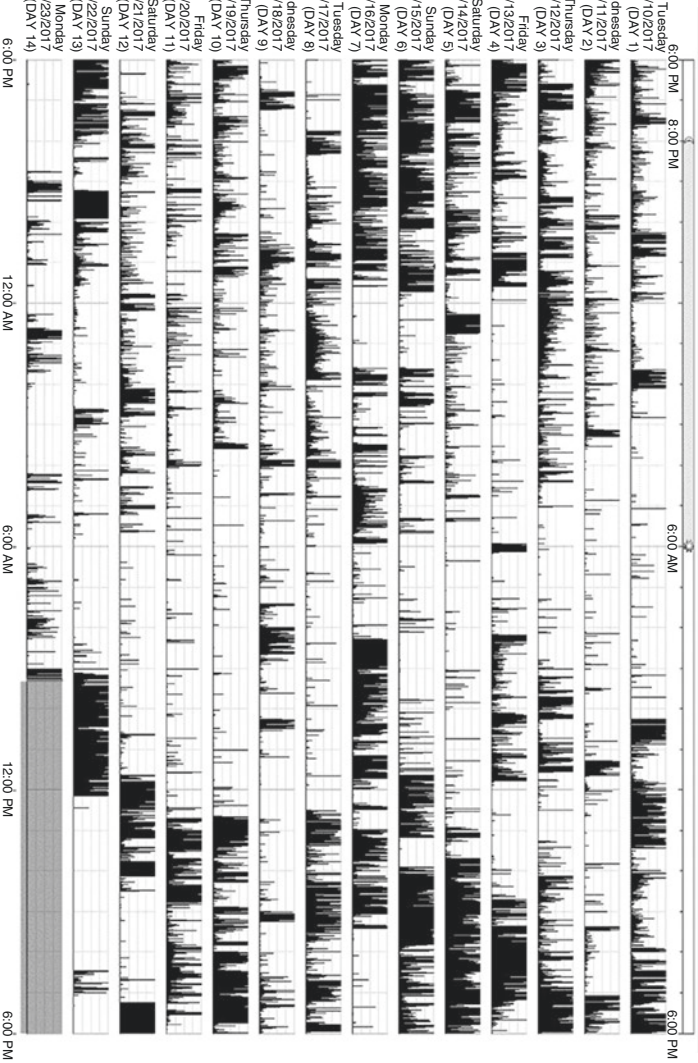

FIGURE 10.1 Two-week actigraphy showing irregular sleep-wake pattern with indiscernible circadian rhythm

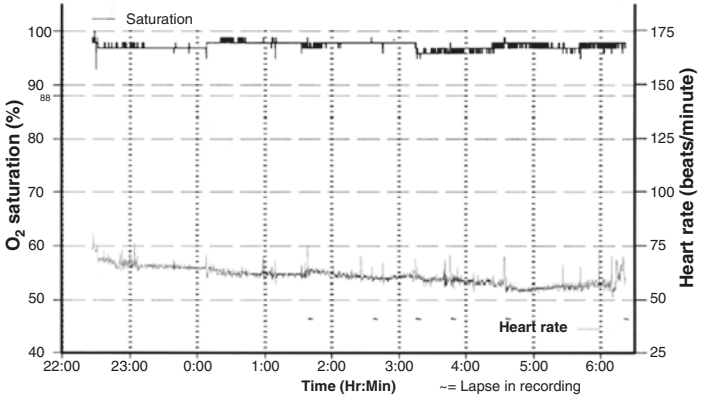

FIGURE 10.2 Overnight oximetry showing normal variations in breathing throughout the night without oscillatory changes concerning for sleep-related breathing disorder

oximetry showed a 4% oxyhemoglobin desaturation index of 1.5 per hour, without any significant oscillatory variation concerning for sleep-related breathing disorder (see Fig. 10.2). A serum ferritin level was obtained and was normal at 109 ng/mL.

Question

What is the cause of this patient's nighttime wandering and irregular sleep schedule and how can we best treat it?

Differential Diagnosis and Diagnosis

There are many possible causes of nighttime wandering in institutionalized patients with dementia and consideration should be given to the different possibilities described below.

Sleep-related breathing disorder (SRBD) with subsequent confusional arousals would need to be considered in individuals with risk factors for this, including a BMI greater than or

equal to 30 kg/m^2, increased neck circumference, crowded oropharynx, history of loud or frequent snoring, snort arousals, and/or witnessed apnea during sleep reported by family or staff members [1]. Studies have shown SRBD to be more prevalent in AD than in the general population [2]. An overnight oximetry screen can be performed to help rule out SRBD [3]. Overnight polysomnography or home sleep apnea testing may be needed if overnight oximetry is difficult to interpret or is suggestive of SRBD.

Restless legs syndrome (RLS) with nighttime wandering secondary to the urge to move the lower extremities should also be considered. A careful history should be taken from patients and caregivers regarding their nighttime routines. Symptoms of RLS may be difficult to elicit in patients with dementia, and if this is thought to be likely, measuring a serum ferritin level may prove helpful with diagnosis and treatment [4]. Although not specific for RLS, the presence of significant periodic limb movements noted on overnight polysomnography may provide supportive evidence for this diagnosis [5].

Delirium is another important consideration in patients with underlying dementia and nighttime wandering episodes [6]. Delirium has a prevalence rate of 1–2% in the general population and 14–24% in hospitalized individuals [7]. The diagnostic criteria for delirium per the *Diagnostic and Statistical Manual of Mental Disorders* 5th edition (DSM-5) require an acute change in consciousness or cognition with evidence that this is caused by a general medical condition. An abrupt change in sleep pattern in conjunction with an altered/fluctuating level of consciousness may indicate possible delirium. Causes of delirium are varied and can be multifactorial in nature including possible urinary infection, urinary retention, constipation, and medication side effects [7]. A detailed history and physical examination should be completed to help determine potential cause(s) of delirium if suspected.

Consideration must also be given to comorbid psychiatric illnesses such as anxiety and depression which can perpetuate insomnia and vice versa [8].

Environmental factors may also play a role in sleep disruption in institutionalized individuals, such as noise disturbance, lack of light exposure, decreased exercise, and limited intellectual stimulation [6, 9].

Substance- and medication-induced causes of sleep disturbance must be assessed. Excessive or evening intake of caffeine can contribute to sleep disruption in elderly patients. Adverse side effects of common medications may include insomnia. Donepezil, which is commonly used in patients with Alzheimer's dementia, can cause insomnia [10]. Medications with stimulating effects, such as theophylline, taken too close to bedtime can also result in insomnia [6]. A thorough review of medication lists should be performed.

Finally, a circadian rhythm disorder should be considered. Given the actigraphy results showing an absent circadian rhythm, the negative overnight oximetry screen, and the normal ferritin level, the most likely diagnosis in this case is irregular sleep-wake rhythm disorder (ISWRD), which is discussed further.

General Remarks

A robust and consistent circadian rhythm is an important component of normal sleep and is the driving force behind our regular, near 24-hour day/night cycle [6]. Dysregulation of this system in patients with neurodegenerative disease processes is thought to be related to degenerative changes in the suprachiasmatic nuclei of the hypothalamus which sets the body's biological clock. Changes in the body's ability to regulate its biological clock results in an irregular pattern of sleep [11, 12]. The behavioral changes secondary to sleep dysregulation are among the leading factors associated with institutionalization of patients with neurodegenerative disease processes [13].

Many different treatment options have been studied for ISWRD. Melatonin supplementation was thought to be an obvious choice given the likely degeneration of the suprachiasmatic nuclei and its effect on melatonin production [14]. However, a recent Cochrane review found no improvement

in sleep problems in patients with dementia who were given melatonin up to 10 mg nightly, and the most recent American Academy of Sleep Medicine (AASM) practice guidelines recommend against the use of melatonin for ISWRD in patients with dementia [15, 16]. The circadian rhythm task force of the AASM based their recommendation on the lack of evidence for improvement in sleep-related symptoms with melatonin and the possible side effect of worsening mood disorders in patients with dementia [16, 17].

The Cochrane review also analyzed the evidence for the use of trazodone and ramelteon in sleep disturbances in dementia. The studies on ramelteon, a melatonin receptor agonist, showed no improvement in sleep disturbances [15]. There was weak, low-quality evidence that trazodone resulted in an improvement in total nocturnal sleep time at a dose of 50 mg nightly for 2 weeks [15]. However, it did not affect the number of nighttime awakenings or the time spent awake after sleep onset [15]. The authors noted a lack of randomized controlled trials assessing benzodiazepines and nonbenzodiazepine hypnotics for sleep problems in dementia. Currently, the AASM practice guidelines recommend against the use of sleep promoting medications in ISWRD as the risks of these medications may outweigh any possible benefits [16].

Atypical antipsychotics have also been utilized in these clinical situations. However, there is evidence of an increased risk of sudden cardiac death in patients with dementia treated with atypical and typical antipsychotic medications [18].

Behavioral management strategies such as distraction and redirection have been employed as well as environmental changes, such as implementing an exercise program, strategic avoidance of light, and sleep-wake schedule prescriptions. One randomized controlled trial analyzed the benefit of implementing an exercise program along with reduction of nighttime noise and light disruption in a nursing home setting, compared to the control population who did not receive these interventions [19]. The researchers found that the use of these interventions led to an increase in the percentage of time spent asleep and a decrease in daytime agitation [19]. Another randomized controlled trial assessed the effects of an exercise

program combined with sleep hygiene education and increased light exposure consistent with phototherapy in patients with Alzheimer's dementia [20]. This combined intervention showed a reduction in time spent awake at night and a decrease in nighttime awakenings [20]. The AASM does not currently recommend for or against exercise programs as a treatment for ISWRD and recommends against combined therapies that utilize melatonin [16]. However, given the low risk associated with these behavioral strategies, they can be considered as treatment options in individual patients.

Phototherapy is the only evidence-based therapy in adult patients that is currently recommended by the AASM practice guidelines. This consists of 2500–5000 lux white broad-spectrum light therapy for a 1–2-hour duration between 0900 and 1100 hours daily, for a duration of 4–10 weeks [16, 21, 22]. Two trials were reviewed by the task force regarding the use of phototherapy to treat ISWRD. Both study populations comprised of institutionalized patients with dementia [21, 22]. One study showed no difference in nighttime sleep duration or daytime wake activity on actigraphy after light therapy induction alone [22]. The other showed improvement in behavioral symptoms, including a decrease in wandering [21]. Phototherapy, however, may be labor- and time-intensive for some individuals. It can be associated with adverse side effects such as eye irritation and agitation [23, 24]. In view of these drawbacks, the benefits versus risks should be weighed carefully before recommending this treatment option.

Pearls/Take-Home Points

1. When assessing an elderly patient with sleep complaints, it is important to consider a broad differential diagnosis.
2. Behavioral management strategies may offer some benefit and could be considered as low-risk treatment options.
3. Phototherapy appears to be of the greatest benefit in treatment of irregular sleep-wake rhythm disorder.

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Suggested Reading

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Chapter 11
My Grandmother Falls Asleep Watching TV. Is She Depressed?

Candace Meinen, Bhanu Prakash Kolla, and Meghna P. Mansukhani

Clinical History/Case

A 91-year-old white woman with a past medical history significant for sick sinus syndrome, status post permanent pacemaker implantation, systemic hypertension, mild mitral valve regurgitation, osteoporosis, and mild cognitive impairment residing in an independent living facility presents with a chief complaint of excessive sleepiness, particularly in the evening hours. She is accompanied by her granddaughter, who supplements history. The patient states she has difficultly staying awake in the evening hours. She usually falls asleep on the couch while watching television after dinner for a variable amount of time. She goes to bed at 9:30 p.m. She denies difficulty falling asleep but notes difficulty staying asleep, with early morning awakening around 3 a.m. She states that

C. Meinen · M. P. Mansukhani
Center for Sleep Medicine, Mayo Clinic, Rochester, MN, USA

B. P. Kolla (✉)
Department of Psychiatry and Psychology, MayoClinic, Rochester, MN, USA
e-mail: kolla.bhanuprakas@mayo.edu

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she feels refreshed upon awakening but begins to feel drowsy in the late afternoon with an Epworth Sleepiness Scale score of 14 out of 24. She does not have a bed partner, but her granddaughter denies hearing snoring or noting pauses in her breathing when she visits in the evening. She denies all other sleep complaints. Her granddaughter has been researching this issue on the internet and is worried about possible depression. The patient denies feelings of low mood or hopelessness. She states she still finds enjoyment in her activities but is worried about her ability to participate in evening activities due to her sleepiness. She is currently taking alendronate 70 mg once weekly, simvastatin 40 mg nightly, lisinopril 40 mg daily, ginkgo biloba 40 mg three times daily, calcium 600 mg daily, and vitamin D 2000 IU daily.

Examination/Mental Status Exam

Physical examination shows a blood pressure of 108/56 mmHg with a regular heart rate and rhythm at 60 beats/minute. Body mass index (BMI) is 21 kg/m^2 and neck circumference is 34 cm. Examination of the oropharynx shows normal lateral and anteroposterior diameters without significant tonsillar hypertrophy. Friedman palatal position is class II. There is mild overbite without overjet noted. Cardiac examination is significant for a 2/6 holosystolic murmur heard best at the apex. Pacemaker pocket is present on the left chest wall. Lungs are clear to auscultation. Mini-Mental Status Examination shows a score of 21/30.

Special Studies and Results

Patient Health Questionnaire 2 (PHQ2) was completed and was negative. A 2-week sleep diary was recommended which showed sleeping during the late afternoon and early evening hours with early morning awakenings (see Fig. 11.1). Overnight oximetry showed a 4% oxyhemoglobin

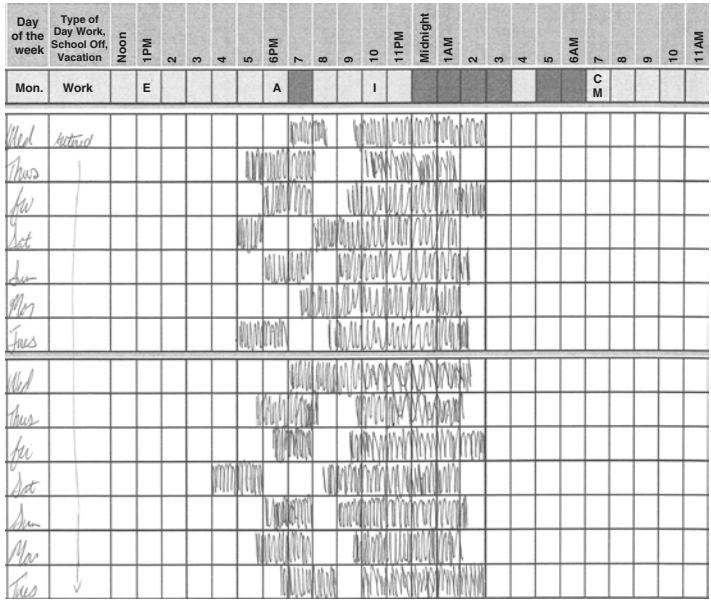

FIGURE 11.1 Two-week sleep diary

FIGURE 11.2 Overnight oximetry showing normal variations in breathing throughout the night without oscillatory changes concerning for sleep-related breathing disorder

desaturation index of 0.0/hour, without any significant oscillatory variation concerning for sleep-related breathing disorder (see Fig. 11.2). A serum ferritin level was obtained and was normal at 83 ng/mL.

Question

What is the cause of this patient's excessive daytime sleepiness, and how can we best treat it?

Differential Diagnosis and Diagnosis

Excessive daytime sleepiness can have a substantial effect on an elderly individual's functional status, cognitive function, incidence of falls, and cardiovascular events [1–4]. Elderly individuals are already prone to feelings of isolation and functional decline which can increase the risk of development of depression as they age [5]. This can be worsened further by the feeling of "missing out" on daytime activates and socialization due to excessive sleepiness. Determining the cause of their excessive daytime sleepiness and initiating treatment could potentially lead to a better quality of life in the elderly.

Sleep-related breathing disorder (SRBD) with subsequent excessive daytime sleepiness would need to be considered in individuals with risk factors for this, including a BMI greater than or equal to 30 kg/m^2, increased neck circumference, crowded oropharynx, history of loud or frequent snoring, snort arousals, and/or witnessed apnea during sleep reported by family or staff members [6]. Studies have shown SRBD to be more prevalent in the elderly population than in the general population [7]. An overnight oximetry screen can be performed to help rule out SRBD [8]. Overnight polysomnography or home sleep apnea testing may be needed if overnight oximetry is difficult to interpret or is suggestive of SRBD.

Restless legs syndrome (RLS) with frequent or prolonged nighttime awakenings secondary to the urge to move the lower extremities should also be considered in a patient with excessive daytime sleepiness. A careful history should be taken from patients regarding their nighttime routines. Symptoms of RLS may be difficult to elicit, and if this is thought to be likely, measuring a serum ferritin level may

prove helpful with diagnosis and treatment [9]. Although not specific for RLS, the presence of significant periodic limb movements (PLMs) noted on overnight polysomnography may provide supportive evidence for this diagnosis [10]. PLMs in isolation, i.e., without associated RLS, if accompanied by significant sleep fragmentation, can also result in excessive daytime sleepiness.

Consideration must be given to comorbid psychiatric illnesses, especially depression, which can present with symptoms of early morning awakening and excessive daytime sleepiness [11]. Depression has been shown to cause advancement of the sleep-wake cycle and has been linked to increased mortality in the elderly population, thus making it important to diagnose and treat in this population [11, 12]. Multiple tools have been developed to screen for depression in the general population including the PHQ2, which has been demonstrated to have reasonable sensitivity with the addition of the PHQ9 questionnaire if positive [13]. A specific geriatric depression screening tool, called the Geriatric Depression Scale (GDS), has been shown to adequately screen for depression in the elderly population [13]. Currently, the United States Preventive Services Task Force (USPSTF) recommends screening all adults, regardless of risk factors, for depression but does not recommend a specific tool for screening [14]. If depression is a concern, screening for this with either the PHQ2 or the GDS would be appropriate.

Insomnia, particularly maintenance insomnia, resulting in early morning awakening and curtailed sleep duration with consequent daytime sleepiness, should also be part of this differential diagnosis. A good history can help distinguish insomnia from other sleep disorders. The use of a sleep diary and actigraphy can also be useful in further evaluation [15].

Substance- and medication-induced causes of excessive daytime sleepiness must be assessed. Adverse side effects of many common medications include sedation. A thorough review of medication lists should be performed.

Finally, a circadian rhythm sleep-wake disorder should be considered in the differential diagnosis of excessive daytime

sleepiness. Given the findings on the sleep dairy, the negative overnight oximetry screen, and the normal ferritin level, the most likely diagnosis in this case is advanced sleep-wake phase disorder (ASWPD), which is discussed further.

General Remarks

Advanced sleep-wake phase disorder (ASWPD) remains a rare condition and is mainly seen in the elderly population with an estimated prevalence of 1–7% [16]. The suprachiasmatic nucleus (SCN) of the hypothalamus regulates the endogenous clock or circadian rhythm [17]. Increasing age appears to impair normal clock function [17]. Multiple studies have shown the effect that aging has on sleep-wake, hormonal, temperature, and various other physiological rhythms in humans [17–20]. Dijk et al. showed that earlier wake times in the elderly population were associated with 1-hour advancement in core body temperature rhythm and melatonin production [20]. Other causes of AWSPD have been linked to decreased light exposure in evening hours and familial variants [16]. The circadian rhythm is further affected by entrainment through external input which has been shown to be affected by the development of cataracts causing decreased responsiveness to light [21].

Multiple treatment modalities have been assessed. Chronotherapy, consisting of prescribed sleep-wake scheduling was assessed in a case report by Moldofsky et al. [22] A nursing home resident with known AWSPD underwent delay of his bedtime by 3 hours every 2 days over a 2-week period and was able to discharge home, symptom-free [22]. This was able to be maintained on a 5-month follow-up visit [22]. However, chronotherapy can be difficult to comply with long term and can be time-intensive for the patient.

Along with sleep-wake scheduling, timed physical activity has been suggested for ASWPD. There is little data in the medical literature to support its use [23]. However, possible side effects of this therapy would be minimal, and physical

activity would likely be recommended with other comorbid disorders as well.

Treatment with melatonin could theoretically help with delay of the sleep-wake phase given the interaction between melatonin administration and changes in circadian rhythm. However, to date, there have been no systematic studies assessing this relationship in ASWPD, and currently the American Academy of Sleep Medicine (AASM) task force on the treatment of circadian sleep-wake disorders lists the administration of early morning melatonin as an optional treatment for ASWPD without supportive evidence [23].

Phototherapy has also been attempted with some promising results. It should be noted that many of the favorable studies assessed the benefit of phototherapy in subjects with insomnia without a clear diagnosis of AWSPD [23]. One randomized control trial assessed the effects of white broad-spectrum light at 265 lux compared to dim red light at 2 lux and showed no significant difference in outcomes including change in circadian phase [24]. The largest effect with phototherapy was seen in a study conducted by Campbell and colleagues assessing the effect of bright white light at 4000 lux versus dim red light at 50 lux in 16 patients with AWSPD during the evening hours [25]. There was a significant increase in total sleep time and concomitant delay in circadian phase [25]. Phototherapy, however, may be labor- and time-intensive for some individuals. It can be associated with adverse side effects such as eye irritation and agitation [26, 27]. Currently, the AASM practice guidelines provide a weak recommendation for the treatment of ASWPD with evening light therapy [23].

Pearls/Take-Home Points

1. Excessive daytime sleepiness may be an important factor affecting the health as well as quality of life of the elderly, and further work-up should be completed if this is distressing to the patient.

2. Depression has been linked to an increase in mortality in the general population, and screening for a mood disorder when patients present with sleep complaints is an essential part of the work-up.
3. Advanced sleep-wake phase disorder can be difficult to diagnose, and a thorough history to rule out all other possible causes is important.
4. Phototherapy appears to be of the greatest benefit in treatment of advanced sleep-wake phase disorder.

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Chapter 12
Severe Sleep Disruption in PTSD: Trauma-Associated Sleep Disorder

Matthew S. Brock, Vincent Mysliwiec, and Sean Shirley

Clinical History/Case

The patient is a 45-year-old retired US Army Master Sergeant with post-traumatic stress disorder (PTSD) and mild traumatic brain injury (TBI) referred to the sleep disorders center for nightmares as well as difficulty falling and staying asleep.

Sleep-Wake History

The patient reports a bedtime of 2100 with a sleep-onset latency of 45 minutes. On most nights, he wakes up approximately 3 hours after falling asleep feeling panicked secondary to one of his nightmares. Upon awakening he is often drenched in sweat, breathing rapidly, and feels his heart racing and pounding in his chest. He usually calms down and

M. S. Brock · V. Mysliwiec (✉) · S. Shirley
Department of Sleep Medicine, Wilford Hall Ambulatory Surgical Center, JBSA Lackland USAFB, San Antonio, TX, USA

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falls back asleep but often has a similar awakening from a second nightmare. He leaves bed at 0400. The patient's Insomnia Severity Index is 28/28 consistent with severe insomnia, Epworth Sleepiness Scale score of 19/24 indicating severe sleepiness, and Pittsburgh Sleep Quality Index of 20 classifying his sleep as poor in quality.

While stationed in Japan several years prior to presentation, he was diagnosed with mild obstructive sleep apnea (OSA). His OSA is well controlled on continuous positive airway pressure (CPAP) at 6 cm H_2O. For the difficulties falling and staying asleep, his psychiatrist prescribed trazodone 50 mg at bedtime and zaleplon 10 mg. Neither of these medications has improved his sleep. He attributes his insomnia to his nightmares, which are a major source of daytime and nocturnal anxiety. His anxiety has been refractory to clonazepam, which he previously took at night, but now takes only in the morning.

During his military career, the patient had five deployments (Philippines, Africa, Afghanistan, Pakistan, and Iraq). He reports his nightmares began in 2011 (approximately 6 years ago) following a combat deployment to Iraq. They occur almost nightly and are all combat-related. What follows is a description of his most common nightmares that are replicative of his deployment-related experiences:

- Nightmare #1: In his most frequent nightmare, the patient is standing outside of a prison where Taliban fighters are detained. One of the prisoners eludes his guard and escapes. After getting outside, the prisoner runs at the patient, who is caught off guard. The patient reaches for his sidearm and begins yelling at the prisoner to "get the f*** down," "you come any closer and I am going to shoot you in the forehead you motherf***er." Prior to getting his gun in position, the prisoner is shot by another soldier and falls dead, approximately 10 feet from the patient.
- Nightmare #2: Another nightmare involves an unfortunate day when the patient's unit was hit by a mortar attack, rendering him momentarily unconscious. Following the blast, the patient regains consciousness and finds himself

mostly uninjured, though his ears are ringing and his lungs are filled with smoke. He crawls in bloody dirt, obstructed by loose stones and body parts. Nearby, a young Captain is badly wounded and virtually unrecognizable due to a missing arm and leg and shrapnel lodged throughout his face, torso, and remaining limbs. The patient did not have formal medical training, but makes tourniquets from his clothes. Upon finishing the tourniquets, the patient holds the Captain in his arms, and the wounded Captain dies shortly thereafter.

- Nightmare #3: In this nightmare, he finds himself at the site of a plane crash in Iraq moments after it occurs. The patient helps carry bloody mutilated bodies off of the plane and puts the corpses in large black bags before placing the bags on ice. He yells out at other nearby soldiers that "we gotta move quick" and "we gotta get these bodies out of here."

The patient's bed partner reports that he has disruptive nocturnal behaviors 4–5 nights per week associated with his nightmares. These behaviors include thrashing, defensive posturing, punching, and vocalizations that range from indecipherable moaning to yelling phrases laced with expletives. The patient always remains in bed and has not caused injury to his bed partner, though she builds a wall of pillows between them.

Psychiatric History

He was diagnosed with PTSD following his deployment to Iraq as well as depression and anxiety. He suffers from frequent suicidal ideation as well as deep survivor's guilt, particularly in relation to the young Captain he tried to save. He regularly sees a psychiatrist and psychologist, and in addition to clonazepam for his anxiety, he was prescribed duloxetine for depression. Notably, the duloxetine was started several years after the patient began having nightmares and disruptive nocturnal behaviors. For his nightmares, imagery

rehearsal therapy (IRT) was attempted but discontinued as it led to heightened anxiety. Previous use of clonazepam at night did not improve his nightmares or disruptive nocturnal behaviors. Prazosin was not attempted due to a history of vasovagal syncope and frequent lightheadedness.

Examination/Mental Status Exam

The patient is 67 inches tall and 164 lb. His appearance is appropriate with good hygiene, but he appears anxious, avoids eye contact, and never appears at ease. He is alert and oriented to person, place, and situation with intact immediate and delayed recall. His speech is spontaneous, clear, and relevant without obvious cognitive impairment. His mood is depressed and affect congruent. His thought processes are logical and content relevant with good judgment and insight. He has no suicidal or homicidal ideation at this time. His neurologic exam, performed by a neurologist, was normal with the exception of enhanced physiologic tremor of his hands bilaterally.

Special Studies

Polysomnography (PSG): A PSG was performed with the patient on CPAP. His sleep apnea was well controlled with a residual AHI of 0/hour. Lights out was at 23:11 with sleep latency = 33 minutes, total recording time = 410 minutes, total sleep time (TST) = 356.5 minutes, and sleep efficiency = 86.9%. His wake after sleep onset was 20.5 minutes, and he spent 21 minutes in stage N1 (5.9% of TST), 217 minutes in stage N2 (60.9% of TST), 60 minutes in N3 (16.8% of TST), and 58.5 minutes in stage R (16.4% of TST). His arousal index = 3.7/hour with eight arousals during REM sleep. No complex behaviors occurred with his arousals. During REM sleep there was prominent REM sleep without atonia (RWA). On review of the video portion of the PSG, the patient moved his legs on two occasions as well as his arm and his foot.

Relative tachycardia (>10 beats/minute increase) was observed during one of these episodes. No epileptiform activity was observed in the electroencephalogram.

Neuroimaging: A brain MRI with and without gadolinium was performed and was unremarkable with no evidence of acute or evolving intracranial process.

Question

Are the patient's replicative trauma-related nightmares (TRN) with associated disruptive nocturnal behaviors and autonomic hyperactivity consistent with an established REM-related parasomnia, or do the aggregate of symptoms represent a novel sleep disorder?

Differential Diagnosis and Diagnosis

The patient's constellation of symptoms leads to a differential diagnosis that includes several sleep disorders.

REM Sleep Behavior Disorder

Patients with REM sleep behavior disorder (RBD) present with vivid, often violent dreams and dream enactment behavior that may be injurious to the patient and bed partner. This disease classically occurs in older adults and is associated with neurodegeneration, specifically α-synucleinopathies such as Parkinson's disease. Dream enactment behavior is frequently captured on a single video PSG. Despite vigorous movements there is a relative paucity of sympathetic output (i.e., no increase in heart rate). Clonazepam is the drug of choice for treatment of RBD, reducing injurious behaviors. Dreams in RBD are not temporally related to trauma and not replicative of prior events. In this case, the patient is relatively young with no evidence of a neurodegenerative disorder. Additionally, dream enactment behavior was absent on PSG,

and autonomic hyperactivity is reported frequently at home and was observed on PSG. Regarding treatment, the patient's nightmares and disruptive nocturnal behaviors did not respond to nocturnal dosing of clonazepam.

Medication-associated RWA is reported with antidepressants, specifically serotonin reuptake inhibitors (SSRI), serotonin-norepinephrine reuptake inhibitors (SNRI), and tricyclic antidepressants. The patient in this case was taking duloxetine, an SNRI. However, while RWA is increased in patients taking SSRI or SNRI, patients on these medications are not at an increased risk for disruptive nocturnal behaviors or RBD. Additionally, the patient in this case reported his nightmares, and disruptive nocturnal behaviors began prior to starting the SNRI.

Nightmare Disorder

In nightmare disorder, another REM-related parasomnia, patients suffer from recurrent disturbing dreams that often result in awakening and cause clinically significant distress or impairment in social or occupational functioning. Nightmares are not associated with nocturnal movements or disruptive nocturnal behaviors, and autonomic hyperarousal is minor or absent, even during highly disturbing dreams. In this case, the patient is suffering from replicative TRN, but his often-violent disruptive nocturnal behaviors and surges of sympathetic activity evidenced by his nocturnal hyperhidrosis, tachycardia, and hyperventilation are not consistent with nightmare disorder.

Other Sleep Disorders

Severe OSA may mimic RBD with symptoms of dream enactment behavior, nightmares, and vocalizations. However,

RWA is not a feature of severe OSA, and treatment with CPAP leads to resolution of RBD-like symptoms. In this case, the patient's mild OSA is adequately treated with CPAP. Periodic limb movement disorder (PLM) is frequently reported in patients with PTSD. Movements of the arms and legs may be viewed as disruptive nocturnal behaviors by a bed partner, but the graphic vocalizations, autonomic hyperactivity, and replicative TRN cannot be explained by PLM. Nocturnal epilepsy can present with stereotypical complex behaviors and vocalizations; however, in this case, the patient's highly variable disruptive nocturnal behaviors and vocalizations are related to his nightmares, and there was no evidence of epileptiform activity on the patient's PSG.

Diagnosis: Trauma-Associated Sleep Disorder

The patient's constellation of replicative nightmares, autonomic hyperactivity, and disruptive nocturnal behaviors developing after trauma are consistent with a diagnosis of trauma-associated sleep disorder (TSD), a proposed novel REM-related parasomnia. Clinical features of TSD include an inciting traumatic event (often in the setting of sleep deprivation/disruption), altered dream mentation related to trauma, disruptive nocturnal behaviors including abnormal vocalizations or abnormal motor behaviors during sleep, and symptoms of autonomic hyperarousal during sleep including tachycardia, tachypnea, and diaphoresis (see Table 12.1). PSG may demonstrate RWA and/or rarely dream enactment behavior in REM sleep. As in this patient's case, the overall sleep architecture during an attended PSG may be relatively normal despite severe sleep disruption in their habitual sleeping environment.

Table 12.1 Proposed diagnostic criteria for TSD

1. Onset after combat or other traumatic experiences (often in the setting of sleep deprivation/disruption)
2. A history of altered dream mentation that is related to prior traumatic experience
3. Self or witnessed reports of disruptive nocturnal behaviors to include at least one of the following:
   (a) Abnormal vocalizations
      (i) Screaming or yelling
   (b) Abnormal motor behaviors in sleep
      (i) Tossing, turning, or thrashing
      (ii) Combative behaviors such as striking bed partner
4. Symptoms of autonomic hyperarousal or PSG monitoring demonstrate one of the following:
   (a) Tachycardia
   (b) Tachypnea
   (c) Diaphoresis
   (d) If documented on PSG, these findings are not due to sleep-disordered breathing
5. PSG may demonstrate:
   (a) REM sleep without atonia (variable amounts of RWA)
   (b) Dream enactment behavior in REM sleep
6. Absence of EEG epileptiform activity on PSG

Adapted from Mysliwiec et al. (2014); with permission

Results (Outcome of Case)

Following diagnosis, safety measures were instituted in the patient's bedroom including padding sharp corners around the bed. The patient was treated with prazosin and titrated up to 7 mg nightly. Above this dose, he experienced lightheadedness. While he continued to have nightmares, they were less severe and did not cause him distress. For example, in his plane crash nightmare, he loads corpses into bags, but there is no blood, and the action feels mechanical, as if he is on an assembly line. Further, his nightmares no longer awakened him, and his sleep was more refreshing. He also reported that

without his nightmares haunting him, he no longer has suicidal ideation. The patient's bed partner noted his disruptive nocturnal behaviors and vocalizations were decreased, occurring less than once per week and were less violent in nature.

General Remarks

After a traumatic experience, sleep disturbances are commonly reported. TSD encompasses the TRN, disruptive nocturnal behaviors, and autonomic discharges observed during sleep in trauma survivors. As in this case, the majority of reported cases consistent with TSD involve relatively young adult males, but it may occur in patients of any age or gender. The traumatic experience is typically extremely stressful, often occurring under intense duress for a prolonged period of time. In our patient's case, the inciting trauma was combat-related, but other forms of trauma including natural disasters or domestic abuse may incite TSD. Sleep deprivation/disruption likely contributes to the onset of TSD, and symptoms typically develop within weeks to months but may persist for years or even a lifetime.

Nightmares in patients with TSD tend to be replicative of the patient's traumatic experience and often include elements of death or dying, combat, and imminent threat to the patient's safety. The disruptive nocturnal behaviors accompanying the TRN are the most distinctive feature of TSD. Vocalizations ranging from grunting and mumbling to frank screaming and yelling expletives have been described. Movements including thrashing and tossing/turning may occur, or movements may be more purposeful, consistent with dream enactment behavior such as punching or choking a bed partner. Sympathetic nervous system hyperactivities including tachycardia, tachypnea, and night sweats are also usually present. On PSG, the most commonly observed finding is relative tachycardia during REM sleep in association with phasic RWA. Notably, the total amount of RWA may not be increased as it is suspected that RWA coincides with the

occurrence of nightmares with or without associated disruptive nocturnal behaviors. Though symptoms may occur frequently at home, nightmares and disruptive nocturnal behaviors are rarely captured during PSG. This phenomenon may be due to the fact that the monitored environment and presence of another person in the vicinity of the patient provide a sense of safety which may limit the probability of nightmare occurrence.

As in the case illustrated in this chapter, TSD patients may have other related medical problems such as TBI as well as sleep and psychiatric disorders. Both insomnia and OSA are frequently diagnosed in patients with TSD. These disorders are also diagnosed in patients with PTSD, and in fact, TSD and PTSD commonly co-occur. However, TSD and PTSD are distinct disorders that can be mutually exclusive. Specifically, TSD is exclusively a nocturnal disorder and has been reported in patients without a PTSD diagnosis. While nightmares are reported in up to 80% of patients with PTSD, TSD transcends the established definition of nightmares by the presence of disruptive nocturnal behaviors and autonomic hyperactivity.

The ideal therapy for TSD would target the underlying mechanisms responsible for the symptoms the patient experiences. While the neurobiological underpinnings of TSD require significant research, there is likely dysfunction in the neural network responsible for processing fear and controlling emotional processes during normal dreaming including the amygdala, medial prefrontal cortex, hippocampus complex, and anterior cingulate cortex. Additionally, hyperadrenergic activity that follows trauma leads to hypermetabolism in the locus coeruleus, excessive norepinephrine, and a nocturnal state of sympathetic hyperactivity that can cause tachycardia, diaphoresis, increased muscle tone (i.e., RWA on PSG), and disruptive nocturnal behaviors. This enhanced sympathetic activity may be counteracted by medications such a prazosin, an alpha-1-adrenergic receptor antagonist that is active in the central nervous system. Prazosin has been effective in reducing nightmares and TRN in combat veterans with PTSD and

has reduced the nightmares and disruptive nocturnal behaviors of patients afflicted with TSD. Notably, clonazepam, the treatment of choice for RBD, has not proven effective in reducing the symptoms of TSD. Ensuring the safety of the patient and bed partner by padding sharp corners, removing loose rugs, and locking up weapons is of the utmost importance. In severe cases, encouraging the bed partner to sleep separately may be warranted.

TSD is a complex disorder brought on by physiologic changes in the central nervous system following trauma. All trauma survivors should be specifically asked about nightmares and disruptive nocturnal behaviors as they are likely much more common than currently recognized. Comorbid sleep and psychiatric disorders and their treatments, including antidepressants, could potentially confound or exacerbate this diagnosis. Thus, an appropriate evaluation of trauma survivors, involving a multidisciplinary team, is required. Recognition of TSD as a unique parasomnia with distinct etiological, clinical, and treatment-based responses is essential to adequately address the severe nocturnal manifestations of this disease.

Pearls/Take-Home Points

- Sleep disturbances are common following a traumatic event and require a high index of suspicion to detect.
- Nightmares are an underrecognized cause of refractory sleep disturbances.
- Patients with nightmares and disruptive nocturnal behaviors require an attended in-lab PSG.
- In many cases, accurately detailing the frequency and nature of sleep disturbances related to trauma requires interviewing the patient's bed partner.
- Nightmares, including TRN, are rarely captured on PSG. This may be due to a perceived feeling of safety the patient experiences in a monitored environment, resulting in decreased hyperarousal.

- TSD is a proposed parasomnia that incorporates the TRN and disruptive nocturnal behaviors that occur following a traumatic event. The differential diagnosis for TSD includes RBD, nightmares, night terrors, and parasomnia, unspecified.
- Prazosin appears to be an effective treatment for the symptoms of TSD, whereas clonazepam, the traditional therapy for RBD symptoms, does not.
- Counseling both the patient and bed partner about potentially injurious behavior can prevent harm. A safe sleeping environment includes padding sharp edges around the bed, securing weapons or potential weapons, and sometimes having the bed partner sleep separately.

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Chapter 13
Zolpidem: The Arrested Woman with No Recollection of Events

Vijayabharathi Ekambaram and Britta Klara Ostermeyer

Clinical History/Case

Ms. Miller was a 35-year-old married, working mother of two boys. She worked as a paralegal for a large law firm and struggled with dual responsibility-related stress. Her husband, an engineer, fell at a construction site and was at home on medical leave, which put even more pressure onto Ms. Miller to earn a good salary to support her family.

Ms. Miller, who has no prior personal or family history of psychiatric or sleep disorders, saw her primary care physician (PCP) with complaints of stress and initial insomnia. Her PCP prescribed zolpidem 5 mg, one to two pills at bedtime as needed, when she could not fall asleep. The next evening, Ms. Miller took two zolpidem pills (5 mg each) for the first time in her life at around 11:00 p.m. At about 11:20 p.m., she was in her bed and asleep, as per her husband. The next morning at about 8:00 a.m., Ms. Miller awoke and found herself in police custody at the local police station with no recollection of how she got there.

V. Ekambaram · B. K. Ostermeyer (✉)
Department of Psychiatry and Behavioral Sciences, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA
e-mail: britta-ostermeyer@ouhsc.edu

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She was informed that she was driving while intoxicated at around 1:00 a.m. and hit and seriously injured a pedestrian. When police arrived, Ms. Miller was able to follow simple directions and complete the sobriety test; however, she was unsteady and fell down twice. Ms. Miller had no recollection at all the following morning of driving, injuring another person with her car, or having been arrested.

Physical Examination/Mental Status Examination

The police took Ms. Miller to a nearby emergency center (EC) for an evaluation as she convincingly insisted that she had no recollection of last night's events and mentioned that she had taken a new sleeping pill prescribed by her PCP for the first time. In the EC, Ms. Miller was cooperative and forthcoming with the examination and also requested that her husband be called. She was wearing a night gown, was disheveled, and was genuinely confused about last night's events. She exhibited no abnormal movements, and her gait was normal. She described her mood as "stressed out" and her affect was anxious. Her speech and thought processes were normal, and she stated no perceptual abnormalities and no suicidal or homicidal ideations. She was oriented to person, date, time, place, and situation, and her cognition was intact. She was able to name recent events in the popular media and was able to do serial 7 s correctly, and her abstract thinking was normal as well. She was 64 inches (162 cm) tall and weighed 115 lbs. (52.2 kg). Her BMI was 19.89 kg/m^2, and her vital signs were normal.

Results

Ms. Miller's forensic blood toxicology screen was positive for zolpidem with a level of 140 ng/mL and negative for alcohol. Her urine drug screen (UDS) showed presence of zolpidem

Table 13.1 Polysomnography of Ms. Miller

Lights out	23:30
Total recording time	530 minutes
Total sleep time	480 minutes
Sleep efficiency	90.5%
Sleep latency	10 minutes
Wake	50 minutes
Stage N1	95 minutes (19.8% of total sleep time)
Stage N2	270 minutes (56.3% of total sleep time)
Stage N3	15 minutes (3.1% of total sleep time)
REM	100 minutes (20.8% of total sleep time)

but no other drugs. Findings of brain CT scan, EKG, blood counts, and chemistries were within normal limits. Ms. Miller underwent a diagnostic polysomnography (PSG), and the results are shown in Table 13.1.

During the sleep study, Ms. Miller slept in all positions. Mild snoring but no obstructive events were noted. Oxygen saturation was maintained above 96% throughout the night, and normal REM sleep with atonia was maintained. There were no periodic limb movements seen, and EEG montage did not detect any epileptiform activity. The study documented normal sleep stage architecture, and no complex behaviors or non-REM parasomnias were noted.

Differential Diagnosis

Sleep walking and sleep-related, complex behaviors, including sleep driving or sleep eating, have been documented with zolpidem ingestion and other hypnotic sedative medications

for insomnia. Whether Ms. Miller's sleep driving and aberrant behavior is induced by zolpidem is the primary question of interest. To answer this question, we need to consider the following:

1. Personal history: Ms. Miller had no prior history of non-REM parasomnias (such as sleep walking or sleep terrors during childhood) nor did she have a history of alcohol abuse, illicit drug abuse, fever, or sleep deprivation. She did, however, have personal stress, which is one of the risk factors for zolpidem-induced sleep-related, complex behaviors (see Table 13.2). Her negative history for sleep-related behaviors and for substance use supports that Ms. Miller's sleep driving was zolpidem-related, so-called Z-drug-induced sleep-related, complex behavior.
2. Family history: Ms. Miller had no family history of any sleep disorders. Typically, in individuals with somnambulism, someone in the extended family has a positive history of non-REM parasomnias. Since Ms. Miller has no such family history, it is more likely that her sleep driving was zolpidem-induced.
3. Timing of episodes: Z-drug-induced-parasomnia starts typically within 3 hours of drug ingestion. Ms. Miller's events started at 1:00 a.m. (2 hours after her medication ingestion which was at 11:00 p.m.). This time of onset further supports Z-drug-induced-parasomnia.
4. Toxicology data: Urine and blood samples help to establish the presence of zolpidem in sleep driving cases. While urine samples can confirm the presence of the common metabolite "ZCA" (zolpidem carboxylic acid) for up to 72 hours after zolpidem ingestion, blood levels allow for timing and dose calculations, i.e., likely dose amount taken and likely time of ingestion [1, 2]. Ms. Miller's urine sample was positive, and her blood revealed a zolpidem level of 140 ng/mL, which confirms the presence of zolpidem and supports zolpidem-induced sleep-related, complex behaviors. Studies reveal that higher doses of zolpidem are more conducive of sleep-related, complex behaviors. Ms. Miller's higher zolpidem blood level also supports

that she suffered from sleep-related, complex behaviors when she was driving.

5. Sleep studies and other relevant data: Ms. Miller's PSG documented normal sleep stage architecture. PSG and other diagnostic studies, such as CT scans and brain MRIs, are not used as confirmatory tools for somnambulism unless there is a suspicion of other sleep disorders (sleep apnea) or neurological disorders. While the Food and Drug Administration (FDA) data indicates that zolpidem typically does not significantly change sleep architecture, it may decrease REM sleep, which then can cause a corresponding increase in non-REM stage [3, 4], thus placing patients at higher risk for non-REM parasomnias, including Z-drug-induced sleep-related, complex behaviors.
6. Cognitive function: As per clinic reviews of Pressman (2011), sleep driving is categorized into two conditions [5]. The first category, sleep driving, occurs as a variant of sleep walking disorder in individuals with a genetic predisposition or positive personal history of somnambulism. These individuals with such genetic predisposition are more susceptible to sleep driving when there is co-occurrence of priming factors, such as stress or sleep deprivation. During a sleep driving episode, when these typical sleepwalkers (with positive personal or family history) are confronted, they may become agitated or violent. For example, when police officers confront them, they are usually not able to interact appropriately, nor do they understand any requests or instructions, and are usually unable to perform sobriety tests [5]. The second category consists of individuals with sleep driving induced by so-called Z-drugs. These individuals usually do not have any positive family history or personal history of parasomnias. They are prone to these events when they take higher medication doses, mix medications with other CNS depressants (such as alcohol), or have other concomitant sleep disorders (such as sleep apnea). The occurrence of sleep-related, complex behaviors, such as driving, stops immediately after discontinuation of the Z-drug. Z-drug-induced sleep-related, complex behaviors differ from typical

sleep walking. Based on roadside reports during arrests, Z-drug-induced drivers typically have some degree of preserved cognitive function despite their anterograde amnesia. They are better able to interact and understand police officers' requests and can often perform sobriety tests. Unlike typical sleepwalkers, Z-drug-induced drivers were found to have flaccid muscle tone, poor motor control, dysarthria, lack of balance, and unsteady gait. These impairments are believed to be due to Z-drugs' actions on the $GABA_A$ receptor complex. Also, the degree of impairment usually correlates well to the Z-drug blood plasma level [5, 6]. In our case, Ms. Miller was able to interact and follow police officers' directions during her arrest and was able to pass the sobriety test. However, she did have some unsteadiness, fell, and also experienced anterograde amnesia. These findings are compatible with Z-drug-induced sleep-related, complex behaviors.

Final Diagnosis

Ms. Miller's history, signs, and symptoms are compatible with Z-drug-induced sleep-related, complex behaviors and not typical non-REM parasomnia sleep walking.

Discussion

Zolpidem (Ambien®) is an FDA-approved imidazopyridine hypnotic sleep medication which has been on the US market since 1992 [1]. While it is one of the most commonly prescribed medications in the USA, it has received growing attention for sleep-related, complex behaviors, including sleep walking, sleep eating, having sex while asleep, and sleep driving. In 2007, the FDA placed a specific warning on all hypnosedative sleep medication regarding sleep-related behaviors and abnormal thinking and behaviors, such as parasomnia-like behaviors, disinhibition, aggressiveness,

mood alterations, and anterograde amnesia. The incidence of such complex behaviors is approximately 5% [1, 7].

Zolpidem has become popular since it is thought to not greatly alter sleep architecture, is believed to have low rates of daytime sleepiness and a low abuse potential, and facilitates sleep onset within approximately 30 minutes with an average peak concentration at 90 minutes. While zolpidem binds to the $GABA_A$ receptor much like benzodiazepines, zolpidem is more selective to the α-1 receptor subtype, which was believed to cause more sedation with less memory impairment and less daytime sleepiness [1].

However, patients taking zolpidem show significant memory impairments and psychomotor performance problems at 1 and 4 hours after ingestion. Zolpidem does decrease REM sleep with a corresponding increase in non-REM time, which increases the risk of non-REM parasomnias since patients spend more time in non-REM sleep. Risk factors for parasomnia (see Table 13.2) are personal or family history of parasomnia as well as sleep deprivation, stress, fever, and alcohol or drugs. Of note, the risk for zolpidem-induced sleep-related, complex behaviors is dose-related, i.e., higher zolpidem doses increase the risk [1].

It is believed that zolpidem can cause three different sleep-related scenarios [1]: (1) After taking zolpidem patients may stay awake and exhibit disinhibition and hallucinations and may speak in coherent sentences but have anterograde amnesia for events. (2) Patients may fall asleep after taking zolpidem but then arouse from sleep while still under its influence. These patients may speak coherently but usually act out of character and also exhibit anterograde amnesia. (3) Zolpidem may also induce or aggravate parasomnias, such as non-REM stages 3–4 sleep walking, with incoherent sleep and purposeless actions.

Surprisingly, zolpidem can cause persistent hallucinations and sleep-related, complex behaviors when prescribed concurrently with antidepressants [8]. While the exact cause remains unclear, the hypothesis is that both zolpidem and antidepressants suppress REM sleep, which causes a cor-

responding non-REM sleep increase. As we know, sleep walking disorder is associated with an increase in slow wave sleep (stage 3 non-REM). Thus, it is postulated that the combination of zolpidem and antidepressants can create an increased amount of slow wave sleep and can occasionally cause a rapid entry into slow wave sleep [8, 9].

There is also a proposed theory [10] postulating that zolpidem can cause desensitization of $GABA_A$ receptors. This desensitization then creates increased activity of serotonergic neurons causing some delay in compensatory decrease in serotonin release through the autoregulatory mechanism regulated by $5HT_{1A1B}$ receptors. According to this model, the delay between desensitization of the $GABA_A$ receptors and a compensatory decrease in serotonin release can create a window of time for parasomnia occurrence. If during this window a short-acting hypnotic like zolpidem is given, there is possibility of dreamlike mentation or parasomnia occurrence depending upon autoregulation of serotonin release and upon individual differences in receptor desensitization. Therefore, additional caution should be applied when zolpidem is prescribed in combination with antidepressants [10].

There are several known potential risk factors which can induce Z-drug-induced sleep-related, complex behaviors, and Z-drug-prescribing clinicians need to be familiar with such risk factors (see Table 13.2).

According to zolpidem's drug prescription information, after the ingestion of a 5-mg dose of zolpidem, a mean peak concentration of 59 ng/mL (range 29–113 ng/mL) was found, and after taking a 10-mg dose of zolpidem, a mean peak concentration of 121 ng/mL (range 58–272 ng/mL) was found. For both doses, time to maximum concentration was 1.6 hours, and the drug half-life was approximately 2.6 hours. The SSRI fluoxetine prescribed concurrently with zolpidem increases zolpidem's half-life by 17%, while sertraline increases zolpidem's half-life by 43% [11, 12].

In 2013, the Food and Drug Administration (FDA) required zolpidem manufacturers to lower the approved dose of zolpidem based on data showing that higher morning blood levels in some people caused impaired driving and alertness. Thus, the FDA recommended that manufacturers

Table 13.2 Potential risk factors for Z-drug sleep driving

Risk factors
1. Concomitant ingestion of CNS depressants (alcohol, sedating medications) or antidepressants (SSRI, SNRI)
2. Concomitant sleep disorder (sleep disorder breathing or periodic limb movement disorder)
3. Personal history of parasomnia
4. Family history of parasomnia
5. Hypnotic sedative ingestion during stressful events, sleep deprivation, or agitated state
6. Hypnotic sedative ingestion at times other than habitual bedtime
7. Living alone
8. Individuals with cognitive impairment (dementia, delirium, intellectual disability) or with a history of poor management of pills

Modified and adapted from Poceta [12]

decrease the recommended dose of zolpidem in women, elderly, and debilitated patients to 5 mg due to slower zolpidem elimination rates in those populations [13].

Zolpidem also has received considerable forensic psychiatry and courtroom attention with a growing number of patients blaming their behavior either on "the pill made me do it" or on sleep walking [1]. Criminal defendants who used alcohol and/or illegal drugs at the time of their crimes are held responsible for their actions. Courts hold that people realize that such substances can negatively impact behavior, and the legal system does not intend for people to use voluntary intoxication as an excuse to escape the consequences of criminal behavior. However, prescription medication use may be considered for an involuntary intoxication defense and may render the defendant not culpable as long as the defendant can show that he/she had no prior knowledge of adverse reactions and behaviors at the time of ingestion [1]. It is important that a defendant prove that he/she indeed took the medication and was under the influence at the time of their crime(s) by obtaining blood and urine toxicology samples at the time of arrest. While urine samples can simply prove the presence of medication(s), blood levels can reveal plasma concentration, which then allows for

calculations of likely ingested medication amounts and medication concentrations at the time of the crime(s).

If the defendant is unable to prove that he/she involuntarily ingested the medication(s), he/she may argue a case of voluntary intoxication. While this still usually renders the defendant culpable, it may lower the severity of the charges, i.e., it may negate specific intent in a murder resulting in a lesser charge of manslaughter. Since Ms. Miller suffered from zolpidem-induced sleep-related, complex behaviors and had no prior knowledge that she would react idiosyncratically to zolpidem, she may qualify for an involuntary intoxication defense, therefore, potentially rendering her not culpable for driving under the influence and hitting a pedestrian with her car.

Pearls/Take-Home Points

- Z-drugs and other hypnotic drugs can induce sleep-related, complex behaviors, such as sleep driving and sleep walking.
- Z-drug drivers may present with some preservation of cognitive and social function, may interact appropriately, follow directions, and pass sobriety tests despite of their anterograde amnesia and unsteady gait.
- Urine and blood toxicology is necessary in establishing the diagnosis. Drug levels help determining 1) the likely time of ingestion and 2) the likely Z-drug amount ingested.
- While sleep studies are not used to confirm Z-drug-induced sleep-related, complex behaviors, they can help to rule out triggers, such as sleep apnea.
- Caution when prescribing zolpidem with an antidepressant as this combination can cause persistent hallucinations and sleep-related, complex behaviors.
- Although voluntary alcohol and illicit drug intoxication still render a person responsible for their actions, persons with Z-drug-induced sleep-related, complex behaviors may argue a case for involuntary or voluntary medication intoxication.

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Chapter 14
To Treat or Not to Treat: Case of SSRI-Induced RBD

Muna Irfan and Carlos H. Schenck

History

A 45-year-old married man without any history of sleep disorder gradually developed depressive symptoms for the first time in his life, without any identified precipitant. His wife of 24 years observed changes in his mood and activity level, as he became less interested in his usual activities, and his company became progressively less enjoyable for her, as he became reticent, kept to himself more and more, was less interested in physical intimacy, and had lost inter-

M. Irfan (✉)
Department of Sleep/Pulmonary, VA Minneapolis, Minneapolis, MN, USA

Department of Neurology, University of Minnesota, Minneapolis, MN, USA
e-mail: irfan007@umn.edu

C. H. Schenck
Minnesota Regional Sleep Disorders Center, Minneapolis, MN, USA

Department of Psychiatry, University of Minnesota, Minneapolis, MN, USA

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est in going out with friends. His wife urged him to see his physician, who found no medical basis for these mood changes, such as hypothyroidism, and so fluoxetine was prescribed for his apparent depressive disorder. Within 4 weeks, he was almost back to his usual self, as also noted by his wife, and so they were pleased to resume their normal lives. However, about 4 weeks later (8 weeks after starting fluoxetine, 20 mg q AM), he started having "wild and vivid dreams" of being confronted by aggressive strangers who wanted to steal his wallet or his car keys, and when they grabbed him, he hit them back, but he was actually striking his wife in bed. His wife noticed that besides his hitting or kicking her a few nights weekly, he was also beginning to moan and talk in his sleep every night. She also noted him to jerk his arms and legs while remaining asleep. A few months later, he started jumping out of bed while dreaming of escaping attackers, and he would periodically bruise himself while knocking over bedside objects and bumping into furniture. His wife started hearing him utter threats, make derogatory comments, and shout and swear in his sleep while apparently dreaming. Since his wife regularly observed that his eyes were closed during these episodes, it reinforced her assumption that he was asleep and dreaming and not willfully in control of his actions. Despite these marked changes in his sleep and dreams, the fluoxetine therapy continued to be effective in fully controlling his depression.

The wife was perplexed by these strange nighttime behaviors. While his demeanor and interaction with his wife were quite agreeable during the daytime, at night she started keeping pillows between them to dampen the impact of any violent movements, and sometimes she would sleep in a separate bed.

For the preceding few years, the patient had noticed some intermittent difficulty with constipation and alteration in his sense of smell. However, no one had ever observed a resting tremor or any postural or gait disturbances.

After mutual discussion, they approached his psychiatrist and were referred to a sleep physician.

The patient had no clinical history apart from his recently diagnosed depression that was fully controlled with fluoxetine, which had triggered his sleep and dream disturbances. He had mild snoring but no excessive daytime sleepiness. There was no history of restless legs, cataplexy, sleep paralysis, or hypnagogic/hypnopompic hallucinations. He did not smoke and was a moderate drinker, without any history of substance abuse. He and his wife were happily married and had three children. He was a computer architect who was successfully employed at a software company. His performance on various projects remained at his expected high level of proficiency without any concerns for lapses in memory and judgment. Similarly, at home, his spouse and children had not noted any decline in cognitive and functional domains.

Examination

During the clinical sleep interview with the patient and his wife, responses to a comprehensive questionnaire that included sleep, medical, neurologic, and psychiatric history and review of systems were reviewed.

His Epworth Sleepiness Scale score of 8/10 was normal. His Montreal Cognitive Assessment score was 30/30. His Patient Health Questionnaire (PHQ-9) score was 4, which indicated no depression. Upon interview, he was a pleasant and cooperative man. BMI was 29. Neck circumference was 17 inches. Oropharyngeal examination revealed Friedman Class III. No overjet was noted. Heart rate and rhythm were regular. Lungs were clear to auscultation. No peripheral edema was detected.

He interacted appropriately with his wife, who affirmed that he had always been a kind man without any tendency for emotional irritability, swearing, or violence. His nocturnal episodes of physically aggressive, profanity-laced, dream-enacting behaviors were in stark contrast to his usually calm and collected personality noted while he was awake. His wife expressed with consternation that he was “a different man now when he falls asleep.” The patient was very concerned and sought advice as to how to fix the problem.

Family History

The family sleep history involved a distant uncle who was diagnosed with Parkinson's disease (PD) at the age of 60. Interestingly, he used to thrash around in bed most nights while having "wild dreams" that closely resembled what was happening to the patient. Medication history and treatment outcome were not known in his case.

Video-Polysomnographic Findings

After the clinical encounter, it was decided to proceed with a video-polysomnogram (vPSG) with an extended electroencephalographic (EEG) montage and supplemental electromyographic (EMG) monitoring of the upper and lower extremities including bilateral anterior tibialis muscles. The PSG was attended by a sleep technologist, and recording was accompanied by continuous, time-synchronized, audiovisual monitoring. Total sleep time was 449 minutes, with 87% sleep efficiency. Sleep latency was 15 minutes and REM sleep latency was 85 minutes. Sleep stage distribution was normal and showed stage N1, 6%; stage N2, 49%; stage N3, 20%; and REM, 25%. Periodic limb movements (PLMs) were present in NREM sleep (15/hour) and, in REM sleep (10/hour), usually unassociated with any signs of arousal. There were no abnormal arousals from N3 sleep recorded. REM sleep was abnormal, with excessive transient muscle activity especially in the legs, and there was prominent loss of submental EMG atonia during all four REM periods, estimated to be present during >40% of total REM sleep 30-second epochs. Frequent bursts of high voltage, phasic EMG twitching with gross limb movements and complex behaviors were noted. Figure 14.1 illustrates a 30-second epoch of PSG recording showing excessive phasic muscle activity in the limb leads. These abnormalities became more frequent and intense with each successive REM period. He

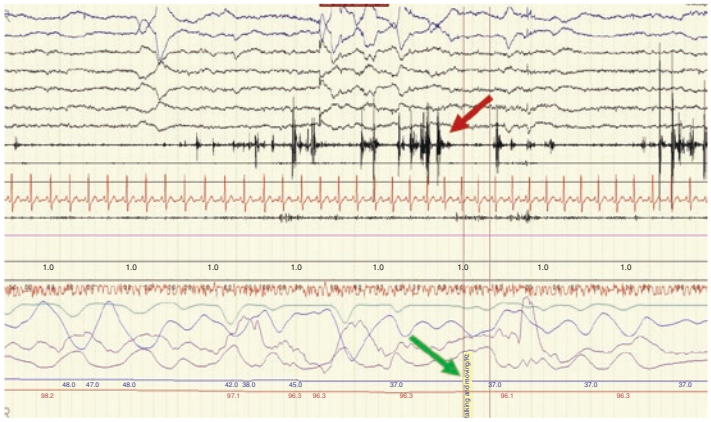

FIGURE 14.1 Illustrates PSG clip of increased muscle tone in chin EMG leads in REM sleep denoted by red. Green arrow denotes annotation by sleep technician when the patient talked and moved in REM sleep describing dream enactment behavior

would moan, holler, and shout, at times with expletives, while physically engaging in combative/defensive behavior, such as throwing punches, or crouching in bed apparently in combat against an assailant while dreaming. He often flailed his arms and kicked his legs with rapid jerky movements. Upon the sleep technologist's attempt to arouse him, he rapidly became alert and oriented and reported dreaming just before awakening. The dreams were "my typical dreams that I have at home, people or animals attacking or chasing me on a street, and I have to fight back or run for my life." He acknowledged shouting and swearing at his assaulters.

No sleep-disordered breathing was detected during the PSG (AHI <3/hour), and no clinical or electrical seizure-like activity was recorded. Upon awakening spontaneously in the morning, the patient reported feeling rested and was able to recall several of his vivid dreams. He thought that his sleep in the lab was representative of his usual sleep at home.

Differential Diagnosis

The differential diagnosis of dream-enacting behaviors includes REM sleep behavior disorder (RBD), NREM sleep parasomnias (sleepwalking, sleep terrors), high-magnitude and frequent periodic limb movements, and nocturnal seizures [1, 2]. Obstructive sleep apnea (OSA) can also mimic RBD, known as pseudo-RBD. It manifests as abnormal behavior with dreaming occurring during an arousal from increased respiratory effort at the end of an obstructive or hypopnea event [3]. In our case, the historical account, along with the clinical and PSG evaluations, did not uncover any diagnosis other than RBD as the cause of his violent sleep problems.

RBD is a parasomnia characterized by recurrent dream enactment during REM sleep marked by the neurophysiological substrate of increased EMG tone and/or increased phasic EMG twitching on the PSG. According to the International Classification of Sleep Disorders, 3rd Edition [ICSD-3] [4], both the clinical history of abnormal sleep behaviors (usually manifesting as dream enactment) and objective evidence of REM sleep without atonia (RSWA) are required to establish the diagnosis. The illustrative features in our case include increased EMG tone and increased phasic twitching in REM sleep, along with REM sleep behavioral findings which are diagnostic for RBD, consisting of vocalizations and complex, vigorous, and violent behaviors.

RBD in the elderly has a high association with future development of alpha-synuclein neurodegenerative disorders such as Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA) [1, 5–8].

While there are other neurological conditions that can be associated with RBD as well, especially narcolepsy type 1, medication-induced RBD is especially common in the adult population <50 years of age. In our case the occurrence of de novo dream-enacting behaviors after initiation of the SSRI agent fluoxetine points decidedly toward this being a case of SSRI-induced RBD. Also, it has been noted that

medication-induced RBD cases tend to have increased phasic EMG activity in the legs, predominantly in anterior tibialis leads, as illustrated in our case.

While there are some clinical features, such as diminished sense of smell, constipation, and a family history of PD with presumed RBD, which raise concern for RBD as a prodromal marker of a neurodegenerative disorder, the temporal onset of symptoms after administration of SSRI points toward antidepressant use as an inducing or unmasking factor. It is also supported by work from Postuma et al., who suggested that even though patients with antidepressant-associated RBD had a lower risk for neurodegeneration during the time period of their study, compared to idiopathic RBD patients not taking antidepressants, biomarkers of alpha-synuclein neurodegeneration were still found robustly in this antidepressant-associated RBD patient group. Thus, RBD emerging with antidepressant pharmacotherapy may be an early signal of an underlying alpha-synuclein neurodegeneration [9].

Clinical Approach

In an otherwise healthy man in his 40s with well-controlled depression who is diagnosed with RBD, careful consideration for clinical conditions, medications, and other risk factors known to induce or aggravate RBD should be undertaken. REM sleep atonia is vulnerable to a wide variety of insults, ranging from narcolepsy and its pharmacotherapy, psychotropic medications (TCAs, SSRIs, MAOIs, venlafaxine, mirtazapine), alcohol and stimulant abuse (and abstinence), and excessive caffeine/chocolate consumption in the evening. A wide variety of neurological disorders other than neurodegenerative diseases and narcolepsy can cause RBD. Any pathology or lesion can trigger RBD by compromising the brain stem neuronal centers and/or pathways subserving the REM atonia circuitry and/or by disinhibiting the circuitry for motor pattern generator activity in REM sleep [1, 5].

Patients aged 50 years or older diagnosed with RBD should undergo detailed neurologic history, examination, and neuropsychological screening and longitudinal neurologic follow-up to ensure early detection of signs of development of neurodegenerative disorder. Counseling of the patient and spouse about the risk of evolution to neurodegeneration is crucial and reiterates the need for yearly surveillance. It is currently unknown whether younger subgroups of RBD patients (e.g., younger adults, females, narcoleptics, medication-induced, alcohol/drug abuse-induced) are also at increased risk for future alpha-synuclein disorders. This applies to our patient who is in his 40s. With dose reduction of the offending antidepressant agent, or switch to a less offending agent, alleviation of RBD symptomatology can occur, although there have been cases where RBD may persist unabated. In cases of antidepressant-induced RBD in younger populations, the risk of phenoconversion is unclear, and so longitudinal follow-up is warranted.

Management

In our case, a detailed discussion about the diagnosis of RBD and the triggering role of an SSRI antidepressant agent was held with the patient and the spouse. He was also instructed to ensure the safety of his immediate bedside environment, such as moving any furniture or objects with sharp edges farther away from the bed and to make sure that the bed was not close to a window. After discussion, especially keeping the risk of injury to bedpartner in mind, the patient decided to follow the recommendation to taper off fluoxetine, in consultation with the treating psychiatrist. Bupropion, a dopaminergic-noradrenergic agent, was started at a dose of 150 mg in the morning, and after 3 days, the dose was increased to 150 mg twice a day with the second dose not to be taken after 6 p.m. due to a potential negative impact on sleep. A follow-up appointment in 3 months was scheduled, at which time the patient and his spouse thankfully reported that the nocturnal vocalizations and aggressive physical

dream enactment improved to only a few minor jerky limb movements at night. His mood remained non-depressed and pleasant, and so bupropion was an effective antidepressant that did not trigger RBD.

Our patient responded to switching off his antidepressant medication, but in certain clinical situations, dose reduction or substitution might not be possible. Careful consideration of the choice of antidepressant based on side effect profile and the risk-benefit ratio should be undertaken. While treatment guidelines for RBD induced by antidepressants are not well defined, we can extrapolate from guidelines suggested for typical RBD. The frontline treatment strategy is ensuring environmental safety (level A evidence according to AASM guidelines). Pharmacological treatment options include bedtime clonazepam, 0.5–1.0+ mg, and/or melatonin 3–15 mg (both level B) [10–12].

For RBD patients not responsive or intolerant to clonazepam or melatonin, dopaminergic agents can be considered as adjunctive therapy. Side effects from clonazepam therapy of RBD are uncommon but can include morning sedation, memory impairment, sexual dysfunction, and depression/personality changes. Melatonin can elevate blood pressure in some patients. Pramipexole carries a small risk for inducing paranoia and behavioral dyscontrol, which resolve with discontinuation of the medication. Other medications for treatment-resistant cases of RBD cited in case reports include clonidine, a potent REM-suppressing antihypertensive drug, tricyclic antidepressants (imipramine, desipramine), anticonvulsants (carbamazepine, gabapentin), and anticholinesterase agents (donepezil) [11].

Discussion

RBD, a potentially injurious parasomnia, is well established as a prodromal feature with prognostic implications for the future development of alpha-synuclein neurodegenerative disorders in adults ≥50 years of age [12–14]. There is an emerging body of literature suggesting the complex nature of

the association between RBD and psychiatric diseases and antidepressant use. The natural course and progression of RBD in psychiatric disorders and antidepressant use are not clearly established [15, 16].

Several studies have identified that antidepressant use can induce RSWA and increase the likelihood of RBD [13, 17]. Table 14.1 lists some of the incriminating antidepressants. Winkelman et al. postulated that RBD induction in patients

Table 14.1 Antidepressants associated with RBD [13, 18–28]

A	SSRIs
	Fluoxetine
	Sertraline
	Paroxetine
	Escitalopram
	Citalopram
B	TCAs
	Imipramine
	Clomipramine
	Amitriptyline
	Nortriptyline
C	Mixed mechanisms (including SNRIs)
	Mirtazapine
	Venlafaxine/desvenlafaxine
	Duloxetine
D	MAO inhibitors
	Phenelzine
	Selegiline
E	Antipsychotics
	Quetiapine

with antidepressants could be attributed to serotonergic activity and its potential influence on REM tone indirectly at the brain stem level and directly at the spinal level [26]. One study showed the presence of RBD in 10% of depression patients after treatment with sertraline as compared to 3% before treatment [27]. Another study reported the lifetime prevalence of RBD-like symptoms with antidepressant use of 5.8% and a 1-year prevalence of 3.8% [15]. It has also been noted that dose reduction or changing of the offending agent may improve the RBD but with persistent RSWA still noted in many cases. A patient in his 30s with depression and obsessive-compulsive disorder treated with fluoxetine who developed RBD was noted to have RSWA on repeat PSG 19 months after its cessation [18]. Parish described a case of a 50-year-old male who developed RBD with flailing of arms in a combative mode and kicking of legs who described having dreams of "fighting with Saddam Hussein" while on paroxetine therapy, which resolved on cessation of this agent [24]. While several studies have corroborated the link of RBD with SSRIs, TCAs, and MOAIs [1, 12, 15, 27], even SNRIs such as venlafaxine and duloxetine have been shown to induce RBD [19, 20]. Such a case was described in a 62-year-old lady who developed PSG-confirmed RBD with enactment of dreams, in which attempts at fighting an assailant resulted in biting her grandson [20]. Also, mirtazapine, a tetracyclic antidepressant with complex adrenergic, serotonergic, and antihistaminic properties, has been shown to induce RBD in PD patients [21].

A recent study demonstrated increase in phasic and tonic REM tone in drug-naïve depression patients, suggesting that REM sleep motor control might be disrupted in these patients at baseline [22]. Also, the residual persistence of RSWA and RBD symptoms in some cases despite medication cessation argues against a strictly de novo induction by antidepressants. Postuma et al. showed that RBD patients taking antidepressants had a lower risk of conversion to a neurodegenerative disorder but also demonstrated the presence of several neurodegenerative biomarkers such as olfaction loss, constipation, color vision, and subtle motor

symptoms in these patients, which were indistinguishable from those in patients who developed neurodegenerative disease, as discussed above. The interpretation of the findings suggested that use of antidepressants in these patients accelerated or unmasked the appearance of RBD without accelerating the risk of emergence of alpha-synuclein disorder [9]. Further investigations are warranted to elucidate the natural history of RBD in psychiatric patients with antidepressant use and their discontinuation.

There are some demographic differences noted in RBD associated with antidepressants from typical RBD, such as age younger than 50 years, female preponderance, and unclear association of phenoconversion to neurodegenerative disorders in the former category. "Early-onset RBD," occurring in adults younger than 50 years old, is less frequently associated with neurodegeneration and is noted more often with the use of antidepressants, narcolepsy type 1, and parasomnia overlap disorder [23]. Interestingly, the rate of injurious behaviors is roughly the same in both groups, which highlights the need for early clinical recognition and management.

The antidepressant bupropion is the preferred medication, given its dopaminergic property. Not one case of bupropion-induced or aggravated RBD has been reported clinically, albeit a recent study has suggested increased RSWA even in patients with bupropion use [22].

Additionally, post-traumatic stress disorder may also aggravate RBD and, in some cases, may induce RBD, but this remains a controversial topic warranting further investigation [28, 29].

It is imperative for psychiatrists to be familiar with various aspects of RBD and the issues governing the selection of antidepressants in psychiatric patients. Early detection and intervention can help manage morbidity resulting from injuries to the patients and their bedpartners. The need for longitudinal surveillance with comprehensive neurological and psychiatric examination should also be emphasized. Counseling of patients and families should be handled tactfully as the association with future development of neurode-

generation is not clear at this juncture while we await further exploration into this condition representing the overlaps among the realms of psychiatry, sleep, and neurology.

Clinical Pearls

- RBD is characterized by a clinical history of aggressive dream enactment behavior and evidence of increased EMG tone during REM sleep on PSG.
- The behavioral manifestations can range from vocalizations (sleep talking), hollering, swearing, and shouting to aggressive dream-enacting behavior simulating either defending against or attacking an assailant.
- RBD can result in significant morbidity by inadvertent injuries to the patient or bedpartner during recurrent episodes.
- Antidepressants are associated with aggravation or induction of RBD and RSWA in psychiatric patients, commonly seen in patients younger than 50 years old.
- There is also some suggestion that antidepressants can unmask the emergence of latent RBD (perhaps in the early stage of alpha-synuclein neurodegeneration) rather than induce de novo isolated RBD.
- Bupropion is the pharmacotherapy agent of choice for treating depression comorbid with RBD, as there has not yet been any reported case of bupropion-induced or aggravated RBD.
- Dose reduction or switching of the offending agent can help alleviate RBD, but often RSWA can persist.
- Patients and family members should receive counseling regarding future implications for PD and related disorders, which await further elucidation.
- Regular surveillance of these patients with comprehensive psychiatric and neurological examination is warranted.

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Chapter 15
Trauma-Related Nightmares

Katherine E. Miller, Joshua N. Friedlander, Joanne L. Davis, and Noelle E. Balliett

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K. E. Miller (✉)
National Center for PTSD, Dissemination and Training Division, VA Palo Alto Healthcare System, Menlo Park, CA, USA
e-mail: Katherine.miller13@va.gov

J. N. Friedlander
Behavioral Health Directorate, Walter Reed National Military Medical Center, Bethesda, MD, USA

J. L. Davis
Department of Psychology, The University of Tulsa, Tulsa, OK, USA

I. S. Khawaja, T. D. Hurwitz (eds.), *Comorbid Sleep and Psychiatric Disorders*, https://doi.org/10.1007/978-3-030-11772-6_15

N. E. Balliett
Outpatient Mental Health, VA Puget Sound Healthcare System, American Lake Division, Tacoma, WA, USA

Clinical History

Ms. R. was a 42-year-old woman who presented to her primary care physician complaining of frequent episodes of "scary dreams" and feeling exhausted. During these dream episodes, she would wake up with heart palpitations and shortness of breath, and her bedsheets would be soaked with perspiration. Upon awakening, she would rapidly and fully orient to present time and place. These episodes were associated with significant daytime fatigue and anxiety. She was finding it difficult to concentrate at work. Ms. R. reported having scary dreams periodically since childhood and included content such as becoming lost or being unprepared for a task. However, 5 years ago she was raped by an acquaintance which exacerbated the frequency and severity of the dreams. She reported having nightmares three or four times weekly since the time of the rape. The content of her dreams was nearly always the same, with a few changes to the characters and location over time. Generally, the dream involved being in an isolated environment with a man, who was forcing her to engage in sexual acts while she struggled to get free.

On a typical night, Ms. R. took 3 mg of over-the-counter melatonin and went to bed at midnight, after forcing herself to stay awake until she could no longer keep her eyes open. She typically fell asleep within 30 minutes. Around 2:00 a.m., she would awaken from these dreams with panic symptoms (e.g., sweating, racing heart, dizziness). Due to the physiological arousal, it would take 1–2 hours for her to calm down and return to sleep. She would typically smoke a cigarette and watch television to relax. About once a month, she would be unable to return to sleep. She napped for 1–2 hours almost daily, preferring to sleep during daytime hours as she reported rarely having any scary dreams during these naps.

She denied snoring or gasping during the night; however, she could not be certain since she slept alone.

Examination

Ms. R. was cooperative with the examination. Although she was alert and oriented, she appeared tired and reported feeling "exhausted." She displayed no problems with ambulation or gross motor control. Cognitive functions were intact. Speech was of normal rate, logical, and goal directed. She displayed no evidence of a thought disorder or other psychotic processes. Mood was depressed. Affect was generally flat, although she became tearful when discussing her nighttime disturbances. She denied suicidal or homicidal ideation, intent, or plans. Results from a physical examination and urine analysis were unremarkable.

Special Studies

Due to Ms. R.'s daytime fatigue, an ambulatory home sleep apnea test was ordered to rule out the possibility of a sleep-breathing disorder. A week of actigraphy and a daily sleep and nightmare log were ordered to collect approximate sleep-wake patterns. Due to her trauma history and panic symptoms, Ms. R. was referred to a psychologist for a mental health examination, which included the Clinician-Administered Posttraumatic Stress Disorder Scale for the Diagnostic and Statistical Manual of Mental Disorders-5 (CAPS-5; [21]). Ms. R. was also administered a battery of self-report questionnaires to assist with diagnosis and conceptualization, including Trauma-Related Nightmare Survey (TRNS; [15]), Patient Health Questionnaire (PHQ-9; [19]), Fear of Sleep Inventory-Short Form (FOSI-SF; [20]), Pittsburgh Sleep Quality Inventory and Addendum (PSQI; PSQI-A; [14, 17]), Insomnia Severity Index (ISI; [13]), and the Epworth Sleepiness Scale (ESS; [18]).

Results

Results from the home sleep apnea screen identified mild sleep-breathing issues, with an apnea-hypopnea index of three per hour. This result was deemed not clinically significant for active treatment. Additionally, the ESS score was six, within a normal level of daytime sleepiness. Ms. R. wore a wrist actigraph and completed a sleep and nightmare log for 1 week (see Table 15.1). On this log, she recorded five nightmares, across three nights, ranging from moderate to extreme severity. Nightmares occurred on days that she endorsed greater distress before bed. Ms. R.'s time to bed was later when she reported longer naps and earlier on days following nightmares. In addition to nightmares, she reported negatively valenced dreams, which did not cause waking, throughout the week. The actigraphy data generally corroborated her sleep log and showed an increase of wake time and light exposure on nights of a recorded nightmare. Additionally, low daytime activity was observed following the nights of a documented nightmare.

The psychological evaluation revealed that Ms. R. had a history of childhood physical and emotional abuse, in addition to the rape. The rape was identified as her index, or worst, trauma experience. Ms. R. met diagnostic criteria for PTSD, mild severity. Specifically, she reported distressing dreams (Criterion B), avoiding the location of the rape (Criterion C), change in thoughts and exaggerated blame of self since the rape (e.g., I can't trust men; it is my fault – I should have fought harder; Criterion D), and difficulty sleeping and concentrating (Criterion E). She also endorsed mild depression symptoms on the PHQ-9 and clinical insomnia, moderate severity, on the ISI. Data from the other self-report assessments provide additional information for conceptualization. On the TRNS, Ms. R. reported having nightmares during the first half of the night, each rated as extremely disturbing. The content of her nightmares were related to themes of safety, powerlessness, and intimacy. Following a nightmare, she reported smoking a cigarette, watching television until

Table 15.1 One week completed sleep and nightmare log

Daily sleep log

Complete immediately after waking up

Note: Nightmares include negative emotions and *do* cause you to wake up. Dreams *do not* cause you to wake up

	Example	**9/2/15**	**9/3/15**	**9/4/15**	**9/5/15**	**9/6/15**	**9/7/15**	**9/8/15**
In total, how many minutes did you nap or doze yesterday?	0	72	60	45	60	80	65	30
Before going to bed, I thought about nightmare ___ (*Not at all 0–1–2–3–4–5 A lot*)	3	3	5	4	3	4	5	3
Before bed, my general level of distress was ___ (*Not at all 0–1–2–3–4–5 extreme*)	3	2	5	4	4	3	5	3
What time did you get into bed?	2300	2400	0100	2230	2400	0130	0130	2300
What time did you try to go to sleep?	0000	2410	0100	2245	2400	0130	0145	2310
How long did it take you to fall asleep?	60	10	20	30	35	15	40	20

(continued)

Table 15.1 (continued)

Daily sleep log

Complete immediately after waking up

Note: Nightmares include negative emotions and *do* cause you to wake up. Dreams *do not* cause you to wake up

	Example	**9/2/15**	**9/3/15**	**9/4/15**	**9/5/15**	**9/6/15**	**9/7/15**	**9/8/15**
How many times did you wake up, not counting your final awakening?	3	1	2	1	2	1	3	1
In total, how long did these awakenings last?	90	20	120	15	45	20	90	35
What time was your final awakening?	0600	0700	0900	0700	0730	0815	0745	0700
If you woke earlier than your desired final awakening, how many minutes earlier?	30	0	0	0	0	0	0	0
What time did you get out of bed for the day?	0700	0720	0900	0745	0745	0830	0745	0745

How would you rate the quality of your sleep? ☐ Very poor ☐ Poor ☐ Fair ☐ Good ☐ Very good	Poor	Fair	Very poor	Fair	Poor	Poor	Very poor	Fair
Last night, I had ____ (#) nightmares	3	0	2	0	1	0	2	0
My nightmare was ____ severe (*Not at all 0–1–2–3–4–5 extremely*)	3		4		3		5	
Last night, I had ____ (#) dreams	1	0	1	2	1	1	0	1
My emotions in my dream were ___ (*Positive 0–1–2–3–4–5 negative*)	1		3	5	3	4		3
Last night, I took/used ____ to help me sleep. List time	1 beer 2100	Mel	Mel/ Cig	Mel/ Cig	Mel	Mel/ Cig	Mel/ Cig	Mel
Comments								

feeling sleepy, and attempting to fall asleep on her couch. She indicated significant complaints about the quality of her sleep and endorsed night sweats, nighttime nervousness, and anger on the PSQI and PSQI-A. Lastly, consistent with the pre-bedtime distress reported on the sleep log, Ms. R. reported significant fear of sleep on the FOSI-SF, specifically trying to stay alert while in bed, avoiding going to sleep because of bad dreams, and feeling terrified to return to sleep following a nightmare.

Question

Should the PTSD diagnosis or the nightmares be considered the primary concern for treatment?

Differential Diagnosis and Diagnosis

In addition to the PTSD diagnosis, there are several potential sleep-related diagnoses to consider in this case, including a breathing-related sleep disorder, a non-rapid eye movement sleep arousal disorder (sleep terrors), nightmare disorder, REM sleep behavior disorder (RSDB), panic disorder, and insomnia disorder. Due to the minimal level of obstructive apneas and hypopneas found from the home sleep apnea test, a breathing-related sleep disorder was ruled out. Next, a diagnosis of sleep terrors was considered. Sleep terrors fall within the non-rapid eye movement sleep arousal disorders and are characterized by abrupt terror arousal from sleep, with little unresponsiveness to external comfort; however, there is typically no recall of imagery or remembrance of the episode in the morning. In contrast, nightmares are defined as story-like sequences of dream imagery, which incite dysphoric emotions. Upon complete awakening, they are well remembered and can be described in detail [12, 16].

Ms. R. recalls the episode and content of the dream and is awakened by them; therefore, her experience more closely resembles nightmares than a sleep terror. Since nightmares are a symptom of PTSD, nightmare disorder should only be considered if the nightmares preceded the onset of the PTSD diagnosis or remain following the resolution of other PTSD symptoms, and their frequency necessitates independent clinical attention [12]. In the present case, while Ms. R. experienced nightmares in childhood, it is difficult to ascertain whether they were associated with a PTSD diagnosis at that time. Therefore, Ms. R. was not diagnosed with a separate nightmare disorder diagnosis. Yet, clinical attention to the nightmares remained warranted due to the frequency and severity of the nightmares, the subsequent daytime dysfunction, and, to address her primary complaint, even in the presence of other PTSD symptoms.

REM sleep behavior disorder (RSBD) was also considered. RSBD is characterized by vocalization and/or complex motor behaviors during REM sleep, most frequently in the later portions of night, and upon awakening the individual is fully alert and oriented. RSBD tends to occur in older males; the onset is not typically associated with trauma and is associated with underlying neurodegenerative disorders and some psychotropic medications. Ms. R. did not report any nighttime injuries, and actigraphy data did not indicate a high level of wake bouts. Due to the low prevalence rate and lack of evidence of other diagnostic features, RSBD was ruled out. Ms. R.'s nightmares were associated with panic attack symptoms; however, panic disorder was also ruled out because she denied experiencing unexpected or daytime panic attacks. Lastly, while Ms. R. reported significant dissatisfaction with sleep quality and quantity, a separate insomnia disorder diagnosis was not assigned because her difficulties initiating and maintaining sleep are adequately explained by fear of sleep and the nightmare occurrences.

The final diagnosis was PTSD.

General Remarks

Trauma-related nightmares are characterized as chronic, distressing dreams following a traumatic event that cause nocturnal waking, with recall of dream narrative [7]. The prevalence rate of nightmares in trauma survivors varies considerably across studies, ranging from 19% to 96% [5, 6], due to differences in definitions, measurement tools, and PTSD diagnostic status of samples. Nighttime hyperarousal is particularly associated with trauma-related nightmares, in that individuals with nightmares have more nocturnal awakenings and reduced slow wave sleep, suggesting a more alert brain [9]. While non-trauma-related nightmares tend to occur in the latter half of the sleep cycle, there is some evidence that trauma-related nightmares may occur in the first part of the sleep cycle [8]. Preliminary data also suggests that nightmare reports are significantly related to decreased parasympathetic activity [10].

It is important to illustrate from the above discussion that while Ms. R. met criteria for PTSD, clinical attention to nightmares is warranted due to the frequency and associated impairment of the nightmares and to address her primary complaint. Attention only to PTSD broadly may underemphasize the prominence of the nightmares and associated nocturnal and daytime symptoms, limiting the opportunity for targeted intervention. Additionally, research demonstrates that nightmares and insomnia symptoms often do not respond adequately to PTSD-focused treatments, despite improvements in other symptom domains [3, 11]. In contrast, treating nightmares and sleep problems may reduce symptoms of PTSD and depression [2]. The assessment approach discussed for this case illustrates the importance of identifying factors that contribute to and maintain the nightmares. For example, it is common for individuals presenting with trauma-related nightmares to have a fear of the dark or sleep, attempt to recoup the sleep loss by napping during the day, and use avoidance or other unhelpful coping strategies to

gain some control over a seemingly uncontrollable situation. The nightmare content does not have to closely resemble the event but may include themes related to the actual traumatic events the individual experienced. Nightmare content that more closely resembles the traumatic event is frequently reported as more distressing than less similar nightmare content. Tracking via the sleep and nightmare log can also aid in conceptualization and highlight patterns for the individual. In this case, daytime distress and anticipatory anxiety prior to bedtime was associated with the likelihood of experiencing a nightmare and, consequently, the following day and night schedules were impacted. These patterns suggest that Ms. R. was stuck in a negative perpetuating cycle.

In addition to determining an accurate diagnosis, this assessment approach also supports treatment planning for targeting the primary complaint. Cognitive-behavioral therapies for nightmares (CBT-N) are available and have evidence for reducing nightmare frequency and severity, as well as improving depression and PTSD symptoms [4]. Exposure, relaxation, and rescripting therapy (ERRT; [1]) is a CBT-N specifically targeting trauma-related nightmares. This treatment targets the perpetuating factors identified in the assessment process through psychoeducation, modification of sleep habits and stimulus control, relaxation techniques, and nightmare exposure and thematic rescripting.

Psychoeducation, which provides rationale for the treatment and the theories behind the nightmare cycle, is thought to directly target anticipatory anxiety both with regard to treatment expectations and provide corrective information regarding what factors are involved in the probability of having a nightmare. Indirectly, psychoeducation works with other components, particularly sleep behavior modification, to address maladaptive sleep habits by educating the client about bedtime routines that may increase chances of disrupted sleep and/or nightmares. The behavioral and environmental changes that occur with sleep habit modification not only encourage new behaviors to facilitate sleep but also

indirectly challenge unhelpful beliefs about one's sense of control over sleep. The component of stimulus control is also used to address the amount of time one spends in bed while not sleeping and aids in the re-conditioning of the bed to associate it only with sleep, as opposed to nightmare experiences and other conditioned hyperarousal. ERRT also includes progressive muscle relaxation and diaphragmatic breathing, which are common relaxation techniques aimed at reducing and controlling physiological arousal. The use of these relaxation techniques immediately before sleep is also aimed at decreasing the cognitive and physiological arousal associated with fear of sleep and sleep-related anticipatory anxiety. The combination of these techniques directly targets the daytime distress and arousal factors of the nightmare cycle. Finally, the exposure component of ERRT involves having the client provide a written and oral account of his or her nightmare content. It is thought that exposure helps to identify unresolved, trauma-related emotional content and themes manifested in nightmares. The exposure also serves to activate the fear network while simultaneously increasing a sense of mastery through confrontation of the nightmare content. The act of rescripting, or changing of the nightmare content based on the identified themes, serves as the presentation of new, fear-incongruent information. Together, the exposure and rescripting components target the fear network and provide a mechanism by which to reduce the fear associated with the content. Additionally, the nightly rehearsal of the changed content can disrupt the association between fear and the nightmare content, offering the client a more adaptive appraisal of the meaning of his or her nightmare(s).

Overall, by targeting the individual's primary complaint first, the experience of symptom reduction may motivate the individual for additional treatment, as needed. Additionally, improvements in sleep quality and quantity may also increase an individual's ability to regulate emotions and to feel more equipped when facing daytime stress. It is also thought that consolidated sleep may be helpful to facilitate extinction learning, which could be particularly helpful for individuals

receiving PTSD-focused treatment after working on their nightmares. The clinical advantage of targeting nightmares prior to or following PTSD-focused interventions is currently under investigation.

Pearls and Take-Home Points

- Sleep disturbances, including recurrent nightmares, following trauma exposure are considered hallmark symptoms of PTSD [8] and may significantly contribute to the development and maintenance of PTSD.
- Focusing solely on the PTSD diagnosis may ignore the prominence and associated functional impairment of nightmares in the complete clinical picture.
- A comprehensive assessment approach of trauma-related nightmares should be the first step in developing an appropriate treatment plan. Although there are similarities in presentations, individuals with trauma-related nightmares vary in their coping skills, resources, trauma histories, and other physical or psychopathological difficulties that impact the conceptualization of the problem. Factors identified as contributing to the maintenance of the nightmare cycle can then be targeted in treatment.
- Due to the pernicious nature of trauma-related nightmares, targeted interventions may be necessary. For some individuals, targeting PTSD symptoms as a whole may not be enough to eradicate the nightmares. There is growing evidence that brief psychotherapeutic approaches for nightmares can mitigate both the frequency of the nightmare occurrences and the associated distress. For example, ERRT is a three- to five-session manualized protocol that can be provided in individual or group format. The treatment is typically conducted once per week over 3–5 weeks, and sessions run approximately 1 hour each.

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Chapter 16
Things That Go Bump in the Night

Abhisek Chandan Khandai and Hrayr P. Attarian

Clinical History

Ms. C is a 32-year-old woman with a history of bipolar disorder who presents to the sleep center's outpatient clinic for the evaluation of unusual behaviors in her sleep for over 10 years.

Ms. C's automatic sleep-related behaviors, including sleepwalking and sleep eating, started at age 20. Around the same time, she had two psychosocial stressors: moving away to college and being diagnosed with bipolar affective disorder. Witnesses described these episodes as repetitive, purposeful goal-directed behaviors including wandering around the apartment, eating, and sometimes filing papers. All these episodes occur within the first 45 minutes of sleep. She is not responsive during these, however, sometimes wakes up shortly after the events, and has a vague and partial recollection of what has occurred. She reports no injuries to herself or others during these events except for once, at age 23, when

A. C. Khandai
Department of Psychiatry, Northwestern McGaw Medical Center, Chicago, IL, USA

H. P. Attarian (✉)
Department of Neurology, Northwestern Medicine, Chicago, IL, USA
e-mail: h-attarian@northwestern.edu

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she fell during a sleepwalking spell. Sleep eating has resulted in weight gain of 15 lbs. or more. She denies incontinence or oral trauma. She denies any daytime events of impaired or loss of awareness; she denies loss of consciousness, staring spells, or convulsions. She denies daytime fatigue and daytime sleepiness. The severity and frequency of these episodes wax and wane in response to stress. Currently she has them once or twice a night, 3–4 times a week, each lasting 2–5 minutes which is significantly less as her anxiety level and stress is less.

Between ages 9 and 18, she had absence seizures confirmed by EEG and treated with valproic acid, which was then tapered off at age 18.

At age 21, as a workup of the above-described events, she underwent EEG, and two MRIs of the brain seizures were ruled out, and she was referred to a sleep specialist who only counseled her on sleep hygiene. Improvements in her sleep hygiene did not change the frequency and the severity of these episodes.

She also had two polysomnograms (PSGs), once at age 20 and once at age 23. Both found no evidence of any primary sleep disorder. The first one did not capture any typical events. The second one captured a few events described as sitting up in bed and writing, talking on the telephone, and eating a granola bar. The four channels of EEG used during this PSG showed posteriorly dominant alpha activity consistent with wakefulness. Patient did not have any recollections of these events. Because these were thought to arise out of wakefulness and she was amnestic for them, she was diagnosed with psychogenic dissociative disorder.

She was prescribed alprazolam for these which she sporadically took with possible reduction in the number of events on nights she took it. She was later switched to lorazepam but she does not take it.

She is on lithium, benztropine, oral contraceptives, and aripiprazole. The timing of the latter was switched to mornings without any impact on her nighttime events.

She has a regular bedtime of 10:30 p.m. and risetime of 6:30 a.m. She sleeps through the night and denies any

disruptions in her sleep other than the events described above. She denies any other sleep-wake-related complaints.

She denies any allergies or any substance use.

Examination/Mental Status Exam

She is a pleasant, slightly overweight, young woman in no acute distress. Apart from a slightly flat affect, her general and neurological exams are normal. Height is 158 cm, weight 65.8 kg, and BM is 26.5 kg/m^2. The rest of her vital signs are also normal.

Labs

Her lithium levels are therapeutic at 0.5 meq/L.

Special Studies

A third overnight PSG was ordered, this time with extended EEG montage (total of 29 channels, 16 of them EEG).

Results

There were multiple arousals and three awakenings from stage N3 sleep. During these three episodes, the patient sat up in bed and looked around confused before returning to sleep. During one episode she mumbled incoherently, and in another she scratched her nose.

There was no epileptiform activity on the EEG and the events arose out of N3 sleep. The EEG pattern during the events was a mix of large amplitude slow delta frequency waves anteriorly and faster, alpha frequency activity in the occipital area. Sleep architecture otherwise was remarkable for increased stage N3 and decreased stage R sleep. Sleep efficiency was

normal. Sleep onset latency was reduced; REM latency was prolonged. There were no other significant abnormalities; specifically motor activity was appropriately suppressed during stage R sleep.

Question

What is the diagnosis: nocturnal seizures, parasomnias, or psychogenic nonepileptic spells?

Differential Diagnosis and Diagnosis

In summary Ms. C is a 32-year-old woman with a history of bipolar disorder who presents to the sleep center's outpatient clinic for the evaluation of unusual behaviors in her sleep for over 10 years.

She has a history of uncategorized epileptiform activity in childhood while awake and sleeping, as well as prior sleep studies, one of which showed alpha activity in posterior channels during these episodes. Initial differential included nocturnal seizures, REM sleep behavior disorder (RBD), NREM parasomnias, and psychogenic disorders.

NREM parasomnias were most likely, given the varied and non-stereotyped nature of these events, nocturnal nature, and longer duration of events (2–5 minutes at a time). Although more often seen in children, NREM parasomnias are often seen in adults as well. PSG confirmed presence of motor activity consistent with NREM parasomnias, with multiple arousals from stage N3 sleep associated with these episodes.

RBD is a possibility given the nocturnal nature of these events and can often lead to injury to the patient, as happened once with this patient. However, the patient denied dream-enacting behaviors and per history episodes tended to occur early in the sleep cycle. RBD events occur most frequently later in the sleep period when REM sleep is more common. In addition, RBD often has its onset later in life

(ages 40–70), whereas this patient started having episodes at age 20. PSG confirmed a lack of motor activity consistent with REM parasomnia.

Prior reported history of seizures during childhood increases the likelihood of the patient having nocturnal seizures; nocturnal seizures can include ambulatory behavior. However, seizures are very stereotyped, and this patient had a lack of stereotyped activity on clinical history. In addition, the duration of events (2–5 minutes) is much longer than those reported for nocturnal seizures. Extended EEG montage confirms a lack of epileptiform activity.

Psychogenic disorders, such as psychogenic nonepileptic spells (PNES) or dissociative events, are possible, given the patient's psychiatric comorbidity. In addition, one prior PSG captured alpha activity (associated with wakefulness) in posterior channels during these episodes, and the lack of recall suggests an amnestic dissociative experience. Per history, the frequency of these events appears related to psychosocial stressors. However, this patient does not report a history of trauma or abuse, which is a far greater driver of PNES or dissociative events than simply psychiatric comorbidity. In addition, stress is a nonspecific factor that also impacts epilepsy and parasomnias. PSG with frontal channels showed activity associated with N3 sleep rather than wakefulness.

General Remarks

Unusual behaviors during sleep represent not only a discomforting and possibly dangerous phenomenon to patients but a diagnostic challenge for clinicians. Given their nocturnal nature and often irregular frequency, characterization of the events themselves can elude patients and their partners. In addition, the presence of psychiatric comorbidity, as well as the lack of easily obtainable diagnostic studies, often leads clinicians to misdiagnosing episodes as psychogenic disorders. While the video-polysomnogram (v-PSG) remains the gold standard for diagnostic clarification, a clearer understanding

of the clinical characteristics of three common conditions leading to unusual nighttime behaviors – nocturnal seizures, REM sleep behavior disorder (RBD), and NREM parasomnias – can also help avoid misdiagnosis and guide more targeted treatment.

Repeated episodic behaviors will naturally lead to consideration of seizures. However, nocturnal seizures represent a particularly challenging form of epilepsy to diagnose. Most often arising from the frontal lobes (nocturnal frontal lobe epilepsy, NFLE), nocturnal seizures often are entirely restricted to sleep, and investigation with MRI and EEG frequently shows no abnormality. Seizures can have bizarre clinical features, such as vocalization, complex automatisms, and ambulation. Seizures with ambulation often involve brief bursts of agitated running or jumping, usually confined to the bedroom. Episodes can be, but are not always, marked by dystonic or tonic posturing, and some cases report an aura – typically a somatic sensation or feeling that their "breath is stuck in their throat." Seizures are frequently clustered, with several on any given night and sometimes 20 or more. They usually occur during stage 2 sleep and so at any time of night. A defining feature of nocturnal seizures is their stereotyped nature. Treatment is predominantly with antiepileptics, with the literature favoring carbamazepine.

REM sleep behavior disorder (RBD) is characterized by vivid dreams accompanied by motor behavior during REM sleep. Almost all patients with RBD have dream-enacting behavior (DEB) – including abnormal vocalizations such as screaming and swearing, limb jerks, and even running and jumping out of bed or attacking bed partners. However, DEB can also occur in untreated obstructive sleep apnea, PTSD, or drug intoxication/withdrawal. Thus, RBD diagnosis requires concurrent abnormal REM activity during these episodes on polysomnogram. The timing of RBD reflects when the patient is in REM sleep, usually during the latter half or even third of the sleep cycle when stage R is more predominant. Onset of symptoms varies, although most develop in the

40–70 age range and may be a harbinger of later neurodegenerative changes such as Parkinson's disease. Polysomnogram shows activity primarily during stage R. Treatment is usually attempted first with clonazepam and/or melatonin; other drugs reported to improve RBD include pramipexole, levodopa, carbamazepine, and quetiapine. Notably, SSRI and SNRI antidepressants can precipitate or aggravate RBD; in patients with both depression and RBD, bupropion may then be favored.

NREM parasomnias, also known as disorders of arousal (DoA), comprise three interrelated entities, confusional arousals, sleepwalking, and sleep terrors, all of which tend to arise out of slow wave (N3) sleep. They are characterized by a state of dissociated consciousness, in between the sleeping and waking state. Episodes often last for several minutes and involve complex motor behavior such as eating and even driving, often outside the bedroom, which the patient will then later not recall or only have vague recollection. While sleepwalking is the most common manifestation, almost all sleepwalkers report co-occurring parasomnias such as sleep talking, nocturnal eating behavior, night terrors, etc.; by nature NREM parasomnias are non-stereotypical in most patients. Episodes will usually occur in the first half of the night, often 1–2 hours after falling asleep; they occur infrequently, rarely more than once or twice a night. While commonly associated with pediatric onset and disappearing in adulthood, they can also persist or appear de novo in adulthood such as in Ms. C. Stress and sleep deprivation often trigger NREM parasomnias; sleepwalking is associated in 25–33% of cases with psychiatric comorbidity, most often depression. Polysomnogram will show activity in stage N3, a mix of both awake and N3 sleep waveforms reflecting the dissociated consciousness state. Treatment of NREM parasomnias is guided primarily by case reports and series as well as expert opinion: the first step is usually with low-dose clonazepam, which is thought to reduce arousals from sleep and presumably prevent the parasomnias. A recent case study

found this effective in almost three-quarters of cases (Attarian and Zhu 2013). Case evidence also exists for sertraline and paroxetine, clomipramine, and temazepam; behavioral strategies include CBT-insomnia, as well as hypnotherapy (even one to two sessions of the latter).

Psychogenic disorders – particularly psychogenic nonepileptic seizures (PNES) or dissociative episodes – are always possible and are particularly tantalizing if clear evidence does not present on EEG or polysomnogram. However, they are rarely seen in true EEG-confirmed sleep, although they can be seen nocturnally from a state misidentified as sleep (termed by some as "pseudosleep"). Remember that psychogenic disorders are by definition a diagnosis of exclusion; in addition, both PNES and dissociative episodes are more specifically correlated with a prior history of trauma or abuse than simply psychiatric comorbidity. This patient did not have a history of trauma or abuse, reducing the pretest likelihood of PNES or dissociative episodes being the diagnosis.

Given differences in clinical characteristics between nocturnal phenomena, clinicians have developed questionnaires and other tools to aid in differential diagnosis. For example, the Frontal Lobe Epilepsy and Parasomnias (FLEP) scale can be used to distinguish between nocturnal seizures and parasomnias (Derry et al. 2006). The gold standard of diagnosis for all three conditions – nocturnal seizures, RBD, and NREM parasomnias – is v-PSG. However, ready availability of this test may be limited, as well as practicality, particularly if episodes are very infrequent. In addition, proper placement of channels is essential in polysomnogram. In this case, the patient had a prior polysomnogram, with alpha activity noted in posterior (occipital) channels; this suggested the patient was awake during the episodes, and along with reported amnesia, this led to a (mis)diagnosis of psychogenic dissociative disorder. However, latter v-PSG included frontal leads, which showed episodes occurring during stage N3 (see Fig. 16.1). This helped make the correct diagnosis of NREM parasomnias.

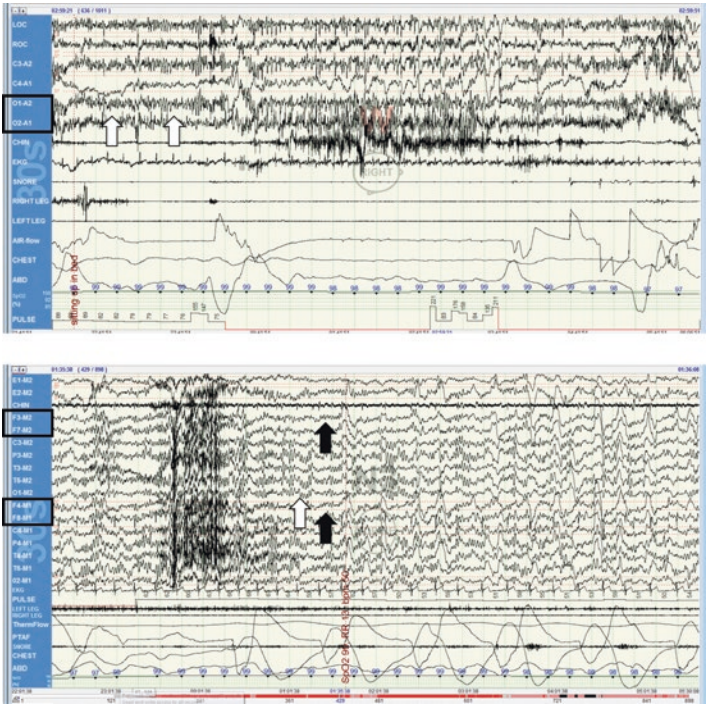

FIGURE 16.1 Two polysomnograms of a patient with NREM parasomnias. The upper PSG (earlier) showed alpha activity (white arrows) in occipital leads ("O"), leading to a misdiagnosis of psychogenic disorder. The lower PSG (latter), including frontal leads ("F"), shows slow-wave activity (black arrows) coexisting with alpha activity (white arrow), characteristic of NREM parasomnias

Take-Home Points

- The differential for nocturnal behaviors includes nocturnal seizures, NREM parasomnias, and RBD, which can be distinguished both by careful history and on polysomnogram.
- When evaluating nocturnal behaviors, particularly NREM parasomnias, extended EEG montage is necessary as NREM parasomnias often show a mix of awake and N3 sleep waveforms.
- Psychiatric comorbidity in general should not automatically lead to a diagnosis of psychogenic disorder in diagnostic dilemmas, particularly as they are more correlated specifically with a history of trauma or abuse.

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Chapter 17
Medication-Induced Nightmares

Abhisek Chandan Khandai, Elizabeth E. Sita, and Hrayr P. Attarian

Clinical History

A 23 year-old male medical student presented on self-referral to our Sleep Disorders Center with a chief concern of difficulty waking up in the morning. He reported onset of sleep troubles around the age of 15 or 16. At that age he began to routinely nap in the early evening from 7 to 10 p.m., awakened to complete his school tasks, and then returned to sleep from 4 to 7 a.m. Over the years, he found himself having more and more difficulty feeling sleepy prior to 3 or 4 a.m., even after eliminating his evening naps. Consequently, he found it exceedingly difficult to wake up in the morning before 10 or 11 a.m. At presentation, he noted some urgency to correct his schedule, offering concern about his ability to adhere to the

A. C. Khandai
Department of Psychiatry, Northwestern McGaw Medical Center, Chicago, IL, USA

E. E. Sita
Department of Psychiatry, Northwestern Medicine, Chicago, IL, USA

H. P. Attarian (✉)
Department of Neurology, Northwestern Medicine, Chicago, IL, USA
e-mail: h-attarian@northwestern.edu

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requisite schedule of a second year medical student and beyond, as he desired a surgical career down the line.

He estimated sleeping 5–7 hours per night, with report of daytime sleepiness only on nights of inadequate sleep (<7 hours) and an Epworth Sleepiness Scale (ESS) score of 10/24. He reported a target bedtime of 12 p.m. with lights simultaneously out and a target wake-up time of 7 a.m. On nights when adhering to these targets, he experienced a sleep latency of 1–2 hours and was rarely able to rise with his alarm in the morning. However, upon going to bed when naturally sleepy, around 3 or 4 a.m., he experienced a sleep latency of only a few moments and, if allowed, would awaken naturally and refreshed around 11 a.m. He reported rare and brief nighttime arousals to use the restroom, with little to no difficulty returning to sleep. He endorsed occasional, limited caffeine use and had not napped during the day or early evening since high school.

Notably, he had recently started taking over-the-counter melatonin 0.5 mg by mouth at bedtime but found it difficult to adhere to this medication with any regularity. On evenings when he took melatonin, he experienced vivid nightmares of someone breaking into his home during which he would sometimes awaken kicking his legs. Moreover, he endorsed associated and abnormal sleep behaviors, such as locking a door unintentionally or resetting alarms. On nights without melatonin, he denied sleepwalking or dream reenactment, had never experienced sleep talking, and had no childhood history of night terrors.

On review of systems, he denied snoring, being awakened gasping for air, witnessed apneas, bruxism, dry mouth, or morning headaches. He further denied sleep attacks, hypnic hallucinations, sleep paralysis, cataplexy, restless legs, or symptoms of post-traumatic stress disorder. His past medical history was notable only for bilateral inguinal hernia repair in childhood. He was on no prescription medications, took only melatonin over-the-counter as above, and had no known drug allergies. His social history was negative for tobacco or illicit drug use, and he endorsed rare, limited alcohol use. Family history was negative for sleep-wake disorders, sleep-disordered breathing, narcolepsy, or restless leg syndrome.

Examination

The patient was noted to have a body mass index of 22.1 kg/m^2 and was generally well-appearing and in no acute distress. His examination was largely unremarkable, with a Mallampati class I airway, with 0–1+ tonsils, normal turbinates, no septal deviation, and a neck circumference of 39.4 cm. His cardiovascular, respiratory, abdominal, and neurologic exams were within normal limits.

Special Studies

In view of his abnormal sleep patterns, 2 weeks of actigraphy monitoring were obtained.

Results

Sleep-wake data were generally in keeping with the patient's presentation at intake, albeit his schedule was a bit earlier than initially reported. Over a period of 2 weeks, he demonstrated an average bedtime of 12:42 a.m. with an average wake-up time of 8:53 a.m. He attributed this shift to the act of monitoring his sleep, which he felt helped him adhere to a more regular schedule. He was subsequently started on a regimen of 10,000 lux of light for 30 minutes to 2 hours at 9 a.m. each morning and instructed to walk back his bedtime/wake-up time by 15 minutes every day from 1 a.m. and 9 a.m., respectively, until achieving his desired sleep schedule of 11 p.m. to 7 a.m.

Question

What medications are likely to induce nightmares?

Diagnosis

The clinical history and actigraphy findings for this patient were fairly straightforward and suggestive of a delayed sleep-wake phase disorder, which one would generally treat with a

combination of bright light therapy and melatonin. However, given the emergence of vivid nightmares and abnormal sleep behaviors with melatonin, the patient was advised to discontinue this medication, with subsequent and near-immediate resolution of associated symptoms.

Remarks

Nightmares are vivid dreams containing intense negative emotions that can result in the dreamer awakening from sleep. Classically defined as a parasomnia, when recurrent (at least once a week) and bothersome, they can rise to the level of nightmare disorder. Nightmares occur almost exclusively during REM sleep, which is more prevalent during the second half of the sleep period [1].

Recurrent nightmares are fairly common in childhood (20–39%), and so nightmares are often thought of as a childhood disorder. However, they are not uncommon in the general population: among adults, 5–8% of adults report frequent nightmares (one or more per week), and 35–45% report at least one nightmare per month. Women have consistently been found to report more nightmares than men, particularly in young adults [2].

Frequent nightmares are associated with a variety of neurologic and psychiatric disorders, including depression, anxiety, schizophrenia, post-traumatic stress disorder, and Parkinson's disease. While often misconceived as a benign if irritating phenomenon, nightmares are associated with other sleep problems, including insomnia and daytime fatigue [3]. Worryingly, nightmares also constitute an independent risk factor for developing PTSD, as well as both attempted and completed suicide [1, 4]. Unfortunately, nightmares are rarely reported to healthcare providers, and most patients do not believe nightmares are treatable [1].

Nightmares must be clinically differentiated both from night terrors and REM behavior disorder (RBD). Although commonly confused with night terrors or pavor nocturnus,

night terrors represent a separate phenomenon occurring primarily during slow-wave sleep (SWS) and so primarily in the first half of the night. In contrast to nightmares, night terrors are marked by the patient screaming and appearing awake but still being in a state of sleep; night terrors are vaguely remembered if at all, as opposed to the vivid detailed remembrance of nightmares. While RBD also occurs in REM sleep, they are defined by the loss of normal muscle atonia, and so patients physically act out their dreams (or nightmares).

Given the previously mentioned high background incidence of nightmares in the general population, it can be difficult to assess true causality in a medication-associated case of nightmare. Most clinical studies, particularly older ones, either did not assess for nightmares or lumped them in with other sleep disturbances. The vast majority of evidence comes in the form of case reports, and most causality is inferred from temporality and clinical judgment of the authors. In addition, the true pharmacologic mechanisms for most medication-induced nightmares remain unclear, although two commonly held mechanisms are alterations in REM or effects on neurotransmitters associated with sleep (serotonin, dopamine, norepinephrine) [5].

However, several classes of medications – antidepressants, dopaminergic agents, GABA agonists, antihypertensives, infectious agents, and melatonin/melatonin agonists – are associated with nightmares and should be taken into account when attempting to determine the etiology of possible medication-induced nightmares.

Several classes of antidepressants are associated with nightmares as adverse effects, although the mechanism by which it occurs – REM suppression or other serotonin-related effects – remains to be elucidated. While depression itself is associated with sleep disturbances including nightmares, studies do show an independent association of antidepressants with nightmares. While monoamine oxidase inhibitors (MAOIs) and then tricyclic antidepressants (TCAs) are classically associated with more nightmares, they are also associated with

selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). Within SSRIs, paroxetine is particularly associated with nightmares as an adverse effect, with fluoxetine to a lesser extent and sertraline occasionally. Within SNRIs, venlafaxine has several reports of nightmares. In contrast, buspirone and trazodone are not typically associated with nightmares. Of note, reports also exist of nightmares during SSRI/SNRI discontinuation, possibly due to REM rebound, and emphasizing the need for careful down-titration of such agents [2].

Dopamine analogues and agonists are also associated with nightmares, such as levodopa, pergolide, cabergoline, and ropinirole. However, Parkinson's disease – a frequent target of dopaminergic agents – is itself associated with nightmares; differentiating causality between the disease and the drug can be challenging. In addition, several amphetamines such as fenfluramine and chlorphentermine have patient reports of nightmares, further strengthening an argument that dopamine plays a part in nightmare pathogenesis [5].

Benzodiazepines and other hypnotics, such as triazolam and zopiclone, have also been reported to cause nightmares. In addition, nightmares may also occur during withdrawal from both alcohol and benzodiazepines, likely due to REM rebound [2].

Beta-blockers are often associated with patient reports of nightmares, particularly more lipophilic beta-blockers such as propranolol and labetalol. The likely mechanism is through their effects on CNS adrenergic receptors and possibly through REM suppression. Other antihypertensives associated with nightmares include certain ACE inhibitors such as enalapril, quinapril, and losartan – possibly through effects on norepinephrine – as well as reserpine, which suppresses REM [2].

Interestingly, several infectious disease agents have been reported to cause nightmares, such as erythromycin, ciprofloxacin, ganciclovir, and amantadine. The mechanism remains unclear, although it may relate more to alterations of the immune system due to the infectious agent and resultant effects on the sleep neuroendocrine system vs a direct effect of the drug itself [2, 5].

In this case, the patient had previously been on melatonin. Melatonin is a neurohormone, synthesized mainly by the pineal gland, and secreted primarily at night in a circadian rhythm. By acting primarily at melatonin receptors at the suprachiasmatic nucleus (SCN), it helps regulate the sleep-wake cycle. Clinical use has thus focused on its use in insomnia and circadian rhythm sleep disorders. Sold over the counter in the United States, it is often assumed to be safe. However, several adverse effects have been reported with melatonin, including gastrointestinal disorders, hypotension, headaches, and indeed nightmares [6]. In addition, newer melatonin-receptor agonists such as Ramelteon also have case reports of nightmares as adverse effects [7].

When evaluating a patient for nightmares, it is important to evaluate both frequency and severity of nightmares, as well as assessing for associated neurologic and psychiatric conditions. If nightmare temporality is associated with a medication trial, particularly those recently discussed, it can be prudent to downtitrate and discontinue the agent, with the awareness that sudden discontinuation can itself often precipitate REM changes and nightmares. Finally, if nightmares persist despite discontinuation of the hypothesized causative agent, further assessment should be made, given the very real deleterious effects of nightmares.

Pearls

- Recurrent nightmares occur in 20–39% of children but also 5–8% of adults.
- Nightmares are associated with several neurologic and psychiatric conditions, including depression, anxiety, schizophrenia, PTSD, and Parkinson's disease.
- Nightmares are underreported and are associated with several deleterious consequences, including increased risk of suicide.

- Nightmare-inducing medications include antidepressants, dopaminergic agents, GABA agonists, antihypertensives, infectious agents, and melatonin/melatonin agonists. Nightmares can occur with both use and withdrawal.
- Melatonin is not a completely benign agent, despite being over-the-counter in the United States, and is associated with nightmares as well as other adverse effects.

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Chapter 18
Uncontrollable Urges to Gamble Following Treatment with Pramipexole (Mirapex)

Austin W. Blum and Jon E. Grant

Clinical History/Case

Mr. S is a 58-year-old man with a diagnosis of restless legs syndrome (RLS) which, prior to treatment with the dopamine agonist pramipexole, prevented him from getting restorative sleep. Three months after starting treatment with pramipexole, Mr. S reported improvement in RLS—he was sleeping well and waking refreshed—but he had also begun to gamble excessively. One afternoon, while driving home from his job in human resources, Mr. S saw a billboard for a casino that triggered a strong internal urge to gamble. Instead of going home, he drove to the casino and quickly won $150 playing video poker. Over the next several weeks, Mr. S started to visit the casino two or three

A. W. Blum · J. E. Grant (✉)
Department of Psychiatry and Behavioral Neuroscience, University of Chicago, Chicago, IL, USA
e-mail: jongrant@uchicago.edu

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nights per week after work. Since commencing this behavior, he has lost up to $500 per night after playing for several hours. While at work, Mr. S frequently becomes preoccupied with calculating the odds of different video poker machines and thinking about which machines are "due" to pay a jackpot. When his urges to gamble have become uncontrollable, he has left work early to go to the casino. These behaviors have resulted in several reprimands from his manager about his lack of reliability. Mr. S sees nothing wrong with his gambling behavior even though it is highly uncharacteristic for him. In the past, he had gambled on sporting events with friends and coworkers, but these activities were recreational in nature and did not cause problems. He has no psychiatric history and has not used illicit substances.

Examination/Mental Status Exam

The patient is euthymic. The neurological examination shows no focal abnormalities.

Special Studies

Mr. S underwent the Minnesota Impulsive Disorders Interview (Grant 2008) and met seven criteria for gambling disorder. In terms of severity of behavior, we assessed Mr. S using the Yale-Brown Obsessive-Compulsive Scale adapted for Pathological Gambling (PG-YBOCS; Pallanti et al. 2005), and he scored a 28 out of 40, reflective of moderately severe gambling behavior. No imaging or laboratory tests were performed as they are unnecessary for the clinical assessment of disordered gambling. Urine toxicology was performed to rule out impulsive behavior in the context of alcohol or drug use. The Mini-International Neuropsychiatric Interview (MINI) was conducted to examine other mental disorders often associated with impulsive behavior and to assess common comorbidities.

Results

See above. Urine toxicology was negative, and the MINI failed to note any other mental health diagnoses.

Question

Can treatment with pramipexole cause compulsive gambling or other addictive behaviors? If so, how?

Differential Diagnosis

The disordered gambling behavior in this case is most consistent with the adverse effects of pramipexole, a dopamine agonist (see "Comment"). It is important to note the strong temporal relationship in this case between the use of pramipexole and the onset of symptoms. Excessive gambling behavior may also play a role in the clinical presentation of several other psychiatric disorders:

- *Gambling disorder*. The persistent and recurrent maladaptive gambling behavior in this case supports a diagnosis of gambling disorder (see *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (*DSM–5*)). If urges to gamble diminish when a medication such as pramipexole is reduced in dosage or discontinued, however, then a diagnosis of gambling disorder would not be indicated.
- *Bipolar disorder*. Excessive gambling behavior may occur as part of a manic episode in bipolar disorder. Mr. S reports gambling behavior while also reporting a stable mood. Additionally, he denies any history of grandiosity or impulsive behaviors other than gambling.
- *Substance abuse*. Excessive gambling can occur when a patient is abusing substances, especially stimulants (e.g., cocaine, amphetamines resulting in impulsive behaviors) or alcohol (disinhibiting the person to act impulsively). Mr. S has not used illicit drugs and does not drink alcohol.

Comment

A small percentage of people with RLS appear to develop impulsive behaviors after starting treatment with dopamine receptor agonist drugs. These behaviors may include not only disordered gambling but also binge eating, compulsive shopping, or a preoccupation with sex, referred to as compulsive sexual behavior or hypersexuality. In such cases, patients (such as Mr. S) often report these behaviors as ego-syntonic rather than excessive or abnormal.

Our understanding of impulsive behaviors associated with dopamine agonists has been promoted by reports of serious side effects submitted to the US Food and Drug Administration (FDA). In one study of adverse drug events reported to the FDA over a 10-year period, dopamine receptor agonists were associated with nearly half (n = 710; 44.9%) of all impulse control disorders that were attributable to a drug (Moore et al. 2014). Impulsive behaviors related to dopamine receptor agonists occurred in patients with a median age of 55 years (interquartile range, 46–63 years) and were more common in males (65.8% of patients). The most common impulsive behaviors reported in these individuals were disordered gambling (39.7%), hypersexuality (29.4%), and compulsive shopping (12.8%) (all at rates higher than found in the population at large). Binge eating was relatively less common (7.7%), although it too was at a rate higher than in the community. The dopamine receptor agonists had been prescribed for RLS in 23.8% of cases (169 events); most prescriptions were for Parkinson disease (61.7%). Although the association between dopamine receptor agonist therapy and impulse control events was strong overall (proportional reporting ratio (PRR) = 277.6), most events occurred with either pramipexole (n = 410; PRR = 455.9) or ropinirole (n = 188; PRR = 152.5), both of which have preferential affinity for the dopamine D_3 receptor. A weaker signal was detected for aripiprazole (n = 37; PRR = 8.6), a partial agonist at dopamine D_2/D_3 receptors. These findings support a close link between the use of dopamine receptor agonists and the development of specific impulsive behaviors.

A clinical picture of disordered gambling linked with dopamine agonist therapy has been provided in a small case series reported by Tippmann-Peikert et al. (2007). In this case series, three patients with RLS became compulsive gamblers after being treated with either pramipexole or ropinirole. None had a prior history of gambling problems. After starting dopamine agonist therapy, all patients described being preoccupied with gambling, needing to gamble with an increasing amount of money, restlessness or irritability when unable to gamble, and loss of control over gambling behavior. Two of the patients ultimately experienced financial losses greater than $100,000. The gambling symptoms abruptly stopped when the dopamine agonist was tapered or discontinued, suggesting a causative mechanism.

Second-generation dopamine agonists such as pramipexole are hypothesized to trigger disordered gambling and other impulsive behaviors by directly stimulating dopamine D_3 receptors. Neuroanatomically, D_3 receptors are highly concentrated in limbic regions of the brain, including a key component of the mesolimbic dopaminergic ("reward") pathway: the nucleus accumbens (NAc)/ventral striatum. Excessive dopaminergic drive in the NAc has been strongly implicated in the development of addiction, including disordered gambling. Based on these findings, some researchers have proposed that drugs with a strong D_3 receptor preference (particularly pramipexole) may overexcite dopaminergic neurons in the NAc, resulting in the onset of problematic incentive- or reward-based behaviors such as compulsive gambling. (A more extensive discussion of possible pathophysiological mechanisms can be found in Voon et al. (2007).)

It is unclear, however, why only a subset of patients treated with dopamine agonists become excessively engaged in rewarding behaviors. One hypothesis is that these patients have an underlying biological vulnerability—such as a polymorphism in the gene that codes for the D_3 receptor—conferring risk for addiction. It is also uncertain why patients treated with dopamine agonists tend to develop problems with gambling as opposed to other rewarding behaviors (e.g., compulsive shopping, hypersexuality, or binge eating).

One animal study has found that pramipexole renders unpredictable rewards more attractive (Johnson et al. 2011), suggesting that gambling in particular may become more rewarding as a consequence of treatment. Regardless of the exact mechanism that may explain these complex behaviors, clinicians should be alerted to the risk of impulsive behaviors associated with the use of dopamine agonists.

Conclusion and Clinical Pearls

Second-generation dopamine agonists (i.e., pramipexole, ropinirole) are linked to impulsive behaviors such as disordered gambling, hypersexuality, and compulsive shopping. These behaviors typically resolve when the dopamine agonist is reduced or replaced with an alternative medication. To reduce the risk of complications, clinicians should obtain a personal and family history of impulsive/compulsive disorders prior to prescribing dopamine agonists and use the lowest effective dosage (Weintraub 2008). Once treatment has begun, patients should be monitored for the development of problematic behaviors using the Minnesota Impulsive Disorders Interview or an equivalent instrument. Early recognition of impulsive symptoms in patients treated with dopamine agonists may significantly improve their quality of life.

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Chapter 19
RLS Caused by Over-the-Counter Medications/ Bruises on My Legs

Elisa Basora, Anna Wani, and S. Kamal Naqvi

Chapter Outline

- Sleep disorders may have different presentations for which sleep history is fundamental in identifying and characterizing them.
- Common over-the-counter medications can cause significant side effects that could precipitate or worsen other medical conditions.
- Sleep disorders are commonly linked to psychiatric illnesses with similar symptoms, difficult to distinguish one from the other.
- Restless legs syndrome in the pediatric population encompasses a broader criteria than adults and is more challenging to identify.

E. Basora (✉) · S. K. Naqvi
Department of Pediatrics – Respiratory Medicine,
UT Southwestern Medical Center, Dallas, TX, USA
e-mail: elisa.basorarovira@utsouthwestern.edu

A. Wani
Department of Pediatrics and Family Community Medicine, UT Southwestern Medical Center, Dallas, TX, USA

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Clinical History/Case

A 17-year-old female was brought by ambulance to a local emergency department with altered mental status and hypersomnolence after she was found unarousable at home by her mother. An empty bottle of diphenhydramine was found next to her bed. Patient was also found to have dry oral mucosa, flushed face, tachycardia, and nausea. Once alert, patient reported that she ingested 30 over-the-counter 25 mg diphenhydramine tablets, due to difficulty to fall asleep. She was adamant that this gesture was not an intentional overdose. Her symptoms usually start with leg discomfort after dinner accompanied with more than 2 hours of sleep-onset latency. She "punches" her legs in the evening to get relief from the restlessness in her legs. Symptoms started 5 years ago after a motor vehicle accident with subsequent lower back injuries. Diphenhydramine dose was increased over time, without medical supervision. There is no past medical or surgical history and was not taking any other medications. The review of systems was positive for depressive mood with no suicidal ideations, anxiety at bedtime, and daytime sleepiness and was negative for drug use, trauma, or abuse. Strong family history of restless legs syndrome in her mom and aunt.

Examination/Mental Status Exam

Physical exam revealed a drowsy young female with slow mentation, otherwise intact neurologic status. Pulse was 96 beats/minute, respiratory rate was 16 breaths/minute, and blood pressure was 100/60 mmHg and SpO_2 of 97%. No increase work of breathing. The remainder examination of the cardiovascular and pulmonary systems was normal. Her oropharynx was Mallampati grade II, tonsil size 1+. Skin examination showed bruising on both upper thighs at different stages of healing (Fig. 19.1).

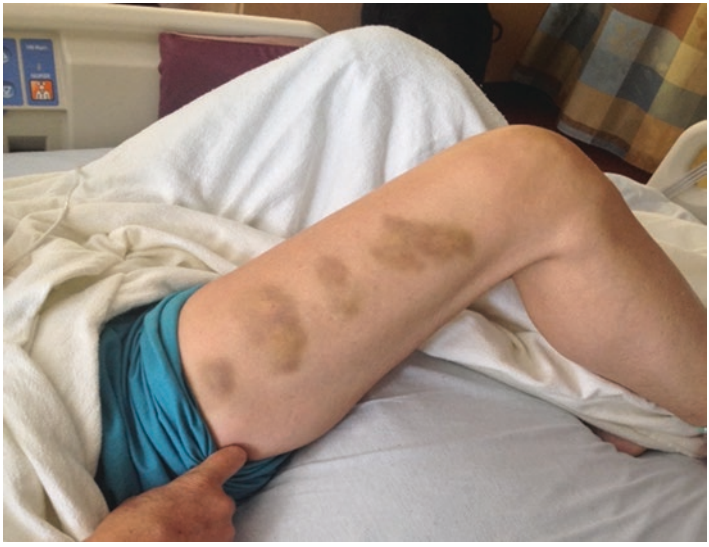

FIGURE 19.1 Patient with bruises at different stages of healing on right upper thigh

Special Studies/Results

Laboratory testing did not show any other intoxications. No electrolytes abnormalities. Sinus rhythm on electrocardiogram (EKG). Ferritin level was 67 ng/mL (normal range: 10–70 ng/mL). Head CT scan was unremarkable.

Question

1. What is the cause of sleep-onset insomnia in this young female?
2. What made her "insomnia" worse?

Answer

1. Restless legs syndrome (RLS)/Willis-Ekbom disease (WED)
2. Diphenhydramine (antihistamine medications)

Differential Diagnosis and Diagnosis

During the evaluation of insomnia, it is important to identify essential features in the sleep history to differentiate between other sleep disorders. The *International Classification of Sleep Disorders* (ICSD-3) defines insomnia as the persistent difficulty of sleep initiation, duration, consolidation, or quality that results in daytime impairment. Insomnia can be classified as chronic, short-term insomnia or other disorder contingent on frequency and duration of symptoms. Medical illnesses and psychiatric disorders are often associated with insomnia.

In this case, difficulty to fall asleep was associated with other sleep disorder, restless legs syndrome, main etiology of patient's sleep-onset insomnia, and/or nonrestorative sleep. Important aspects of her history and physical exam were the key to pinpoint this clinical diagnosis. The delayed diagnosis and her lack of awareness of the effects of diphenhydramine on RLS prolonged and complicated her illness and resulted in self-injury and hospitalization.

Restless legs syndrome, also known as Willis-Ekbom disease (WED), is a common disorder that affects 7% of the American and European adult population. It is also frequent in the pediatric population, affecting 2% of children between 8 and 17 years old. There is a higher prevalence of RLS/WED cases in female sex, increasing age, and patients with a positive family history. Other factors as iron deficiency, medications, chronic renal failure, pregnancy, and immobility may precipitate and worsen symptoms. Medical conditions as ADHD, depression, anxiety, narcolepsy, neuropathy, and thyroid and heart disease have strong associations with RLS.

It is classically described as an urge to move the legs when resting, with commonly associated dysesthesia, circadian appearance, and temporary relief by motion. These four criteria can be used for adolescent and adult population. However, in children from ages 2 to 12 years, pediatric RLS criteria consist of the above symptoms, child's own description of leg discomfort and two of three supportive criteria that includes sleep disturbance, family history of RLS, and/or periodic limb movements of sleep index >5/hour. Many common classes of medications such as antihistamines, anticholinergics, antidepressants,

and dopamine receptor antagonists can exacerbate RLS symptoms. A histaminergic abnormality related to increased hypocretin has been the proposed mechanism for RLS exacerbation with antihistamines. These symptoms can be severe, RLS can cause sleep-onset or sleep-maintenance insomnia, unrestorative sleep, and poor quality of life. In this case, she had an intentional non-suicidal ingestion of high doses of diphenhydramine in an attempt to treat her insomnia. Her depressive mood can be associated with a comorbid psychiatric condition or a manifestation of many years of sleep frustration.

Increased sleep-onset latency is one of the most common sleep disturbances in children and adolescents with psychiatric disorders. It is comorbid with anxiety, depression, bipolar, and obsessive-compulsive disorder. Patients with schizophrenia may also exhibit insomnia as paranoia interferes with the ability to fall asleep. Disruptions of sleep can have an emotional impact leading to changes in behavior and development of psychiatric illnesses. Untreated psychiatric conditions can be the cause of perpetual sleep disturbances with further deterioration of neurobehavioral functions.

RLS therapy starts by treating the underlying cause, discontinuation of RLS symptom activator drugs, iron supplementation, and behavioral modifications as caffeine avoidance, good sleep hygiene, avoiding exercise before bed, warm bath, and relaxation techniques. Other treatments as dopaminergic drugs, anticonvulsants, benzodiazepines, and opioids have been used off-label as no current FDA-approved options are available in children.

Pearls/Take-Home Points

- RLS can be associated with insomnia, nonrestorative sleep, and disturb sleep quality.
- RLS can be caused or exacerbated by commonly used medications like antihistamines.
- Comprehensive evaluation and medication review by healthcare providers should be performed in all patients with sleep disturbances.
- Psychiatric illnesses should always be taken into consideration when treating patients with sleep disorders.

Suggested Reading

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Chapter 20
Is This Akathisia or Restless Legs?

Differentiating Akathisia from Restless Legs Syndrome

Ahmed Qureshi and Khurshid A. Khurshid

Introduction

Restless legs syndrome (RLS) is common in patients with psychiatric disorders. It has a prevalence rate of 5–15% in the general population. The disorder is thought to be related to dysfunction of iron and dopamine metabolism in the central nervous system. Epidemiology indicates that there is a two to fourfold increase in risk of developing depressive disorders in those with RLS as compared with healthy controls [1]. Additionally, it can be a result of medication used to treat psychiatric symptoms such as antidepressants or antipsychotics [2, 3, 4]. According to the DSM-5, restless legs syndrome is defined by an "urge to move the legs, usually accompanied by or in response to uncomfortable and unpleasant sensation in the legs." The urge begins or worsens

A. Qureshi
Department of Psychiatry, VA Medical Center, Orlando, FL, USA

K. A. Khurshid (✉)
Department of Psychiatry, University of Massachusetts Medical School, Worcester, MA, USA
e-mail: khurshid.khurshid@umassmemorial.org

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during periods of rest or inactivity, is partially or totally relieved by movement, and is worse in the evening or night compared to during the day or occurs only in the evening or night. These symptoms must occur at least three times per week and have persisted for at least 3 months and must cause distress in distress or impairment in important areas of daily functioning. The diagnosis is excluded in cases when the symptoms are better explained by an existing mental condition, medical condition (i.e., peripheral vascular disease, tissue damage), or recreational drug use [5].

Akathisia is a syndrome that is characterized by its relationship to dopamine and the use of psychiatric medications. The DSM-5 defines acute akathisia by subjective complaints of restlessness, often accompanied by observed excessive movements (such as leg movements, pacing, rocking from foot to foot, or inability to stand or sit still) developing within the first few weeks of starting or raising the dosage of a medication or after reducing the dosage of a medication used to treat extrapyramidal symptoms [5]. It prohibits patients from sitting still or lying quietly in bed. Due to a psychological urge, patients often march with their legs, shuffle in place, or rock back and forth. This condition is thought to have originated from excessive dopamine blockade.

These two syndromes are often confused with each other. A few key features can help distinguish akathisia from RLS: (1) patients with akathisia do not have the paresthesias that RLS patients do; (2) in akathisia, the movements are not related to sleep; and (3) movement does not relieve the urge in Akathisia [2, 6]. We describe a case below that illustrates this difference and how knowledge of these differences can result in effective treatment of patients' symptoms.

Case Scenario

The patient is a 70-year-old male with a history of treatment-resistant major depressive disorder who was admitted to a psychiatric unit for treatment of his severe depression

anxiety with ECT. The patient exhibited severe recurrent episodes of depressed mood, anhedonia, poor energy, weight loss, and problems with sleep onset and maintenance and passive death wish. He also exhibited symptoms of anxiety and severe restlessness. On admission, the patient was minimally verbal due to severe depression but was demonstrating significant pacing throughout the day. Additionally, the patient's wife reported significant leg movements which did not relieve the patient's restlessness which had been going on for months. He was prescribed pramipexole by a neurologist which offered minimal treatment of his "restless legs" that his wife was concerned about. On day 1 of admission, it was observed that his symptoms of restlessness persisted throughout the day with a lack of diurnal variation.

Past Medical History

Coronary artery disease, hypertension, hyperlipidemia, benign prostatic hypertrophy.

Medications

His current prior-to-admission medications were pramipexole 2 mg po qhs, olanzapine 10 mg po qhs, duloxetine 60 mg po qdaily, atorvastatin 20 mg po qhs, ramipril 5 mg po qdaily, and tamsulosin 0.4 mg po qpm.

Family History

His family history was positive for depression in his father, brother, and paternal grandfather. He was unaware if they were treated with medication for depression, and there was no family history of suicide.

Vital Signs/Mental Status Exam

His vital signs were blood pressure 129/78, pulse 66, respiration rate 16, and temperature 96.8 F. He appeared well groomed and appeared stated age, though he was pacing the hallway slowly. He was guarded with interview and had poor eye contact. He appeared to have psychomotor agitation with significant restlessness. In terms of gait, he had normal stance but had a hunched posture and ambulated slowly. His speech was hesitant, soft, and slow. He identified his mood as depressed and appeared constricted in affect. His thought process was linear, and his thought content demonstrated passive death wish but without psychotic symptoms or delusional thinking. His memory appeared intact, and he was alert and oriented to person, place, time, and situation. His insight was fair though his judgment was limited.

Differential Diagnosis

- Restless legs syndrome.
- Neuroleptic-induced akathisia.
- Major depressive disorder, severe, recurrent, without psychotic features.
- Generalized anxiety disorder.
- Substance intoxication.
- Substance withdrawal.
- Adult attention hyperactivity disorder.

Labs

Relevant labs include hemoglobin 12.0 g/dL (normal), mean corpuscular volume 96.2 fL (normal), ferritin 173.9 ng/mL (normal), iron 54 μg/dL (normal), total iron binding capacity 330 μg/dL (normal), iron saturation 16% (low), TSH 0.421 mIU/L (normal), vitamin B12 level 736 pg/mL (normal), urinalysis negative, and urine drug screen negative.

Final Diagnosis

- Neuroleptic-induced akathisia.
- Major depressive disorder, severe, recurrent, without psychotic features.

Question 1

What interventions would you recommend for this patient?

Case Follow-Up and Discussion

Given the lack of diurnal variation and the presence of antipsychotics in his medication history, his olanzapine dose was reduced to 5 mg on day 3 of admission with some improvement in symptoms. Given that olanzapine was giving him some benefit in terms of antidepressant augmentation and the persistence of his residual restlessness, the treatment team decided to start propranolol on day 9 of admission which resulted in resolution of his symptoms. The patient was ultimately diagnosed with acute akathisia likely induced by his olanzapine. In terms of his depression, the patient went on to receive a course of ECT leading to improvement in depression.

Restless leg syndrome and akathisia are common in patients with psychiatric disorders. These two disorders can exacerbate psychiatric symptoms. They can also be a treatment-emergent adverse effect. It is important to recognize these two disorders. Tables 20.1 and 20.2 indicate some of the similarities and differences between RLS and akathisia. In this case, given the lack of diurnal variation in symptoms, failure of movements to provide relief and response to pramipexole, and near resolution of symptoms by reducing his neuroleptic dose and the initiation of propranolol, the patient above likely had akathisia induced by olanzapine. Akathisia is usually caused by dopamine-blocking agents,

Table 20.1 Similarities between RLS and akathisia

1. Sensation or feeling of restlessness
2. Urge to move
3. Caused by central dopamine blockade or dopamine hypofunction

Table 20.2 Differences between RLS and akathisia

1. Leg discomfort	No particular leg discomfort
2. Restlessness in legs or arms	Overall restlessness
3. Worse or only in evenings/ nighttime	No diurnal variation
4. Family history of RLS	No family history of RLS
5. No improvement with beta-blockers	Improvement with beta-blockers

and treatment is either removing the offending agent or treatment with a beta-blocker. In contrast to this, though RLS can be triggered or exacerbated by the use of certain antidepressants and antipsychotics and removing the offending agent can be significantly helpful, treatment of restless legs often requires the use of dopamine-blocking agents or the use of iron supplementation (in cases of iron deficiency) to provide relief [1, 2]. Given the clinically divergent treatment approaches to each condition, this case illustrates the importance of using key clinical features to distinguish between restless legs syndrome and neuroleptic-induced akathisia.

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Chapter 21
Depression and Insomnia

LaDonna Saxon

Chapter Outline

- Insomnia may occur as a symptom of depression or be a separate clinical condition that may co-occur with depression and other mental health conditions.
- Taking a thorough sleep history is necessary to diagnose and identify behavioral targets for intervention.
- Treating insomnia directly can improve depressive symptoms in many patients.

Clinical History/Case

A 64-year-old married, cisgender male was referred to mental health by his primary care physician due to concerns of depression and poor sleep, which are known to co-occur [1]. The patient is most concerned about ongoing sleep problems,

L. Saxon (✉)
Department of Mental Health, Veterans Affairs Medical Center, Dallas, TX, USA
e-mail: ladonna.saxon@va.gov

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to which he attributes low energy, difficulty concentrating, and irritability. He is also concerned that his lack of sleep may contribute to errors with his mother's medications, as he is her primary caregiver. He acknowledges some periods of low mood but attributes this to his lack of restorative sleep. In addition to insomnia, the patient's medical history is significant for hypertension, which is well controlled with medication. He also has chronic arthritis pain for which he uses over-the-counter oral medications and topical creams. He is a previous tobacco user, now abstinent for 15 years. He endorsed a remote history of occasional cannabis and methamphetamine use but denied any use in the past decade. On average, he consumes 1–2 alcoholic beverages weekly and 1 pot of coffee daily. His only allergy is to the medication flagyl.

Sleep History

Patient reports having disrupted sleep for approximately 6 years, with the onset coinciding with job loss. He has a history of shift work but rotated to a 7 a.m.–4 p.m. shift consistently for the last 5 years of his employment. Patient denied any significant difficulty adjusting to an earlier work schedule, as he stated he always felt better working during the day. Despite his age, gender, body mass index of 32, and diagnosis of hypertension, the patient did not have obstructive sleep apnea per a recent sleep study summary report from a non-network provider. Patient denied symptoms of restless leg syndrome, any history of sleepwalking, late night binge eating, or nightmares. The patient attributes the onset of sleep problems to frequent worry about being able to meet his financial obligations and low self-worth after not being able to find further employment and financially support his family. At the time of this assessment however, he no longer reported significant worry about finances as he says his family made adjustments to their current income constraints. Clinical interview revealed numerous behaviors that adversely impact sleep such as napping during the day, spending excessive time

in bed while not sleeping, irregular rise times, and excessive caffiene intake. When unable to fall asleep, the patient tends to lay in bed ruminating about possible ill effects of not sleeping. The patient was asked to maintain a sleep diary for 2 weeks after the initial consultation to provide supporting documentation of sleep habits. The results indicated an average latency to fall asleep of 99 minutes, with 94 minutes awake after sleep onset. His average time in bed was just over 10 hours with his total sleep time just under 6 hours, yielding a sleep efficiency of 59.35%.

Assessment Measures

Several assessment measures were completed at the initial appointment, including the Insomnia Severity Index (ISI) [2], on which he scored in the severe clinical insomnia range, and the Epworth Sleepiness Scale [3] on which he scored a 6 (normal range). On the Smith Measure of Morningness/Eveningness [4], he scored in the intermediate range, reflecting neither a strong preference for being awake in the early morning nor late evening hours. Given the patient's early reports of worry interfering with sleep, self-criticalness related to his employment status, and endorsement of symptoms that can overlap with insomnia and mood disturbances (irritability, fatigue, changes in sleep, and difficulty concentrating), he was asked to complete a Generalized Anxiety Disorder Assessment-7 (GAD-7) [5] and a Beck Depression Inventory-II (BDI-II) [6]. On the GAD-7, he scored in the mild range, endorsing symptoms consistent with his sleep complaints: difficulty relaxing, being irritable, and feeling restless. He described the restlessness as occurring at night when he had trouble getting to sleep. During the day he said he was "too busy with chores" to feel restless. On the BDI-II, he scored in the severe range of depressive symptoms. Symptoms endorsed on the measure included sadness, feelings of worthlessness, indecisiveness, loss of interest in sex, and increased appetite in addition to the common symptoms already previously described. He adamantly denied any

thoughts of self-harm, citing religious beliefs and obligations to family as barriers to such acts. The patient stated that he did not begin experiencing sadness and worthlessness until approximately 6 months after his job loss, as he was initially optimistic he would find work. Moreover, he states that while now he feels sad 1–2 days/week, he states that he does not experience sadness every day and his current mood represents a significant improvement than in the past, an improvement he attributes to his role in helping his family members. The patient also stated that although his appetite is increased, he attributes this to his increased role in preparing meals for family; because food is a significant part of each day, he is eating more. Overall, while some depressive symptoms are present, his endorsements on the BDI-II alone seem to be an overestimate of his current level of mood disturbance when his clinical interview is taken into account.

Special Studies

No special studies were ordered.

Consultation

Discussed nighttime urination frequency with patient's primary care provider who subsequently instructed client to switch his furosemide dose, prescribed for hypertension management, from evening to morning.

Question

1. What are the precipitating factors related to the onset of insomnia?
2. What are the perpetuating factors related to the maintenance of insomnia?

Answer

1. Job loss and subsequent psychiatric distress
2. Spending excessive time in bed not sleeping, irregular rise times, naps, excessive caffeine intake, depression

Diagnosis

Based on the clinical history, it is likely that the patient previously met criteria for major depressive disorder (MDD); however at the time of this evaluation, he does not meet criteria for MDD as he does not meet the hallmark symptoms of depressed mood or loss of interest or pleasure in most activities, most of the day nearly every day per the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5) [7]. Because he does seem to experience some residual symptoms of sadness, worthlessness, and loss of interest in sex, in addition to common and overlapping symptoms associated with insomnia, a diagnosis of unspecified depressive disorder can be justified at present. The patient also meets criteria for insomnia disorder, persistent. As outlined in the DSM-5, a diagnosis of insomnia disorder is given when it occurs as an independent condition or is comorbid with another psychiatric disorder, provided that the insomnia is sufficiently severe to warrant independent clinical attention. In this patient's case, insomnia is the primary presenting concern causing him distress and the sole reason he sought out mental health assistance.

Treatment

An explanation of evidence-based psychotherapy as well as medication management was outlined as possible ways of addressing his depressive symptoms directly. Additionally the client was provided an overview of cognitive behavioral

therapy for insomnia (CBT-I) and its efficacy [8–10]. In collaboration with the client, the decision was made to initiate CBT-I as a first-line treatment, as CBT-I alone has been found to reduce depressive symptoms to nonsignificant levels, particularly if the depressive symptoms are mild [11]. CBT-I commonly includes aspects of stimulus control, sleep restriction, and cognitive therapy. Relaxation training and sleep hygiene education are also often included, and this case was no exception. The patient also agreed to gradually reduce his coffee intake from one pot per day to two cups in the morning.

Over the course of 6 weeks of CBT-I therapy, the patient's sleep latency onset decreased to an average of 10 minutes, and minutes awake after sleep onset decreased to an average of 20 minutes. Additionally, he spent less time in bed when not sleeping. These changes resulted in significantly improved sleep efficiency (90%). His total sleep time increased to 7 hours. Contributory factors to his success included sleep drive strengthening though the elimination of daytime napping, improved stimulus control by not remaining in bed when not sleeping, and changing his dosing of furosemide from evenings to mornings. Additionally the patient's willingness to decrease his coffee intake was helpful in that it not only reduces the stimulating effect of caffiene, but also its dieuretic effect, which also likely contributed to his nightime wakings. Over the course of the therapy, his ISI decreased to 8 (subclinical insomnia), and his BDI-II decreased to 12 (minimal depressive symptoms).

Pearls/Take-Home Points

- Insomnia is often comorbid with other mental or medical disorders.
- CBT-I has been shown to produce improvements in commonly measured sleep parameters among patients with concurrent medical and/or mental health diagnoses.
- It is not always necessary to maximize treatment of other conditions before proceeding with CBT-I.

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Chapter 22
Insomnia and OSA

Elizabeth E. Sita and Hrayr P. Attarian

Clinical History

A 30-year-old woman presented on referral from her primary care physician for evaluation of insomnia. She reported onset of sleep difficulties at the age of 12 after her elderly grandmother experienced a sleep-related seizure; since that time she endorsed regular nighttime awakenings, which she attributed initially to a desire to monitor her grandmother, although this pattern persisted following her grandmother's death. On average, she estimated sleeping 3–4 hours per night, with substantial daytime fatigue and a borderline Epworth Sleepiness Scale (ESS) score of 10/24.

She reported a consistent bedtime of 11 p.m. with lights simultaneously out and a sleep latency of only a few minutes. However, she awoke regularly each night around 2 or 3 a.m. There was uncertainty regarding the cause of this arousal, but it was noted that upon awakening she experienced "racing thoughts" and was unable to return to sleep for any meaningful

E. E. Sita (✉)
Department of Psychiatry, Northwestern Medicine, Chicago, IL, USA

H. P. Attarian
Department of Neurology, Northwestern Medicine, Chicago, IL, USA
e-mail: h-attarian@northwestern.edu

I. S. Khawaja, T. D. Hurwitz (eds.), *Comorbid Sleep and Psychiatric Disorders*, https://doi.org/10.1007/978-3-030-11772-6_22

period of time for the remainder of the night. She instead slept in short periods and experienced 2–3 prolonged awakenings. During these she often read, attended to work-related matters, or did relaxation exercises before getting out of bed at 7 a.m. to start her day. She was briefly prescribed trazodone 50–75 mg at bedtime, which she took for roughly 1 year with little reported benefit or change in sleep patterns. She denied caffeine use or daytime naps.

On review of systems, the patient noted being told by others that she snored loudly and also endorsed intermittent nasal congestion. She did not recall ever being awakened gasping for air nor had such an event or an observed apnea been reported by others. She denied bruxism, dry mouth, or morning headaches. She denied sleepwalking or talking yet endorsed jerking her legs from time to time. She also endorsed rare dream-enacting behavior that resulted in light bruising during a dream about falling down the stairs. There was also a brief period of time in which she experienced distal upper and lower extremity paresthesias several years prior to her presentation. However, this sensation was not associated with time of day or made worse by inactivity and did not remit with movement; the phenomenon resolved within a year and without intervention. She further denied sleep attacks, hypnic hallucinations, sleep paralysis, cataplexy, nightmares, or symptoms of post-traumatic stress disorder.

Her past medical history was notable for obesity, asthma, and gastroesophageal reflux disease, as well as seasonal and food allergies. She was managed on fluticasone-salmeterol 100–50 mcg/dose 1 puff twice daily, albuterol sulfate 108 (90 base) mcg/dose 1–2 puffs every 4–6 hours as needed for shortness of breath, and epinephrine 0.3 mg/0.3 mL IM once as needed for anaphylaxis. She also intermittently took over-the-counter medications for seasonal allergies as well as an oral contraceptive.

Her social history was negative for tobacco or illicit drug use, and she endorsed only occasional alcohol use. She reported frequent travel for work as a financial advisor and observed that she slept better when traveling, particularly to

the East Coast. Family history was negative for obstructive sleep apnea, narcolepsy, or restless leg syndrome, although she believed her mother experienced unspecified and untreated difficulties with sleep.

Examination

The patient was noted to have a body mass index of 39.17 kg/m^2 but was otherwise well-appearing and in no acute distress. Her examination was remarkable for a Mallampati class II airway, with visible anterior pillars and uvula but enlarged adenoids obstructing view of the posterior pillars. She was without septal deviation but did have enlarged turbinates with copious secretions. Neck circumference was 43.2 cm. Her cardiovascular, respiratory, abdominal, and neurologic exams were unremarkable.

Special Studies

In view of her report of snoring as well as an examination remarkable for obesity and a somewhat crowded airway with increased neck circumference, a home sleep apnea test (HSAT) was ordered, and a type III unattended seven channel polysomnogram was obtained (Fig. 22.1). Findings demonstrated an apnea-hypopnea index (AHI) of 10.3 with more frequent events appreciated in the supine position (AHI 29.2); her peripheral capillary oxygen saturation, or SpO_2, nadir was 84% (Table 22.1).

Results

The clinical history, physical examination, and polysomnographic findings were suggestive of a mild obstructive sleep apnea, and the patient was advised to initiate automatic continuous positive airway pressure (auto-CPAP) with 5–15

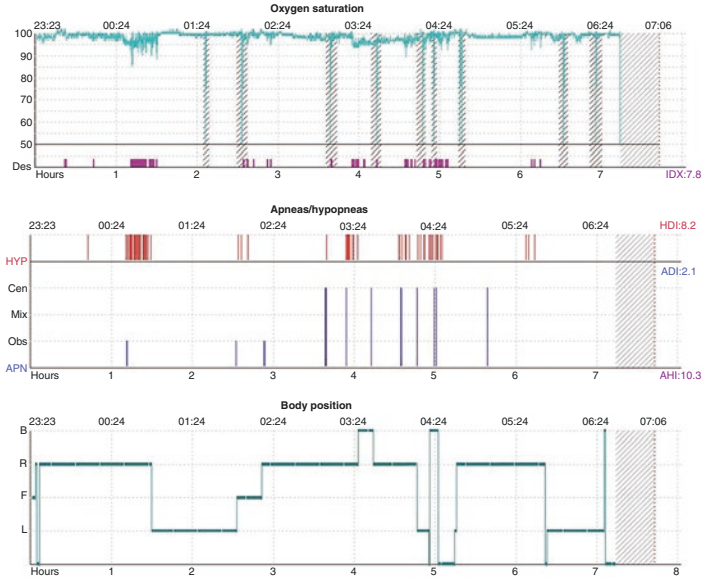

FIGURE 22.1 Data graphs from polysomnogram obtained during home sleep test

centimeters of water pressure (cwp). Cognitive behavioral therapy for insomnia was also recommended given evidence of middle insomnia, although the patient completed only initial intake without additional sessions. At subsequent follow-up appointments, she reported good adherence with CPAP and significant improvement in symptoms of insomnia with complete resolution of her presenting concerns at the 1.5 year mark. At this time, data from her CPAP machine demonstrated 90% usage with an AHI of only 0.4 at a median pressure of 7.6 cwp (Table 22.2).

Question

What is the relationship between insomnia and obstructive sleep apnea?

Table 22.1 Summary of polysomnographic findings

Time (minutes)	Total	Supine	Left	Right	Prone	Sitting
	433	18	116	253	21	23
Apneas	Total	Central	Obstructive	Mixed	Apnea index	Average duration (s)
	15	10	5	0	2.1	16
Hypopneas	Total					Average duration (s)
	59					28
Positional AHI	Total	Supine	Left	Right	Prone	Sitting
	10.3	29.2	3.1	12.8	8.4	5.2
O_2 saturation (% time in range)	Baseline	61–70%	71–80%	81–90%	91–100%	SpO_2 nadir
	97%	0.00%	0.00%	0.49%	99.45%	84%

Table 22.2 Summary of findings on CPAP download after 1.5 years of treatment

Usage days	Total (%)	≥4 hours (5)	<4 hours (%)
	27/30 (90)	27 (90)	0 (0)
Usage hours	Total	Average (days used)	Median (days used)
	174 hours 59 minutes	6 hours 29 minutes	6 hours 53 minutes
Pressure	Median (cwp)	95th Percentile (cwp)	Maximum (cwp)
	7.6	10.7	12.2
Events/ hour	AI	HI	AHI
	0.3	0.1	0.4

Differential Diagnosis

The initial history obtained from this patient was most suggestive of a primary insomnia disorder, specifically middle insomnia, also known as sleep maintenance insomnia. However, a breathing-related sleep disorder was also on the differential by history and exam, and a mild obstructive sleep apnea was confirmed on polysomnogram. While primary insomnia and obstructive sleep apnea may be comorbid, in this instance the patient's difficulty maintaining sleep resolved completely with adherence to CPAP therapy. This suggests that her middle insomnia was a symptom of OSA rather than a comorbid disorder.

Remarks

Insomnia and obstructive sleep apnea are the most common disorders of sleep, and there is growing appreciation for clinically meaningful overlap and comorbidity among the two, as

can be seen in this case. Historically, insomnia and OSA were conceptualized as divergent disorders, with the former seen as a process of hyperarousal and associated fatigue and the latter dominated by excessive sleepiness owing to micro-arousals and fragmented sleep. However, a growing body of literature suggests more convergence than previously recognized and highlights the need for awareness of a complex interplay between the two.

Insomnia is a heterogeneous disorder with both sleep and waking symptoms. It is generally characterized by subtype based on sleep-specific concern, namely, difficulty falling asleep or initial insomnia, difficulty maintaining sleep or middle insomnia, early morning awakening or late insomnia, or some combination thereof. Notably, it is often the functional impairment, rather than the sleep-specific concern, that leads people to seek treatment. Patients report daytime symptoms such as fatigue, cognitive disruptions to attention, concentration, and/or memory, as well as emotional disturbances including irritability and depressed mood, which in turn may contribute to social, academic, or vocational limitations [1]. Experts generally agree that, when attempting to characterize insomnia, qualitative concerns owing to the extent of daytime impairment be taken into consideration along with more quantitative, sleep-specific symptoms. For research purposes, quantitative symptoms are often characterized as sleep-onset latency or waking after sleep onset for longer than 30 minutes occurring three times per week for at least 6 months [2].

Obstructive sleep apnea is a disorder characterized by complete or partial upper airway collapse leading to frequent apneic and hypopneic events in spite of persistent efforts at ventilation. Severity is generally graded by the number of events per hour of sleep as defined by the apnea-hypopnea index (AHI), with 5–14 events considered mild OSA, 15–29 events moderate, and 30 or more events severe. The textbook presentation of OSA is that of a middle-aged, obese man with excessive sleepiness who reports gasping/choking arousals, disruptive snoring, witnessed apneic episodes, and early

morning headache. However, not all patients with OSA fit this stereotype, and symptoms should not be dismissed in those who do not present with the characteristic "Pickwickian" habitus. Neck circumference, nasal congestion, narrowed nasal cavities, micrognathia, retrognathia, tonsillar hypertrophy, and the postmenopausal hormonal milieu also play an important role and should be considered [3].

Although insomnia and OSA are often conceptualized in opposing fashion, there are many areas of overlap in clinical presentation, particularly as it relates to daytime symptoms and functional impairment (Fig. 22.2). In addition to frequent nighttime awakenings, patients with insomnia or OSA often report unrefreshing sleep, cognitive disturbance, and psychological difficulties, as well as decreased quality of life with limitations in social, academic, and vocational endeavors. It is not surprising, then, that an association between the two was first observed by Guilleminault and colleagues in 1973. This seminal paper reported two cases of patients with chronic insomnia subsequently found on respiratory studies to suffer apneic episodes while sleeping. The authors postulated that concurrent insomnia and sleep apneas represented an as of

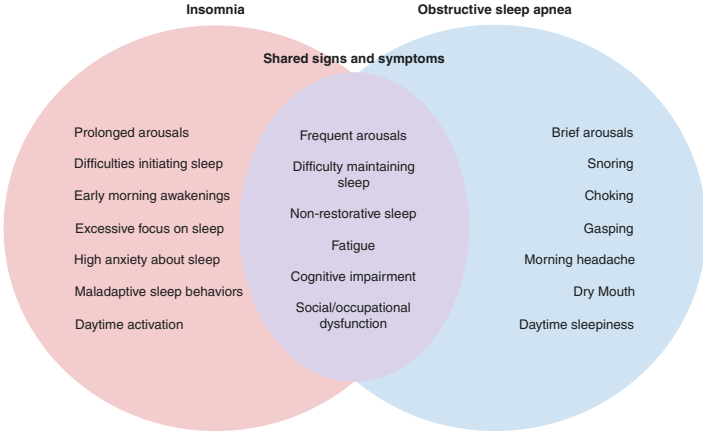

FIGURE 22.2 Interplay of signs and symptoms in insomnia and obstructive sleep apnea. Adapted from Luyster et al. [29]

yet unappreciated but clinically significant syndrome in the field of sleep medicine [4].

It was nearly 30 years before renewed interest was demonstrated in Guilleminault's initial observations. In 2001, Krakow and colleagues reported a 50% prevalence of clinically apparent insomnia in a retrospective analysis of 231 patients with objectively diagnosed sleep-disordered breathing, namely, obstructive sleep apnea or upper airway resistance syndrome [5]. Subsequent research confirmed high rates of concurrence, with estimates of insomnia ranging from 34% to 84% among select patient populations with confirmed OSA [6, 7]. Similarly, rates of OSA have been reported from 17% to 71% among various samples of patients with clinically diagnosed insomnia [8, 9]. The wide variability in prevalence is likely multifactorial, reflecting features of the patient group sampled as well as variability in diagnostic criteria employed for each disorder.

While insomnia and OSA both carry increased risk of adverse cardiovascular events, the literature is equivocal as to whether these risks are additive when both disorders are present. For example, Vozoris reported after retrospective analysis of a large national epidemiologic database that patients with both insomnia and OSA and with OSA alone had elevated rates of hypertension, diabetes, congestive heart failure, myocardial infarction, and stroke. However, rates between groups did not differ to a degree of statistical significance [10]. A subsequent retrospective analysis of a second large national database by Gupta and Knapp found, to the contrary, that rates of essential hypertension were significantly higher among those with insomnia and OSA compared to those with OSA alone; this study also found a significantly increased risk for cerebrovascular disease among the former group, although the finding was limited by the number of cases, which was too low to meet reliability criteria [11].

More consistently, research has demonstrated an additive adverse effect on quality of life among patients with insomnia and OSA compared to OSA alone. Patients with both disorders report significantly greater rates of sleep disturbance –

including sleep-onset latency, sleep maintenance, and sleep efficiency – as well as more daytime impairment, including poor attention/concentration, higher rates of absenteeism, and overall self-report of worse physical and mental health [12–14]. They also report significantly higher rates of chronic pain, experience significantly more symptoms of depression and anxiety as measured by the Beck Depression and Anxiety Inventories, and generally hold more dysfunctional health beliefs regarding sleep and sleep behaviors [15, 16].

There are multiple theories to characterize the pathophysiologic interplay between insomnia and OSA. However, no single theory thus far has provided a unified explanation, and it is exceedingly likely that the interaction is multifactorial and quite complex. It has been suggested that insomnia is a consequence of the pathophysiology of OSA, that insomnia may perpetuate symptoms of OSA, and, more recently, that insomnia and OSA are reciprocally related and each may in turn exacerbate the other.

Proposals include the observation that brief arousals (be they obstructive or otherwise) may be perceived as extended periods of wakefulness, which may then be characterized as insomnia [17]. It has also been noted that obstructive arousals may lead to sympathetic nervous system activation, which may then contribute to subjective and objective symptoms of anxiety. Anxiety in turn may lead to maladaptive sleep behaviors (such as clock-watching or worrying about sleep) that promote or perpetuate insomnia [18]. It has been observed that sleep loss from insomnia may reduce upper airway tone, thereby exacerbating OSA, with evidence that sleep deprivation/fragmentation leads to more frequent and more severe apnea [19, 20]. Finally, it has been suggested that insomnia and OSA may occur on opposite sides of a sleep fragmentation continuum. To this end, activation of the hypothalamic-pituitary axis (HPA) has most recently been implicated. This is in large part due to growing appreciation for the metabolic and endocrine effects of both insomnia and OSA, making the HPA a potential shared pathway through which one disorder may influence the other [21].

Treatment approaches for both insomnia and OSA are well-defined and evidenced-based. However, the standard of care when both disorders are present is less clear and an area of ongoing research. Currently, the gold standard for the treatment of non-acute insomnia is cognitive behavioral therapy for insomnia (CBT-I) with a select role for augmentation with benzodiazepine receptor agonists (both non-benzodiazepine and benzodiazepine agents), exogenous melatonin, or a melatonin receptor agonist when clinically indicated. A number of medications are also used off-label in the treatment of insomnia, including antidepressants, antipsychotics, and mood stabilizers with sedative-hypnotic properties. First line for the treatment of moderate-to-severe OSA is CPAP therapy. More conservative approaches in the setting of mild disease include weight loss, positional therapies, and oral devices. Surgical approaches such as uvulopalatopharyngoplasty or hypoglossal nerve stimulator implantation may be appropriate in select cases, although they are generally not recommended.

Anecdotal evidence and emerging research suggest that outcomes are improved by treating both disorders in the case of concurrence. Patients treated for insomnia who remain symptomatic have demonstrated benefit from evaluation for and treatment of even mild cases of OSA or other sleep-related breathing disorders [22, 23]. Alternatively, responders versus nonresponders in the treatment of OSA have been differentiated by the absence or presence of symptoms of insomnia, accordingly [24]. Further, there is evidence of worse adherence to CPAP therapy among patients with insomnia, although some discrepancy exists as to which type of insomnia portends worse outcomes [25–27]. Regardless, it has been suggested that CPAP therapy may exacerbate certain types of insomnia by increasing anxiety associated with the bedroom and the CPAP device itself. Fortunately, CBT for CPAP adherence has demonstrated efficacy and can be incorporated into traditional CBT-I approaches. From a pharmacologic standpoint, non-benzodiazepine agents for insomnia, with the exception of zolpidem, appear to have

minimal adverse effect on symptoms of OSA. Traditional benzodiazepines, on the other hand, have been found to reduce upper airway tone [28] and may increase the time to arousal following an event and decrease the hypoxic/hypercapnic ventilatory response. Caution should accordingly be exercised when utilizing pharmacologic approaches in the management of patients with both insomnia and OSA.

Pearls

Insomnia and obstructive sleep apnea are common sleep disorders with a high rate of concurrence. Appropriate characterization of insomnia in patients with sleep-disordered breathing is critical to predict outcomes and define treatment. Likewise important is appreciation for the risk of OSA in patients presenting with insomnia. The interplay between both disorders is complex and yet to be fully elucidated. While some patients experience remission of insomnia with OSA treatment, others find treatment exacerbates or unmask insomnia. Conversely, patients with treatment-refractory insomnia or who demonstrate limited benefit from CBT-I may well have undiagnosed or undertreated OSA. Outcomes and treatment adherence tend to be worse among patients experiencing symptoms of both disorders rather than one disorder alone. Case-by-case assessment is thus necessary to determine appropriate treatment interventions and mitigate modifiable risk factors.

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Chapter 23
Insomnia and Caffeine

Gregory S. Carter and Hisham Hamdan

Clinical History

Mr. R was a 55-year-old man who presented to sleep clinic for the evaluation of sleep maintenance insomnia for the past 10–15 years. Initially, he was awakening every hour throughout the night. He was placed on gabapentin 300–600 mg followed by trazodone 50 mg, amitriptyline 25 mg, doxepin 6 mg, Belsomra 10 mg, melatonin 5 mg, and Lunesta 2 mg, in various combinations. He routinely went to bed at 9:00 p.m. on weekdays and 10:00 p.m. on weekends. He reported falling asleep within 5 minutes of lying down. Even with medication he awakened three times a night and was unable to return to sleep for between 30 and 60 minutes following each of these awakenings. He would stay in bed until he was able to return to sleep. Most nights he would awaken at 4:00 a.m. and be unable to return to sleep. He could not describe any factor that caused him to awaken or be unable to return to sleep. He micturated once per night. He did not have any pain or discomfort. He denied depression or anxiety. He slept in the same bed with his wife who reported some snoring if he had consumed a beer, which he did 3–5 nights a week. He estimated his sleep time at

G. S. Carter (✉) · H. Hamdan
Department of Neurology and Neurotherapeutics, The University of Texas Southwestern Medical Center at Dallas, Dallas, TX, USA
e-mail: Gregory.carter@utsouthwestern.edu

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6 hours per night with medication. He denied tingling or unpleasant feelings in his leg or a need to move his legs at night. His bedroom was comfortable. He exercised five mornings per week. He felt very sleepy during the day which he self-treated with ten 12 ounce mugs of "strong" brewed coffee between 6:00 a.m. and 12:00 p.m. every day. He did not use tobacco. He worked four 10 hour days per week in a local retail pharmacy.

Examination/Mental Status Exam

On examination he was a well-nourished white male in no distress with an Epworth Sleepiness Scale of 15/24. His vital signs were all normal, though his pulse was 52. His body mass index was 25. His general and neurological exams were normal.

Special Studies

He received a nocturnal in-laboratory-attended diagnostic polysomnogram (Fig. 23.1) followed by a multiple sleep latency test the following day. He was asked to avoid alcohol, nighttime sedatives and caffeine for 2 weeks prior to undergoing sleep testing.

Results

The diagnostic polysomnogram revealed a total sleep time of 418 minutes for a sleep efficiency of 89.9%. His sleep latency was 12.5 minutes, and his REM sleep latency was 66 minutes (both in the low normal range). He spent 25% of the night sleeping in the supine position. His arousal index of 22 was borderline elevated. His periodic limb movement index was normal at two limb movements per hour of sleep. His overall apnea hypopnea index was normal at 1.3 respiratory events per hour of sleep. His oxygen saturation averaged 95%, and he spent no time with abnormal oxygen saturations. His diagnostic polysomnogram was interpreted as normal.

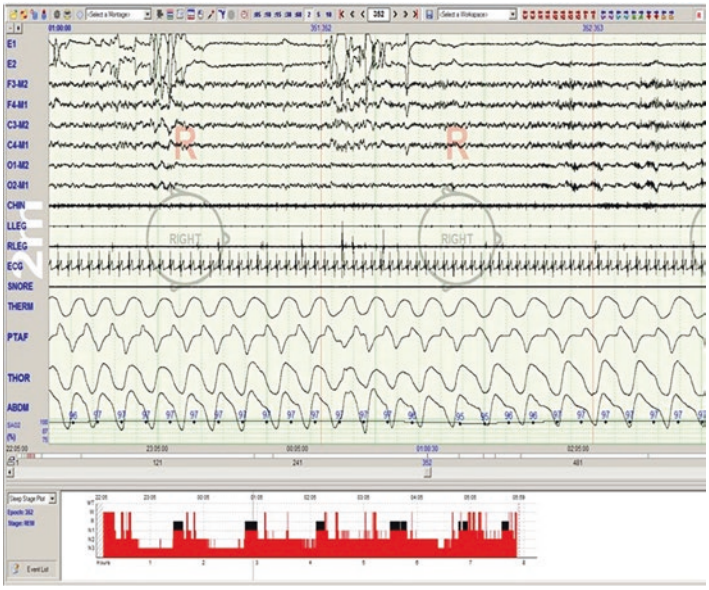

FIGURE 23.1 The above represents a 24 seconds excerpt from the polysomnogram during phasic REM sleep with a summary hypnogram of the entire night below

The following day he received a multiple sleep latency test (MSLT) consisting of five naps at 8:00 a.m., 10:00 a.m., 12:00 p.m., 2:00 p.m., and 4:00 p.m. While no REM sleep episodes were seen on any of those naps, the sleep latencies were 1.0 minute, 2.0 minutes, 5.0 minutes, 3.5 minutes, and 3.0 minutes, respectively. His mean sleep latency for the five naps was 2.9 minutes. This mean sleep latency was consistent with a severe tendency to sleepiness.

Question

What effect does high-dose caffeine have on sleep, especially when the last dose is consumed more than 9 hours before bedtime?

Differential Diagnosis and Diagnosis

On the basis of his history, exam, plus a normal nocturnal polysomnogram and severely shortened mean sleep latency on his MSLT, he was diagnosed with idiopathic hypersomnia without long sleep time which he was self-treating with high doses of caffeine. His complaint of intractable insomnia was secondary to excessive caffeine consumption. Over a 6 hour period, every morning he was consuming, conservatively, 1650 mg of caffeine. He reported that he needed to take that much coffee to awaken and stay awake over the course of the day.

The differential diagnosis includes alcohol-related obstructive sleep apnea and alcohol-related sleep maintenance insomnia or alcohol (and/or caffeine)-related periodic limb movement disorder. His report that he saw no differences in his sleep with or without consuming beer in the evening; his wife's confirmation that he did not consume more that 1–2 beers in an evening; and her report that he did not snore loudly or kick his legs following beer consumption make an alcohol-related sleep disorder less likely.

General Remarks

Caffeine is the most widely consumed psychoactive substance in the world today. An 8 ounce brewed coffee contains, on average, 135 mg of caffeine; however depending on preparation, this number could be as high as 200 mg. The average 50–64-year-old adult consumes 226 mg of caffeine daily. When consumed orally caffeine is rapidly and completely absorbed.

Caffeine works by antagonizing adenosine A1 and A2A receptors and thus inhibiting the action of adenosine to decrease neural firing and neurotransmitter release. Though there is individual variation, the average elimination half-life of caffeine is close to 6 hours. The metabolism of caffeine to paraxanthine by the cytochrome P450 hepatic enzymes can

be further prolonged in heavy consumers (like the case above) due to accumulation of metabolites inhibiting caffeine clearance.

Population surveys have indicated that high caffeine consumers (defined as consumption greater than 500 mg per day) had a higher incidence of severe daytime sleepiness, shorter sleep duration, and poorer subjective sleep quality. Studies including polysomnogram measures showed dose-related changes in sleep latency, wakefulness after sleep onset, sleep duration, and sleep efficiency. Slow wave sleep was attenuated by caffeine consumption even after salivary levels of caffeine were no longer detectable. The timing of consumption is important as smaller doses closer to bedtime will have a greater effect on sleep onset, whereas heavy consumption greater than 8 hours prior to bedtime will more likely cause an effect on sleep maintenance.

Pearls/Take-Home Points

The quality of sleep is altered by caffeine with the effects dependent on the timing of consumption, the amount consumed, and individual differences in caffeine sensitivity; thus assessment of consumption from all potential sources should be a part of the evaluation of any patient with the complaint of insomnia.

Even small amounts of caffeine (100 mg or less) consumed within 6 hours of bedtime can produce increases in sleep latency and changes in the microarchitecture of sleep.

Large doses of caffeine (greater than 1000 mg) consumed greater than 6 hours of bedtime produce increased wakefulness after sleep onset, decreased total sleep time, and decreased slow wave sleep producing a vicious cycle of nocturnal sleep deprivation worsening daytime sleepiness, the latter leading to ever greater consumption of caffeine.

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