A Clinical Casebook of Sleep Disorders in Women

Safia S. Khan
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Editors

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- *Our work and home families that energize us!*
- *Our patients that inspire us!*

Preface

Whether presenting in isolation or combination with other illnesses, sleep disorders are prevalent among women during their lifespans. Sleep architecture and physiology reveal subtle differences among the sexes although sleep disorders are disproportionately higher among women. This book will go through a series of clinical cases to understand the presentation and management of various sleep disorders, focusing on women in various stages of their life cycle.

In the first two books, *Comorbid Sleep and Psychiatric Disorders: A Clinical Casebook* and *Sleep Disorders in Selected Psychiatric Settings: A Clinical Casebook*, editors Imran S. Khawaja and Thomas D. Hurwitz explored the association between sleep and psychiatric disorders.

In this third volume, we discuss 20 cases to highlight unique aspects of sleep disorders among women, the primary audience being all clinicians taking care of women's health. We review cases of sleep disturbance among young teenagers, adolescents, and middle-aged women with a spectrum of sleep-related breathing disorders, sleep-related movement disorders, hypersomnia, parasomnias, insomnia with hormonal changes, and some unique cases encountered in our clinical practices. Pregnancy-related sleep disorders pose an interesting dilemma as this is a transient phase. Menopause and pre-menopausal stages lead to a noteworthy change in sleep architecture, sometimes associated with insomnia with or without sleep-related breathing disorders.

Sleep disturbances in pregnancy can lead to long-term adverse maternal and fetal health effects.

This book will present trainees and experienced clinicians with a valuable guide to managing sleep disorders among women. This book is a compilation of succinct, interesting clinical cases, each followed by relevant questions to stimulate the reader. We thank our contributing authors for their dedication to the field of medicine and hope this book will spark further research to enhance our knowledge in the arena of sleep disorders in women.

Dallas, TX, USA — Safia S. Khan
Grapevine, TX, USA — Imran S. Khawaja

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About the Editors

Safia Sameem Khan is a Fellow of the American Academy of Family Physicians with specialization and board certification in Sleep Medicine. Dr. Khan is the Program Director for the Sleep Medicine Fellowship at the University of Texas Southwestern Medical Center in Dallas, TX, USA.

She completed her residency training in Family and Community Medicine at Texas Tech University Health Sciences Center, El Paso, TX, after completing medical school at Quaid-e-Azam Medical College, Pakistan. She trained for a Sleep Medicine Fellowship at the University of Texas Southwestern Medical Center (UTSW) in Dallas, TX, where she is currently working as an Assistant Professor, training the sleep medicine fellows and family medicine residents.

Dr. Khan has been an inductee of the Gold Humanism Honor Society since 2014. Her special interests are sleep disorders in women and primary prevention and early detection of sleep disorders in the general population.

Imran Shuja Khawaja is a Diplomate of the American Board of Psychiatry and Neurology specializing in Psychiatry and Sleep Medicine. He completed residency training in Psychiatry at Westchester Medical Center/New York Medical College, Valhalla, NY, and a fellowship in Sleep Medicine from Mayo Clinic, Rochester, MN.

Dr. Khawaja has fellow status with the American Academy of Sleep Medicine. He received a Bush Foundation Medical Fellowship in 2008.

He is a Clinical Professor in the Department of Psychiatry at the University of Oklahoma, OK.

Dr. Khawaja is the CEO of MD TruCare, PA, in Grapevine, TX, and Fort Worth, TX.

Dr. Khawaja is particularly interested in better understanding the relationship between sleep disorders and psychiatric conditions. He has published more than 100 publications, including research papers, review articles, editorials, case reports, and book chapters. He has also published two academic books with Tom Hurwitz, MD, entitled *Comorbid Sleep and Psychiatric Disorders: A Clinical Casebook* and *Sleep in Selected Psychiatric Setting: A Clinical Casebook*.

He has also published three self-help books with Rizwan Shuja: *The Power of Your Dream Self Image*, *The Cycle of Fulfillment*, and *Mental/Emotional Fulfillment*.

Part I

Menstrual Cycle and Sleep Changes

Sleep Changes with Menarche

1

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Clinical Case

A 14-year-old girl presents to clinic with daytime sleepiness, has had increased daytime napping, mood swings and poor school performance for the last 4 months. Menarche occurred 1 year ago with dysmenorrhea and heavy bleeding. Reports weight gain of 20 pounds, with anxiety and depression. She was evaluated by her primary care physician; the physical exam was unremarkable, and it showed Tanner stage 3 for breast and pubic hair growth. The infectious disease workup was negative. The patient was referred for a sleep evaluation.

Regarding her past medical history, she was born full term with no complications during childhood. She has a history of allergic rhinitis that is worse during the spring and fall. She is up to date with her immunizations.

Her list of medications includes over-the-counter cetirizine for allergic rhinitis. Denies intake of supplemental vitamins. She regularly takes ibuprofen during her period due to dysmenorrhea. Her family history is positive for diabetes and hypertension in her father, paternal grandmother has history of restless legs syndrome, and her maternal cousin was diagnosed with narcolepsy with cataplexy at age 15.

Her sleep habits revealed exposure to blue light (phone, computer) at bedtime occasionally. She complains of an urge to move her legs to relieve discomfort that starts during the evening and worsens at bedtime, this sensation delays her sleep onset. She also reports multiple nighttime awakenings, especially during her period, awakenings are due to pain, and has difficulty falling back to sleep. Her total sleep time was estimated to be 6–7 h per day, during weekends when she was pain free, she was able to sleep longer up to 9–10 h with later morning awakenings. Three times per week she had early start times for track and field practice, lately she had missed many due to excessive sleepiness. She took 1–2-h naps during the day, she persisted feeling tired after awakening from the naps. Her review of systems is significant for multiple nighttime awakenings due to pain with periods, she denies history of snoring.

She has history of painful cramping during menstrual periods with heavy bleeding, lasting 9–10 days (about 1 and a half weeks). Unintentional weight gain of 20 pounds in the last year. Her grades in school have declined due to missing deadlines to return homework.

Special Studies A 2 weeks actigraphy report was obtained, confirming insufficient sleep time of 6–7 h mostly consistent with weekdays and during the nights of her menstrual period there were more frequent awakenings, there was occasional inconsistent naps during the day following the night of excessive awakenings.

A ferritin level was ordered due to the history of heavy bleeding along with the reported urgency to move her legs at sleep onset. Her ferritin level was 19 micrograms/liter (mcg/l). A sleep study was considered due to history of weight gain, despite lack of history of snoring, however, because her BMI was within a normal range with absence of physical findings suggestive of narrow airway a sleep study was not obtained.

Management Good sleep hygiene was implemented, that included avoidance of daytime naps after 4 pm. Blue light exposure was stopped 2 h before bedtime and caffeinated drinks (sodas, teas, coffee) were eliminated after 3 pm. She was started on supplemental iron for the treatment of restless leg syndrome with the goal of reaching a ferritin level above or equal to 50 mcg/l. She was referred to an adolescent clinic for management of dysmenorrhea as her symptoms persisted despite adequate trial of non-steroidal anti-inflammatory medication use.

General Discussion

Menarche and Sleep

Menarche is defined as the first menstrual cycle in adolescent girls and is the beginning of the reproductive phase. It is influenced by genetic, biological, nutritional, and psychosocial factors [1, 2]. In developed countries the median age is: 12–13. The serum levels of melatonin have a close relation to sleep, and it is also a hormone related to menarche/menstruation as described by Takahashi et al. in 1968. Melatonin is secreted in the pineal gland during the night and has an inhibitory action on reproductive function [2].

In one study the dim light melatonin onset (DLMO) was shown to correlate with Tanner staging, indicating that in more mature teens, the onset of biological night is later [1]. Reduction of slow-wave sleep (SWS) and greater daytime sleepiness in girls is also associated with later Tanner stages [3]. Data also shows adolescent sleep has a slowing accumulation and tolerance of sleep homeostatic pressure which indicates a greater ability to maintain wakefulness. These changes also correlate with decline in delta spectral power and steep decline in deep sleep [4].

Menstrual cycles in high school students have been reported to be linked to the irregularity of sleep time. Based upon these findings, it would be suggested that sleep disturbance is associated with the onset of menarche [2, 5]. To further explore causes for sleep disturbance among adolescents; refer to Table 1.1.

Sleep Evaluation Questionnaires

A detailed and unbiased sleep intake should be obtained as with sleep history, the perception of the patient, parent or clinician can mislead the facts. Sleep and wake times should be documented in a sleep diary over a period of minimum 2 weeks. In cases that show discrepancy even after the information obtained from a sleep diary, the use of actigraphy or attended sleep study can be a helpful tool. See Table 1.2 for sleep history questions. Sleep study is recommended to evaluate for sleep breathing disorder if suspected, it can be helpful to determine other disorders like periodic limb movement disorder [6].

Table 1.1 List of causes for sleep disturbance among pre-teens and teenagers. (This table is an original and has never been printed online or on paper)

Primary sleep disturbances
• Insomnia
• Circadian rhythm disorders (delayed sleep-wake phase disorder (DSWPD))
• Sleep related movement disorders (restless leg syndrome (RLS), parasomnias)
• Obstructive sleep apnea (OSA)
Mental health and psychiatric causes
• Depression
• Anxiety
• Attention deficit/hyperactivity disorder (ADHD)
• Childhood conduct problems (CP)
• Premenstrual dysphoric disorder (PMDD)
• Bullying
• Social isolation
Medication/substance use
• Stimulants
• Alcohol
• Drugs of abuse
Physical/endocrine causes
• Night-time menses
• Premenstrual symptoms (PMS)
• Thyroid or other hormonal imbalances
Environmental causes
• Digital technology
• Adverse childhood experiences (ACES)

Table 1.2 Recommended sleep history questions for assessment of sleep disorders (This table is original and has not been published)

Sleep history questionnaire
• Sleep environment (noise, temperature, comfort)
• Bedtime routine
• Sleep onset (weekdays, weekends, holidays)
• Sleep onset latency
• Awakenings
• Reason for awakenings if present
• Wake up time (weekdays, weekends, holidays)
• Naps
• Medications
• Difficulty falling back sleep after awakenings
• Parasomnias
• Bedwetting
• Kicking, jerking
• Urgency to move legs, leg discomfort (restless legs)
• Nightmares
• Snoring
• Coughing
• Presence of pain
• Use of electronics
• Caffeine intake (sodas, coffee, tea, energy drinks)

Physiologic changes of Sleep during Adolescence

The "perfect storm" was described by Carskadon in 2011, referring to changes that occur during maturation in adolescence where intrinsic mechanisms in combination with social and emotional aspects converge in the sleep wake cycle changes [1, 7]. A delayed shift in the intrinsic rhythmic system as adolescents mature has been described, resulting in later bedtimes. Sleep hygiene with the use of blue light devices further delays the sleep onset time. In the other hand the social aspects that promote early awakenings are sport practices and early start school times along with a delayed sleep onset can result in insufficient sleep during weekdays, resulting in sleepiness or tiredness during the day.

While evaluating an adolescent due to sleepiness or insomnia, a detailed history must be obtained with specific times of sleep onset, awakenings, total sleep per night and sleep hygiene. A list of differential diagnoses for excessive sleepiness in adolescents is narrated in Table 1.3. Sufficient sleep should be evaluated to

Table 1.3 A quick reference for evaluation and characteristics of disorders of excessive sleepiness among adolescents (This table is original and has not been published)

Evaluations and diagnoses of disorders leading to daytime sleepiness in adolescents			
Diagnoses	Evaluate	Characteristics	Initial treatment options
Insufficient night-time sleep	Total sleep time should be adequate for age	Daytime sleepiness, cognitive decline, poor academic performance	Consistent sleep schedule, modify activities and routine to allow adequate sleep time
Restless legs syndrome	Ferritin levels below 50 micrograms/L. leg discomfort, urgency to move legs to find relief, kicking.	Delayed sleep onset, sleep disruption resulting in reduced sleep time.	Initial therapy is to increase ferritin levels to 50 or above micrograms/L with oral iron supplementation, monitor for constipation after iron therapy initiation.
Obstructive sleep apnea	Snoring, AHI above 5 events/h	Disrupted sleep, lack of restorative sleep, waking up with dry mouth, performance and cognition can decline	If indicated consider CPAP, ENT evaluation, if overweight initiate weight loss plan, medications for allergic rhinitis to keep patency of nasal passages. Alternatively, dental device for mandibular advancement, hypoglossal nerve stimulator device implant, and surgery for tonsillectomy or maxillary expansion

(continued)

Table 1.3 (continued)

Evaluations and diagnoses of disorders leading to daytime sleepiness in adolescents			
Diagnoses	Evaluate	Characteristics	Initial treatment options
Delayed sleep-wake phase syndrome (circadian rhythm disorder)	Late sleep onset, late morning awakenings	Can be misdiagnosed as insomnia, patient is sensitive to blue light exposure that will result in delayed sleep onset	Scheduled melatonin, timed bright light therapy, sleep hygiene, gradual advancement of delayed sleep phase, anchoring wake up time, motivation to wake up earlier like work/school
Unhealthy sleep habits	Blue light exposure, caffeine intake	Inconsistent sleep schedule, use of electronics at bedtime, late naps, caffeine intake	Sleep hygiene improvement, avoidance of nicotine, caffeine and blue light emitting devices prior to bedtime
Chronic medical conditions (pain, dysmenorrhea, endocrine as hypothyroidism)	Medical conditions that can cause sleep disruption	Chronic medical conditions can result in sleep disruption due to pain, feeding times, coughing etc.	Individualized therapy by condition.
Premenstrual syndrome (PMS)	Present in 20% of female adolescents	Sleep disruption and delayed of sleep onset due to pain and discomfort.	Non-steroidal anti-inflammatory drugs, selective serotonin reuptake inhibitors
Chronic psychiatric conditions (anxiety, depression)	Screen for general anxiety and depression	Mind racing, or engagement of activities or thoughts that delay sleep, insomnia.	Cognitive behavioral therapy, medications customized to symptoms
Narcolepsy	Sufficient sleep time with fragmented sleep and refreshing naps.	Narcolepsy with or without cataplexy must be differentiated. Onset usually during adolescence.	Individualized therapy by sleep physician, close monitoring
Idiopathic Hypersomnolence	Diagnoses of exclusion	Thorough investigations needed.	Individualized therapy by sleep physician, close monitoring, optimizing sleep hours
Klein-Levine syndrome	Periods of somnolence are episodic.	Episodes of sleepiness that lasts days to weeks, that resolve spontaneously, appears confused during brief episodes of wakefulness, improves with aging.	Support therapy, hydration, and observation at home during episodes, mood stabilizer (lithium) has shown to reduce frequency of episodes.
Drug induced somnolence	Review medications and toxicology screening if deemed necessary	Prescription medications that can cause sedation, hypersomnolence as anticonvulsants, unintended ingestion, recreational.	Review dosing and medications, avoiding exposures, addiction rehabilitation.

determine further interventions and consider other differential diagnoses. Recommended sleep length guidelines have been proposed by the National Sleep Foundation and the American Academy of Sleep Medicine and a consensus statement published in 2016 [7, 8]. The recommended amount of sleep for teenagers 13 to 18 years of age should sleep 8–10 h per 24 h [8].

Treatment

The prevalence of sleep problems in adolescents in most studies range from 20–40% [9, 10], with most adolescents having sleep deficiency or sleep problems as the need for sleep is not reduced in adolescence [10]. Adolescent sleep often impacts the circadian timing system which leads to long sleep onset latency, shorter sleep duration, irregular sleep schedules, and delayed sleep phase (later bedtimes) [3, 4, 10, 11].

Premenstrual and menstrual problems such as irregularity, dysmenorrhea, cramping, bloating is common in female adolescents and can impact sleep. In women, insomnia is estimated to be 1.41 times more prevalent in females when compared to males [Confidence interval – 1.28–1.55] [12]. In girls who have had menarche, more than a twofold risk for insomnia was found when compared to boys of the same age in a population-based study [10]. In addition, adolescent girls who are depressed have been found to report more problems with sleep than depressed boys [12]. Interestingly, estradiol and progesterone are thought to be protective factors for the development of sleep disordered breathing (SDB), so females are found to have an unchanged prevalence of SDB post menarche when compared to their male counterparts after puberty [12].

Treatment should be individualized for each disorder and treatment offered customized to patients and family dynamics. Table 1.3 elicits a brief description of treatment options for each of the disorders considered in the different diagnoses.

Consequences of Inadequate Sleep

Insufficient or poor sleep among adolescents range from excessive daytime sleepiness, mental health problems, poor academic performance, increased risk of obesity, reckless behavior, drowsy driving, and substance use [11, 13]. Worldwide, adolescents experience poor sleep patterns and insufficient sleep on school days with the proportion of adolescents meeting sleep recommendations ranging between 32% to 86% [14]. Adequate sleep of 8–10 h per 24 h is recommended by the American Academy of Sleep Medicine and is associated with better health outcomes including improved attention, behavior, learning, memory, emotional regulation, quality of life, and mental and physical health [8].

Take Home Points

- Parents, health professionals and teachers should educate children and adolescents regarding sleep hygiene, adjusting schedules and time management.
- Delayed school start time or adjusted schedules as recommended by the American Academy of Pediatrics may be beneficial for this population given the changes in bio-regulatory systems that young women go through due to menarche [1, 13, 15, 16]. Delayed high school start time has been shown to decrease daytime sleepiness, increase satisfaction with sleep, and increase total sleep time on weeknights by 45 mins [13].
- During menarche changes are multifactorial and assessment of sleep quality is relevant during well child checkups to screen for any disturbance and refer to a sleep specialist, healthy sleep contributes to healthy physical and mental development, allowing our adolescents to thrive to their full capacity.

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Insomnia in Pregnancy: A Review

2

Rabab Naqvi, Zaiba Jetpuri, and Anna Wani

Clinical History

Ms. IC, a 30 year old female in the third trimester of her second pregnancy (G2P1A0 at 31 weeks), presents to the clinic with complains of inability to fall asleep at 9 pm when she goes to bed, it takes her 2–3 h to fall asleep and occasionally she will need a melatonin 5 mg pill to get to sleep. She likes to watch the 10 pm news in bed before turning off the TV at 10:30 pm. She will occasionally toss and turn before she is finally able to doze off. She has to wake up by 6 am to get her 7 year old son to school every day. On the weekends, she likes to sleep in and gets out of bed at 10 am. Her symptoms have been going on for over a year, she is particularly concerned now as she recently read that risk for cesarean delivery is much higher in women with sleep disorders during pregnancy. She has excessive daytime sleepiness and will take a short nap at lunch 3–4 days a week.

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Physical exam is limited as this interview was done through telehealth visit owing to the COVID-19 pandemic.

Question 1 What diagnostic tests are recommended for further evaluation of insomnia in this patient?

(a) Overnight sleep study
(b) Arterial blood gases
(c) Clinical history and actigraphy
(d) CBC, CMP, urinalysis

Question 2 Risk for which of the following complications is highest among women with sleep disorders during pregnancy?

(a) Hypospadias, congenital cardiac malformations
(b) Preterm birth, depression, increased risk for cesarean delivery
(c) Restless legs syndrome and deafness
(d) Intrauterine growth retardation

Discussion

Insomnia during pregnancy is common, with a prevalence of 20–60% of pregnant women reporting symptoms [1] , compared to 6–10% of the non-pregnant population [2] . Insomnia is defined as a dissatisfaction with the amount or quality of sleep along with impairment of daily activities or increased levels of stress, which occurs at least three times weekly for 3 months and not due to a secondary condition or substance use (Fig. 2.1). Research suggests the prevalence of insomnia is higher during pregnancy, with symptom prevalence increasing with each trimester [2]. Women with higher vulnerability toward sleep disorders including stress reactivity [3] as well as mothers over the age of 20 [4] were found to have increased prevalence of insomnia symptoms. Using polysomnography, it has been found that pregnant women have increased time spent awake after falling asleep, decreased REM sleep, and increased time spent in lighter stages of sleep [2]. Sleep disorders during pregnancy are important because poor sleep is associated with poor obstetric and mental health outcomes, including increased likelihood of preterm birth, caesarean delivery [5], as well as postpartum depression [6]. There are similarities between the sleep alterations seen in pregnancy and the changes in sleep seen in psychiatric disorders including depression, mania, and Obsessive – compulsive disorder [2].

The differential for insomnia symptoms in pregnant patients is vast (Fig. 2.2). There are a number of predisposing factors including family history, incidence of insomnia in previous pregnancies, history of mental illness, personal medical history, as well as currently ongoing medical conditions [2] (Fig. 2.3). Physiologic alterations brought on by pregnancy can trigger insomnia symptoms as well. Changes in circadian rhythm during pregnancy brought on by hormonal fluctuations have been found to cause changes in sleep during pregnancy. Management of these

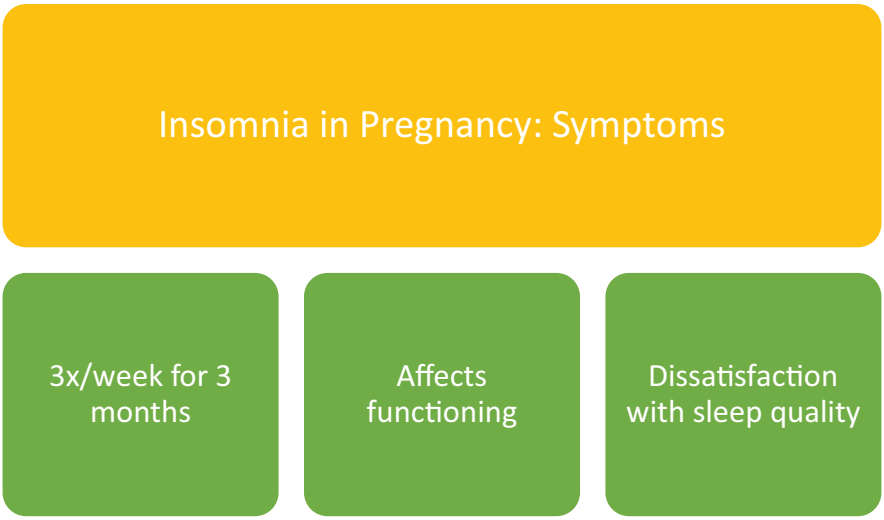

Fig. 2.1 The symptoms required to make a diagnosis of insomnia include disturbed sleep experienced at least 3 times a week which affects functioning in daily activities, causing dissatisfaction with sleep quality

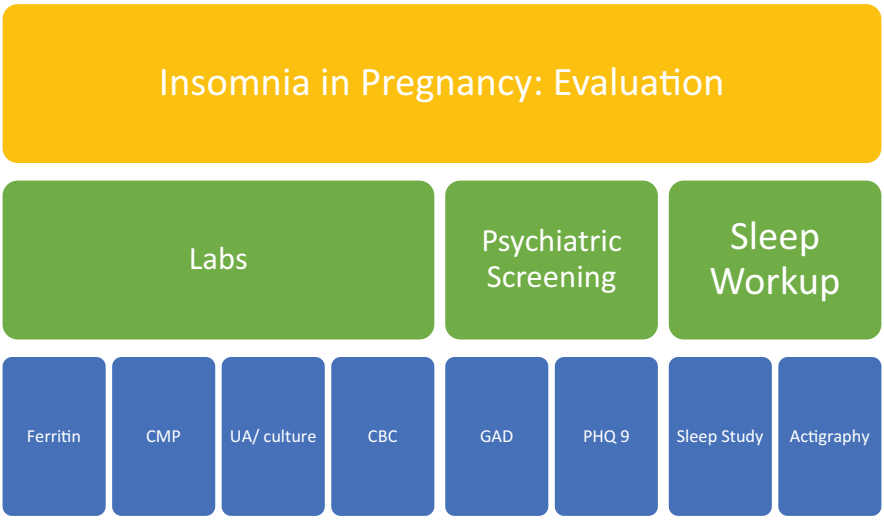

Fig. 2.2 In evaluation of insomnia symptoms in pregnant patients, there are a number of labs which should be completed in order to rule out possible diagnoses causing sleep disturbances. Ferritin should be obtained in order to evaluate for iron deficiency anemia which is an underlying cause for Restless legs syndrome. A complete metabolic panel will provide information about liver function to rule out intrahepatic cholestasis of pregnancy. The CMP will also provide electrolyte levels, which can help to find causes of cramping. A urinalysis and culture will rule out urinary tract infections, which may be an underlying cause for illness and discomfort. A complete blood count will also help to rule out infection and anemia. Psychiatric workup is crucial due to the strong association between psychiatric health and sleep, which may be exacerbated by stressors brought on during pregnancy (Fig. 2.3). The evaluation for insomnia is completed by ruling out other sleep disorders including obstructive sleep apnea and restless legs syndrome using polysomnography and actigraphy

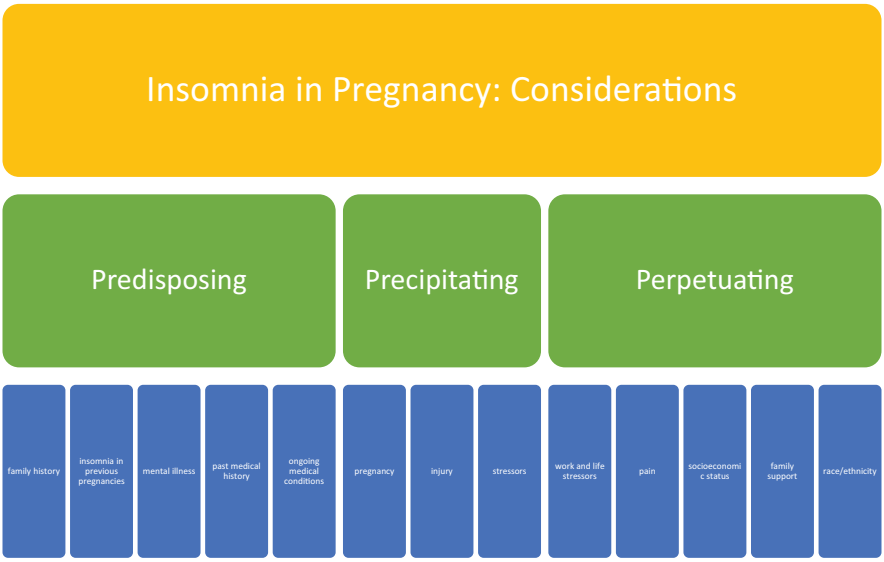

Fig. 2.3 Various lifestyle factors must be considered when making a diagnosis and creating a treatment plan for patients with insomnia symptoms in pregnancy

changes to improve sleep is found to reduce incidence of postpartum depressive symptoms [7]. Hormonal and physical alterations brought on by pregnancy, as well as increased incidence of urinary tract infection, often lead to increased urinary frequency which increases the number of awakenings during the nighttime, further disrupting sleep [8]. Other changes in the body can give rise to insomnia symptoms as well, including discomfort and pain due to increased physical stress on the body, injury or comorbid conditions brought on by pregnancy, and increased stress associated with pregnancy [2].

Factors that may perpetuate the issue depend largely on the patient's lifestyle, and adjustments to these factors should be considered when creating a treatment plan for patients experiencing insomnia-related symptoms during pregnancy. Lifestyle factors that can be altered to improve sleep include sleep hygiene, stress and pain management, family/social support, and work requirements (Fig. 2.3). Other perpetuating factors which should be considered may range from socioeconomic standing, race/ethnicity, and medical history [9] (Fig. 2.3). These factors may be difficult to alter, but to gain a thorough understanding of the disease process they should be factored into the evaluation of pregnant patients experiencing these symptoms as well. Finally, a PHQ-9 depression scale and General Anxiety Depression scale should be completed for every patient because up to 40% of all cases of insomnia are associated with common psychiatric conditions such as depression and anxiety, and these patients should be referred for further workup if appropriate [10].

In addition to social and historical data collection during evaluation of these patients, laboratory values can be crucial tools in narrowing down the etiology behind the disease (Fig. 2.2). Iron studies and complete blood counts help to assess

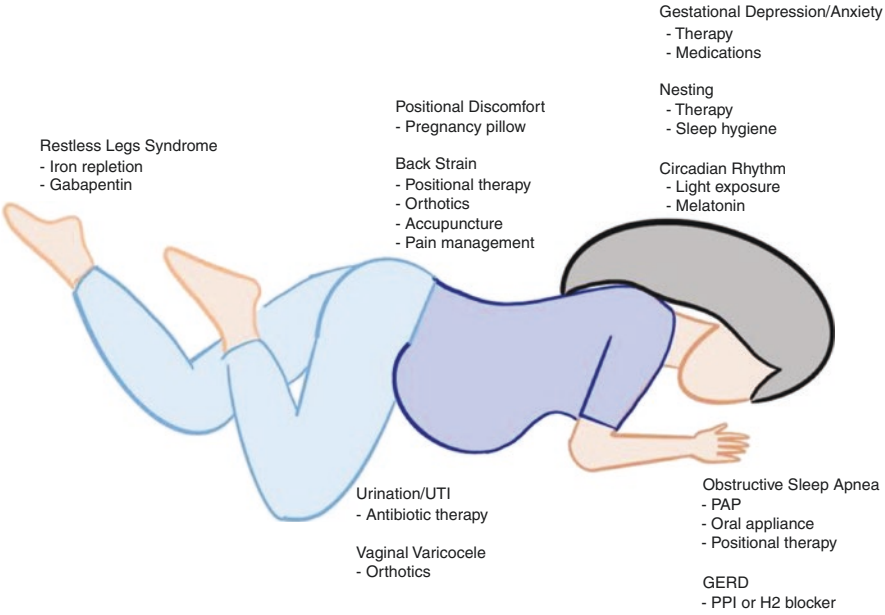

Fig. 2.4 Due to the multidisciplinary nature of sleep, there are several conditions which should be ruled out before considering the diagnosis of primary insomnia in pregnant patients. These are conditions which may be brought on during pregnancy and may cause symptoms causing sleep disturbance

for iron deficiency anemia, which is associated with *restless legs syndrome* (Fig. 2.4). The prevalence of restless legs syndrome has been found to be two to three times higher in pregnant populations compared to the general population [11]. Obtaining a complete metabolic panel can be beneficial to check for the possibility the patient has an electrolyte or mineral disturbance which may cause leg cramping [12] (Fig. 2.2). Urinalysis and urine culture can help to rule out urinary tract infection which is often brought on by the structural and physiologic changes of pregnancy and can lead to pyelonephritis and bacteremia as well as complications with pregnancy due to ongoing infection [13] (Fig. 2.2). Ongoing infection leads to a host of symptoms which cause discomfort and increased frequency of urination.

The final step to evaluate these patients is determining whether insomnia symptoms are truly insomnia or whether they are related to a different disorder. In order to confirm a patient is experiencing insomnia, a patient must have difficulty falling asleep, staying asleep or nonrestorative sleep; these symptoms are present despite adequate opportunity and circumstance to sleep; this impairment in sleep is associated with daytime impairment or distress; and this sleep difficulty occurs at least 3 times per week and has been a problem for at least 1 month [14] (Fig. 2.1). Once most of these qualifications are met, a patient can undergo a sleep study which will help to evaluate for obstructive sleep apnea or other primary sleep disorder, narrowing down the differential to primary insomnia [10] (Fig. 2.2). Sleep apnea in obese

pregnant women has been found to have a prevalence of 15–20% compared to 4–19% of women overall. Given the increased rates of obesity worldwide and the natural increase in weight during pregnancy, it is important to rule out sleep apnea in pregnancy. There are also complications which may arise secondary to untreated obstructive sleep apnea in pregnant patients, including hypertensive disorders of pregnancy and cardiovascular disease [15]. Actigraphy using total sleep time, sleep onset latency, and number of awakenings greater than 5 mins has been found to be a useful tool in assessment of insomnia [16].

There are several medical diagnoses that can lead to pain and discomfort in pregnancy which can lead to symptoms of insomnia (Fig. 2.4). Physical examination should be completed to assess for venous insufficiency, which can lead to discomfort while sleeping [17]. Round ligament pain as well as increased incidence of hemorrhoids can cause pain leading to trouble sleeping [18]. Gastroesophageal reflux disease is common in pregnancy due to the positional changes of organs in the body, and it has been found to cause disturbances in sleep as well [19]. Intrahepatic cholestasis of pregnancy causes a buildup of bile acids, which leads to pruritis and can cause symptoms of insomnia due to discomfort during sleep [20]. General pain and aches brought on by the increased physical demands of pregnancy can be managed with physical and occupational therapy as well as orthotics and products such as pregnancy pillows.

Answers

Question 1: Clinical history and actigraphy.

Question 2: Preterm birth, depression, increased risk for cesarean delivery.

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Restless Legs Syndrome in Women: A Case Report

3

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Introduction

Restless legs syndrome (RLS) is a common movement disorder. It is characterized by an uncomfortable urge to move the lower limbs, particularly when the patient is at rest, symptoms are temporarily relieved by movement and worsen in the evening and at night following a circadian rhythm [1].

The prevalence of RLS varies with age, sex, and associated medical conditions. Studies report a 2–4% prevalence of RLS in European populations [2]. The incidence is almost two-fold greater in women than in men [3–6]. The age of onset may also be influenced by sex: in the REST PC study, women reported a lower age of onset than men, but more studies are needed [5]. The reasons for sex differences are uncertain but it has been suggested that iron deficiency, pregnancy, and hormonal changes may be important contributing factors [5, 6].

RLS is important not only due to its high prevalence but also due to its health consequences. Difficulties initiating or maintaining sleep are usually reported, resulting in lower quality of life [2]. Symptoms of anxiety and depression are also frequent in RLS patients [5]. In addition, RLS has been associated with higher cardiovascular risk [7]. Periodic limb movements (PLMs) are considered a supportive

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diagnostic criterion of RLS and are the main motor sign of RLS during sleep and, although they are not specific, they are present in about 80–89% of RLS patients [1, 8]. PLMS have been associated with high blood pressure and might be a risk factor for cardiovascular and cerebrovascular diseases [2].

Because of both the increased risk in women and the health consequences of this disorder, special attention must be paid to ensure an accurate diagnostic and therapeutic plan. Also, a careful evaluation of other comorbidities is mandatory, as many can trigger or worsen RLS symptoms. Here we present a typical case of RLS.

Case Report

A 52-year-old woman with RLS presented for a second opinion. Her medical history was significant for irritable bowel syndrome, celiac disease, uterine fibroids, and iron deficiency anemia. At the time of her visit, she was undergoing treatment with oral iron therapy and trazodone. She reported a family history of RLS. She had suffered from RLS since she was 20. Her symptoms included an uncomfortable urge to move the legs when at rest in the evening or at night, and symptoms were partially relieved by movement. She had difficulties initiating sleep, she usually went to bed at 11 PM and fell asleep at 5 AM. Her bed partner reported vigorous legs movements while she was asleep. She described excessive daytime sleepiness (Epworth Sleepiness Scale score 20) and difficulty concentrating. Symptoms were more intense when she was menstruating. Menstruation was irregular and stronger during the past year but she had no hot flashes. She denied previous hemostasis dysregulation, other bleedings, or anticoagulant/antiagregant treatments.

She gave birth when she was 25 years old. In the past, she had received pramipexole, clonazepam, and mirtazapine for RLS, and oral iron therapy and tranexamic acid for anemia. She reported no improvement. Her neurological examination was normal.

Polysomnography showed prolonged sleep latency, high levels of sleep fragmentation, and a PLM index of 63 per hour during sleep and 80 per hour during wakefulness. The multiple suggested immobilization test (m-SIT) showed 30 PLMs per hour. Transcranial sonography showed bilateral hypoechogenicity in the substantia nigra (0.18 $cm^{2)}$ (Fig. 3.1). Relevant results from the laboratory test were: hemoglobin 12.9 mg/dl (>12.16 mg/dl), serum iron 86 mcg/dl (60–160 mcg/dl), serum ferritin 15.8 ng/dl (30–200 ng/dl), serum transferrin 295 mg/dl (212–360 mg/dl), transferrin saturation 23.3% (20–50%), follicle-stimulating hormone (FSH) 33mUI/ml (1.27–19.29 mUI/ml), luteinizing hormone 12mUI/ml (2–10 mUI/ml), estradiol 18 pg/ml (30–400 pg/ml), dehydroepiandrosterone sulfate nmol/L 0.74 (0.64–4.19 nmol/L) and androstenedione 0.91 nmol/L (1.6–33-nmol/L). The fecal occult blood test was negative and the colonoscopy was normal. Transvaginal ultrasound showed two uterine fibroids: one type 5 in the anterior surface of the uterus (76x55mm) and the other a type 4 in the isthmus (24 × 25 mm).

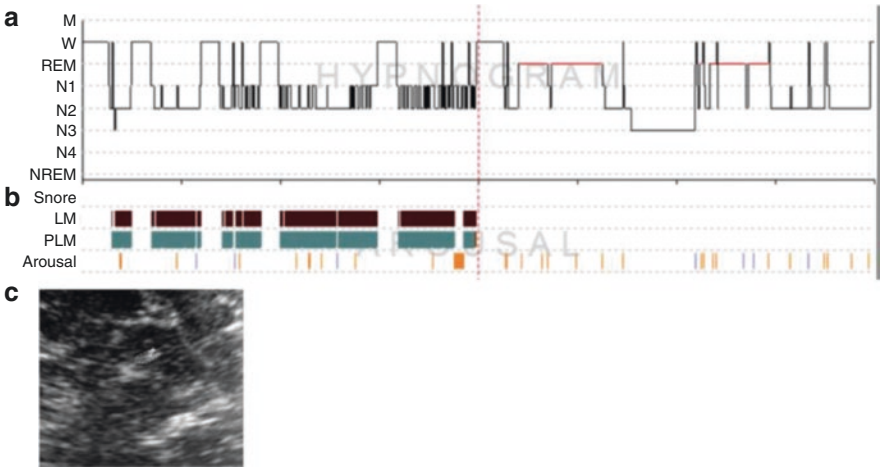

Fig. 3.1 Complementary study results. Figure **a** and Fig. **b** show polysomnography results. Fig. **a** shows the sleep cycles with a prolonged sleep latency and high levels of sleep fragmentation. Fig. **b** shows a high PLMs index. Figure **c** show hypoechogenicity in the substantia nigra in transcranial sonography. (These figures are original and have not been published previously)

She was diagnosed with RLS and iron deficiency anemia due to metrorrhagia and celiac disease. As symptomatic treatment she received gabapentin and stopped trazodone, and, because of celiac disease, which likely hinders oral iron absorption, was prescribed intravenous (IV) iron therapy consisting of 1000 mg of ferric carboxymaltose. A gynecologist diagnosed her with perimenopause and metrorrhagia, recommended medroxyprogesterone acetate and tranexamic acid. During short-term follow-up, as she showed no improvement, was prescribed pramipexole. Serial blood tests initially showed systemic iron worsening due to metrorrhagia despite IV iron supplementation, so oral contraceptives and oral iron therapy were started. During follow-up, the patient presented a progressive improvement in her metrorrhagia and RLS, so symptomatic treatment was reduced.

Discussion and Conclusions

RLS diagnosis is essentially clinical according to the International Restless Legs Syndrome Study Group Consensus Diagnostic Criteria established in 2014 (Table 3.1) [1]. There is controversy about sex differences in clinical presentation. Holzknecht et al. reported that women have more severe symptoms on the IRLSSG severity scale, the RLS-6, and the Clinical Global Impression [9]. While Bentley et al. have shown that women more often have a combination of three possible symptoms of RLS such as involuntary movements when awake, sleep onset difficulties, and frequent awakenings at night [10]. Other studies have not shown significant differences [3]. Our patient met all criteria for RLS and also reported severe difficulties initiating sleep.

Table 3.1 International Restless Legs Syndrome Study Group Consensus Diagnostic Criteria for Restless Legs Syndrome [1]

Five essential criteria for RLS:
1. An urge to move the legs usually but not always accompanied by or felt to be caused by uncomfortable and unpleasant sensations in the legs.
2. The urge to move the legs and any accompanying unpleasant sensations begin or worsen during periods of rest or inactivity such as lying down or sitting.
3. The urge to move the legs and any accompanying unpleasant sensation are partially or totally relieved by movement, such as walking or stretching, at last as long as the activity continues.
4. The urge to move the legs and any accompanying unpleasant sensations during rest or inactivity only occur or worse in the evening or night than during the day.
5. The occurrences of the above features are not solely accounted for as symptoms primary to another medical or behavioral condition

PLMs are supportive criteria in RLS and give an indirect index of severity. Although they are not specific, they are highly suggestive of RLS [1]. Holzknecht et al. reported a lower index in women than in men [9]. Our patient reported a high PLM index in polysomnography and in m-SIT, higher than that reported by Holzknecht et al. Polysomnography showed lower percentages of N1 and higher N3 in women with RLS than in men, but no other sex differences were found. In our case, polysomnography showed low percentages in N1 and N3 with a high percentage in N2 [9].

As per the diagnostic criteria, other conditions that may mimic RLS such as peripheral neuropathy, nocturnal leg cramps, medication-induced akathisia, and peripheral vascular disease should be evaluated [2]. In our patient, the medical history and neurological examination were not suggestive of any other condition.

The pathophysiology of RLS is not completely understood, but many medical conditions have been associated with it. The most consistent neuropathological finding associated with RLS is iron deficiency. Although most RLS patients may have normal serum iron levels, they show low iron parameters in cerebrospinal fluid and some specific brain regions, such as the substantia nigra. This situation, defined as brain iron deficiency (BID), leads to several alterations in neurotransmitters that are secondarily related to RLS symptomatology. RLS has also been related to genetic factors. In recent years, several mutations have been identified as risk factors for RLS. Most of these genes are related to brain iron homeostasis [2].

Clinicians should also look for causes of secondary RLS. Systemic iron parameters, liver and kidney blood tests, electrolytes, vitamin levels, and thyroid hormones should be investigated. In our patient, the laboratory test showed iron deficiency even though she had been receiving oral iron supplementation for years. The evaluation was completed with a transcranial ultrasound that demonstrated a reduction of iron content in the substantia nigra, a common finding in RLS [2], see Fig. 3.1). There is controversy about the sex differences in brain iron and more studies are needed [6].

The causes of iron deficiency should be investigated and corrected whenever possible. In our patient's medical history, three possible causes of iron deficiency

were identified. First, the patient was diagnosed with a bowel syndrome, so a fecal occult blood test and colonoscopy were performed to exclude intestinal leaks. In addition, she had celiac disease, a condition in which iron absorption may be decreased. Finally, the most common cause of iron deficiency in women of reproductive age is of gynecological origin. In this case, we had two gynecological factors that could impact the bleeding pattern in this patient:

On the one hand, perimenopause would be an important factor in gynecological bleeding. The physiologic changes of the menopausal transition stem primarily from the decline in ovarian function. Various markers of ovarian aging have emerged to determine transitions within perimenopause. Traditionally, FSH has been utilized as a measure of ovarian aging, but assessing this gonadotrophin has its limitations given its indirect correlation with ovarian functional decline [11].

Body mass index (BMI) and race impact hormones. Women with obesity have a lower rise in FSH and a less steep decline in estradiol as they traverse the final menstrual period. African American and Hispanic women have higher FSH and lower testosterone compared to other ethnic groups based on an analysis of 2930 women from the SWAN Study (The Study of Women's Health Across the Nation) [11]. This suggests that changes rather than absolute levels of estrogen may be responsible for the initiation of symptoms. Furthermore, hormone replacement therapy (HRT) in menopause has not been completely effective. Therefore, its role is inconsistent.

Anovulation occurs most commonly in the early reproductive years and later perimenopausal years. Episodes of bleeding can range in those periods from light and infrequent for two or more months to episodes of unpredictable and extreme heavy menstrual bleeding (HMB).

A different disorder can occur in ovulatory women: the luteal-out-of-phase event. These women ovulate but recruit follicles early in the luteal phase, resulting in high circulating estradiol levels and associated HMB. This ovulatory dysfunction can occur with a polycystic ovarian syndrome, obesity, hypothyroidism, hyperprolactinemia, anorexia, extreme exercise, and significant weight loss [11]. In women with abnormal uterine bleeding (AUB) evaluation should be directed toward identifying treatable causes, which may include thyroid function testing.

AUB presents a unique challenge in perimenopause, as physiologic hormonal changes may mimic, or mask pathologic diagnoses. These presentations often warrant further evaluation to rule out serious conditions such as hyperplasia or cancer and to guide treatment options. For perimenopausal women, the PALM-COEIN classification of AUB applies and should be utilized to establish a differential diagnosis of bleeding and to guide evaluation and management [12]. Evaluation should include a thorough menstrual, medication, and family history, and assessment for endocrine dysfunction or bleeding disorders. The examination should evaluate BMI, the thyroid, uterus, and cervix via both a speculum and bimanual assessment. This information will help guide laboratory testing, which may include complete blood count, iron studies, thyroid assessment, or evaluation for coagulation disorders. Transvaginal ultrasonography is the imaging modality of choice to identify uterine and endometrial structural abnormalities. Endometrial biopsy is indicated

for persistent AUB, or in those with risk factors, including chronic anovulation and obesity. Once the evaluation is complete, tailored management options can be discussed [11].

Furthermore, leiomyomas (myomas or fibroids), which are benign monoclonal tumors arising from smooth muscle cells of the myometrium, develop during the reproductive years. They are the most common pelvic tumor (estimated prevalence of 70% in white women and more than 80% in black women) [12]. Risk factors for developing leiomyomas include African American ethnicity, early menarche, early oral contraceptive use, low parity, obesity, diet (increased meats, glycemic index, or alcohol consumption), hypertension, and family history. Symptoms include painful menses or HMB and bulk-related symptoms such as pelvic pressure, urinary frequency, bowel symptoms, or reproductive dysfunction. Whereas in other cases, many leiomyomas are asymptomatic, and their presence is not the cause of AUB. Clinical diagnosis may be based on results of pelvic examination with pelvic ultrasound as the standard test. The FIGO classification of leiomyoma location helps define the relationship of leiomyomas in reference to the endometrium or the visceral peritoneum [13].

To summarize, regarding RLS pathophysiology and prevalence, three factors have been proposed for sex differences:

The first factor is iron metabolism: systemic iron parameters are lower in women than in men after the age of 15. However, differences in RLS prevalence do not occur until after the age of 30. Sex differences in peripheral iron status do not suffice to increase the risk of RLS unless there was an additional factor that affects iron stores [3, 5, 6]. As iron plays a central role in the pathophysiology of RLS, and among women of reproductive age common causes of iron deficiency are related to the gynecological sphere, a complete evaluation should be performed in this regard.

The second factor is pregnancy, during which RLS prevalence increases to 20%. The pathogenesis is unclear but family history and multiparity are independent factors. Other risk factors such as iron and folate deficiency and hormonal changes have been suggested [4]. Although RLS is usually transitory, it increases the risk of developing chronic RLS four-fold. Nulliparous women have the same prevalence as men [3, 5, 6].

Third and last, hormonal changes have been associated with the frequency and severity of RLS fluctuation in relation to the menstrual cycle, pregnancy, and menopause. However, these fluctuations do not follow a fixed pattern since there is a high prevalence of RLS during pregnancy when estrogen levels are high but also during menopause when they are lower [3, 6].

Regarding RLS treatment, reversing iron deficiency is essential. Supplementation is indicated if transferrin saturation is less than 45% and serum ferritin is less than 300 ng/mL. The choice of oral or IV iron should be tailored to the patient's needs [2]. In the present case, the response to oral iron was unlikely, so according to the current guidelines, IV iron was initiated. For this reason, the patient received 1000 mg ferric carboxymaltose. It was, however, mandatory to stop blood losses. In our patient, we had to treat both AUB due to perimenopause and the presence of leiomyomas.

Perimenopause can last for a variable amount of time, the median is 4 years. Changing hormone levels manifest through varying symptoms that can present complex clinical management situations for physicians. Understanding the physiology of the decline in ovarian function can help guide management.

The many treatment options for leiomyomas can help individualize therapy to symptoms. Asymptomatic leiomyomas usually do not need to be treated, except in some cases associated with fertility treatments. When HMB is the only symptom, medical therapies may be highly effective, including tranexamic acid, nonsteroidal anti-inflammatory drugs (NSAIDs), contraceptive hormones, danazol, GnRH agonists, aromatase inhibitors, selective progesterone receptor modulator (SPRMs), and selective estrogen receptor modulator (SERMs). In a review by Talaulikar [14], tranexamic acid reduced bleeding by 30–60%, and the levonorgestrel-releasing intrauterine system (LNG IUS) significantly decreased bleeding while increasing ferritin and hematocrit levels [12]. The GnRH agonists can be used preoperatively to reduce leiomyoma volume, correct anemia, and reduce intraoperative blood loss [12]. Uterine-sparing options include myomectomy, uterine artery embolization, magnetic resonance imaging-guided focused ultrasound, or laparoscopic radiofrequency ablation. All of these treatment options have been shown to improve symptoms. Although hysterectomy remains the treatment for leiomyoma symptoms after childbearing is completed and when other options fail.

Finally, regarding symptomatic treatment, it is first of all recommended to avoid therapies that can worsen RLS. These therapies include prokinetic agents, antipsychotics, vestibular sedatives, antihistamines, and antidepressants [2]. In our patient, previous treatment with mirtazapine and trazodone—sedative antidepressants frequently used to treat insomnia—may have worsened RLS symptoms.

Symptomatic RLS treatment should be tailored to the individual according to risk-benefit. Non-pharmacological treatment should be recommended in all patients. Common recommendations are moderate exercise, cold water, massages, compression devices, reduced intake of stimulants, vibratory stimulation, and avoidance of sleep deprivation [2, 5]. Although iron replacement therapy was initiated in our patient, it usually takes at least 6 weeks to show effect, we therefore also initiated symptomatic treatment. The first line of treatment has classically been dopaminergic agents such as levodopa, pramipexole, ropinirole, and rotigotine. Long-term complications such as augmentation are changing this trend. Other treatments for RLS are α2δ-ligand, benzodiazepines, and opioids. It is recommended to start with an α2δ-ligand as they have been demonstrated to be safe and effective in the long-term. Opioids are recommended in severe RLS or in cases of augmentation. In our patient, the first choice of treatment was an α2δ-ligand (gabapentin) [2]. During follow-up, as symptoms did not improve, a low dose of a dopamine agonist was added (pramipexole) and she was monitored for augmentation. There are no specific recommendations for symptomatic treatment in women.

In conclusion, RLS is a common neurological disorder that is more frequent among women. Differences between men and women might be related to iron deficiency, pregnancy, and hormonal changes. The most consistent medical condition associated with RLS is iron deficiency. In women, iron deficiency anemia related to

gynecological issues should be carefully evaluated and corrected to minimize blood losses. As far as RLS treatment is concerned, oral or IV iron replacement therapy should be always considered, as well as symptomatic treatment whenever necessary. A close follow-up and a multidisciplinary approach are mandatory in RLS.

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Sleep Deprivation in a Postpartum Woman with Short Sleeper Syndrome

4

Christine Liu

Clinical History

Chief Complaint "I just don't feel like myself! I can't keep up with things anymore"

Ms. J.L. is a 30-year-old G1P1 with no past medical history except notable short sleeper syndrome, who is 4.5 months postpartum and status post primary C-section for labor dystocia.

Her husband took 2 weeks off to help right after delivery, but since he is a pilot, she continued to let him sleep and was their son's primary caretaker. Immediately after delivery, she was breastfeeding and formula-feeding for 2 weeks, but then transitioned to just formula because her son had difficulties maintaining a good latch.

The first month, she fed him every 2 hours for about 30–40 minutes each time; because she also changed a diaper each feed, she found she would lay down for no more than 1 hour between feeds, but she would have a tough time falling asleep or even staying asleep because of her attentiveness to the movements and sounds of her baby in the co-sleeper next to her bed. Because family lived a state away, she was mostly alone during the day with the baby, doing all household chores herself. She tried to prioritize sleep because she anticipated fatigue, but she found that though she laid down for about six to eight times during the day, she likely slept for 4–5 hours total a day, if that, the first month---all in 40-minute to 1-hour increments.

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J.L. did not feel too fatigued this first month, except she was increasingly irritable and snappy at her husband.

Then the second to the third month, baby transitioned to feeding every 2–3 hours. J.L. began sleeping 1–2 hours between feeds at night, averaging 1.5 hours each time, for a total of 4.5–5 hours a day. The baby was more awake between feeds, so she tried to read to him and have him do tummy time as much as possible when she took him home from daycare. After 2 months of maternity leave, J.L. went back to work as a part-time home health occupational therapist. She saw patients for four 1-hour sessions a day, but with driving and charting time, really worked 8 hours a day. She had a few incidents of dozing off at red lights, which scared her into taking two 15-minute naps between patients during the day to help her stay awake driving. While she had some irritability and forgetfulness the second month, she now felt "flat" and disengaged going into her fourth month postpartum, even with patients, with whom she used to love interacting. She started to feel more isolated. Friends asked to visit, but she preferred to be by herself. She felt guilty because she would doze off when feeding the baby and was afraid, she would drop him. She could not understand why, when she used to sleep 5 hours a day, she felt fine, but now was increasingly fatigued.

After 4 months, she began feeding the baby every 3–4 hours. J.L. would doze off when typing her charts at home, would occasionally confuse her patient cases, and felt anxious she was underperforming. She would eat more snacks to stay up at night and gained 12 pounds post-pregnancy. She asked her supervisor to work 3 days a week rather than 5, but due to staffing issues, she was asked to work 5 days a week for one more month. After talking with her supervisor, J.L. had her first panic attack. J.L. would feed the baby twice at night now and sleep up to 3 hours at a time for two sessions, sometimes getting up 6 hours of sleep total. She felt increasingly fatigued and could not figure out why, especially if she were sleeping more hours at night and catching two 15-mins naps during the day. Over time, J.L. had a harder time falling asleep and staying asleep, so her 3-hour-at-a time of sleep at night became closer to 2-hour sessions. She tried to take naps on the weekends when her husband was home, but though she slept up to 2 hours more on those days and could fall asleep quickly and stay asleep, fatigue persisted. She sometimes falls asleep in mid-conversation with her husband. She felt she was letting her husband, baby, friends, and work colleagues down. She felt increasingly more withdrawn and detached.

Physical Exam

BP 114/74 mmHg, HR 78 bpm, RR 12 breaths/mins, 187 lb., 5′6″, BMI 30.2 kg/m^2.

General: alert, oriented.
ENT: no thyromegaly or thyroid masses.
CV: regular heart rate and rhythm.
Psych: linear and fluent speech, normal insight and eye contact, depressed affect, shifted often in her seat, no suicidal or homicidal ideation.

Neuro: no focal deficits.
PHQ9 depression screen: 12.
GAD7 anxiety screen: 7.
Epworth Sleep Scale: 16.

Lab Results

CBC, CMP, thyroid panel, Vitamin B12 and D within normal limits.

Actigraphy: decreased sleep efficiency, increased intra-daily variability, increased sleep periods, increased wake after sleep onset (WASO), increased sleep fragmentation index.

Sleep diary: difficult for patient to remember to do because of life demands.

Question 1
What is the next best step in the management of sleep disturbance for this patient?

A. Sertraline 25 mg by mouth 2 hours before bedtime
B. Asking for help to get at least 7 hours of uninterrupted sleep at least 3–4 times a week
C. Napping 30 minutes during the day straight, rather than two 15-minute sessions
D. Taking 3-hour naps on Saturday and Sunday

Question 2
Treatment for which of her associated conditions will best result in improvement of her sense of well-being and fatigue?

A. Postpartum depression
B. Anxiety with panic attacks
C. Postpartum sleep deprivation
D. Obesity

Differential Diagnoses

Postpartum depression.
Anxiety disorder.
Postpartum sleep deprivation.
Chronic insomnia.

Diagnosis

Postpartum sleep deprivation

Discussion

The average adult needs 7–9 hours of sleep a day, going through continuous five 90-minutes sleep cycles or more to feel refreshed. For the postpartum woman, frequent awakenings to tend to her newborn (waking after sleep onset), disruption of the 90-min sleep cycle (increased sleep fragmentation), with noticeably short intervals of sleep which can prevent achieving refreshing and rejuvenating sleep. Early sleep deprivation can cause problems with fatigue and irritability, which can then progress to decreased concentration, memory, increased reaction time and motor coordination/reaction time. This is especially problematic not only for the new mother but also for her infant. Long-term sleep deprivation can lead to symptoms of postpartum depression and anxiety and critical malfunction [3].

Short sleepers, by definition, usually need less than 6 h of sleep to feel refreshed. They do not need naps or stimulants to keep them awake and fully functional. This pattern of sleep is most often noticed in adolescence. Recent studies show that short sleeper syndrome can be caused by a gene mutation in *DEC2* (variant known as *BHLHE41)* [2, 4]. There seems to be no long-term negative health sequelae for short sleepers, as opposed to many morbidities in normal sleepers who sleep less than 6 hours (cardiovascular disease, cancer, obesity, mood disorders, compromised immune systems, decreased libido). Short sleeper syndrome new mothers may at first think they can get by with the same or less amount of sleep than they did prior to delivery. However, they too are equally subject to the effects of sleep deprivation when they experience more disrupted sleep, shorter sleep cycles, and overall decreased amount of sleep from their baseline.

Often **new mothers** may instinctively, as nurturers, try to do most things for their newborn. They may consider sleep deprivation as the norm for all mothers and may have personal preferences or real or perceived societal pressures to not reach out for help. However, studies show that mothers who reach out for support or who have a natural support system do better when queried about well-being at every stage of the postpartum period.

As clinicians, educating new moms about their need for sleep that is uninterrupted for their natural sleep cycle, the amount of sleep they need, and the benefits of reaching out for support can help mitigate the development of sleep deprivation even before it starts. Teaching expectant moms that fully breastfeeding yields more sleep for moms than bottle-feeding can also help [1]. The causes are still being explored, but some suggest that less blue light stimulation (not needing to get up and make a bottle and then being more aroused) can be a possibility. We can further support the new mother even in the antepartum period by recommending not only pregnancy and prenatal support groups, but also postpartum support groups, encouraging them to sign up even before they deliver. Encouraging new mothers to do a sleep diary can help them be more aware of their sleep patterns before they become

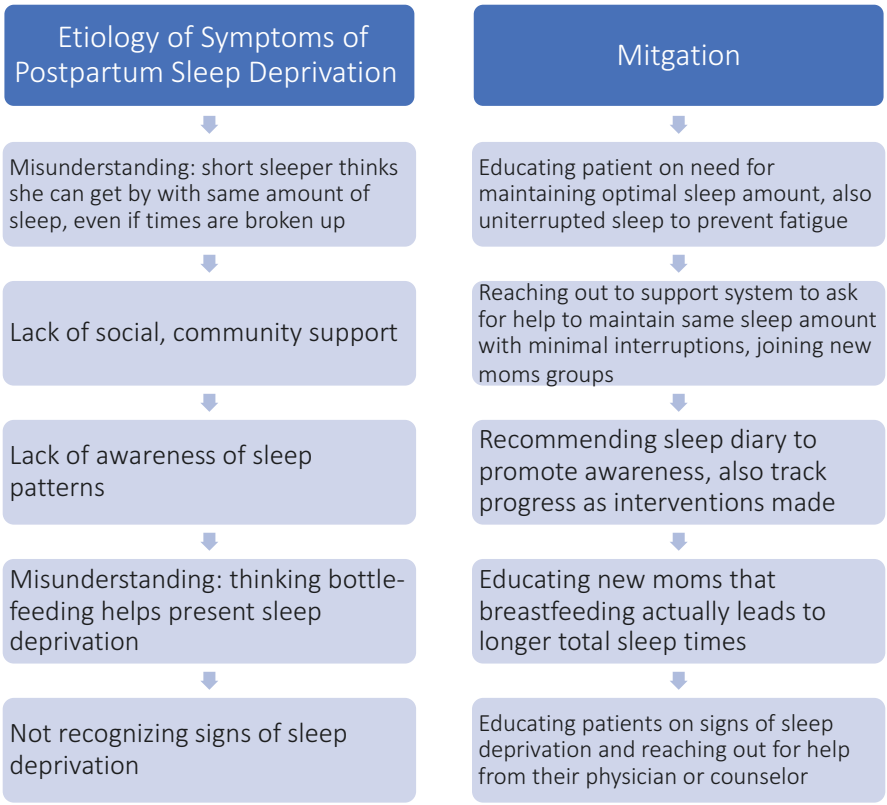

Fig. 4.1 Etiology of symptoms of postpartum sleep deprivation and mitigation strategies. (This is an original graph that has not previously been published)

very sleep deprived. Alerting new moms about symptoms of depression, anxiety, decreased functioning that can come from sleep deprivation can make them more motivated to prevent chronic sleep deprivation and be aware of when to reach out for help from their physician or to seek behavioral health support if they develop more serious signs of sleep deprivation.

Destigmatizing the need for support from family, friends, or even hired helpers by normalizing it in routine screening and discussion can support the new mom during the antepartum and postpartum periods. Refer to Fig. 4.1. Family physicians, pediatricians and obstetricians building in questions not only about postpartum depression, but also about symptoms of sleep deprivation screening into their routine postpartum clinic follow-ups may find they catch symptoms of sleep deprivation earlier, which can be addressed as soon as possible for the promotion of health of the mother and newborn.

Answers
1. b
2. c

Pearls/Take-Home Points

While not all postpartum sleep deprivation can be avoided, mitigating exacerbating attitudes or behaviors by offering education and support of the new mom can be helpful in preventing negative sequelae of sleep deprivation.

Educating women with short sleeper syndrome about their specific need for consistent, uninterrupted sleep of the same quantity before and after delivery can especially prevent morbidity, and, reduce exhaustion in this special population.

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Part II

Sleep-related Disorders of Breathing in Women

5 Can Snoring Cause Me to Be Tired and Sleepy? Upper Airway Resistance Syndrome in Women

Zakarya Irfanullah and Imran S. Khawaja

Clinical Case History

A 52-year-old Caucasian female college professor presented to a sleep clinic with no past medical history. She endorsed persistent daytime sleepiness and inability to concentrate every day for the past 6 months. Her husband had told her that she had started snoring, but she did not believe it. Her performance at work had dropped, and she had associated symptoms of difficulty focusing and mental fatigue. She wondered if she had attention deficit hyperactive disorder (ADHD). She denied any typical symptoms of depression but admitted to having frequent awakenings with a dry mouth at night. She, however, did not have any trouble going back to sleep most nights.

Examination and Mental Status Exam

The patient was tall and slightly overweight on general physical examination with a BMI of 32. She exhibited classical craniofacial abnormalities of long face syndrome with a narrow and short chin and retrognathia. On further clinical examination, dental overjet and ogival hard palate were observed. Her mood was euthymic, with affect being appropriate to her mood. She was cooperative, and appeared tired. A

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mental state examination did not reveal any evidence of paranoia or any other psychotic symptoms. The patient reported feeling unrefreshed after sleeping for the past several months.

Special Studies

A full blood panel recently conducted by her primary physician revealed no abnormalities. The sleep doctor recommended formal polysomnography (PSG) instead of a Home Sleep Apnea Test (HSAT) as the patient did not have a high probability of sleep apnea.

The sleep study revealed the presence of respiratory effort-related arousals (RERAs) and few apneas and hypopneas. On the attended polysomnogram, an apnea-hypopnea index (AHI) of four events per hour (normal is <5). The respiratory disturbance index (RDI), a combination of the AHI and RERA Index, was 7/h.

Results

As per the physician's recommendation, the patient underwent maxillofacial surgery to correct her craniofacial abnormalities. She began using a mandibular advancement device for her retrognathia in addition to initiating CPAP therapy while sleeping. On her first visit post-op, the patient reported a remarkable improvement in her daytime fatigue and sleepiness.

Diagnosis, Differential Diagnosis, and Discussion

Chronic sleep loss associated with sleep disorders imposes an increasingly significant burden on public health. Close to 60 million Americans now suffer from a chronic sleep disorder. This impacts daily functioning by decreasing attention, memory, and concentration, decreasing workplace productivity and quality of life, and increasing the incidence of road traffic accidents [1].

Guilleminault et al. in 1993 [2], first described upper airway resistance syndrome (UARS). UARS exists on the spectrum of sleep breathing disorders that ranges from simple snoring to obstructive sleep apnea. It is defined by the presence of excessive daytime somnolence that cannot be explained by another cause and is associated with greater than 50% of respiratory events that are nonapneic and non-hypopneas. The prevalence of UARS is found to be 3.1% (4.4% in women and 1.5% in men), making it more common in women [3].

UARS is characterized by repetitive respiratory effort-related arousals (RERAs) that induce microarousals from sleep that are sufficient to cause clinical pathology in the form of daytime sleepiness, functional impairment, and potential cardiovascular complications but are not profound enough to result in oxygen desaturation, thus differentiating it from obstructive sleep apnea (OSA) [4].

RERAs can be measured directly via esophageal pressure, by assessing changes in pulse transit time as a proxy for respiratory effort, or by evaluating respiratory flow limitation with either a nasal cannula or a pneumotachograph.

Daytime somnolence remains the most consistent clinical finding in UARS. Apart from this, UARS shares much the same clinical symptomatology as OSA, with patients reporting insomnia (in 20% of cases with UARS), nocturia, poor concentration, headaches, irritable bowel syndrome, and vasomotor rhinitis. In addition to all the downstream consequences of unrefreshed sleep, patients often complain of depressed mood and consequently seem to be on more antidepressants, hypnotics, and stimulants than if they are not treated for UARS [5]. On clinical examination, the craniofacial abnormalities that constitute 'classical long face syndrome' involving a short and narrow chin, reduced mouth opening, and retrognathia have been reported as being specific to UARS [6].

The daytime sleepiness seen in UARS can be similar to lethargy secondary to iron deficiency anemia, especially in females. For this reason, a full-blood panel is recommended to rule out this diagnosis.

UARS can be differentiated from OSA by the absence of apneas and the fact that there is no significant oxygen desaturation during RERAs. Although UARS falls on the spectrum of sleep breathing disorders of which OSA is the most severe, OSA is not the natural progression of UARS, although OSA can develop in a patient with UARS if they gain significant weight over time [4].

The pathophysiology of UARS centers around velo and oro-pharyngeal collapsibility, which depends on the balance between collapsing factors and protective factors. Collapsing factors include upper airway narrowing and pharyngeal collapsibility [7]. This is often seen in the case of patients with classical long face syndrome, where the craniofacial abnormalities favor collapsibility of the upper airway. This collapsibility is countered by strong pharyngeal reflexes and upper-airway dilating muscular activity [8].

UARS has been correlated with adverse cardiovascular outcomes, although more definitive studies on this relationship are warranted. Nonapenic non-hypopneic events, as seen in UARS, are succeeded by elevations in arterial pressure in proportion to the degree of arousal [9]. It has been posited in observational studies that the mechanical act of snoring itself gives rise to carotid atherosclerosis, with the carotid bifurcation most affected because of its proximity to the hypopharyngeal wall [10]. In addition to this, repeated micro-arousals in RERAs are associated with transient arterial blood pressure fluctuations and rises in CO2 [11]. With all of this said, the data to support the claim that UARS results in cardiovascular morbidity is still quite tentative, and further longitudinal studies are needed.

In terms of treatment, there is insufficient data on the long-term outcomes of any particular modality. However, CPAP tends to be the standard of care for patients with UARS. Given that specific craniofacial abnormalities have been shown to exacerbate upper airway collapsibility, the use of mandibular advancement devices and maxillofacial surgery to correct long face syndrome has also become common practice; however, once again, further studies on the long-term benefits of these interventions are required.

Consequently, maxillofacial surgery and mandibular advancement devices have become part of the standard of care for individuals with UARS and classical long face syndrome. However, further studies on the outcomes of this surgical intervention in UARS are warranted.

Conclusion

UARS is a phenomenon that affects women more often than men, and usually presents as daytime somnolence. It shares much of the same clinical symptomatology as OSA although it is not profound enough to cause oxygen desaturation. CPAP is currently the mainstay of care, however, efficacious treatment modalities for UARS remains an area of further exploration.

Pearls/Take-Home Points

- UARS is common in women with craniofacial abnormalities and obesity
- UARS causes symptoms similar to OSA
- Treatment of UARS may have a beneficial effect on daytime sleepiness and fatigue by eliminating sleep fragmentation.
- Clinicians should ask patients about snoring, mainly if they are complaining of daytime sleepiness, and fatigue, and other medical conditions like anemia, hypothyroidism and vitamin D deficiency have been ruled out.

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Is It Snoring or Sleep Apnea; Should I Be Worried?

6

Abha Patel, Joy Bernardo Ramos, and Safia S. Khan

Clinical Case 1

Ms. K is a 45 year old woman, a retired military veteran with a PMH of generalized anxiety disorder, depression, migraine headaches, chronic insomnia, chronic PTSD, and obesity who presented to the sleep clinic for evaluation of sleep apnea as a contributing factor to her headaches. While active duty, she had undergone a sleep study approximately 11 years before presentation to our sleep lab. She reported snoring and daytime sleepiness at that time, prompting the sleep study. Of note, her prior polysomnography (PSG) test was significant for reduced sleep efficiency, but her apnea hypopnea index (AHI) was normal at 2.3 events/h. She did have a somewhat elevated respiratory disturbance index (RDI) of 6.8 events/h of sleep.

During her current presentation to our sleep clinic, she endorsed a 10-to-15-pound weight gain since her initial sleep study. She also reported snoring and daytime fatigue. Her Epworth Sleepiness Score (ESS) was 9/24.

At the time of her initial sleep study, the patient was pre-menopausal. However, 4 years prior to presentation in our clinic, she underwent a total hysterectomy with bilateral oophorectomy. With regard to her sleep, she noted worsening sleep maintenance insomnia and night sweats since menopause. Her sleep schedule was as

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follows: time in bed 10 p.m., sleep onset latency 15–60 mins, multiple arousals throughout the night with difficulty falling back asleep, wake up time 7 a.m. She estimated a sleep time of 5–6 h nightly. She did not routinely take naps.

She denied tobacco use, drank alcohol minimally on a social basis, and denied recreational drug use. She did drink 1 cup (10 oz) of coffee most mornings.

Active Medications Venlafaxine, Trazodone, Maxalt.

Exam She was alert and oriented to person, place and time. She appeared overweight, but maintained good muscle tone. Her neck circumference was 14 inches, height was 66 inches, and weight was 190 Ib. with a BMI of 30.7. Her oral cavity revealed a Mallampati of 2 out of 4 with an elongated uvula.

Special Studies

1. Initial PSG:
   Total sleep period 409.9 mins, total sleep time 375.6 min, sleep efficiency 82.4%.
   AHI 2.3 events/hr., RDI 6.8 events/hr., SaO2 nadir 91%, SaO2 mean 96%.
2. Follow up home sleep apnea test (HSAT), (see Table 6.1 and Fig. 6.1) AHI: 7.4; Supine AHI: 7.9, REM AHI: 2.2, RDI: 22.5/h lowest SpO_2 83%, and time below 88% O2 was 0 min

Table 6.1 Portable sleep apnea monitoring test showing mild OSA, note AHI: 7.4; Supine AHI: 7.9, REM AHI: 2.2, RDI: 22.5/h lowest SpO_2 83%, and time below 88% O_2 was 0 mins (This table is original and has not been previously published online or in print)

Sleep	Sleep Latency (min): 31	REM Latency (min): 65	Sleep Efficiency: 83%
	Estimated%REM: 18.3%	Est%deep sleep: 9.9%	Est%light sleep: 71.7%
Respiration (3%)	pAHI: 7.4/h	pAHI in REM: 2.2/hr	pAHI in supine pos: 7.9/h
		pAHI in non-REM: 8.6	pAHI in non-supine pos: 3.5
	pRDI: 22.5/h	pRDI in REM: 16.0/h	pRDI in supine pos: 22.2/h
Snoring	Average level: 40 dB		
Body position	Supine: 407.0 min. (89.0%)	Lateral 4.5 min. (1.0%)	Prime: 47.0 min. (10.0%)
Heart rate (bpm)	Average HR: 52	Maximum HR: 89	Minimum HR: N/A
Oxygen saturation (4%)	Overall ODI**: 2.0/h	ODI in REM 1.5/hr	ODI in supine pos: 2.1/h
	Avenge SpO2: 96%	Minimum SpO_2: 90%	Total # of OD events: 15
	SpO_2 < =88: 0.0 mins		

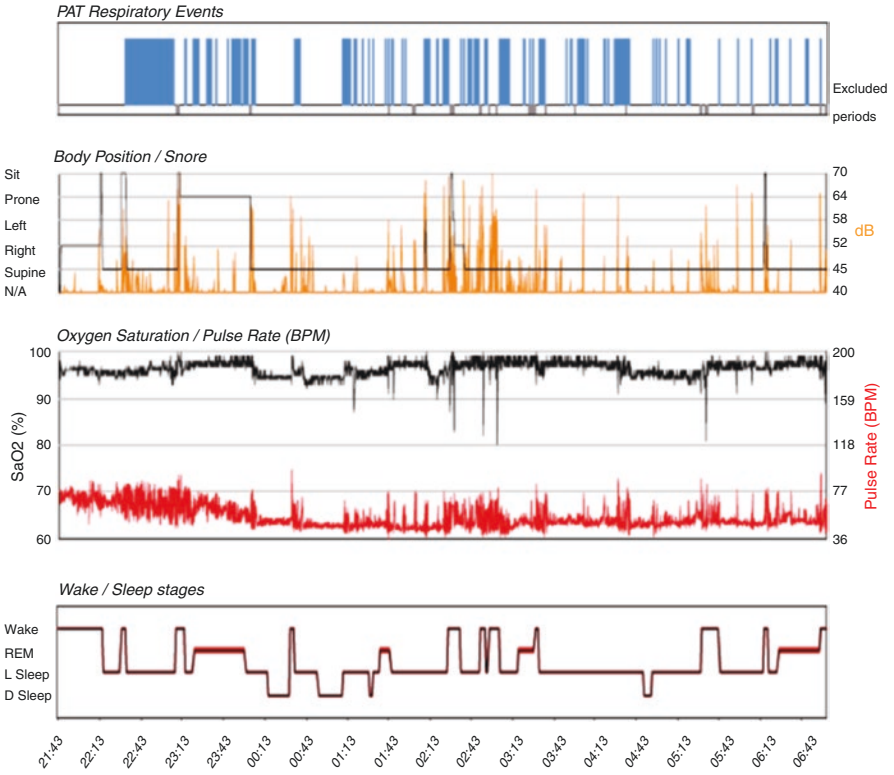

Fig. 6.1 Hypnogram of portable monitoring showing mild OSA, showing peripheral arterial tonometry (PAT) events, body position/ snoring, oxygen saturations/pulse rate, and wake/sleep stages. Note snoring as high as 70 dB (This figure is original and has not been previously published online or in print)

Case Follow Up

After completion of her HSAT, the patient had clinic follow up to discuss her diagnosis of mild severity OSA. She opted to start treatment with auto-CPAP with a plan to re-evaluate her insomnia and hypersomnia symptoms after optimization of her underlying OSA.

Question 1
How may have menopause changed this patient's sleep quality?

A. Reduced airway collapse
B. Increased upper airway resistance
C. Reduced oxygen saturation
D. Increased oxygen saturation

Question 2
What role does gender play in women regarding the diagnosis and presentation of sleep apnea?

A. Mostly present with typical symptoms of loud snoring, witnessed apneas
B. Have higher risk of obstructive sleep apnea compared to men
C. Do not respond well to therapies for sleep apnea
D. Mostly present with non-specific symptoms of fatigue, headaches, mild snoring

Clinical Case 2

Ms. SS is a 35 years. old lady of African American descent who has history of snoring for many years. Recently, she was on a camping trip with her friends and was informed of recurrent witnessed apneas while sleeping. She does not have any significant past medical or surgical history. She is a financial advisor, has a busy work life. She eats an extremely healthy diet and exercises regularly at the local gym for 40–60 mins daily. She enjoys hiking and off-road biking. She is not worried about snoring as it is not affecting her sleep and she wants to know if anything needs to be done about this. She takes an afternoon nap on the weekends, attributes the tiredness on the weekdays to her work and on the weekends to her busy exercise routines. Her Epworth Sleepiness Scale Score was 12/24.

Physical Exam Normal general physical exam for cardiovascular, respiratory, neurologic, and abdominal systems. Head and neck exam shows Mallampati: II, tonsils: 1+, uvula midline with tapering long end, neck circumference of 13″, BMI (Body Mass Index): 24.

Special Studies CBC (complete blood count), CMP (comprehensive metabolic panel), TSH (thyroid stimulating hormone), Vitamin D levels were all unremarkable.

Question 3
Ms. SS has a low STOP BANG score of 3. What diagnostic test is indicated for evaluation of snoring in this patient?

A. Actigraphy study
B. In-lab sleep study
C. Home sleep study
D. No testing is necessary

Question 4
What is the initial treatment option for simple snoring?

A. Tonsillectomy
B. CPAP (continuous positive airway pressure)

C. Dental device for mandibular advancement
D. Uvulopalatopharyngoplasty (UPPP)
E. Avoidance of supine sleep
F. Elevate head of the bed

Discussion

Snoring is a common complaint associated with sleep disordered breathing. Due to its high prevalence, snoring is often overlooked as a predecessor to a more significant issue of all severities of sleep disordered breathing. Of the different manifestations of sleep disordered breathing, OSA is the most common. Many people accept snoring as a cultural and aging norm, and do not feel the need to have their snoring evaluated. Snoring has been found to occur in over half of the adult population [1].

Clinicians must not overlook snoring with sleep apnea and its potential effects on the patient, bed partner, and family. The association of obstructive sleep apnea with cardiovascular and metabolic disease has been well established. In recent years, the role of gender and aging in OSA has been increasingly studied. Specifically, the effect of menopause in women with OSA has been more clearly identified. Here we will review the defining characteristics of OSA and the role that gender plays in diagnosis and disease manifestation.

OSA, as described by the International Classification of Sleep Disorders, third edition must meet the following criteria: The patient must present with symptoms of sleep disordered breathing or have significant co-morbid disease associated with sleep disordered breathing plus five or more predominantly obstructive events on PSG (see Table 6.2 and Fig. 6.2) or HSAT (see Table 6.1 and Fig. 6.1). If the patient has 15 or more predominantly obstructive events per hour of sleep, then associated symptoms or comorbid disease are not needed to establish the diagnosis. Symptoms

Table 6.2 In-lab polysomnography example of mild OSA, tabular information showing; AHI: 5.1, Supine AHI: 12.9, REM AHI: 0, lowest SpO_2 85%, and time below 88% O_2 was 1.1 mins (This table is original and has not been previously published online or in print)

Sleep architecture	
Lights out	23:01
Lights on	05:35
Total recording time (min)	394.0
Total sleep time (min)	374.5
Sleep efficiency (normal is >80–90%)	95.1%
Sleep latency (min)	0.5
REM latency (min)	0.0
WASO (min)	19.0
% supine of TST	23.6%
Time supine (min)	88.5
% non-supine TST	76.4%
Time non-supine (min)	286.0

(continued)

Table 6.2 (continued)

Sleep stages			
Pre-TX	Mins	% TST	Normal
Stage N1	37.0	9.9%	<5%
Stage N2	330.5	88.3%	50%–60%
Stage N3	7.0	1.9%	15%–20%
Stage R	0.0	0.0%	20%–25%

Cardiac events	
Average HR Sleep	74
Highest HR during sleep	106

Pre-treatment arousal events (Arousal index = AI)			
PLMS Arousals	0	PLMS AI	0.0
Resp. arousal	71	Resp. AI	11.4
Spont. Arousals	33	Spont. AI	5.3
Snore arousals	0	Snore AI	0.0
Total arousals	104	Total AI	16.7

PLMS	
# of PLMS	0.0
PLMS index	0.0

Respiratory events	
Obstructive Apneas	1
Obstructive hypopneas	31
Central apneas	0
Mixed apneas	0
Total apneas + hypopneas	32
Apnea index	0.2
Hypopnea index	5.0
AHI supine	12.9
AHI non-supine	2.7
Overall AHI (Normal: <5/h)	5.1
REM AHI	0.0
RERAs	58
RERA index	9.3
Total events	90
RDI	14.4
Minimum SpO_2	85%
Mean SpO_2	94%

of OSA typically include daytime sleepiness, fatigue, nonrestorative sleep, insomnia, breath holds, witnessed apneas, snoring, choking, or gasping episodes in sleep. Co-morbid diseases associated with OSA can include hypertension, mood disorders, cognitive dysfunction, heart disease, arrythmias, or diabetes [2].

Despite the wide range of symptoms and co-morbid disorders associated with OSA, presentation typically manifests as repeated apnea and hypopnea events often resulting in intermittent hypoxia. These events are known to cause increases in sympathetic tone and oxidative stress, often leading to elevated cardiovascular risk over time. Interestingly, while men are more likely to present with snoring, choking

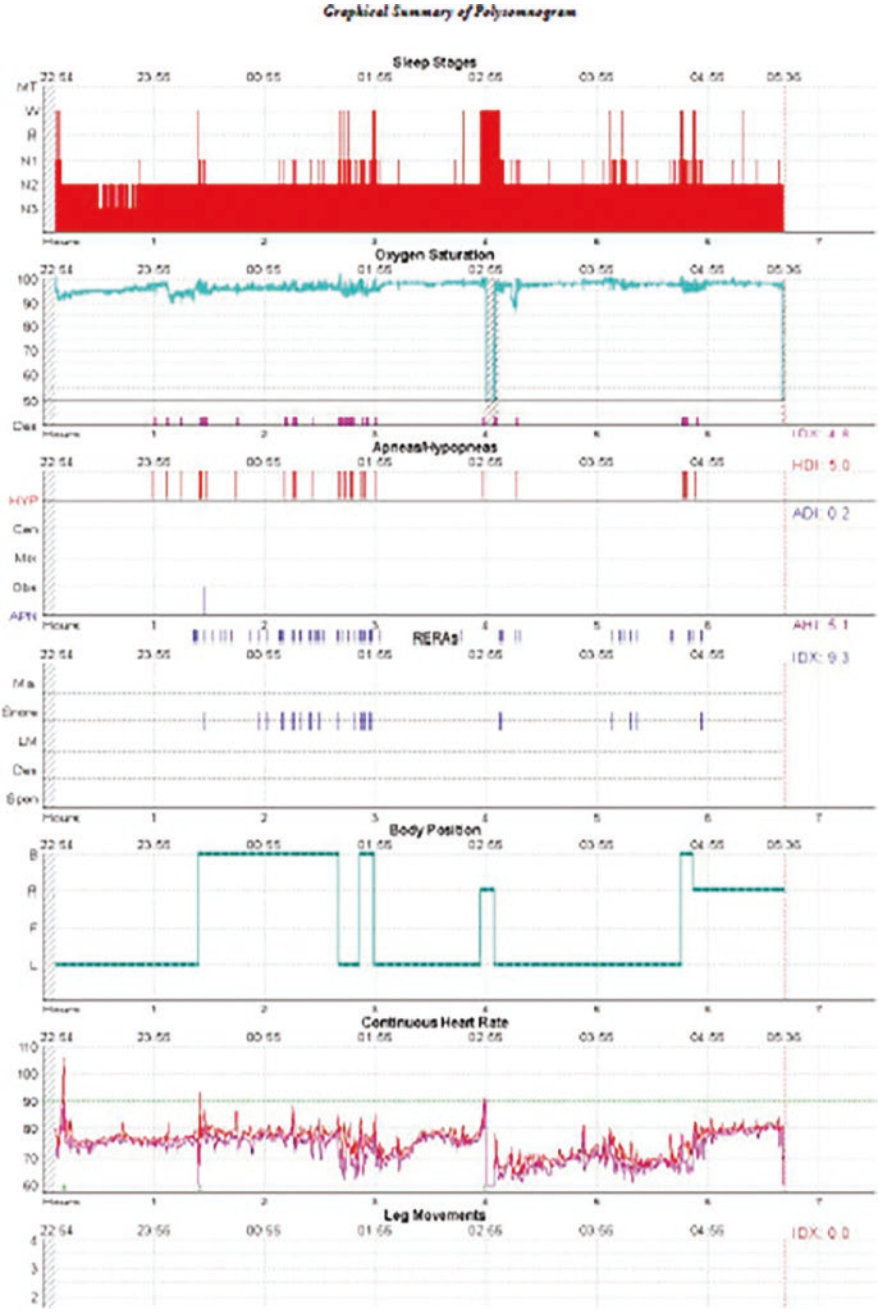

Fig. 6.2 Hypnogram for in-lab polysomnogram showing sleep stages, oxygen saturation, apneas/hypopneas, (respiratory effort related arousals (RERAs), body position, heart rate, and leg movements (This figure is original and has not been previously published online or in print)

episodes, and daytime sleepiness, women more often report nonspecific symptoms such as fatigue, headaches, lack of energy and mood disorders [3]. Of note, snoring, stopping breathing in sleep, and daytime sleepiness are all part of the STOP-BANG screening criteria for sleep apnea, whereas headaches and mood disorders are not included. Moreover, female gender is not considered a predictor of OSA in the SOTP-BANG screening criteria [4] possibly reducing its sensitivity in women.

A 2018 study looking at the impact of gender and menopausal status on sleep disordered breathing (SDB), nicely delineated differences in prevalence, presentation, and associated co-morbid diseases based on sex and hormonal changes in patients. The overall prevalence of sleep disordered breathing (defined as an AHI > 5/h) was significantly higher in men (83.8%) compared with pre-menopausal women (35.1%) [5]. However, post-menopausal women had a prevalence of sleep disordered breathing of (71.6%) [5] due to increased upper airway resistance to flow and increased upper airway collapsibility. There were also differences in clinical presentation noted. For example, women with SDB were significantly more likely to have hypertension, depression, headaches, mild snoring and fatigue, compared to men. Moreover, men with SDB were significantly more likely to have diabetes, while both pre-and post-menopausal women did not have a significant increase in incidence of diabetes [5].

Diagnostic Testing; Utility of in-Lab Versus Home Testing

The Portable Monitoring Task Force of the American Academy of Sleep Medicine (AASM) recommends that use of portable monitoring or home sleep apnea tests should only be performed in combination with a complete sleep evaluation [6]. An in-lab polysomnography test (see Table 6.2 and Fig. 6.2) is particularly ideal for patients who have congestive heart failure, neuromuscular disease or diaphragm weakness, restrictive lung disease, COPD, and obesity hypoventilation syndrome [6]. Furthermore, patients with neurological history such as nocturnal seizures, stroke, Lewy Body Dementia, Parkinson's Disease, and multisystem atrophy would benefit from an in-lab study given EEG monitoring, EMG monitoring, and video monitoring. If a portable home sleep test was to be conducted on a patient with severe insomnia, their sleep issues may be underestimated if little sleep is recorded relative to total time of recording [6]. In case initial test is negative with home testing or with attended polysomnogram and there is suspicion of OSA then repeat testing with attended polysomnogram is recommended [6].

A diagnosis of OSA is not confirmed in the absence of polysomnogram or portable home testing, even in the case of strong suspicion utilizing clinical tools (pulse oximetry alone), questionnaires and other algorithms [6].

In addition to these recommendations, portable monitoring is beneficial for patients who have circadian rhythm disorders like shift work, as they are able to go to sleep and wake up on their own schedule with no pressure having to sleep within a restricted timeframe. Portable monitoring (see Table 6.1 and Fig. 6.1) is also useful for patients with anxiety disorders surrounded by sleeping in a different

environment aside from their own bed. Depending on busy lifestyles, home/work demands, and transportation, portable monitoring can be very convenient for many patients. Portable/home sleep apnea tests have been additionally useful during the COVID-19 pandemic that necessitates halting attended sleep studies during peak surges of the pandemic.

Treatment

There are many options to treat obstructive sleep apnea depending on comorbidities, severity of sleep apnea, symptoms, and patient willingness. Particularly in sleep apnea with mild severity as well as snoring, patients can choose one or multiple modes of treatment in conjunction with one another, with initial intervention being avoidance of supine sleeping position. Patients with UARS (Upper Airway Respiratory Syndrome) or snoring, who are not able to access PAP (Positive Airway Pressure) therapy from an insurance perspective, or mandibular advancement device fit by a dentist, should consider positional therapy (avoidance of supine sleep), weight management, elevating head of bed, snore guards, and nasal strips for some relief from snoring.

Recommendations for treatment with PAP therapy are clearly outlined in the AASM Clinical Practice Guidelines for treatment of OSA. It is noted that patients and clinicians should both agree that PAP is the preferred treatment choice. This is important, as many patients may be reluctant to even try PAP without appropriate education and guidance. Considering auto-CPAP or in-lab titration study to determine optimum treatment pressures should be discussed by taking into consideration comorbidities [7]. Occasionally, there is evidence of significant central sleep apnea events (>5/h) with initiation of PAP therapy, this is effectively treated with bilevel PAP with a backup rate or timed mode.

The most apparent symptomatic benefits from proper treatment of OSA include improvement in snoring, daytime sleepiness, quality of life, and mood. With the elimination of respiratory effort related arousal events, treatment of mild sleep apnea improves sleep consolidation and reduces arousals. Additionally, various randomized controlled trials have revealed that CPAP therapy reduces the risk for major adverse cardiovascular events when CPAP is used greater than 4 h each night [8]. There has also been various evidence in support of sleep apnea treatment and its benefits in neurodegenerative disorders such as Parkinson's disease and Alzheimer's disease [9].

Conclusion

The patient presented in the first case, had more atypical symptoms of OSA such as migraine headaches, depression, nonspecific fatigue, and insomnia. The patient in the second case had less likelihood of having obstructive sleep apnea due to lower BMI, less crowded upper airway, and an active lifestyle. Understanding gender

differences and the effect on SDB can better identify which patients are at low or high risk of disease, and obtaining the appropriate sleep study will lead to lower chances of missing a diagnosis of OSA and UARS. As medicine in general moves towards individualized or personalized care, understanding the different predictors of disease and phenotypes of disease manifestation may lead to better overall patient outcomes.

Take Home Points

- Though snoring is very common, often goes under-reported among women. If it is accompanied by other symptoms such as excessive daytime sleepiness or fatigue, witnessed apneas, or insomnia, further evaluation with polysomnography or portable home sleep apnea monitoring is recommended.
- There are specific recommendations regarding whether in-lab polysomnography or portable monitoring is indicated, and it is outlined in guidelines developed by AASM task force.
- Treatment for obstructive sleep apnea will vary depending on clinical presentation, symptoms, severity of sleep apnea, comorbidities, and patient willingness.

Correct Answers

1. B
2. D
3. B
4. E

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7 Case of Obesity Hypoventilation in an African American Lady with Underlying Hypertension, Diabetes and Mood disorder

Abha Patel

Clinical History/Case

Ms. B is a 52 years old postmenopausal African American female with a past medical history of benign essential hypertension, morbid obesity, depressive disorder, diabetes mellitus, obstructive sleep apnea (OSA), and hypersomnia. Medications at time of presentation included metoprolol, lisinopril, atorvastatin, metformin, lithium, bupropion, and desvenlafaxine. She was referred to the sleep clinic for daytime sleepiness and headaches despite previous good CPAP compliance. She had been first seen at our institution in 2011 and had done well on CPAP therapy. Her initial diagnosis of OSA was in 2004, and her most recent diagnostic sleep study from 2007 was significant for moderate OSA with an apnea hypopnea index (AHI) of 28.3 evens/h. She was on CPAP 8 cm H_2O based on a titration study at time of presentation, but was no longer consistently using her PAP device. She had prior excellent compliance, but noted that recently the CPAP was not helping. She was waking up with frequent morning headaches, daytime fatigue, and described poor sleep quality. Since her initial OSA diagnosis, she had gained 40 pounds due to a more sedentary lifestyle. Her Epworth sleepiness scale (ESS) was 16/24.

She did not have history of smoking, drinking alcohol, or use of recreational drugs. She was drinking 1–2 (10 oz) cups of coffee daily. The caffeine did not help with her daytime sleepiness.

Her sleep schedule was as follows: time to bed 11 p.m., sleep onset latency 15–25 mins, wake time 7:30 a.m., estimated sleep time 6.5 hours. She also endorsed an hour-long nap daily.

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Examination

She was alert and oriented to person, place, and time. Height was 66 inches and her weight was 251 Ib. with a BMI of 40.5. Her oral cavity revealed a Mallampati of 4/4. She also had central obesity on exam.

Special Studies

Serum bicarbonate levels on basic metabolic panel:

Baseline: 23.3 mmol/L
At time of presentation: 27.7 mmol/L
After initiation of BIPAP: 22.7 mmol/L

Polysomnography A one-night polysomnography (PSG) was performed on her baseline CPAP setting of 8 cm H_2O with continuous transcutaneous CO_2 monitoring.

Time in bed (TIB) 429.6 mins, total sleep time (TST) 337.5 mins, sleep efficiency of 78.6%, sleep latency 27.7 mins, Wake after sleep onset (WASO) 64.4 mins, Stage N1 was 25.5 mins, Stage N2 was 196.5 minutes, Stage N3 was 0 mins, and stage REM was 115.5 mins.

The PSG demonstrated good control of her OSA on CPAP 8 cm H_2O. The patient's residual AHI corrected to normal (AHI 2 events/h) on PAP therapy. However, her awake upright CO_2 level was 45 mmHg, but peaked at 64 mmHg during REM sleep. Despite CPAP use, her CO_2 level continued to remain above 55 mmHg for majority of her sleep time (see Figs. 7.1 and 7.2).

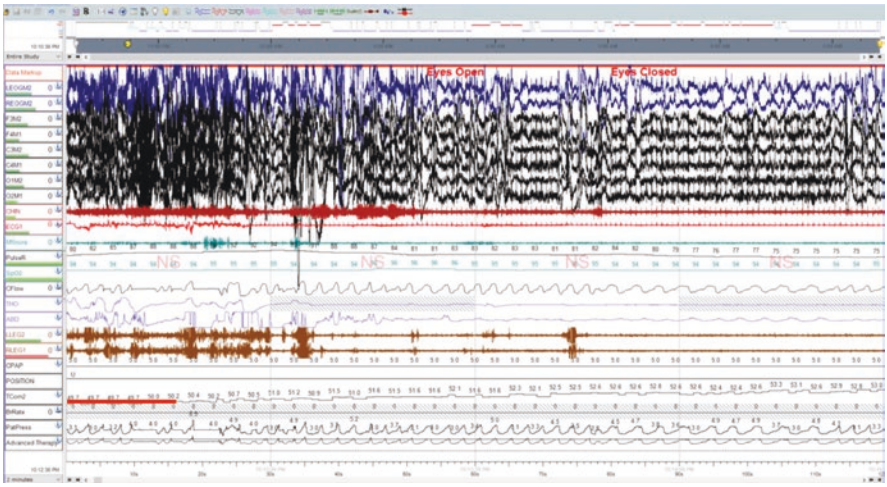

Fig. 7.1 Baseline awake CO_2 levels were normal at 45 mmHg. The red line demonstrates the elevation of transcutaneous CO_2 levels while the patient was awake in the supine position at the start of the study. (This figure is an original and not been published)

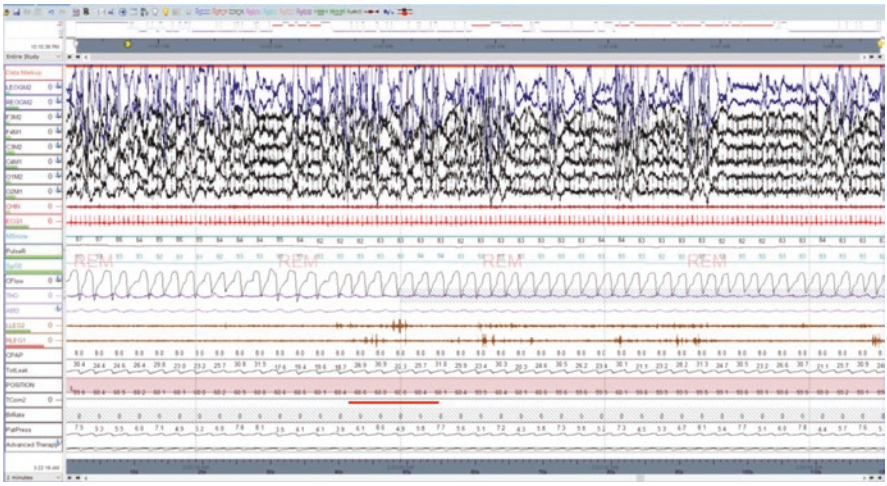

Fig. 7.2 The red line depicts the further increase in transcutaneous CO_2 level while the patient is in REM sleep. (This figure is an original and not been published)

Question

Why did her symptoms persist despite good control of her sleep apnea on CPAP therapy?

A. Due to hypoxemia
B. Due to hypercapnia
C. Due to sub-optimally treated OSA
D. Due to insufficient number of hours of CPAP usage.

Final Diagnosis

Obesity hypoventilation syndrome.

General Remarks

Obesity hypoventilation syndrome (OHS) has three defining criterions based on the International Classification of Sleep Disorders, third edition. Patients must have an elevated carbon dioxide level (CO_2) greater than 45 mmHg to mark the presence of hypoventilation. Typically, CO_2 levels are highest overnight, but then normalize as the day progresses. Patients must also have documented obesity with a BMI > 30 kg/m^2. In addition to these criteria, it is essential to rule out other potential causes of hypoventilation such as COPD or neuromuscular disease, as they can mimic OHS symptoms.

Common clinical symptoms of OHS include morning headaches, mood disturbances, fatigue, and cognitive impairment. Patients may also present with associated polycythemia, hypoxemia, or clinical signs of cor-pulmonale. Our patient described persistent daytime fatigue as well as morning headaches despite adequate treatment with CPAP therapy. Of note, her serum bicarbonate level was elevated above 27 mmol/L, which should increase the suspicion for OHS given her clinical presentation. OHS is often overlooked in patients that have good sleep apnea control on PAP therapy. While multiple studies, including RTC data, have demonstrated that CPAP is equivalent to non-invasive ventilation (NIV) for treatment of OHS [1], this is not always the case. In our patient OHS symptoms persisted despite good control of her sleep apnea, which may in part be due to the degree of her obesity. Ultimately, she did respond to NIV therapy using BIPAP.

In many sleep disorders, the role played by gender has been well described. For example, the effect of menopause in women with OSA has been clearly documented [2]. Gender effects of OHS have only more recently been described in the literature. Based on various studies, the overall prevalence of OHS in the general population is thought to be between 10–20% [3]. There is conflicting data on whether OHS is more prevalent in men or women. A recent study evaluating 617 women and 1076 men with OSA, found that OHS was present in 96 women (15.6%) compared to 48 (4.5%) men. Majority of the women in this study were postmenopausal, which may account for the increased prevalence of OHS in women. In fact, the prevalence of OHS was only 5.3% in pre-menopausal women, but 21% in post-menopausal women. Interestingly, women with OHS were associated with increased risk of hypertension and diabetes compared to male patients, even after controlling for BMI and symptoms [4, 5]. Our patient was postmenopausal, morbidly obese, and had a history of hypertension and diabetes. Whether or not any of these factors impacted her OHS significantly is still not clear. More research is needed to determine how gender effects OHS and development of comorbid conditions.

Clinical Pearls

- OHS is often under recognized and should be considered in obese patients with poor symptom control despite good PAP compliance.
- OHS may be associated with a higher risk of hypertension and diabetes in women.

Answer
B. Due to Hypercapnia

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Part III

Hypersomnias in Women

Idiopathic Hypersomnia

8

Venkata M. Mukkavilli

History

Patient is a 24-year-old female, who is a first year medical student was referred by primary care physician for excessive sleepiness, and suspected narcolepsy.

She started experiencing excessive daytime sleepiness in senior year high school and has gotten worse over the past 6 months. She managed without much difficulty in college by attending afternoon classes. Her problems started in med school as she struggles to wake up in the morning and often has difficulty staying awake in classes. She was found napping in the class many times and is lagging in her grades.

Her normal sleep schedule is from 9 PM to 7 AM and extends sleep on weekends. She sleeps around 10–11 h and takes a nap for 30–60 mins on weekdays. On weekends and holidays, she sleeps for 12–14 h at night and takes 1–2 naps during the day. She falls asleep very easily, sleeps well through the night and never feels refreshed in the morning or after taking a nap. Extending sleep on weekends did not improve her excessive daytime sleepiness. She drinks 2 cups of coffee in the morning and 3–4 energy drinks throughout the day to stay alert. Coffee and energy drinks were helpful in the past but doesn't work anymore to keep her alert during the day.

She denied hypnogogic, hypnopompic hallucinations, and cataplexy. She reports experiencing sleep paralysis once 2–3 years ago. She snores rarely, but denied witnessed apneas. She denied restless leg symptoms and parasomnias.

She has history of seasonal allergies and takes fexofenadine in spring for 2–3 months, and is currently taking birth control pills. She also reports history of depression 5 years ago lasting for 6 months after a breakup and received counseling.

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She was not prescribed any antidepressant medications. She denied symptoms of depression or anxiety at present. She also denied recreational drug use. She drinks alcohol socially. Patient reports her maternal grand mother was also a long sleeper like her but never sought any treatment.

Physical Examination

Vitals: BMI = 27.2. BP = 112/76 mmHg, Pulse = 74.

Patient appeared sleepy and tired otherwise her general physical examination was completely normal.

Laboratory Tests

Complete blood count, serum chemistry panel, thyroid functions, Vitamin B12 and Vitamin D were within normal range. Urine drug screen on the morning of the MSLT was negative.

Actigraphy and Sleep Log

Reviewed patient's smart watch sleep data and sleep log. It revealed average sleep was 10.5 h on weekdays and 12.3 h on weekends, two weeks prior to the sleep study.

Epworth sleepiness score: 17/24.

Polysomnogram and MSLT

Diagnostic PSG: Polysomnogram revealed sleep latency of 7.5 mins, total sleep time was 432 mins and sleep efficiency of 92.7%. Sleep architecture showed increased REM sleep. Apnea hypopnea index was 1.2. Periodic limb movement index was zero. Details of the PSG and attended nap study/MSLT is shown in Table 8.1, and Fig. 8.1. MSLT revealed mean Sleep latency of 3.6 mins in five naps and no SOREMs. Details of the attended nap study/MSLT is shown in Table 8.2, and Fig. 8.2.

Question What diagnostic criteria differentiates idiopathic hypersomnia from narcolepsy in this patient with mean sleep latency of 3.6 minutes?

Answer options:

(a) Sleep efficiency of > 87%
(b) REM latency of 25 minutes in PSG
(c) Total sleep time > 360 min
(d) Absence of sleep onset REM periods

Table 8.1 Results of PSG in a tabular form (This figure is original and has never been published online or in print)

Time at light out	21.24
Time at light on	06.04
Total recording time	520 mins
Total sleep time	482 mins
Sleep efficiency	92.7%
Sleep latency	7.5 mins
REM latency	25.5 mins.
WASO	23 mins.
Stage N1	4.8%
Stage N2	51.8%
Stage N3	2.1%
Stage REM	41.3%
AHI	1.2/h
Periodic limb movement index	0/h
Arousal index	3.1/h

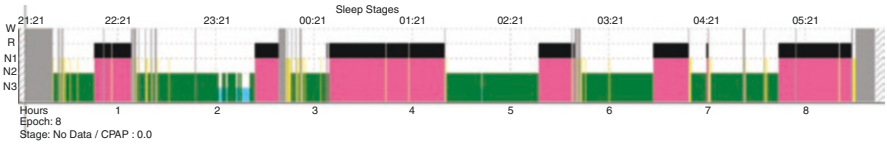
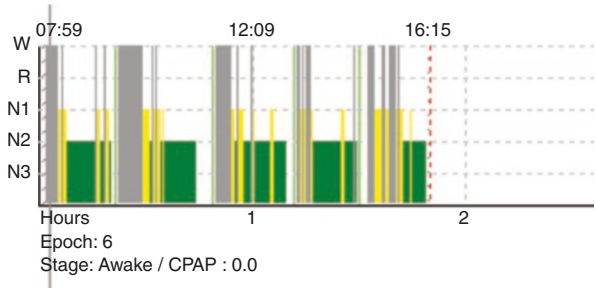


Fig. 8.1 Hypnogram of overnight PSG (This figure is original and has never been published online or in print)

Table 8.2 Results of MSLT (This figure is original and has never been published online or in print)

Naps	Nap 1	Nap 2	Nap 3	Nap 4	Nap 5
Recording time (minutes)	20.5	20	19.5	18.5	17
Total sleep time (minutes)	13.5	14	14	13	11.5
Sleep latency (minutes)	3.5	7	4.5	1	2
Onset to REM sleep	No REM	No REM	No REM	No REM	No REM

Fig. 8.2 Hypnogram of MSLT showing sleep onset in the 5 naps. Yellow indicates stage N1 sleep, green indicates N2 sleep, gray indicates wake stage. (This figure is original and has never been published online or in print)



Diagnosis and Treatment

Clinical history, physical examination and sleep study is suggestive of idiopathic hypersomnia. Patient was recommended both behavioral approaches including sleep hygiene, strategic naps, and pharmacological treatment. She was started on Modafinil 100 mg by mouth daily and subsequently increased to twice daily at 7 AM and 1 PM in 6 weeks. Also, counseled patient about drug-drug interaction with birth control pills, voiding the effectiveness of birth control pills, and advised to use alternate methods of contraception.

Differential Diagnoses

Hypersomnia due to sleep apnea.
Major depression.
Hypersomnia due to medications.
Hypersomnia due to substance use.
Narcolepsy type 1 or 2.

Discussion

Sleepiness is a core feature of multiple disorders and no validated biomarkers that is diagnostic of IH, a careful history and diagnostic testing can distinguish IH from other possible disorders.

The possible diagnosis is idiopathic hypersomnia due to excessive daytime sleepiness, irrepressible need to sleep and daytime lapses into sleep, absence of cataplexy, and her MSLT shows no sleep onset REM periods (Table 8.2, Fig. 8.2). Her mean sleep latency is 3.6 mins and average total sleep time in 24 h is more than 11 h. Other supportive symptoms of IH are severe and prolonged sleep inertia (sleep drunkenness), unrefreshing naps, high sleep efficiency (>90%).

The ICD 3 diagnostic criteria for idiopathic hypersomnia are periods of irresistible need to sleep on daytime lapses into sleep coding for at least 3 months, absence of cataplexy, and MSLT shows less than 2 sleep onset REM periods. Either mean sleep latency less than or equal to 8 mins, or total 24 sleep time is more than 660 mins on a 24-h PSG, or monitored by wrist actigraphy in association with a sleep log. Rule out insufficient sleep syndrome, another sleep disorder, other medical or psychiatric disorder or use of drugs and medications.

The age of onset varies but it is frequently present between the age of 10 and 30 years. The prevalence of IH in general population is approximately 50 per million people. Females may be affected more frequently than men. There are no consistent findings showing association between HLA markers for diagnosis of IH[2]. Cerebrospinal fluid hypocretin-1 levels are normal in IH. A recent meta-analysis of 10 studies on nocturnal sleep in IH patient showed decreased slow wave sleep and increased REM sleep compared to controls.

Narcolepsy type 1 and type 2. The distinction between IH and Narcolepsy type I are fairly distinct. Narcolepsy type 1 (NT1) patients have cataplexy, fragmented nocturnal sleep, and generally short naps are refreshing. In contrast, the distinction between IH and Narcolepsy type 2 (NT2) is more difficult. Sleep paralysis and sleep related hallucinations are commonly seen in patient with NT2 but they are also seen in a quarter of IH patients. Genetic testing HLA DQB1*0602 is not positive in all patients with NT2 unlike in Narcolepsy type 1. The differentiation between IH and Narcolepsy type 2 entirely rests on the presence or absence of 2 sleep-onset REM periods (SOREMs) [1].

Distinguishing between circadian rhythm disorder, delayed sleep phase syndrome (DSPS) and IH is difficult as DSPS patients will frequently present with the combination of daytime sleepiness and sleep drunkenness, which are seen in Idiopathic hypersomnia. Insufficient sleep syndrome can also present with daytime sleepiness, irritability, attention deficit and fatigue but it improves with prolonged sleep time unlike in IH[3]. History, sleep log and actigraphy are very important in distinguishing these disorders from IH. IH can be sometime confused with chronic fatigue syndrome but patients with chronic fatigue syndrome generally complain fatigue rather than excessive daytime sleepiness and doesn't resolve with sleep or rest.

Hypersomnia due to medications and substances occurs because of current medications like sedative/hypnotics, muscle relaxants, opioids, antidepressants, antiallergy, antiepilepsy drugs, and other centrally acting medications or substance use or withdrawal of caffeine, nicotine. Commonly used substances causing excessive sleepiness include marijuana, barbiturates, benzodiazepines, gamma hydroxybutyrate, opiates, and alcohol. It can be distinguished from IH with a careful history and toxicology screen. Similarly, hypersomnolence due to medical condition and neurological conditions is generally apparent from history and physical examinations.

One of the most challenging differential diagnoses is hypersomnolence associated with psychiatric disorders. ICSD 3 does not assign causality in the diagnosis because of uncertainty about the nature of the relationship. A judgement about whether the main diagnosis is IH or primary psychiatric should be ascertained. Patient did have a history of depressive illness in the past, but she clearly denied depressive symptoms. Also, in depression patients may have excessive daytime sleepiness but generally sleep varies from day-to-day and it is often associated with poor sleep at night.

Treatment of Idiopathic Hypersomnia

Treatment of idiopathic hypersomnia includes both nonpharmacologic and pharmacologic treatment. Nonpharmacologic treatment includes behavioral approaches and sleep hygiene but generally these are unhelpful. Different medications have been tried in idiopathic hypersomnia patients, including, stimulants antidepressants, sodium oxybate, clarithromycin, flumazenil, clonidine, levodopa, bromocriptine,

selegiline and amantadine. Overall, two thirds of the patient reported symptoms improvement with modafinil or amphetamine. Around one third of the patient's reported spontaneous remission of symptoms.

Outcome of the Case

Patient responded to modafinil treatment and Epworth score in 3 months follow up was 10/24 showing significant improvement.

Take Home Pearls

1. Idiopathic hypersomnia is a diagnosis of exclusion and requires exclusion of other causes of hypersomnolence in addition to sleep log, actigraphy, sleep study.
2. Modafinil is the first line drug for treatment of Idiopathic hypersomnia.
3. Modafinil will decrease the level or effect of hormonal contraceptives (estrogen) by hepatic/intestinal enzyme CYP3A4 metabolism. Health care professionals should discuss with patient about drug-drug interaction and advise to use other contraceptive methods while taking modafinil and for 2 months after stopping modafinil.
4. Spontaneous improvement in EDS may occur in up to one-third of patients.

Correct Answer
d

Reference

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Complicated Delayed Sleep Wake Phase Disorder in a 59-Year-Old Woman

9

Marilyn K. Culp, Shan R. Luong, and Gregory S. Carter

Clinical History

A 59-year-old female who does not work outside her home or keep a routine daily schedule presented with the complaint of insomnia. She describes herself as a "night owl." Her past medical history includes depression, excessive daytime sleepiness and mild obstructive sleep apnea (OSA). The latter was diagnosed 9 years ago but not treated due to its mild severity with an apnea hypopnea index of seven events per hour of sleep with no worsening in REM sleep. She has been sleepwalking and sleep eating for the past 10 years. She has taken appropriate safety measures to keep herself safe when sleepwalking and locks up unhealthy foods. While she has taken zolpidem in the past, she continues to sleepwalk occasionally off zolpidem. She has gained approximately 10 pounds since her last sleep study 9 years ago. She denies symptoms of restless legs. She did two out of eight sessions of cognitive behavioral therapy for insomnia cognitive behavioral therapy for insomnia (CBT-I) 2 years ago but did not finish the course.

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She goes to bed at 1:30 AM but does not fall asleep until 2:30 AM on average. She then wakes up between 6:00 AM and 7:00 AM, arising to use the restroom. If she has nothing to do that day, she will take an additional alprazolam 1 mg and return to her bed, rapidly falling asleep until 10:30 AM. She naps in the late afternoon 3–4 times weekly, sleeping for an average of 1 h. She reports sleeping between 4.5 and 8 h per 24-h period distributed randomly throughout the week.

Her morning medications include bupropion XL 300 mg and venlafaxine 225 mg. At bedtime she takes alprazolam 1 mg, triazolam 0.5 mg and quetiapine 25 mg. Quetiapine was started 1 year ago to allow a taper of alprazolam which the patient had escalated to 3 mg. The triazolam dose had gradually increased over time to aid sleep onset.

Physical Examination

Physical exam reveals a pleasant 59-year-old lady who appears her stated age. She is alert and fluently conversive without dyspnea. BMI is 30. HEENT exam revealed a crowded oropharynx, Mallampati Class 4. Neck circumference is 16 inches. Heart, lung, musculoskeletal, and neurological exams were all normal.

Question 1
Due to a history of insomnia, OSA and a suspicion for a delayed circadian rhythm, which of the interventions and evaluations should be considered?

(a) Repeat a sleep study to assess for worsening of her obstructive sleep apnea
(b) Recommend that she should stop taking alprazolam 1 mg in the mornings.
(c) Obtain actigraphy and a sleep log for 7–14 days
(d) All of the above

Answer: D

The patient has gained weight since her last sleep study 9 years ago when she was found to have mild OSA. The weight gain and current post-menopausal state may have worsened the severity of her obstructive sleep apnea (OSA), contributing to her sleep disturbances at night. Insomnia, excessive daytime sleepiness, sleepwalking and sleep eating are all sleep disorders that may be exacerbated by untreated OSA [1]. Though alprazolam is FDA indicated for generalized anxiety disorder and panic attacks, the patient's use of alprazolam 1 mg in the morning to return to sleep implies an unfortunate dependence on this drug that should be discouraged. Keeping a sleep diary with or without actigraphy can help to define the patient's sleep/wake schedule. Actigraphy may be helpful in comparing the patient's perception of their sleep expressed in the sleep log to the objective information provided by actigraphy.

The following actigraphy in Fig. 9.1 was obtained.

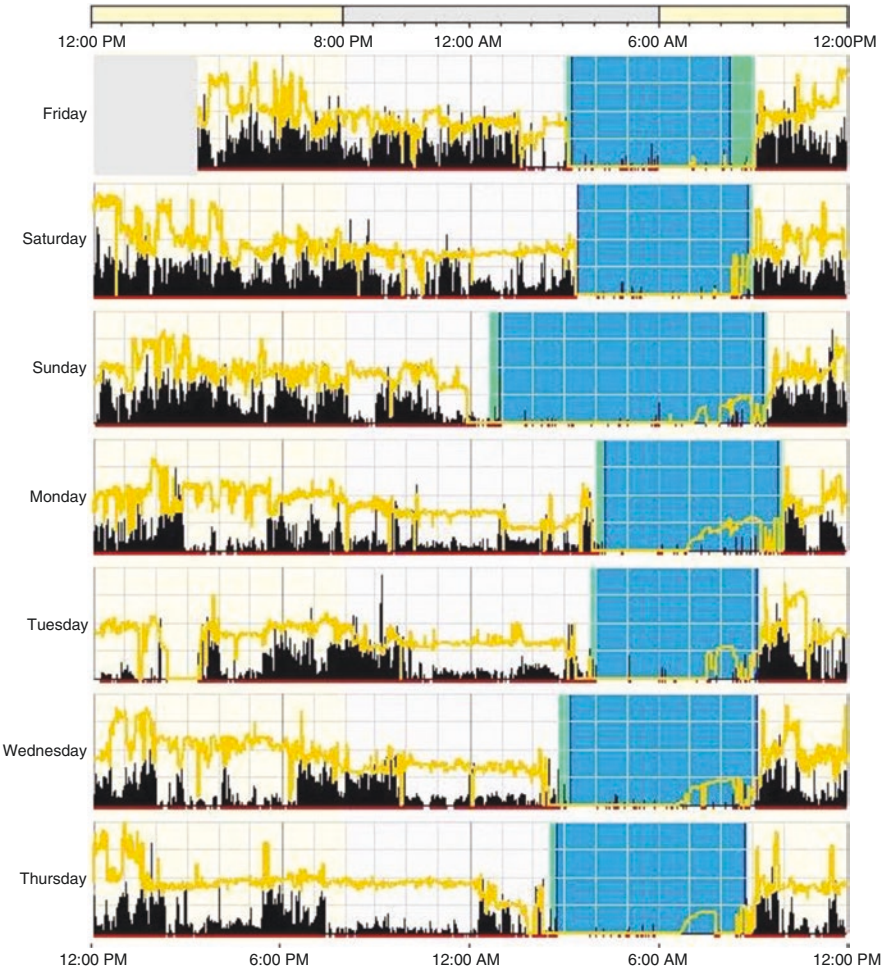

Fig. 9.1 Actigraphy. The blue bars represent sleep, light green represents resting, black represents activity and yellow represents light exposure (this figure is an original and has not been printed in the past)

Question 2

What sleep wake phase pattern is represented by the actigraphy?

A. Advanced sleep wake phase
B. Delayed sleep wake phase
C. Irregular sleep-wake phase
D. Non-24-h sleep-wake rhythm disorder

Answer: B

The pattern is consistent with a delayed sleep phase. Sleep onset is variable from 1 am to 4 am with wake times between 8:30 am and 10 am. Once the patient was asleep, sleep was consolidated. The patient's sleep log approximated the actigraphy data demonstrating that she had an accurate perception of her sleep times.

Data

Home sleep study.

AHI 7/h, REM AHI 16/hour, no significant hypoxia.

Total sleep time from 2:31 am to 8:42 am.

Question 3

As noted above, the patient's repeated sleep study shows a similar AHI of 7/h but a REM AHI that is higher at 16/h Treating her obstructive sleep apnea may also help with which of the following?

A. Sleep-related eating disorder
B. Sleepwalking
C. Insomnia
D. Sleep-wake circadian disorder
E. All the above

Answer: E.

Treating OSA has been shown to improve all the above [1]. Obstructive sleep apnea has been shown to decrease melatonin secretion at night and alters clock gene transcription. Long term treatment with CPAP has shown promising results as a counter to these disruptions.

Treating OSA can improve insomnia, excessive daytime sleepiness, sleepwalking and sleep eating behaviors. CBT-I is the only treatment that has received a strong recommendation in the 2021 updated treatment guidelines for chronic insomnia. CBT-I is effective in reducing and even eliminating the need for benzodiazepine medications [2].

Treatment of OSA with CPAP or a mandibular advancement device (MAD) are both appropriate interventions. A MAD is an appropriate intervention for treating mild to moderate OSA. It is not as efficacious as CPAP but is preferred by some patients. Studies have shown adherence to oral appliances is equal to or better than to CPAP [3, 4].

Obstructive sleep apnea is much less common in women than men, a fact which is well recognized. What is not recognized is that OSA may present differently in women. In women, untreated OSA may manifest with symptoms of insomnia, restless legs, hallucinations, and depression [5].

Question 4
After treating OSA and resuming CBT-I, which of the following interventions would not likely have any effect on advancing the patient's circadian rhythms?

A. Melatonin 0.5 mg at 8:30–9:30 pm
B. Melatonin 5 mg within an hour of bedtime
C. Discourage use of electronics within an hour of bedtime.
D. Encourage mid-day sunlight exposure.
E. Encourage the patient to establish a consistent wake time, setting that wake time to allow a minimum of 5 h of sleep per night.

Answer: B.

Melatonin at 0.3 –3 mg has been shown to advance human circadian rhythms when given 4 h before the desired bedtime. Likewise, exposure to morning sunlight after the core body temperature minimum (CBTmin) will advance the circadian rhythm. CBTmin occurs approximately 2–3 h before the habitual wake time and this patient's wake time is averaging 10:30 AM. Thus, exposure to sunlight before 7:30 AM could move her circadian rhythm in an unwanted clockwise direction Once she becomes accustomed to awakening at an earlier clock time, morning sunlight upon awakening would be appropriate.

To summarize the effects of melatonin and light on the circadian phase: morning light "pushes" the CBTmin counterclockwise and melatonin "pulls" the CBTmin counterclockwise, thus advancing the circadian rhythms. All television, computer, laptop, tablet, and cell phone screens are enriched with blue light. Blue is the color of the daytime sky, and our retinas transfer the intensity of that wavelength directly to the drivers of our circadian rhythms, delaying sleep onset. This effect of blue light can be shown by its suppression of melatonin secretion. Thus, avoiding electronic screens within 1–2 h of bedtime allows sleep onset.

Discussion

The suprachiasmatic nucleus (SCN) located in the anterior hypothalamus serves as the master clock for the human body which results in a 24-h diurnal sleep/wake cycle or circadian rhythm which affects all organ systems. The structure and neuronal constituents of the SCN are different in women compared to men. Studies have shown that women have an earlier dim light melatonin onset (DLMO) and reach their minimum core body temperature earlier in the night than men [6–8]. Women have been found to have a shorter circadian period of 24 h 5 mins than men whose circadian period was 24 h 11 mins. Significantly more women have an intrinsic circadian period shorter than 24 h, 35% of women compared 14% of men [6–8]. Whether or not these differences contribute to more circadian rhythm disorders in women is unclear but delayed sleep wake phase disorders occur equally in men and

women. Adolescents and adults are affected with between 0.48% [9] and 3.3% [10] of adolescents estimated to be affected by delayed sleep wake phase disorder. Delayed sleep wake phase disorder tends to run in families. Polymorphisms of the clock gene CRY 1 are contributory to a delayed sleep phase and are inherited in an autosomal dominant fashion [11, 12].

Patients with delayed sleep wake phase disorder will often describe themselves as "night owls," preferring to go to bed two or more hours later than the bedtime required for adequate sleep duration. When they are required to wake up to meet their work, social or academic schedules they become chronically sleep deprived. When allowed to sleep and awaken ad lib on weekends or during vacations, they much prefer to sleep from the early morning hours until the early afternoon hours. On that schedule, they have no trouble falling asleep and their total sleep time is normal.

Treatment

The treatment for delayed sleep wake phase disorder includes the following behavioral, medication, and light therapies. Success is highly dependent on patient motivation to change.

Behavioral Interventions

Behavioral interventions include minimizing caffeine, nicotine, marijuana, and alcohol as these substances can affect normal sleep architecture. Establishing a routine bedtime and wake time is essential for circadian entrainment. Avoiding bright light exposure from electronic screens within 2 h of bedtime helps minimize delay in melatonin secretion. Organizing a daily routine for eating, exercising, and meeting work/family/social obligations is important. Avoidance of the following habits is also helpful: daytime napping, sleeping-in on weekends for more than 60 mins past weekday wake times [13] and exercising within an hour of bedtime [14].

Medication

Evening melatonin (0.5 mg) given 4 h before the patient's preferred bedtime can be helpful in advancing sleep time. Higher doses of melatonin 3 mg–5 mg given within 1 h of bedtime can be helpful for the sedative effects but does not advance the circadian rhythm as melatonin is already being secreted at that point by the pineal gland [6–8]. The natural process of dim light melatonin onset (DLMO) occurs about 2 h prior to habitual sleep onset. Prescription sedative hypnotics are not routinely recommended [2].

Light Therapy

The normal circadian period is approximately 24.2 h. Thus, a slight phase advance is required daily to maintain entrainment with the light-dark cycle of 24 h on earth. Sunlight is the most impactful zeitgeber or time cue that influences circadian entrainment and provides an alerting benefit. Other zeitgebers include eating schedule and routines involving exercise, work and social activities. Morning light exposure *after* the core minimum body temperature (CBTmin) which occurs approximately 2–3 h before preferred/habitual wake time can also help to advance the onset of sleep time. Conversely, light exposure *before* the CBTmin will cause further phase delay. Avoiding light exposure from electronic screens within 1 h before bedtime is also helpful [15].

Light from the blue light spectrum (450 to 495 nm) has the most potent effect on circadian entrainment due to activation of melanopsin which is a photopigment located within intrinsically photosensitive reginal ganglion cells. Melanopsin signals the SCN via the retinohypothalamic tract (RHT) to send inhibitory input to the pineal gland and thus suppressing melatonin secretion and delaying sleep onset [7]. During daytime sunlight exposure, the blue light component of sunlight provides inhibitory tone to the pineal gland to help maintain wakefulness. Sundown naturally provides withdrawal of this inhibitory tone and allows DLMO to occur which promotes sleep onset 3–4 h later. Electronic screens emit blue light, thus avoiding electronic screens in the evenings within an hour of bedtime allows sleep onset.

Sunlight exposure 3–4 h after CBTmin provides the maximum phase advance. CBTmin occurs 2–3 h before spontaneous awakening. This means light exposure for 30 mins starting with spontaneous awakening to 2 h after awakening provides the maximum phase advance. Sunlight is the strongest zeitgeber but light boxes providing an intensity of 10,000 lux can also be used indoors, placed 2.5 m (approximately 8.5 feet) or further away from the patient where it is comfortable in the peripheral visual field [15].

Clinical Pearls

- Delayed circadian rhythm sleep phase often presents with the clinical complaint of insomnia.
- Sunlight is the most impactful zeitgeber or time cue factor that influences circadian entrainment.
- Until the circadian and homeostatic drives are matched, hypnotic medications will be minimally successful to engage sleep.
- Morning light “pushes” and evening melatonin “pulls” the minimum core body temperature, thus advancing sleep onset timing for a patient with a delayed sleep phase.

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Medication Management of Patient with Narcolepsy During Pregnancy and Lactation

10

Safia S. Khan and Cephas Mujuruki

Clinical History

ZZ is 27 years old lady, G2P0A1 at 12 weeks gestational age, she presents to the sleep specialist's clinic for management of excessive sleepiness and daytime tiredness due to narcolepsy without cataplexy. She was on a combination of wake promoting, stimulant and rapid eye movement (REM) sleep suppressant medications (modafinil, methylphenidate and clomipramine for REM sleep suppression) prior to conception of her baby. These medications were discontinued when she started planning for pregnancy about 6 months earlier as she had suffered a spontaneous early fetal loss in previous pregnancy at 8 weeks gestational age. She is working as an office administrator and is nervous due to her history of excessive daytime sleepiness in the absence of the wake promoting and stimulant medications. She has not been able to keep a job for more than 8–12 months in the last 5 years due to excessive daytime sleepiness leading to missed days at work, tardiness and instances of dozing off. This has led to increased anxiety and stress related to return to work for her.

She was diagnosed with narcolepsy without cataplexy at age 17 years when she developed sudden episodes of overwhelming sleepiness in high school despite

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sleeping usual number of hours at night. Past medical history is significant for seasonal allergies, managed with steroidal nasal spray and over-the-counter allergy medications as needed.

There is no significant family history of cardiovascular, endocrine or sleep disorders.

Physical Exam

Cardiovascular, respiratory, psychiatric and neurologic exam is within normal.

Sleep Study Results

Her initial sleep study showed sleep efficiency of 91%, frequent spontaneous arousals, reduced REM sleep latency of 34 mins and did not show any evidence of obstructive sleep apnea. Subsequently mean sleep latency test was done that showed mean sleep latency of 2 mins for 5 attended naps with 3 episodes of sleep onset REM periods in the absence of medications affecting sleep-wake stages.

Question 1
What medications can be used for narcolepsy during pregnancy that have lower risk of congenital malformations?

(a) Modafinil/Armodafinil and fluoxetine
(b) Amphetamine-dextroamphetamine and fluoxetine
(c) Methylphenidate and clomipramine
(d) Sodium oxybate and modafinil/armodafinil

Question 2
What medications are associated with reduced efficacy of contraceptives and should be avoided in child-bearing age women who are sexually active due to risk of congenital malformations?

(a) Modafinil/Armodafinil
(b) Amphetamine-dextroamphetamine
(c) Methylphenidate
(d) Sodium oxybate

Question 3
Is vaginal delivery an option for this first-time mom who has narcolepsy without cataplexy?

(a) No, cesarean delivery is the only option
(b) Yes, vaginal delivery is an option

Question 4
Risk of spontaneous abortion is greatest for which of the following medications that should be avoided during pregnancy and nursing, by patients with narcolepsy?

(a) Modafinil/Armodafinil
(b) Amphetamine-dextroamphetamine
(c) Methylphenidate
(d) Sodium oxybate

General Discussion

Narcolepsy is a rare disorder characterized by excessive daytime sleepiness and REM sleep dissociation including sleep paralysis, sleep-related hallucinations, and cataplexy in the case of narcolepsy type 1, and absence of cataplexy in the case of narcolepsy type 2. Narcolepsy affects approximately 0.02–0.18% of the population in the United States and western Europe without significant gender differences [1]. Cataplexy is the sudden occurrence of muscle weakness in association with emotions like laughing, joking, excitement, or anger. It has long been considered a pathognomonic symptom for this disorder. This is differentiated from epilepsy based on the fact that there is rare incidence of injury with cataplexy as patients can sense it and safely sit or lay on the floor to avoid injury in majority of cases. Also, there is no loss of consciousness or confusion during cataplexy episodes which last anywhere from a few seconds to a few minutes. Whereas, epilepsy is of sudden onset, variable duration, with loss of motor control and associated confusion or postictal state.

Normal pregnancy is associated with subjective and objective increased daytime sleepiness which is more pronounced in the first and last trimester in a majority of normal women due to the effects of pregnancy-related surge of hormones and increased body metabolism. These symptoms of excessive sleepiness are amplified many-fold for women with narcolepsy. Without a curative therapy for narcolepsy, management involves treating the symptoms narrated above especially excessive daytime sleepiness and cataplexy when present. Most women of child bearing age are uninformed of the risks, harms and benefits of medications for narcolepsy prior to conception, these are discussed weeks after conception when critical neurodevelopment has already taken place.

Treatment of Narcolepsy in Non-pregnant Women and Men

The mainstay of treatment in narcolepsy with and without cataplexy is:

1. Wake-promoting medications (modafinil, armodafinil, pitolisant, solriamfetol),
2. Stimulants (amphetamine, dextroamphetamine, methylphenidate),

3. REM sleep suppressants classified as tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and selective norepinephrine reuptake inhibitors (SNRIs)
4. CNS depressant (sodium oxybate) which improves night time sleep thus reducing daytime sleepiness and also treating cataplexy.

For most of these medications human data are insufficient to determine risk to fetus if used in pregnancy or during lactation. REM suppressants (fluoxetine, clomipramine) have more published data to support safe use during pregnancy and lactation in women with narcolepsy and advise appropriate screening for congenital malformations [2]. Non-pharmacologic interventions of frequent strategic naps, sleep extension and frequent breaks to move around, have been the safest treatment options for women in the pre-conception, early, middle and late gestational periods.

Change in Labelling of Drugs Safety for Pregnancy and Lactation

In 2015, the US Food and Drug Administration (FDA) retired the drug categories for pregnancy (ABCDX) for several reasons [3, 4]. This was replaced by the FDA Pregnancy and Lactation Labeling Rule (PLLR) with efforts to improve drug information for the patients and physicians [3]. Information of drug effects on human pregnancy, labor, birth, lactation, effects on female and male subjects of reproductive potential is included in the PLLR, encouraging consideration of these risks compared with the untreated disease [4].

Treatment of Narcolepsy in Pregnant Women

The risks and benefits of narcolepsy medications have to be weighed in the context of fetal harm and maternal benefits (see Fig. 10.1). Maternal symptoms and ability to manage the excessive sleepiness during the day without medications or with the minimal effective dose of medications dictates the shared decision-making process with these patients.

In a large Danish study, published in 2020, using the Danish national health registries, all pregnancies from 2004 to 2017 were identified [5]. Data for medication exposure in early pregnancy was reviewed, of these 49 pregnancies (0.006%) had exposure to Modafinil, 963 (0.12%) exposed to methylphenidate, and 828,644 were unexposed pregnancies [5]. Among modafinil-exposed pregnancies there were six major congenital malformations (cardiac, craniofacial), 43 in the methylphenidate-exposed women, and 32,466 in the unexposed group [5]. This translated to an absolute risk of 12% for modafinil, 4.5% for methylphenidate, 3.9% for unexposed women [5]. The adjusted odds ratio (OR) was 3.4 (95% CI, 1.2–9.7) when comparing modafinil to methylphenidate and 2.7 (95% CI, 1.1–6.9) when comparing modafinil to unexposed pregnancies [5].

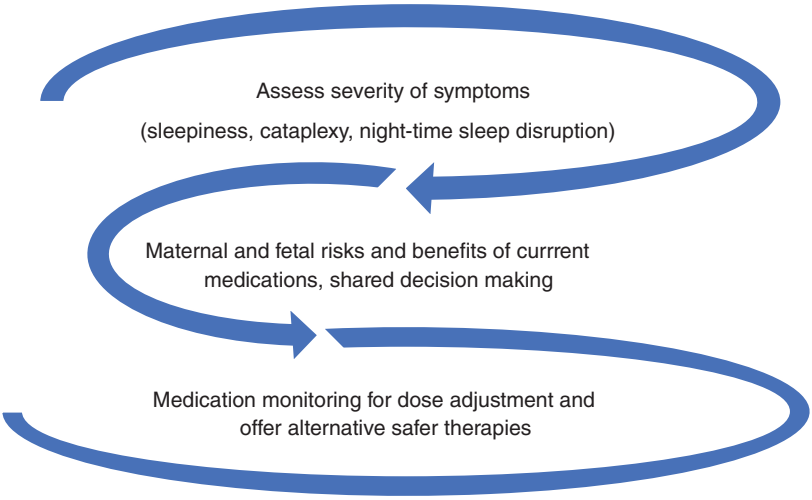

Fig. 10.1 Factors to consider when prescribing and monitoring medications for patients with narcolepsy before, during and after pregnancy. (This figure is an original and has not been printed online or in paper)

Stimulant medication use in the context of pregnancy and narcolepsy may be limited, however, more data is available for stimulant use in women with attention deficit hyperactivity disorder (ADHD) and antidepressant use of REM suppressants. Results for stimulant use for ADHD in pregnancy can be extrapolated for justifying use of or avoidance of stimulant medications in narcolepsy patients. These drugs cross the placental barrier and can potentially affect neurologic development as the primary mechanism of action of stimulants is increase in synaptic norepinephrine-dopamine concentrations (methylphenidate, dextroamphetamine, lisdexamfetamine), or increase in synaptic concentrations of norepinephrine (atomoxetine) or serotonin (fluoxetine, sertraline, clomipramine) [6]. Increased spontaneous abortions, low birth weight, increased rate of prematurity, withdrawal symptoms in infants (jitteriness, drowsiness, respiratory depression) and maternal complications of preeclampsia, gestational hypertension, placental abruption, intrauterine fetal death and infant death have been described in women exposed to some of these CNS stimulants when prescribed for ADHD [6].

Modafinil and armodafinil are medications that reduce contraceptive effectiveness by way of induction of cytochrome P450 enzymes (CYP3A4) [7], which reduces maximal plasma levels of ethinyl estradiol. Ethinyl estradiol is a vital component of almost all combined oral contraceptive pills. Therefore, alternative methods of contraception like intrauterine device and barrier contraception is recommended for pregnancy prevention.

Use of sodium oxybate during pregnancy has not shown teratogenicity in limited human case reports and animal studies [8]. Embryo-lethality has been seen in animal studies. Increased risk of spontaneous abortions has been noted from pregnant women exposed in the first trimester [8]. Therefore, it is recommended to discontinue this medication prior to conception in cases of planned pregnancies for women with narcolepsy.

REM suppressants have a unique role in reducing cataplexy by way of reducing REM intrusion during wakefulness in narcolepsy type 1. Venlafaxine is the most widely used REM sleep suppressant in patients with narcolepsy, other agents include fluoxetine, protriptyline, and clomipramine. These medications are associated with neonatal withdrawal syndrome or serotonin syndrome, slight increase in congenital malformations [9] based on limited pregnancy data. Abrupt withdrawal of SSRIs has been known to trigger status cataplecticus with prolonged period of cataplexy, therefore, careful tapering is recommended if discontinuation of medication is the chosen option for risk reduction.

Treatment of Narcolepsy During Labor and Delivery

In 2013, the results from a retrospective cohort study of 249 female narcolepsy patients with cataplexy ($n = 216$) and without cataplexy ($n = 33$) in 12 European countries. This study showed more obstetric complications in patients with narcolepsy with cataplexy, although these were not severe [1]. Higher rates of cesarean sections ($p < 0.05$), older age during first pregnancy ($p < 0.01$), and higher weight gain in pregnancy ($p < 0.01$), were noted in the narcolepsy-cataplexy group [1].

In rare cases, cataplexy has interfered with vaginal delivery in the cases of spontaneous or induced labor and thus increasing risks associated with emergency cesarean deliveries [1]. Monitoring of labor in a center where vaginal and if needed cesarean delivery can be performed is recommended to reduce risk of fetal or maternal harm during the process of child birth.

Prescribing in Breast-Feeding Mothers

The physical and emotional demands of caring for a newborn can be exhausting for new mothers and will intensify symptoms of narcolepsy. Although the opportunity for frequent napping is there during puerperium, the averseness to be sleepy most of the day is understandable when patients are off stimulant medications. Presence of medications in breast milk although mostly inevitable, it is dependent on two main factors; time of medication intake relative to time of breast feeding, and, dose of medication.

The benefits of breast feeding on the social, mental and physical development and well-being of babies are firmly established. These benefits far outweigh the undefined risks of medications used for narcolepsy during breast feeding. Therefore,

breast feeding should be encouraged for the first few months of life and avoidance of stimulant medications while breast feeding should be advocated.

Evidence of specific fetal harm is largely lacking for most pharmacotherapies used by nursing mothers with narcolepsy. Sodium oxybate is not recommended for nursing women, it is advised to either discontinue the medication or discontinue breast feeding in order to reduce risk of harm to the baby as it is expressed in breast milk [8]. Most stimulant medications can be found in small quantities in breast milk or in infant urine, although their effects on sleep disturbance are not elicited. Methylphenidate is present in small amounts in the breast milk and not detected in infant blood, therefore, its use during nursing is considered safe [6]. Amphetamines are present in a higher concentration in breast milk leading to significant infant exposure, therefore, these are contraindicated during nursing [6].

Safety instructions similar to the ones given for epilepsy patients are important in all stages of pregnancy, delivery, and while nursing for mothers with narcolepsy [10]. These include and are not limited to; avoidance of driving and operating heavy machinery when sleepy, avoidance of unsupervised water activities, avoidance of bathtubs for infant, use of a wheeled carrier for baby inside and outside the home, considering breast feeding in laying position and using social support when available. The goal of treatment of women with narcolepsy before, during and after pregnancy is to provide a safe, nourishing environment for both; the baby and the mother.

Take Home Points

- It is important to provide adequate education for risks, harms and benefits of medications used for narcolepsy before conception, during the early, middle and late gestation and during the nursing period.
- Labor and delivery monitoring in a facility where option of vaginal and cesarean delivery is available will reduce risk of fetal and maternal complications.
- Medication exposure risk is present through breastmilk; therefore, it is recommended to avoid use of narcolepsy medications when nursing. Breast feeding is to be encouraged for established benefits**.**
- Potential risk of injury to the baby in case of motor vehicle accidents, accidental falls or injury due to excessive sleepiness and sudden sleep attacks in the untreated mothers with narcolepsy presents a huge threat for infant survival. This is a strong impetus for determination of medication safety in the treatment of narcolepsy in all stages of reproduction.

Answers

Question 1: c. Methylphenidate and clomipramine.

Question 2: a. Modafinil/Armodafinil.

Question 3: b. Yes, vaginal delivery is an option.

Question 4: d. Sodium oxybate.

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Part IV

Menopause Related Sleep Disorders

Sleep Disturbances Due to Hot Flashes in the Post-Menopausal State

11

Mahdi M. Awwad

Clinical History

Ms. M.P. was a 55-year-old female presented to the sleep clinic with complaints of difficulty falling asleep and remaining asleep for the last 3 years now. She finds that she is staying awake roughly 2 h after lying in bed. She stays up two to four times a week, working and browsing social media to keep up with long distance family. She also wakes up about 3 times a night with hot flashes. Currently unsure about snoring but noted her late-husband complained of her snoring years back. She does state not feeling refreshed when waking up in the morning. She drinks coffee in the morning but still exhibits some midday fatigue. She eats dinner around 8 p.m. and is up until 12 a.m. watching TV, and browsing through social media. Her only prior issues with sleep were in relation to her husband passing away 7 years ago when she struggled with depressive symptoms, but noted significant improvement in her mood when she focused her time at her firm/work. She has used melatonin 5 mg when she previously struggled with sleep but has not tried it this time. No other past medical or surgical history. Her only medications consist of a daily multivitamin.

Examination BP 129/78, pulse 73/min, temp 36.7 °C (98 °F), respiratory rate 20, height 5′6″ (1.68 m) weight 196 lbs. (88.9 kg) SpO2 99%, BMI (Body mass index) is 31.6 kg/m^2. Mallampati score of 1 and normal neck circumference of 36 cm. Otherwise, normal overall and neurological examination. PHQ9 score was noted to be 2.

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Special Studies

Polysomnogram Results Diagnosis: Moderate obstructive sleep apnea.

- Decreased sleep efficiency of 69%,
- Increased sleep fragmentation with an arousal index of 17/hr.
- Increased WASO (wake after sleep onset) period of 80 min.
- AHI (apnea-hypopnea index) of 4.1
- No evidence of significant hypoxemia
- No periodic limb movements were observed during the study

Question What is the diagnosis? What would you recommend to improve sleep quality?

Differential Diagnosis and Diagnosis

Ms. M.P. most likely presented with insomnia associated with being in a post-menopausal state. Her history revealed she did not struggle previously with insomnia outside of her bereavement period. There was some snoring in her history but unable to note any apnea episodes as she sleeps alone currently. Her examination did not elude to findings related to sleep apnea like high BMI, large neck circumference and high Mallampati score. Her PHQ9 score was not elevated, eluding her sleep disruptions have little to do with mood disorders. It shows she does exhibit systemic symptoms of menopause, mainly hot flashes, that are noted to also disturb her sleep. Her polysomnogram noted increase disruption, arousal and wake times with decrease efficiency. AHI did not meet criteria for sleep apnea nor was there findings of periodic limb movements to indicate diagnosis of RLS.

Discussion

Menopause can be both physically and psychologically challenging. Menopause related metabolic changes are responsible for mood variations, eating disorders, hunger, impulse control, temperature irregularity and sensitivity, and sleep disturbances [1]. The most common sleep related concern in the post-menopausal state is insomnia and nighttime awakenings. Hormonal changes, including higher FSH and lower estrogen levels, were associated with increased arousal frequencies as well as decrease in falling asleep and maintaining sleep [2]. There have been studies noting a higher apnea-hypopnea index (AHI) and lower arterial oxyhemoglobin saturation but failed to find differences in PSG relating to increasing OSA in menopausal state [2]. There have been noted high frequency beta EEG activity, suggesting greater cortical hyperarousal during sleep than premenopausal patients, thought to be explained by increased frequency of self-reported hot flashes [2]. Women with moderate and severe hot flashes were noted to be three times more likely to report

frequent arousals compared to those without hot flashes, with more recent studies showing this association. Hot flashes have been related to more awakening episodes, WASO and stage 1 sleep [2]. There were also noted reduced total sleep time (TST) and more wakefulness after sleep onset (WASO) [3]. Women who undergo surgical menopause tend to experience worse sleep quality compared to those who experience non-surgical menopause, and might benefit from behavioral interventions [2]. The likelihood of having chronic insomnia symptoms increased with the severity of hot flashes [3]..

The prevalence of restless leg syndrome (RLS) and periodic limb movement disorder (PLMD) increases with age, and RLS is furthermore common in women overall [3]. The incidence of PLMD was unrelated to hormone (E_2 or FSH) levels, meaning it's more related to aging than menopause [4].

In regards to other sleep disturbances in postmenopausal women, there are more likely to screen positive for OSA, as do older men [4]. There is an increased risk of OSA in the postmenopausal patient in comparison to the premenopausal patient, especially with gained weight after menopause. Women are more symptomatic with a lower AHI in comparison to men, having more prolonged partial upper airway obstruction and report insomnia related to sleep disordered breathing more often [3]. In the case of OSA, treatment is positive airway pressure. Hormonal therapy is not recommended to treat sleep apnea [4]. Menopausal status has not been associated with sleep maintenance insomnia, daytime somnolence, nor restless leg syndrome [5].

Treatment

Treatment for insomnia due to hot flashes in menopause includes behavioral, herbal and pharmacological management. Sleep hygiene [6] and Cognitive-behavioral treatment of insomnia (CBT-I) is considered the main treatment for patients with chronic insomnia [3, 6], including those with hot flashes. 8-weeks of CBT-I led to a reduction in insomnia symptoms, with maintained reductions at 6 months post-treatment. There are also non-pharmacological approaches for treating menopausal insomnia, including acupuncture, yoga, massage, exercise, tai chi [3, 6] and nutritional supplements containing soy isoflavones have been tried, with mixed effects [3]. It is important to review patient's history and medication list for conditions and meds associated with patient's insomnia. Treatment options for hot flashes of menopause are listed in Table 11.1. Recommend to avoid hypnotics as primary therapy for chronic insomnia in adults; these should be short term and supplemented with CBT-I and sleep hygiene [6] Patients with menopause noted to show the most effective improvement with hormone replacement therapy, compromising of estrogen with or without progestin. It is typically used in patients who suffer from systemic symptoms of menopause, hot flashes being one of them. It is not prescribed without complete review of patient's history and evaluation of risk for negative effects of hormone replacement therapy. There is increased risk of venous thromboembolism (oral not transdermal), breast cancer and endometrial cancer (if used without

Table 11.1 Treatment options for hot flashes of menopause (This table is original, it has not been produced in print or online before)

Treatment options for hot flashes of menopause	
Behavior interventions	• Avoid caffeinated drinks • Avoid nicotine • Dress up in layers • Regulate environmental temperature • Regular exercise, meditation and yoga • Weight management • Dietary changes (avoidance of carbs, addition of soy, nuts, fish)
Herbal supplements	• Black cohosh • Ginseng • Valerian root extract • Soy isoflavones • St. John's wort
Medications	• Hormone replacement therapy (Estrogen, progesterone) via pill or patch • Serotonin selective re-uptake inhibitors (Paroxetine, Fluoxetine, Sertraline) • Gabapentin, Pregabalin • Clonidine

progestin). Indications and contraindications reviewed prior to prescribing hormone replacement therapy. In regards to isolated improvement of sleep is mixed, but mainly have shown improvement in vasomotor symptoms and follow with subjective sleep disruption [3].

Pearls/Take Home Points

- Insomnia is a common sleep finding in postmenopausal patients, especially those who suffer from hot flashes and other vasomotor symptoms.
- Increased risk of OSA in postmenopausal women, being more symptomatic with lower AHI in comparison to men.
- Identification of factors for sleep changes in postmenopausal individual patients help guide treatment intervention.
- Hormone replacement therapy is an effective treatment of vasomotor symptoms in menopause if no contraindications noted.
- Cognitive-behavioral treatment of insomnia (CBT-I) is the mainstay treatment of patients with insomnia due to menopause.

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12 Hypoglossal Nerve Stimulator in the Treatment of Obstructive Sleep Apnea in a Menopausal Woman with CPAP Intolerance

Safia S. Khan

Clinical Case

Ms. NM is a 66 years old lady, diagnosed with severe obstructive sleep apnea (OSA), has an apnea-hypopnea index (AHI) of 38/hour. She has failed continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BPAP) due to anxiety and claustrophobia. She was evaluated for obstructive sleep apnea when she presented for treatment of chronic sleep maintenance insomnia, history of frequent nocturnal gasping episodes and nocturia with more than three arousals a night. She has history of snoring that significantly worsened after menopause. She is curious to learn about the association of sleep apnea with menopause. She does have complains of excessive daytime sleepiness that improves somewhat after her daily naps post lunch. Since being diagnosed with obstructive sleep apnea and unable to tolerate the CPAP, her anxiety related to this diagnosis has worsened her insomnia. She has been evaluated by the dentist and found to be ineligible for the dental device due to loss of complete set of teeth and significant history of osteoporosis making her a poor candidate for teeth implants. She is desperate for treatment of her insomnia and sleep apnea so that she can start to feel like her normal self again.

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Physical Exam

Blood pressure: 139/92 mm of Hg, Pulse: 72/min
Mallampati: II, tonsils 1+, slight nasal septal deviation to the left with reduced airflow to the left. Rest of the physical exam is unremarkable.

She undergoes evaluation for hypoglossal nerve stimulator by the otolaryngologist, a drug-induced sleep endoscopy (DISE) showed antero-posterior pharyngeal wall collapse making her a suitable candidate for hypoglossal nerve implant. She proceeded for the surgery and then presents to the sleep medicine clinic for activation of the HGNS device 4 weeks after device implant and uneventful recovery.

The internal medicine resident working with you in clinic is surprised to hear about worsening of sleep apnea with menopause and also would like to know more about indications and contraindications for this implanted device in the management of obstructive sleep apnea.

Question 1
What is the association of obstructive sleep apnea with menopausal status?

What are the common indications and contraindications for hypoglossal nerve stimulator implant?

Discussion

Definition and Diagnosis of Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is a sleep related breathing disorder characterized by intermittent reduction in airflow due to partial or complete collapse of the upper airways including the soft palate, tonsils, tongue and oropharyngeal passages [1]. Home sleep study or attended in-lab polysomnography (PSG) are the tests performed for diagnosing OSA. In adults this flow reduction is quantitatively measured by reduction in airflow of more than 90% for at least 10 s called an apnea, or reduction in airflow by 30% for at least 10 s associated with drop in oxygen saturation of 4% or 3% with an arousal called a hypopnea.

An apnea-hypopnea index of more than 5 to <15/h is defined as mild OSA, ≥15 to <30/hour is moderate OSA and ≥ 30/h is described as severe obstructive sleep apnea.

The frequent apneas and hypopneas lead to tissue hypoxia resulting in inflammation at the cellular and tissue level, and, over a period of months and years will lead to increased risk of hypertension, diabetes, cardiovascular, cerebrovascular and mental health disorders. Therefore, it is crucial to treat OSA in a timely manner and reduce the risk of irreversible end organ damage.

Treatment Options for Obstructive Sleep Apnea

Treatment recommendations for OSA may vary according to the severity of OSA and tolerance for the nasal or oro-nasal interface (also known as the mask) that delivers pressurized room air from the CPAP/BPAP device. For mild OSA in the absence of comorbid conditions, avoidance of supine sleeping position, weight loss, avoidance of sedating medications, mandibular advancement device, uvulopalatopharyngoplasty, and CPAP/BPAP are reasonable options. For mild OSA with comorbidities, moderate and severe OSA treatment, the recommended option is positive airway pressure (PAP) therapy. PAP delivers room air with pressure to splint open the upper airway and improve airflow acting by acting as a virtual stent in the upper airway. However, for patients that do not tolerate PAP therapy for various reasons, alternative options to consider are; mandibular advancement device, surgery for tonsillar hypertrophy or maxillary expansion, tracheostomy, bariatric surgery, and hypoglossal nerve stimulator.

Obstructive Sleep Apnea in Menopausal Women

Women go through significant hormonal changes throughout their lives from menarche to pregnancy, then reduced fertility as part of ovarian aging and eventually menopause in the fifth decade. Menopause is retrospectively marked by the absence of menstrual cycles for at least a duration of 12 months [2]. Surgical menopause is achieved in case of surgical removal of both ovaries.

While the hormonal fluctuations and events leading up to menopause are beyond the scope of this chapter, major hormonal changes at menopause are briefly stated here. At menopause there is a noticeable reduction in the production of estrogen and progesterone hormones by the ovaries, despite elevated levels of gonadotropins (LH and FSH). Progesterone is correlated with airway patency, lack of this hormone due to menopause leads to easy collapsibility of the upper airways, at a propensity similar to airway collapse among men. Absence of periods (amenorrhea) due to secondary causes like endocrine disorders, thyroid disorders, pituitary dysregulation, polycystic ovaries, or pregnancy, and lactation predisposes to sleep disordered breathing similar to menopause [3].

Progesterone is a potent respiratory stimulant, and, in combination with estrogen it reduces airway collapse by increasing genioglossus contractility. During menopause, progesterone depletion is associated with increased respiratory instability, and reduced respiratory drive increasing risk of OSA and sleep disordered breathing [2]. In addition, there is tendency for excessive weight gain due to changes in lifestyle, comorbid conditions, reduction of body metabolism and increased life stressors. These factors also contribute to worsening of OSA and sleep disorders in women at the time of menopause. Obstructive sleep apnea often presents with symptoms of chronic insomnia specifically frequent arousals, disturbed sleep, nocturia and, excessive daytime tiredness among menopausal women.

Hypoglossal Nerve Stimulator Device

Upper airway stimulation device is an implantable cranial nerve XII stimulator device with a central processor called implantable pulse generator (IPG) implanted in the upper right chest wall subclavicularly typically as an outpatient surgical procedure under general anesthesia [4]. The IPG is connected to a motor and a sensory lead to coordinate forward protrusion of the tongue by way of stimulation of unilateral genioglossus muscle when inspiration is initiated at the level of the intercostal muscles and pleura.

Sequential steps involved in the process of treatment with HGNS are listed here:

- Diagnosis of moderate to severe obstructive sleep apnea
- Failed CPAP/BPAP or intolerance to CPAP/BPAP
- Drug induced sleep endoscopy ➔ favorable antero-posterior collapse of upper airway
- Surgical implantation of hypoglossal nerve stimulator device
- Activation of HGNS device, determine sensation and functional threshold for stimulation
- Set range for stimulation with patient education for titrating up the voltage over next few weeks
- Instructions on increasing the voltage to cause more robust forward protrusion of the tongue are given in detail during the activation visit
- In-lab attended HGNS titration sleep study
- Determine optimum HGNS setting with lowest corrected AHI, ideally in both REM and NREM sleep
- Trouble shoot device setting and stimulation as needed
- Follow up sleep study after 6–12 months to observe and document efficacy of treatment
- Yearly follow up for device monitoring (usage download) and adjustments if needed
- Repeat sleep studies as deemed necessary by sleep physician or at 1 and 5 years if necessary to discern optimal management of obstructive sleep apnea.

Indications

Common indications and contra-indications, irrespective of gender, for upper airway stimulation with the hypoglossal nerve stimulator device are listed here [5], this is not an exhaustive list and certain exceptions may apply on a case-by-case basis:

- Age more than 18 years
- Patients with moderate to severe obstructive sleep apnea who have failed positive airway pressure (PAP) therapy due to persistently high AHI of more than 15/hour.

- Patients with moderate to severe obstructive sleep apnea who cannot tolerate positive airway pressure (PAP) therapy due to difficulty tolerating the mask, pressures or inability to use PAP therapy for more than five nights a week and for more than 4 h a night.
- Mild sleep apnea in association with significant comorbidities.

Contraindications

Few contraindications and limitations, irrespective of gender, for using HGNS device are listed here, again this is not an exhaustive list and certain exceptions may apply on a case-by-case basis:

- Body mass index (BMI) $\geq$32 kg/m^2
- Central sleep apnea and sleep related hypoventilation or hypoxia
- Obstructive sleep apnea with more than 25% central apneas
- Patients requiring frequent MRI, although newer IPG versions are MRI compatible
- A complete concentric collapse of the palate/oro-pharynx
- Patient unwilling to treat obstructive sleep apnea
- Patients requiring frequent MRI scanning.
- Patients with cognitive or functional deficits limiting use of the remote for HGNS device.

While rare, HGNS implant may need to be removed in case of recurrent infections at the surgical sites or in case of absolute need for MRI or other procedures interfering with use of the HGNS device.

Limitations

While HGNS implant has been a life-changing and life-saving therapy for most candidates for this surgery, it also comes with its challenges. Few exclusions for eligibility of HGNS are mentioned here, more information should be explored prior to the surgical implant. The IPG is battery operated, this battery has the capability to last upwards of 10 years. The device is turned on each night by the patient 30 to 60 minutes before going to bed with the intention of being asleep when the stimulation begins to improve tolerance and promote sleep. Four to six weeks after surgical implantation of the device, the patient returns to the sleep medicine clinic for activation of the device and to adjust a range of settings that will effectively help forward protrusion of the tongue past the lower incisor teeth ideally by a minimum of 2 mm.

Education for limitations, mechanical side effects of repetitive tongue stimulation, awareness of potential interactions with wireless devices and chargers,

welding and MRI compatibility are some of the important topics of discussion at the initial activation visit. Extreme sports and extreme weather conditions may affect device performance and further investigation in these situations is an area of research opportunity.

This device has opened many more opportunities for optimal therapy of obstructive sleep apnea among CPAP/BPAP intolerant patients looking for treatment options for this disorder irrespective of gender. Non-invasive ventilation with CPAP and BPAP remains the treatment of choice for management of all severities of OSA with superior evidence for controlling and monitoring AHI while using CPAP/BPAP.

Take Home Points

- Evaluation for sleep disorders particularly obstructive sleep apnea is warranted with significant life changes, especially in the peri and post-menopausal age.
- Treatment options for patients with CPAP intolerance include surgical implantation of hypoglossal nerve stimulator device. This device periodically enables forward protrusion of the tongue to increase airway patency, thus effectively reducing and eliminating sleep disordered breathing.
- A detailed discussion of pros and cons of surgical implantation of hypoglossal nerve stimulator is recommended for patients who have CPAP and BPAP intolerance.

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13 Onset of Chronic Insomnia Due to COVID-19 Pandemic in the Setting of Severe Anxiety in an Elderly Widow

Ariel Park and Safia S. Khan

Clinical History

Ms. E is a 75 years old widow with a significant past medical history of well-controlled hypertension, hyperlipidemia, gastroesophageal reflux, major depression, and coronary artery bypass grafting for occlusive coronary artery disease. She presents to the Sleep Medicine clinic for evaluation of insomnia that started around 6 months ago. She endorsed symptoms of severe anxiety and reports having "a feeling of doom" with insomnia. She goes to bed between 8 and 9 PM each night, takes 3–4 h to fall asleep and wakes up at 5 or 6 AM. She stays in bed until 10 AM unless she has a doctor's appointment in which case she will get out of bed earlier. She likes to keep the TV on at night and during the day to give her a feeling of not being alone. She described this sudden onset of inability to fall asleep and stay asleep coincided with the death of her spouse of more than 40 years. She and her late husband enjoyed dining with friends 2–3 times a week prior to the pandemic. They provided each other company during the COVID-19 pandemic related isolation

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recommended to reduce spread of this contagious respiratory virus. She endorsed underlying anxiety as a perpetuating factor for her insomnia. Her psychiatrist had prescribed Citalopram for anxiety, she discontinued this after taking it for a couple of weeks due to the side effect of dizziness. Since her husband's death, 8 months ago due to COVID-19 infection, she has been staying alone in the family home, and gets visited by her son twice a month. She does not have friends that visit her due to COVID restrictions on socialization, and was never engaged in any church or religious group activities prior to the start of the pandemic. She denied any panic attacks, suicidal or homicidal thoughts.

Her medications include losartan, montelukast, rosuvastatin, spironolactone and aspirin.

She has tried Zolpidem, Eszopiclone, Trazodone, Hydroxyzine, Doxepin, Clonazepam and Alprazolam with little to no success. Each medicine was tried for 3–5 days and then discontinued for lack of effectiveness and risk of addiction feared by the patient. She is reluctant to try any sedative medications due to potential risk for addiction or accidental over-sedation. She is looking for 'an instant fix' to the problem, is very nervous that she has to wait 4 weeks for a follow up appointment, and wants to return for follow up within a week. She is convinced she has the most severe case of insomnia, and the recommended sleep hygiene and any medications we prescribe will not work for her.

Physical Examination

Physical exam shows vitals; HR: 86/min, RR: 16/min, BP 138/81 mm of Hg, Epworth sleepiness scale score of 0. Psychiatric exam: anxious mood, fluent speech with normal vocabulary, made appropriate eye-contact, no suicidal or homicidal ideations. Cardiovascular, respiratory and neurologic examination is within normal.

Lab Test Results

Complete blood counts, basic metabolic panel, hepatic panel, thyroid stimulating hormone and vitamin D levels are within normal.

An attended sleep study (polysomnogram) shows sleep efficiency of 69% with total sleep time of 410 minutes, no evidence of clinically significant obstructive sleep apnea or periodic limb movements. Sleep architecture is significant for prolonged sleep latency and prolonged wakefulness after sleep onset.

Question 1 What is the next best step in the management of sleep disturbance for this patient?

A. Start low dose melatonin 6 hours prior to bedtime and high dose melatonin at bedtime
B. Cognitive behavior therapy for insomnia

C. Reassurance and restriction of time in bed
D. Bright light therapy in the morning
E. Referral to psychiatrist

Question 2 Treatment of which one of her associated conditions will result in resolution of her insomnia complaints?

A. Elevated blood pressure
B. Anxiety disorder
C. Grief
D. Delayed sleep phase circadian rhythm disorder

Differential Diagnoses

- **Delayed sleep phase circadian rhythm disorder**
- **Poor sleep hygiene**
- **Adjustment insomnia**
- **Panic attacks with anxiety disorder**
- **Chronic insomnia**
- **Grief reaction**

Diagnosis

Poor sleep hygiene with excessive time in bed.

General Remarks

Since COVID-19, also known as SARS-CoV-2, has been declared as a pandemic in 2020, extensive public health measures have been implemented to reduce COVID-19 transmission. These measures include social and physical distancing, limiting activities or access to resources, facilities, or institutions, and even isolation or quarantine of individuals. Unfortunately, this pandemic continues to cause considerable deaths worldwide and substantial mental health disorders among affected populations. Studies have shown a number of risk factors to mental health problems during this pandemic, including anxiety and stress associated with the risk of being infected, death or infection of loved ones, containment measures, and social isolation and loneliness [1]. Insomnia is one of the resulting mental health problems along with depression, anxiety, PTcSD, and more [2]. In one meta-analysis, the global prevalence rate of sleep problems was 35.7% [3]. Also, among those who experience social isolation, nearly a third of them developed insomnia [1]. In another study, sleep problems worsened about 10% or more during this pandemic.

Confinement was particularly associated with poor sleep quality, problems falling asleep, and decreased use of hypnotics [4].

Identification of the predisposing, precipitating and perpetuating factors of insomnia is important in addressing the core reason for development of insomnia. In this particular patient the predisposing and perpetuating factor is the underlying untreated anxiety disorder. The precipitating factor for her insomnia is the COVID-19 related isolation, and the sudden death of her spouse due to this contagious illness.

The first line treatment for insomnia during the pandemic remains non-pharmacological approaches, such as optimizing sleep hygiene and cognitive behavioral therapy (CBT) (refer to Fig. 13.1) [3]. Cognitive behavioral therapy for insomnia (CBT-I) helps patients identify and target the various cognitive and behavioral factors leading to sleep disruption. Examples include sleep education, sleep restriction therapy, stimulus control therapy, and sleep hygiene interventions. Patients typically achieve the greatest benefit from CBT-I after four to eight sessions. Although in-person therapy may not be readily available for patients during the pandemic, there are a number of CBT programs available on the internet and via telemedicine.

When CBT-I alone is insufficient to treat insomnia, pharmacotherapy can be incorporated in addition to behavioral strategies and treatment of underlying conditions such as anxiety. In the case of Ms. E, resolution of insomnia will not improve the anxiety, however, treatment of anxiety will definitely improve or resolve the insomnia associated with it. Pharmacotherapy is not recommended to be used alone without promoting healthy sleep habits or incorporating CBT-I when available [3]. There is a range of medications used to treat insomnia including medications approved for insomnia treatment, off-label prescription medications, over the

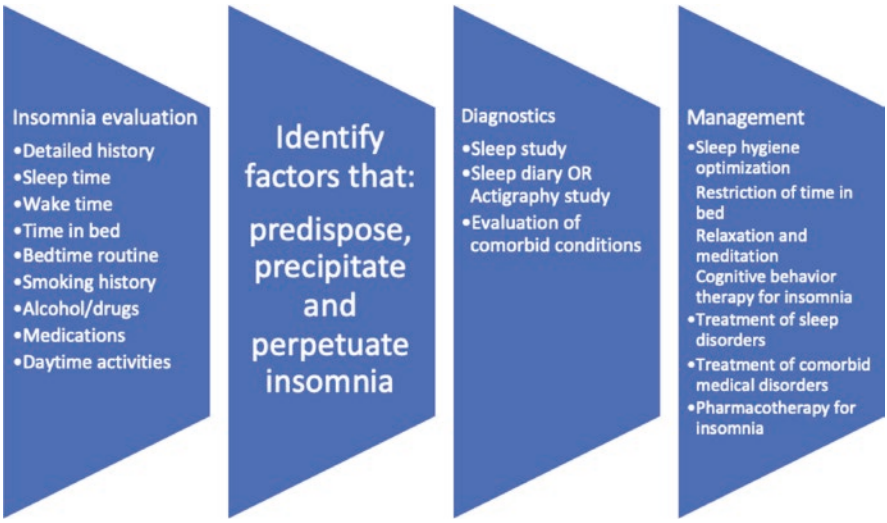

Fig. 13.1 Algorithm for management of insomnia among elderly (this is an original table, has not been published online or in print)

counter sleep aids, and supplements. When choosing appropriate medication, it is important to identify whether patients are struggling with sleep-onset, sleep-maintenance, or both. Also, medication selection process may require even more fine tuning based on treatment response, medication availability and cost, side effects, contraindications, and patient preference [5].

Best Answers

1. **Reassurance and restriction of time in bed**
2. **Anxiety disorder**

Pearls/Take Home Points

- **Identification of the causes of insomnia is of utmost importance in the treatment of sleep disturbances during a pandemic.**
- **Treatment of comorbid medical and psychiatric conditions will improve sleep disturbance and reduce need for pharmacotherapy in the elderly population with significantly increased risk of adverse effects from sedatives and hypnotics.**
- **Hypnotics when used in conjunction with behavior therapy, with caution, improve health and reduce comorbidities.**

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Part V

Sleep and Psychiatric Disorders in Women

Bipolar Disorder Related Sleep Disturbances in Women

14

Darlene Rae King, Sravan Narapureddy, and Meitra Doty

Clinical Case

Ms. GH is a 34-year-old female with a history of HTN and obesity who presents to the sleep clinic for an evaluation of intermittent insomnia. Every 3–4 months, she will experience a period of 3–5 days of insomnia. During this time, she notices that she is more irritable, anxious and motivated to meet her goals. She often has racing thoughts that keep her awake at night, and even though she is in bed by 11 PM, she is unable to sleep for hours. She will often get up, work on projects, clean her home or shop online. She feels energized during these times, but also stressed because she knows she needs sleep. She wants to maintain a regular schedule, so she will continue to attempt to sleep with no success. She may only get about 2–3 h of sleep per night during these episodes of insomnia. Her partner has noticed this pattern and becomes concerned for her but has thought she was just under a lot of stress at work and trying to meet deadlines. She often buys a lot of things online during this time, adding to clutter in their home. She will develop plans for how to improve the organization of their home, purchase things online in waves to help with this and then work tirelessly installing and organizing things. She becomes easily irritated and angry if these efforts are interrupted. After this period of 4–5 days, she will "crash" and sleep excessively. She also notices impairment in her memory and concentration, and decreased mood. Ms. GH has never been admitted to a psychiatric hospital and she has never attempted suicide in the past. She does remember getting depressed several times in her life. Listening to her describe these times, her symptoms at the time met criteria for major depressive disorder. She was able to work and maintain her daily activities, so she did not seek help. Her father had a history of

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alcohol use disorder and coronary artery disease, and her older sister has a polysubstance use disorder. Her father, now deceased from a fatal arrhythmia, was the CEO of a company. He was always very preoccupied with work—a very social and ambitious person. At times reckless, he ended up losing millions of dollars throughout the course of his life on business deals that went south. At one point, after investing in a large business venture, he flew across the country on a whim and was detained at a regional airport for public intoxication and irritability towards airport staff. He was taken to the local psychiatric emergency room and diagnosed with "manic-depressive disorder", but he always said that was a big misunderstanding and that he was improperly diagnosed. Her sister has had many episodes of severe depression. They are not on speaking terms. Her sister leads a very chaotic life and has polysubstance use disorder. When Ms. GH was younger, she found these periods of insomnia helpful in allowing her to be extremely productive, but now that she is older, she finds the recovery period more difficult and feels like these episodes are taking a toll on her physically and mentally. Her treatment goal is to have a more balanced sleep schedule that is not so unpredictable and riddled with bouts of insomnia followed by excessive sleepiness that interferes with her ability to work and maintain life commitments.

Physical Exam

Blood pressure 139/92 mmHg, Pulse 75 bpm
Mallampati: I, tonsils removed, no nasal septal deviation
No other significant findings on physical exam

Questions
What disorders would you include in your differential for Ms. GH?

How do you interpret Ms. GH's family history? How does her family history influence your differential?
When you have a patient with potential bipolar disorder, how do you treat their insomnia?
What are the next steps in providing for a patient with potential bipolar disorder?

Discussion

Bipolar disorders were classically described by Emil Kraepelin as 'manic depressive psychosis' consisting of manic or depressive periods with symptom free intervals of normal functioning. Today, the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5-TR) further subdivides Bipolar and Related Disorders primarily into bipolar I disorder, bipolar II disorder, and cyclothymic

disorders [1]. Bipolar I is defined by having at least one lifetime episode of mania that was not due to substances/medications or a general medical condition and may be preceded or followed by a hypomanic or major depressive episode. Conversely, Bipolar II is defined as a current or previous history of a hypomanic episode and major depressive episode without ever having a full manic episode. Cyclothymic disorders are defined as periods of depressive symptoms and hypomanic symptoms but without meeting the criteria for a major depressive episode or hypomania for at least 2 years in adults. Thus, it is essential to assess the timeline, quality, quantity, and duration of mood symptomology to assign the proper diagnosis [1].

Hypomania Vs. Mania

To better understand and appropriately diagnose these conditions, we also need to understand the terms mania, hypomania and depressive episodes. A manic episode is a distinct 1-week period characterized by a persistent elevation in mood or irritability. The peak age of onset of mood elevation is between the ages of 15 and 25 years [2]. Patients who have had mania describe their experiences as feeling "euphoric" or "feeling on top of the world." [1]. Other core symptoms of mania include decreased need for sleep and an increase in energy. This is to be separated from insomnia in which patients want or feel the need to sleep but are unable to. During this time patients demonstrate an increase in goal-directed activity participating in numerous activities that can range from organizing or cleaning their homes to starting political campaigns. They also often experience elevated self-esteem, sometimes to the point of grandiosity believing they have special skills or fame despite not having any experience or talent in that field. Other common symptoms include speech that is loud, rapid, and pressured (difficult to interrupt). Sometimes, the individual's thoughts are even more rapid than their speech and can be evidenced by switching topics in the middle of conversation mid-sentence (i.e., flight of ideas). Patients also commonly demonstrate labile mood shifting rapidly and inappropriately from giggling to crying to laughing. Their labile mood, grandiosity and poor judgement often lead to involvement in reckless activities such as spending sprees, excess substance use, hypersexuality or excess gambling. At times, manic symptoms are severe to the point of having psychotic symptoms such as auditory or visual hallucinations and delusions.

What separates a manic episode from a hypomanic episode is social or occupational impairment and duration. Manic episodes are defined by at least three of the above symptoms (four or more if irritability is more predominant than elevated mood) lasting most of the day for an entire week and resulting in dysfunction (i.e., significant financial loss, getting fired or divorced) or being hospitalized. Hypomanic episodes also need three or more of the above symptoms (four or more if irritability is more predominant than elevated mood lasting most of the day for four days but not severe enough to cause marked social or occupational dysfunction nor necessitate hospitalization. Of note, if psychotic features are present with the mood elevation, then the patient has mania by definition [1].

Depressive Episodes

Depressive episodes are characterized by depressed mood or anhedonia (loss of interest of pleasurable activities). During these episodes patients also have changes in their sleep and appetite, feel fatigued, often feel worthless and have a more difficult time concentrating. More severe cases are associated with recurrent thoughts of death or suicide and or visible restlessness or slowing down of their actions [1]. Depression is the most common presentation of bipolar disorder particularly in women and can commonly lead to misdiagnosis as unipolar depression. It is imperative that all patients with depression be screened for bipolar disorder as depressive episodes in those with bipolar disorder are notoriously hard to treat and do not respond well to typical depressive treatments and can even switch patients to mania.

Influence of Family History

When evaluating for bipolar disorders, it is important to elicit whether there is a family history of mood disorders. Estimates suggest that bipolar disorder is heritable in the range of 60–85% of the time [3]. While no single gene is identified as the cause of bipolar disorder, genome wide association studies have found multiple loci with small effect sizes that seem to explain approximately 25% of the overall heritability of bipolar disorder [4]. It is hypothesized that these genetic variants in combination with environmental stress such as physical or sexual abuse, major life events and other chronic stressors result in the phenotypic presentations of bipolar spectrum illness [5].

Diagnosing Bipolar Disorder

The key to diagnosing bipolar disorder lies in identifying the presence of a history of mania or hypomania. A thorough history, collateral information and mental status examination are the first line tools for diagnosis. Self-rated questionnaires like the Mood Disorder Questionnaire (MDQ) or the Young Mania Rating Scale (YMRS) can be useful to identify a history of hypomania/manic episodes, however, should not replace a thorough clinical evaluation [6]. See Table 14.1 below that summarizes the type of mood elevation and depressive episodes necessary to diagnose bipolar related disorders. While there are no laboratory or imaging studies to diagnose bipolar disorder, it is critical that appropriate medical work-up is done to rule out medical or substance induced etiologies of mood disturbance.

Reviewing Ms. GH's presentation, we can identify that she meets criteria for a diagnosis of bipolar II disorder. Her episodes of decreased need for sleep, increased energy, increased goal directed activity, marked irritability and notable behavioral change lasting 3–5 days without significant social or occupational dysfunction or need for hospitalization is characteristic of a hypomanic episode. For a diagnosis of bipolar II disorder, a patient must meet criteria for a hypomanic episode and a

Table 14.1 Mood Elevation and Depressive Episodes seen in Bipolar Disorders compared to other mood disorders

Diagnosis	Mood elevation	Depressive episodes
Bipolar I Disorder	At least one manic episode required	With or without the presence on major depressive episode
Bipolar II Disorder	At least one hypomanic episode required & no history of manic episode	At least one major depressive episode
Cyclothymic Disorder	Multiple episodes of hypomanic symptoms that don't meet criteria for hypomania/mania	Multiple periods of depressive symptoms that don't meet criteria for major depressive episode
Substance/ Medication Induced Bipolar Disorder	Prominent mood elevation that can meet criteria for hypomania/mania	With or without the presence of depressed mood or anhedonia
Major Depressive Disorder	Typically, absent. Irritability is common and can sometimes have mixed features of hypomanic symptoms but do not meet full criteria for hypomania/mania	Prominent depressive symptoms meeting criteria for major depressive episode

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current or past major depressive episode which is met as Ms. GH also noted multiple periods in her life that likely met criteria for depressive episodes. Further evidence for a bipolar spectrum illness is present with her father's history of manic episodes requiring hospitalization and treatment.

Differential Diagnosis

Differential diagnosis of bipolar disorders includes Substance Induced Mood Disorder, Major Depressive Disorder, Generalized Anxiety Disorder, Trauma-related disorders, Attention-Deficit/Hyperactivity Disorder (ADHD) and personality disorders [7]. Table 14.2 below highlights the similar symptomology across this differential that can result in a diagnostic challenge.

A patient with bipolar disorder is most likely to present to clinic during a depressive episode. This increases the risk of mis-diagnosing Bipolar Depression with Major Depressive Disorder, which research has shown may delay the correct diagnosis by up to 2 years in women as compared to men [8]. Considering the multiple disorders on the differential, insomnia is a common complaint which can often be confused with hypomania or mania, especially in patients with substance use, among other disorders. It is important to characterize the quality, duration, associated mood symptoms and sleep environment when evaluating a primary psychiatric cause of insomnia. When a patient shares symptoms of potential bipolar I or II disorder, an important follow up question is to ask about use of substances. Patients with substance use disorders, especially stimulant use disorder, often have symptoms that mimic mania, hypomania or anxious/depressive episodes and cannot be reliably diagnosed with a primary mood disorder (MDD, GAD or Bipolar) until they have been abstinent from the substance for at least 6 months [9]. Withdrawal

Table 14.2 Common Symptoms and Special Considerations for Bipolar Disorders and other select psychiatric disorders

	Mania	Hypomania	Major depressive episode	Sleep disturbance	Impulsive behavior	Inattention	Special considerations
Bipolar I Disorder	+	+/−	+/−	+	+	+	Symptoms occur primarily during episodes and are absent when not in episode
Bipolar II Disorder	−	+	+	+	+/−	+	Symptoms occur primarily during episodes and are absent when not in episode
Cyclothymic Disorder	−	−	−	+	+/−	+/−	Shifting mood symptoms that do not meet criteria for mania, hypomania, or major depressive episode
Substance/Medication Induced Bipolar Disorder	+/−	+/−	+/−	+	+	+	Mood elevation predominant and develop in the setting of substance intoxication or withdrawal or medication exposure
Major Depressive Disorder	−	−	+	+	−	+	Mixed symptoms of mood elevation can be present but cannot meet full criteria for mania/hypomania. Symptoms occur primarily during episodes and are absent when not in episode
Generalized Anxiety Disorder	−	−	−	+	−	+	
Trauma-Related Disorders	−	−	−	+	+/−	+	Can have marked irritability/anger, reckless behavior, persistent negative emotional states that occur in the setting of exposure to trauma and symptoms being or worsen after traumatic event
Attention-Deficit/ Hyperactivity Disorder (ADHD)	−	−	−	+/−	+	+	Symptoms present prior to 12 years of age. Often comorbid with bipolar disorders
Personality Disorders	−	−	−	+/−	+	+/−	Have significant mood dysregulation and often incorrectly diagnosed as mood episodes. Often comorbid with bipolar disorders

Legend: (+) commonly present; (−) typically absent; (+/−) can be present or absent
This table is original and has never been printed online or on paper

from alcohol, methamphetamine or other stimulants continue to affect sleep and mood long after the initial medical withdrawal symptoms have subsided. Regardless of whether a patient has a primary mood disorder or substance induced mood disorder, treatment of symptoms may still include pharmacological management. For example, depressive symptoms can be treated with an SSRI; manic symptoms an antipsychotic or mood stabilizer and close follow up can be scheduled to continue to tailor treatment to the patient's symptomatology [9].

Bipolar disorder can also be mistakenly diagnosed in patients with trauma-related disorders, ADHD, or personality disorders because of overlapping symptoms between disorders. It is also likely that trauma-related disorders may develop as a sequelae of bipolar disorder from increased risk-taking behaviors during manic or hypomanic episodes [10]. Patients with early childhood traumatic experiences also have an increased risk of developing bipolar disorder and/or borderline personality [11]. Symptoms such as impulsivity, emotional dysregulation, substance use and sensation seeking behaviors overlap in borderline personality disorder, ADHD, bipolar and PTSD [12]. When there is a suspicion for ADHD, trauma-related disorder, personality disorder or bipolar disorder, a referral to a psychiatrist to further evaluate symptomatology and diagnosis is key as there are many nuances involved in making the correct diagnosis.

Special Considerations for Bipolar in Women

There is a growing body of evidence to suggest that some women with bipolar disorder are more sensitive to normal physiological fluctuations in hormones that occur over the course of the menstrual cycle and may experience cyclical changes in mood [8]. One review including 25 studies showed that two-thirds of women with bipolar disorder had pre-menstrual exacerbation of mania or hypomania [8]. When looking at studies on bipolar disorder; however, it is important to look at the diagnostic criteria used in the study because of the high risk of misdiagnosis of bipolar disorder in patients with trauma, substance use or personality disorders.

Women with bipolar disorder are also at increased risk of relapse in the peripartum period, especially if they discontinue their medication while pregnant. The overall risk of relapse in the post-partum period is about 23% for those who continue their medications compared to 66% for those not on medication. Postpartum psychosis is also common with bipolar disorder and can occur within 2 weeks of delivery with 50% of cases occurring on postpartum days 1 to 3 [8].

There are a collection of small studies looking at the menopausal transition in women with bipolar disorder. There is some evidence that the menopausal transition is a time of increased risk for depressive episodes in women with bipolar disorder. However, the menopausal transition has also been associated with increased risk of MDD in women without any prior history of MDD. Overall, more research in this population is warranted [8, 13].

Treatment and Referral to Psychiatry

Proper treatment of bipolar disorder will resolve symptoms of insomnia due to mania or hypomania [14]. If the patient is currently on an antidepressant and you suspect a current hypomanic or manic episode, consider stopping this medication or alerting the physician prescribing it. Unopposed antidepressants can increase the risk of triggering a hypomanic or manic episode and are typically used in conjunction with a mood stabilizer [14, 15]. Providing the patient with education on mood disorders and referring them to a psychiatrist for evaluation and treatment will help provide relief of symptoms. For patients who present with a confirmed diagnosis of bipolar disorder and are seeking treatment for a sleep condition, avoid interventions that may restrict sleep as sleep deprivation can increase the risk of mania or hypomania. For patients with comorbid sleep apnea, providing treatment for obstructive sleep apnea alongside a psychiatric evaluation is key.

Take Home Points

- Gender differences in bipolar disorder related sleep disturbances have not been well studied and results can be complicated by different approaches to diagnosing bipolar disorder.
- Trauma related disorders and personality disorders can often mimic symptoms of bipolar disorder, leading to misdiagnoses.
- When bipolar disorder is suspected, a referral to a psychiatrist is recommended for full evaluation and treatment.
- When treating patients with bipolar disorder, avoid treatments that may cause sleep deprivation as this increases the risk of triggering a manic or hypomanic episode.
- For patients with comorbid sleep apnea, providing treatment for obstructive sleep apnea alongside a psychiatric evaluation is key.

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Part VI

Special Topics

Intractable Insomnia in a Woman with Otherwise Successful Treatment of Breast Cancer

15

Shan R. Luong, Marilyn K. Culp, and Gregory S. Carter

Clinical History

This 42-year-old woman with left-sided stage 3 breast cancer who has been successfully treated with left total mastectomy, radiation therapy, and chemotherapy (doxorubicin, cyclophosphamide, paclitaxel) presents with complaints of poor sleep at night. She has concomitant depression, is on escitalopram 20 mg daily. She has struggled with insomnia for 10 years, but her difficulties sleeping worsened after cancer treatment a year ago. She completed a course of cognitive-behavioral therapy for insomnia (CBT-I) prior to her diagnosis of cancer 3 years ago which helped but did not completely resolve her symptoms. She tried over-the-counter melatonin 5 mg and diphenhydramine 25 mg with little benefit. A trial of zolpidem led to sleep walking. Since her diagnosis of cancer, she has been using lorazepam 0.5 mg at night to help her fall asleep but complains of a hangover effect in the mornings. Without lorazepam, it can take 1–3 h to fall asleep. She usually takes lorazepam at 9:00 PM, watches TV in bed, then, attempts to go to sleep at 10:00 PM on weekdays

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and 11:00 PM on weekends. It takes her 15 min to fall asleep and she awakens twice during the night. It takes her an hour or more to fall back asleep after these arousals. She wakes up with her alarm at 7:00 AM on weekdays and 9:00 AM on weekends and averages 6.5 h of sleep at night but still feels tired on arising. For the past 3 months, she has had increased difficulty arising on time to get to work in the morning. She drinks four 20-ounce Dr. Peppers during the day with the last as late as 6:00 PM (total of 273 mg of caffeine). She does not nap during the day.

Examination/Mental Status Exam

On exam, she is a thin woman who appears tired. Her general and neurological exams are within normal limits with the exception of a Mallampati score of 3 out of a possible 4 due to a low-lying soft palate and brisker than expected patellar reflexes.

Question 1 Given the symptoms of difficulty getting out of bed in the mornings, what is the best treatment option for this patient?

A. Increase escitalopram to 60 mg after breakfast daily
B. Switch from lorazepam to triazolam 0.25 mg at bedtime
C. Start bupropion 37.5 mg after breakfast every morning
D. Switch from lorazepam to trazodone 150 mg at bedtime
E. Increase her Dr. Pepper consumption to eight 20-ounce bottles per day

Answer: B. Patient is currently experiencing insomnia with sleep onset and sleep maintenance. Though she is on a low dose benzodiazepine, lorazepam is less potent than triazolam which has a very strong affinity for benzodiazepine receptor. The half-life of lorazepam is also on the intermediate side of 14 hours whereas the half-life of triazolam is 2.5 h. Our patient is experiencing improvement in sleep onset with the use of lorazepam but is reporting excess sedation in the mornings. Using a shorter-acting benzodiazepine such as triazolam may improve her morning sedation.

Depression is prevalent in patients with cancer. Though this patient does not specifically state worsening mood, other manifestations of depression can be insomnia and fatigue. The maximum studied dose on efficacy, safety, and tolerability for escitalopram is 50 mg and little is known on the efficacy and safety profile of 60 mg dosing. Jumping directly from 20 to 60 mg daily is excessive and may cause unintended adverse effects.

While bupropion (Choice C) can have an alerting effect and can be used as an adjuvant antidepressant, the dose given here is too small to have an adequate beneficial effect. A starting dose of 75 mg would be more likely to be helpful.

Though trazodone (Choice D) is a medication that is used in depression with a sedating effect, the American Academy of Sleep Medicine (AASM) 2017

guidelines did not recommend its use for insomnia due to lack of supporting data. In off label use, a starting dose of 25–50 mg is generally used to avoid morning sedation.

Increasing Dr. Pepper consumption to eight 20-ounce bottles per day is equivalent to roughly 550 mg of caffeine. Prior studies have shown that 400 mg of caffeine taken at 0, 3, or even 6 h prior to bedtime significantly disrupts sleep including limiting total sleep time by more than 1 h and decreasing the amount of slow wave sleep [1]. Thus, Choice E is not correct as increasing her soft drink intake does not address her main complaint of initial difficulty getting out of bed in the morning and would also lead to worsening insomnia at night.

Question 2 Which of the following choices is the least likely in her diagnostic differential given the above clinical history.

A. Chemotherapy-induced circadian disruption
B. Depression
C. Lorazepam addiction
D. Iron deficiency-related restless legs syndrome
E. Sleep-related breathing disorder

Answer: C. There is no evidence that a lorazepam dose of 0.5 mg nightly causes physical addiction. While she may have psychological dependence at this dose, there is no evidence that sudden stoppage of this dose will risk serious withdrawal symptoms. That said, it is important to monitor prescription drugs to guard against multiple providers prescribing the same controlled substances and that the medications are being used appropriately by the patient. If she is using additional lorazepam at night from other providers to help her fall asleep, this could lead to over-sedation and difficulty waking up in the mornings. Anthracycline-based chemotherapy, such as doxorubicin, can disrupt the circadian rhythm and worsen fatigue. This can lead to behavioral changes that lengthen the time in bed and delay morning arising which further leads to poor sleep at night. Other co-existing symptoms of uncontrolled pain, depression, fatigue, additional stressors from the diagnosis of cancer are all interrelated to sleep disturbances and can be potential exacerbating factors. Primary sleep disorders such as sleep disordered breathing and restless legs syndrome induced by low iron levels in women need to be considered in women with serious illnesses undergoing chemotherapy.

Question 3 Which of the following additional strategies would be the most helpful for this woman's insomnia?

A. Sleep hygiene alone
B. Sleep restriction and stimulus control
C. Further testing with actigraphy and sleep study

D. None of the above as she has already completed CBT-I previously with minimal benefit and further testing is unnecessary for the diagnosis of insomnia
E. B and C

Answer: E. CBT-I provides a multimodal approach to help identify negative thoughts, feelings, and behaviors that lead to insomnia and to reconstruct them to promote sleep. There are several areas in our patient's sleep routine that could be improved upon. Though she has completed CBT-I before, the strategies are only effective if they are used consistently. She may even benefit from a repeat session of CBT-I with updated feedback from a Sleep psychologist on her current sleep needs. To start, she can improve sleep hygiene by avoiding screen time within an hour of bedtime. The brightness from the TV screen can delay melatonin secretion. Activities such as coloring or reading a non-thrilling printed book under a dimmer light setting would be less stimulating. Avoiding caffeinated drinks after lunch time would help decrease its alerting effect and its disruption on sleep architecture. Establishing a routine bedtime and wake up time on weekdays as on weekends would promote consistent sleep schedules. However, sleep hygiene alone is not enough to treat insomnia and it needs to be combined with other techniques. As part of stimulus control, her bedroom and especially bed should be reserved for sleep only and her wind-down activity should take place in a separate space. Her current time spent in bed ranges from 10 to 12 h (including time spent watching TV in bed) and her estimated sleep time is 6.5 h per night with an average sleep efficiency of 60%. Initially limiting her time in bed to 6.5 h can increase her sleep pressure and improve her sleep efficiency. She should keep a sleep log and gradually increase her time in bed by 15–20 min weekly as her sleep efficiency improves. This should ideally be done under monitoring by a Sleep psychologist and patient warned about possible sleepiness. This patient has intractable insomnia, and it is reasonable to also evaluate her for co-existing sleep-related breathing disorder with a sleep study. Women with untreated obstructive sleep apnea (OSA) are more likely to complain of insomnia, restless legs, depression, nightmares, palpitations at night, and hallucinations than men [2]. Also, a 1–2 week actigraphy monitoring could help further clarify her sleep-wake cycle and provide a more objective measure of estimated total sleep time.

Discussion

The most common types of cancer in women in the United States are breast cancer, lung cancer, and colorectal cancer in descending order [3]. This accounts for an estimated 50% of all new cancer diagnoses in women in 2020 in the US [3]. Patients with cancer have reported significant disruption to their daily lives. A survey of 212 patients in the UK showed that the four primary areas of impairment are work, recreation and pastimes, home management, and sleep [4]. These patients reported sitting or lying down to rest for much of the day with insomnia at night [5]. In one

study, over 60% of women with breast cancer reported one or more of the following sleep disturbances of excessive daytime sleepiness, sleep-onset insomnia, sleep-maintenance insomnia, early morning awakenings, and insufficient sleep [5].

As in our patient presented above, the difficulties with the onset and maintenance of sleep also tend to occur in a cluster with depression, pain, and debilitating fatigue [6]. These symptoms can have bidirectional relationships where worsening of one symptom can lead to or worsen other symptoms [6]. Higher levels of depression, pain, and life stressors at baseline tend to have a positive predictive value for developing sleep disturbances at 4-, 8-, and 12-month follow-ups after the diagnosis of cancer [7]. Stress, poor social support, and depression can also lead to activation of the hypothalamic-pituitary-adrenal (HPA) axis which then changes hormone levels that can impair immunity and alter circadian rhythms [8]. The cancer-related circadian dysregulation leads to altered rest-activity cycles and further hastens tumor growth via its effects of altered hormone levels in tumor cells, effects on tumor versus host metabolism, immunosuppression, and decreased tolerability of cancer treatments where timing of normal circadian rhythms is assumed [8].

Treatments with chemotherapy tend to exacerbate sleep disturbances. Compared to cancer-free matched controls, patients at cycle 4 of chemotherapy report taking longer daytime naps and having worse sleep quality, fatigue, depression, disrupted circadian rhythms, and worse quality of life [9]. Though some of those symptoms returned to baseline one-year post-treatment, they were still worse when compared to the normal controls [9] (see Fig. 15.1a). Actigraphy in women undergoing anthracycline-based chemotherapy, such as doxorubicin, showed significantly lower levels of activity and less variability between daytime and night activity (Fig. 15.1b) compared to normal controls (see Fig. 15.1a) [10]. This tends to be due to an increased amount of time spent in bed that is reflective of their worsening fatigue, which then can be insomniogenic leading to "shallower" nocturnal sleep with more stage I sleep and less slow-wave sleep [11]. There are also changes to circadian rhythm variables which include decreased circadian rhythmic cycles (lower amplitude, lower mean activity level, less rhythmicity) and later starting time of activities in the morning and settling down earlier in the evening which suggest shorter days [12]. First administration of an anthracycline chemotherapy was associated with a transient disruption, while repeated cycles of chemotherapy dosing resulted in progressively worse and more enduring impairments in circadian rhythms in women with breast cancer [12].

Treatment for insomnia remains focused on cognitive behavioral therapy for insomnia (CBT-I) and other mindfulness therapies. The components of CBT-I include sleep hygiene, stimulus control, cognitive therapy, circadian entrainment, relaxation techniques, and sleep-restriction (Table 15.1). A meta-analysis of 20 studies involving 1162 patients treated with CBT-I showed a statistically significant improvement in sleep with average decrease in sleep onset latency (SOL) by 19 minutes, decrease in wake after sleep onset (WASO) by 26 minutes, and increased sleep efficiency (SE) by 9.9% [13]. Pharmacologics have a weak recommendation as studies have shown an increase in short-term mortality associated with hypnotic use

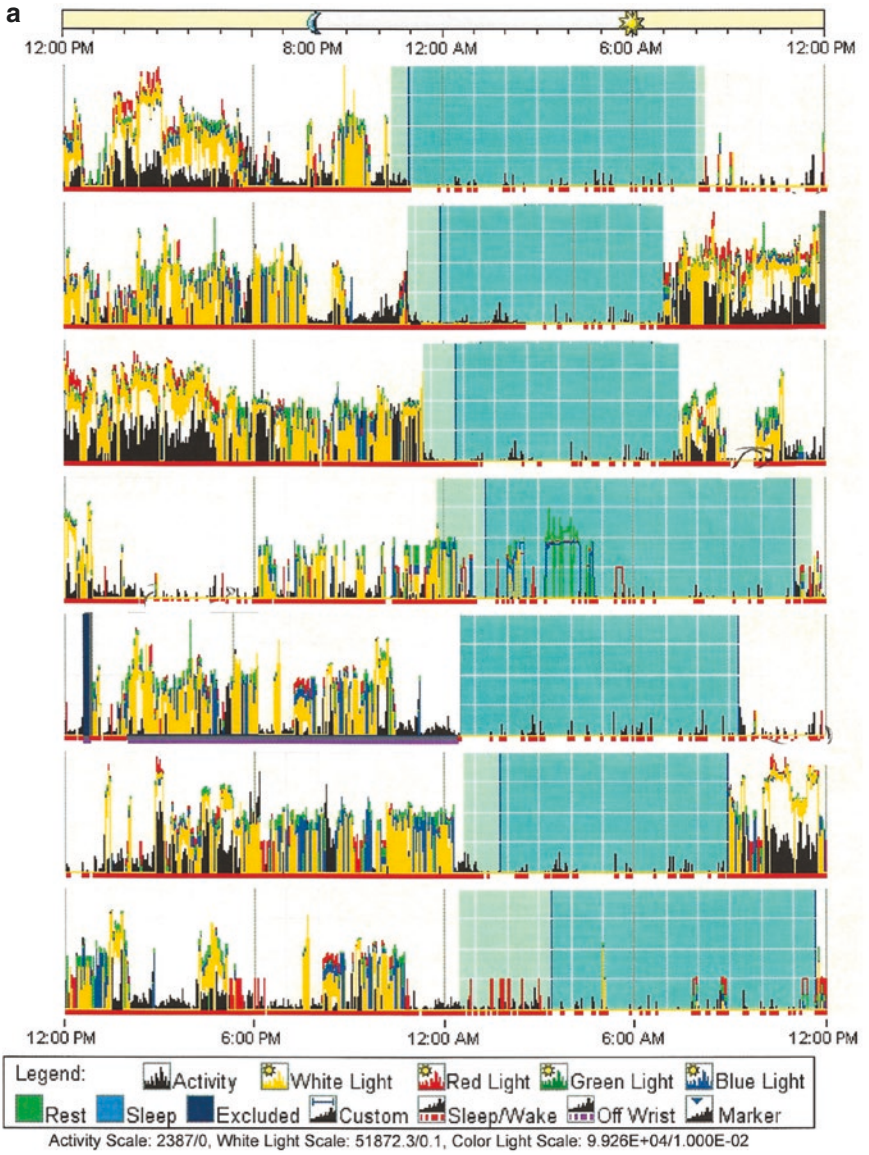

Fig. 15.1 (**a**) Actigraphy of normal control shows variability between daytime and nighttime activities. The shaded light blue area shows adequate estimated sleep time at night where activity level is at its lowest. (This figure is original, has not been published in the past). (**b**) Actigraphy of cancer patient shows decreased variability between daytime and nighttime activities. The shaded light blue area shows decreased estimated sleep time at night where there are periodic elevations in activity level suggesting fragmented sleep. (This figure is original, has not been published in the past)

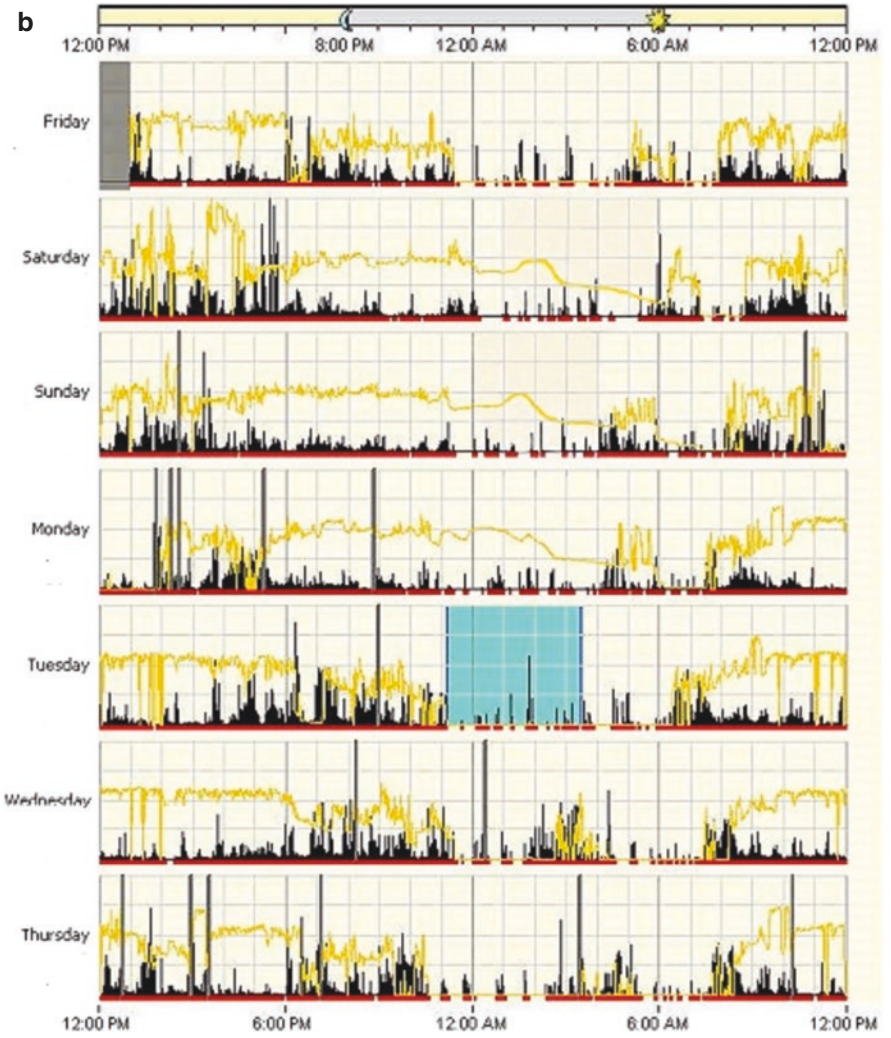

Fig. 15.1 (continued)

where all-cause mortality increased 2.38-fold within 2 years (benzodiazepines increased risk five-fold, whereas non-benzodiazepine sedative hypnotics doubled the risk). This increase in mortality was confined to a relatively short period following the initiation of hypnotic use, with no association between hypnotic use and long-term mortality [14]. Though the American Academy of Sleep Medicine recommends limiting hypnotic use to 2–4 weeks, it also recognizes that long-term use may be indicated in those with severe or refractory insomnia or chronic comorbid illness. It is also important to recognize that sleep disturbance in cancer is seldom a single phenomenon and is usually associated with concomitant depression, anxiety,

Table 15.1 Components of CBT-I (This figure is original, has not been published in the past)

Component	Brief description
Sleep Hygiene	Maintaining a bedroom environment and a set of daily routines that promote consistent and uninterrupted sleep.
Stimulus Control	Conditioning a set of behaviors to strengthen the association between bed and sleep and avoiding behaviors that would cause an association of bed with other stimulating activities.
Cognitive Therapy	A form of behavioral treatment to become more aware of inaccurate or negative thinking about sleep and insomnia so that it can be reshaped with positive concepts about sleep and its effects.
Circadian Entrainment	Utilizing the light-dark cycle to help synchronize the circadian rhythm.
Relaxation Techniques	Methods of relaxation to limit cognitive stimulation and reduce bodily tension to promote sleep. Techniques include progressive muscle relaxation, meditation, mindfulness, breathing techniques, and guided imagery.
Sleep Restriction	Limiting the amount of time spent in bed to increase sleep drive and improve sleep efficiency. The amount of time is gradually increased as sleep efficiency improves.

and pain disorders that need to be adequately treated as well. Closer monitoring and dose adjustments must take place when a combination of sedative hypnotics and opioids is used. A retrospective cohort study of Washington Medicaid patients found that the addition of sedative-hypnotic to an opioid was associated with 6.4 times the risk of opioid overdose death compared to opioid alone [15]. This risk increased 12.6 times with a further addition of skeletal muscle relaxants [15].

Take Home Pearls

- It is important to screen for sleep disturbances such as insomnia in patients with cancer as these can side effects of cancer chemotherapy and/or radiation therapy.
- Co-existing symptoms of uncontrolled pain, depression, fatigue, additional stressors from the diagnosis of cancer are all interrelated to sleep disturbances and can be potential exacerbating factors for insomnia.
- Treatment for insomnia focuses on cognitive behavioral therapy for insomnia (CBT-I), other mindfulness therapies, in association with sedative hypnotics where indicated.
- The components of CBT-I include sleep hygiene, stimulus control, cognitive therapy, circadian entrainment, relaxation techniques, and sleep-restriction.
- Closer monitoring and dose adjustments must take place when a combination of sedative hypnotics and opioids is used.

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Parasomnias in Women

16

Stephanie M. Stahl and Cynthia Bodkin

Case 1

A 41-year-old woman with a past medical history including depression, on escitalopram, presented to the sleep medicine clinic for episodes of eating during sleep without recall of these events. The onset was about 5 years prior. She decided to pursue evaluation due to an approximate 9.1 kg weight gain since onset despite daytime calorie restriction and other dieting. She initially became aware of her behaviors after several instances of finding wrappers from candy and food, and empty soft drink cans in her bed that she did not recall consuming. Other examples over the years included she found evidence one morning that appeared she had sliced and eaten part of a stick of butter and had found evidence of using the stove that she did not recall. The episodes often occurred several times per week. She denied restless legs syndrome (RLS). She lived alone and was uncertain if she snored, had other obstructive sleep apnea (OSA) symptoms, or had periodic limb movements in sleep (PLMS). She had sleepwalking in early childhood but had no known occurrences since. A presumptive diagnosis of SRED was made. A polysomnogram (PSG) was completed to evaluate for OSA or other cause of sleep disturbance that may be contributing to these episodes. The study revealed mild OSA with

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Table 16.1 Classification and types of parasomnias. (This is an original and has not previously been printed)

NREM parasomnias	Confusional arousals Sleepwalking Sleep terrors Sleep-related eating disorder
REM parasomnias	REM sleep behavior disorder Recurrent isolated sleep paralysis Nightmare disorder
Other parasomnias	Sleep-related dissociative disorders Exploding head syndrome Sleep-related hallucinations Sleep enuresis

an apnea-hypopnea index (AHI) of 7.9/h, normal REM atonia, a sleep efficiency of 76%, an arousal index of 23.1/h with several awakenings occurring from stage N3 sleep, and a periodic limb movement of sleep index of 8.4/h. During her PSG, she had an episode of awakening from stage N3 sleep where she sat up in bed for approximately 1 minute and then laid back down and returned to sleep. Electroencephalography (EEG) showed wakefulness during the episode; however, she had no recollection of this event the following morning (Table 16.1).

Discussion

SRED is considered a NREM-related parasomnia. The ICSD-3 diagnostic criteria for SRED requires (1) the presence of recurrent episodes of dysfunctional, involuntary eating that occur after an arousal during the main sleep period; (2) consumption of peculiar forms or combinations of food or substances, sleep-related injurious behavior while in pursuit of food, or adverse health consequences from the recurrent nocturnal eating; (3) partial or complete loss of awareness during the episode with impaired event recall; and (4) the disturbance is not better explained by another condition, medication, or substance [1]. People with SRED often consume odd food combinations or harmful substances, such as frozen pizza or soap. Injury is not uncommon as the person attempts to pursue or make the food while not fully aware. Injuries reported include cuts from use of utensils and burns. Poisoning from toxic substances can occur. Interestingly, alcohol consumption is rare. Adverse health effects can also occur. Consumption of high-calorie foods are common, which can lead to significant weight gain. Patients with diabetes or other metabolic abnormalities may have other deleterious consequences. Dental caries and tooth injury can also occur [1]. The main differential in SRED is night eating syndrome (NES), which is excessive eating near bedtime or eating after nocturnal awakenings with conscious awareness, although these two conditions can occur concurrently.

SRED is common, especially in people with another eating disorder. The prevalence of SRED is not well studied; however, one study reported the prevalence in a college student sample was 4.6% compared to 16.7% in those involved in an inpatient eating disorders group and 8.7% in an outpatient eating disorders group [2].

SRED is much more common in women at 60-83% of cases. The age of onset averages between 22 and 39 years old [1, 3]. Nightly eating episodes are common with up to six occurrences per night reported [3].

SRED can be idiopathic but is often associated with medications, other medical problems, or other sleep problems including other parasomnias, PLMS, OSA, RLS, narcolepsy, and irregular sleep-wake circadian rhythm disorder. SRED does not appear to be associated with insomnia. Medication-induced SRED is most commonly associated with zolpidem but has been reported with several medications including other sedative hypnotics, psychotropic medications, and anticholinergics. Sleepwalking in childhood; eating disorders in childhood or adulthood; recent cessation of tobacco, alcohol, or substance use; and stress may be predisposing factors [1, 3].

In SRED, PSG often shows reduced sleep efficiency with frequent arousals from sleep, particularly from stage N3 sleep, with a mean arousal index of 21/hour reported [3]. Confusional arousals and complex behaviors may be observed on video during PSG. PLMS with arousals are common and OSA may be seen, although severe OSA is not common [3]. The eating episodes typically occur within 1 min of awakening from stage N2 or N3 sleep. During the episodes, the EEG often shows a pattern of wakefulness, indicating a dissociation between conscious awareness and wakefulness.

Limited research is available regarding the treatment of SRED. Safety precautions should be discussed. Precautions to consider include putting alarms on bedroom doors, locking up kitchen knives and other potentially harmful utensils, and childproofing stove knobs. If an associated sleep condition is present, such as RLS, frequent PLMS, or OSA, then treatment of the underlying condition may improve the eating episodes and should be considered first-line treatment. Medication options reported to improve SRED include selective serotonin reuptake inhibitors, topiramate 100–400 mg/day, and clonazepam 0.5–2.0 mg/day [4, 5]. Topiramate has also been shown to provide benefit in NES [5]. While impaired cognition is commonly reported with topiramate, a small study showed no impairment in cognition when used in SRED and NES, and rather, improved alertness was reported in 50%. In this group, benefit was maintained with topiramate with return of symptoms upon discontinuation. Weight loss is common with topiramate. This small study evaluating patients with NES and SRED reported a mean weight loss of 11.1 kg with a mean decrease in body mass index from 30.0 to 26.1 [5].

Outcome of Case

She was started on continuous positive airway pressure (CPAP) with some benefit in daytime sleepiness and perceived sleep quality; however, the frequency of the sleep-related eating improved but persisted. She was then started on topiramate initially at 25 mg at bedtime and was increased by 25 mg every two weeks as needed and tolerated. With 150 mg at bedtime, she had resolution of sleep-related eating.

She had mild hand and feet paresthesias with topiramate, but she felt the benefits outweighed this effect and she opted to continue the medication. Over the next couple of years of follow up, she did lose approximately 11.3 kg. With this weight loss, she stopped using her CPAP machine as she no longer felt improvements with it in the setting of the weight loss. She has continued topiramate with no further episodes of sleep-related eating to her knowledge and no additional adverse effects.

Case 2

A 28-year-old man with a past medical history including asthma presented to the sleep clinic by himself with a chief complaint of violent behavior in sleep. He noted the episodes started 5 years ago around the time he got married. His wife reported that he attacked her in his sleep. His wife has woken up with bruises, and one episode she had a rope wrapped around her wrist upon awakening. He was also told by his wife that other times he would stare at her as if he was going to attack her. His wife reported that he is angry and aggressive toward her during these episodes and these events last 2-15 minutes. One episode even occurred during the day while he was sitting on sofa reading on his phone without recall of falling asleep. The episodes were causing a strain on their marriage, leading to discussions about divorce. He denied waking up in the wrong room or a strange place. He had roommates in the past that did not report similar episodes. No one had witnessed these episodes except for his wife. He had no memory of these events. He used to sleep well without any problems prior to getting married. However, he had developed anxiety about going to sleep as he was scared he would hurt his wife and started sleeping in his workshop. His sleep latency was about 1 hour, and he slept approximately 6 h on weeknights and 8–9 h on weekends. His Epworth Sleepiness Scale was 12. He denied urinary or bowel incontinence or tongue biting during these episodes. He had no prior history of sleep walking or other abnormal behaviors during sleep. He denied cataplexy, sleep paralysis, hypnagogic hallucinations, RLS, or falling out of bed. He denied tobacco or recreational drug use and would drink 1–2 alcoholic beverages per year. He had a normal routine EEG prior to his clinic visit. He was scheduled for an in-laboratory PSG; however, prior to completing this study, his wife came to the sleep clinic as a patient.

The wife is a 26-year-old female with a past medical history including PTSD with a recent suicide attempt and rheumatoid arthritis who presented with a chief complaint that her husband was abusing her in his sleep. She reported waking up with bruises and injuries. She stated that she had no memory of these events. These episodes did occur a few times before meeting her husband. Since marriage, episodes occurred 2–3 times a month. She denied urinary or bowel incontinence or tongue biting with these events. She went to bed at 9 p.m. and rocked for 1–2 h before falling asleep. She obtained approximately 8–9 h of sleep per night. She reported daytime sleepiness, restless sleep, and an episode of sleep waking about 3 years prior to presentation. She denied cataplexy or sleep paralysis. She reported struggling with knowing what is reality and what is a dream and reported déjà vu

episodes during the day. Her medications included buspirone, cyanocobalamin, escitalopram and tofacitinib. She denied any significant recreational drug or alcohol use.

Her psychiatric history included PTSD. She reported being physically, emotionally, and sexually abused by her mother's boyfriend at a young age. She had a suicide attempt 2 months prior to presentation by overdosing on sertraline, diphenhydramine and benzonatate and was subsequently admitted to the intensive care unit for management. She reported a history of nonepileptic psychogenic seizures and had no memory of major life events, such as weddings, birth of children or graduation.

After the initial visit, the husband set up a video camera in the bedroom and recorded videos of her punching herself in the face during sleep. She underwent a PSG with 7.08 h of sleep, a sleep efficiency of 78%, a REM sleep latency of 267 minutes, an overall AHI of 4.2/h, and an oxygen saturation nadir of 90%. A multiple sleep latency test (MSLT) demonstrated a mean sleep latency of 15 min and 6 s and no sleep-onset REM periods. Her urine drug screen on the day of the MSLT was negative. She also underwent a 3-day extended video EEG where she had a nonepileptic event of tremoring of the right hand which transformed to whole body tremoring. She had another event out of REM sleep that began after 10 min of wakefulness, where she was noted to swat at the air with her left hand and thrashed with asynchronous movements. This event, with off and on motor movements, lasted about 9 min with the EEG demonstrating wakefulness during this entire episode.

Discussion

Sleep-related dissociative disorders (SRDDs) were included as an entity within the "other parasomnias" section of the International Classification of Sleep Disorders, second edition. It is considered a dissociative disorder that emerges during sleep periods with well-established EEG of wakefulness after stage N1, N2 or R sleep [6]. The Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) describes dissociative disorders as "a disruption of and/or discontinuity in the normal integration of consciousness, memory, identity, emotion, perception, body representation, motor control, and behavior. Dissociative symptoms can potentially descript every area of psychological functioning." [7] SRDDs were not included in the ICSD-3 because of difficulty classifying the disorder under the committee's guidelines [8]. However, sleep medicine providers must be aware of SRDDs. In this particular case, both the husband and wife had been diagnosed with a parasomnia prior to being referred to our sleep center.

There are many parallels between SRDDs, RBD and NREM parasomnias, such as similar complex behaviors, injuries, a state of dissociation, and occur during the sleep period. Therefore, differentiating the disorders can be very challenging. People with SRDDs typically have a history of physical or sexual abuse often as a child and are more often women. Mood disorders, PTSD, suicide attempts,

self-mutilating behaviors and psychiatric hospitalizations are common in patients with SRDDs. Episodes captured on PSG demonstrate a behavior out of clear wake EEG compared to RBD with a REM EEG and NREM parasomnia which can be N1, N2, N3 or awake EEG [1, 6, 8]. People with SRDDs may have dissociative events during the daytime as well. Therefore, asking if the behaviors occur outside of the sleep period is of importance.

Treatment is focused on psychotherapy. Medication may be used to treat comorbid psychiatric disorders, such as mood disorders. Clonazepam, which is often used to treat parasomnias, frequently has a lack of response in people with SRDD or can make symptoms worse [8]. Therefore, if a patient diagnosed with a parasomnia is not responding to clonazepam, SRDDs should be considered.

Outcome

Based on all the information obtained, including the wife's psychiatric history with a recent suicide attempt, the husband's video, PSG, MSLT and prolonged video EEG, she was diagnosed with a SRDD. The patient's psychologist was contacted and informed of the findings. Her psychologist had also been concerned about the possibility of dissociative symptoms. She is currently undergoing extensive psychotherapy. The husband decided not to move forward with his PSG in light of the video he had captured of his wife. Providing the couple with information on this diagnosis has relieved some of the stress they were experiencing in their marriage.

Teaching Points

- Parasomnias are states of dissociation characterized by undesirable physical events or experiences that occur during sleep or transitioning into or out of sleep. They can be associated with violent behaviors and are often treatable.
- Sleep-related eating disorder is NREM-related parasomnia most commonly seen in women that must be differentiated from night eating syndrome where recall or awareness of the nocturnal eating is present.
- Sleep-related dissociative disorders should be considered in the differential in patients with parasomnias especially if they have failed standard treatment.

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Fatigue in a Transgender Man

17

Emily Levy Kamugisha and Micah Nishigaki

Clinical History

Mr. AH is a 38-year-old African American male (assigned female at birth) who presented to clinic for daytime sleepiness and fatigue for a few months. He has had to increase his caffeine consumption to avoid falling asleep while at work as a hospital administrator. He often falls asleep while watching T.V. with his partner in the early evenings. He has a past medical history of polycystic ovary syndrome (PCOS), major depressive disorder (well controlled on sertraline 100 mg 1 tab by mouth daily for the past 2 years), obesity, and hypertension. He began socially transitioning to male in his early thirties and began testosterone therapy about 1.5 years ago. He had a mastectomy 3 years ago. On review of systems, he reports morning headaches occurring a few times per week, and no significant weight changes since beginning testosterone therapy. His partner (who is present for the visit) reports that Mr. AH snores. He denies a known history of obstructive sleep apnea (OSA) and has never had a polysomnography in the past. He is a non-smoker. He drinks 2–4 alcoholic beverages on the weekends. He uses no illicit drugs.

He generally goes to sleep at 10:30 p.m. nightly and sleeps uninterrupted until 6:00 a.m. He sleeps in a cool, dark room in a bedroom that is not street-facing. He and his partner share a bed. He watches T.V. prior to bed and sometimes eats in his bed.

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Physical Examination and Objective Metrics

Vital signs: Blood Pressure 154/83 mmHg; Heart Rate 86 beats per minute; Respiratory Rate 15 breaths per minute; Temperature 98.8 °F; Body Mass Index 33.31 kg/m^2
General appearance: Pleasant, obese gentleman in no apparent distress, non-toxic
HEENT: Neck circumference of 44.7 cm, normocephalic and atraumatic. No thyromegaly. Mallampati class III.
Cardiovascular: Regular rate and rhythm, no murmurs/rubs/gallops, no JVD, no pedal edema
Respiratory: Lungs clear to auscultation bilaterally, no crackles/wheezes/rhonchi, no increased work of breathing on room air
Gastrointestinal: normoactive bowel sounds, abdomen soft, non-tender and non-distended without rebound or guarding
Neurological: Alert and oriented, CN II-XII grossly intact, no focal deficits appreciated
MSK: Moving all extremities spontaneously, normal bulk and tone
Skin: No rashes or lesions, skin warm and well perfused

STOP-BANG score: 5
Epworth Sleepiness Scale (ESS): 14/24 (abnormal sleepiness)

Lab Results

No electrolyte abnormalities, mild microcytic anemia (with iron studies to indicate iron deficiency anemia), normal TSH, HgA1c 5.7%.

Special Studies

Polysomnogram Overnight home sleep study (Fig. 17.1a,b,c) showed AHI of 11.2/h with an RDI of 21.3/h and a sleep efficiency of 94%.

a

Sleep	Sleep Latency (min): 6	REM Latency (min): 71	Sleep Efficiency: 94%
	Estimated % REM: 23.2%	Est % Deep Sleep: 17.7%	Est % Light Sleep: 59.0%
Respiration (4%)	**pAHI: 11.2/hr**	pAHI in REM: 16.7/hr	pAHI in Supine pos: 12.1/hr
		pAHI in Non-REM: 9.6	pAHI in Non-supine pos: 8.9
	pRDI: 21.3/hr	pRDI in REM: 27.1/hr	pRDI in Supine pos: 21.2/hr
Snoring	Average level: 40 dB		
Body Position	Supine: 451.5 min. (72.0%)	Lateral: 58.5 min. (9.5%)	Prone: 118.5 min. (19.0%)
Heart Rate (bpm)	Average HR: 58	Maximum HR: 95	Minimum HR: 39
Oxygen Saturation (4 Percent)	Overall ODI**: 6.3/hr	ODI in REM: 12.1/hr	ODI in supine pos: 7.0/hr
	Average SpO2: 95%	**Minimum SpO2: 89%**	Total # of OD Events: 66
	SpO2 <=88: 0.0 minutes		

Impression

The overall AHI was 11.2 per hour, consistent with mild obstructive sleep apnea. Hypopneas were scored using 4% desaturations. Supine AHI was 12.1 and REM AHI was 16.7. Lowest SpO2 was 89% and time less than or equal to 88% was 0.0.

b

Sleep Summary

Start Study Time:	10:52:00 PM
End Study Time:	9:57:43 AM
Total Recording Time:	11 hrs, 5 min
Total Sleep Time	**10 hrs, 28 min**
% REM of Sleep Time:	23.2

Respiratory Indices

Total Events		REM	NREM	All Night
pRDI:	223	27.1	19.6	21.3
pAHI:	117	16.7	9.6	11.2
ODI (4%):	66	12.1	4.6	6.3
pAHIc:	7	0.8	0.6	0.7
% CSR:	0.0			

Indices are calculated using technically valid sleep time of 10 hrs, 27 min. Central-Indices are calculated using technically valid sleep time of 10 hrs, 24 min.

pRDI/pAHI are calculated using oxyhemoglobin desaturations ≥ 4%

Oxygen Saturation Statistics

Mean: 95 Minimum: 89 Maximum: 99

Mean of Lowest Oxygen Saturations (%): 93

Oxygen Desatur. %:	4-9	10-20	>20	Total
Events Number	66	0	0	66
Total	100.0	0.0	0.0	100.0

Oxygen Saturation	<=88	<70
Duration (minutes):	0.0	0.0
Sleep %	0.0	0.0

Pulse Rate Statistics during Sleep (BPM)

Mean: 58 Minimum: 39 Maximum: 95

* **Mean Snoring DB:** Mean volume detected during sleep.
** **Oxygen desaturation index (ODI):** The number of oxygen desaturations divided by the monitoring time *** (for HOAT).
*** **Monitoring time (MT):** Total recording time minus periods of artifact and time the patient was awake as determined by actigraphy, body position sensor, respiratory pattern, or patient diary.
**** **Valid Sleep Time:** Total time patient was asleep minus periods of artifact where PAT or Oximeter were deemed invalid.

c

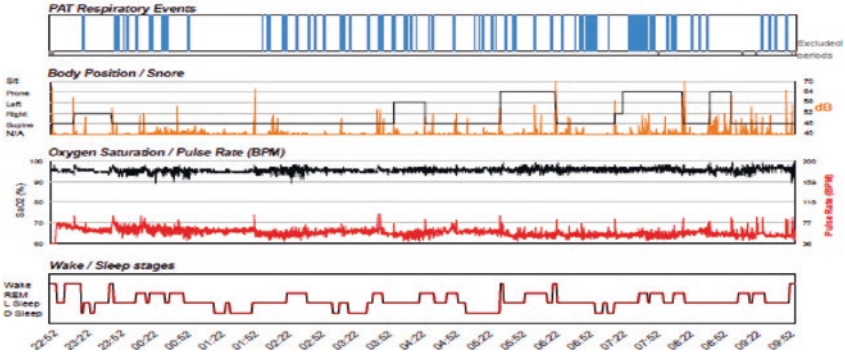
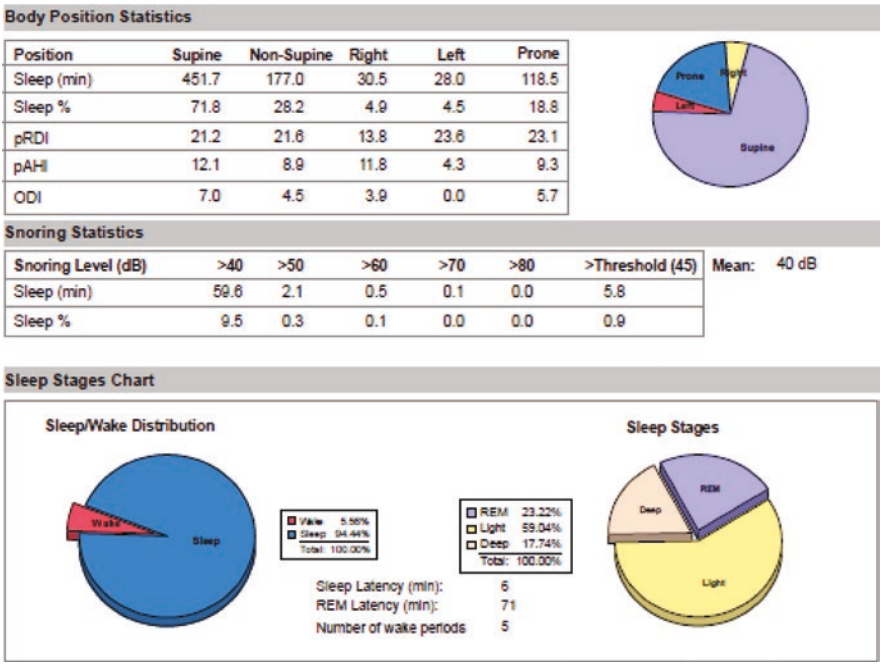


Fig. 17.1 (**a**, **b**, **c**) Overnight home sleep study. (This figure is an original and has not been published). (**a**) Tabular information of the home sleep study with narrative for impression. (This figure is an original and has not been published). (**b**) Tabular information showing sleep study start and end times, % REM sleep, types of events in the REM and NREM stages of sleep, oxygen desaturation events, and pulse rate statistics. Hypnogram (graphical information on the lower half) of the home sleep study shows respiratory events, body position, snoring (dB), oxygen saturation, heart rate, and sleep wake stages. (This figure is an original and has not been published). (**c**) Tabular information for the home sleep study showing respiratory events and sleep time in the various body positions, snoring statistics and pie chart showing sleep stages. (This figure is an original and has not been published)



Body Position Statistics

Position	Supine	Non-Supine	Right	Left	Prone
Sleep (min)	451.7	177.0	30.5	28.0	118.5
Sleep %	71.8	28.2	4.9	4.5	18.8
pRDI	21.2	21.6	13.8	23.6	23.1
pAHI	12.1	8.9	11.8	4.3	9.3
ODI	7.0	4.5	3.9	0.0	5.7

Snoring Statistics

Snoring Level (dB)	>40	>50	>60	>70	>80	>Threshold (45)
Sleep (min)	59.6	2.1	0.5	0.1	0.0	5.8
Sleep %	9.5	0.3	0.1	0.0	0.0	0.9

Mean: 40 dB

Sleep Stages Chart

Fig. 17.1 (continued)

Results

Overnight home sleep study (Fig. 17.1a, b, c) showed mild obstructive sleep apnea.

Question: What Is the Diagnosis?

Differential Diagnosis and Diagnosis

The patient presented with daytime sleepiness, fatigue, snoring, and morning headaches. His mild iron deficiency anemia may contribute to his fatigue. The Epworth Sleepiness Scale helped distinguish that his predominant symptom is daytime sleepiness rather than true fatigue. He has no recent travel to suggest jet lag as contributing to his sleepiness. Similarly, he does not participate in shift-work which can impact sleep. He has reasonable sleep hygiene practices although he does utilize screen time prior to sleep, which could impact his sleep quality. Although poor sleep hygiene may be contributing to some of his daytime sleepiness, his history is much more suggestive of sleep-disordered breathing, with concerning symptoms for obstructive sleep apnea. His history of PCOS and obesity also place him at higher risk for this diagnosis. With the provided history, we do not know if his

hypertension is essential hypertension or secondary hypertension but it is possible his hypertension is a manifestation of his previously undiagnosed and untreated obstructive sleep apnea. His polysomnogram confirmed a diagnosis of obstructive sleep apnea.

General Remarks

Sleep-Disordered Breathing

Sleep-disordered breathing is an umbrella term that encompasses pathology due to disordered respirations during sleep, and includes other diagnoses such as obstructive sleep apnea, central sleep apnea, and sleep-related hypoventilation. In sleep apnea, people experience a decrease or complete cessation of airflow for at least 10 seconds. These respiratory events can be classified as apneas or hypopneas depending on the degree of airflow reduction. Apneas are further sub-classified into obstructive, central, or mixed apneas based on respiratory effort during the apnea event [1].

Obstructive apneas are complete or near-complete airway collapses resulting in at least a 90% decreased airflow in the setting of continued respiratory effort for at least 10 seconds, while obstructive hypopneas are partial airway collapses leading to at least a 30% reduction in airflow in the setting of continued respiratory effort for at least 10 seconds and associated with a 3% decrease in oxygen saturation [1, 2]. Such respiratory events are induced because of either easily collapsible airways, via a reduction in genioglossus and upper airway dilator muscle activity, or because of airway or craniofacial abnormalities, like tonsillar hypertrophy or a shortened mandible, which can cause obstruction [1]. Central apneas are the absence of or decrease in airflow of at least 90% along with an absence of respiratory effort for at least 10 seconds [1, 2].

OSA: Clinical Screening, Diagnosis, and Consequences

The apnea-hypopnea index (AHI) is used to calculate the severity of OSA and is measured as the total number of respiratory events (apneas and hypopneas) to the total number of hours of sleep on polysomnography (PSG). This is the gold standard to diagnose OSA. An AHI score of 5–14 per hour usually indicates mild sleep apnea, 15–29 events per hour defines moderate sleep apnea, and an AHI greater than 30 is severe sleep apnea. OSA is defined as an AHI of 15 per hour or an AHI of 5 per hour plus one or more of the following symptoms: excessive daytime sleepiness, nonrestorative sleep (that is, the lack of feeling refreshed after what is perceived as normal sleep), waking up with breath holding, reports of loud snoring and/or interrupted breathing, gasping or choking, or co-morbidities including hypertension, cerebrovascular accident, type 2 diabetes mellitus, mood disorder, heart failure, atrial fibrillation, cognitive dysfunction, or coronary artery disease [1].

Apneic events cause hypoxemia which usually returns to baseline upon normal respirations (arousal from sleep). However, this results in fragmented sleep, leading to poor sleep quality, fatigue, and excessive daytime sleepiness. Further downstream consequences of OSA include high blood pressure, cardiac arrhythmias, congestive heart failure, obesity, and strokes among other co-morbid conditions [1]. Given the long-term consequences of OSA, it's important for clinicians to keep OSA on their differential if these symptoms or co-morbid conditions present in the patient's history. In the clinical setting, clinicians can screen for OSA with the STOP-BANG questionnaire, which is a concise, validated tool that inquires about snoring (S), tiredness (T), observed (O) apneas, blood pressure (P), BMI (B), age (A), neck (N) circumference, and male gender (G; biological sex). Scores of 0–2 indicate low risk for moderate to severe OSA, 3–4 indicate intermediate risk, and 5–8 (8 is the highest score) indicates high risk for moderate to severe OSA [3]. Another scale to use in the outpatient setting is the Epworth Sleepiness Scale (ESS), which is used to quantify the severity of reported daytime sleepiness in a patient's history. The ESS score ranges from 0–24 with anything greater than 10 out of 24 points considered excessive daytime sleepiness [4]. For our gentleman from clinic, he had a STOP-BANG score of five, already stratifying him in the high-risk category for OSA, and an ESS score of 14, indicating pathologic daytime sleepiness. These scores should prompt a sleep medicine clinic referral and/or polysomnography for further workup.

Gender Affirming Care: Hormonal Treatment for Transgender Persons

Particular to our patient's history is his initiation of testosterone therapy to transition from female to male 1.5 years ago. Hormone therapy is a mainstay of treatment for transgender individuals who seek masculinization or feminization; testosterone therapy for transmen (or those transitioning from female to male), and estrogen in combination with an androgen blocker for transwomen (individuals transitioning from male to female) [5]. The goal of testosterone therapy is to provide male sex characteristics to transgender men [5] so they can live their lives as men, such that their outward appearance matches their gender identity. Several months to years after initiating testosterone therapy, transgender men can start to see the desired effects such as voice deepening, increased lean muscle mass, and increased facial and body hair (with some undesired effects such as acne or alopecia). In addition to the physical benefits of hormone therapy, providing these medical therapies is associated with improved mental health of transgender individuals such that those receiving cross-sex hormonal treatments compared to those who don't initiate hormonal therapy have improved mental health – with a decrease in gender dysphoria, stress, anxiety, and depression [5]. In the short-term, testosterone therapy is considered safe; however, the long-term effects are still under investigation due to a lack of long-term safety data in the transgender population [5].

Anatomical Oropharyngeal Differences Between Genders

There may be some physical differences that ultimately influence the prevalence of OSA when comparing males and females. For example, a longer airway, which is seen in healthy biological males compared to biological females (independent of height), are more susceptible to airway collapse [6, 7]. Biological males may have a larger soft palate compared to biological females, which can predispose them to OSA [6]. Another anatomical contributor is the thicker tissue of the lateral walls of the pharyngeal airway in biological males, which leads to an increase in the extraluminal pressure and a decrease in the intraluminal pressure, making it easier for the airway to collapse [7]. Additionally, larger neck circumferences, which biological males tend to have compared to biological females, increase the risk of sleep apnea [6, 7] (as seen in the STOP-BANG scoring questionnaire) [3]. These anatomical features based on biological sex may explain the greater prevalence of OSA in biological males versus biological females.

Effects of Hormones on Airway Collapse

There are also neurochemical components, such as androgens, that seem to play a role in OSA. For example, research in the past several decades have demonstrated the increasing importance of testosterone's impact on sleep. Both initial (though limited due to the quality) research and more recent, robust studies have suggested that there is an increase in AHI or exacerbation of sleep apnea in cisgender men who have received testosterone therapy [7]. Additionally, women with PCOS, who tend to have higher than normal levels of testosterone, also have higher reported rates of OSA compared to reproductively healthy women [8]. Paradoxically, there have been multiple studies demonstrating older men (age $\geq$ 65) with OSA have lower testosterone levels, leading to lower sleep efficiency and higher AHI scores. However, after controlling for the BMI of participants, the relationship was no longer significant, indicating that obesity may play a role in the relationship between OSA and testosterone levels [7]. Prior research has documented a link between obesity and a decline in testosterone, as well as weight loss and increased testosterone levels [9], indicating that OSA may be more related to the physiological results from weight change and possibly age rather than testosterone levels in these older gentlemen. With all of this said, it's not fully understood how testosterone is related to sleep, and more studies need to be conducted to understand the influence of sleep from both physiological testosterone changes and exogenous testosterone administration.

It is believed that progesterone and estrogen may play a role in OSA but data are conflicting [7, 10]. For example, post-menopausal women who have not received hormonal therapy have a higher prevalence of OSA compared to pre-menopausal women or post-menopausal women receiving hormonal treatment [7]. Progesterone has been implicated as a protective factor against OSA (especially with combined estrogen and progesterone therapies) [10]; progesterone levels increase the tone of

the genioglossus muscle [11], keeping the airway patent by reducing airway collapsibility, and may be one reason why OSA is seen less in pre-menopausal women than in post-menopausal women (as progesterone levels decrease with age) [12]. Of note, however, the suppression of sex hormones in healthy women does not seem to manifest OSA symptoms [7]. There is mixed data on pregnant women, who have higher levels of estrogen and progesterone; some studies report increased incidence in OSA severity in pregnant women, while others suggest mild OSA in pregnant women whom would otherwise be at higher risk due to severe obesity [7, 8]. Finally, estrogen replacement therapy has shown only marginal improvement in OSA frequency and no significant effect on partial airway obstruction as a cause of sleep disordered breathing [13]. Due to the low evidence on benefits of estrogen in OSA, there aren't guidelines that support the use of estrogen as an aid to improve OSA.

OSA in Transgender People

There have been a few cases that suggest the use of exogenous testosterone (for transition-related therapy) can increase the risk of OSA. Two cases have demonstrated the emergence of OSA after initiation of testosterone supplementation in persons transitioning from female to male despite stability in weight/BMI and neck circumference (other known risk factors for OSA) [14]. In one case, however, preceding the diagnosis of OSA, the patient had a total hysterectomy and bilateral salpingo-oophorectomy, [14] decreasing the female sex hormones that could have played a protective factor against the development of OSA [10]. It is unclear if this may have contributed to the development of OSA in addition to the exogenous testosterone administration. These cases further highlight that testosterone may increase the risk of OSA, but more importantly, there remains a complex and unknown relationship between sex hormones and sleep in general.

Transgender medicine is an evolving field in medicine; the long-term consequences of hormone therapy for transitioning individuals remain mostly uncharacterized, especially with respect to sleep [14]. Additionally, much of the research on sex-hormone administration and sleep has been conducted on cis-gendered individuals, with mixed data on exactly how sex hormones influence sleep and respiration [7, 8, 10]. As testosterone and estrogen administration are common therapies for gender-affirming treatment [5], it is important for further research to be conducted to better understand the influence of hormones on sleep in transgender individuals.

Pearls/Take Home Points

- Obstructive sleep apnea is characterized by symptoms of excessive daytime sleepiness (which can be measured with a validated tool such as the Epworth Sleepiness Scale), nonrestorative sleep, waking up with gasping/choking/breath holding, and loud snoring. Associated co-morbid conditions may include

hypertension, cerebrovascular accident, type 2 diabetes mellitus, mood disorder, cognitive dysfunction, or coronary artery disease.
- Biological sex may lead to anatomical differences that predispose males assigned at birth to obstructive sleep apnea.
- The role of endogenous and exogenous sex-hormones on sleep, both in the cisgender and transgender community, remains an evolving area of research and discovery.

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Part VII

Neurologic Disorders with Sleep Disturbance

Parkinson Disease and REM Sleep Behavior Disorder in Women

18

Cynthia Bodkin and Stephanie M. Stahl

Case 1

A 55-year-old right-handed woman with a past medical history including hypertension and osteoarthritis presented to the sleep medicine clinic for dream enactment of approximately 15 years duration. Symptoms initially started with yelling in sleep, but in the last 5 years, she had been physically acting out her dreams. Some examples include she has jumped out of bed, causing her to hit her nose on a nightstand leading to epistaxis, and she has run across the bedroom into an armoire during sleep. Through a different provider she was started on clonazepam 0.5 mg at bedtime, which helped reduce the severity of the behaviors, but she continued to have these episodes 1–2 times per week. She had an initial polysomnogram (PSG) about 10 years prior, which she reported did not show sleep apnea, but she was also told that she did not have any REM sleep during this study. She reported two episodes of nocturnal hallucinations but did not have daytime hallucinations. Other recent symptoms included constipation and sometimes she felt like she was in a fog and would lose her train of thought; however, she denied other memory or cognitive issues. She denied tremors, gait difficulties, falls, dizziness, or urinary problems. She had been taking both metoprolol for hypertension and citalopram for anxiety

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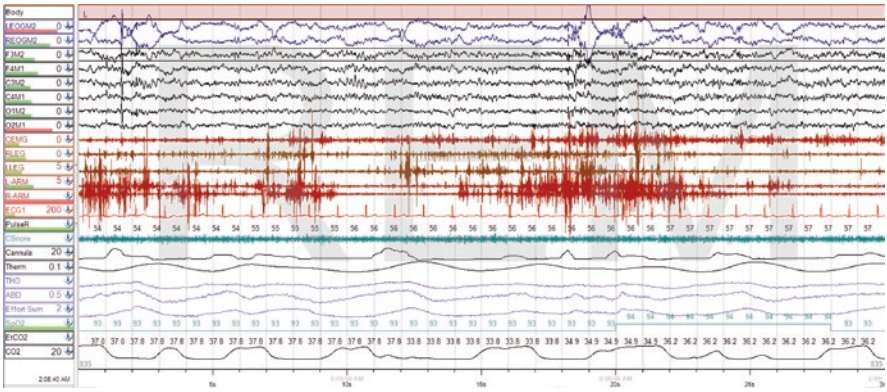

Fig. 18.1 REM without atonia on polysomnography seen in chin, arm and leg electromyography leads. (This figure is original and has not been printed online or on paper)

for about 5 years. She had one caffeinated beverage most mornings and rarely drank alcohol. Her family history included a maternal grandmother with PD. Her father used to sing and yell in his sleep, but he did not have physical acting out of dreams. Her physical exam was notable for a slight decrease in rapid alternating movements and serial finger tapping in her right hand compared to the left and slight right wrist cogwheel rigidity. She did not have a tremor and had a normal gait and good facial expression. She had a repeat in-laboratory PSG which was negative for obstructive sleep apnea (OSA) with an apnea-hypopnea index (AHI) of 0.8/h and oxygen saturation nadir of 91%, but the study did show multiple epochs of REM without atonia (RWA) as demonstrated in Fig. 18.1.

Discussion

RWA is excessive muscle activity during REM sleep defined in the American Academy of Sleep Medicine scoring manual as the presence of tonic/sustained activity with ≥50% of the epoch containing excessive chin activity or phasic/transient muscle activity in ≥5 mini-epochs of 3-second duration in a 30-second epoch [1]. Dream enactment behavior with RWA meets criteria for RBD [2]. The differential diagnosis of RBD includes non-rapid eye movement -related parasomnias, nocturnal seizures, PLMS, pseudo-RBD caused by OSA, sleep-related dissociative disorders, and post-traumatic stress disorder (PTSD).

The estimated prevalence of RBD is 0.5–2%; however, dream enactment behaviors are reported in up to 13% of community-dwelling older adults [3]. RBD is less common in women, accounting for approximately 13–22% of RBD cases overall [4, 5]. However, in people less than 50 years old, the frequency in men and women is equal [3, 6]. One study reported the mean age of onset of RBD symptoms at approximately 60.9–62.0 years old (range 36–84) and mean age of RBD diagnosis of 64.4–69 years old (range 37–85) [4, 5]. RBD is often associated with or a prodrome to an alpha-synucleinopathy neurodegenerative condition (i.e., dementia with Lewy

Bodies (DLB), PD, or multiple system atrophy (MSA)) [5, 7]. The median interval between onset of RBD symptoms and diagnosis of a neurodegenerative condition is reported to be 11 years [5]. Time from RBD diagnosis to a defined neurodegenerative condition is 33.1% at 5 years, 75.7% at 10 years, and 90.9% at 14 years [5]. However, onset of a neurodegenerative symptoms can be prolonged up to 50 years [7]. Evidence of a synucleinopathy is found in 94% of patients with RBD at autopsy [8]. Other causes of RBD include narcolepsy, autoimmunity, paraneoplastic conditions, brainstem lesions, and substance or medication-induced, particularly serotonin reuptake inhibitors, selective norepinephrine inhibitors, and tricyclic antidepressants. However, medication-induced RBD is not clear if it occurs in isolation or creates early unmasking of RBD in people with an underlying alpha-synucleinopathy [3]. Limited data suggests that beta-blockers may also cause RBD [9].

Management of RBD includes removal of potential contributing medications, if possible, safety precautions, and medications to reduce dream enactment behaviors. Safety precautions to review with patients include locking bedroom doors and windows, putting alarms on windows and doors that go outside, keeping the bedroom floor clear of clutter to prevent tripping if the patient gets out of bed, removal of glass and other breakable items in the bedroom, removal of furniture with sharp edges or putting padding on corners, moving the mattress to the floor if falls out of bed are occurring, moving the bedroom partner to a different room if needed, and removal of firearms from the bedroom and keeping them in a locked, secured place far from the bedroom. If dream enactment behaviors are infrequent and mild, such as only minor hand movements during sleep, close monitoring and safety precautions may be initially sufficient. However, once behaviors become frequent, more pronounced, and/or injury to oneself or the bedroom partner occurs, medication to reduce these behaviors should be considered. Melatonin and clonazepam are the front-line options for RBD. Clonazepam has more adverse effects, including worsened OSA and increased risk of cognitive impairment, confusion, and falls, which patients with RBD are already at risk for; therefore, melatonin is often the preferred initial choice. In RBD, melatonin is typically started at 3 mg at bedtime and increased as needed and tolerated to reduce the dream enactment. Median effective dose of melatonin is reported to be 6 mg with some people requiring 15–25 mg to sufficiently reduce dream enactment behaviors. Melatonin, unlike clonazepam, has been shown to reduce RWA on PSG. Clonazepam is usually initiated at 0.25 mg at bedtime with the median effective dose of 0.5 mg. Although these medications are typically effective in reducing the severity and frequency of dream enactment, complete cessation of behaviors is rare [3, 10].

Patients with dream enactment behaviors, particularly those presenting at ages ≥50 years old, should be screened for and counseled about the risk of a neurodegenerative condition. Symptoms to evaluate and monitor for that may be suggestive an alpha-synucleinopathy include hyposmia, memory impairment, visuospatial difficulties, tremor, gait difficulties, falls, hallucinations, orthostasis, and constipation. A thorough neurologic exam should be conducted regularly, including assessment of cognition, gait, tremor, cogwheel rigidity, bradykinesia, and hypomimia. Pending symptoms, neuropsychological testing, neuroimaging, and/or evaluation of alpha-synucleinopathy biomarkers may be indicated for further evaluation.

Outcome of Case

Due to potential contributions from medications, metoprolol was changed to lisinopril, but she was unable to wean citalopram. She started melatonin 3 mg near bedtime and later increased to 6 mg. With the addition of melatonin, she was able to reduce clonazepam to 0.25 mg at bedtime. With these changes, her dream enactment behaviors decreased in frequency and severity, but she does still have minor movements during sleep. A brain MRI with and without contrast showed mild scattered punctate foci of T2 hyperintensity in the subcortical and deep white matter of the bilateral cerebral hemispheres and pons consistent with chronic microvascular ischemic changes but was otherwise unremarkable. Her subtle abnormalities on neurologic exam are suggestive of an underlying alpha-synucleinopathy. She was counseled on safety precautions and risk of a neurodegenerative condition. Neuropsychologic testing was ordered due to minor cognitive complaints and for a baseline evaluation and was found to be normal. Healthy diet and exercise were also encouraged.

Case 2

A 62-year-old woman with PD presented to the clinic due to difficulty sleeping. She first noted symptoms of PD about 5–7 years prior with tremor in her right hand and trouble keeping up with her husband when walking. At the time of her evaluation, she was on carbidopa/levodopa 25/100 mg 1 tablet 3 times a day, ropinirole 4 mg 3 times a day, and melatonin 3 mg at bedtime. She felt her motor symptoms were moderately controlled. She described herself as never being a great sleeper, but in the past 1–2 years she had trouble falling asleep and staying asleep. She would typically go into the bedroom around 9 pm and watch television until 10 pm. At 10 pm she would try to fall asleep but would take 90–120 minutes. Once a sleep, she would wake up 3–4 times per night for 30–90 minutes. Sometimes she felt she did not sleep at all. She typically got out of bed at 9 am. During the day, she was sleepy with an Epworth Sleepiness Scale (ESS) of 19/24. She took 1–2 scheduled 60-minute naps per day but also had many episodes of dosing off throughout the day. Her husband noted she snored for the past 2 years but denied dream enactment behaviors. She voiced she could not “shut off my brain” and was anxious at night thinking about her disease, especially when her arm tremor started. Due to being disabled and embarrassed and anxious to out in public, she spent most of the day at home. She had a PSG which demonstrated poor sleep efficiency at 65.1%, multiple awakenings with an arousal index of 32.2/h, a periodic limb movement index (PLMI) of 19.6/h and periodic limb movement arousal index of 5.2/h, decreased slow wave sleep with stage N3 accounting for 7% of her sleep, and an AHI of 14/h.

Discussion

Sleep disorders are one of the most common non-motor symptoms of PD. Based on a survey performed in 1988, 98% of patients with PD experience sleep disturbance either with difficulties at night or during the daytime [11]. The difficulties can include insomnia, hypersomnia, restless legs, RBD, circadian rhythm disorders and OSA. Managing the motor symptoms in PD is extremely important; however, one should not overlook non-motor symptoms, especially sleep disturbances.

A meta-analysis of PSG findings in patients with PD compared to healthy controls found decreased total sleep time, slow wave sleep and REM sleep. While wakefulness after sleep onset, REM sleep latency, the AHI and PLMI were increased in PD. [12] Lower scores on the mini mental status exam were associated with decreased total sleep time and slow wave sleep. However, eliminating the impact that antiparkinsonian medications and benzodiazepines have on the differences in PSG findings is difficult.

Medications that are frequently used in patients with PD can contribute to sleep difficulties. Studies have demonstrated that some of the sleep disturbances in patients with PD occurred after initiation of antiparkinsonian medications, causing insomnia and/or hypersomnia [13]. Dopamine agonists can cause sleep attacks and daytime sleepiness as well as insomnia and hallucinations. The dose of the dopamine agonists play a role on their effects, where sleep may improve at lower-doses but cause more wakefulness at higher doses [13]. Selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs) and acetylcholinesterase inhibitors are associated with insomnia and/or hypersomnia [14]. Conversely, treating a patient's depression, anxiety and/or cognitive symptoms with these medications may help sleep. SSRIs and SNRIs are also associated with RBD, and PLMS, and RLS and, therefore, must be used with cation in with patients with these conditions.

Aside from insomnia and hypersomnia, other sleep issues are common in patients with PD. The incidence of sleep apnea in patients with PD has been controversial. However, the meta-analyst demonstrates a higher AHI in men with PD compared to healthy controls. Although a difference was not seen in female patients [12]. RLS has been associated with PD however, differentiating RLS from akathisia, nocturnal hypokinesia, leg cramps and/or dystonia can be difficult without a formal history and exam [12].

The patient's motor symptoms can also contribute to difficulty initiating and maintaining sleep due to struggles rolling over in bed and adjusting sheet/clothes as well as a tremor occurring once awoken. Longer-acting dopamine agonists are often helpful at nighttime to improve the motor symptoms that are disrupting sleep without having any higher incidence of side effects compared to immediate release [13].

Just like patients without PD, a detailed sleep history is important to evaluate their sleep difficulties. The evaluation may include PSG and rating scales, such as the Parkinson's disease sleep scale, Pittsburgh Sleep Quality Index, Stanford

Sleepiness Scale and ESS. Patients with PD often have more than one sleep disorder; therefore, evaluating the appropriate response to treatment and re-evaluation for other co-morbid sleep disorders is of importance and often requires a step-wise approach to treatment.

As with all patients with sleep disorders, management should start with sleep hygiene education and non-pharmacological treatments when possible. Adjustments to current medications may be needed to minimize side effects or to optimize symptom control. As with many patients with chronic illnesses, their sleep schedule may suboptimal. They often sleep in, especially if they had trouble falling asleep the night before, due to no constraints on their schedule. Gradually with time the sleep schedule often worsens. A decrease in light dark ratio was found on actigraphy in patients with PD [15] A lack of adequate light exposure during the day and too much light exposure in the evening and night can perpetuate circadian rhythm disorders. Therefore, it is important for patients with PD to get adequate light exposure during the day and avoid bright lights if able in the evening and throughout the night. Exercise has also been shown to have a positive effect on sleep quality among patients with PD. [16]

Pharmacological treatment is often needed to improve quality of life. Specific treatment is similar to treating sleep disorders in patients without PD with a few caveats. Benzodiazepine agonists s must be used with caution given concern of respiratory depression, especially in someone at risk for sleep-disordered breathing. Benzodiazepines may also worsen cognitive disfunction, which patients with PD are at risk for. Iron therapy lacks evidence in treating RLS in patients with PD. Wake promoting medications, such as modafinil, and stimulants can be used for daytime sleepiness; however, they have to be used with caution in an older population due to increased risk of cardiovascular disease.

Outcome of Case

This patient demonstrates the multiple sleep difficulties a patient with PD may suffer from. She was tried on continuous positive airway pressure for her mild OSA but felt it only made her insomnia worse and failed to see improvements in her daytime sleepiness. She was instructed on improving her sleep hygiene, such as eliminating electronic use 2–3 h before bedtime and matching time in bed to time asleep as she had been spending 12 h in bed but felt she was only sleeping 6 h. Light therapy in the morning and appropriate exercise were recommended. With the help of her neurologist, she was tapered down on the immediate release ropinirole, and carbidopa/levodopa was increased during the day and along with switching to long acting ropinirole at bedtime. After the above changes her sleep had improved with a bedtime of 11 pm, sleep latency of 30–50 min, two-three 30-minute awakenings at night and getting out of bed at 7 a.m. Her daytime sleepiness improved with ESS down from a 19 to 11/24. She was only taking one 30-minute nap per day and was no longer having sleep attacks. Because of continued anxiety and depression, she

was started on sertraline 50 mg daily and referred for cognitive behavior therapy (CBT). For treatment of her mild sleep apnea, she was referred to dentistry for a mandibular advancement device. At the last visit she was not interested in any wake promoting medication or stimulant medications and wanted to first see how she felt after CBT and mandibular advancement device use.

Take Home Points

- REM sleep behavior disorder is less common in women and is highly associated with alpha-synucleinopathy neurodegenerative conditions (i.e., PD, DLB, MSA). Safety precautions and medications to reduce severity of behaviors are the mainstays of management.
- Patients with PD frequently have sleep disturbances that require a detailed history and evaluation. Comorbid sleep disorders are common, and therefore, continual evaluation into their sleep disturbances is required.
- The neurodegeneration related to PD and the medications used to treat PD symptoms can lead to multiple sleep disturbances. Treatment requires collaboration between the sleep physician and neurologist.

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Disordered Sleep in a Female Caregiver

19

Khanh Truong and Tamara McGregor

Clinical History/Case

Ms. MP is a 78-year-old woman with hypertension and osteoarthritis who is seeking medical help for a 6-month history of fatigue and sleep difficulties. She denies snoring, restless legs, nocturia, racing thoughts, caffeine/alcohol use, nightmares, or significant pain. Her sleep problems began with the increased care needs of her husband, an 84-year-old man with advanced dementia now receiving hospice care for worsening end-of-life symptoms such as immobility, incontinence, and confusion. She notes feeling overwhelmed and isolated with caregiving needs despite help from hospice staff. Even with breaks, she continues to suffer from poor interrupted sleep throughout the night such as waking up 3–4 times at night to check on her husband or redirect her husband back to bed. She admits that she watches TV at night to stay alert and provide help to her husband. She has trouble sleeping at night and is only able to sleep much better from 7 AM to 1 PM when the hospice staff for the day is there. The patient has tried over-the-counter diphenhydramine and melatonin but feels groggy in the daytime. She rates her sleep quality as "very bad."

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Examination/Mental Status Exam

Her physical exam showed: BP: 160/85, Pulse 84, Temp: 36.3 (97.4F), Height 5′ 4″, Weight 172lbs, SpO2 100%, BMI 29.5 kg/m^2. She appears tired but the rest of her examination is normal. Her Pittsburgh Sleep Quality Index (PSQI) score is 14.

Question 1 Given the above symptoms, what is the most likely diagnosis for this caregiver?

(a) Chronic insomnia
(b) Circadian rhythm disorder, advanced sleep phase
(c) Circadian rhythm disorder, shift work type
(d) Circadian rhythm disorder, delayed sleep phase

Question 2 What other screening tools may be helpful in distinguishing other causes of sleep disturbance in this caregiver?

(a) PHQ-9
(b) STOP-BANG
(c) ISI (Insomnia Severity Index)
(d) All of the above

Question 3 What is the first line of treatment for sleep disturbances?

(a) Zolpidem
(b) Sleep hygiene education
(c) Diphenhydramine
(d) Melatonin

Differential Diagnosis and Diagnosis

Patient has a PSQI score of 14 which is concerning for poor sleep quality. Since patient is the sole caregiver for her husband with dementia with abnormal sleep-wake patterns, daytime drowsiness and difficulty with sleep initiation and having trouble to go to sleep symptoms would put her at risk for circadian sleep-wake rhythm disorders. In this case, this patient suffers from delayed sleep-wake phase disorder. She has a STOP-BANG score of 3 due to uncontrolled blood pressure, age and daytime sleepiness, is at low to moderate risk for obstructive sleep apnea. Her positive PHQ-9 also implicates depression so a Geriatric Depression Scale will be helpful to distinguish depressed mood as a comorbid cause/result of her disordered sleep. Other differential diagnoses that we need to consider include alcohol abuse, drug abuse, and stimulant usage.

From Fig. 19.1, primary care physicians can use this algorithm to appropriately recognize the need for further management.

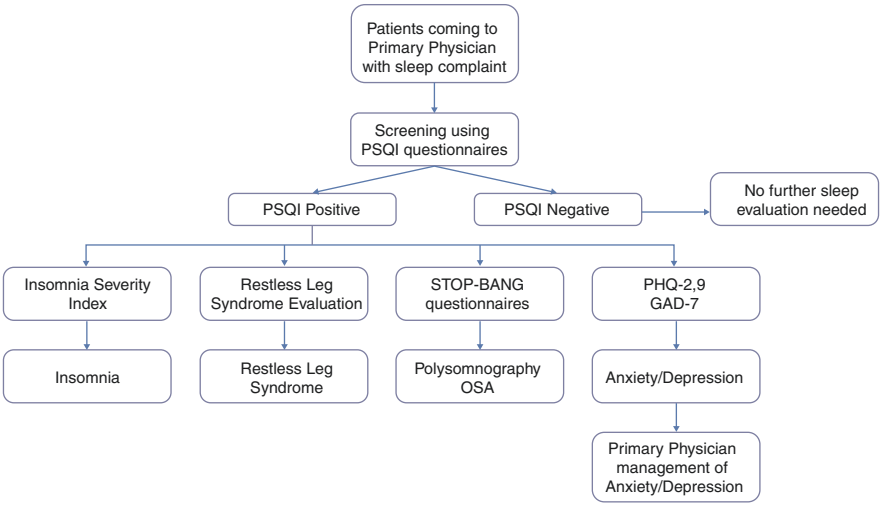

Fig. 19.1 A modified algorithm for primary care physicians for patients with sleep disorders (This algorithm is an original and has never been printed online or in print)

General Remarks

A caregiver's sleep disturbances occur most often when providing around-the-clock care to a patient with dementia. This care involves, and is not limited to tasks such as going to the bathroom, redirecting them back to bed, or providing emotional reassurance. It may be difficult for caregivers to fall back to sleep after being awakened by the care recipient, which may cause them to nap during the day, drink coffee frequently, or spend more time in bed to "catch up" to sleep lost.

Risk factors for sleep-wake disturbance among caregivers are age, female gender, caregiver burden, depression, and poor physical health [1]. These caregivers are at higher risk of developing sleep disturbances such as increased sleep latency, decreased sleep maintenance and circadian rhythm disturbances [2].

Diagnosis Sleep-wake disturbances in this case are consistent with delayed sleep phase circadian rhythm disorder. The circadian system modulates sleep, wakefulness and other physiological systems including the daily rhythms of core body temperature, melatonin secretion, cortisol and appetite. The circadian system also controls wakefulness during the usual waking phase and helps us fall asleep by promoting sleepiness. Diagnosis of circadian rhythm sleep wake disorders is made by obtaining detailed clinical history including bed time, wake up time, time in bed, and naps during the day. A sleep diary and actigraphy study will affirm the suspected diagnosis. Sleep study is warranted in case of suspicion of concomitant sleep disorders.

Treatment The treatment of sleep-wake disturbances including circadian disorders, insomnia, sleep hygiene disorder, should be individualized according to patient needs and symptoms, especially as a caregiver in this setting. Differentiating insomnia from circadian rhythm disorders will help customize therapy.

Non-pharmacologic Therapy

- First-line therapies for patients with difficulty initiating sleep is behavioral and nonpharmacological therapies such as sleep hygiene education, optimizing dark/lighting, noise reduction and consistent bedtime and awakening times [3] before attempting pharmacotherapy.
- Such behavioral, non-pharmacological treatment should include keeping a sleep diary, consistency of the sleeping environment such as reducing noise at night, keeping the bedroom dark at night and bright during the day, sleep hygiene education (avoid naps, turn off lights, electronics, TV, limit caffeine, limit alcohol, and avoid eating late at night).
- A consistent sleep-wake schedule is also important, particularly maintaining regular wake-up time.
- For delayed circadian rhythm disorder, light therapy is an optimal strategy. We recommend exposure to bright light (~10,000 lux) within 30 min of waking up, or spending time outdoors with direct sunlight exposure and avoiding wearing sunglasses [3]. Sunlight provides ~120,000 lux, this entrains the body to stay alert and awake directly after light exposure and will enable falling asleep 14–16 h later.
- In the case of caregivers; it is important to identify resources for obtaining help as much as possible to reduce caregiver burn out and reduce morbidity among caregivers.

Pharmacologic Therapy

- The use of low dose melatonin of 0.5–1 mg can help fall asleep earlier when taken 4–6 h prior to desired bedtime by promoting the earlier production of melatonin.
- Higher dose melatonin of 3 or 5 mg can be taken at bedtime. Though, larger melatonin dose has hypnotic effects.

Sleep deprivation from sleep-wake disturbances can affect cognitive functions such as alertness and attention [4], resulting in mental health problems such as depression or anxiety [5, 6], and are associated with higher BMI and other health problems [7]. Therefore, physicians should identify caregivers who are at high risk of developing sleep disturbance and provide appropriate treatment and support to prevent further complications.

Pearls/Take Home Points

- Sleep disturbances occur frequently among caregivers who provide care to patients with dementia
- Risk factors for sleep disturbances include age, female gender, caregiver burden and depression.
- Treatment should be tailored and personalized. First-line treatment should be behavioral changes and non-pharmacological before introducing pharmacotherapy.
- The use of a sleep diary can help elucidate caregiver patterns/habits.
- Treatment for caregiver sleep disturbances must consider multiple factors: simple dosing of hypnotic medications without full analysis of cause is not advised.
- Primary care physicians should recognize patients with high risks to provide proper treatment.

Correct Answers

1. **D**
2. **D**
3. **B**

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Poor Sleep in a Cancer Patient Receiving Palliative Care

20

Aditi Singh and Tamara McGregor

Clinical History/Case

Ms. LN is a 68-year-old woman with Stage IV ER+/PR+/HER2+ invasive left breast cancer with osseous metastases to skull, ribs, lumbar spine, right humerus, and left tibia, status post bilateral salpingo-oophorectomy who is currently undergoing palliative therapies including oral chemotherapy medications and hormone therapy. Targeted radiation therapy to L2 vertebral body and R humerus relieved her pain. She has no organic or brain metastases on recent imaging. She is brought to the palliative care clinic by her caregiver daughter for a complaint of insomnia in that she is only sleeping in 2–3-h fragments, often seems to roam about the house at night and is drowsy throughout the day. Ms. LN is distressed by this new symptom and seeking treatment for her insomnia.

Further history is negative for significant daytime napping, falls, caffeine intake, or any new nutritional supplements. Review of systems over the past 2 weeks is positive for: fatigue, hot flashes, decreased oral intake of liquids/solids, bony pain in posterior right ribs (better since directed radiation therapy and low-dose opioids),

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decreased ambulation/mobility. Her daughter is concerned because her mother is answering questions very slowly and seems less engaged with her young grandchildren. Current medications include losartan, anastrozole, capecitabine, tucatinib, and hydrocodone 5 mg (3/day as needed), trazodone 50 mg was stopped 2 months ago as it was no longer effective for sleep.

Physical/Mental Status Examination

Vitals: BP 140/80, HR 80, Temp 36.7°C, RR 18, 96% O2 sat, BMI: 26, 4 lbs. weight-loss from last visit.

Well-developed petite female, appears tired, in no acute distress, looks to her daughter to answer questions.

Her physical exam is otherwise unremarkable except for post-surgical mastectomy changes to the left chest wall.

Neuro exam/MSE: not normal. Pt is drowsy, able to state her name, but not place or time.

Paucity of speech with slow, 1–2-word responses, no slurring but needs prompting/repetition of questions and frequent redirection (poor attention).

Motor and sensory exam were not completed as the patient was not able to follow commands.

Question 1 What initial workup is recommended in this scenario?

(a) Comprehensive metabolic panel: Na+, K+, CO2+, Cl, BUN, Creatinine, Glucose, Calcium, Albumin, Total Protein, AST, ALT
(b) Urinalysis and culture
(c) Complete Blood Count with differential and TSH (Thyroid Stimulating Hormone)
(d) Brain imaging
(e) All of the above

Question 2 What interventions might be helpful in the management of this patient's sleep disturbance?

(a) Medication review for side effects
(b) Reorientation
(c) Assess for unresolved pain, constipation
(d) Improve nutrition and hydration
(e) All of the above

Question 3 What diagnostic tool may prove most helpful in this scenario?

(a) Geriatric Depression Scale
(b) Confusion Assessment Method

(c) PHQ-9
(d) GAD-7
(e) Mini-COG

Results (Abnormal Bolded)

Na + 138, K+ 4.0, Cl 104, CO2 24, Glucose 97, BUN 15, Creatinine 1.0.
Albumin 2.9, Total protein 6.0, AST 28, ALT 32.
Calcium total 13.4, Calcium (albumin-adjusted) 14.3.
EKG was normal, no QT abnormalities or ST changes.
CT (Computed Tomography) Head without contrast showed No acute intercranial abnormalities.

Differential Diagnoses

Delirium #1—The patient meets criteria for delirium based on the Confusion Assessment Method tool (CAM) done at bedside. Refer to Table 20.1. While there are multiple etiologies for delirium, in this case, the patient had malignant hypercalcemia likely related to her bony metastases as the suspected cause for her delirium and disrupted sleep

Table 20.1 Confusion assessment method [1]. A helpful and efficient diagnostic tool that can be used at bedside to help rule out delirium (This table is an original and has not been published online or in print)

Confusion assessment method (CAM)	
The diagnosis of delirium by CAM requires the presence of BOTH feature *A* and *B*	
A. Acute onset and **fluctuating course**	**B. Inattention**
Is there evidence of an acute change in mental status from patient baseline? Does the abnormal behavior: • Come and go? • Fluctuate during the day? • Increase/decrease in severity?	Does the patient: • Have difficulty focusing attention? • Become easily distracted? • Have difficulty keeping track of what is said?
AND the presence of EITHER feature *C* or *D*	
C. Disorganized thinking	**B. Altered level of consciousness**
Is the patient's thinking • Disorganized • Incoherent For example, does the patient have: • Rambling speech/irrelevant conversation? • Unpredictable switching of subjects? • Unclear or illogical flow of ideas?	Overall, what is the patient's level of consciousness: • Alert (normal) • Vigilant (hyper-alert)? • Lethargic (drowsy but easily roused) • Stuporous (difficult to rouse) • Comatose (unarousable)

Medication side effects—current meds/supplements should always be suspected/reviewed as:
- Opioids can contribute to delirium but can also disrupt normal sleep architecture. If lethargic or decreasing level of consciousness, naloxone may be administered.
- Many chemotherapy agents can contribute to insomnia.
- Hormone therapy (commonly used for estrogen/progesterone receptor positive breast cancer) causes significant flushing, hot flashes which may affect sleep.
- Polypharmacy may contribute to renal/hepatic injury or interactions leading to encephalopathy.

Infection—UTI/other infections should always be considered

Brain metastases—recent imaging clear, but would maintain surveillance for further metastases

Head trauma—no fall history, but consider brain trauma with progressive worsening of a mental status change

Subclinical seizure activity—no reports of seizure activity, but this patient is at risk for subclinical seizure activity due to metastases, electrolyte imbalance, head trauma

Depression—decreased mood, low energy, insomnia, poor appetite, restlessness can present with difficulty initiating or maintaining sleep and mental status changes

Hypothyroidism or "euthyroid sick"—endocrine abnormalities are common in cancer patients receiving multiple medications/treatments

CVA—Stroke must be considered in a cancer patient with new mental status changes as they could be more prone to hemorrhagic or thrombotic complications.

Discussion

Hypersomnia Versus Insomnia in Delirium

Daytime drowsiness, erratic episodic sleep patterns, and a new change in mental processing led this patient's daughter to seek help for her mother's "insomnia." Delirium, defined as an acute, fluctuating syndrome with disturbance in attention, awareness, and cognition, is an emergency and demands rapid evaluation [2]. Refer to Table 20.2 for assessing common causes of delirium. While delirium is usually reversible and common in older sick or hospitalized patients, it may indicate a life-threatening condition and necessitates a search for an underlying cause. Delirium can complicate hospital stays for older individuals, contribute to falls and injury, delays in treatment, earlier institutional care initiation, and poor medical outcomes.

Table 20.2 Common Causes of Delirium: "DELIRIUM" [6] (This table is an original and has not been published in print or online)

D	**Drugs**	• Anticholinergic drugs such as tricyclic antidepressants, antihistamines, and antipsychotics in patients with underlying dementia as it may cause hyponatremia • Sedative hypnotics such as benzodiazepines as they may worsen sedation, respiration, and increase falls • Muscle relaxers, and opioids such as meperidine • Anti-seizure medications • Consider drug/alcohol withdrawal or acute intoxication and toxicity • A urine or serum drug toxicity panel should be considered as well as acetaminophen and blood alcohol levels if indicated
E	**Eyes and ears**	• Hearing loss and poor vision may contribute to symptoms of confusion • This can be avoided by ensuring patients have access to their glasses and hearing aids, opening windows during the daytime, and having a clock in the room is also helpful to orient patients to time of day
L	**Low oxygen states**	• Labored breathing and decreased oxygen saturation, for example in the case of a COPD exacerbation or pulmonary embolism, can manifest in a hypoactive delirium state • Assess for accessory muscle use and provide supplemental oxygen if needed
I	**Infection**	• Urinary tract infections, pneumonia, sepsis, cellulitis, and meningitis should be considered in an older adult presenting with confusion • Obtain complete blood count, urinalysis, urine/blood cultures, and chest X-ray as clinically indicated, especially if immunocompromised state (receiving cancer therapies)
R	**Retention**	• Urinary retention can cause kidney injury and worsen confusion, monitor urinary output, and use a bladder ultrasound to ensure patient is not obstructed • Constipation can worsen urinary retention and increase the risk of urinary infections and diverticulitis • Increase in dietary fiber or addition of an osmotic laxative may help
I	**Ictal state, immobilization**	• Have a low-threshold to obtain an EEG to assess for seizure activity, asymmetry, or brain injury • Immobilization can lead to hypercalcemia due to bone breakdown, bedsores, and ulcers, and increase risk for deep vein thromboses • Promote early mobilization to preserve muscle strength, increase lung expansion, and prevent constipation • Avoid restraints if possible
U	**Undernutrition, underhydration**	• Assess thiamine, vitamin D, or vitamin b12 deficiencies • Encourage fluid intake and ensure adequate nutrition • If a patient is unable to eat by mouth, consider enteral or tube feeds
M	**Metabolic**	• Obtain a complete metabolic panel to assess for hyponatremia, hypocalcemia, hypoglycemia, acute renal or hepatic failure/encephalopathy • Initial workup should include a TSH and ammonia level

Reversible Versus Irreversible Delirium

All-cause delirium is often divided functionally into reversible vs. irreversible though the reversibility of the problem is usually not immediately obvious. Reversible delirium should be treated by eliminating the cause, if found and securing the safety of the patient. Irreversible delirium (especially if near end-of-life and with progressively worsening symptoms) can portend a very poor prognosis.

Hyperactive Versus Hypoactive Delirium

Delirium that is hyperactive in nature (less common than its calmer hypoactive counterpart), is usually recognizable with increased speech, fearfulness, psychomotor agitation among other symptoms. Conversely, hypoactive delirium symptoms may mirror sedation, dementia or somnolence and are frequently missed on initial examination [3]. Caregivers may complain of frequent daytime napping and unrestful sleep at night as well as a fluctuating state of awareness. Other signs can include decreased responsiveness, apathy, flat affect, and withdrawal from surroundings. Clinicians may blindly assume that the patient's slowed mentation or confusion is baseline and not recognize the acuity of the problem. Prolonged episodes of hypoactive delirium may be mistaken for dementia. Obtaining corroborating history from patient family members or caregivers is essential to establish a baseline mental status and to recognize a change in that status. Maintaining a high-level suspicion for delirium may help avoid medical mistakes.

Treatment

In the case discussed above, the patient was admitted urgently to hospital for delirium likely related to cancer-related malignant hypercalcemia. Her altered level of consciousness and acute cardiotoxic risks necessitated urgent treatment and monitoring. While hypercalcemia was likely the etiology for this patient's symptoms, in most at-risk patients, a single cause is not usually identified but instead due to a number of contributing factors or complications.

Treatment of delirium should focus on identifying and managing the causative medical conditions, providing supportive care, preventing complications, and reinforcing preventive interventions. Pharmacologic interventions should be reserved for patients who are a threat to their own safety or the safety of others and/or for those patients nearing death [4]. In older persons, delirium increases the risk of functional decline, institutionalization, dementia, and death. Caregivers may complain of increased daytime sleepiness and patients may be incorrectly diagnosed with insomnia or sleep apnea. Addition of sedative hypnotics may worsen symptoms and lead to a negative reinforcement loop [5].

Clinical Pearls/Take Home Points

- Delirium is a reversible process that can have a myriad of causes, a single cause is rare, and the process is usually the result of many factors.
- Preventive measures to decrease delirium and early recognition utilizing simple bedside assessment tools can decrease prolonged symptoms and complications for patients at risk.
- Antipsychotic medications should be used as a last resort in treating delirium and should not be used indiscriminately in persons with delirium who have not been rigorously evaluated.
- Avoid benzodiazepine or other sedative-hypnotic use in older adults as first choice for insomnia, agitation, or delirium.

Correct Answers

1. E
2. E
3. B

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