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Sleep Disorders in Women

A Guide to Practical Management

2nd Edition

Humana Press

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Second Edition

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To the memory of my father, Pierre:
May it live in the minds of all those whose lives he touched.

Hrayr P. Attarian, M.D.

To my daughters, who bring the greatest joy to my life.

Mari Viola-Saltzman, D.O.

Series Preface

As already emphasized in the first edition of Dr. Attarian's *Sleep Disorders in Women: A Guide to Practical Management,* which was published in 2005, women are subject to relatively unique sleep disorders some of which occur more frequently and with different clinical features than in men. This remains a very unique book and now, 5 years later, enough new information has accumulated to warrant an expanded second edition on the subject, this time edited by Dr. Hrayr P. Attarian together with his colleague Dr. Mari Viola-Saltzman. Sleep disorders that occur in women are usefully presented in this volume according to the age and stage of a woman's life, a particularly important concept given the endocrine swings which occur during women's lives.

The current volume adds more than ten new authors and includes several new and extensively rewritten chapters to those of the first edition. As expected, the rewritten chapters have been updated and contain many additional references, thereby speaking to the rapidly accumulating information in the field. Two new chapters deserve mention. One of these concerns insomnia during menopausal transition and the other is a guide for the nurse practitioner and physician's assistant. As stated by the editors, *Sleep Disorders in Women: A Guide to Practical Management,* 2nd edition, is designed to introduce primary care physicians and other health care providers to this important area of sleep disorders as they occur in women. Due largely to the efforts of the editors and authors who have contributed to these two volumes, sleep disorders in women are becoming better recognized and more effectively treated.

Boston, MA, USA — Daniel Tarsy, M.D.

Second Edition Preface

Gender bias has long been an issue in medical research, and this bias has translated to the care of patients. Fortunately, it is becoming less prevalent, but it still is a significant problem, especially in conditions traditionally thought of as "male illnesses."

Sleep medicine, a relatively young field, has not been immune to gender bias. It has been a well-established fact that symptoms of obstructive sleep apnea (OSA) do not necessarily differ between genders, yet, until recently, it took twice as long for a woman with OSA to get correctly diagnosed than a man with the same condition. In certain circles, unfortunately, it had been a common practice to attribute any type of sleep symptom in women to a psychiatric illness or related to menopause, which would lead to a delay in diagnosis and treatment.

Thanks to pioneers in sleep research such as Dr. Terry Young and others, these trends are slowly changing. OSA was first described in middle-aged overweight men, and, because it was looked for only in that population group for a long time, no one looked for it in women or other population groups. Certain features associated with OSA unique to middle-aged men were automatically assumed to be applicable to other population groups. However, research in the past 10–20 years has produced a wealth of data regarding the prevalence and uniqueness of sleep disorders in women. The interplay of reproductive hormones, the endocrinological changes that women go through during various life stages, and both normal and disordered sleep is being explored in more depth. Despite all these advances in our understanding of sleep disorders in women, we are still just scratching the surface of this fascinating and multifaceted field.

Sleep Disorders in Women: A Guide to Practical Management, 2nd Edition*,* is divided into five parts. The first part is an overview discussing epidemiology, workup, and normal sleep changes. The next four sections are divided by reproductive stages (adolescence, premenopausal state, pregnancy, and menopause), with chapters in each section devoted to specific disorders such as insomnia, restless legs syndrome, OSA, and others.

In order to write a book that covers the multifaceted aspect of sleep medicine, one needs a multidisciplinary team of specialists. The authors of these chapters are well-respected and well-published researchers and clinicians in this field and come from a variety of backgrounds. *Sleep Disorders in Women: A Guide to Practical Management,* 2nd Edition*,* is intended to introduce primary care physicians and health care providers to the discipline of sleep disorders in women. It summarizes the latest, cutting-edge research and presents it in a succinct and clinically relevant manner. The goal of this book is to help physicians recognize the symptom patterns of sleep disorders in their female patients, guide them in diagnosing and treating these patients in a timely fashion, and help in the elimination of gender bias in sleep medicine research and care.

We hope that *Sleep Disorders in Women: A Guide to Practical Management,* 2nd Edition, will fill an important niche in the medical literature by being the first multidisciplinary, comprehensive review written for physicians on sleep disorders in women.

Chicago, IL, USA — Hrayr P. Attarian, M.D.
Evanston, IL, USA — Mari Viola-Saltzman, D.O.

First Edition Preface

Gender bias in medical research and care is a well-established fact. It has, fortunately, become less prevalent now than in the past, but still is a significant problem, especially in conditions traditionally thought of as male illnesses. Sleep medicine, a relatively young field, has not been immune to gender bias. It has been a well-established fact that symptoms of obstructive sleep apnea (OSA) do not necessarily differ between genders, yet until recently it took twice as long for a woman with OSA to get correctly diagnosed than a man with the same condition. In certain circles, unfortunately, it has been a common practice to attribute any type of sleep symptom in women to a psychiatric illness, which leads to delay in diagnosis and treatment. Thanks to pioneers in sleep research, such as Dr. Terry Young and others, these trends are slowly changing. OSA was first described in middle-aged overweight men and because it was only looked for in that population group for a long time, no one looked for it in women or other population groups. Certain features associated with OSA unique to middle-aged men were automatically assumed to be applicable to other population groups. Research in the past 10–15 years, however, has produced a wealth of data regarding the prevalence and uniqueness of sleep disorders in women. The interplay of reproductive hormones, the endocrinological changes that women go through during various life stages, and both normal and disordered sleep is being explored more in depth. Despite all these advances in our understanding of sleep disorders in women, we are still just scratching the surface of this fascinating and multifaceted field.

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In order to write a book that covers the multifaceted aspect of sleep medicine, one needs a multidisciplinary team of specialists. The authors of these chapters are well-respected and well-published researchers and clinicians in this field and come from a variety of backgrounds, making the book multidisciplinary.

Sleep Disorders in Women: A Guide to Practical Management is intended to help introduce primary care physicians and health care providers to the multifaceted discipline of sleep disorders in women. It summarizes the latest, cutting-edge research and presents it in a succinct and clinically relevant manner. Its goals are to help physicians recognize the symptom patterns of sleep disorders in their female patients, guide them in diagnosing and treating these patients in a timely fashion, and help in the elimination of gender bias in sleep medicine research and care.

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Chicago, IL, USA Hrayr P. Attarian, M.D

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Part I
Overview

Chapter 1
Introduction

Hrayr P. Attarian

Sleep complaints, in general, are common in the health care field, and they are twice as prevalent in women [1]. Women with sleep disorders have been persistently under diagnosed. This is primarily owing to a strong gender bias when it comes to both diagnosing and researching sleep disorders [2], and partially because of a difference in the way symptoms are perceived by women as opposed to men [3]. Furthermore, most representative norms are from studies based primarily in men, while there are clearly established gender differences in both normal and abnormal parameters [4–6]. This is because there are important (and well recognized) sleep-related physiological differences in women.

Women are generally underrepresented in sleep and sleep disorders research. Until a decade ago, 75% of sleep research had been conducted in men [7]. This has fortunately started to change, especially after the National Sleep Foundations 2007 Sleep in America poll which focused primarily on women [8–10]. The past 4 years have produced a wealth of information on various sleep disorders and their particular impact on women. Despite this "boom" in medical literature, the majority of women with sleep disorders go undiagnosed [11]. With this rapid increase in new information and the continued gender discrepancy, a second edition of this book was planned. This new edition includes an updated chapter on the epidemiology of sleep disorders in women. It discusses and summarizes the latest research results from around the world, primarily prevalence of insomnia in women in several countries, and gender differences in the prevalence of parasomnias, restless legs syndrome (RLS), and sleep-related breathing disorders (SBD), particularly obstructive sleep apnea (OSA).

It is a clearly established fact that sex hormones influence sleep and circadian rhythms, and sleep in turn affects the episodic secretion of gonadotropin hormones [12, 13]. Gender-related differences in sleep and its regulation therefore influence

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the risks for and mechanisms of sleep disorders [14]. Physiological changes that occur during puberty, the menstrual cycle, pregnancy, and menopause can have profound effects on sleep quality, daytime functioning, and quality of life in women from adolescence throughout adulthood [14]. In the overview section of this volume (Part I), there are updated and expanded chapters on the impact of different endocrine and other physiological changes both on sleep and sleep disorders.

Starting with menarche, there are distinct differences in sleep patterns and susceptibility to sleep disorders between the sexes. Although the male preponderance of OSA is present in the prepubertal stage [15], both insomnia and hypersomnia become more prevalent in females after puberty, and there are distinct differences in adolescent circadian rhythm changes between boys and girls [16–18]. We have included a section on adolescent sleep (Part II), with an expanded and updated chapter on circadian dysrhythmias and hypersomnia around and shortly after menarche and a completely rewritten chapter on insomnia in adolescent girls.

The higher prevalence of insomnia, hypersomnia, and RLS remains higher in women throughout their adult life. Although OSA in premenopausal, nonpregnant women is much less prevalent than in men of the same age, in the setting of polycystic ovarian syndrome (PCOS), the risk of OSA significantly increases and treatment of one condition impacts that of the other [19]. In addition, a rare but unique disorder called menstrual hypersomnia can be quite disabling and yet responds very well to hormonal treatments [20]. Recently, a few studies have also concentrated on gender differences in parasomnia presentations and treatments [21]. In Part III, we have updated and expanded chapters discussing specifically RLS as it pertains to women, parasomnias from women's perspective, nonhormonal insomnia treatments as they pertain to women, hypersomnia in women, and two chapters on OSA in women (one in premenopausal and nonpregnant population and the other in those with comorbid PCOS).

Another arena where there has been a significant increase in research is sleep and its disorders in pregnant women. Poor sleep quality both in early and late pregnancy, for example, is associated with preterm birth [22]. Untreated OSA is also associated with preterm birth [23], and the risk of OSA dramatically increases during pregnancy (prevalence of about 25%) [24]. OSA also increases the risk of small for gestational age infants, lower birth weights, births with lower Apgar scores, more caesarean sections, and maternal preeclampsia [23]. Another sleep disorder whose prevalence dramatically increases during pregnancy is RLS. Multiple studies from all over the world have reported significantly increased prevalence of RLS in pregnant women and an equally dramatic improvement in its symptoms after delivery. Although the pathophysiology is unclear, it may be due to a combination of high estrogen and altered iron metabolism [25]. OSA and RLS are not the only causes of sleep disturbances in pregnancy; over half of pregnant women complain of poor sleep in the third trimester [26]. History of sleep disruptions in late-stage pregnancy is associated with a higher incidence of postpartum blues [27].

Thus, this volume includes updated and expanded chapters that specifically discuss insomnia and sleep disturbances in pregnancy, OSA and other SBD in pregnant women, and RLS during pregnancy with a focus on treatment modalities as

pharmacological agents are usually not recommended because of risk of teratogenicity. All these chapters are found in Part IV.

Many women during the menopausal transition (perimenopause, menopause, postmenopause) complain of sleep disturbances [28], some of which are attributed to hot flashes, night sweats, and other health variables associated with menopause [29]. Insomnia is reported in about 42% of menopausal women [29]. A host of papers have been published recently looking at various treatment options including hormonal treatment (HRT), pharmaceuticals, and holistic interventions like yoga, massage, and herbs [30–33]. In our section on Menopause (Part V), we have added a new chapter on the practical management of insomnia in menopause and updated and expanded the chapter on the pathophysiology of insomnia in perimenopausal women. Menopause may also be a significant risk factor for OSA [34]. It has been suggested that one of the reasons for this increased prevalence of OSA in postmenopausal women is sex hormone deficiency [35]. Some studies have shown that women on HRT might be at lower risk [36, 37]. Given the obvious concerns about risk of other diseases associated with HRT, it is to be used cautiously. To address these controversies and other associated with menopause and OSA, we have included an updated chapter on OSA and menopause. RLS also becomes more prevalent both with age and menopause, which also tends to be less prevalent with HRT [38]. We have an updated chapter on menopausal RLS addressing the pathophysiology and treatment of RLS in menopausal women.

The last several years have seen an increase in the number of mid-level primary care providers (nurse practitioners and physician assistants). An updated overview chapter geared toward these mid-level professionals is included in this volume in order to help individuals in these professions best diagnose and treat sleep complaints in women.

We hope that this updated and expanded second edition will be helpful to health care providers managing the myriad of sleep disorders in their female patients and that it will also increase the awareness of these disorders in a population in whom they are often missed.

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Chapter 2
Epidemiology of Sleep Disorders in Women

Hrayr P. Attarian

Historical Perspectives

Sleep medicine as a field was not established until the early 1970s after the discovery of obstructive sleep apnea syndrome (OSAS) in Europe in 1965 [1, 2] and the establishment of the first sleep laboratory at Stanford in 1972. The term "polysomnography" was coined by Dr. Jerome Holland at Stanford, in 1974, to describe the studies that were done during all night sleep.

In the early years of sleep medicine, sleep centers concentrated on diagnosing and treating OSAS and, less frequently, Narcolepsy. Both conditions were thought rare; in fact, OSAS was initially described as a rare disorder of overweight men.

We now know that OSAS is a very common disorder that affects both men and women (premenopausal women less than postmenopausal women) and can affect both overweight and normal weight people.

Restless legs syndrome (RLS), another well-described sleep disorder, was thought of rare until recently as well, and now is known to be quite prevalent especially in women.

In addition, the increased recognition and acceptance of insomnia, a condition more prevalent in women, as a sleep disorder in its own right have established the fact that sleep disorders are quite common and are not gender-specific disorders of the male population.

The recent findings of the association of sleep duration and mortality have shown some gender differences as well, with both sexes having higher mortality if they slept 5 or less hours or 10 or more hours but these extremes of sleep were only a risk factor for cardiovascular morbidity and mortality in women [3].

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Below I will discuss the prevalence of the complaint of difficulty sleeping and excessive daytime sleepiness (EDS) in women. I will also discuss the gender differences in the prevalence of the two most common sleep syndromes: OSAS and RLS.

Insomnia

The complaint of insomnia is more prevalent in women. Several studies looking at different aspects of insomnia have confirmed this fact. Bixler et al. in 1979 published the results of their survey of 1,006 Los Angeles metropolitan area where they looked at the prevalence of sleep disorders in general. They found a 42.5% prevalence of insomnia. Trouble falling asleep was 14.4%, and difficulty with frequent nighttime awakenings was 22.9%. Women, especially postmenopausal women, were more affected than men [4]. Karacan and colleagues also reported a similar prevalence in their community survey, with again a female preponderance [5]. Liljenberg et al. surveyed randomly selected members of the population aged 30–65 years from two geographically different rural parts of central Sweden: 7.1% of the women and 5.1% of the men reported difficulty in falling asleep; 8.9% of women and 7.7% of men reported trouble with nocturnal awakenings. Using a stringently defined concept of insomnia as a disorder of initiating sleep (DIS), the prevalence rate of insomnia among women was 1.1%, and among men it was 0.5%. Defining insomnia as a disorder of maintaining sleep (DMS), the prevalence among both women and men was 1.1%. Defining insomnia as a disorder of initiating and maintaining sleep (DIMS), the prevalence rate was 1.7% among women and 1.4% among men. Liljenberg concluded that the reason for the lower prevalence of insomnia in this study was because they used more stringent criteria for the definition of insomnia [6]. Morgan et al. surveyed 1,023 randomly chosen elderly members of the community in Nottinghamshire, England, and discovered subjective insomnia at least "sometimes" in 37.9% of the sample, with women having a higher prevalence than men [7]. For example, in Sweden, Liljenberg reported the following in 1988: Females significantly more often reported difficulty in falling asleep (7.1% of the women and 5.1% of the men). Among women 8.9% and among men 7.7% of individuals reported trouble with nocturnal awakenings. Using a stringently defined concept of insomnia as a DIS, the prevalence rate of insomnia among women was 1.1% and among men it was 0.5%. Defining insomnia as a DMS, the prevalence among both women and men was 1.1%. Defining insomnia as a DIMS, the prevalence rate was 1.7% among women and 1.4% among men [6]. In one Brazilian town, the prevalence of insomnia was 38.9%, being higher among women (45.3%) than among men (28.8%) [8]. In Hong Kong, females were found to be about 1.6 times at higher risk for insomnia than males [9]. In Kuwait, it was found that 14.6% of boys and 20.3% of girls reported difficulty initiating sleep, while 8.6% of boys and 15.7% of girls reported difficulty maintaining sleep. Girls had higher mean scores in most of a 12-point insomnia scale items [10]. In Germany, the prevalence of severe insomnia was found to be 5% in women vs. 3% in men [11]. Over the years, multiple other survey-based studies have

come up with robust data to support the increased prevalence of insomnia in women in different adult population groups in several other countries as well and among the elderly [12, 13] (the Netherlands, Greece, the UK, India, Japan, France, Spain, Korea, Sweden, Canada, China) [14–26]. Women are also more likely to use sleep aids for insomnia and have more insomnia-related depression [27].

National Sleep Foundation started their annual polls in 1995, and every year they have demonstrated about 1.5–2/1 female to male preponderance of different insomnia complaints. The poll of 2007 focused primarily on women and their sleep habits. They phone surveyed a random sample of 1,003 women ranging from 18 to 64 years old between September 12 and October 28, 2006, and 29% of women reported rarely if ever getting a good night's sleep, with an additional 32% reporting a good night's sleep only a few times a week. Sixty-seven percent reported having sleep problems at least a few nights a week, while 46% reported it happening almost every night. Among the respondents, 11% had the diagnosis of insomnia and 7% were being treated for it, but full 29% used some sort of sleep aid every night or almost every night. The older the women the more likely it was that they suffered from insomnia. Other risk factors included menopause, pregnancy, RLS, snoring, and other medical problems. A study in Japan surveyed 555 nurses for symptoms of insomnia. The prevalence of insomnia among shift-working nurses (29.2%) was three to four times higher than that in the general population [28]. That out of 522 female staff nurses those with insomnia had increased tobacco use compared to those who slept well [29]. Substance use was also reported in a US study among shift-working nurses with insomnia [30]. Shift work in women is therefore a significant risk factor for insomnia and subsequent tobacco and alcohol use. More women complain of ambient noise-related sleep disruptions than men (78.3% vs. 48.6%) as shown in an Indian study of the impact of noise in urban areas on health [31], and women's sleep is more prone to disruption due to job-related stress [32]. Lastly, single women have more complaints of insomnia than partnered ones according to a US survey of a multiethnic middle age group [33]. Short sleep duration is also associated with central obesity in young women as shown by Theorell-Haglow et al. [34]. African American women were more likely to have poor sleep objectively than Caucasians or Asian Americans after adjusting for other variables [35].

It is therefore clearly established that insomnia is a much more prevalent complaint in women than men. This gender difference seems to be present only in adolescents [36] and adults. A few studies looking at the prevalence of insomnia in prepubertal children have not demonstrated this gender difference [37–40]. This could very well be due to hormonal changes occurring during the menstrual cycle, during pregnancy, and after menopause. It has been well documented that there is an increase in subjective sleep complaints during the late luteal phase [41], and dysmenorrhea is associated with decreased sleep efficiency and worsening daytime functioning [42]. Luteal phase is also associated with increased mood problems [41]. Due to both unique hormonal changes and mechanical problems (including backache, urinary frequency, heartburn, fetal movement, and spontaneous awakenings), significant number of women experience insomnia during pregnancy [43]. Insomnia starts becoming prevalent in the 23–24 weeks of gestation. By the third trimester, only

1.9% of women fail to experience nocturnal awakenings [43]. This is indirectly reflected in studies from Europe that show increasing use of benzodiazepines as pregnancy progresses (8.3% in the first trimester, 14.2% in the second trimester, and 23.7% in the third). These papers, however, do not differentiate between benzodiazepine use for insomnia vs. anxiety [44, 45].

Despite the complaint of insomnia, partially due to napping and partially due to "sleeping in," there is an overall increase in total sleep time in pregnancy despite a reduction in sleep efficiency. A mean increase in sleep duration of 0.7 h during the first trimester, compared to the prepregnancy period, has been reported, and a mean increase of more than 30 min of total nocturnal sleep time was recorded at 11–12 weeks of gestation in 33 women who underwent in-home polysomnography prior to conception and during each trimester of pregnancy [43]. Shorter sleep duration in the first year postpartum is also associated with increased adiposity up to 3 years postpartum in the form of higher waist circumference and higher retention of pregnancy weight [46]. And, lastly, there is a high level of sleep disturbance (42–54%) [47–50] in menopausal women. The odds of complaining of severe insomnia was 2- to 3.5-fold higher in menopausal women compared to premenopausal women, and hysterectomy specifically is an independent risk factor for insomnia [51]. Insomnia worsens as menopause progresses [52]. Caucasian menopausal women have slightly higher chance of sleep maintenance issues, but there are no real significant differences across different ethnic groups when it comes to overall prevalence of insomnia in menopause [53, 54].

Insomnia was associated with higher levels of anxiety, depression, stress, higher systolic and diastolic blood pressures, greater waist/hip ratios, and significant economic burden in the form of absenteeism, consumption of medical services, and decreased productivity [55].

Although cross-sectional analyses indicate that sleep disturbance may be independent of menopausal status, transition into postmenopausal status is associated with deleterious changes in sleep among women, and it is unclear whether receiving hormone replacement therapy prevents this [47, 49]. Interestingly, when subjective and objective sleep measures were compared in peri- and postmenopausal women, perimenopausal and postmenopausal women, relative to premenopausal women, were less satisfied with their sleep, but did not have diminished sleep quality measured by polysomnography [56]. In conclusion, although prevalence rates of insomnia varies from study to study (depending on the definition of insomnia used) and from one geographical area to another, the female preponderance is always the one constant.

Hypersomnia or Excessive Daytime Sleepiness

The complaint of hypersomnia, regardless of cause, is more prevalent in women as well. This has been confirmed time and time again in different populations around the world. One of the most important studies done in Sweden showed a prevalence of EDS 23.3% in women and 15.9% in men despite the fact that women generally

reported longer total sleep time. They also looked at psychological status and discovered a higher prevalence of anxiety in women; however, this alone was not enough to explain the more prevalent complaint of EDS [57]. A Japanese study showed a prevalence of EDS 13.3% in women and 7.2% in men [58]. Similar results of a higher prevalence in women were found in Brazil [59]. This gender difference appears to be a phenomenon of the adolescent and postadolescent population. Adolescent girls reported slightly but significantly more sleep per night than boys (5–20 min) according to two-cross sectional surveys of adolescents [60, 61], while in another study that followed 3,134 adolescents for 1 year the female sex was one of the risk factors for curtailed sleep [62, 63].

These two findings may not be as contradictory as they appear on the surface, as girls may need to sleep more but because of societal restrictions are getting less sleep than their male counterparts. Studies from other countries have shown curtailed sleep time in preadolescent boys vs. girls or no difference between the sexes, suggesting a cultural component to the number of hours of sleep children get [64, 65].

Long sleep duration in middle aged women, but not in men, is a risk factor for weight gain as demonstrated in a Finnish public health study that followed 7,332 individuals for up to 7 years [66]. This also could be due to middle aged women being more sleep deprived than their male counterparts, therefore reporting longer catch up sleep. In the elderly group, women who napped regularly or slept more than 9 h a day were at a higher risk for mortality from causes other than cancer [67].

Idiopathic hypersomnia with long sleep time tends to have a female preponderance of 2/1 [68]. Children have not demonstrated this gender difference in the complaint of EDS in various ethnic groups [69]. Even in special groups such as patients with major depression, EDS was more prevalent in women that men; the study was conducted in matched opposite sex dizygotic twins [70]. In pregnancy, EDS is a common first-trimester complaint that may precede the realization of pregnancy [43].

Interestingly though, men tend to report falling asleep unintentionally more than women do. In a survey aimed at Chinese medical students, 20.3% of men vs. 8.8% of women reported habitually falling asleep in class [71].

Obstructive Sleep Apnea Syndrome

In the landmark study published in *New England Journal of Medicine* in 1993, Young et al. studied 602 employed men and women 30–60 years of age. The estimated prevalence of sleep-disordered breathing defined as an apnea–hypopnea score of 5 or higher was found to be 9% for women and 24% for men. They also estimated that 2% of women and 4% of men met the minimal diagnostic criteria for the sleep apnea syndrome (an apnea–hypopnea score of 5 or higher and daytime hypersomnolence). Male sex and obesity were strongly associated with the presence of sleep-disordered breathing [72].

Most population-based studies estimate a sex-specific prevalence of two- to threefold greater risk for men compared with women [73], but little progress has been made in understanding the reasons for the risk difference. This male preponderance has been shown in groups as young as 2–6 years of age where, across three ethnic groups (Caucasian, Black, and Hispanic), boys were 2.9 times more likely to have obstructive sleep apnea than girls [74]. This held true for Chinese preadolescents as well where the prevalence of OSA in boys was 5.8% vs. 3.8% in girls [75], in Brazilian children 7–11 years of age [76], 3/2 in Turkish children 7–13, and in Turkish adolescents (1.5/1) [77].

The role of sex hormones in OSA pathogenesis has been hypothesized to account for this disparity [78]. Clear sex differences in upper airway shape and genioglossal muscle activity during the awake state, in craniofacial morphology, and pattern of fat deposition have been proposed to account for a higher male risk of OSA as well [79]. However, no conclusive findings have emerged [79].

Bixler et al. in 2001 further studied the gender difference in the prevalence of OSA and sleep-disordered breathing (an apnea–hypopnea score of 10 or higher and daytime hypersomnolence). The overall incidence for women was 1.2%, and for men was 3.9%. Premenopausal women had a prevalence of 0.6%, and postmenopausal women had a prevalence of 1.9%. When they further subdivided postmenopausal women into two groups, one on HRT and the other not on HRT, they discovered that the prevalence in the first group was only 0.5% vs. 2.7% in the second [80]. This difference between those with and without HRT (especially estrogen) was also demonstrated in another study in 2003 [81]. Age also has an impact on the prevalence of sleep apnea in women. In the same landmark study, Bixler et al. demonstrated that the prevalence in women 20–44 was 0.7%, in women 45–64 1.1%, and in the age group 65–100 3.1% [80]. Weight also has an impact in increasing the prevalence of OSA in women but not to the degree it does in men. Again, in their study, Bixler et al. demonstrated that women with a BMI of under 32.3 kg/cm^2 had a prevalence of 0.4% and women with BMI equal or more than 32.3 kg/cm^2 had a prevalence of 4.8% [80]. This is in concordance with previous studies that have shown the prevalence among obese women (BMI over 27.3 kg/m^2) to be 3–7% [82, 83]. In contrast, the impact of weight in men is much more pronounced. The prevalence for obese men (BMI over 27.8 kg/m^2) is 40–76.9% [82, 83]. Interestingly enough, this male prevalence is what is seen in a group of women with polycystic ovarian syndrome (PCOS). Women with PCOS have hirsutism, obesity, infertility, and enlarged polycystic ovaries. They also have increased androgen production and disordered gonadotropin secretion; it results in chronic anovulation [84]. Studies have shown an OSAS prevalence of 17%–69.9% (depending on the definition of OSA used) in women with PCOS [84–86]. OSA is independently associated with higher risk of metabolic syndrome (central obesity, hypertriglyceridemia, and low high density lipoprotein [HDL]) in women, both pre- and postmenopause. The prevalence of metabolic syndrome increases from 10.5% in women without OSA to 57.1% in those with severe OSA. Moreover, the apnea-hypopnea index (AHI), the nadir oxygen saturation, and the oxygen desaturation index (ODI) are each independently associated with metabolic syndrome [87].

Habitual alcohol intake also increases the risk of OSA in women by twofolds after controlling for other variables [88]. Compared to men with similar OSA severity, women are heavier users of health care resources because of poor perceived health status and the overuse of psychoactive drugs [89].

Pregnancy is another situation where women are at particular risk for OSA [79]. There are, unfortunately, very few studies addressing this. Twenty-seven percent of otherwise healthy women report snoring in the third trimester [43]. Three hundred fifty pregnant women and 110 age-matched nonpregnant women were surveyed at two US Army hospitals. Frequent snoring was reported in 14% of the pregnant women vs. 4% of the nonpregnant women [90]. Both frequency and loudness of snoring, and episodes of awakening with a choking sensation, appear to increase during pregnancy, with half of the women in one study reporting snoring and 14% reporting choking awakenings at 35–38 weeks of gestation, vs. 37% and 4%, respectively, at 8–12 weeks of gestation [79]. Another survey of 502 Swedish women at the time of delivery found that 23% reported snoring often or always during the week before delivery, whereas only 4% reported snoring before pregnancy. Most of the time, the snoring increased during the third trimester [91]. There is evidence that the impact of pregnancy on snoring resolves within several months after delivery [79].

The high prevalence of snoring and choking awakenings during pregnancy suggests that pregnancy may be associated with OSA; however, there are few data regarding the prevalence of OSA during pregnancy [79]. In the largest reported study, polysomnography was performed in 11 snoring women early in the third trimester. All had an AHI less than 5, although all had evidence of increased upper airway resistance characterized by either crescendo respiratory effort or abnormal sustained increases in respiratory effort, occurring more commonly than in nonsnoring control subjects [92]. The mechanisms underlying the increase in snoring during pregnancy are uncertain, but may include excess weight gain [79], diffuse pharyngeal edema of pregnancy, or the effect of sleep deprivation on pharyngeal dilator muscle activity [79].

In conclusion, OSAS is common in women but not as common as in men. Weight, menopause, age, and endocrine disorders have an impact on increasing the prevalence of OSAS in women.

Restless Legs Syndrome

RLS, one of the most common sleep disorders, was first described in 1,672. RLS is characterized by uncomfortable, tingling, crawling, burning, prickly limb sensations associated with an irresistible urge to move the limbs to obtain relief, typically occurring while sedentary or at sleep onset [93]. Hanson et al. in their series in 2003 found a female to male ratio of 2:1 [93]. These results were replicated in the UK by Van De Vijver et al. in 2004 [94]. Similarly, increased prevalence of RLS in women was found in several other studies [95–97]. This female preponderance, however, seems to be limited to adults as trials among adolescents have not shown a difference

between the sexes (prevalence and correlates of RLS in adolescents). Berger et al. looked at the relationship between parity and increased prevalence of RLS. Nulliparous women had prevalences similar to those among men; the risk of RLS increased gradually for women with one child (odds ratio, 1.98; 95% confidence interval, 1.25–3.13), two children (odds ratio, 3.04; 95% confidence interval, 2.11–4.40), and three or more children (odds ratio, 3.57; 95% confidence interval, 2.30–5.55) [98]. There was also a gradually increasing risk of RLS with increasing age that was demonstrated in all of the above studies [99]. Pregnancy also is a significant risk factor. Pregnant women have at least two or three times higher risk of experiencing RLS than the general population. It develops more frequently during the third trimester and disappears within the first month after delivery in most cases. One of oldest RLS studies reported a prevalence of 19.5% in 500 pregnant women. Four weeks after delivery, only three women still had RLS symptoms [100]. A large Japanese study involving 16,528 pregnant women reported an RLS prevalence of 19.9%. The prevalence of RLS increased with the length of pregnancy: 15% in the first trimester and 23% in the last trimester [101]. Another Italian study of 606 women using more standardized screening questionnaires reported a prevalence of 26.6%, with almost 2/3 of women never having experienced RLS prior to their pregnancy [102].

A similar study from Brazil reported an RLS prevalence of 13.5% in 524 women; 94.4% were in the second or third trimester. RLS prevalence and severity increased by trimester [103]. Yet another large survey of 1,022 pregnant women living in a French town showed that 24% of women were affected by RLS during their pregnancy. The disease was strongly related to the third trimester of pregnancy [104]. Women who had transient RLS during their pregnancy had a fourfold increased risk of developing chronic RLS [105, 106]. These studies were all done in the US and Europe, where the overall prevalence of RLS is estimated to be 10.0%–12.9% [107, 108].

In Asia, the prevalence of RLS is much lower at 3% or less [109–111]. Despite the lower prevalence, the ratio of female to male is high and so is the overall prevalence in pregnancy. One study from India reported a F/M of 7/1 [112]. A Japanese study targeting pregnant women found the prevalence in this particular group to be 19.9% [101].

This increased prevalence of RLS in women and especially its association with pregnancy has been thought to be related to reduced iron, ferritin, and/or folate levels [43]. RLS is much more prevalent in women, especially with pregnancy and menopause, even in ethnic groups where RLS is relatively uncommon.

Periodic limb movement disorders (PLMD), on the other hand, do not have as robust a sex predilection, with isolated PLMD being equal in both sexes [113] while PLMD with RLS is more prevalent in women [114].

Other Sleep Disorders

Not much is available about gender differences in other sleep disorders except for the rare condition sudden unexpected nocturnal death syndrome, which tends to be significantly more prevalent in men. In REM parasomnias for example, REM

sleep behavior disorder tends to be more prevalent in men (M/F = 2/1) [115, 116] while recurrent sleep paralysis and hypnic hallucinations separately or together do not have a gender predilection, and nightmares are more prevalent in women [117–120].

A recent study from Portugal found that girls ages 7–10 had a higher prevalence of bruxism (56.5%) than boys (43.5%) of the same age [121]. In adults, however, there seemed to be no difference between genders in the prevalence of bruxism [122]. Two epidemiologic studies reported higher prevalence of sleepwalking in women [122, 123], but sleep terrors did not show a gender predilection [124], nor did other parasomnias such as catathrenia, sleep eating, and confusional arousals [125].

Circadian rhythm sleep disorders seem to vary with sex as well. Teenage girls reach the peak of their adolescent delay in their sleep phase by age 17 while boys reach the peak by age 21. The prevalence of delay, however, is about the same regardless of gender. Premenopausal adult women, however, tend to have significantly more advanced sleep phase than men of the same age [126, 127].

Conclusion

The complaint of both insomnia and hypersomnia is more prevalent in women. Of the two most common sleep syndromes, OSAS is relatively rare in premenopausal nonpregnant women while its prevalence increases during pregnancy and menopause.

RLS is much more prevalent in women, and that prevalence amplifies as women become pregnant and when they reach menopause. Interestingly, parity itself increases the prevalence of RLS in women even after delivery while RLS exacerbations during pregnancy tend to disappear with delivery.

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Chapter 3
Sleep Disorders in Women: A Guide for the Nurse Practitioner and the Physician Assistant

Nancy I. Resi

Introduction

Sleep disorders are among the most common complaints in the primary care setting [1]. The universal phenomena of sleep should occupy approximately one-third of one's life. While 7–9 h of uninterrupted sleep per night is the norm, the average woman's sleep falls short of the norm at 6 h and 40 min and is often interrupted [2].

The quality and quantity of sleep can be impacted by both hormonal and vasomotor symptoms as well as social issues such as marital, financial, and child care responsibilities. Poor sleep, from either sleep loss or deprivation, may lead to excessive daytime sleepiness and fatigue. Poor sleep is associated with significant health, safety, and economic consequences, considerably impacting one's overall performance at school, in the workplace, social interactions, and quality of life.

Despite the significant socioeconomic impact from sleep disorders, it is often not addressed in the primary care setting [3–5]. Sleep disorders are common, and it is estimated that 35–40% of the population will have difficulty with falling asleep or with daytime sleepiness [4]. At the present time, the United States Preventative Services Task Force, which guides preventive care recommendations, has not advocated for routine screenings of sleep disorders [3, 6].

In the previous edition of this book, the chapter on this subject was authored by Diana Monaghan, PA-C.

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Sleep and Premenstrual Syndrome

Fifty to 80% of women experience premenstrual symptoms (PMS), which may range from mild to severe. Almost 20% of women have severe PMS and another 3–8% qualify for premenstrual dysphoric disorder (PMDD) [7]. PMDD often includes a myriad of symptoms, such as mood changes, behavioral symptoms, and somatic complaints, which can impact work and social relationships [8]. Insomnia, which will be addressed later in this chapter, and hypersomnia are some of the sleep-related changes women experience.

Fatigue, sleepiness, and tiredness are terms which are often used interchangeably. It is, however, important to distinguish between these terms. In 2004, Dittner et al. defined fatigue as "extreme and persistent tiredness, weakness or exhaustion; mental, physical or both" [9]. Sleepiness refers to the perception of one's likelihood of falling asleep [10].

In 2007, Baker et al. investigated both sleep quality and sleep composition in women with PMS using electroencephalography (EEG) [11]. This study revealed that women with severe PMS perceive poor quality of sleep with PMS symptoms in the late leutal phase (LLP) of their cycle. Interestingly, there was no alteration in sleep structure with PMS, and there were no abnormal disturbances of sleep on polysomnogram (PSG).

Following this study, Baker and Colrain [12] evaluated daytime sleepiness and psychomotor performance in women with severe PMS and healthy controls in the LLP compared to the follicular phase of the menstrual cycle. They found that women with severe PMS felt sleepy and fatigued and showed mild psychomotor slowing with PMS symptoms in the LLP. However, these women were able to maintain their cognitive processing skills despite their perception of sleepiness and slower performance in the LLP.

Pregnancy and Sleep

Sleep complaints are more common among pregnant women than their nonpregnant counterparts. According to the National Sleep Foundation, nearly 80% of women reported more disturbed sleep during pregnancy than any other time during their life [13]. Pregnancy is associated with physiologic and hormonal changes and changes in sleep architecture. Pregnant women may suffer from poor quality of sleep, difficulty falling asleep, and frequent arousals which tend to increase after the first trimester [14]. This is often due to the rise in progesterone, leading to excessive daytime sleepiness. Other factors, such as nocturia, inability to assume one's standard position of sleep due to enlargement of the abdomen and low back pain, can also cause sleep disturbances during pregnancy.

Nicotine use stimulates the central nervous system, promoting wakefulness and an increased sleep latency [15]. Pregnant smokers have difficulty with sleep onset,

excessive daytime sleepiness, non-restorative rest, and difficulty awakening. Ohida et al. found that women exposed to passive smoke also have increased difficulty with sleep [16].

Restless legs syndrome (RLS) is also more common in pregnancy. This may be related to low iron storage or hormonal changes [17]. Several studies have shown that pregnancy has a significant impact on the risk for developing RLS for those with a family history of RLS, thus accounting for gender differences in the overall RLS data [17, 18].

The prevalence of snoring in pregnant woman is higher than in nonpregnant woman and reported to be between 14 and 45%. However, the prevalence of obstructive sleep apnea (OSA) in pregnant women is less clear since no large studies have been conducted. OSA in women in the general population is estimated to be 0.7–6.5% [19]. As the general population is becoming more obese, there is an increase in obesity-related conditions such as OSA also complicating pregnancy [20, 21]. There are increased risks for complications in pregnant women with OSA including low birthweight (LBW), preterm birth, small for gestational age (SGA), cesarean section (CS), low Apgar score (at 5 min after delivery), and preeclampsia. Among 66% of pregnant women who report preeclampsia during pregnancy, 32% have premature labor.

There are no pregnancy-specific guidelines for treatment of OSA in pregnancy. Recommendations are based on guidelines for the general population, which include treatment focused on normalizing the apnea hypopnea index (AHI). The standard treatment is continuous positive airway pressure (CPAP), oral appliances, and behavior modification, which will be discussed later in this chapter [22].

Middle Age Women and Sleep

Sleep disturbances are widely reported by middle age women. Both age and the menopausal transition contribute to these sleep disturbances. Much of the research has focused on the relationship between sleep, sex hormones, and body temperature. Kravitz et al. in the Study of Women's Health Across the Nation (SWAN) found that 35% of women age 40–55 years experienced difficulty with sleep [23]. Most of the complaints are related to sleep maintenance insomnia with early morning awakenings. The precipitating factors for this are onset and exacerbation of vasomotor symptoms such as hot flashes, night sweats and cold sweats along with changes in the reproductive hormone levels, particularly follicle stimulating hormone (FSH). It is unclear whether the vasomotor symptoms initiate the arousal or the hot flash occurs after the arousal [24]. This results in older women who spend the same amount of time in bed as their younger counterparts, sleeping approximately 2 h less [25]. Several studies have shown that vasomotor symptoms affect up to 40% of postmenopausal women's sleep [26, 27]. Murphy and Campbell found that elevated lutenizing hormone (LH) levels were correlated with sleep disturbances in women. Perimenopausal women's daytime levels of LH correlated with the number of nocturnal awakenings [28].

Overall, sleep quality may not change during the menopausal transition. However, sleep quantity, which is affected by specific symptoms such as hot flashes and depression, have been associated with menopause [29].

Insomnia

Insomnia is a condition in which individuals have difficulty falling asleep, staying asleep or awakening too early [30]. This equates to a mean sleep onset of greater than 30 min to fall asleep, or a total sleep time of less than 6 h during three or more nights per week [30]. The end result is a poor quality of sleep, which does not allow the individual to feel refreshed upon awakening. Insomnia may contribute to motor vehicle accidents, decreased work productivity and efficiency, absenteeism, and a decreased quality of life [31].

Insomnia is the most chronic sleep complaint in primary care [32]. Unfortunately, many patients do not discuss this problem with their provider, even though one study documented that 75% or responders indicated that they had experienced a problem with sleep several nights per week in the past year [33].

The prevalence of insomnia increases with age. In one study of elderly individuals, 57% had complaints consistent with insomnia and only 12% reported normal sleep [34]. Elderly individuals will often attempt to combat insomnia with over-the-counter medications or alcohol [30].

Adult women are more likely to report insomnia than men. This is often related to vasomotor symptoms and depression. Approximately two-thirds of patients with depression will have insomnia in the form of sleep-onset difficulties [35].

Acute insomnia lasts up to 4 weeks and can be precipitated by work shift changes, major changes in one's life such as the loss of a loved one or daily life stressors such as small children awakening during the night. Air travel (jet lag), especially traveling over time zones, is also likely to cause difficulty sleeping. Symptoms of this are more common when traveling from west to east and in the elderly [36].

Chronic insomnia occurs for a period of time greater than 4 weeks. It is a poor quality of sleep which often presents with daytime symptoms such as daytime fatigue, malaise, irritability, and limited ability to concentrate and recall information [37].

Insomnia is a syndrome, not a disorder. Therefore, the treatment will depend on the underlying cause. Both pharmalogic and non-pharmalogic treatments are indicated for insomnia. However, the mainstay of treatment for insomnia remains good sleep hygiene (Table 3.1) and cognitive behavioral therapy [38].

Obstructive Sleep Apnea Syndrome

OSA is characterized by apneas and hypopneas, lasting at least 10 s. OSA is often associated with aging, obesity, snoring, and excessive daytime sleepiness. Patients may also report difficulty maintaining sleep and/or non-restorative sleep. The lesser

Table 3.1 Sleep hygiene

Maintain a regular sleep schedule
Bed at the same time, up at the same time 7 days per week
Do not use the bedroom for activities other than sleeping or sex
Avoid napping during the day
Avoid exercise no later than 3 h before bedtime
Avoid caffeine after 12 noon
Avoid alcoholic beverages
Do not smoke or use tobacco
If not asleep within 30 min, get out of bed, go to another room and do something calming. Return to bed only when sleepy

Insomnia Case History

S.K., a 38-year-old, divorced mother of a 10-year-old son presented with a 2-year history of difficulty sleeping. She had relocated 6 months earlier to be closer to her parents and brother following her divorce. Most of her life she had slept well; however, following her divorce, she got into the habit of going to bed with a glass of wine to relax. She found that she was able to fall asleep within 1 h but would awaken multiple times during the night worrying about her son.

S.K. had a normal examination. No laboratory tests were indicated.

The patient was advised to avoid all alcohol, caffeine, and exercise no later than 6 h before going to bed at 9:00 pm. She was further advised to use the bedroom for sleep and sex only. If she awoke and could not return to sleep within 30 min, she planned to go into the living room and knit, which was her source of relaxation. When she became sleepy again, she was to return to bed. Additionally, she was started on Ambien 10 mg at bedtime and referred for cognitive behavioral therapy for insomnia.

The patient returned in 4 weeks and was improved. She was able to fall asleep within 45 min of taking Ambien and would awaken only 1–2 times during the night and was able to fall asleep within 15 min. On a subsequent visit, she had stopped Ambien and had only intermittent nights of difficulty sleeping.

severe form of OSA is upper airway resistance syndrome (UARS). This is characterized by increased upper airway resistance which can also lead to snoring and daytime sleepiness [39]. It occurs when the airway narrows causing more subtle hypopneas associated with arousals from sleep [40].

In the past it was believed that OSA was uncommon in women. More recently, studies have shown that OSA affects men twice as much as women [41]. Women are

more affected by UARS than men due to differences in upper airway anatomy. Additionally, it has been estimated that more than 90% of women with sleep apnea are not diagnosed [42].

In terms of reporting, women tend to have higher consumption of health care compared to men; although women with symptoms of OSA may also fail to get feedback from their bed partner [43]. When women are seen for OSA, they report "atypical" OSA symptoms [44]. They often complain of sleep onset and sleep maintenance insomnia [40]. They may also complain of depression, anxiety, leg cramps, and myalgias [40, 43, 45].

The PSG is the gold standard test for diagnosing OSA. This is best accomplished in an attended laboratory setting. Unattended, in-home portable equipment monitoring might be an alternative for some patients. During the PSG, specific measures of sleep architecture, sleep efficiency, respiratory events, and leg movements are studied. The AHI and respiratory disturbance index (RDI) indicate the severity of sleep apnea. The diagnosis of OSA is confirmed if the index is greater than 5 events per hour for mild OSA; moderate OSA is usually an AHI greater than 15 but less than 30, and an index greater than 30 is usually considered severe [46, 47].

CPAP remains the primary treatment for mild, moderate, and severe OSA [47]. However, if OSA is mild, alternative treatment options might be considered. This includes avoiding the supine position during sleep, as OSA is usually more severe in this position due to a gravitational effect. Avoiding alcohol or sedatives before bedtime may also reduce sleep disordered breathing during sleep. Weight loss is another effective treatment. Oral appliances may also be considered and should be devised by a dentist who specialized in sleep medicine. These devices are intended to improve upper airway patency during sleep by enlarging the upper airway and decreasing the potential for collapse. Lastly, surgery may also be an option to reduce obstructions in the nasal and/or oropharyngeal spaces [47].

Restless Leg Syndrome and Periodic Limb Movements of Sleep

Restless leg syndrome (RLS) is a sensorimotor disorder characterized by an irresistible urge to move the legs. RLS symptoms are often difficult to describe and have been also labeled as a painful, burning, itching, tugging, electrical current, restlessness, and/or a creepy-crawling sensation. This sensation occurs predominately during the evening and/or during periods of immobility, and movement tends to relieve it [46, 48]. RLS is a clinical diagnosis and does not require a sleep study to diagnose it

The prevalence of RLS is approximately 2:1 for women compared with men, and it occurs in 5–15% of the population [49]. The cause of primary RLS is unknown. However, 50% of patients have a positive family history, suggesting there is a

genetic basis for the disorder [50]. Secondary RLS occurs due to a number of disorders including iron deficiency, pregnancy, uremia, diabetes mellitus, rheumatic disease, and venous insufficiency [50].

Approximately 80% of individuals with RLS will also have periodic limb movements of sleep (PLMS). In this disorder, limb movements occur every 20–40 s during the night with each jerk causing a brief awakening. Most commonly, it consists of flexion of the knees and hips, dorsiflexion of the foot and great toe, though it can occur in the arms as well. PLMS occurs during non-REM sleep. The bed partner will often be the first to take notice of the disorder. Typically, PLMS symptoms increase with advancing age. The prevalence of PLMS in older adults is 45% [51]. It is also exacerbated by low ferritin and with medications such as tricyclic antidepressants and selective serotonin reuptake inhibitors [49].

Treatment for RLS and PLMS is necessary only when it is clinically significant, or when the symptoms impair the patient's quality of life, daytime functioning, social functioning, or sleep. First-line therapy for RLS and PLMS are the dopamine agonists ropinirole and pramipexole [50]. Patients who have iron deficiency should be treated with iron supplements. Second-line therapy may include carbidopa-levadopa, gabapentin, benzodiazepines, and/or opioids. However, augmentation or worsening of symptoms with an earlier onset may occur in up to 80% of patients using carbidopa-levadopa.

Restless Leg Case History

G.C., a 56-year-old married woman, presented with a 3-year history of leg pain and restlessness. Recently she had flown to Paris on an overnight flight anticipating a full night of sleep. She found, however, that her legs were "wiggly" which prevented her from attaining any sleep. Her normal routine included sleeping 10 h at night and napping 2 h during the day. She reported awakening 3–4 times during the night to urinate. G.C. described her legs as having "small worms crawling under my skin." When this sensation was severe, it would also lead to a painful sensation in the legs. She would bang her legs on the recliner, get up and pace or rub her legs to alleviate these symptoms. Her husband did not notice any jerking or kicking of her legs during the night.

G.C. had a normal exam including muscle stretch reflexes and sensory exam. Thyroid profile and ferritin were within the normal range.

She was started on ropinirole 0.25 mg in the early evening and titrated up her dose to 1.5 mg per night. On reevaluation, she continued to have resolution of her symptoms, was sleeping only 8 h per night, and she no longer required a nap during day.

Narcolepsy

Narcolepsy is a disorder involving the brain's inability to stabilize the sleep–wake cycle. Onset of narcolepsy is typically in adolescence, but it is often not diagnosed until adulthood. Although it affects only 1–2% of the population, it can be a devastating disease. Symptoms of narcolepsy worsen during the first few years and last throughout the lifetime [52].

Narcolepsy is characterized by excessive daytime sleepiness and inappropriate transitions from wakefulness to REM sleep [53]. It may occur with or without cataplexy. Cataplexy is defined as sudden episodes of bilateral loss of muscle tone, usually triggered by strong emotions such as crying or laughter. It often affects the face, neck, and knees. Cataplexy is pathognomonic for narcolepsy, and the presence of it requires no further diagnosis. Nacoleptics may also complain of hynagogic/hypnopompic hallucinations, REM sleep behavior disorder (or the abnormal enactment of dreams), and/or sleep paralysis. Hypnagogic/hypnopompic hallucinations are vivid, often frightening perceptual experiences which occur during the transition time between sleep and wakefulness. Sleep paralysis causes a panicked sensation in an individual because they feel as if they are paralyzed when waking from REM sleep [50].

Diagnosis of narcolepsy includes an overnight PSG with at least 6 h of sleep, followed by a multiple sleep latency test (MSLT). Even those presenting with cataplexy, usually undergo these studies for insurance documentation purposes. Stimulants and psychoactive medications should be stopped for 7–10 days prior to the study. Antidepressants, such as SSRIs should also be stopped for at least 2 weeks prior to testing to avoid REM rebound effects [51]. The PSG may show spontaneous awakenings, decreased sleep efficiency, and an early REM sleep onset. The MSLT, which is performed the day after the PSG, consists of 4–5 nap periods. Patients with narcolepsy will have a mean sleep onset latency of less than 8 min. In addition, 2 or more of the nap periods need to demonstrate REM sleep to establish the diagnosis of narcolepsy [50].

Narcolepsy is treated with pharmacologic agents which promote wakefulness such as modafinil, methylphenidate, or amphetamine derivatives. Sodium oxybate may be useful to improve cataplexy and excessive daytime sleepiness and consolidate REM sleep [50, 54]. However, it is a salty liquid that needs to be administered twice at night, once at bedtime and then the patient must set an alarm to wake up a few hours later to take the second dose. Antidepressants, such as venlafaxine, are also used to treat cataplexy [50, 54]. Nonpharmacologic therapy with regular bedtimes and short nap periods during the day will also improve alertness.

Conclusion

Sleep disorders place a significant burden on overall health and well-being. A large number of women with sleep disorders remain undiagnosed. If a patient has a concern about sleep, it often goes unmentioned or will be brought up at the end of the

visit. This is compounded by the fact that sleep is not routinely screened for in the primary care setting [3, 55]. Awareness of sleep disorders in women, who often have unique clinical presentations, should be increased and addressed.

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Chapter 4
Life Cycle Impact on Sleep in Women

Margaret Moline and Lauren Broch

Introduction

Across the life cycle of women, the quality and quantity of sleep can be markedly impacted by both internal (e.g., hormonal changes and vasomotor symptoms) and external (financial, marital, and child care responsibilities) factors. This chapter will outline some of the major phases of the adult life cycle in women that have been associated with sleep problems. The main messages from this chapter include that sleep disturbance and sleep disorders are common in women and increase across the lifespan for a variety of reasons; once identified, the sleep problem is generally best addressed by the standard therapeutic approach, although special cases arise in pregnant and lactating women due to concern for the fetus and child; and little systematic, large-scale research has been performed in virtually every area reviewed. This chapter is organized into sections that address sleep problems associated with the menstrual cycle, pregnancy, postpartum, and the perimenopause.

Anecdotal reports recommend treatment that addresses specific physical discomforts experienced by women at many of these phases (e.g., analgesics for premenstrual pain, pregnancy pillows for backache, hormone replacement therapy (HRT) for hot flashes). The importance of developing standard treatment recommendations is stressed, especially since the development of chronic insomnia has been linked to precipitating events. In addition, primary sleep disorders (e.g., sleep apnea, restless legs syndrome, RLS) have been shown to increase during pregnancy and menopause, but treatment recommendations may be contraindicated for pregnant women. Thus, there may also be the need to develop unique therapeutic strategies for women [1].

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Sleep Disruption Related to the Menstrual Cycle

Studies of the influence of phase of the menstrual cycle on sleep began in 1966 with the paper by Williams' group [2]. The literature since that time continues to be limited and contradictory, in part due to numerous methodological issues that make designing studies in this area a challenge. Lee and Shaver [3] discussed many of these methodological factors, including:

defining menstrual phases, considering menstrual cycles are not uniform in length both among women and between consecutive cycles;
documenting the timing of ovulation, demarcating follicular from luteal phase;
a wide age range in the perimenopausal interval;
oral contraceptives use;
life situations.

Parry and colleagues [4] and Shechter and Boivin [5] also highlight the inconsistency of results due to methodological issues. For example, the sleep of a woman with normal menstrual cycles and young children at home may differ from that of a woman without children [6]. This may translate into differences observed in the laboratory between "normal" cohorts and clinical populations studied in treatment trials. In addition, many studies of women across the menstrual cycle have included only small numbers of subjects [6, 7].

The International Classification of Sleep Disorders (ICSD) lists several sleep disorders related to the menstrual cycle in their own category: Menstrual-Associated Sleep Disorder. These include premenstrual insomnia, premenstrual hypersomnia, and menopausal insomnia. The rationale for the latter category is not clear since, by definition, menopausal women have no menstrual cycles. Schenck and Mahowald [8] recommended adding another disorder, premenstrual parasomnia, to the category based on their clinical observations.

Despite the inclusion of premenstrual insomnia in the ICSD, Manber and Armitage [7] discussed the lack of research on this entity. In apparently the only research study focusing on this issue, Manber's group [9] used sleep logs and actigraphy to study women with psychophysiological insomnia across the menstrual cycle. They found that daily irregularity in the insomnia pattern outweighed any menstrual cycle effect. A case report [10] documented a phase delay in core temperature in association with premenstrual insomnia. More research will be required to validate this diagnosis.

Menstrual cycle influences on sleep have been reported in survey studies of women and by women with premenstrual syndrome (PMS) [11]. One report suggests that the perception of sleep quality declines premenstrually and in the early follicular phase without an impact on sleep continuity [12]. Irregular menstrual cycles have also been associated with more subjective reports of sleep difficulties, including insomnia [13].

Survey studies [14–16] suggest that the late luteal phase may be associated with more frequent subjective sleep disturbances, including restless sleep, sleep disturbances, unpleasant dreams, and unrefreshing sleep, even in women without PMS. As reviewed by Baker and Driver [17], studies report that subjective sleep

quality is lowest before and during menses. PMS is a common problem characterized by mood and/or physical symptoms that appear regularly in the luteal phase and remit during or shortly after the onset of menses. Severe, predominantly mood and anxiety symptoms that markedly impact a woman's ability to function at home or the workplace or in her relationships with others can lead to an additional diagnosis, premenstrual dysphoric disorder (PMDD). PMDD is a psychiatric diagnosis, listed under the affective disorders. It is classified in the DSM-IV-TR as "depressive disorder not otherwise specified."

Sleep complaints, either insomnia or hypersomnia, are prominent in this disorder. Women with PMS and PMDD report sleep-related complaints including "insomnia, hypersomnia, tiredness or fatigue, disturbing dreams or nightmares, lethargy, and inability to concentrate" [18]. In a recent paper, women with severe PMS reported subjective sleepiness and fatigue, with psychomotor slowing on symptomatic days compared to their symptom-free intervals and to control women [19]. However, objective measures of sleepiness in that study did not show significant group or phase of cycle differences.

Since PMDD may be a variant of an affective disorder, and since patients with major depression have well-characterized sleep abnormalities, the sleep of women with premenstrual conditions was compared to women with major depression. There are also suggestions that women with PMDD may have underlying circadian rhythm abnormalities in temperature [20, 21], in melatonin [22, 23], or in the coupling of rhythms [24] that could impact sleep.

There has been limited research using polysomnography across the menstrual cycle [14, 15, 22, 23, 25–29]. Several of these groups did not report major reproducible differences in sleep architecture in women, with PMS/PMDD compared to control women or in the control women themselves [30]. Driver and colleagues [25] reported an increase in spindle frequency during the luteal phase. A recent study by Shechter and colleagues [31] used polysomnography to study eight healthy controls during the mid-follicular and mid-luteal phases. While they found small statistically significant increases in sleep onset latency and decreases in percent of REM sleep, they concluded that sleep homeostasis is unaffected by the menstrual cycle. As reviewed by Shechter and Boivin [5], there exist important methodological issues that need to be addressed, in addition to larger numbers of patients participating in clinical studies. Taken together, it appears that there are no clear menstrual cycle changes in sleep architecture [30] with the timing and composition of sleep relatively stable across the menstrual cycle in healthy women. Further, the sleep of women with PMS does not share the key features of sleep of depressed women.

However, women do complain of difficulty sleeping in the premenstrual phase, often in parallel with other symptoms [30]. There have been no definitive clinical trials that have specifically addressed the treatment of women with premenstrual insomnia [32]. Thus, the management of disrupted sleep in this population should be similar to the treatment of sleeping problems at other times. Consideration should also be given to addressing physical symptoms such as pain, headache, and bloating

that may make the patient uncomfortable. Limiting caffeine and salt intake and consuming frequent small meals have been reported often as behavioral measures for common premenstrual symptoms of insomnia, bloating, and food craving, respectively [33]. While there are few supporting data for these recommendations, nevertheless they may be helpful in mitigating difficulty falling asleep due to caffeine or acid reflux, for example. Regular aerobic exercise has some research support as a treatment for some symptoms of PMS [33], but exercise should be avoided too close to bedtime [34].

Treatments for PMS/PMDD such as the selective serotonin reuptake inhibitors may also be effective in reducing sleep complaints, although their specificity in addressing insomnia (or hypersomnia) per se has not been reported to date [32].

Another important disorder related to the menstrual cycle that may impact sleep is dysmenorrhea. Dysmenorrhea refers to severe pain associated with menstruation. It can also include painful cramping before the onset of menstrual flow. Dysmenorrhea is common, but apparently only one paper on this population has been published in the sleep literature [35]. Subjects with dysmenorrhea reported more subjective fatigue than control subjects. Given that pain can contribute to insomnia [36], therapeutic interventions for dysmenorrhea may ameliorate the sleep complaints, a question that should be addressed in controlled research studies.

Several reports describe hypersomnia episodes that were temporally linked to the menstrual cycle [37–39]. However, there have been no definitive clinical trials that have specifically addressed the treatment of women with premenstrual hypersomnia.

As mentioned previously, premenstrual parasomnia is not currently listed in the ICSD. Schenck and Mahowald [8] described two female patients who each had sleep terrors and injurious sleepwalking that were linked to the premenstrual phase. With treatment, one by self-hypnosis and the other by self-hypnosis and medication, symptoms were decreased. To date, however, there have been no definitive clinical trials that have specifically addressed the treatment of women with premenstrual parasomnia. However, if the behaviors occurring during the episodes are dangerous, benzodiazepine medication (the standard treatment for parasomnias) might be considered. Clinicians who encounter female patients past menarche with complaints of parasomnias will hopefully inquire about the temporal association of symptoms with menstrual cycle events to help establish the clinical validity of this diagnosis.

Sleep Problems During Pregnancy

While pregnancy, childbirth, and postpartum can be fulfilling and exhilarating experiences for women, these periods are also fraught with considerable sleep disruption. Reports of altered sleep during pregnancy range from 13 to 80% in the first trimester and increase to 66–97% by the third trimester [40–42]. The marked rise in gonadal steroid hormones during the first trimester and the added physical discomfort associated with the growing fetus during the second and third trimesters are obvious reasons

for sleep disturbance. The addition of the diagnosis of Pregnancy-Associated Sleep Disorder in the ICSD validates sleep difficulties during pregnancy. However, as Santiago and colleagues point out [43], physicians may presume a sleep problem is due to normal physiologic changes during pregnancy and overlook the possibility of a primary sleep disorder such as sleep apnea or RLS.

Sleep research during pregnancy has been limited by varying data collection procedures, small and often nonrepresentative samples, poorly controlled studies, pooled data that may obscure individual variation, cross-sectional designs, and studies that are descriptive rather than hypothesis-driven. Unfortunately, few generalizations exist beyond women's almost universal complaints of disrupted sleep and fatigue during the first trimester, varying degrees of a grace period in the second trimester, and substantial sleep disruption during the third trimester and postpartum. As Lee [44] discusses in a comprehensive review of the literature, research on sleep during childbearing has received little attention since the pioneering work of Karacan and colleagues in the 1960s [45]. Furthermore, little to no research exists on possible treatments for sleep disruption and safe, effective treatment of primary sleep disorders during pregnancy and postpartum.

Subjective studies during pregnancy [40, 41] find that the most common reasons cited for altered sleep are dependent upon the trimester. In the first trimester, women complain of nausea and vomiting, urinary frequency, backaches, and feeling uncomfortable and fatigued. By the second and third trimesters, fetal movements, heartburn, abdominal discomfort, cramps or restless legs, and shortness of breath are also reported. In addition to physical discomfort, women report that emotional concerns such as dreams about the fetus and anxiety over the eminent change in lifestyle are playing a role in pregnant women's insomnia. A most provocative finding in the Mindell and Jacobson's study [41] was that despite the fact that virtually all women at the end of pregnancy reported poor sleep, only one third of women considered they had a current sleep problem. The authors suggest that pregnant women may resign themselves to poor sleep because they believe it is an expected and perhaps untreatable part of pregnancy.

Both subjective and objective studies mainly concur in showing that, early on in pregnancy, most women become sleepier and their nighttime sleep may become more disrupted. Mean sleep durations are between 7½ and 8½ h, and total sleep time (TST) increases roughly ½ to 1 h per day when compared to pre-pregnancy levels. As the pregnancy progresses, however, sleep becomes more fragmented, with a resulting decrease in TST back to pre-pregnancy levels and lower by the end of pregnancy. Hedman and coworkers [46] surveyed 325 pregnant Finnish women and found an interaction between trimester and mean hours of total self-reported sleep, with women reporting sleeping 8.2 h in the first trimester, 8.0 h in the second trimester, and 7.8 h in the third trimester. Studies of the sleep architecture of the pregnant woman demonstrate increased stage one sleep (light sleep), increased awakenings, and reduction in REM sleep [42]. While findings regarding slow wave sleep are equivocal [44], objective sleep studies confirm the universal complaints of disrupted sleep, particularly as the pregnancy progresses, in showing increased wake after sleep onset.

To compensate for disrupted nighttime sleep and the soporific effects of rising hormones, pregnant women alter their sleep habits by sleeping later, especially on weekends, and napping more often. Studies agree that the most commonly endorsed complaints are of physical discomfort, but reported prevalences of sleep problems can vary widely and depend to some degree on the format of the survey studies (e.g., self-report, questionnaires, sleep logs, Likert scales). Although hormonal and physical changes contribute profoundly to sleepiness and sleep disruption, age, parity, and history of mood disorders can affect sleep as well [44]. Alterations in sleep and wake schedules, anxiety, and primary sleep disorders also contribute to an unknown extent.

The treatment of sleep problems during pregnancy consists primarily of addressing the specific physical discomfort experienced by the woman (e.g., backache, nausea, urinary frequency). Anecdotal reports from pregnant women suggest that certain interventions—such as a reduction in spicy foods and caffeine, sleeping with the head elevated and taking antacids for heartburn, a reduction of fluid intake in the evenings to decrease nocturia, pregnancy pillows and side sleeping positions for back discomfort—may improve a pregnant women's sleep. Stress-related insomnia during pregnancy has not been studied; however, general recommendations include meditation, stress management therapies, and psychotherapy to relieve anxiety and depression that may be associated with pregnancy.

In studies of nonpregnant women and in men, it has been shown that alterations and irregular sleep schedules such as napping or sleeping later in response to sleep disruption may result in the development of poor sleep hygiene and conditioned anxiety over the sleep process, which in turn may contribute to a more chronic form of insomnia in some women. However, there are no behavioral studies showing that poor sleep hygiene in pregnant women results in a more lasting insomnia or that good sleep hygiene treatment, on the other hand, benefits the pregnant woman. The most obvious reason for the lack of behavioral treatment studies in pregnant women is due to the possible deleterious effects of pharmacotherapy on the developing fetus but likely also to the false belief that sleep problems during pregnancy are inevitable and untreatable.

For similar concerns regarding the developing fetus, little research exists regarding sleep aids. In one of the earliest survey studies [40], 12% of pregnant women reported using sleep aids. It is likely that fewer women now take sleep medication, since medication recommendations during pregnancy have become more stringent. A Medline search of literature between 1966 and 2011 [47] revealed that the currently available literature is insufficient to determine whether the potential benefits of benzodiazepines to the mother outweigh the potential risks to the fetus. In fact, recommendations regarding the use of over the counter or prescription sleep aids during pregnancy extrapolate mainly from the relatively few studies done in nursing mothers.

A case series [48] showed that nursing infants' exposure to mother's use of benzodiazepines was relatively limited. In particular, the review reported that it appears to be safe to take diazepam during pregnancy. On the other hand, the review cites there have been case reports of sedation, poor feeding, and respiratory distress

in nursing infants, particularly with diazepam use. However, when the data have been pooled, the findings suggest a low incidence of adverse events, particularly with low dosages of benzodiazepines. General guidelines for physicians treating pregnant women are as follows:

1. Determine if the medication is necessary.
2. Choose the safest drug available (e.g., diazepam, lorazepam, clonazepam) at the lowest dosage for the shortest duration.
3. Avoid the first trimester if possible [47, 49].

Sleep Disorders During Pregnancy

Given the changes in pulmonary mechanics during pregnancy, the incidence of snoring and sleep-disordered breathing during pregnancy has become a topic of interest. While progesterone, a respiratory stimulant, may play a protective role, there are at least theoretical concerns that narrowed upper airways coupled with increased body habitus may result in compromised breathing during sleep in pregnancy. It is well known that snoring increases during pregnancy, especially during the third trimester, with estimated frequencies increasing from 4% in the nonpregnant woman to ranges of 14–35% during pregnancy [50–52].

These findings are important since snoring during pregnancy has been linked in some studies to maternal and fetal complications [42, 51, 53]. In one case report, a 25-year-old woman in her third trimester (37 weeks) being evaluated and treated for preeclampsia overnight was also confirmed to have sleep apnea, with maternal oxygen desaturations and concurrent fetal heart rate decelerations [54]. She then delivered an infant that was small for gestational age (SGA). Although several studies have found maternal snoring to be a risk factor for maternal hypertension and preeclampsia [51, 53], Tauman and colleagues [55] did not find an increased incidence in low birth weight (LBW) in the infants of mothers who snored during pregnancy.

While the effects of snoring on the pregnant woman and the developing fetus are still unclear, there appears to be a strong link between sleep apnea and maternal hypertension and preeclampsia which, in turn, has been shown to result in an increased risk to the developing fetus. A recent study by Chen and colleagues [56], in which 791 pregnant women with OSA were compared to 3,955 pregnant women without OSA, found that pregnant women with OSA were more likely to develop preeclampsia and have a cesarean section and were at increased risk for having LBW, preterm, and SGA infants.

There is also mounting evidence that the prevalence of sleep apnea increases in pregnancy, particularly in those women who have a preexisting tendency toward sleep-disordered breathing (e.g., obese, loud snorers), and worsens in those women who already have sleep apnea [57, 58]. A study by Shepertycky et al. [59] suggests that sleep apnea may present differently in women since women recently diagnosed with sleep apnea were found to be more likely to have signs and symptoms of hypothyroidism, depression, and insomnia than were men with sleep apnea.

Nasal continuous positive airway pressure (CPAP) has been used effectively in a number of pregnant women and was found to reduce nocturnal blood pressure increments in women with preeclampsia [51]. In a study by Guilleminault and colleagues [60], pregnant women diagnosed with sleep-disordered breathing either early on or pre-pregnancy and treated with nasal CPAP with repeat titrations at 6 months gestational age (GA) had full term pregnancies and delivered healthy-sized infants. At least half of the pregnant women needed CPAP-pressure readjustment at 6 months GA.

Recommendations for pregnant women with symptoms suggestive of sleep apnea include screening and an overnight polysomnogram. In women found to have severe OSA and in those women with mild to moderate OSA who are symptomatic, nasal CPAP treatment is the standard treatment. Conservative measures (e.g., avoidance of excess weight, positional therapy, elevation of head of the bed and avoidance of sedatives) were also recommended [61].

Future research should first assess for upper airway resistance syndrome, a more subtle form of sleep-disordered breathing, by utilizing more sophisticated breathing equipment, and then further investigate the relationship of sleep-disordered breathing with maternal and fetal complications.

In addition to sleep apnea, RLS increases during pregnancy, particularly during the final trimester, and then decreases after delivery [41, 44]. The International RLS Study Group defines RLS as (1) an urge to move one's legs, usually accompanied by an unpleasant or uncomfortable sensation in the legs that is (2) worse when at rest and during the evening and nighttime and (3) is partially or totally relieved by movement. RLS can result in difficulty falling and staying asleep. Lee's group [62] found that the prevalence increased from 0% of the 30 women pre-conception to 13% in the first trimester, 18% in the second, and 23% by the third trimester. Only one subject continued to have restless legs after delivery. When compared to those without complaints, the women with restless legs had lower ferritin levels (<50 Ug/dL) and significantly lower folate levels before and during pregnancy. They suggest that these findings support the role of iron and folate in the etiology of RLS during pregnancy.

Indeed, Botez and Lambert [63] found that the prevalence of RLS in pregnant women taking vitamins with folate (9%) was lower than those taking supplements without folate (80%). However, Manconi and colleagues [64] point out that larger studies are needed to evaluate the importance of folate and iron supplementation during pregnancy in preventing RLS. With regard to fetal development, a recent study [65] found that low maternal vitamin B-12 during pregnancy was associated with excessive infant crying, although there was no relationship between folate levels with infant crying.

Most dopaminergic agents used to treat idiopathic RLS fall into category C drugs (uncertain safety in pregnancy—animal studies; show an adverse effect; no human studies) with the exception of pergolide (category B—presumed safety based on animal studies) [66]. However, there are no published studies using pergolide in pregnant women with RLS. Conservative treatments for RLS include avoidance of caffeinated beverages and nicotine, restriction of carbohydrate-rich food, treatment of anemia

(if present), calf stretches, massage, warm or cold compresses, and vitamins with folate. Also, OTC sleep aids that contain diphenhydramine and other antihistamines should be avoided, since they can worsen RLS symptoms. Given the precipitous increase in RLS in pregnancy, research should be undertaken to address other possible nutritional supplements for this problem.

Sleep Problems During Postpartum

The postpartum period, which is associated with considerable sleep disruption, begins with delivery and ends for most women approximately 6–12 months later when the infant is sleeping through the night. The postpartum distress that most women experience (estimates range from 35 to 80%) occurs 3–5 days after birth. The more serious form of postpartum depression that generally occurs within 2–4 weeks after delivery may require more significant intervention including antidepressant treatment and therapy. Ten to fifteen percent of women will develop postpartum depression, and, of that group, only one-third of these women have had a prior history of affective disorder [67].

While postpartum sleep loss is both intuitive and well documented, interpretation of the small number of objective and subjective sleep studies has been challenging [68]. First, data collection procedures vary widely, especially the earlier research in which the mother's sleep was studied without the infant present. More recent postpartum sleep studies have been conducted in a naturalistic setting with the infant at home or in the hospital room. Second, there is great variability in prior sleep deprivation and sleep/wake patterns. In addition, it is difficult to obtain reliable data because PSG studies can be intrusive and lead to sleep disturbance itself and survey studies require daily tracking of sleep behavior that is difficult for most new mothers. Finally, other important variables (e.g., parity, length of labor, time of day, type of delivery, feeding method, postpartum day studied) are often not considered.

The most common reason cited for maternal awakenings in postpartum studies is the infant's sleep and feeding schedule [69, 70], but there is considerable discrepancy in the average TSTs reported (ranges from 4 to 7.5 h), due to small sample sizes and the variability of sleep during the first few postpartum weeks [71, 72]. There is some suggestion that slow wave sleep is somewhat preserved due to the effects of chronic sleep deprivation [71]. As in pregnancy, women compensate for lost nighttime sleep by sleeping on a more irregular schedule and napping to some extent while the infant naps [73], although the ability to nap is affected by parity. Gay and Lee [74] compared new mothers and new fathers using wrist actigraphy and found that while both partners' sleep was more disrupted when compared to the third trimester of pregnancy, new moms slept less at night but new dads had less TST when compared to their partners' sleep postpartum. Beyond the obvious sleep disruptions caused by the infant, recent studies suggest a myriad of other factors (e.g., emotional and physical health of mother, parity, methods

of birth and feeding, infant's sleep/wake rhythm, co-sleeping) that further affect postpartum sleep.

In a polysomnographic study investigating parity, Waters and Lee [75] found that, although both first-time mothers and mothers with children at home did not differ in TSTs during the third trimester, first-time mothers had a decrease in sleep efficiency from the third trimester to 1 month postpartum, while multiparas' sleep efficiency remained relatively stable. A most provocative finding in the Waters and Lee study is that new mothers had more fatigue than experienced mothers yet scored lower on a measure of participation in household chores. The authors propose that the differences in sleep and fatigue found in novice and experienced mothers reflect the new challenges in maternal role acquisition in the primigravida group. They also suggest that the process of integrating and achieving competence in mothering behaviors together with the sleep deprivation may put new mothers at risk of developing postpartum depression.

Feeding method may also impact the sleep of mothers with infant children, although this subject has not been well studied [76]. Quillin's study showed that those mothers who breast-fed had more awakenings within the first month postpartum and tended to sleep less during the night than women who bottle-fed. However, in another study [77], lactation was associated with significant increases in slow wave sleep in women who breast-fed when compared to women who bottle-fed. Mosko and colleagues [78] conducted laboratory polysomnography on bed-sharing and solitary-sleeping breastfeeding Latino infant and mother pairs. Although they found differences in arousals and a small decrease in slow wave sleep in the bed-sharing condition, there was no difference in overall nocturnal wakefulness and TSTs between the two conditions.

While all these aforementioned variables impact mother and baby's sleep, studies show that, ultimately, mothers' sleep will improve along with babies' development. Subjective and objective studies conducted on new mothers and their infants show that, by around 3 months, the infants' sleep and wake patterns become more regular and, in turn, the mothers' sleep becomes more continuous [70, 79]. In a study conducted in England, 50% of the babies were found to sleep through the night by 8 weeks and 75% by 3 months [79]. Factors that affected sleeping through the night at an earlier age were a heavier birth weight, female gender, younger mothers with less stress, co-sleeping less than 2 h or not at all, no central heating, and the baby not sharing a room with a sibling. While many infants sleep through the night by a year old, Ferber [80] reports that bothersome nocturnal awakenings continue to occur in 23–33% of 1- and 2-year-old children in the USA.

Recommendations for new mothers include the old adage "sleep when you can" which is essentially to sleep on a somewhat irregular schedule to conform to the infants erratic pattern of sleeping. And while this type of schedule has not been formally researched, anecdotal reports suggest that it may help to stave off severe sleep deprivation for many women. However, the long-term effects of an irregular sleep/wake regimen have been associated with insomnia in other populations [32]. Establishing a clear circadian pattern (day–night difference) in the child's bedroom will also facilitate adjustment to night sleeping. Commonly used

behavioral interventions such as controlled crying and systematic ignoring have also been shown to decrease infant sleep problems in randomized controlled trials [81]. In addition, education regarding normal sleep cycles and maintaining regular bedtime routines and schedules and consistent nap schedules can help establish a more predictable sleep and wake rhythm in the baby [82].

The potential for sleep deprivation during pregnancy and postpartum to negatively impact the mother and child has been an emerging body of literature. Sleep patterns have been shown to affect such variables as labor, delivery, the infant's health, and postpartum depression. Lee and Gay [83] found that women who slept less than 6 h during late pregnancy had longer labors (29 h vs. ≤20 h) and were 4.5 times more likely to have C-sections than pregnant women who slept more than 6 h. Other studies have also found a positive association between sleep duration and quality with type of delivery, length of labor stages, pain perception as well as with the neonates' Apgar score, gestational age, and birth weight [84, 85].

To determine a possible mechanism for the relationship between sleep deprivation and poor maternal-fetal outcomes, Okun and colleagues [86] studied IL-6 levels in 19 healthy women during mid- and late pregnancy. They found that pregnant women with higher levels of IL-6 had self-reported shorter sleep durations and lower sleep efficiency. They propose a mechanism in which sleep deprivation causes an increase in pro-inflammatory serum cytokines (e.g., IL-6) that then results in adverse maternal and fetal outcomes such as postpartum depression, preterm delivery, and LBW. The emerging literature on sleep deprivation and maternal-fetal outcomes is further summarized in an article by Chang and coworkers [87]. These findings have led Lee and Gay [83] to recommend that physicians and other health care providers not only discuss sleep quantity and quality with their pregnant patients but strongly emphasize to their pregnant patients that they are, in a sense, "sleeping for two."

While some authors have suggested that sleep deprivation during pregnancy may be associated with postpartum depression [87], Wolfson and colleagues [88] found that women with depressive symptoms 2–4 weeks postpartum were more likely to nap and have increased TSTs during the third trimester. However, there was no difference in TST between depressed and nondepressed women postpartum. They suggest that women with increased sleeping during pregnancy have more difficulty tolerating postpartum sleep deprivation that may then result in depression.

Although the relationship between prenatal sleep and postpartum depression remains unclear, the negative effects of sleep deprivation during the postpartum period on depression are clearly established [89]. Toward this end, the Women's Health Concerns Clinic at St Joseph's Healthcare has developed an intervention for women at high risk for postpartum depression (e.g., those with subclinical symptoms during pregnancy, those with personal or family history of depression), with promising results [90]. In an effort to minimize sleep deprivation, patients thought to be at risk for postpartum depression are offered longer hospital stays, private rooms, demand feedings rather than routine feedings, maternal choice regarding the

infant staying in the room, limited visiting hours, and, in some cases, sedatives, during the first postpartum week.

Although sleep aids are generally avoided in healthy women during the postpartum period, sleep aids may be warranted when the effects of sleep deprivation and insomnia may affect the new mother's welfare and her ability to take care of her infant. General accepted guidelines [49] regarding medication during lactation include:

1. Establish the risk/benefit ratio to determine if the medication is necessary.
2. Choose the safest drug available (e.g., is safe when administered directly to infants, has a short half-life and high molecular weight, a low milk: plasma ratio, has a high protein binding in maternal serum, is ionized in maternal plasma, and is less lipophilic).
3. Consult with the pediatrician when possible. Also, the mother should take the medication after breastfeeding and/or right before the infant's longest sleep period and arrange monitoring of the infant's serum drug levels if the mother's medication is possibly injurious to the infant.

As mentioned, the Medline review article [47] conducted a search with the terms "benzodiazepines," "diazepam," "chlordiazepoxide," "clonazepam," "lorazepam," and "alprazolam" and found 118 articles. The data for each medication were summarized, and it was found that diazepam was not recommended during lactation due to potential effects of lethargy, sedation, and weight loss in infants. Chlordiazepoxide and lorazepam were found to be safe during lactation.

A case series [48] measuring infants' serum levels of psychotropic medication and active metabolites from mothers taking psychotropic medications showed that medications were not detected in infant serum when mothers had taken these agents solely during the postpartum period. Also, mothers did not report any difficulties with their infants.

In closing, postpartum sleep in new mothers is seriously disrupted. This disruption is likely due to a multitude of factors that include parenting approaches, infants sleep/wake schedule, bed-sharing, parity, breastfeeding, how and where an infant is readied for sleep, the tenor of the parents' interaction with the child, and general household demeanor. The parents' general physical and emotional health, cumulative sleep deprivation, and their ability to bounce back from severe sleep disruption must also be considered.

Future research needs to investigate effective treatments for infants' irregular sleep and wake schedules. Many of the factors affecting the infant and mother's sleep are likely amenable to intervention that benefits the mother without compromising the infant. Yet, in common with research on sleep during pregnancy, there are little to no evidence-based data on which to base treatment recommendations for postpartum sleep disruption. Since sleep deprivation has been linked to postpartum depression in some women and there is an emerging literature suggesting that it may negatively impact the developing fetus and child as well, the importance of finding preventive interventions and workable treatment alternatives in this population is not trivial.

Sleep Problems During Perimenopause

There is an increased prevalence of insomnia in menopausal women [91], with estimates of complaints of insomnia in peri- and postmenopausal women ranging from 44% [92] to 61% [93]. While menopause can reduce the reported quality of sleep, the reasons for sleep problems are often multifactorial, which also explains their already high frequency in midlife [91]. Fatigue is also reported frequently in menopausal women [94]. Several major causes have been proposed to account for poor sleep in perimenopausal women:

1. Sleep disruption associated with hot flashes.
2. Increased incidence of obstructive sleep apnea.
3. Mood disorders.
4. Inadequate sleep hygiene leading to a chronic insomnia.
5. Pain disorders.
6. Movement disorders.

Not surprisingly, the focus of therapeutic interventions has been on HRT as well as on standard treatments for these six disorders. The results of the Women's Health Initiative (WHI) [95] put into question the safe use of HRT as a treatment option for menopausal women [96]. As with the conclusions reported next in this chapter, the implications of the WHI apply primarily to the particular hormone preparation used in that study, which was oral conjugated equine estrogen and medroxyprogesterone. There are theoretical reasons, at least, to suspect that transdermally delivered estradiol and oral progesterone may not, necessarily, have the same adverse events. Since some women choose to remain on HRT, and there may be future long-term safety and efficacy data available on the newer HRT formulations, it is reasonable to discuss the role of this therapy in treating sleep disorders in menopausal women.

Hot Flashes

Hot flashes are one of the oldest reported causes of sleep disruption. However, the debate continues as to whether they actually are associated with sleep disruptions [97]. On polysomnography, some authors found an association of hot flashes with nocturnal awakenings [98] and decreased sleep efficiency [99, 100]. Additional studies, some involving the same authors, have found no correlation between the presence of hot flashes and polysomnographic measures of poor sleep [101, 102]. It is suggested that one of the methodological problems with the older studies is that they did not screen for concomitant sleep disorders or drug use as other causes of sleep disruption [102].

In addition to the lack of clarity on the role of hot flashes in perimenopausal insomnia, the efficacy of HRT in treating this problem has been debated. Two papers analyzing the effect of oral synthetic estrogen on objectively determined hot flashes

and sleep found improvements in both [103, 104]. In contrast, another study analyzing the combination of estrogen and progesterone [105] found no difference in objective hot flashes between treatment and placebo.

Not only do the objective studies disagree, but those studies looking at patient self-reports of hot flashes also conflict. Two double-blind crossover studies, one with transdermal estrogen [106] and the other with oral synthetic estrogen [107], found a decrease in subjectively reported hot flashes. On the other hand, a double-blind placebo-controlled study using oral synthetic estrogen [104] did not result in a greater decrease in subjectively reported hot flashes in the treatment of the two groups.

In summary, there are objective and subjective data that both support and refute a role of HRT in treating hot flashes. Nonetheless, if a woman is complaining of hot flashes, particularly at night, it would seem prudent to treat these symptoms, whether using a form of HRT or other treatment. Hot flash frequencies vary directly with temperature. Sleeping in a cool environment can decrease the frequency of hot flashes [108, 109], so one could also advise women with hot flashes to lower the temperature in the bedroom. It should also be noted that behavioral treatments for hot flashes have shown some efficacy in decreasing the frequency of hot flashes [97].

Sleep-Disordered Breathing

Sleep-disordered breathing is another proposed cause of poor sleep in perimenopausal women. The incidence of sleep-disordered breathing increases with menopause [110]. After controlling for age, BMI, and several lifestyle factors [111], postmenopausal women were 2.6 times more likely than premenopausal women to have sleep-disordered breathing. Proposed mechanisms for this apparent rise have included a change in the distribution of body fat with an increase in the waist:hip circumference ratio [112] and a decrease in sex hormones, in general [113], and progesterone, a known respiratory stimulant, in particular [7].

The literature on HRT and sleep-disordered breathing is divided into cross-sectional analyses and prospective clinical trials. The majority of the results from the large cross-sectional studies favor a positive effect of HRT (either estrogen or estrogen and progesterone) on sleep-disordered breathing, with two showing statistically significant decreases in the prevalence of sleep-disordered breathing among women using HRT vs. those not [114, 115]. One study found somewhat decreased odds of having sleep-disordered breathing with HRT use [111]. Thus, epidemiological data suggest a therapeutic effect of HRT.

The prospective drug trials have shown an effect in mild but not in moderate or more severe obstructive sleep apnea. A pilot study using the newer, more physiologic forms of HRT (transdermal estradiol with oral progesterone) in postmenopausal women with mild to low-moderate sleep-disordered breathing found

an effect with estrogen that disappeared with the addition of progesterone [116]. Treatment did not normalize the apnea-hypopnea index (AHI), leaving residual mild sleep-disordered breathing. However, the study was both of short duration and small sample size. Another pilot study using estradiol and a synthetic progestin (trimegeston) demonstrated normalization of the AHI in subjects with mild obstructive sleep apnea [117]. These studies suggest that HRT may be effective in treating mild sleep apnea.

The results of using HRT to treat moderate or more severe sleep-disordered breathing are not as promising. One study of HRT use in women with high to moderate sleep-disordered breathing found a statistically significant improvement with HRT but not resolution of the sleep-disordered breathing [118]. A second study similarly looked at subjects with moderate to severe sleep-disordered breathing before and after HRT [119] and found no overall improvement with HRT. These findings, however, are neither surprising nor disappointing since the gold standard of treatment for moderate to severe sleep-disordered breathing is nasal CPAP.

Mood Disorders

Mood disturbances can affect sleep. In well-controlled studies, sleep tended to be more disturbed and sleep quality more impaired during perimenopause, especially in predisposed women with a history of a mood disorder [120]. Both depression and anxiety can be associated with less refreshing and more fragmented sleep [121]. It is unclear if the hormonal changes of menopause, per se, can account for depression and anxiety in this population [122] or if the depression and anxiety that can be associated with menopause represent unresolved grief [123], a response to life circumstances [124], or relate to the presence of hot flashes [123]. Nonetheless, there are patients for whom psychotherapy was necessary to treat insomnia despite diminution of hot flashes with HRT (using transdermal estradiol and a progestin) [125]. There are many more studies that look at using HRT (either estrogen alone or estrogen and a progestin) to treat perimenopausal depression. Not surprisingly, some find efficacy [126] and others do not [101, 127]. Thus, it is important to consider a mood disorder when a woman is complaining of poor sleep in association with menopause.

As with all cases of insomnia, one should look for a precipitating cause that then has perpetuating factors, generally the result of inadequate sleep hygiene. In an excellent review of this topic, Krystal and colleagues [123] propose a primary insomnia of menopause in which a precipitating factor (sometimes hot flashes) resolves, but perpetuating factors (elements of inadequate sleep hygiene) then intervene, maintaining the insomnia. Clearly, the treatment for this would be the standard insomnia therapies—patient education about principles of good sleep hygiene, sleep restriction, and relaxation techniques, among others.

Pain Disorders

Pain disorders may also lead to decreases in sleep quality [91]. Fibromyalgia and other disorders should be addressed in this population, since their prevalence increases with age in women [96].

Movement Disorders

While RLS prevalence is not directly correlated with menopause, the frequency increases with age [96]. Estrogen replacement therapy has been studied for RLS [128] against placebo and was not shown to alter the incidence, intensity, movement durations, or movement intervals.

Sleep Problems in General

In addition to treating specific causes of insomnia, many studies look at using HRT to treat sleep complaints, in general. As with the efficacy of HRT in treating hot flashes, there are conflicting data on the efficacy of HRT in treating disturbed sleep during menopause. The older literature from the 1970s documented improved sleep parameters with oral synthetic estrogens as measured with PSG [107, 127]. In contrast, later studies using transdermal estrogen [106, 129] and one using oral conjugated estrogen and an oral progestin [105] showed no objective, polysomnographic improvements. In the two studies using transdermal estrogen, however, the subjects noted a subjective improvement in their sleep. Another trial suggests that progesterone (vs. a synthetic progestin) may be necessary to see a beneficial effect of estrogen on sleep [103]. Again, a subjective improvement was noted even in the group in which there was no objective improvement. Therefore, there are data that support a therapeutic effect of HRT on sleep as well as data that suggest a subjective improvement of HRT on sleep without an objective correlate.

Turning from HRT to non-pharmacological therapies for menopause-related insomnia, several approaches have been investigated, including stretching and exercise. A study looking at the efficacy of stretching vs. exercise on symptoms of insomnia in a group of postmenopausal women not using HRT found that stretching was more effective than exercise. There was an effect seen with exercise in the morning for more than 3 h per week [130]. A behavioral treatment for hot flashes was discussed earlier [97].

When evaluating a menopausal woman with sleep complaints, the clinician should take a thorough sleep history to look for symptoms that would suggest the primary sleep disorders, having a higher suspicion for sleep-disordered breathing than one might otherwise in younger women, and inquiring about pain and

movement disorders. Treatment generally would be as usual (e.g., nasal CPAP for moderate or severe sleep-disordered breathing) while recognizing the important but as yet unresolved question about the efficacy of HRT for mild sleep-disordered breathing. Then, one should assess whether or not the patient is experiencing hot flashes—even if she is unaware of them occurring at night—and treat these appropriately. Depression and anxiety should be in the differential diagnoses and treated. One should look for an initiating event (hot flashes, personal trauma) that has since dissipated or been treated, but that resulted in an irregular sleep-wake schedule or other elements of inadequate sleep hygiene (e.g., increased caffeine consumption, napping) and treat these problems. Finally, one could recommend a program of stretching or other behavioral techniques [91] to increase relaxation and, hopefully, promote more restful sleep and consider the use of HRT.

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Chapter 5
Normal Reproductive and Endocrine Life Stages: The Impact on Sleep Disorders

Rochelle Goldberg

Introduction

Sleep disorders affect people at all stages of life. For women, sleep complaints may vary by hormonal status as well as life stage. Certain broad perceptions about sleep and sleep disorders are supported by population surveys [1]. In earlier research, most study populations that included women did not differentiate findings by gender. Even in studies of women with sleep disorders, the potential effects of hormonal condition or reproductive status were not identified. These topics have been more frequently addressed in recent years. Women develop more sleep problems during pregnancy and with menopause [1–3]. Postmenopausal and elderly woman have more insomnia complaints while sleep-disordered breathing (SDB) increases in the peri- and postmenopausal population [4]. This chapter provides an introduction to recent findings on sleep and women from menarche to menopause.

Menarche and Adolescence

Insomnia

A prospective study in adolescents, 13–16 years, identified a lifetime prevalence of insomnia in 10.7%, of which 88% had current history based on *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, (DSM-IV) criteria. Sleep onset complaints occurred in 68.5%, sleep maintenance problems in 26.2%, and

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non-restorative sleep in 48.1%. Many children had a combination of complaints. Comorbid psychiatric diagnoses, including mood disorders, anxiety, behavioral problems, and substance abuse, were found in 52%. Prior to menarche, there was no gender distinction, while menarche was associated with a 2.75-fold increased risk of insomnia. The authors also evaluated for possible delayed sleep phase syndrome (DSPS), which was not found to explain the sleep onset complaints in this group [5].

Normal hormonal changes through the menstrual cycle may favor sleep stability mid-cycle and sleep fragmentation during menses [6]. These changes may be associated with reports of insomnia or hypersomnolence. Several studies reported subjectively longer sleep durations but more fragmented sleep premenstrually [7–9], while others did not support these findings [10, 11].

Restless Legs Syndrome

Restless legs syndrome (RLS) is a clinical diagnosis characterized by an unpleasant sensation, usually in the lower extremities, accompanied by an irresistible urge to move the legs. Symptoms typically occur in sedentary situations and tend to be associated with difficulty initiating sleep [12]. The prevalence in the general population ranges from 2 to 5% [13] and goes up to 20% in the elderly [14]. It occurs in about 2% of peri-pubertal and post-pubertal children (ages 12–17). Within this group, 52% indicate moderate to severe symptoms two or more times per week. Difficulty with sleep onset and nocturnal awakenings were also common [15–17]. Over 70% had a positive family history (one or both biological parents). Growing pains were identified in 80.6% vs. 63.2% of controls [16–18], as was a low serum ferritin [16, 17]. The influence of gender is less clear (15 vs. 17).

Sleep-Disordered Breathing

Puberty is also associated with changes in upper airway morphology that may potentiate SDB. In a study of 226 adolescents, ages 11–19 years, symptoms of SDB were identified by questionnaire. Subjects then had home testing with respiratory monitoring and actigraphy. Unlike their male counterparts, females did not show an increase in snoring and respiratory disturbance index (RDI) at postpuberty compared to prepuberty. Gender differences in RDI normalized when adjusted for waist-to-hip index. The findings suggest that female sex hormones may exert a protective effect on the pathogenetic factors associated with SDB [19]. This is also consistent with the potential hormonal effects on the increased SDB in women in later life stages. While the presentation of SDB in adolescence may mirror features in the adult population, teens may present with more inattention, hyperactivity, insomnia or delayed sleep phase features [20].

Sleepiness

Daytime sleepiness increases with puberty and adolescence regardless of gender. In a study by Carskadon, children grouped by Tanner stage showed significant reductions in slow-wave sleep time as well as a greater degree of daytime sleepiness in later Tanner stages 3–5. These findings are not explained by abbreviated night sleep. The results support that children in early adolescence are sleepier than during their prepubertal years [21]. The additional sleep loss, related to earlier school start times and other circadian factors, may further compromise daytime function at this life stage [22].

Narcolepsy is most often diagnosed in early adult years, although many identify symptoms starting in childhood and adolescence. In a retrospective analysis of the Stanford Center narcolepsy database, 40% of the 1,219 cases identified symptoms before age 15 years. This is consistent with the reported prevalence in earlier publications and the delay in symptom onset to diagnosis of about 10 years [23, 24]. Weight gain within 6 months of onset and early puberty were found in this group [25].

Pregnancy

Sleep disturbance during normal pregnancy is well recognized. A pregnancy-associated sleep disorder is generally defined as poor sleep quality or hypersomnolence, occurring at the start of or within the gestational period and resolving postpartum. Polysomnographic features may demonstrate sleep fragmentation or extended sleep duration. The multiple sleep latency reveals a reduced sleep latency. In addition to the hormonal and other physiologic changes throughout pregnancy, comorbid sleep disorders will also affect sleep.

Insomnia

Insomnia is a common pregnancy-related sleep complaint. Nocturnal awakenings, reported by sleep diary and polysomnography, increase 1.4-fold during the first two trimesters and twofold by the third trimester compared to pre-pregnancy. Reasons for awakenings included nocturia (51.4% in first and third trimester), nausea, fetal movements, joint pains, and general discomfort [26]. Another study found one-third of women had sleep problems in pregnancy described as nighttime awakenings, with more difficulty returning to sleep in 97.3% of women by the third trimester. Women also reported waking earlier in the morning and difficulty falling asleep. Restless legs occurred with the highest frequency in the last quarter of pregnancy (91.9%). This study was a single application questionnaire, so it did not

evaluate individual responses over the gestational period [27]. In another study, by the third trimester, altered sleep (nocturnal awakenings with heartburn, discomfort, and cramps) occurred in 68%, with longer sleep times in 19%, and 12 of the 100 subjects reported new use of hypnotics [2]. Poor sleep quality, measured by the Pittsburgh Sleep Quality Index (PSQI) [28], occurred throughout pregnancy, becoming more prominent by the third trimester (39.0%, up to 53.5%). Predictors of sleep disturbance included age greater than 35 years and African-American and Hispanic race/ethnicity [29]. A retrospective study reported an increase in complaints of non-refreshing sleep and frequent awakenings from the second and third trimesters in up to 75% of women [30].

Restless Legs Syndrome

Studies of RLS during pregnancy identify prevalences ranging from 11 to 27%. Not all studies applied the more stringent International Restless Legs Syndrome Study Group (IRLSSG) criteria, which may explain differences in reported RLS prevalences [31]. Symptoms may also worsen during pregnancy for women with preexisting RLS [32]. There was a prevalence of RLS of 27% from an interview study of 606 pregnant women. Preexisting RLS occurred in 10% of all women, whereas 17% noted onset of RLS during pregnancy with postpartum resolution of symptoms. Although the symptoms were not severe, they contributed to reported longer sleep latency and decreased total sleep time (TST) [33, 34]. A 19.9% prevalence was reported in a national questionnaire study in Japan that included 16,528 subjects. They also found that RLS was associated with current smoking, use of alcohol or medication for sleep, and longer duration of pregnancy [35]. In nulliparous healthy women, there was an increase in RLS symptoms from 17.5 to 31.2% from the first to the third trimester. More subjects identified severe symptoms (15.2–27.1%) with later trimester [30]. RLS was also reported in 32% of 186 French patients during the third trimester. Symptoms resolved in 64.8%, generally within 2 weeks postpartum. There is no correlation with parity, iron intake, RLS severity, delivery methods or complications, newborn weight or breastfeeding [36]. Another study, however, found an increasing risk of RLS in subsequent pregnancies with an odds ratio of 1.98 with first child to 3.04 with second child and 3.57 with three or more pregnancies [37].

There was an increased risk of RLS in pregnancy for those with a family history of RLS. The prevalence was greater in parous vs. nulliparous women (49.5 and 33.7%, respectively) but not for nulliparous women vs. men (33.7 and 30.0%, respectively). This indicates that pregnancy is a major risk for development of RLS in familial RLS and seems to account for the gender differences in RLS prevalence for the general population [38].

An epidemiological study also found an association of iron deficiency and RLS. Although mild, the decrease in plasma iron and hemoglobin is significant [34]. Another study of pregnant patients with RLS (overall prevalence of 23%) identified low ferritin and folate at preconception and throughout pregnancy [39]. These

findings are consistent with the role of iron metabolism in RLS pathogenesis [40]. The substantially greater iron and folate requirements during pregnancy suggest a possible mechanism for the increase of RLS in pregnancy.

In summary, pregnancy is associated with an increased prevalence of RLS. For women with preexisting RLS, symptoms worsen during pregnancy. Symptom frequency and severity is greatest during the third trimester. Pregnancy-related RLS (which usually resolves postpartum) is likely to recur with future pregnancies and is more likely with a family history of RLS. A deficiency of iron and folate may underlie the increased risk for RLS during pregnancy.

Sleep-Disordered Breathing

The hormonal and physiological changes occurring during pregnancy affect upper airway function and respiration, and have the potential to exacerbate SDB. Changes that increase the risk for sleep apnea include gestational weight gain, nasopharyngeal edema, decreased functional residual capacity, and increased arousals. Others that may reduce the risk include an increase in minute ventilation, lateral sleep position preference, and decreased rapid eye movement (REM) sleep time [41]. Concerns for sleep apnea during pregnancy relate to both maternal health and that of the fetus.

Snoring is more common during pregnancy than in nonpregnant women and after delivery. This corresponds to a smaller upper airway (at the oropharyngeal junction and mean pharyngeal space) during third trimester than in postpartum and nonpregnant women [42]. By third trimester, 27% of normal pregnant women reported snoring [43]. Self-reported snoring occurred in 14% of women by the second or third trimester compared to 4% of control, nonpregnant, premenopausal women ($p<0.05$). Self-reported apnea was similar between groups. There was no difference in mothers' daytime sleepiness, mean birth weight, or APGAR scores for infants born to snoring mothers [44]. The prevalence of snoring decreased, returning to pre-pregnancy levels, by 3 months postpartum [45]. In contrast, another study found higher rates of gestational hypertension, preeclampsia, and small for gestational age (SGA) infants in habitual snorers than in non-snorers [46]. Snoring was a risk factor for gestational hypertension in obese subjects [47]. In patients with pregnancy-associated hypertension or preeclampsia, there was a greater likelihood of increased upper airway resistance or airflow limitation [48, 49]. Snoring may be also associated with lower APGAR scores, but has not been found to have a consistent association with low birth weight [46, 50].

Studies of pregnant women found an increase in symptoms of SDB in pregnant vs. nonpregnant participants and in pre-pregnancy vs. third trimester women [51]. There are a few studies in small patient groups that include polysomnography. These indicated that, while snoring is common, the prevalence of sleep apnea is low. In a study of multiple pregnancies, a single polysomnogram (PSG) conducted at 30–36 weeks gestation found no evidence of obstructive sleep apnea (OSA), although episodes of increased airway resistance occurred in four subjects [52]. In a small study

with non-obese controls, obese pregnant women were found to have an apnea hypopnea index (AHI) no higher than in those in early pregnancy. Only one subject developed an AHI above ten by the third trimester [53]. Another polysomnographic study of obese pregnant and non-obese pregnant controls, reported a significantly higher AHI of 1.7 vs. 0.2 ($p<0.05$) at 12 weeks gestation. Increases in snoring and AHI in the obese group occurred at 30 weeks gestation. Gestation length and fetal outcome (birth weight) were comparable between groups. One obese mother had an AHI of greater than ten on the second study and developed preeclampsia. Respiratory events normalized in this woman at 6 months postpartum [47]. Additional studies indicate that SDB symptoms are associated with a risk for gestational hypertensive disorders, diabetes, and unplanned caesarian sections [54, 55].

Sleep-Disordered Breathing and Positive Airway Pressure

A study of 11 women with preeclampsia showed increased upper airway resistance in all subjects. Treatment with an auto-titrating positive airway pressure (PAP) unit resulted in reversal of flow limitation and prevented the nocturnal blood pressure increments noted previously [56]. A randomized, controlled trial for chronic snoring in pregnant women with a history of hypertension or identified hypertension compared PAP plus antihypertensive medications to antihypertensive treatment alone. The PAP-treated subjects (AHI <5) had lower mean daytime blood pressure with less antihypertensives than controls. The PAP subjects also favored better pregnancy outcomes (APGAR, birth weight, healthcare utilization, and preeclampsia) [57].

In summary, these studies suggest that snoring is commonly reported during pregnancy. While sleep apnea is not common in normal healthy, non-obese pregnant women, the obese pregnant woman may have an increased risk for SDB. Furthermore, comorbid SDB may increase the risk for maternal and fetal complications; therefore, symptoms of snoring or sleep apnea should be considered. Nasal PAP may reduce the risk for pregnancy or fetal complications in these patients.

Childbearing Years

Insomnia

The complaint of insomnia is noted to vary with the menstrual cycle in women through their childbearing years. In one prospective study, subjective poor sleep quality occurred in the 3 days prior to menses thru the first 4 days of menses. However, the objective measures of sleep quality, sleep onset latency, TST, and nocturnal awakenings did not differ significantly [58]. These findings are similar to other population studies [59]. The International Classification of Sleep Disorders identifies premenstrual insomnia and premenstrual hypersomnolence [60]. These

are characterized as complaints of insomnia or daytime sleepiness, respectively, that occur prior to or during menses. Symptoms are denied otherwise during the menstrual cycle. Despite these designations and broad anecdotal observations, there is little beyond case reports to support these diagnoses.

Sleep Apnea

Young and middle-aged (premenopausal) women are also at risk for sleep apnea. In a community sample of women aged 30–39, 6.5% had mild OSA (AHI > 5 per hour) and 4.4% had moderate to severe apnea (>15 per hour). Similar frequencies are reported in other studies [61, 62]. Women more often report insomnia and nocturnal palpitations and are less likely to be told of witnessed apnea than men in this age range. They more often have depression, hypothyroidism, asthma, allergies, migraines, fibromyalgia, and irritable bowel syndrome than men [63, 64]. Up to 93% of women with sleep apnea are unrecognized [65]. Perhaps, the less typical symptomatology and comorbidities mask identification of this problem. Nonetheless, women with OSA are also at risk for incident hypertension (odds ratio 2.9 over 4 years), coronary artery disease, atrial fibrillation, and stroke [66–69].

In the childbearing population, the potential effects of unrecognized sleep apnea on sex hormones and the menstrual cycle may also impair fecundity [70, 71]. In addition, women with polycystic ovarian syndrome have a 70% prevalence of sleep apnea. Infertility, relating to anovulation and excess androgens, is common in this condition, which occurs in 5–10% of women [72]. Several preliminary studies suggest that women with dysmenorrhea may have an increased risk of SDB, and that treatment with PAP may have a favorable effect [73].

Menopause

Insomnia

Symptoms of sleep fragmentation and non-restorative sleep are common during menopause. While these symptoms are often noted in conjunction with vasomotor features (e.g., hot flashes), hormonal changes alone may disturb sleep. There is also an increased risk of primary sleep disorders presenting with complaints of impaired sleep. Vasomotor symptoms are observed in 68–85% of women and are often reported in conjunction with nocturnal awakenings [3, 74]. Subjective and objective sleep measures were assessed in a general population of women aged 44–56 years using the PSQI and PSG. Subjects with complaints of poor sleep were recruited by newspaper advertisements. A primary sleep disorder was found in 53% (clinically significant sleep apnea, periodic limb movements or both) and 56% had hot flashes measured during the PSG. The reduced sleep efficiency seemed to be related to the disturbances from the primary

sleep disorders, not the vasomotor symptoms [75]. Higher anxiety scores and hot flashes, in the first half of the night, were correlated with increased subjective sleep disturbance [76]. The subjective sleep disturbance, labeled as chronic insomnia with nocturnal awakenings in menopausal women, was associated with higher healthcare utilization and compromised quality of life and work productivity [77]. Another community-based study identified self-reported sleep disturbance in 38%. The complaints were best associated with the stage of menopausal transition rather than age [78].

Subjective and objective sleep quality was evaluated in a community-based sample of 589 postmenopausal women. Subjective sleep complaints were common and significantly more serious than in premenopausal controls. Perimenopausal and postmenopausal women had twice the odds of reporting sleep dissatisfaction. In the subset of women with vasomotor complaints, there was a significant difference in reports of sleep dissatisfaction and sleep-related hot flashes. Despite the subjective complaints, postmenopausal women had better sleep quality with an increased TST, better sleep efficiency, and greater percentage of slow-wave sleep during PSG. Sleep fragmentation was more prominent in the premenopausal subjects. Hormone replacement therapy (HRT) was not found to have favorable effects on the objective measures of sleep. Rather, sleep onset, sleep efficiency and duration and depth of sleep were better in the postmenopausal group without HRT [79].

Subjective sleep complaints, however, may respond more favorably to HRT. Subjects taking HRT reported improvement in falling asleep, less restlessness, and fewer nocturnal awakenings. They were also less tired during the day. Although improvements were most striking in those with severe vasomotor symptoms, insomnia complaints were also favorably affected by HRT in those without vasomotor symptoms [80]. In another randomized control study of HRT, the treatment group had improvements in vasomotor symptoms, night sweats, and insomnia [81].

There are likely different contributors to the disturbed sleep in menopause, and the dichotomy of symptomatic vs. objective measures is consistent with these observations. Treatment considerations for insomnia in the postmenopausal woman must therefore address goals of subjective sleep response, while weighing the risk of treatment against more equivocal objective finding.

Restless Legs Syndrome

Berger et al. found an overall increased prevalence of RLS with age using the IRLSSG criteria [31]. Although hormonal status was not indicated, the increase in RLS for women 50–59 years old (19.4%) was significant compared to the younger groups (approximately 10% for women 30–39 and 40–49 years old), suggesting that RLS is more prevalent in peri- and postmenopausal women. There was no attempt to determine incidence within the groups [37]. A study of RLS in women aged 18–64 years (mean age 45 years) found a prevalence of 11.4% (16 women, 14 of whom were older than 34 years). Hormonal status was not identified [82]. Menopausal women with vasomotor symptoms may also identify more RLS [83]. Patients with

late-onset (>45 years old) RLS may have a more rapid course than the often described waxing-and-waning characteristics reported in younger age groups [84].

These studies are consistent in showing an increased prevalence of RLS with age in women. A hormonal mechanism is likely since RLS increases in the perimenopausal age subgroup and in those with vasomotor symptoms.

Sleep-Disordered Breathing

A number of protective factors have been proposed to explain the observed differences in sleep apnea prevalences in men and women. Physiological changes, particularly relating to sex hormones coincident with menopause, may also help explain observed differences in the prevalence of SDB in postmenopausal women. Premenopausal women, in contrast to men, have gynecoid rather than android fat distribution, less fat deposition in the neck, a stiffer upper airway, more active genioglossal muscle tone, and better immediate load compensation favors pharyngeal patency [85–87]. Progesterone is a respiratory stimulant, and the decreased levels of this hormone with menopause are also implicated in the increased prevalence of sleep apnea in postmenopausal women [88].

Bixler et al. found an increase in sleep apnea with menopause. Women were grouped as premenopausal, postmenopausal without HRT, and postmenopausal with HRT. Menopausal status favored SDB, whereas HRT subjects had a prevalence similar to that of premenopausal subjects. Obesity may facilitate SDB in this group as well. All of the premenopausal and postmenopausal HRT subjects with SDB were obese, and only 49.4% of those postmenopausal without HRT were obese [89]. In a study of obese subjects, Resta et al. found significant differences in anthropometric parameters and sleep apnea in pre- and postmenopausal women. Neck circumference, percentage of predicted normal neck circumference, waist-to-hip ratio, RDI, and prevalence of SDB were higher in the postmenopausal group. The body mass index (BMI) was significant as well ($p < 0.01$) [90]. There was also an association of SDB and body fat distribution (assessed by skin-fold sum). The women with SDB had higher BMIs and body fat than the general population [91]. Another retrospective study also documented a higher prevalence of SDB in postmenopausal women, but did not show any difference in BMI or general symptoms of SDB between groups. The higher BMI was associated with greater sleepiness [92].

Menopause may also be an independent risk factor for SDB. The SDB prevalence was higher across menopausal groups. This difference persisted when controlled for age and BMI. There were no further increases in SDB for subjects beyond 5 years of menopause, suggesting a latent period for the development of the disorder. In this study, a small protective effect of HRT was noted [93]. The increase in SDB in the postmenopausal population persisted after controlling for BMI and neck circumference, again suggesting a risk inherent in the menopausal state [4]. Studies of the effect of HRT on SDB and upper airway responsiveness were inconclusive, with small to negative results [94, 95].

These studies support an increased risk of OSA during the transition to menopause. The risk appears to be independent of BMI, neck circumference, and age. The role of HRT in modifying upper airway mechanics, SDB and related sleep characteristics remains unclear.

Conclusion

Women describe sleep complaints and sleep disorders at all ages. Differences in hormonal state or endocrine life stage may modify the risk for specific sleep problems. Sleep apnea remains largely unrecognized throughout life stages. A better understanding of hormonal effects and interactions with age and comorbidities in the prevalence of sleep disorders in women is needed, although studies continue to support these associations. There is increasing evidence for the risk for sleep disorders in women at different life stages. These conditions, untreated, have significant health and quality of life implications. Studies that respect not only gender and age, but differences in cyclical hormonal effects and life stage contribute to a better understanding of disease mechanisms, clinical risk factors, adverse health effects, and treatment opportunities.

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Part II
Adolescents

Chapter 6
Delayed Sleep Phase Syndrome in Adolescents

John Garcia and Garrick Applebee

Introduction

Delayed sleep phase syndrome (DSPS) is present to some degree in most if not all adolescents. It is thought to be a normal biological developmental phase. Weitzman et al. first described DSPS in 1981 [1], and Carskadon et al. in 1993 [2] first linked it to the biological process of puberty. Its mean age of onset is 15.4 years [3].

The International Classification of Sleep Disorders describes DSPS as a disorder in which the major sleep episode is delayed in relation to the desired clock time, resulting in complaints of sleep onset insomnia and/or difficulty in awakening at the desired time. Symptoms must be present for at least 1 month, and other explanations to account for excessive daytime sleepiness must be excluded [4]. This chapter will briefly summarize basic science regarding circadian rhythm disorders, review clinical research regarding DSPS, and discuss treatment options as well as hope for future directions.

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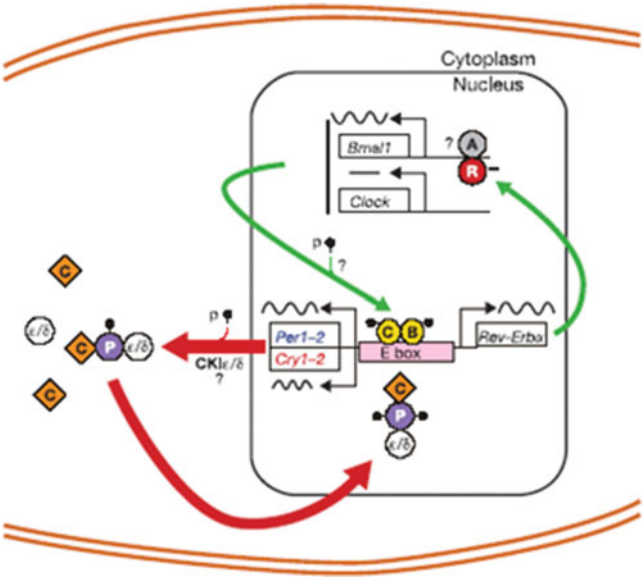

Fig. 6.1 Mammalian circadian clockwork model (Reproduced with permission of Macmillan Publishers Ltd from Reppert SM, Weaver DR. Coordination of circadian timing in mammals. Nature 29 August 2002; 418:035–941)

Review of Basic Science Surrounding Circadian Rhythm Control

Light is the most powerful entraining agent of the circadian system. Retinal ganglion cells mediate the effects of light to the suprachiasmatic nucleus (SCN) in the hypothalamus through the chemical mediator melanopsin. Activated by melanopsin, the SCN increases its uptake of glucose, leading to the expression of genes including *per*, *clock*, and *tim*. Cytochromes in the cells of the SCN also play a role in the expression of *per*, *clock*, and *tim*. Oscillations generated by rhythms in gene and protein expression create long feedback loops (Fig. 6.1). These long feedback loops ultimately regulate the release of hormones such as melatonin in the pineal gland and numerous peripheral circadian rhythms of the body, including thyroid stimulating hormone (TSH) release, cortisol secretion, and core body temperature control [5].

These create the circadian rhythm known as process C. The two-process model proposed by Borbely in 1982 describes a model where process C is affected by sleep homeostasis process, also known as process S [6]. Process S describes the physiology that sleep propensity increases as duration of wakefulness accumulates and dissipates during sleep (Fig. 6.2). Interaction of process S and process C leads to the manifest sleep–wake cycle.

Research regarding sex differences in circadian timing has yielded variable findings. A recent study comparing young adults did show differences between the sexes, with women having earlier timing of the circadian rhythm phases of melatonin secretion and

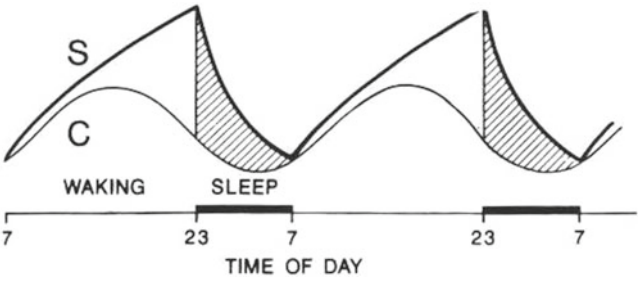

Fig. 6.2 A two-process model of sleep regulation showing that DSPS may involve problems related to the homeostatic regulation of sleep (Reproduced with permission from Borbely AA. A two-process model of sleep regulation. Human Neurobiology 1982 Oct; 9(3):195–204)

core body temperature related to men, despite similar actual sleep–wake times [7]. Further research in this area may help us better understand the pathophysiology of DSPS in adolescent girls.

Delayed Sleep Phase Syndrome

Clinical Research

Teens have an increased incidence of circadian rhythm disorders, particularly DSPS. The incidence of DSPS in teens is 7% [8], ten times greater than that of middle-aged adults [9]. Contrary to popular belief, Carskadon has revealed that there is a physiologic imperative to delayed sleep seen in teens in general, and more strikingly in teens with DSPS. They have delayed release of melatonin, and this biologic imperative seen in DSPS contrasts with conventional wisdom that rationalizes teen sleep patterns as simply the consequence of social pressures [10]. Others have suggested that people with DSPS have an increased sensitivity to evening light, which may also influence their circadian rhythm [11].

Research has also revealed alterations in sleep homeostasis process in teens with DSPS. In one study, patients with DSPS did not exhibit recovery sleep during the subjective day despite sleep deprivation. The authors suggest therefore that DSPS may involve problems related to the homeostatic regulation of sleep after sleep deprivation [12]. Development of DSPS may therefore be an interplay of biological changes to both process C and process S in the adolescent population.

Sequelae of Delayed Sleep Phase Syndrome

Regular sleep deprivation related to the truncation of the normal sleep period is seen frequently in adolescents with DSPS. The impact of this includes daytime

sleepiness, deficits in cognitive functioning, difficulty with mood regulation, and increased propensity for accidents [13]. Tardiness to school and academic difficulties, especially in classes in the early part of the day, are common concerns. Eveningness has also been associated with increased trends toward substance use, which for adolescent girls can also be influenced by age of menarche [14]. These impacts should all be considered in the evaluation and treatment of teens with this disorder.

Clinical Evaluation

Patients with DSPS can often present complaining of an inability to fall asleep. This can be differentiated from sleep onset insomnia by procuring additional history, including whether the patient is able to sleep later in the morning if given the opportunity (uncommon in psychophysiological insomnia), and what the patient's sleep patterns are like on vacation or weekends. DSPS patients generally have less sleepiness if they are allowed to have a delayed schedule (as on vacation), whereas abnormal sleep patterns and fatigue persist with those patients with insomnia. Sleep logs are a useful subjective measure of the overall sleep pattern and can be instructive in demonstrating these patterns to the patient. Actigraphy is an excellent objective measure [15]. Guidelines for the clinical use of actigraphy in evaluation of circadian rhythm disorders including DSPS are available [16]. Actigraphy is especially useful when sleep logs are not completed or unreliable. The morningness eveningness questionnaire (MEQ) measures a person's biologic activity tendencies within the day span, and can be useful as a supportive clinical tool [17].

DSPS Case History

Erica is a 15-year-old female who presents with a several year history of difficulty falling asleep. Her parents complain that they have difficulty walking her in the morning. In fact, over the past 5 months she has missed 35 days of school because her parents were physically unable to help her out of bed. Truancy officers are threatening remedial action. 24-h history reveals that she goes to bed at 11 PM. She often does not fall asleep until between 1 AM and 4 AM (Fig. 6.3). She denies feeling anxious while lying in bed. She does not have leg restlessness nor does she complain of pain anywhere in her body preventing sleep onset. Once asleep she remains so without arousals. Her parents begin calling her at 7 AM. After several calls, they will try and rouse her from bed physically. Often they are unable to awaken her. On weekends, holidays and days she does not go to school, she awakens between noon and 2 PM. During summer vacation when she sleeps ad lib, she does not complain of excessive daytime sleepiness. During the school year, she shares that she falls asleep in her first three classes most days.

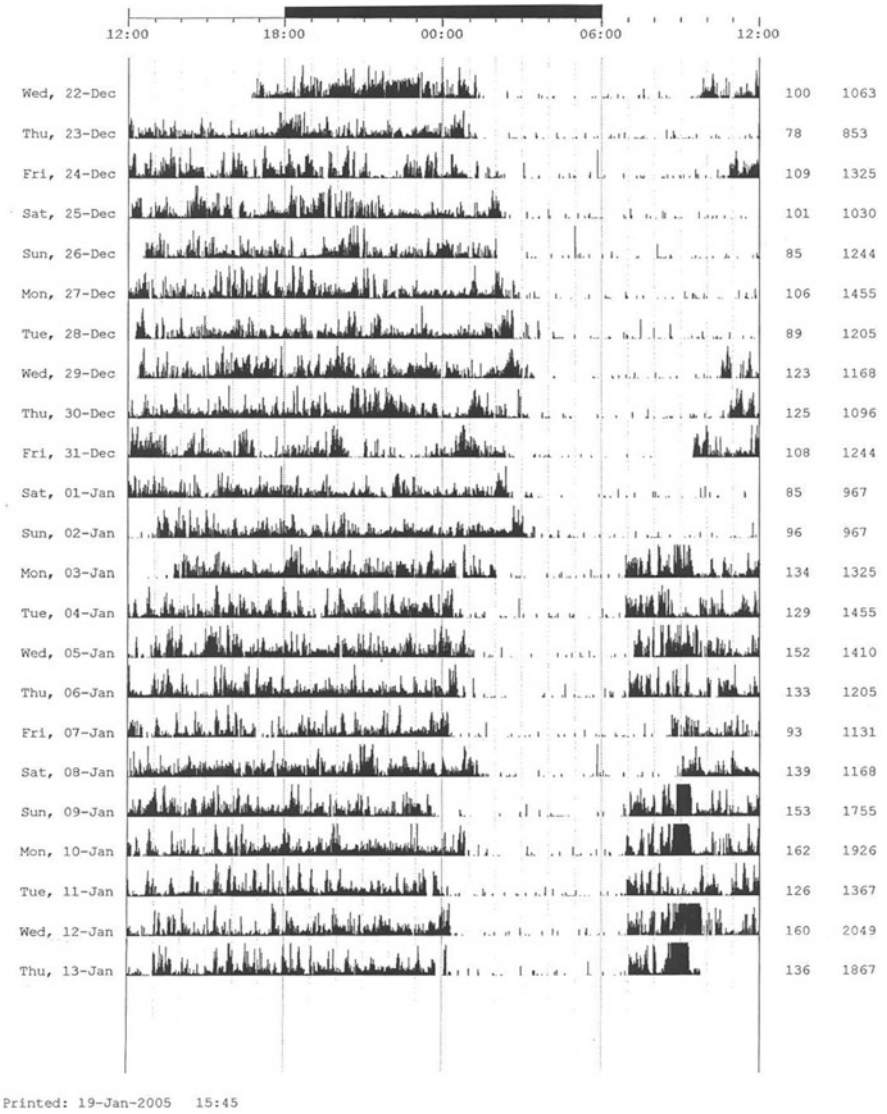

Fig. 6.3 Actigraphy showing the subject's delayed sleep phase

Treatment

Treatment of circadian rhythm disorders falls into three categories: phototherapy, chronotherapy, and pharmacotherapy. The motivation of the teen should be assessed as regular use of the interventions discussed next requires discipline. The teen must be involved in the implementation. If resistance is encountered, searching for an

underlying cause such as depression should be pursued. If depression is present, treating it simultaneously is necessary [18].

Timed light exposure or "phototherapy" involves increasing morning light and decreasing evening light [19]. In North America, increasing morning light may mean using a "light box" 2,500 lx between 6 and 9 AM has been shown to advance sleep as measured by changes in core temperature and improved morning alertness on multiple sleep latency tests. *Ultraviolet* light should be filtered. Patients may also benefit from avoidance of exposure to bright light in the evening [19, 20]. This can include avoidance of artificial sources of light such as television and computer screens.

Rescheduling treatment, known as "chronotherapy," involves the timing of wakefulness and sleep to minimize excessive daytime sleepiness. A general review of sleep hygiene is recommended. Specifically, wake time on the weekends should not be more than 2 h later than wake time during the weekdays. Daytime napping should be avoided.

Standard chronotherapy involves phase advancement. To implement this, the wake time and bedtime are made 15 min earlier each day until the target wake time is achieved [21]. Rarely, physicians promote phase delay [21, 22]. Progressive phase delay involves delaying the bedtime and wake time 2–3 h each 24 h period until the target sleep onset and wake times are achieved. Phase delay is generally reserved for the more severely DSPS patients as it is more difficult to implement with typical daytime responsibilities. Unfortunately, chronotherapy alone often fails [23].

The physician can act as an important advocate for teens with DSPS. Standard high school early morning start times are not in alignment with the physiologic sleep/wake patterns of teens in general and are grossly incompatible and may be academically devastating for teens with DSPS. Writing a letter for a 9 AM school start time is not unreasonable.

Pharmacotherapy is limited to melatonin. Several studies have shown that melatonin advances the sleep phase of patients with DSPS [24–26]. In early studies, 5 mg of melatonin were given 5 h before the mean group sleep onset time. The majority of patients reported a small advance in their sleep phase [27]. Recent studies have revealed that small doses (0.3 mg) of melatonin were as effective as larger doses and timing 6.5 h before dim light melatonin onset (DLMO) provided the best response [28]. The National Sleep Foundation has warned against using melatonin in patients with immune disorders and lymphoproliferative disorders and patients who take corticosteroids or other immunosuppressants [4]. Melatonin is not approved by the Food and Drug Administration (FDA) in the United States [29]. There is not enough evidence to support the use of sedative hypnotics in treatment of DSPS. There is also no evidence to support the use of stimulant medication to promote alertness in patients with DSPS [30]. It must be admitted that many teens are not successful in the implementation of these just described interventions. There is known heterogeneity of genetic mutations manifesting as DSPS. This includes the 4-repeat allele of the per gene3 [31], a gene encoding arylalkylamine (serotonin) N-acetyltransferase (AA-NAT) and HLA-DR1 [32, 33]. It is likely that some mutations are more amenable to treatment than others. Rather than blaming the patient, this should lead the physician to recommend adaptation of the external environment. One strategy is the integration of school

officials and truancy officers in the creation of a plan that helps the teen to graduate. This may mean advocating for evening classes with credits that apply to graduation.

Future Directions

The field needs to improve the objective verification of this diagnosis instead of relying only on self-reported information. This could be done using DLMO serum or salivary assays. This will allow differentiation of circadian rhythm disorders from chronic insomnia [34]. Exogenous melatonin is only effective when given before DLMO. An easy to use assay would make diagnosis more accurate and treatment more effective. Currently, these assays are only available for research purposes in Europe. A clinically available application should be ready within 5 years [35].

Challenges for future research include determining the degree of contribution of homeostatic vs. circadian processes in DSPS. Mary Carskadon is currently studying the homeostatic contribution to DSPS by a method she calls forced desynchrony [36]. Forced desynchrony imposes a 20-h day on individuals involved in the study for 2 weeks. The hypothesis is that the homeostatic process will be revealed as the available sleep time is shifted away from the circadian phase. Finally, conducting treatment research aimed at determining efficacy, effectiveness and mechanism or mechanisms of action is necessary [14]. The field is in need of a more effective chronobiotic agent [30].

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Chapter 7
Defining, Assessing, and Treating Adolescent Insomnia and Related Sleep Problems

Brandy M. Roane

Sleep During Adolescence

Adolescence is a developmental stage that encompasses numerous neuroendocrine and structural brain changes. The reactivation of the hypothalamus–pituitary–gonadal axis triggers the onset of puberty following a dormant period during childhood. The brain undergoes structural reorganization throughout the second decade of life with the most prominent being the pruning of synapses in the cortex [1], which influences physiological correlates of sleep [2]. For instance, adolescents experience a sharp decrease in slow-wave sleep.

Maturation also brings about a change to both processes that regulate the timing of sleep during adolescence. Postpubertal adolescents show a slower accumulation of Process S, or homeostatic sleep pressure, during wake compared to pre- and early pubertal adolescents following sleep deprivation [3]. In essence, older adolescents are able to sustain wakefulness for longer. Puberty is also associated with a delayed phase preference [4]. Carskadon and colleagues showed in controlled laboratory studies that pubertal stage is positively associated with later circadian timing when the sleep/wake schedule is fixed [5, 6]. What these studies show is that adolescents exhibit a tendency to phase delay as they mature despite consistent external light/dark cues. One explanation for this delay may be adolescents experience a lengthening of their intrinsic circadian clock period [7, 8].

Despite this emergence of a delayed preference and notable delays in bedtimes as adolescents mature, their actual sleep need of approximately 9.2h does not change [9].

Note: In the previous edition of this book, the chapter on this subject was authored by Amy R. Wolfson, Ph.D., Alison Quinn, and Anna Vannucci.

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In a 6-year longitudinal study, Carskadon and colleagues found when adolescents were placed in a laboratory setting, which removed environmental factors from influencing sleep time, they continued to exhibit similar sleep needs across all pubertal stages [9]. Thus, they concluded that the external environment was contributing to the reduction in sleep time and not a biological need for less sleep.

Highlighting their conclusions is the well-documented emergence of the "typical" adolescent schedule that occurs once school begins and a weekday nonnegotiable earlier rise time is imposed [10–13]. Adolescents' tendency to phase delay coincides with a shift to earlier school start times that arise with the transition from middle school to high school. In addition, other environmental and societal factors such as homework [14] and extra-curricular activities [12, 15] impinge upon the 24-h day. The resulting schedule forces adolescents to rely on shortened school night sleep periods and extended nonschool night sleep periods to accommodate the increased demands.

Carskadon and colleagues noted that the transition from summer to earlier school start times was associated with increased sleep deprivation and daytime sleepiness [16]. Their findings are not surprising, when you consider the irregular schedules adolescents keep. On average, pre- and young adolescents extend their sleep by 0.5–1h on nonschool nights while this extension jumps to 1.5–2h on nonschool nights for older adolescents [16–18]. The extended nonschool night sleep is more commonly known as the "catch-up," an attempt to pay back the sleep debt accrued during the school week. For the more fortunate who maintain a fairly stable schedule and do not rack up a high debt, this catch-up is manageable; however, for those adolescents who maintain a highly irregular schedule, "catch-up" is not possible. Instead, they fair worse as shown by higher reports of behavior and academic problems, daytime sleepiness, and depressed mood [11].

Emergence of Gender Differences

Many of the neuroendocrine and structural brain changes adolescents experience result in a differentiation of the sexes [19, 20]. During adolescence, observable differences between the sexes arise in their sleep patterns [21, 22], sleep hygiene practices [23], and rates of insomnia [24]. Lee and colleagues noted females reported earlier rise times on weekdays, but later rise times on weekends compared to males, which indicates that females have more variable sleep schedules [21]. Similarly, female adolescents reported more time in bed and later rise times on the weekends compared to males according to Laberge and colleagues [22]. They also noted increased difficulties falling asleep were associated with later weekend wake times. More recently, sleep hygiene practices of children and adolescents have come into focus. Eggermont and Van den Bulck found female adolescents were less likely to use computer games, but more likely to use music and books as sleep aids compared to males [23].

The most striking distinction is the divergence between the sexes in rates of insomnia that occur post-menarche with a well-documented increased risk for adolescent females of 2.75 [24]. Prior to menses onset, boys and girls show no difference in insomnia rates. Adult studies show that this sex-specific divergence in reports of insomnia remains until postmenopause [25].

Investigators acknowledging differences in the genders have looked to the menstrual cycle in hopes of further elucidating mechanisms driving the higher occurrence of sleep disturbances in women [26–30]. Shibui and colleagues found decreased amplitude in the core body temperature rhythm, an increase occurrence of slow-wave sleep during the daytime, and an increased report of daytime sleepiness during the luteal phase compared to the follicular phase in eight young women (age 20–23 years) [29]. They proposed that the increased reports of daytime sleepiness may be the result of the increased slow-wave sleep experienced during the daytime, which may be connected to the changes in thermoregulation during the luteal phase. Schechter and colleagues replicated the decreased amplitude findings in eight women (mean age 26 years), but took Shibui and colleague's study further by examining ovarian hormones, subjective and objective sleep, and circadian variation of core body temperature, melatonin, and sleep. They observed that increased progesterone concentrations were correlated with a blunted nocturnal decline in core body temperature and decreased amplitude [28]. The young women also reported longer sleep-onset latencies and more sleepiness upon awakening during the mid-luteal phase compared to the mid-follicular phase. Objective polysomnogram (PSG) findings showed a decrease in time in rapid eye movement (REM) sleep.

Other investigators have evaluated subjective reports of sleep disturbance. Manber and Bootzin studied 32 healthy young women (mean age 38.7 years) across two menstrual cycles and found women reported increased disturbed sleep during the late luteal phase [27]. These women reported increased difficulties falling asleep, poor quality sleep, and low sleep efficiencies. Baker and Driver sought to hone in more specifically on when women reported the most sleep disturbance during the menstrual cycle by confirming ovulatory cycles. They found 26 healthy young women (mean age 21 years) reported poor sleep quality during a specific timeframe—the last 3–6 days of the late luteal phase and first 4 days of menstruation [30].

The studies in healthy adult women reveal changes across the menstrual cycle are associated with sleep disturbances [26–30]; however, the associations are complex. In part, the complexity revolves around the menstrual cycle and its heterogeneity, particularly in adolescent females. A number of variables work together to impact the diversity seen across females. For instance, several factors impact age of puberty onset such as higher body mass index (BMI), socioeconomic conditions, nutrition, and preventive health care [31]; age of puberty onset then correlates with age of menarche. Following menarche is the interval between the first and second cycle, which is often the most irregular [31]. Irregularity continues throughout adolescence with a regular cycle establishing closer to the sixth gynecologic year [32, 33]. Once a "regular" cycle is established, this cycle varies across women. Thus, the menstrual cycle is highly diverse, and comparisons across women can be difficult at times.

If we consider the Spielman's Behavioral Model of Insomnia that looks to predisposing, precipitating, and perpetuating events to explain the onset of insomnia [34], then the female menstrual cycle is a perfect storm for encouraging insomnia to manifest and maintain. First, the menstrual cycle occurs roughly every 21–45 days during the first 3 years [35, 36]. Therefore, the menstrual cycle acts as both a precipitating and perpetuating event. Adolescent girls who experience sleep disturbances that coincide with their menstrual cycle will do so frequently and repeatedly. Second,

the menstrual cycle is typically variable in length for the first 3 years [31, 35, 36], so, while they experience a menstrual cycle frequently, it will not be so routinely that they easily associate their sleep disturbance with their menstrual cycle. Third, postpubescent adolescent females are prone to a delayed circadian phase [4], which increases the difficulty they experience with falling asleep. Fourth, many of the over-the-counter medications used to treat symptoms associated with the menstrual cycle include caffeine that can further exacerbate sleep disturbances.

The data in young women in their early 20s to late 30s provide strong evidence that women experience sleep disturbances across their menstrual cycle, with the most vulnerability to sleep disturbances being the last few days of the late luteal phase and first few days of the menstruation period. No studies that this author could locate evaluated these phenomena in adolescent females, which is unfortunate.

Assessment of Sleep Disorders in Adolescents

As a child matures, parents become less involved in the bedtime routine and thereby know less of what goes on once the older child or adolescent goes to bed. Parents' lack of knowledge surrounding bedtime may play a part in the underdiagnosis of sleep disturbances in adolescents [37]. Specifically, in younger children, the parents initiate the office visit; however, for adolescents, the parent may not always know the sleep disturbance is occurring. A study by Schreck and Richdale found parents' knowledge about sleep and sleep disorders was poor, but their knowledge about sleep disorders in older children and adolescents was significantly worse [37]. For instance, nearly a third of parents reported they did not know if adolescents snored on a nightly basis or if adolescents slept more on school nights or nonschool nights.

Unfortunately, parents are not alone in their lack of knowledge. Owens found only 46% of pediatricians felt confident in their ability to screen for sleep problems, with 25.3% feeling confident in their ability to treat sleep disorders [38]. Even more alarming, only 43.9% actually screened for sleep problems in adolescents. Psychologist are not fairing any better according to a study by Meltzer and colleagues that polled directors of clinical psychology internships and graduate programs [39]. They reported only 16% of these programs have faculty with a specialization in sleep, and 31% offered training in sleep disorders treatment. These findings highlight the need for more individuals that specialize in sleep disorders; however, a clinician with a good understanding of what to look for and when to refer can handle many of the common difficulties adolescents face.

Many clinicians assessing sleep disorders mistakenly focus solely on the nighttime features of the disorder. Doing so is like saying night and day are two distinct time periods and an adolescent's behavior is not impacted at all by what occurs in the other time period. Anyone who has experienced a night of disturbed sleep can attest to poorer functioning the next day and vice versa: events from your day can intrude upon your sleep.

In order to assess both night- and day-time features of a sleep disturbance, a thorough evaluation of a sleep disturbance should focus on four domains: (1) sleep/wake schedule, (2) bedroom environment, (3) bedtime skills and interactions, and (4) daytime skills and behaviors [40]. Information collected in these four domains can inform your diagnosis and help with treatment planning. Gathering information in these four domains is best done through a multi-method clinical assessment [40, 41]. This assessment should involve a clinical interview, sleep diary data, and standardized assessments (as needed). Prior to the initial visit, adolescents should complete a sleep diary for 2 weeks. Actual diary data are more reliable than having adolescents retrospectively recall average amounts of sleep across the whole week or average sleep on weekend vs. weekday nights. Retrospective recall often is problematic as parents and adolescents typically recall the worst night and last night. A diary reduces this likelihood by providing night-to-night data on the adolescent's sleep/wake schedule. These data also provide a baseline to assess severity and treatment gains. In addition to a sleep diary, actigraphy may prove to be helpful in validating the self-report sleep diary both for baseline assessment and for treatment outcomes [42, 43].

Once the adolescent and family arrive, additional information is collected through the clinical interview and questionnaires, if necessary. The clinical interview will provide you with an opportunity to make behavioral observations and to collect information to inform your diagnosis. Within the interview, collect information on the adolescent's various histories including sleep, medical, developmental, school, psychosocial, and family [41]. Assess the adolescent's daytime functioning both at school and within the home. Also, collect the family's sleep disorder history. Both the adolescent and parents need to provide information during this step, as each will provide valuable information that will help with the diagnosis and treatment planning. During your clinical evaluation, you also want to make behavioral observations regarding how the adolescent looks (e.g., sleepy, alert, sad), parent–child interactions (e.g., do they getalong well, combative, does the parent know what is going on), and any other notable concerns that present. These observations are as important as the information they actually tell you. Since most of the interventions used with adolescents are behavioral in nature, establishing goals during this initial phase is useful as well. By having parents and the adolescent identify goals right away, you focus in on what each party is wanting from treatment, which helps with planning and implementation.

Standardized assessments and questionnaires can be useful in providing additional points of data to inform your clinical interview. For adolescents, a few that would provide beneficial information, noninvasive information, and informed decision-making are the Pubertal Development Scale (PDS) [4, 44], Morningness Eveningness Questionnaire (MEQ) [45], Adolescent Sleep Hygiene Scale (ASHS) [46], and Dysfunctional Beliefs and Attitudes about Sleep (DBAS) [47]. The PDS is a 5-item self-report measure that requires adolescents to report on changes in height, body hair, skin, voice, and facial hair (boys only) and breast and menstruation (girls only). Scores are classified into five pubertal developmental stages (prepubertal, early pubertal, midpubertal, late pubertal, and postpubertal). If concerns arise that the sleep disturbance is occurring within the context of the adolescent female's menstrual

cycle, it is recommended that the subject keep a premenstruation diary for several consecutive months [48]. The MEQ is a 19-item self-report measure that assesses circadian phase preference. Adolescents endorse the time they would prefer specified activities (e.g., school, taking test) to occur. The ASHS is a 33-item assessment that requires adolescents to self-report the frequency they engage in sleep-facilitating and sleep-inhibiting behaviors. The DBAS is a 16-item self-report measure of sleep-related beliefs and attitudes toward sleep.

Insomnia, disrupted sleep, insufficient sleep, and circadian disorders have a high rate of comorbidity with depressed mood [11, 49–52]. Thus, including a measure of depressed mood in your assessment may be beneficial. In addition, other assessments may be warranted if concerns are raised about specific psychological disorders.

Adolescence and Insomnia

Insomnia, broadly defined, refers to difficulties falling asleep, staying asleep, or awakening too early or sleep that is non-restorative. Both the *International Classification of Sleep Disorders,* 2nd Edition (ICSD-2) [53] and *The Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR) [54] require an accompanying daytime impairment and the complaint to be present for at least 1 month. While the DSM-IV-TR distinguishes between primary insomnia and insomnia due to an Axis I or II disorder [54], the ICSD-2 designates 7 types of insomnia based on their presentations [53]. For instance, adjustment insomnia is caused by an immediate stressor and is an acute case of insomnia, whereas idiopathic insomnia has no identifiable cause and has been present throughout the patient's life. The ICSD-2 also categorizes inadequate sleep hygiene as a type of insomnia. For the purposes of this chapter, inadequate sleep hygiene is discussed as a distinct disorder from insomnia, and differentiating between the two is discussed later on.

Another way of classifying insomnia is by the primary time the sleep difficulty occurs. Distinctions made in this way result in three "types" that include sleep-onset insomnia—difficulties initiating sleep; maintenance insomnia—difficulties maintaining sleep throughout the night; and terminal insomnia—awakening before the desired rise time.

The Spielman Behavioral Model of Insomnia [34] focuses on physiological, psychological, and behavioral factors and their role as predisposing, precipitating, and perpetuating events in the etiology of insomnia. This model was mentioned briefly previously in the context of the menstrual cycle being a possible initiating and maintaining event for sleep disturbances in female adolescents. Predisposing factors typically refer to underlying pathophysiological mechanisms. The etiology of insomnia is unclear; however, recent evidence supports genetics as playing a role in predisposing individuals to insomnia [55], while another line of research suggests that hyperactivity of corticotropin-releasing factor neurons predisposes individuals to insomnia [56].

Psychological precipitating events, or events that "trigger" the onset of insomnia, include mood disorders, anxiety disorders, and other psychological disorders. Liu and colleagues found nearly 73% of adolescents with major depression reported sleep disturbances, mostly insomnia [51]. The relationship between insomnia and depression is complex. The two disorders are frequently comorbid, and insomnia symptomology during adolescence strongly predicts future depression [50, 57, 58]. Adolescents with bipolar disorder also report high rates of insomnia [59]. Like adolescents who experience mood disorders, adolescents with anxiety disorders frequently report insomnia. Alfano noted 54% of children and adolescents with anxiety disorders reported trouble sleeping [60].

Physiological precipitants include underlying sleep disorders such as obstructive sleep apnea (OSA) or restless legs syndrome (RLS). Other physiological events include the use of caffeine, medication, alcohol or drug use or abuse, and medical conditions such as chronic pain [61]. Another important consideration when working with adolescents is that the hormonal changes during adolescence create an environment of unique physiological precipitating events. Just as the menstrual cycle creates a perfect storm for adolescent females, changes in adolescents' sleep-wake bioregulatory processes and subsequent delays in their circadian rhythms [1–6] may act as precipitating events for adolescents predisposed to insomnia. For these adolescents, the delay they experience in their circadian rhythms may trigger the onset of acute insomnia. The extended wakefulness when trying to adjust to an early school day schedule creates a potential for compensatory behaviors and dysfunctional beliefs about sleep to develop that transforms acute insomnia into chronic insomnia. Initially, the time awake is filled with laying in bed; however, repeat appearances of time awake can lead to the development of compensatory behaviors such as watching TV, playing video games, texting and reading in bed in an effort to become sleepy and fall asleep. As a result, the pairing of bed with sleep is overshadowed by other pairings, all with wakefulness at their core. The time awake in bed may also lead to anxiety about not falling asleep and provides a prime opportunity for adolescents to ruminate over the inability to sleep, which facilitates the formation of dysfunctional beliefs about sleep [62]. The subsequent daytime consequences such as daytime sleepiness, inattention, and mood disturbance [63, 64] that result from the insomnia sleep pattern and delays in the circadian rhythms reinforce the compensatory behaviors and dysfunctional beliefs about sleep.

Connections between insomnia, phase preference, and circadian rhythms exist. For example, adults with an evening-type preference report higher levels of daytime sleepiness [65, 66] and maladaptive beliefs about sleep [67] compared to morning types. Adults with sleep-onset insomnia exhibit a phase delayed circadian core body temperature rhythm [68], while adults with early morning awakening insomnia show a phase advanced circadian core body temperature rhythm [69]. Adults who exhibited an advance in their circadian core body temperature rhythm reported shorter and more restless sleep [70]. Ong and colleagues evaluated phase preference in adults seeking treatment for insomnia [71]. They found evening types reported longer total time in bed, great variability in their sleep/wake patterns, higher rates of dysfunctional beliefs about sleep, and higher depression scores than morning and neither types.

While the connections between insomnia, phase preference, and circadian rhythms mostly appear in the adult literature, at least one study has shown some indices that these connections are present in adolescents. Adolescents with substance abuse disorders and self-reported sleep difficulties evidenced later dim light melatonin onset (DLMO) than those without self-reported sleep disturbances [72]. Later DLMOs in this group were also associated with longer sleep-onset latencies.

Insomnia obviously has a circadian dysregulation component to its presentation. For adolescents, this circadian dysregulation is likely going to favor a delayed phase tendency. Therefore, teasing apart a diagnosis of insomnia vs. delayed sleep phase disorder (DSPD) may be a challenge. DSPD presents like sleep-onset insomnia, but the complaint of sleep-onset insomnia is schedule-specific [73]. In addition to difficulties initiating sleep when constrained by a "normal" schedule, these adolescents experience difficulties waking in the morning. Thus, difficulties initiating sleep and waking only present when the adolescent attempts to fall asleep at a "normal" societally induced sleep/wake schedule. When left to fall asleep and awake without constraints, such as on vacation, sleep initiation occurs without a lengthy sleep-onset latency and adolescents maintain sleep for a full sleep period [73, 74].

Lastly, behavioral and environmental factors that contribute to the perpetuation or maintenance of insomnia are wide-ranging. The development of unhelpful beliefs about insomnia can contribute to the disorder [47]. Exposure to light prior to bedtime can reduce melatonin levels sufficient to exacerbate adolescents already delayed phase [75]. The "typical" adolescent schedule creates a weekend phase delay that subsequently impacts sleep onset for the beginning of the school week [76]. In addition, many of the sleep hygiene behaviors can contribute to the maintenance of insomnia.

Prevalence rates of insomnia range from 4 to 39% in adolescents, while new onset rates are 5–23% and chronic insomnia rates are 2–20% [24, 77–80]. Rates vary due to differences in criteria for insomnia within each study. Roberts and colleagues estimated DSM-IV criteria for insomnia, which resulted in a prevalence rate of 7.03% and incidence rate of 5.5% [77]. They reported rates of 34.71% for chronicity and 65.29% for remission. Johnson and colleagues defined insomnia as difficulties initiating or maintaining sleep or non-restorative sleep for at least a month with reports of significant distress or impairment plus a frequency of at least 4 times per week [24]. Based on this, 9.4% of adolescents met criteria for insomnia. They also evaluated the role DSPD may play in contributing to insomnia diagnosis. Of the 1,014 adolescents in the study, 19 met criteria for DSPD within the last 2 weeks; however, DSPD did not significantly account for the insomnia cases. Of the 95 adolescents with insomnia, 4 met criteria for DSPD and 91 did not.

Treatment of Insomnia in Adolescents

The differential diagnoses of insomnia include DSPD, inadequate sleep hygiene, and behavioral sleep restriction. Aside from these, considerations should be made for underlying sleep and/or medical disorders. OSA can present with complaints of

frequent night awakenings, but symptoms such as loud snoring, gasping for air, pauses in breathing, night sweats, and enuresis may be present. Similarly, periodic limb movement disorder (PLMD) can present with middle of the night awakenings, whereas those with RLS may complain of sleep-onset insomnia. OSA and PLMD are diagnosed with PSG. If symptoms of another Axis I disorder are present, further evaluation is warranted. Treatment will not necessarily change for insomnia as recent studies show treatment of insomnia reduces symptoms of comorbid depression [81, 82]; however, treatment of the comorbid disorder will need to be taken into consideration.

Clinicians working with adolescents lack the breadth of empirical evidence for treatment outcomes compared to clinicians who work with adult populations. As a result, inferences are drawn from the adult literature coupled with the scant literature showing treatment outcomes in adolescents [83–85]. Weil and Goldfried implemented self-relaxation training to treat insomnia in an 11-year-old [84], and Barowsky and colleagues treated onset and maintenance insomnia in three adolescents with biofeedback [85]. Bootzin and his colleagues treated adolescents (with substance abuse disorders and self-reported sleep problems or daytime sleepiness) with a poly-therapeutic treatment approach, consisting of stimulus control therapy (SCT), bright light therapy, cognitive therapy, mindfulness-based stress reduction, and sleep hygiene education [83]. This study provides the most solid evidence to date that some of the empirically validated approaches used in adults improve sleep disturbances in adolescents as well. A few limitations with this study make drawing conclusions about treatment outcomes difficult because it was unclear if the treatment was the driving factor in changes in sleep (i.e., participants were substance abuse patients) and the control group was not valid. Fortunately, through the efforts of pioneers in the field who work with adolescents, more studies are underway that use many of the treatments outlined in this chapter.

The various behavioral and cognitive strategies for the treatment of insomnia are used as either monotherapies or combined into the polytherapeutic intervention called cognitive behavioral therapy for insomnia (CBTi). CBTi typically includes SCT, sleep restriction therapy (SRT), cognitive therapy with relaxation techniques, and sleep hygiene education. The rationale behind CBTi is that it combines both cognitive and behavioral interventions to address the multifaceted nature of insomnia. Some of the monotherapies that comprise CBTi have solid empirical evidence while others do not [86]. However, no studies to date have dismantled CBTi to determine if all components typically included are necessary [87].

SCT strengthens the association between sleep and the bedroom by removing sleep-incompatible associations [88]. In order to remove wake-promoting associations, access to the bed is made contingent on being sleepy. If the adolescent is not sleepy, then he or she is not to enter the bed. Instead, the adolescent should engage in a mundane activity in dim light to reduce stimulation and impact of light on the circadian timing system. Through repeated experiences of falling asleep quickly in bed, the bed and bedroom are reestablished as cues for sleep. SCT consists of five key instructions: (1) go to bed only when sleepy, (2) get out of bed when unable to sleep within 15–20min, (3) use the bed for sleep only, (4) wake-up at the same time each morning, and (5) no daily naps.

SRT increases the likelihood of falling asleep quickly by reducing the allowable time in bed [89]. By restricting the total time in bed, homeostatic sleep pressure continues to build throughout the day because continued wakefulness is required for a longer period of time before getting into bed. The result is a quicker sleep onset and reduction in sleep fragmentation. Pretreatment sleep diary data inform the treatment prescribed total sleep time and required wake-up time. The wake-up time typically remains constant across all 7 days of the week and is based on the earliest time the adolescent has to be awake during the week. Once the adolescent achieves a sleep efficiency over 85% ([total sleep time/total time in bed] × 100), their total time in bed is increased by 15min. This incremental increase occurs each week until the optimal time in bed is achieved. Both SCT and SRT will likely increase daytime sleepiness because the adolescent will be getting out of bed when sleep is not occurring (SCT) and will have restricted access to bed (SRT). The practitioner should be sure to discuss the implications of decreased total sleep times with the adolescent and parents, so they understand potential ramifications of increased daytime sleepiness and do not end treatment prematurely.

Cognitive therapy for insomnia focuses on identifying unhelpful beliefs about sleep and replacing these with more adaptive substitutes [90, 91]. Unhelpful beliefs about sleep are identified through the interview and standardized assessments, such as the DBAS [47]. Once unhelpful beliefs are identified, it is important to work with the adolescent to challenge and replace these through education and behavioral experiments.

Various relaxation techniques can be used with CBTi, including progressive muscle relaxation (PMR), diaphragmatic breathing, visual imagery, meditation, and/or yoga. Until recently, PMR had the most evidence to support it in the treatment for insomnia [86, 87]; however, more recent work combining mindfulness meditation with CBTi shows very promising results [92–94]. The overarching goal of relaxation training is to induce relaxation through diverting focus. For instance, PMR trains adolescents to focus on tensing and relaxing muscle groups while mindfulness meditation teaches adolescents to be aware of their thoughts and actions in the present only. Each teaches sustained focus, which allows the body time to relax. Relaxation therapy is a skill that requires daily practice. Adolescents should initially practice it before bed and not when they require it to help them go to sleep or return to sleep.

Sleep hygiene education will be more fully covered under the inadequate sleep hygiene treatment section since it is ineffective as a stand-alone treatment for insomnia [95]. Yet, sleep hygiene education and medication are the most common treatments in primary care for insomnia in adults. However, empirically validated standards of care for prescribing hypnotic medications in children and adolescents do not exist [96]. In addition, medication may provide acute symptom relief, but studies in adults with insomnia show medication is unable to sustain long-term effectiveness [87] (see Table 7.1).

Table 7.1 Cognitive and behavioral therapies for insomnia

Stimulus control therapy (SCT)
Go to bed when sleepy
Get out of bed when unable to sleep within 15–20min
Use bed for sleep only
Wake-up at the same time each morning
No daily nap
Sleep restriction therapy (SRT)
Set total sleep time based on pretreatment sleep diaries
Wake time should be based on earliest required wake-time during the week and remain constant across all 7 days
Slowly extend total sleep time by 15min if sleep efficiency is >85% until optimal sleep time is achieved
Decrease total sleep time by 15–30min if sleep efficiency is <85%
Cognitive therapy
Identify unhelpful beliefs about sleep through interview and assessment
Challenge and replace unhelpful beliefs about sleep through education and behavioral experiments
Relaxation training
Find a technique preferable to the adolescent such as progressive muscle relaxation, diaphragmatic breathing, visual imagery, meditation, or yoga
Practice daily for 20–30min before bedtime

Delayed Sleep Phase Disorder

Adolescents, prone to a delayed circadian timing system, are especially susceptible to DSPD compared to other age groups. DSPD is thought to be due to a misalignment between the intrinsic circadian timing system and imposed sleep/wake schedule [73, 74, 97]. An important note is these adolescents are not experiencing the expected delay that their peers experience. Instead, their intrinsic circadian timing system is delayed by several hours with sleep onset occurring as late as 1–6a.m. [53]. As indicated previously, these adolescents present with sleep-onset insomnia and difficulties awakening when a "normal" sleep/wake schedule is imposed. When allowed to sleep at their preferred time, they do not experience these same difficulties. Unfortunately, society does not afford adolescents the ability to alter their schedules to accommodate their preferred sleep/wake schedule. Thus, these adolescents frequently experience adverse consequences that result from an imposed "normal" schedule including daytime sleepiness, truancy, and depressed mood [98, 99].

The DSM-IV-TR requires a "persistent or recurrent pattern" [54] but does not specify how long this pattern must persist. The ICSD-2 requires at least 7 days of data via a sleep diary or actigraphy monitoring that coincides with a sleep diary [53]. Both diagnostic systems require the disorder to result in impairment in functioning. Applebee and Garcia provide a more thorough discussion of DSPD in Chap. 6 of this book.

Treatment of DSPD

Differential diagnoses to consider are insomnia, inadequate sleep hygiene, and behavioral sleep restriction. Differentiating between an intrinsically delayed phase vs. a behaviorally induced delayed phase requires listening for key distinctions in presentation. With behavioral sleep restriction, adolescents do not tend to complain of sleep-onset insomnia. Adolescents who experience inadequate sleep hygiene engage in behaviors that push their circadian timing system to delay, but if removed from these environmental factors, they would fill a "normal" sleep period without experiencing persistent delays in their circadian timing system. Adolescents who try to avoid school may delay their bedtime on school nights, which results in difficulties waking up on school mornings. Restless leg syndrome should be considered if the adolescent indicates these symptoms are present. If symptoms of another Axis I disorder are present, further evaluation of that disorder is warranted so treatment can be sought in conjunction with treatment for DSPD.

Several treatment options are available for DSPD including chronotherapy, bright light therapy, and exogenous melatonin therapy [97]. Chronotherapy for DSPD entails delaying the adolescent's bedtime by 3h per day until the adolescent's desired sleep/wake schedule is achieved [100]. Bright light therapy phase advances the adolescent's circadian timing system by ending the adolescent's night with bright light. The timing of the light and the light intensity are important. Timing of the light should be based on the adolescent's circadian phase, using the light phase response curve (PRC) to maximize effectiveness. In addition, the brighter the light, the larger the phase advance [101]. Unfortunately, at this time, guidelines have not been established for how long adolescents should use a light device both in terms of minutes or hours per day and number of consecutive days to phase advance [73].

Inadequate Sleep Hygiene

Inadequate sleep hygiene involves engaging in behaviors that interfere with sleep onset or maintenance due to the timing [53]. For instance, drinking a soda in the morning has less influence on sleep onset than drinking the soda in the late afternoon or early evening. Consuming at the later time does not allow a sufficient amount of time for the drug to wear-off before the sleep period. Common contributing factors that are considered inadequate sleep hygiene behaviors are a variable sleep/wake schedule, napping, pre-bedtime activities that influence sleep onset and maintenance (e.g., electronics use, exercise), eating irregular meals, and alcohol or tobacco use.

The various inadequate sleep hygiene behaviors influence sleep differently. For instance, Pollak and Bright found an association between increased caffeine intake and middle of the night awakenings [102]. Mindell and colleagues found 43% school-aged children had a television present in the room and 41% drank caffeinated beverages at least once per day [103]. Interestingly, both were associated with an average reduction in total sleep time per night of 20min compared to their peers who did not have a television present or do not drink caffeinated beverages. Several

studies show electronic use is associated with delayed bedtimes and shorter sleep durations [104–108]. Van den Bulck noted a large percentage of adolescents use their phones immediately after "lights out" for text messaging (55.6%) and for calls (58%), and roughly a fifth continue to use their phones between midnight and 3a.m. for text messaging (20.3%) and calls (17.3%) [107]. Adolescents who used their phones for text messaging or calls after lights out at least once a week were twice as likely to be very tired.

Actual prevalence rates of inadequate sleep hygiene are unknown. Manni and colleagues found 1.6–10.2% of adolescents met criteria for non-restorative sleep and engaged in an improper sleep hygiene behavior [109]. For instance, 10.2% of the adolescents met criteria for poor sleep and reported drinking coffee; 1.6% of the adolescents met criteria for poor sleep and reported using alcohol.

Differentiating Inadequate Sleep Hygiene from Insomnia

As indicated in the treatment section for insomnia, sleep hygiene education is frequently included in the multicomponent approach of CBTi. Good sleep hygiene behaviors are what "good sleepers" tend to do. Through reasoning, you can conclude that "bad sleepers," including people with insomnia, must have poor sleep hygiene practices. This thought process is misleading. Not all individuals with insomnia have poor sleep hygiene practices and not all individuals with poor sleep hygiene behaviors have insomnia, as described in the previous section. In addition, inadequate sleep hygiene can exacerbate the severity level of insomnia in an individual predisposed to insomnia. However, if an individual is experiencing disturbed sleep solely due to poor sleep hygiene, then, once the poor sleep hygiene behaviors are addressed, the sleep disturbance dissipates. Conversely, individuals with insomnia will continue to report insomnia symptoms if only the sleep hygiene behaviors are treated.

Treatment of Inadequate Sleep Hygiene

If evidence from your assessment indicates the adolescent engages in poor sleep hygiene behaviors, then a diagnosis of inadequate sleep hygiene should be given. Adolescents meeting criteria for inadequate sleep hygiene does not preclude them from also meeting criteria for insomnia, circadian rhythm disorder, or behavioral sleep restriction. If inadequate sleep hygiene is part of the diagnosis, then treatment should include sleep hygiene education [110, 111] that specifically targets the areas the adolescent endorses having difficulties with. In general, sleep hygiene education includes ensuring your sleep environment is conducive to sleep, maintaining a consistent sleep/wake schedule, avoiding stimulating activities the hour before bedtime, eating regular meals so you do not go to bed hungry, avoiding naps, eliminating caffeine 4–6h before bed, and staying away from alcohol and nicotine (see Table 7.2).

Table 7.2 Sleep hygiene education for adolescents

Insure your sleep environment is quiet, dark, relaxing so it is conducive to sleep
Maintain a consistent evening routine, bedtime, and rise time with no more than approximately an hour difference between school and nonschool nights
Avoid stimulating activities approximately 1h before bedtime
Eat regular meals and avoid going hungry or eating to excess
Avoid long, unscheduled and late afternoon/evening naps
Avoid consuming caffeine during the day, especially 4–6h before bedtime
Stay away from alcohol and nicotine, as they disturb sleep

Behavioral Sleep Restriction

Adolescents reported an increase in sleep restriction and daytime sleepiness with the transition from summer to earlier school start times [16]. Survey and longitudinal studies show that on average 60% of adolescents report being "too sleepy to get out of bed" [112] or "tired upon awakening" [18] and nearly 70% need a parent to wake them up on school mornings [13].

In addition to biology and school start times, there are other environmental factors such as increased homework load [14], extracurricular activities [12, 15], social activities and media use [23, 104, 113], and reduced parental influence on bedtime [12, 13, 114] that work against adolescents achieving an adequate amount of sleep. They, like their parents, often choose other activities before sleep. Roberts and colleagues reported a prevalence rate of 8.89%, incidence rate of 8.17%, and chronicity rate of 2.9% for restricted sleep (sleeping <6h) on both school and nonschool nights [115]. Rates increased to 19.82% for prevalence, 16.92% for incidence, and 13.13% for chronicity when sleep restriction was limited to school nights only. Sleeping <6h is at least 3h less than the necessary 9.2h required by adolescents. Detriments in performance occur prior to restricting sleep on a nightly basis by 3h. Thus, their study likely is underreporting the actual occurrence of restricted sleep in adolescents.

More extreme findings were reported by the 2006 Sleep in America poll that showed 87% of adolescents slept <9h and 62% slept <8h on school nights [13]. Interestingly, adolescents endorsed sleeping more on nonschool nights; yet, 41% still indicated they slept <9h on nonschool nights. As shown by other studies, adolescents who slept <8h were more likely to endorse negative daytime consequences such as feeling too tired or sleeping, having a depressed mood, daytime sleepiness in school, irritability or crankiness, and consuming more caffeinated beverages.

Differentiating Behavioral Sleep Restriction from Insomnia

Unlike with insomnia, adolescents experiencing behavioral sleep restriction do not report difficulties falling asleep or staying asleep when they attempt to fall asleep at night. On the contrary, they report rapid sleep onset, difficulties awaking in the morning,

and daytime sleepiness due to insufficient sleep periods. What deems the sleep period as insufficient may vary for some adolescents. Most adolescents need around 9.2h; however, some may require more or less as this is an average need. A useful, helpful tool is to collect data on how long the adolescent will sleep if unhindered by a schedule. These data are extremely useful in knowing how much sleep the adolescent needs and in determining if the adolescent is self-imposing sleep restriction for other reasons like underlying insomnia. In addition, considering the sleep needs of the parents can be useful in determining if the adolescent may be a "shorter" or "longer" sleeper. These adolescents will have high sleep efficiencies vs. the lower sleep efficiencies experienced by adolescents with insomnia because the time they spend in bed is spent sleeping. Unfortunately, they simply do not spend enough time in bed sleeping.

Treatment of Behavioral Sleep Restriction

If symptoms for behavioral sleep restriction arise during your assessment, make sure to rule-out several other disorders before you finalize your decision. You should consider OSA and other sleep disorders if symptoms present during the interview and data collection. Also rule-out inadequate sleep hygiene. Adolescents who engage in high levels of electronic use prior to bedtime more frequently have later bedtimes and, therefore, have shorter sleep periods. Once you can rule-out other disorders, then you can conclude that the sleep disturbance is due to behavioral sleep restriction.

The major goal of treatment is to extend the total sleep period. Often, adolescents and parents are skeptical when told they are to extend their total sleep time. Considering they are selectively choosing to shorten the sleep period, you can expect they may not be excited that the goal is to lengthen it. One main consideration is they are not always sure "how to get more sleep" or "where the time will come from." In order to achieve the major goal of sleep extension, you need to help them find the time by working with their schedule and increasing their motivation to place importance upon sleep. Sleep extension may be a gradual process or an immediate process depending on the adolescent and parent. The clinician should plan to work with the family before they leave the visit on how the additional sleep will fit into the adolescent's schedule. Another component is problem-solving with the family. Problem-solving helps the family anticipate difficulties and build skills to overcome problems. Make sure to increase motivation, which may require the use of an adjuvant treatment like motivational interviewing.

Conclusion

Several factors contribute to the onset of insomnia, DSPD, inadequate sleep hygiene, and behavioral sleep restriction in adolescents. Strong evidence links the differentiation in risk for sleep disorders to menarche-onset. Adult studies support connections between the menstrual cycle and insomnia symptoms. However, no studies have fully explored this

connection between the menstrual cycle and sleep disturbances in female adolescents. Biological delays in the adolescent circadian timing system combined with environmental and societal factors further contribute to the onset of sleep disturbances. Improved education regarding sleep and sleep disorders is needed for adolescents, parents, educators, and healthcare providers in order to increase diagnosis and connect adolescents with treatment. In addition, studies providing treatment outcomes specific to adolescents are sorely needed.

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Part III
Premenopausal Women

Chapter 8
Restless Legs Syndrome: An Overview with an Emphasis on Women

David M. Hiestand

Introduction

Restless legs syndrome (RLS), soon to be renamed Willis–Ekbom disease, is a sensorimotor disorder that affects sleep in up to 10% of the population. Individuals experience uncomfortable sensations of the extremities, which occur with inactivity and are relieved with activity. Because of the circadian rhythmicity of these symptoms, RLS symptoms can interfere with sleep onset. Symptom descriptors are varied; some commonly used terms are "creepy-crawly," "uncomfortable," "pins and needles," and "internal itch." Regardless of the descriptor, symptoms of RLS include a compelling urge to move, as they are usually improved with movement, and patients frequently resort to flexing, stretching, and vigorous movement. The end result is typically poor quality of sleep, leading to excessive daytime somnolence and feelings of fatigue. Although the disorder affects both genders, it is more common in women (in most populations studied) and is associated with several medical conditions including uremia, anemia, diabetes, pregnancy, fibromyalgia, and menopause.

The disorder was described by Karl Ekbom in 1945 [1] after an initial description by Sir Thomas Willis in 1865. It was not until 1995, however, that the International Restless Legs Syndrome Study Group (IRLSSG) standardized criteria for the definition and diagnosis of RLS [2]. These criteria were further updated in 2002, and currently the following four diagnostic criteria are considered essential for diagnosis:

1. The patient must have an urge to move the legs, usually accompanied by an unpleasant sensation in the legs.
2. RLS symptoms must be aggravated by rest or inactivity such as lying or sitting.

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3. RLS symptoms must be alleviated by movement, in particular, walking, at least as long as the activity continues.
4. RLS symptoms must be worse in the evening or night either currently or in the past when the condition first started.

Secondary supporting symptoms include having a first-degree relative with RLS, periodic limb movements (PLMs), and relief with dopaminergic agents.

Diagnosis is based purely on clinical grounds, with history making up the key component of the evaluation. In light of the impact on women and the necessity of clinical diagnosis, the practitioner caring for women must be able to recognize the symptoms of RLS, complete necessary diagnostic studies, and initiate therapy.

Another disorder that can coexist and is often confused with RLS is periodic limb movement disorder (PLMD). PLMD, as defined by the *International Classification of Sleep Disorders*, Second Edition, [3], consists of four features: Polysomnography (PSG) demonstrating repetitive, highly stereotyped, limb movements that are:

1. 0.5–5.0 s in duration
2. Of amplitude greater than or equal to 25% of toe dorsiflexion during calibration
3. In a sequence of four or more movements
4. Separated by an interval of more than 5 s (onset-to-onset) and less than 90 s (typically 20–40 s)

Additionally:

- The PLM index exceeds 15 per hour in adults (or 5 per hour in children)
- There is a clinical sleep disturbance or complaint of daytime fatigue
- The limb movements are not better described by another condition or illness

The subjective complaints in this disorder are typically limited to poor sleep and insomnia with a heavy emphasis on PSG findings, distinguishing this disorder from RLS.

Although PLMs may be noted in patients undergoing PSG for other indications, one must remember that PLMs in the absence of symptoms do not establish the syndrome of RLS. Furthermore, a PLM index of more than 5 is commonly found both in normal subjects and in patients with other sleep disorders. In a study of 100 patients including controls, insomniacs, hypersomniacs, narcoleptics, and RLS patients, the prevalence of a PLM index greater than 5 was 55% in controls, 40% in insomniacs, 30% in hypersomniacs, 80% in narcoleptics, and 85% in RLS patients [4].

PLMs are also seen in association with commonly prescribed medications. In a study of nine depressed patients on fluoxetine compared with six depressed patients on no medication, PLMs were observed in 44% of the medicated patients [5]. This finding has been demonstrated with other antidepressants. Bupropion, in contrast, has been shown to decrease the number of PLMs in depressed patients with this disorder [6].

In addition to the association with medications, PLMs are also associated with other sleep conditions, such as narcolepsy, rapid eye movement (REM) sleep

behavior disorder and sleep-disordered breathing, including upper airways resistance syndrome (UARS) [7, 8]. In the case of obstructive sleep apnea (OSA), however, it is unclear whether PLMs are caused by the associated disorder or are merely associated with the arousals that result from that disorder [9].

PLMD can, under appropriate circumstances, be treated with the same medications used to treat RLS. In the absence of subjective symptoms, however, the benefits of therapy must be carefully evaluated. Furthermore, identification and treatment of associated conditions may be a more prudent initial therapy.

Epidemiology

The prevalence of RLS in the population was originally estimated by Ekbom [1] to be 5%, based on his clinical population. The current prevalence estimates have been somewhat controversial, with most studies representing questionnaire responses without clinical validation or characterization of frequency of symptoms. A population-based telephone survey from Kentucky found that 10% of respondents experienced symptoms at least "often." In this study, there was an age-related increase in prevalence, with 3% of those affected being 18–29 years of age and 19% aged 80 or older [10]. This study demonstrated no difference between prevalence in men and women. More recent studies have validated the correlation between increasing prevalence of symptoms with increasing age and have also identified a clear gender difference in symptom occurrence and prevalence.

A recent and relatively large survey of 2,099 rural primary care patients, designed for the purpose of identifying the prevalence of RLS in a general population, revealed that 24% of patients were positive for all four of the cardinal symptoms used to make the diagnosis of RLS. Furthermore, 15.3% of these patients reported symptoms at least weekly [11]. In this study, RLS was more common in women (59%), and patients reporting symptoms were significantly older than patients without symptoms. The demonstration of higher prevalence of RLS symptoms in women is most striking in a study conducted in Germany of more than 4,300 individuals. This was a cross-sectional survey with face-to-face interviews and physical examinations. In this study, the overall prevalence of RLS was 10.6%, and women were twice as likely to have the disorder as men [12]. Furthermore, parity was associated with the prevalence of symptoms. Nulliparous women had equal prevalence to men up to age 64, but those with one child were twice as likely and those with three or more children were 3.5 times more likely to have the disorder. This study was the first to demonstrate an association with parity, which, along with the association with pregnancy and menopause, provides strong support for the role of sex hormones in the etiology and pathophysiology of the disorder.

More refined and involved studies conducted in the last few years have assessed prevalence of symptoms with follow up clinical evaluation to exclude medical and pharmaceutical confounders. In a study by Allen et al., approximately 313,000 people were surveyed with nearly 62,000 respondents. Of these, 4,484 reported

RLS symptoms and 1,400 of these were randomly selected to participate in further testing with clinical evaluation. This study produced a conservative estimate of the US census-weight prevalence of 2.4% for primary RLS [13], with 88% being female. This study also addressed disease-related cost and quality of life burden, demonstrating mean productivity loss of 1 day per week and increasing RLS-related costs with severity of symptoms.

Although age and gender now appear to have clear roles in the prevalence of RLS, there also appear to be racial and ethnic differences. In a study of African American and Caucasian Americans undergoing hemodialysis, RLS symptoms were less common in the African Americans [14] than in the other ethnic groups. To date, there are no specific studies addressing racial differences in a general population, and this remains an area of active investigation.

Similarly, there are few and relatively small studies of RLS prevalence in non-Western populations. In a study conducted in Singapore, less than 1% of individuals reported symptoms of RLS [15]. In a Japanese study, only 5% reported symptoms of RLS, and symptoms were more common in men [16]. In a small study conducted in India, only 6.6% of patients undergoing hemodialysis had symptoms, and 0% of a control group of normal individuals had symptoms [17]. These studies appear to measure overall prevalence in Eastern populations as somewhat less than the prevalence in Western populations and implicate a complex pathophysiology with multiple potential etiologies.

Although more prevalent with advancing age, RLS has been well described even in children [18, 19], in whom the disorder may be misdiagnosed as growing pains or attention deficit hyperactivity disorder (ADHD). There are no specific data on gender difference among children.

Etiology and Pathophysiology

As a result of the findings in epidemiological studies, the etiology and pathophysiology of RLS remains an area of intense research. The disorder is commonly encountered as an idiopathic disorder, although it has been associated with a number of medical conditions. These associated medical conditions include pregnancy, fibromyalgia, rheumatic disease, diabetes, renal insufficiency, vascular insufficiency, iron-deficiency anemia, thyroid disease, and others. When associated with a chronic medical condition, the disorder is sometimes referred to as secondary RLS. Although symptoms seem to improve in both idiopathic and secondary RLS with standard therapies, as outlined here, it is unclear if primary and secondary forms result from the same mechanism.

An understanding of the etiology of this disorder has been derived from evaluation of anatomical studies, neurotransmitter systems and iron metabolism. Further postulated mechanisms are derived from associations with pregnancy and menopause, implicating sex hormones in this disorder.

From detailed studies of the peripheral, spinal, subcortical and cortical components, RLS appears to result from dopaminergic deficits in the central nervous system. This finding has been most convincingly demonstrated from studies of centrally acting dopaminergic agents, which attenuate symptoms, whereas peripherally acting dopaminergic agents do not [20]. The specific mechanism of this phenomenon has not been elucidated.

Similarly, the relationship to iron deficiency has been recognized since the studies of Ekbom [21]. Further studies have consistently validated this finding. In a study of 18 elderly patients with RLS and 18 age-matched controls, serum ferritin was significantly lower in RLS patients and correlated with severity of symptoms [22]. In another study of 27 patients aged 29–81 years, a ferritin level of less than 50 ng/dL was found in all but one patient and correlated with severity of symptoms [23]. In a study examining magnetic resonance imaging (MRI) estimates of brain iron, individuals with RLS had significantly reduced ferritin levels in the substantia nigra [24].

Because the symptoms of RLS typically occur at night, a circadian-related mechanism has been actively investigated. Serum iron levels have been shown to be decreased by 50% at night [25]. Iron is an essential element for the synthesis of dopamine, and dopamine production is increased at night. A prevalent hypothesis is that RLS results from low levels of iron in the brain, which interferes with dopamine synthesis.

The specific localization of dopaminergic dysfunction has been more difficult to elucidate. Functional imaging with single photon computed emission tomography (SPECT) and positron emission tomography (PET) has demonstrated conflicting results related to reduced basal ganglia dopamine receptor binding [26–28]. Therefore, despite strong support for the role of central iron and dopamine metabolism in the etiology and pathophysiology of RLS, further investigation is still needed.

In light of the circadian cycling of symptoms and the known circadian cycling of hormones, a causative mechanism has been postulated. Michaud et al. have shown that PLMs are associated with salivary melatonin secretion [29]. Perhaps paradoxically, however, exogenous melatonin improved PLMs in most patients [30]. Further complicating this analysis was the finding that urinary excretion of 6-hydroxy melatonin does not vary in patients with RLS compared with controls [31], and therefore the relationship between RLS and melatonin requires further investigation.

Further support for hormonal regulation of RLS in women comes from the increased prevalence of symptoms in pregnancy. Pregnant women have a two- to threefold higher risk of symptoms than does the general population. The severity of these symptoms is generally highest during the third trimester, and they tend to disappear around the time of delivery. Therefore, in addition to possible etiologies including iron and folate metabolism, several hormonal changes are prevalent in the third trimester. Prolactin, progesterone, and estrogens are elevated, thus lending support to reports of their role in this disorder. Further research is needed in this area, however, because there is currently no definite evidence of a role for these hormones in the pathogenesis of this disorder.

RLS has been identified as a genetically inherited disorder in some individuals, with a family history present in up to 60% of individuals [32–34]. In individuals

with a family history of RLS, symptoms tend to begin earlier in life [35]. In a large study of mono- and dizygotic twins evaluated for RLS symptoms, heritability was estimated at 54% [36]. In a study of 12 monozygotic twins, RLS was concordant in ten pairs [37]. After initial investigations of two families by genetic linkage mapped associations to chromosomes 12q [38] and 14q [39], further studies have identified 5 genes and 10 different risk alleles for RLS [40–42].

Diagnosis

The diagnostic criteria of RLS, as identified by the *International Classification of Sleep Disorder,* Second Edition, are listed in Table 8.1. The International Restless Legs Syndrome Association also publishes diagnostic criteria similar to those seen in Table 8.1, but adds the following supportive criteria: PLMs in sleep, sleep disturbance especially difficulty in sleep initiation, dyskinesias while awake that occur almost exclusively at rest, positive family history, exclusion of potential underlying causes of RLS and onset at any age with typically chronic and progressive course, and occasional remissions. Emphasis is placed primarily on the history obtained from the patient and, if available, the information from the patient's bed partner. It is important to differentiate between alternative explanations for extremity discomfort. Such alternative diagnoses include diabetic polyneuropathy, leg cramps, and arthritic pains. Upon excluding these diagnoses, a compatible history is all that is needed—and often all that is available—to make a diagnosis. Patients are generally asymptomatic during daytime visits, and physical examination findings are typically normal. Finally, there are no available laboratory markers that can confirm the diagnosis.

In evaluating for alternative diagnoses, a clinical history is generally sufficient. Pain associated with diabetic neuropathy is present during the day and may simply be exacerbated at night. Pain from arthritis also occurs during the daytime, but it also affects the joint(s) more than the distal extremities, is associated with some stiffness, and is generally exacerbated by activity. Leg cramps are typically described as a continual, aching pain in the calves, which is worse at night, worse with

Table 8.1 Diagnosis of RLS in patients older than 12 years

A. The patient reports an urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensation in the legs
B. The urge to move or the unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting
C. The urge to move or the unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues
D. The urge to move or the unpleasant sensations are worse, or only occur, in the evening or night
E. The condition is not better explained by another current sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder

walking, and associated with palpable knots in the calf muscles. Other considerations in the differential diagnosis that have distinct history and physical exam features include akathisia with generalized restlessness and lumbosacral radiculopathy with characteristic radicular physical exam findings. ADHD can also be considered in the appropriate clinical context, though this is typically clinically apparent from daytime symptoms.

In patients with a history compatible with RLS, evaluation for potential secondary causes is also warranted. This evaluation should include a history related to possible anemia, including gastrointestinal blood loss, menstruation, and the like. Determination of serum ferritin level is warranted with treatment, as outlined later in this chapter. Controversy exists regarding the indication for thyroid evaluation. A higher prevalence of RLS was found in patients with hyperthyroidism in one study [12], but routine evaluation in the absence of clinical suspicion is likely not warranted. Because of the high prevalence of PLMs in other disorders, PSG is not indicated unless warranted for the evaluation of other sleep disorders.

Diagnosis in children can be difficult, especially in younger children with limited capacity to conceptualize or articulate symptoms. Given the genetic predisposition of the disorder, in individuals with a family history and complaints of poor sleep, insomnia or growing pains, a high clinical suspicion is warranted. In this scenario, PLMs identified on PSG may be sufficient for diagnosis and treatment.

Symptoms can be characterized by severity and frequency in order to determine the need for and effectiveness of therapy. The IRLSSG has developed and validated a rating scale for this purpose. The scale contains ten patient-reported items assessing frequency and severity of RLS symptoms over the preceding week. Responses are graded from 0 (absent symptoms) to 4 (severe) symptoms [43]. This scale can be useful in the management of patients who are attempting to use non-pharmacologic therapies and for those in whom pharmacologic dose titration is needed.

Management

The goal of therapy is to reduce the severity of symptoms in order to allow the onset and maintenance of sleep. For individuals with infrequent symptoms or symptoms that do not significantly affect quality of life, therapy may be tailored to behavioral and non-pharmacological therapies. Individuals with frequent symptoms or symptoms causing daytime somnolence should be evaluated for secondary etiologies. Once excluded, patients may benefit from the addition of appropriate pharmacotherapeutic agents. Although several agents have been used in RLS, none have yet been approved by the United States Food and Drug Administration.

As previously mentioned, the initial evaluation of patients with symptoms of RLS should include an evaluation for anemia and iron deficiency. Correction of iron deficiency for the treatment of RLS may be all that is required to alleviate symptoms and is encouraged as a first-line approach to this disorder. In individuals with anemia secondary to iron deficiency, an evaluation for pathological etiologies of blood

loss should be initiated and iron supplementation should be instituted. Ferritin levels should be checked at 3-month intervals, with a goal of achieving a serum ferritin level up to 75 ng/dL [23, 44]. Iron can be prescribed in multiple forms. The cheapest preparation, iron sulfate, can be administered in a 325-mg dose three times a day. Most clinicians recommend taking iron sulfate with concurrent administration of 200 mg of vitamin C to enhance oral absorption. Oral iron can cause constipation and abdominal discomfort. It should be taken on an empty stomach to enhance absorption, but if gastrointestinal discomfort occurs, it can be taken with non-dairy, non-fiber containing foods.

Upon elimination or treatment of secondary etiologies of RLS, consideration of non-pharmacological treatments should be considered. Such treatments may include nutritional supplementation, exercise, massage, and sleep hygiene [45, 46]. The use of non-pharmacological approaches to symptoms is particularly important for pregnant women. Patients in the course of the illness, often prior to seeking medical advice, usually discover the best treatment methods. Physical activity such as active stretching prior to bedtime may be of benefit. Hot baths, cold baths, or alternating hot and cold baths may provide some relief of symptoms. Massage can be comforting and alleviate symptoms temporarily. Maintenance of appropriate sleep hygiene is encouraged, because sleep deprivation and fragmentation can exacerbate symptoms. An excellent and up-to-date website for support and medically reviewed information is the Restless Legs Syndrome Foundation website (www.rls.org).

Two non-pharmacologic treatment modalities for which patients may seek medical advice include pneumatic compression devices and near-infrared light (NIR) therapy. Several small studies of pulsed compression devices, utilizing 40 cm H_2O intermittently to the thigh and leg regions for 1 h, have resulted in improvement in IRLSSG and quality of life scores [47–49]. The postulated mechanism of benefit is through the release of nitric oxide from vascular endothelium, which moderates symptoms. NIR is also thought to effect nitric oxide release and has been used in the treatment of neuropathy and wound healing. Two small studies have demonstrated improvement in IRLSSG scores after three-time weekly treatment for 4 weeks [50, 51].

Individuals may also seek to implement complementary and alternative medicine. These therapies may include Vitamins E, D, B, and C along with glucosamine, zinc, folate, and magnesium. While anecdotal evidence may exist for improvement in symptoms for individuals with deficiency, it is difficult to make any recommendation for supplementation based on evidence. Acupuncture and Chinese medical therapies are also used in certain populations, again with limited rigorous evidence for benefit.

For those attempting to utilize non-pharmacological therapies, the avoidance of several medications and dietary substances will also be of benefit. Elimination or restriction of caffeine, nicotine, alcohol, antihistamines, most antidepressants, older antiemetic agents, and antipsychotics may alleviate symptoms.

Although alcohol can promote sleep and reduce RLS symptoms, this effect lasts only 30–90 min, and rebound (discussed later in this chapter) may occur. Although some patients show some improvement from tricyclic and selective serotonin

Table 8.2 Pharmacologic agents used to treat RLS

Agents	Starting dose	Dose range	Class side effects
Dopaminergic precursors			Rebound, augmentation
Carbidopa/levodopa	25/100	25/100–100/400	
Dopamine receptor agonists			Nausea, lightheadedness, nasal stuffiness, constipation, insomnia, compulsive behaviors, rebound, augmentation
Pramipexole	0.125	0.5–2	
Ropinerole	0.25	2–4	
Opioids			Abuse potential, daytime somnolence, constipation or GI upset
Methadone	5	5–10	
Oxycodone	5	5–15	
Hydrocodone	5	5–15	
Tramadol	50	50–100	
Benzodiazepines			REM sleep suppression, daytime somnolence, abuse potential
Clonazepam	0.5	0.5–4	
Temazepam	15	15–30	
Anticonvulsants			Daytime somnolence, ataxia
Gabapentin	200 tid	Up to 2,700 in divided doses	
Pregabalin	150	150–450	

REM rapid eye movement

reuptake inhibitor antidepressants, these agents often intensify symptoms [5]. For patients with depression or nicotine-withdrawal issues, bupropion may be considered. As previously noted, most antidepressants appear to worsen symptoms. Bupropion, a dopamine-active antidepressant, has been shown in one small study to reduce limb movements [6]. H1 antihistamines probably exacerbate RLS symptoms owing to their effects on dopamine receptors. Similarly, older antiemetic agents act on the dopaminergic system, thus potentiating symptoms. Newer antiemetic agents, which are selective 5-HT3 receptor antagonists, will likely have little effect on RLS symptoms.

For patients who fail to demonstrate improvement with conservative, nonpharmacological methods, the choice of medication initiated should be focused on providing the most effective symptom relief with the least number of side effects. Table 8.2 shows the general categories of agents used to treat this disorder.

Although the primary pharmacological agents used have traditionally been dopamine precursors, benzodiazepines and opioids, newer dopamine receptor agonists are increasingly being used as first-line agents [20], particularly for individuals with frequent, chronic symptoms. Dopamine precursors such as carbidopa/levodopa are still used, but patients frequently experience rebound or augmentation.

Rebound is defined as the tendency for symptoms to worsen at the end of the dosing period. This leads to recurrence of symptoms in the late night or early morning. This phenomenon is most common with short-acting, regular-release preparations of carbidopa/levodopa. *Augmentation* is defined as the tendency for symptoms to develop earlier in the day and to be more severe than the symptoms that occurred before treatment began. Augmentation is the most common complication of carbidopa/levodopa therapy. It is treated by withdrawal of the agent over a few days, followed by initiation of a dopamine agonist.

The non-ergot agonists, pramipexole and ropinerole, are currently preferred to ergot agonists because of their more favorable side-effect profiles. These agents stimulate most D2 and D3 receptors. Ropinerole has been demonstrated in several studies to improve symptoms of RLS [52, 53]. The typical starting dose is 0.25 mg taken 2 h prior to major RLS symptom onset. The dose is increased by 0.25 mg every 2–3 days to eliminate symptoms. Most patients typically require 2 mg or less, but some patients may require 4 mg or more. Pramipexole has also been shown to have efficacy in RLS [54–56]. Pramipexole is usually initiated at 0.125 mg, taken 2 h prior to major symptom onset. The dose is increased by 0.125 mg every 2–3 days until symptom relief is achieved. Common daily dosage is usually between 0.375 and 0.75 mg. Augmentation is less common with dopamine agonists than with precursors, but it has been demonstrated in patients taking pramipexole for 2 years [57].

Rotigotine is a newer non-ergot agonist that is administered via a transdermal patch. This agent has been demonstrated to have long-term safety and efficacy after 1 year of therapy [58]. It has been approved for use in Europe, but is still not approved in the USA [59, 60].

While dopaminergic medications are typically well-tolerated, adverse effects are more commonly recognized. Compulsive behaviors are described for both ropinerole and pramipexole [61–63]. Additionally, patients on these agents may demonstrate sleep problems and mood disturbances.

Because of the effectiveness of these dopamine agonists, individuals rarely require treatment with other agents. Willis described the use of opioids in the seventeenth century. Their use has been largely abandoned as a result of the possibility of overuse and dependence. They are, however, generally well-tolerated and offer good long-term efficacy [64].

Benzodiazepines also produce an improvement in symptoms and have been used for decades in the treatment of RLS. Similarly, their use has been avoided recently because of the risk of abuse, side effects, and intolerance. Furthermore, benzodiazepines have a detrimental effect on sleep architecture, suppressing REM sleep.

The final class of medications used includes anticonvulsant agents, with gabapentin currently being the most promising. In one small double-blind, placebo-controlled, crossover study, gabapentin significantly improved RLS symptoms and PLMs [65]. Dosage requirements may be as high as 2,700 mg a day in three divided doses. Patients complaining of pain had the greatest benefit in this study. Pregabalin, an alpha-2-delta anticonvulsant, has also been shown to effect improvement in RLS symptoms [66].

For women who are pregnant or who are considering pregnancy, few data on pharmacotherapy for RLS are available. Iron and folate supplementation should be strongly encouraged, not only as part of routine pregnancy counseling, but also because of the beneficial effects on RLS symptoms in pregnancy [67]. In individuals having symptoms despite appropriate iron and folate supplementation, the choice of therapeutic agent is somewhat limited.

Dopaminergic agonists and precursors are category C agents; therefore, few data are available upon which to base recommendations for or against their use. Benzodiazepines are listed as category D agents, and therefore should be avoided in pregnancy. Among opiates, only oxycodone is a category B agent, with all other commonly utilized opiates being either class C or D. The antiepileptic drugs are class C or D agents. The decision to treat women with RLS during pregnancy, therefore, requires thoughtful discussion about possible risks to the fetus.

In women who are not pregnant and who are not attempting to become pregnant, all therapeutic choices are available. Women are encouraged to take precautions in utilizing these medications without proper birth control methods. Fortunately, there are no specific drug interactions with dopaminergic agonists, dopamine precursors, opioids, benzodiazepines, or antiepileptic agents.

Conclusion

RLS commonly affects women and can significantly affect sleep and quality of life. The etiology of the disorder is multifactorial, but in women it may be influenced by higher rates of anemia and sex hormone levels. Treatment includes correction of iron deficiency, if present, and both non-pharmacological and pharmacological treatments. Current first-line agents include the non-ergotamine dopamine agonists, ropinerole and pramipexole. The use of these agents in women who are pregnant or considering pregnancy should be carefully considered due to potential risks to the fetus.

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Chapter 9
Pharmacological Treatments of Insomnia

Mehmet E. Dokucu

Introduction

The mainstay for treatment of chronic insomnia and the majority of acute insomnia is cognitive behavioral therapy (CBT), often combined with medications in the early phase of CBT, as combination therapy has been shown more effective than either therapy alone [1]. The focus of this chapter is not to discuss in depth the different CBT modalities. For that, the reader is referred to the excellent, concise yet comprehensive *Cognitive Behavioral Treatment of Insomnia*: *A Session-by-Session Guide* by Michael Perlis et al. and published by Springer. Below is a brief summary of the American Academy of Sleep Medicine's (AASM) practice parameters in the use of CBT for insomnia.

Stimulus Control Therapy entails training insomnia sufferers to re-associate the bed and bedroom with sleep and to reestablish a consistent sleep–wake schedule. It is recommended by the AASM for the treatment of chronic insomnia [2].

Relaxation training, involving methods aimed at reducing somatic tension or intrusive thoughts at bedtime that interfere with sleep, is recommended by the AASM for the treatment of chronic insomnia [2].

Sleep restriction consolidation involves reducing the amount of time spent in bed to the actual amount of time asleep, thereby creating a mild sleep deprivation, and then lengthening sleep time as sleep consolidation improves. It is recommended by the AASM for the treatment of chronic insomnia [2].

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Paradoxical intention involves instructing the patient to avoid any effort to fall asleep, thus eliminating performance anxiety, and is recommended for sleep onset insomnia [2].

Biofeedback provides visual or auditory feedback to patients to help them control somatic tension and is recommended by the AASM for the treatment of chronic insomnia [2].

Sleep hygiene, cognitive therapy, and imagery training are not recommended as stand-alone treatments for chronic insomnia [2].

Multimodal approaches both with and without cognitive therapy are recommended as stand-alone treatments for chronic insomnia [2].

Pharmacological Treatments

A National Institutes of Health independent review panel has reported that although pharmacological treatments for insomnia are used more often than they are indicated, long-term benefits are better and more sustainable when combined with cognitive behavioral treatments [1, 3]. Nevertheless, clinicians frequently need to recommend medications in combination with CBT or as stand-alone treatment when CBT fails or is not indicated. Fortunately, newer and likely safer hypnotic agents have become available that allow tailoring of benefits and adverse effects to a specific clinical problem.

Pharmacological Principles

The benzodiazepines bind an allosteric modulation site at the GABAA receptor and greatly facilitate GABA action. Benzodiazepines exert potent anticonvulsant, hypnotic, antianxiety, and myorelaxant effects. The “Z” drugs are specific GABAA or omega-1 receptor agonists that are structurally unrelated to benzodiazepines. They are potent hypnotics but show weak anticonvulsant and myorelaxant properties. Exogenous melatonin and melatonin receptor agonists have both circadian rhythm resetting and soporific qualities (the latter is more likely at higher doses) that last several hours, probably secondary to a decrease in the core body temperature. Their circadian rhythm regulator function occurs through their direct action on the suprachiasmatic nucleus (the mammalian circadian pacemaker). Valerian root is an herbal product that produces sedative effects on the central nervous system. Its mechanism of action is not known; however, some evidence suggests that it may have GABAergic properties. Doxepin, trazodone and over-the-counter antihistamines act by blocking H1 and H2 receptors, therefore inhibiting the alerting effects of endogenous histamine. Gabapentin and other anticonvulsants have unknown mechanism of action as sedative hypnotics.

The Primary Insomnias

According to both the *International Classification of Sleep Disorders*, Second Edition, (ICSD 2), and *DSM IV-TR*, primary insomnia is defined as repeated difficulty with sleep initiation and the inability to obtain sufficient length or quality of sleep to feel refreshed the following morning, as opposed to total sleep time. ICSD 2 further subdivides primary insomnia into subtypes: (1) Psychophysiological insomnia, also termed learned or conditioned insomnia, which is an abnormal associative conditioning response to the bedroom environment; (2) Paradoxical insomnia, formerly called sleep state misperception, which is reported insomnia with symptoms grossly disproportionate to objective findings; and (3) Idiopathic or childhood-onset insomnia, which has no known cause and continues unremittingly throughout life, often starting at birth. The mainstay of the management of primary insomnias is combined CBT and pharmacological therapy. Initiating pharmacotherapy in the acute stages of CBT and later discontinuing it during the maintenance phase improves long-term outcome [1].

Comorbid Insomnias

Menopause-related insomnia is highly associated with perimenopausal hot flashes and affects up to 40% of women. In menopause-related insomnia, hormone replacement therapy may improve insomnia along with menopause-related symptoms. The increased probability of cerebrovascular events and neoplasms associated with estrogen replacement therapy has led to a search for other alternatives to treat hot flashes and insomnia. The herbal supplement black cohosh was studied as an alternative, but the evidence for its efficacy in menopausal insomnia is inconclusive [4]. Gabapentin at doses of 600–2,400 mg/day in divided doses may be a viable option for treating hot flashes and insomnia associated with them [5]. Paroxetine, venlafaxine, and desvenlafaxine are also beneficial for treatment of hot flashes, night sweats, and related sleep disturbances [6]. Ramelteon, a melatonin receptor agonist, is also beneficial for menopause-related insomnia [7]. It does, however, carry the potential to modestly increase prolactin levels in women [8]. Valerian at 530 mg dose has been shown to have modest benefit in improving menopausal insomnia [9]. Melatonin combined with mirtazapine has been shown effective in the treatment of perimenopausal insomnia, but there is the significant side effect of weight gain [10].

When compared to placebo, eszopiclone 3 mg at bedtime improves both the insomnia and the other ancillary symptoms (nighttime hot flashes, etc.) of menopause [11] as do the isoflavones [12]. The data available do not support the use of phytoestrogens (red clover extract and other soy products) [13].

Pregnancy-related insomnia can be secondary to sleep-disordered breathing, restless leg syndrome (up to 33% in the third trimester), pain and anxiety during pregnancy, but it also could be due to hormonal changes. There is increased

Table 9.1 Pregnancy and lactation categories of hypnotic medications

Medication	Class	Half-life (h)	Pregnancy category	Lactation category
Zolpidem	Non-benzodiazepine GABA agonist	1.6–4	C	Minimal infant risk
Zaleplon	Non-benzodiazepine GABAA agonist	1	C	Minimal infant risk
Clonazepam	Benzodiazepine	30–40	D	Infant risk cannot be ruled out
Lorazepam	Benzodiazepine	12	D	Unknown but of concern
Temazepam	Benzodiazepine	3.5–18.4	D	Infant risk cannot be ruled out
Oxazepam	Benzodiazepine	5.7–10.9	D	Infant risk cannot be ruled out
Trazodone	Sedating antidepressant	7–10	C	Infant risk cannot be ruled out
Amitriptyline	Sedating tricyclic antidepressant	9–27	C	Infant risk cannot be ruled out
Quetiapine	Sedating antipsychotic	6–12	C	Infant risk cannot be ruled out
Mirtazapine	Sedating tetracyclic antidepressant	20–40	C	Infant risk cannot be ruled out
Doxylamine	Antihistamine	6–12	B	May inhibit lactation, of concern in infants

Pregnancy categories B, C, D defined by FDA
Adapted with permission from Pavlova M, Sheikh LS. Sleep in women. Seminars in neurology 2011;31(4):397–403

incidence of sleep fragmentation and hence sleep maintenance insomnia especially in the third trimester of pregnancy. Pharmacotherapy of insomnia with hypnotic agents during pregnancy and lactation presents a formidable challenge due to risks and contraindications, especially teratogenicity (Table 9.1). Table 9.1 summarizes the teratogenic potentials of the commonly available sedative hypnotics [14]. Choice of a hypnotic during this period must be based on careful and detailed consideration of clinical and pharmacokinetic factors. No information is available on the pregnancy risks of herbal and dietary supplements (such as melatonin and valerian).

Other comorbid insomnias include restless leg syndrome, insomnia due to other sleep disorders, insomnia due to neurologic, psychiatric, and other medical conditions, and drug-induced insomnia.

Comorbid insomnias most often respond best when their treatment is combined with that of the underlying etiology.

Response to Medications

No reliable studies have looked at the percentage of responders to sedative hypnotics. A few studies show that most people will respond, at least initially, to non-benzodiazepine GABAA agonists and benzodiazepines with improved subjective and objective sleep. Some patients may even experience long-term benefit. The medications used in the treatment of restless leg syndrome have been shown to be 70–100% effective in various individual trials, depending on the product used [15]. No treatment

outcome studies and no head-to-head comparison studies are available. Both the non-benzodiazepine GABAA agonists and benzodiazepines have been shown to be safe and effective in the elderly [16].

Benzodiazepines

Benzodiazepines were developed in the 1960s and were quickly favored over barbiturates, which had significant CNS toxicity, high risk of addiction, and narrow therapeutic window. Benzodiazepines, however, also have significant potential for dependence, cognitive impairment, and fall risks. They all bind the GABA receptors nonspecifically. Until the development of the "Z" or GABAA receptor agonists, benzodiazepines were the preferred hypnotics for insomnia. They were clinically demonstrated to be efficacious and had rare adverse reactions. Benzodiazepines differ from each other mainly by the speed of absorption and half-life of elimination. With the exception of temazepam, none of the FDA-approved benzodiazepines for insomnia are currently in common use. However, benzodiazepines that are not FDA approved for insomnia, such as clonazepam, alprazolam, lorazepam, and diazepam are more frequently prescribed. Diazepam and alprazolam have the fastest oral bioavailability in spite of their diametrically opposite half lives (alprazolam short, diazepam long). Hence, they can both be used for managing initial insomnia or nocturnal panic attacks. For patients whose insomnia is accompanied by significant anxiety that does not respond well to cognitive therapy, benzodiazepines are still the agents of choice for the acute phase of the management but should not be continued for long term due to risks and side effects.

Most benzodiazepine adverse reactions are viewed as extensions of the therapeutic effect beyond the desired time. The use of benzodiazepines has been generally restricted in the treatment of insomnia because of concerns of addiction, dependence, and tolerance. The risk of habituation and abuse, however, is lower than previously thought in patients who are properly diagnosed and use these medications for medicinal purposes. Temazepam, the benzodiazepine most commonly used as a hypnotic, has been shown to be safe even in the elderly [17]. Very short acting benzodiazepines such as alprazolam can cause rebound anxiety and insomnia or troublesome amnesia.

Non-benzodiazepines

Zolpidem, zaleplon, and eszopiclone are hypnotic agents that are chemically unrelated to benzodiazepines although they all bind the benzodiazepine site of the GABA receptor.

Zolpidem is an imidazopyridine and is a safe and effective hypnotic with only mild risk of abuse, dependence, and tolerance, but no withdrawal or rebound

insomnia over long-term use [18, 19], even in elderly patients [20]. It has minimal adverse effects and its elimination half-life is about 2 h, with peak plasma levels achieved within 90 min. Dose adjustment is required only in the setting of liver impairment. Zolpidem is available in a controlled release formulation as well. Compared to the immediate-release formulation, plasma concentrations are maintained for a longer period, and pharmacokinetic analysis has demonstrated that the time to maximum concentration (t_{max}) and terminal elimination half-life ($t_{1/2}$) of 12.5 mg zolpidem extended-release are similar to those of 10 mg zolpidem. These findings indicate a similar rapid onset of action and an elimination profile that reduce the risk of next-day decrements in performance [21]. The extended-release formulation has the advantages of being safe and effective in the elderly population at the 6.25 mg dose [22] and ability to remain safe and effective with both nightly and occasional use over 6 months in chronic primary insomniacs [23]. Several studies with zolpidem given nightly over 6 months have shown continuous efficacy and safety [18]. Low-dose sublingual zolpidem lozenges are also available for sleep maintenance insomnia [24]. Zolpidem, zaleplon, and eszopiclone are safe hypnotics with minimal adverse effects and no dependence, withdrawal, tolerance, or rebound insomnia with up to 12 months of nightly use [25–27], although rare incidents of abuse have been reported, especially in subjects with active polysubstance abuse history [28, 29]. Zolpidem has received notable negative coverage in the lay media for causing automatic sleep behaviors. Automatic behavior with retrograde amnesia for the event is a rare but undisputed side effect of zolpidem. Caution should be observed, especially when prescribed with other sedating or psychotropic medications, at a higher than 10 mg dose, or in the setting of head injury, psychiatric illness, untreated sleep disorders, and previous history of sleepwalking. The single predictive risk factor for complex sleep behaviors with zolpidem is suggested to be usage of doses higher than 10 mg per day [30].

Zaleplon is another effective and safe hypnotic [31], with onset of action in approximately 30 min and duration of action of about 4 h. Peak serum concentrations occur in about 1 h, and elimination half-life is also about 1 h. Because of its short half-life, there is no residual sedation when zaleplon is administered in the middle of the night; making it an ideal medication for sleep maintenance insomnia. As with zolpidem, the dosage of zaleplon requires adjustment with altered hepatic function but not with renal impairment.

While eszopiclone is effective for treatment of insomnia for at least 12 months with no evidence of tolerance, dependence, or abuse, it has caused mild, transient memory impairment in some patients [26, 32]. When coadministered with fluoxetine, it is relatively well tolerated and is linked to rapid, substantial, and sustained sleep improvement, as well as a faster onset of antidepressant response as based on the Clinical Global Impression (CGI) and a greater magnitude of the antidepressant effect [33]. Coadministration of eszopiclone and escitalopram is well tolerated and appreciably improves sleep, daytime functioning, anxiety, and mood in patients with insomnia and generalized anxiety disorder [34]. Zolpidem 10 mg is as effective as eszopiclone 3 mg, and both have been shown to be more effective than placebo in improving polysomnographic measures of insomnia in patients with primary

insomnia [35]. Of note, eszopiclone has been shown effective in menopause-related insomnia as well [36]. Nightly eszopiclone use for 6 months is shown to be cost effective, particularly when the impact on productivity costs is considered [37]. Eszopiclone has a similar safety profile to both zolpidem and zaleplon but exhibits a commonly reported unfavorable side effect of unpleasant taste (34 vs. 3%) in patients taking it vs. those taking placebo [38].

At present, there have been no studies comparing eszopiclone or zolpidem to zaleplon or other older benzodiazepine-type sedative hypnotics. A related medication, zopiclone, is not available in the United States, but has been shown to be helpful in both primary insomnia and shift-work insomnia [39].

Several studies, mainly with zolpidem, have shown that occasional use in conjunction with stimulus control therapy is both effective and safe over longer periods of time [40]. This method of using hypnotics has come into favor as it both maximizes benefits and minimizes tolerance or dependence for chronic insomniacs.

Sedating Antidepressants

Due to concerns of tolerance, addiction, and dependence with barbiturates and benzodiazepines, and because insomnia is commonly associated with depression, sedating antidepressants (specifically amitriptyline and trazodone) have been introduced early into the treatment regimen of insomnia. There has been an upward trend in the number of antidepressants that are prescribed for insomnia in the last decade and a half. Unfortunately, although antidepressants have been used routinely as sleep aids, few studies have examined their efficacy in the treatment of insomnia, and the available data are inconclusive for most of the antidepressants used as such. Moreover, the presence of lingering daytime sedation after nighttime administration and their other adverse effects (with tricyclics aggravation of restless leg syndrome, anticholinergic effects, etc.) make them suboptimal choices for the treatment of insomnia especially in the absence of coexisting depressive symptoms. Paroxetine was shown to be ineffective for primary insomnia in the elderly [41].

Trimipramine and trazodone were the only antidepressants with some clinical data regarding efficacy in insomnia until relatively recently [42]; however, neither are without problems. Trazodone results in residual daytime sedation and can cause rebound insomnia, although it does not tend to aggravate restless leg symptoms and periodic limb movements. Furthermore, there is no evidence that trazodone improves sleep in patients with primary insomnia without comorbid depression [18]. Trimipramine has been shown to improve sleep efficiency but not duration [42].

Antidepressants have, among other adverse effects, lingering daytime sedation after nighttime administration. Studies have demonstrated that doxepin, given in doses of 1 mg, 3 mg, and 6 mg, is effective in the short term in improving the sleep of patients with chronic primary insomnia, with a safety profile comparable to placebo [43, 44].

Sedating Antipsychotics

Quetiapine was recently shown to be effective in treating insomnia associated with comorbid depression, especially one exacerbated by antidepressant therapy [45] or by clozapine withdrawal [46]. However, it showed little effect on primary insomnia in another placebo-controlled, double-blind trial [47]. Quetiapine is not without safety concerns either: studies have suggested an increased prevalence of hyperlipidemia and cardiovascular disease associated with its use [48]. Less commonly, olanzapine is prescribed for insomnia. In the absence of comorbid psychiatric symptoms or disorders, using antipsychotics, even at low doses, is inappropriate, and in the elderly this has been shown to be associated with higher incidence of cardiovascular and cerebrovascular morbidity and mortality.

Alcohol

Twenty-five percent to 30% of patients reporting insomnia self-medicate with either alcohol, over-the-counter hypnotics or a combination of the two [49], with alcohol being the substance most commonly used. However, it affects sleep architecture negatively and causes fragmentation, most likely due to withdrawal effects in the second half of the sleep cycle.

Antihistamines and Over-the-Counter Hypnotics

Although there is little evidence of their efficacy, antihistamines and over-the-counter preparations continue to be the most widely used and recommended hypnotics, despite several studies showing significant adverse effects.

There are no reliable studies demonstrating efficacy of antihistamines in the treatment of insomnia. In fact, the residual daytime sedation of a single nighttime 50 mg dose of diphenhydramine, the active ingredient in most over-the-counter hypnotics, was reliably shown on PET even in the absence of subjective sedation [50].

Anticonvulsants

Tiagabine was initially designed to be an anticonvulsant but has been used off label in a variety of neurologic and psychiatric conditions, and it has received some exposure as a sleep aid. It does not have a significant effect on wake after sleep onset, latency to persistent sleep, total sleep time, or the subjective rating of sleep. Moreover, it leads to sleep architecture changes [51]. Gabapentin is another

anticonvulsant that appears to have some effect in improving sleep efficiency in insomniacs. At relatively low doses of 300–600 mg, gabapentin has been shown to modestly improve sleep efficiency in primary insomniacs [52].

Melatonin Agonists

While there are no safety data or FDA-regulated standard formulation of melatonin, several studies have shown its efficacy in the treatment of circadian rhythm problems. Subjective evidence suggests that it may improve sleep in age-related insomnia, especially when mixed with magnesium and zinc [53]; sleep disturbances in autism and mental retardation [54–56]; schizophrenia [57]; insomnia associated with childhood ADHD [58, 59]; and childhood-onset insomnia [60]. However, the data available are not adequate to support its use as a wide spectrum hypnotic for primary insomnia [61]. Furthermore, despite several recent studies showing a potential benefit in treatment of insomnia in the healthy elderly population using prolonged-release melatonin [62–65], it has been shown to be ineffective in Alzheimer disease-associated insomnia [66]. Nevertheless, new melatonin agonists show modest efficacy in primary insomnia. The only marketed FDA-approved melatonin receptor agonist is ramelteon, a melatonin ML1/MT1 receptor agonist that demonstrates a statistically significant reduction in latency to persistent sleep and a statistically significant increase in total sleep time with no apparent next-day residual effects in patients with chronic primary insomnia. The doses studied were 4, 8, 16, and 32 mg, with the recommended dose found to be 8 mg [67]. Ramelteon has a short half-life of 1–2 h, a t_{max} of three-fourths of an hour and remains effective with continuous use for 5 weeks [67]. In addition, it has been shown to be safe and effective after nightly use for up to a year [68, 69] for alleviating first-night effect in the sleep lab [70], as well as for middle-of-the-night administration for sleep maintenance issues [71] and anxiety-related insomnia [72]. Ramelteon has demonstrated an adverse events profile similar to placebo [67]. It has been found to be safe in patients with mild to moderate obstructive sleep apnea syndrome [73].

Herbal Supplements

The merit of valerian as a hypnotic is still in question. While a recent, comprehensive review showed very weak support for its use as a sedative hypnotic [74], another large placebo-controlled study indicated that 450 mg of valerian improves subjective sleep in cancer survivors [75]. It should also be noted that there are no safety data or FDA-regulated standard formulation of valerian. Case reports, however, raise the concern of valerian-induced hepatotoxicity [76]. Preliminary studies have been conducted on additional herbal supplements, such as essential oil of Citrus aurantium L. (sour orange) [77] and other preparations made from various herbal

ingredients [78]. None of these studies have shown conclusive evidence of clinically significant efficacy for these drugs. However, Neurexan, a sleep aid made up of four different herbs, has been found to be slightly more effective than valerian in improving sleep in patients with chronic insomnia [79].

Agents in Development

There are several products still in phase 2 and 3 trials that show some potential as treatment for insomnia. Among these are orexin receptor antagonists such as almorexant [80–82], 5-HT2A receptor antagonists [83, 84], and H1/H2 antagonists [85].

Conclusion

Chronic insomnia left untreated can be a significant risk factor for the development of depression, anxiety disorders, and hypertension [86]. Similarly, a study has shown that, in nursing homes, insomnia is a stronger risk factor for falls than hypnotic use [87].

All sedative hypnotics are effective, to varying degrees, in decreasing the sleep latency and number of nocturnal awakenings. To maintain long-term improvement of sleep, however, a combination of pharmacological and cognitive-behavioral treatments is needed. The outcome of comorbid insomnias depends on how well underlying conditions respond to treatments.

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Chapter 10
Obstructive Sleep Apnea–Hypopnea Syndrome in Premenopausal Women

Kanika Bagai and Beth A. Malow

Introduction

Obstructive sleep apnea–hypopnea syndrome (OSAHS) is characterized by recurrent sleep-induced collapsibility of the pharyngeal airway. Normal adult women (ages 20–45 years) are a cohort of women in whom menstrual cycles, the use of oral contraceptives, pregnancy, and lactation are associated with a varied hormonal environment. These differences in the hormonal status may in turn potentially change the likelihood for the development of OSAHS in premenopausal women. The clinical spectrum of sleep-disordered breathing includes apnea, hypopneas, and upper airway resistance syndrome (UARS).

Prevalence

The prevalence of OSAHS in premenopausal women is low (0.5%), according to an interview and polysomnogram (PSG)-based survey in a large cohort of women [1]. Interestingly, postmenopausal women on hormone replacement were found to have a similar low prevalence in the same study (0.5%). In these two groups, sleep apnea was exclusively associated with obesity (defined as a body mass index (BMI) $\geq$32.3 kg/m^2). The prevalence of OSA was significantly higher (2.7%) in postmenopausal women not on hormone replacement.

In another study comparing the prevalence and severity of sleep apnea between premenopausal (n=797) and postmenopausal (n=518) women, Dancey et al. [2] found that postmenopausal women had a higher prevalence of OSAHS (47% vs. 21%

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in premenopausal women, with OSA defined as an apnea hypopnea index (AHI) >10/h). In the same study, BMI and neck circumference were higher in postmenopausal women with sleep apnea compared with those in premenopausal women with sleep apnea. While AHI increased with BMI and neck circumference in both groups, in premenopausal women the relation between BMI and AHI was less linear, with a steep slope in the most obese range. The relation between neck circumference and AHI was similar in both groups. Further, sleep apnea severity was noted to be higher in the postmenopausal group, even after adjusting for neck circumference and BMI, suggesting functional differences in the upper airway between the two groups.

In the Wisconsin Sleep Cohort Study [3] consisting of 589 women, the prevalence of sleep-disordered breathing, indicated by AHI cut points of 5–15 events per hour, increased across menopausal categories: 10.8% in premenopausal women, 18.4% in perimenopausal, 27% in perimenopausal/postmenopausal, and 29.1% in postmenopausal women, respectively.

Therefore, menopause seems to increase the risk and premenopausal status and hormone replacement decrease the risk for sleep apnea, suggesting an important role of hormones in the pathogenesis of OSA.

Effect of Hormones on Sleep and Breathing/Role of Hormones in Pathogenesis of OSAHS

Progesterone

Progesterone's effect on sleep in experimental models resembles that of benzodiazepines. Non-rapid eye movement (NREM) sleep latency is shortened, low frequency (theta and delta) electroencephalogram (EEG) activity is reduced, while the high frequency (>10 Hz) activity is increased. High doses of progesterone suppress REM sleep in rats [4].

Progesterone is a respiratory stimulant. Basal minute ventilation and ventilatory responsiveness to hypercarbia were augmented in men receiving medroxyprogesterone acetate, a synthetic progesterone used to stimulate respiration in high altitude polycythemia, chronic obstructive pulmonary disease, and the obesity-hypoventilation syndrome. In non-hypercapnic men with obstructive sleep apnea (OSA), however, medroxyprogesterone did not reduce apnea frequency, duration, or arterial oxygen desaturations [5].

Women experience an increase in ventilatory drive during the luteal phase of the menstrual cycle and during pregnancy. This is thought to be secondary to the increased levels of progesterone [6, 7].

Papovic and White [8] determined the level of the awake genioglossus electromyogram and upper airway resistance (UAR) in 12 pre- and 12 postmenopausal women under basal conditions and during the application of an inspiratory resistive load.

The waking peak phasic and tonic genioglossus electromyelogram (EMG) activity in women tended to be higher in the luteal phase of the menstrual cycle, lower in the follicular phase and lowest in the postmenopausal phase. There was a weak but significant positive correlation between progesterone levels and both peak phasic and tonic EMG activity. It was concluded that female hormones (possibly progesterone) have a substantial impact on upper airway dilator muscle activity. However, the effect of sleep on the upper airway tone was not studied.

Estrogen

Estrogen may have an indirect influence in the control of breathing. Estradiol, via an upregulation of progesterone receptors, may enhance the respiratory stimulant effects of progesterone [9].

Small patient numbers limit almost all of the studies comparing the effect of hormone replacement therapy (HRT) on the severity of sleep apnea, and the results have been varied. In a group of nine healthy, surgically postmenopausal women, Pickett et al. [10] found that combined estrogen–progestin treatment was superior to placebo in reducing episodes of sleep-disordered breathing and in decreasing the duration of hypopneas. Cistulli et al. [11] could not show any benefit with estrogen or with combined estrogen–progestin treatment in 15 postmenopausal women with moderate OSA. A recent pilot study [12] evaluated four postmenopausal women and one perimenopausal woman with clinical symptoms and OSAHS with PSG before and after HRT (estradiol and trimegeston). The subjects had a 75% mean reduction of the severity of sleep apnea as measured by AHI. The variable results of HRT in different studies possibly indicate variability in hormone metabolism in different individuals. Further studies comparing the effects of estrogen replacement and combined HRT are needed to clarify the role of estrogens in the control of breathing and sleep apnea syndrome.

Estrogen replacement therapy has been reported to cause a worsening of asthma symptoms in postmenopausal women with mild-to-moderate asthma. In a study by Lange et al. [13], a weak but positive association was reported between HRT and self-reported asthma and asthma-like symptoms.

Estrogen deficiency has also been suggested to play a role in menopause-associated changes in body fat distribution. During the menopause transition, estrogen levels decline while the ovary continues to secrete small amounts of androgens. Both overall body fat and upper-body adiposity have been associated with increased testosterone levels. In some studies, HRT attenuated the menopause-related acceleration of adipose tissue deposits, which has been attributed to decreased lipoprotein lipase (LPL) activity [14]. Hormonal treatment with either unopposed estrogen or with estrogen in combination with progesterone stimulated LPL activity, minimizing adipose tissue deposits. Change in body fat distribution, especially in the neck region, influence upper airway muscle tone and may facilitate OSA.

Gender Differences in Upper Airway Resistance

Gender plays a role in determining the incidence of OSA in men and women. This has been attributed to the differences in the upper airway function during sleep in patients with OSA.

Trinder et al. [15] studied changes in ventilation and UAR both during sleep onset and over a full NREM sleep period from wakefulness to slow-wave sleep (SWS) in a group of 14 men and 14 women. Airflow was measured by attaching the mask to a pneumotachograph. UAR was calculated by using simultaneous recordings of airflow, mask pressure, and epiglottal pressure. Changes in ventilation and UAR from wakefulness to early Stage 2 NREM sleep were similar in male and female subjects. Once NREM sleep became established and developed to SWS, the pattern of change in UAR varied between men and women. In men, there was a progressive increment in UAR over the sleep period, whereas in women UAR during SWS remained at a level similar to (or only slightly above) that observed in subjects who did not obtain SWS. Ventilation was maintained at similar levels despite the marked difference in UAR. This difference in the effect of sleep on upper airway muscle activity in males and females may contribute to a male predisposition to sleep-disordered breathing.

In a study of UAR and dimensions in healthy young and old men and women [16], young women (mean age 27 ± 1 (18–34)) had narrower airways at all sites compared with young men and older men and women, in both sitting and supine positions. Young women had greater percentage increase in oropharyngeal resistance at high flows between awake and NREM sleep compared with young men. Total respiratory resistance increased between awake and REM sleep in young women and older men only. However, when overall changes from awake to sleep were considered, there were no significant differences between groups of younger and older men and women, and, therefore, the significance of these findings is not known.

Obesity predisposes to OSA. Even though women have a greater total body fat and are more obese as compared to men, the prevalence of OSA is higher in men. In a study [17] comparing the upper airway size in 78 male and 52 female patients, both oropharyngeal junction and pharyngeal cross-sectional areas were significantly smaller in females than in male patients with comparable BMI. There was no correlation between BMI and pharyngeal size in either gender. There was a positive correlation between BMI and AHI in both men and women. Obesity may predispose to UAR through mass loading and alteration of tissue characteristic in addition to fat deposition. Other studies [18] have shown that normal men, despite larger pharyngeal areas as compared to normal women, have a higher pharyngeal resistance than women. This may be due to gender differences in airway compliance and tissue characteristics.

Symptoms

The most common presenting symptoms of OSA are loud snoring, excessive daytime sleepiness, choking arousals, restless sleep, and witnessed apneas. All aspects of quality of life, from physical and emotional health to social functioning, are

markedly impaired by OSA [19]. Other symptoms in premenopausal women can include mood disturbances, irritability, disrupted social interactions, reduced libido, nocturia with disrupted nocturnal sleep, morning headaches, and dry mouth upon awakening. In one study, 43% of the women reported menstrual irregularities [20]. Up to 40% of the women with sleep-disordered breathing disorder attributed divorce or dissolution of a love relationship to their chronic sleepiness and fatigue, and their social isolation to a physical and not a psychiatric problem, such as depression.

Sleep-related breathing disorder in women may be poorly recognized, since women are more likely than men to complain of fatigue and morning headache, and less likely to report restless sleep or to have been told of witnessed apneas during sleep [21]. Despite daytime sleepiness, women are more likely to complain of difficulty falling asleep, and their concerns may be attributed to insomnia.

Before referral to a physician, women tend to have sleepiness or other symptoms related to sleep-disordered breathing for 9.7 ± 3.1 years. The problem receives faster attention in elderly or obese women [20]. When a population with mild OSA and sleepiness was analyzed, 72% of the men were initially given the diagnosis of hypersomnolence or narcolepsy, and one was diagnosed as chronic fatigue syndrome. In contrast, 53% of the women were initially diagnosed and treated for chronic fatigue syndrome [20]. Some groups have found that since women are vastly underdiagnosed, they tend to present with considerably more severe and greater coexisting medical problems. In some series, hypothyroidism was present in almost 20% of the women with OSA [22].

Signs

Morbid obesity is the dominant factor for the appearance of OSAHS in premenopausal women. In one study [23] with 27 women (one-third of whom were premenopausal), participants were referred to the sleep disorders clinic for clear symptoms of OSAHS. Women with OSAHS were found to be significantly more overweight than the 110 men with OSAHS.

Schellenberg et al. [24] studied the physical findings and risk for OSA in 420 patients and tried to identify the upper airway bony and soft tissue structural abnormalities by physical examination (lateral pharyngeal wall narrowing, tonsillar enlargement, enlargement of the uvula or tongue, low lying palate, retrognathia, or overjet) that are associated with an increased risk for OSAHS. After controlling for BMI and neck circumference, narrowing of the airway by the lateral pharyngeal walls and tonsillar enlargement had a significant statistical association (odds ratio 2.0 and 2.6, respectively) with OSA. A subgroup analysis studying differences between men and women showed that no oropharyngeal risk factor achieved significance in women, while lateral narrowing was the sole independent risk factor in men. This study, however, did not distinguish the characteristics of pre- and postmenopausal women.

Another study [25] compared 10 premenopausal women with 13 postmenopausal women and 32 men with OSA. Two premenopausal women had structural

abnormalities of the pharynx, and the remaining eight were significantly more obese than the men with OSA. Thus, premenopausal women with OSA were more likely to be obese and have structural abnormalities of the upper airway than men and postmenopausal women.

Adverse Consequences

OSA has many adverse consequences. Several studies have implicated OSA as a risk factor for the development of hypertension and cardiovascular disease [26, 27]. A study of a large community-based cohort of 6,132 subjects indicated that sleep-disordered breathing was associated with systemic hypertension in middle-aged and older individuals of different sexes and ethnic backgrounds [27]. A prospective study found a dose–response relationship between OSA and the presence of hypertension 4 years later that was independent of confounding variables [28]. Muscle sympathetic nerve activity and nocturnal norepinephrine levels are elevated and thought to be a possible cause for OSA-induced hypertension. OSA has been associated with an increased risk for transient ischemic events and strokes [29]. Intracranial pressures may rise secondary to apneic events, contributing to morning headaches, cognitive impairment, or vascular complications. Dysmenorrhea and amenorrhea are complaints in some women with OSA and may improve with treatment. Finally, there is a strong association between OSA and the risk for motor vehicle accidents [30].

Sleep Apnea Related to Menstrual Cycle

Menstrual cycle fluctuations in progesterone also influence ventilation. During the luteal phase of the menstrual cycle, women have a greater central chemoreceptor drive. Both minute ventilation and ventilatory responsiveness to hypercapnia increase during this phase, presumably due to the physiologic rise in progesterone [31]. However, these ventilatory effects do not ameliorate OSAHS. In studies of premenopausal women with OSAHS, there were no changes in the rate or length of apneas or hypopneas or in oxygen desaturation throughout the menstrual cycle during NREM sleep [31]. Only marginal improvements in these parameters occurred during REM sleep in the luteal phase of the cycle. However, mean arterial pressure responses to apneic events increased significantly in the luteal phase as compared to the follicular phase for both NREM and REM sleep. In women with obesity or anatomically narrow airways, progesterone protects the airways from obstruction by acting as a respiratory stimulant, although this protective effect is counterbalanced by weight gain that exacerbates obesity [32].

Sleep Apnea Related to Pregnancy and Preeclampsia

Pregnancy affects sleep-related respiration independent of changes in sleep [33]. Some variables are detrimental, while others are protective. Detrimental variables include weight gain, uterine enlargement, and nasal obstruction. Weight gain during pregnancy has been correlated with increased upper airway obstruction during laryngoscopy and with increased difficulty with obstetrical intubation [34]. Apart from weight gain, the most obvious mechanical abnormality causing respiratory changes during pregnancy is the enlarging uterus, which elevates the diaphragm. The effect is a decrease in expiratory reserve volume and residual volume, which causes a decrease in the functional residual capacity. This decrease can potentially produce shunting and hypoxemia, as well as reduced lung oxygen stores, contributing to hypoxemia during hypoventilation [33]. During the second and third trimester, nasal obstruction is very common. Increased estrogen levels cause hyperemia and edema of the nasal mucosa with increased secretions. The increased resistance to airflow in the nasopharynx contributes to OSAHS and UARS by creating excessive negative pressure in the collapsible pharyngeal airway.

Protective variables include an increased ventilatory drive from circulating progesterone (reviewed earlier), avoidance of the supine position later in pregnancy due to discomfort, decreased REM sleep (a state during which sleep apnea may occur preferentially due to upper airway hypotonia) due to the effects of high levels of estrogen and progesterone, and the rightward shift of the oxyhemoglobin dissociation curve, which enhances oxygenation to the fetal circulation.

The precise incidence and consequences of sleep-disordered breathing during pregnancy are unknown. Polysomnographic studies performed on six pregnant women at 36 weeks gestation and at postpartum showed that oxygenation was well maintained and the frequency of apneas and hypopneas were significantly reduced during pregnancy [35]. These findings were observed despite reduced functional residual capacity and residual volume, increased alveolar–arterial differences for oxygen, and reduced cardiac output in the supine position.

Several studies have reported an increase in self-reported snoring in pregnancy. A questionnaire study reported frequent snoring as being common in 350 pregnant women compared with 110 age-matched nonpregnant women; however, snoring mothers were not at an increased risk for delivering infants with fetal compromise [36]. In a separate investigation of 502 women screened on the day of delivery with a questionnaire, 23% reported snoring nightly, 14% of them developed hypertension (compared with only 6% of non-snorers), and 10% developed preeclampsia (as compared with 4% of non-snorers). Witnessed apneas were observed in 11% of the habitual snorers, as compared to 2% of the non-snorers. Intrauterine growth retardation (IUGR) occurred in 7.1% of the infants of snoring mothers and 2.6% of the remaining infants. Despite the limitations of the study, it suggests that the consequences of UAR may affect the fetus [37].

Maasita et al. [38] evaluated sleep-related breathing disorder in obese (mean pre-pregnancy BMI >30 kg/m^2) and non-obese (mean BMI 20–25 kg/m^2) pregnant women. During early pregnancy, there were significant differences in the AHI: 1.7 events per hour in the obese group vs. 0.2 events per hour in the non-obese pregnant group ($p=0.05$). There were significant differences in the snoring times, 32% vs. 1% ($p<0.001$) between the obese and non-obese pregnant women.

Izci et al. [39] studied upper airway dimensions in 37 women with preeclampsia, and 50 nonpregnant and 50 pregnant women in their third trimester. Snoring was reported by 75% of the women with preeclampsia. Women with preeclampsia had upper airway narrowing in both upright and supine postures as compared with non-pregnant and pregnant women. These changes could contribute to the UAR episodes during sleep in women with preeclampsia. These alterations during sleep could further increase the blood pressure of this group of pregnant women.

Sleep Apnea Related to Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS) is a common endocrine disorder of premenopausal women and clinically characterized by oligomenorrhea, signs of androgen excess and insulin resistance. Obesity is seen commonly in these women and is frequently central (increased waist to hip ratio).

Vgontzas et al. [40] compared the PSGs of 53 women with PCOS (age range 16–45 year) and 452 control premenopausal women without PCOS (age range 20–42). PCOS patients were 30 times more likely to suffer from sleep-disordered breathing than controls, even when corrected for BMI differences between the two groups. In addition, PCOS patients reported more frequent daytime sleepiness than the controls (80.4% vs. 27.0%, $p<0.001$). The subgroup of PCOS patients who were recommended for treatment for sleep-disordered breathing had significantly higher fasting plasma insulin levels and lower glucose-to-insulin ratio, as compared with patients who did not receive treatment. Plasma free and total testosterone and fasting blood glucose concentrations were not different between the two subgroups of PCOS women. In conclusion, higher fasting plasma insulin levels and low glucose-to-insulin ratio may be stronger markers of sleep apnea than testosterone levels in this group of premenopausal women. Other case series [41] have confirmed the higher prevalence of sleep apnea symptoms and higher AHI in patients with PCOS as compared with women without PCOS.

Sleep Apnea Related to Hypothyroidism

Routine testing for hypothyroidism in women with symptoms of sleep-disordered breathing is unlikely to be useful [42]. However, it is important to recognize that hypothyroidism predisposes to OSAHS. The patients with hypothyroidism should be screened for possible OSAHS with questions regarding snoring and daytime somnolence. If clinically suspected, this should be confirmed with overnight PSG.

Gender Differences in the Polysomnographic Features of Obstructive Sleep Apnea

In several studies, women demonstrate a lower AHI compared with BMI and age-matched men [43, 44]. Ware et al. [44] found that both young and middle aged women had fewer apneic events compared with men of similar age, but older women (ages 60–88 years) had similar apnea severity as age-matched older men. Menopausal status and upper airway muscle tone might play a role for these differences. Female gender and younger age seem to confer benefit by preventing airway collapse in spite of an increased BMI. In other words, for a given value of AHI, women can be more obese than men.

Along the same lines, Walker et al. [45] found a weaker correlation between AHI and BMI in women compared with men. As a result, weight loss in women might not be associated with as marked an improvement in apnea severity as compared with men.

O'Connor et al. [46] studied the influence of gender on the polysomnographic features of OSA in a retrospective study of 830 patients. Women have milder events during NREM sleep and greater clustering of respiratory events during REM sleep as compared to men, resulting in less severity of OSAHS. REM-related OSA (mild OSA which occurred predominantly during REM sleep with total AHI 5–15 events/hour, AHI REM/AHI NREM >2 and AHI NREM <15 events/hour) was disproportionately more common in women that in men. Supine OSA (OSA of any severity, which occurred predominantly in the supine position) was disproportionately more common in men than in women. They further compared the REM difference for men and women within different ranges of BMI (<30, 30–40, and >40) and found no significant effect of BMI.

Premenopausal Versus Postmenopausal OSAHS

In the Wisconsin Sleep Cohort Study [47], perimenopausal and postmenopausal women were twice as likely to be dissatisfied with their sleep as compared with premenopausal women; however, menopause was not associated with decreased sleep quality as assessed by PSG. As the severity of sleep-disordered breathing indicated by AHI categories increased, sleep architecture became less favorable in both pre- and postmenopausal women. At any AHI level, postmenopausal women had more favorable objectively measured sleep quality than did premenopausal women. Thus, menopause is not independently associated with objectively measured diminished sleep quality, and abnormal sleep in midlife women should not be treated as a simple menopausal symptom.

Management

The decision to treat patients should be based on the symptoms and signs of OSAHS and the PSG results. The different methods to treat sleep apnea include behavioral treatment including weight loss, treatment of nasal symptoms, continuous positive airway pressure (CPAP), oral appliances, and surgery.

Behavioral Treatment

It is important to identify any coexistent conditions that contribute to or promote upper airway collapsibility. The same lifestyle modifications, which are recommended to all patients with OSAHS, also apply to the treatment of premenopausal women.

Weight Loss

An association has been noted between OSAHS in premenopausal women and a higher BMI and neck circumference. Dancey et al. [2] noted a steep increase in AHI with increasing BMI in the most obese women. It has also been noted that pre-eclamptic women were heavier than healthy pregnant and nonpregnant women and had higher BMI than the healthy pregnant women before pregnancy [48].

Weight loss, by a combination of diet change and exercise, is of prime importance in decreasing the severity of OSAHS. The degree of weight reduction that will result in an improvement of the AHI is variable and even modest weight loss can result in substantial benefits in some patients [49]. Bariatric surgery has consistently been shown to cause significant improvement in sleep apnea severity [50]. Although bariatric surgery is increasingly performed for refractory medically complicated obesity, its long-term effectiveness in the treatment of OSA in morbidly obese patients is not yet demonstrated [51].

Positional Treatment

Positional therapy holds some promise in the treatment of sleep apnea [51]. Sleeping on the side is also recommended to prevent the tongue from falling back in the supine position and decreasing upper airway dimensions. It is even otherwise the preferred body position during sleep in pregnant women to prevent pressure on the inferior vena cava by the gravid uterus. Elevation of the head of the bed can also be useful.

Avoidance of Agents That Promote Upper Airway Collapsibility

Alcohol should be avoided for at least 6 h before bedtime. Sedatives and heavy meals should also be avoided before bedtime. Sleep deprivation should be avoided as it increases sleep drive on following nights.

Treatment of Nasal Symptoms

It is important to promptly treat allergic symptoms, which cause nasal congestion, as they compound upper airway obstruction. A trial of an inhaled nasal steroid, such

as fluticasone with or without a nonsedating antihistamine, should be used for 4–6 weeks. Surgery may be indicated for a deviated nasal septum or turbinate hypertrophy. Smoking cessation should be encouraged to improve upper airway health.

Continuous Positive Airway Pressure

CPAP is considered the gold standard for the treatment of moderate to severe sleep apnea. In 1999, Loube et al. [52] published a consensus statement and indicated that CPAP treatment should be indicated for all OSA patients with a respiratory disturbance index (RDI) of 30 events per hour, regardless of symptoms, based on the increased risk of hypertension evident from the Wisconsin sleep cohort data. CPAP is also indicated for patients with an RDI of 5–30 events per hour when accompanied by symptoms of excessive daytime sleepiness, impaired cognition, mood disorders, insomnia, or documented cardiovascular diseases to include hypertension, ischemic heart disease, or stroke.

In a study of 334 women with sleep-related breathing disorder [20], treatment with CPAP led to improvement in sleepiness in all cases as well as other symptoms, including dysmenorrhea in the premenopausal group.

CPAP has been tried as the first-line therapy for UARS and is often used as a therapeutic trial to demonstrate improvement in symptoms. In a randomized study conducted on postmenopausal women with UARS and chronic insomnia, radiofrequency reduction of nasal turbinates or turbinectomy or a trial of CPAP showed better relief in daytime fatigue than behavioral treatment alone at 6 months [53]. Some patients with UARS may benefit from CPAP treatment even with a normal apnea index and absence of snoring [50].

In pregnant women with preeclampsia, low level auto-setting nasal CPAP has been safely and effectively used to eliminate inspiratory flow limitation, resulting in a significant lowering of nocturnal blood pressure [54].

The American Academy of Sleep Medicine (AASM) practice parameters consider CPAP an effective treatment of OSA [55]. Initial CPAP follow-up is recommended during the first few weeks to establish utilization pattern and provide remediation if needed. Longer-term follow-up is recommended yearly or as needed to address mask, machine, or usage problems.

Oral Appliances

Oral appliances can be used for the improvement of snoring, OSA or both. The possible mechanisms include mandibular repositioning, tongue advancement, and alteration of palatal and mandibular position or dynamics. According to the American Sleep Disorders Association practice parameters for the use of oral appliances in the treatment of OSA [56], oral appliances are indicated for use in patients with mild-to-moderate OSA who prefer them to CPAP therapy, or who fail treatment attempts with CPAP. Oral appliances may also be useful during the period

of weight loss or adaptation to sleep-position changes. Oral appliances can also achieve satisfactory outcomes in UARS [57]. It is recommended that patients with moderate-to-severe OSA should have an initial trial of nasal CPAP because greater effectiveness has been shown with CPAP than with the use of oral appliances.

Oral appliances are also indicated for patients with moderate-to-severe OSA who are intolerant of or refuse treatment with nasal CPAP and for patients who refuse or are not candidates for tonsillectomy and adenoidectomy, cranofacial operations or tracheostomy. Follow-up PSG is not indicated for patients with either primary snoring or mild OSA, unless symptoms worsen or do not resolve. However, patients with moderate-to-severe OSA should undergo PSG to ensure therapeutic benefit, with the oral appliance in place after final adjustments of fit have been performed, and should have follow-up office visits to monitor compliance.

Oral appliances may cause a worsening of OSA in some patients and appropriate follow-up care is therefore essential. Intolerance and improper use of the device are potential problems for patients using oral appliances, which require patient effort for proper use. Oral appliances may aggravate temporomandibular joint disease and may cause dental misalignment and discomforts that are unique to each device.

Surgery

According to the American Sleep Disorders Association practice parameters [58], nasal positive airway pressure is the recommended therapy for patients with moderate-to-severe OSA. Nasal positive airway pressure may also be the preference of symptomatic patients with mild apnea. Surgery is indicated to treat OSA in patients who have an underlying specific surgically correctable abnormality that is causing the sleep apnea. Surgery may be indicated to treat OSA in patients for whom other noninvasive treatments have been unsuccessful or have been rejected, who desire surgery and who are medically stable to undergo the procedure.

Uvulopalatopharyngoplasty (UPPP), as a sole procedure, with or without tonsillectomy, does not reliably normalize the AHI in moderate-to-severe OSA. Patients need to be carefully selected in order to minimize failure rates [59]. Maxillomandibular advancement (MMA) is indicated for the surgical treatment of severe OSA or for those in whom oral appliances have been considered and found ineffective or undesirable. Use of multilevel or stepwise surgery (MLS) is acceptable in patients with narrowing of multiple sites, particularly if they have failed UPPP as a sole treatment. Laser-assisted uvuloplasty (LAUP) is not routinely recommended as a treatment of OSA. Patients should be advised about potential surgical success rates and complications, the availability of alternative treatment options, such as nasal positive airway pressure and oral appliances, and the levels of effectiveness and success rates of these alternative treatments.

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Chapter 11
Polycystic Ovary Syndrome and Obstructive Sleep Apnea

Mira Aubuchon

Introduction

Polycystic ovarian syndrome (PCOS) is an extremely common disorder in reproductive-age women. Affected patients frequently complain of menstrual irregularities, symptoms of hyperandrogenism, and infertility. The entity was first characterized by Stein and Leventhal in 1935 [1], who observed enlarged ovaries, obesity, hirsutism, and infertility associated with chronic anovulation [2]. Because PCOS is associated in the long term with diabetes, heart disease, and cancer [1], accurate diagnosis and treatment are extremely important. In recent years, it has become increasingly evident that PCOS is also a significant risk factor for obstructive sleep apnea (OSA). OSA is characterized by sleep-disordered breathing (SDB) and can be a debilitating condition leading to serious health problems if not treated or diagnosed adequately.

PCOS Diagnosis

PCOS is complex and consists of a variety of symptoms, but because the basic pathophysiologic defect is unknown, there are no universally accepted criteria at present for diagnosis of PCOS [1]. In the United States, PCOS is defined by the 1990 NIH-NICHD Conference as chronic anovulation and androgen excess, after other causes have been ruled out [3] (Table 11.1). Ovarian morphologic findings are not required, as not all women with PCOS have polycystic ovaries (PCO) by ultrasound [2].

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Table 11.1 Comparison of the NIH and Rotterdam criteria

Criteria	Rotterdam 2003	NIH 1990
Required	Two of the first three, plus 4	1,2, and 4
1. Hyperandrogenemia	✓	✓
2. Chronic anovulation	✓	✓
3. Polycystic ovaries	✓	Not required
4. Exclusion of other causes	✓	✓

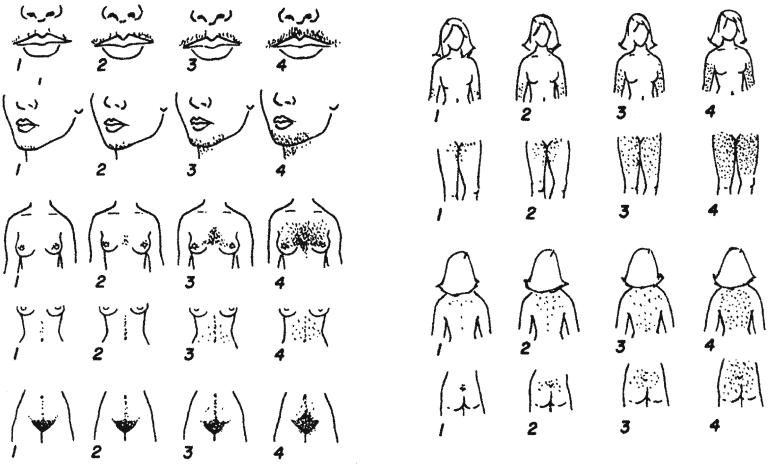

Fig. 11.1 Modified Ferriman-Gallwey scale (reproduced with permission of Elsevier from Hatch R, Rosenfield RL, Kim MH, Tredway D. Hirsutism: implications, etiology, and management. American Journal of Obstetrics and Gynecology 1981; 140(7):815–830)

At the 2003 Rotterdam conference in Europe, the NIH criteria were expanded to include ultrasonographic PCO morphology, as it was felt that this was predictive of ovarian dysfunction [4] (Table 11.1). The Rotterdam consensus determined ultrasonographic criteria for PCO as at least one ovary containing >12 follicles of 2–9 mm diameter and/or ovarian volume >10 mL [4].

Chronic anovulation, while not strictly defined by either criterion, is generally typified as fewer than 6–8 spontaneous episodes of vaginal bleeding per year [2]. Both criteria require exclusion of related disorders such as congenital adrenal hyperplasia, androgen secreting tumors, Cushing's syndrome, and hyperprolactinemia [2, 4].

Clinical hyperandrogenemia is characterized by hirsutism and/or acne [2, 4]. Evaluation should focus on location of terminal hair on upper lip, chin, lower abdomen, and inner thighs, with a Ferriman-Gallwey score of >5 defining hirsuitism [1] (Fig. 11.1).

Biochemical evidence of hyperandrogenism may also be useful for diagnosis, including elevated measurements of total and free testosterone, sex hormone binding globulin (SHBG), androstenedione (A4), and DHEA-S levels, although these may not be accurate in the presence of oral contraceptive pills. Androgen measurements are best performed when clear hirsutism is not present, with some clinicians measuring only a total testosterone, with abnormal considered to be >60 ng/dL, and 17 hydroxyprogesterone (17-OHP) level to rule out congenital adrenal hyperplasia [1]. However, clinical assessment can be somewhat subjective, and biochemical normal ranges are not well established [4].

OSA Diagnosis

OSA is a disorder resulting in episodes of either diminished or absent breathing during sleep. It is characterized by intermittent partial or complete airway obstruction that can lead to oxygen desaturations, blood pressure and heart rate changes, and interrupted sleep [5]. The gold standard for diagnosis is the overnight polysomnography (oPSG), which records the electric potentials of the brain and heart, eye movements, muscle activity, respiratory effort, airflow, oxygen saturation, and leg movements throughout the night [6].

Apnea is defined as complete airflow cessation at the nose or mouth ³10 s, while a hypopnea refers to a 30–50% decrease in airflow ³10 s that is accompanied by oxygen desaturation ³2–4% [6]. Severity is determined by the frequency of apnea and hypopnea events per hour of sleep (apnea-hypopnea index, AHI) as measured by oPSG [5]. AHI can be used interchangeably with respiratory disturbance index (RDI) [6]. OSA syndrome is a term used when PSG findings are accompanied by functional abnormalities such as daytime sleepiness [7].

Symptoms of OSA in adults include daytime sleepiness, partner-witnessed apneic episodes, snoring, or nocturnal gasping [6]. It is also important to elicit a medication history, as OSA may be associated with use of antidepressants or antihypertensives [8]. However, daytime sleepiness alone in obese patients may be a result of metabolic or circadian abnormalities rather than nocturnal sleep disturbances [9]. When PSG was performed on 99 morbidly obese patients in Australia describing symptoms suggestive of OSA, the only symptom that predicted OSA and OSA severity was partner-observed sleep apnea [10] (Table 11.2).

Physical exam may yield evidence of large neck circumference, pitting edema, hypertension, anatomic facial or oropharyngeal abnormalities, and increased weight, although one-third of OSA patients are non-obese [6]. In addition to body mass index (BMI) ³45 kg/m^2, the best clinical predictive measure for OSA was neck circumference followed by waist circumference [11] (Table 11.2).

When laboratory evidence is combined with clinical features, raised HbA1c >6% and fasting plasma insulin >28 mmol/L were most predictive, although HDL <1.17 mmol/L and fasting plasma glucose >5.6 mmol/L were also associated with OSA [11] (Table 11.2).

Table 11.2 Significant factors independently predicting severe obstructive sleep apnea (OSA) as defined by apnea-hypopnea index ³15 in symptomatic severely obese subjects

Variables	OR for OSA (95% CI)	*p* value	Corrected OR for OSA (95% CI)	Adjusted *p* value
Age ³38 years ($n=58$)	3.4 (1.3–9.2)	0.007	4.66 (1.0–22)	0.050
BMI ³45 ($n=51$)	4.3 (1.7–11.1)	0.002	4.6 (1.1–20)	0.043
Fasting plasma insulin ³28 μmol/L ($n=23$)	10.2 (3.4–30)	<0.001	14.7 (2.9–74)	0.001
HbA_{Ic} ³6% ($n=25$)	5.9 (2.2–15.8)	<0.001	4.5 (1.1–18.4)	0.036
Male sex ($n=23$)	5.2 (1.9–14.8)	0.001	7.3 (1.6–31.8)	0.008
Neck ³43 cm ($n=52$)	10.2 (3.7–28)	<0.001	13.2 (2.4–75)	0.004
Partner-observed apnea ($n=37$)	3.3 (1.4–8)	0.006	4.8 (1.2–18.9)	0.024

Adapted with permission from Dixon JB, Schachter LM, O'Brien PE. Predicting sleep apnea and excessive day sleepiness in the severely obese: indicators for polysomnography. Chest 2003; 123(4):1134–41

OR odds ratio; *BMI* body mass index

The differential diagnosis for excessive daytime sleepiness (EDS) includes idiopathic hypersomnia, narcolepsy, atypical depression, periodic leg movements during sleep, central sleep apnea, and insufficient sleep syndrome [6]. Partner-witnessed nocturnal choking, gasping, coughing, or shortness of breath could be attributable to gastroesophageal reflux disease, nocturnal asthma, congestive heart failure, central sleep apnea, nocturnal panic attacks, or sleep-related laryngospasm [6]. The gold standard of objective measurement is PSG in a sleep laboratory because electrode dysfunction can be corrected and sleeping behavior can be observed [6].

In 1999, the American Academy of Medicine Sleep Task Force standardized the severity of OSA using the AHI [7]. A minimum AHI of ³5 events/h is needed for a diagnosis of mild OSA, while moderate and severe OSA are distinguished with AHI cutoffs of ³15 and ³30, respectively [7].

PCOS Epidemiology

PCOS is the most common cause of anovulation and hirsutism in women [12]. Epidemiologic data of PCOS are limited due to the lack of uniform diagnostic criteria as well as selection bias from using patients going to PCOS referral centers [1]. Guzick determined that the best prevalence study was performed in 1998 on an unselected population of 277 women aged 18–45 in Alabama [1]. In the Alabama study, the overall prevalence of PCOS was 4%, with 4–4.7% in whites and 3.4% in African Americans, although the authors gave a possible overall prevalence range of 3.5–11.2% [13]. The 11 women with PCOS ranged in age from 18 to 29 years [13]. Guzick extrapolated these figures to three million current PCOS cases in the United States [1].

In adults, obesity is clearly a risk factor of PCOS. The obesity rate in the United States of women with PCOS is much higher than the general population, respectively 50–60% vs. 30% [14]. However, PCOS is also present in women of normal weight, suggesting other factors may play a role. In the Alabama study, 4 of the 11 (36%) of the PCOS cases were obese with a BMI >30 kg/m^2, indicating a significant number (64%) were non-obese [13].

PCOS prevalence among adolescent females in the United Kingdom is 8–26% [11]. Predictors of PCOS in adolescents include history of low birth weight, onset of pubic hair prior to age 8, African American or Caribbean Hispanic ethnicity, and positive family history of PCOS in first-degree relatives [11]. There appears to be tendency of PCOS patients to cycle more regularly as they get older, which may be attributable to declining androgen levels, particularly for age 42–47 [15].

OSA Epidemiology

It is estimated that 1 in 5 adults has mild OSA and 1 in 15 has moderate-severe OSA [5]. In the OSA population, men outnumber women 8:1 [5]. However, the ratio for unselected populations falls to 2:1, indicating that women may be less likely to be diagnosed [5]. The main risk factors for OSA are male gender, obesity, and older age, but it also occurs in thin, younger women. In a Wisconsin-based population study of 602 state employees aged 30–60, mild OSA rates in women vs. men were 9% vs. 24% and severe OSA rates were 4% vs. 9.1%, respectively [16]. It is estimated that 75–80% of OSA cases in the United States are undiagnosed, which is distressing in light of the effective treatment modalities that are available [5]. In another study involving 1,000 women, the overall prevalence of moderate OSA (AHI >10 with daytime symptoms) was 1.2% and severe OSA was 2.2% [17].

Obesity seems to affect overall prevalence in men much more than in women. In the obese population with BMI >40 kg/m^2, one study reported OSA prevalence rates of 7% of women and 76.9% of men [18]. A longitudinal study indicated that with each 10% gain (up to 20%) in weight, AHI increased by 30%, and the risk for developing moderate to severe OSA is increased sixfold [19]. It should be stressed, though, that OSA does occur in lean women [20].

With respect to ethnic prevalence of OSA, data are conflicting in the United States on prevalence in African Americans vs. Caucasians [7]. In two studies from Hong Kong, prevalence of OSA was 5% in men and 2% in women and was thought to be attributed to factors other than obesity [7].

Severe OSA prevalence rises with age, reaching a plateau of 13% for men and 7% for women after age 65 [5]. OSA prevalence rises with menopause to 29% vs. 10.8% in the premenopause, based on 589 women sampled from the longitudinal Wisconsin Sleep Cohort study, even after controlling for BMI [21] (Fig. 11.2).

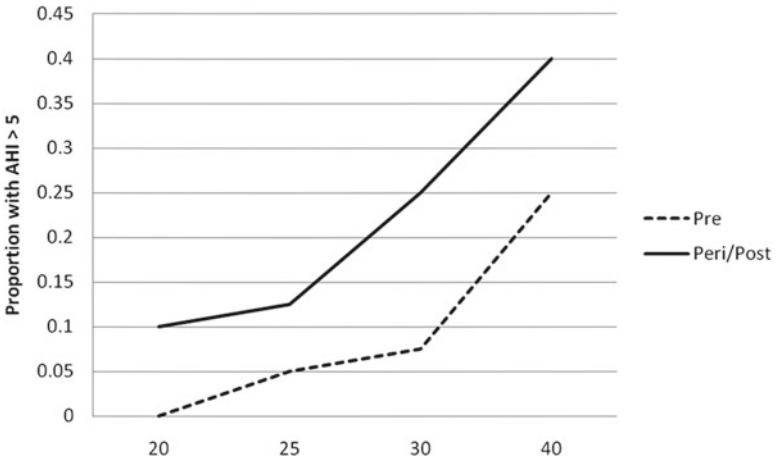

Fig. 11.2 Prevalence of apnea-hypopnea index (AHI) events >5 (*y*-axis) by body mass index (BMI) in kg/m^2 (*x*-axis) according to menopausal status (based on data from Young T, Finn L, Austin D, Peterson A. Menopausal status and sleep-disordered breathing in the Wisconsin Sleep Cohort Study. Am J Res Crit Care 2003;167:1181–1185)

PCOS Sequelae

PCOS patients are often infertile and have a higher rate of endometrial cancer due to unopposed estrogen [1]. Metabolic risks imparted by PCOS include impaired glucose tolerance (IGT), diabetes mellitus (DM), lipid abnormalities, and preclinical atherosclerotic changes [1].

Obese and non-obese PCOS patients have much higher rates of IGT and Type 2 DM, as measured by 75-g oral glucose tolerance test, than non-PCOS similar weight controls and the general population [22] (see Fig. 11.3).

Comparisons of lipid profiles of 195 PCOS patients and 62 controls showed that both lean and obese PCOS groups had higher total cholesterol and LDL-C than the lean and obese control groups, but only obese PCOS had higher triglycerides (TG) [23]. Unexpected findings, as yet unexplained, were the relatively higher HDL-C levels in both weight groups of PCOS participants [23].

PCOS women age ³45 have significantly greater ultrasonographic carotid intima-media wall thickness, which indicates premature subclinical carotid atherosclerosis, than controls of similar age and BMI [24]. The findings imply that subclinical cardiovascular changes that can occur with aging seem to be augmented by PCOS [24]. However, Spanish investigators determined that increases in markers associated with cardiovascular disease such as C reactive protein had the best statistical relationship to obesity, not presence of PCOS or insulin sensitivity [25]. Fortunately, mortality rates do not appear to be increased compared to the national averages, according to a retrospective study in the UK which examined hospital records and death certificates of 786 women with PCOS diagnosed between 1930 and 1979 [26].

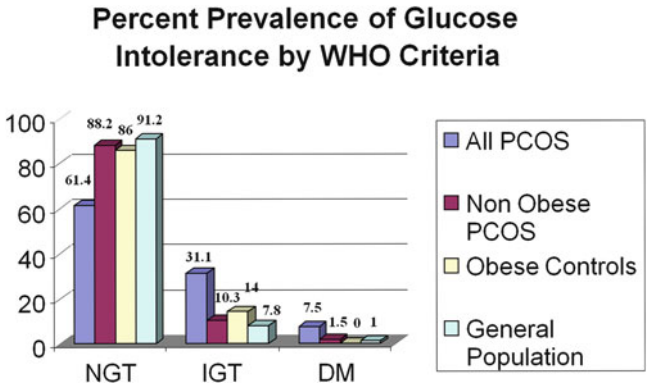

Fig. 11.3 Prevalence of impaired glucose tolerance (IGT) in polycystic ovary syndrome (PCOS) World Health Organization (WHO) (based on data from Legro RS, Kunselman AR, Dodson WC, Dunaif A. Prevalence and predictors of risk for Type 2 diabetes mellitus and IGT in polycystic ovary syndrome: a prospective, controlled study in 254 affected women. J Clin Endocrinol Metab 1999; 84(1): 165–9)

OSA Sequelae

OSA is associated with DM, hypertension, coronary artery disease, congestive heart failure, and stroke [5]. Other comorbid conditions include problems with daytime functioning and motor vehicle crashes [5]. Mortality from untreated OSA is estimated at 2–10% and is attributed to vascular disease [27]. Two studies determined that Type 2 DM and insulin resistance, as measured by homeostasis model assessment, were associated with OSA in men independently of obesity [28, 29]. In the Sleep Heart Health Study, however, a cross-sectional evaluation of 470 diabetic vs. 4,402 non diabetic male and female individuals showed that increases in OSA in the diabetic group were no longer evident after controlling for body habitus and BMI [30].

Evidence for a causal influence of OSA on hypertension was supported by the prospective 8-year Wisconsin Sleep Cohort Study, in which odds ratios for hypertension increased as AHI scores worsened, even after adjusting for age, sex, body habitus, smoking, and alcohol [31]. OSA is also an independent risk factor for coronary artery disease, according to a cross-sectional study of 6,424 participants from the Sleep Health Heart Study who underwent home PSG [32]. The acute hypoxia, CO_2 retention, sympathetic activation, and increases in blood pressure that occur during OSA events may all contribute to eventual coronary vascular damage [33].

Severe OSA also contributes to left ventricular (LV) dysfunction. A prospective study of 169 patients with severe OSA but without preexisting coronary artery disease found a 7.7% prevalence of LV systolic dysfunction that normalized with continuous positive airway pressure (CPAP) treatment [34]. OSA is probably a risk factor for cerebrovascular disease, according to several prospective studies showing similarly high rates of OSA in both stroke and TIA patients compared with controls [35].

Potential mechanisms include arterial hypertension and decreased cerebral blood flow [35]. Patients with OSA also show neurocognitive impairment, which may relate to hippocampal hypoxia [36]. Cognitive dysfunction can encompass learning and memory, attention, executive function, and motor skills [27]. This may relate to the increased frequency of motor vehicle accidents seen in this population, involving more than 800,000 drivers and 1,400 deaths in the year 2000 alone [37].

PCOS Pathophysiology

The exact mechanism by which PCOS develops has yet to be determined. However, insulin resistance and hypothalamic-pituitary hormonal changes likely play a major role (Fig. 11.4).

Insulin resistance (IR) is a state in which high serum levels of insulin are needed to maintain normal glucose tolerance, until pancreatic beta cells can no longer compensate, leading to glucose intolerance and Type 2 DM [38]. Fifty to seventy percent of PCOS patients have some degree of IR, compared to 10–25% in the general population [39].

IR can arise in visceral or intra abdominal fat, such as that found in omentum or mesentery. Visceral fat has much higher cellularity, blood flow, and innervation compared to subcutaneous fat, and is associated with increased free fatty acids [40]. Free fatty acids then lead to diminished hepatic insulin clearance and increased hepatic glucose production [41]. Although strongly associated with obesity, PCOS seems to be an independent risk factor for IR, based on a 1989 study by Dunaif which showed levels of insulin resistance in lean PCOS patients that were similar to obese cycling controls [1].

The ovary, however, remains sensitive to insulin despite the otherwise systemic insulin resistance [1]. Insulin enhances luteinizing hormone (LH) action on theca cells, leading to increased androgen secretion [42]. Hyperandrogenemia is further exacerbated by the suppressive effects of insulin on SHBG synthesis in the liver [2]. Insulin also enhances aromatase activity in granulosa cells, such that tonic low levels of estradiol are produced that negatively feedback on follicle stimulating hormone (FSH) from the pituitary [42], leading to arrested follicular growth and anovulation [1].

In the normal menstrual cycle, gonadotropin release hormone (GnRH) is released in from hypothalamic neurons in a precise pulsatile fashion, which leads to LH pulsatile release from the pituitary. Proper frequency and amplitude of gonadotropin pulses are crucial for hypothalamic-pituitary-ovarian regulation of the menstrual cycle. For as yet unexplained reasons, women with PCOS exhibit alterations of this neuroendocrine axis. In particular, they exhibit increased LH pulse frequency and amplitude, with overall increased LH serum levels [1]. The altered GnRH pulsatility is also thought to play a role in the diminished FSH levels seen in PCOS [1].

The changes in LH pulsatility can be especially appreciated during sleep. Normally cycling women have sleep-related suspension of episodic LH pulsations, especially in the early follicular phase of the menstrual cycle [43, 44]. In women

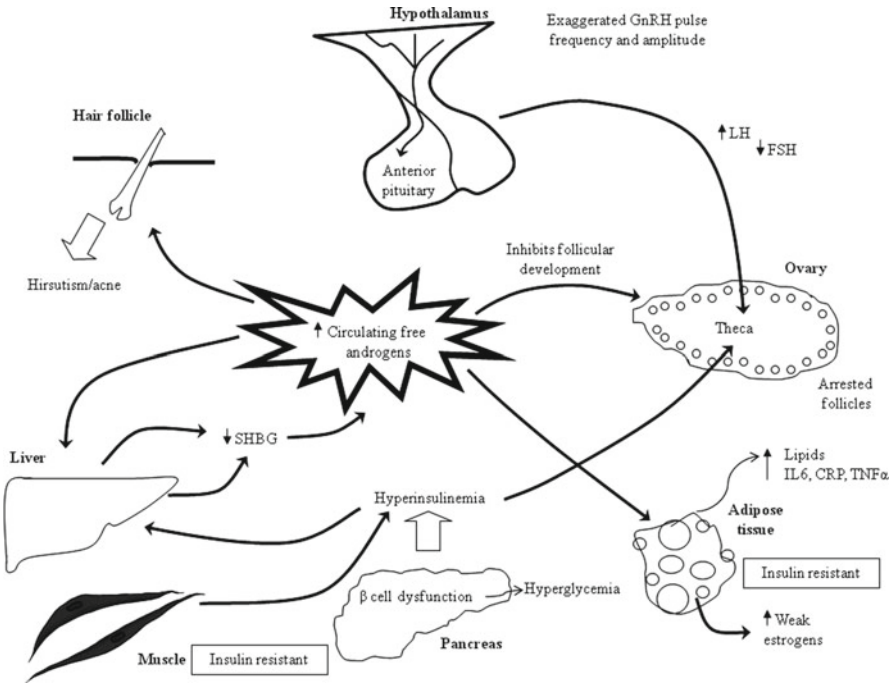

Fig. 11.4 Pathogenesis of PCOS

with PCOS, however, increased frequency of LH pulsations is seen, independent of BMI [42, 45, 46]. The increased pulse frequency of PCOS suggests an aberrant nocturnal pattern of GnRH secretion [47, 48]. The reason for this is unclear.

OSA Pathophysiology

The pathogenesis of OSA is also uncertain, but seems to involve interrelated mechanisms such as upper airway anatomy, pharyngeal muscle activity, body fat distribution, inflammation, insulin resistance, hyperandrogenism, and central respiratory control. These mechanisms, once elucidated, may help to explain the role of gender differences and obesity in OSA.

During wakefulness, the pharyngeal muscles in an OSA patient compensate for a vulnerable airway's propensity to collapse, but activation of those muscles is lost during sleep [49]. Apnea causes hypoxia and hypercapnia that eventually lead to nighttime arousal at which time hyperventilation lowers CO_2 and subsequently reduces central respiratory drive to produce cessation of respiration [49]. This cycle of OSA repeats when the patient falls back asleep [49]. See Fig. 11.5.

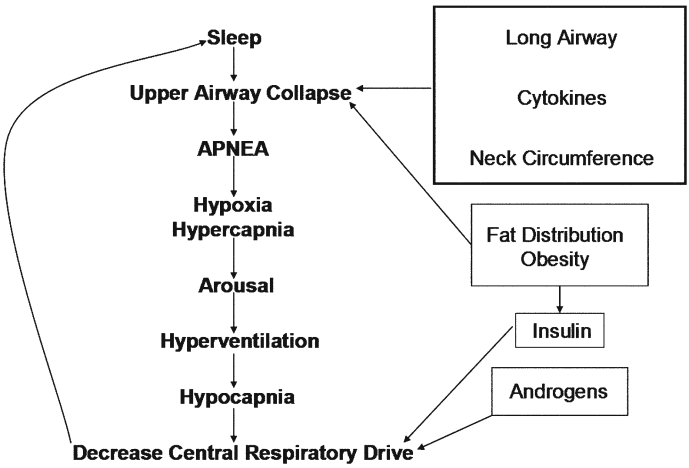

Fig. 11.5 Pathogenesis of obstructive sleep apnea (OSA) (based on data from Jordan AS, White DP, Fogel RB. Recent advances in understanding the pathogenesis of obstructive sleep apnea. Curr Opin Pulm Med Nov 2003;9(6):459–464; and Malhotra A, Huang Y, Fogel RB et al. The male predisposition to pharyngeal collapse: importance of airway length. Am J Respir Crit Care Med Nov 15 2002;166(10):1388–1395)

Men have significantly longer airway lengths than women, even after controlling for body height [50]. The male airways collapse much more readily than those of women, despite having significantly greater airway lumen area [50]. In addition, even healthy men have increased pharyngeal volume and soft palate area compared to women, which could also contribute to increased risk of OSA in susceptible individuals [50]. Although increased neck circumference in men compared to women is thought to contribute to higher OSA rates, men still had higher rates OSA than women even after controlling for BMI, age, and neck-height ratio [51].

Obesity is a well-known risk factor for OSA, but the distribution of subcutaneous body fat is more important than total body fat as predictor of OSA severity; in patients with OSA matched for BMI and waist-hip ratio (WHR), men had greater upper-body fat by subscapular and tricep skin fold measurements and higher AHI than women [52]. Visceral body fat, independently of BMI, is even more predictive than subcutaneous fat for OSA severity ($r=0.07$, $p=0.00$) (Fig. 11.6) [53].

In non-apneic individuals, pharyngeal muscle activity, the genioglossus (GG) in particular, is maintained during sleep, but falls in individuals with OSA [49]. Abnormalities in GG fast-twitch muscle fibers have been demonstrated in both lean and obese OSA [54]. Pharyngeal tissues from OSA patients show significant interstitial and lymphocytic infiltration and decreased levels of an anti-inflammatory enzyme, all of which can lead to pharyngeal vasodilation and upper airway collapsibility [55].

The systemic inflammatory markers TNF-a (alpha) and IL-6 are also significantly increased in men with OSA compared with controls [53] (Fig. 11.7). These cytokines cause sleepiness, increase with BMI, and are associated with OSA

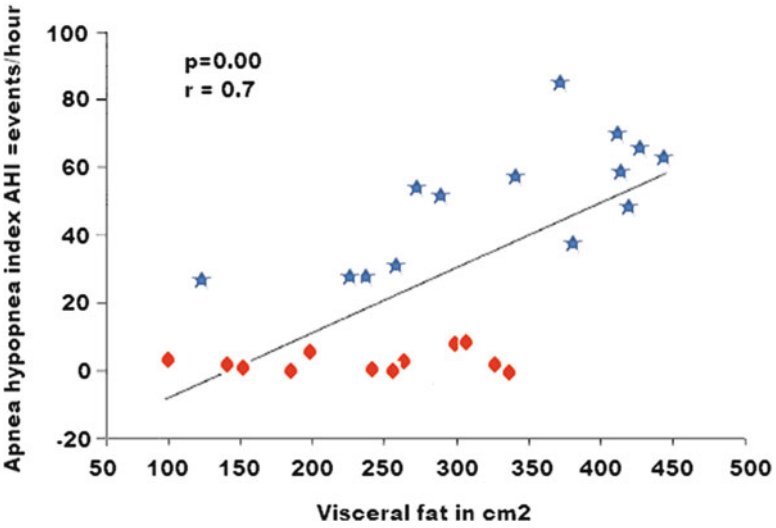

Fig. 11.6 Visceral fat and indexes of sleep apnea (based on data from Vgontzas AN, Papanicolaou DA, Bixler EO et al. Sleep apnea and daytime sleepiness and fatigue: relation to visceral obesity, insulin resistance, and hypercytokinemia. J Clin Endocrinol Metab 2000;85(3) 1151–1158)

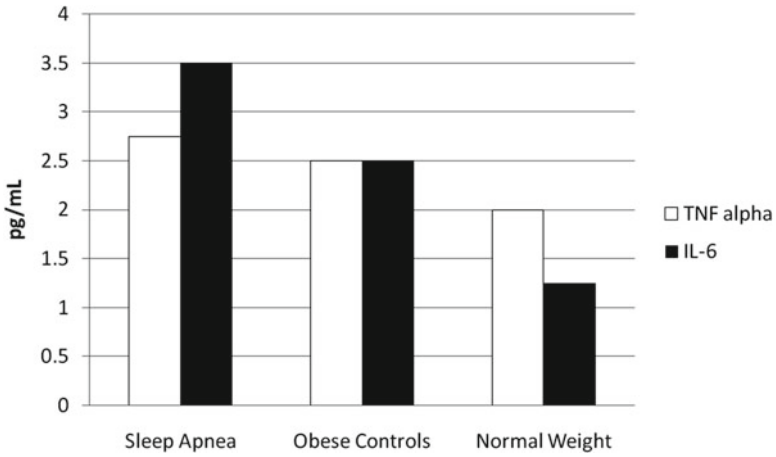

Fig. 11.7 Plasma TNFα (alpha) and IL-6 Levels in sleep apneics and BMI-matched obese and normal weight controls (based on data from Vgontzas AN, Papanicolaou DA, Bixler EO et al. Sleep apnea and daytime sleepiness and fatigue: relation to visceral obesity, insulin resistance, and hypercytokinemia. J Clin Endocrinol Metab 2000;85(3) 1151–1158)

independently of obesity [53, 56]. Compared to obese controls, male obese apneics have significantly higher fasting glucose and insulin levels and more visceral fat, which itself releases cytokines [53] (Table 11.3).

Table 11.3 Plasma glucose and insulin levels in obstructive sleep apneics (OSA) and obese controls

	Obese controls ($n=11$)	OSA ($n=14$)
Insulin (μg/mL) mean ± SE	14.55 ± 2.49	25.70 ± 4.22 ($p<0.01$)
Glucose (μg/dL) mean ± SE	85.4 ± 4.4	106.2 ± 4.1 ($p<0.05$)

Adapted with permission from Vgontzas AN, Papanicolaou DA, Bixler EO, Hopper K, Lotsikas A, Lin HM, Kales A, Chrousos GP. Sleep apnea and daytime sleepiness and fatigue: relation to visceral obesity, insulin resistance, and hypercytokinemia. J Clin Endocrinol Metab 2000 Mar;85(3):1151–8

SE standard error

Gender differences are also observed with respect to central ventilatory control, which may be accounted for by testosterone. Men require less reduction in CO_2 to induce apnea during non-REM sleep than women in either the follicular or luteal phase of the menstrual cycle [57]. Eight healthy mid-reproductive age normally cycling non-obese non-apneic women were given transdermal testosterone for 10–12 days during the follicular phase, which resulted in male levels of testosterone >130 ng/dL [58]. Response to hypocapnia determined at baseline and after testosterone administration showed an increase in CO_2 chemoresponsiveness with testosterone during non-REM sleep, which increases the likelihood of developing apnea [58]. Obese men with OSA have decreased nocturnal LH and total testosterone secretion, by mean and area-under-the-curve (AUC), compared with similar weight controls [59]. A review of the study concluded that although the sample size of 5 was small, the results suggest OSA is associated with pituitary suppression of androgen production [60]. Although these results seem paradoxical, the relative hypoandrogenism may reflect an adaptive response to OSA rather an etiology [60].

OSA and PCOS

Women with PCOS have a markedly increased OSA prevalence compared to the general female population. One study of 23 obese premenopausal women with PCOS found that 69.6% met criteria for symptomatic OSA [61]. Another study reported 44.4% of 18 obese women with PCOS had symptomatic OSA compared with 5.5% in weight and aged matched controls [62]. Adolescent girls with PCOS also have higher rates of SDB and EDS than controls matched for BMI, sex, race, and age [63].

The severity of OSA by RDI does not necessarily depend on higher BMI 61 (Fig. 11.8). However, the severity of OSA by AHI in adult PCOS patients was significantly correlated with WHR and with total testosterone ($r=0.051$, $p<0.03$ and $r=0.052$, $p<0.03$ respectively) [62]. In the adolescent population, metabolic

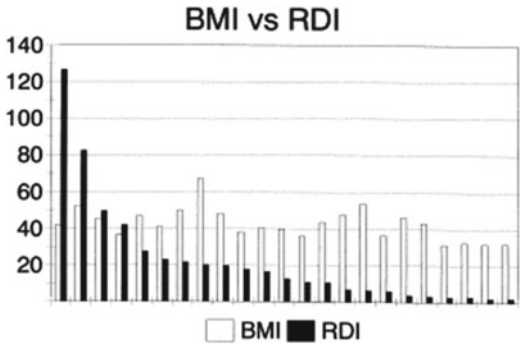

Fig. 11.8 BMI vs. RDI (reproduced with permission of Elsevier from Gopal M, Duntley S, Uhles M, Attarian H. The role of obesity in the increased prevalence of obstructive sleep apnea syndrome in patients with polycystic ovarian syndrome. Sleep Med Sep 2002;3(5):401–404)

Table 11.4 Biochemical profiles of women with polycystic ovary syndrome with and without obstructive sleep apnea (OSA)

	Non-OSA subjects	OSA subjects	*p*
Glucose nmol/L	5.48 ± 0.25	5.65 ± 0.31	NS
Insulin pmol/L	176.71 ± 18.53	306.48 ± 52.39	0.01
Glucose/insulin ratio	0.04 ± 0.003	0.02 ± 0.006	0.05
Free testosterone nmol/L	118.11 ± 16.54	124.81 ± 44.52	NS
Total testosterone nmol/L	284.77 ± 26.41	276.20 ± 73.1	NS

Adapted with permission from Vgontzas AN, Legro RS, Bixler EO, Grayev A, Kales A, Chrousos GP. Polycystic ovary syndrome is associated with obstructive sleep apnea and daytime sleepiness: role of insulin resistance. J Clin Endocrinol Metab 2001;86(2):517–20

syndrome independently predicted SDB and EDS [63]. IL-6 and TNF-α are elevated in PCOS women, but are not associated with OSA, unlike in men [64].

Insulin sensitivity in PCOS women was associated with SDB, which included OSA and upper airway resistance syndrome (UARS) severe enough to warrant treatment, for nine PCOS and three controls displaying SDB [65]. SDB was best correlated with fasting insulin, even after adjusted for BMI, and to a lesser extent with glucose:insulin ratio [65] (Table 11.4). Insulin resistance did not predict SDB in adolescents, however [63].

OSA may in turn worsen insulin resistance, as PCOS women with normal glucose tolerance had higher glucose and insulin levels in the presence of OSA compared to PCOS women without OSA66 (Fig. 11.9). This effect seems to occur in a dose-dependent fashion with severity of OSA and prevalence of glucose intolerance in PCOS women [66] (Fig. 11.10).

To summarize, OSA shows a male gender predilection related to generalized and visceral obesity, elevated androgens, inflammatory mediators, insulin resistance, and upper-body and neck fat. This gender gap narrows, however, in women with PCOS. PCOS patients share many of these characteristics, which may explain their markedly increased risk of OSA compared to the general female population.

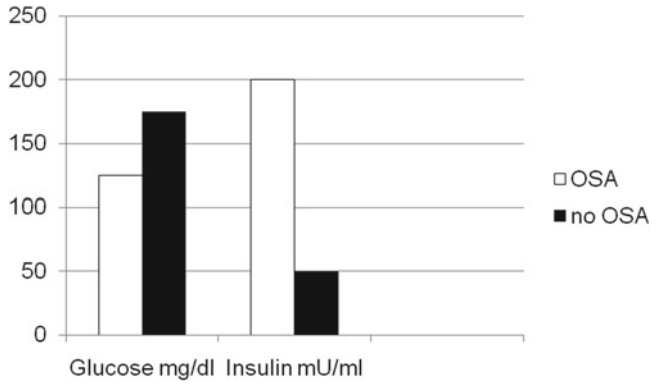

Fig. 11.9 Mean glucose and insulin levels 2 h following 75 mg oral glucose tolerance test in women having PCOS and normal glucose tolerance with and without OSA (based on data from Tasali E, Van Cauter E, Hoffman L, Ehrmann DA. Impact of obstructive sleep apnea on insulin resistance and glucose tolerance in women with polycystic ovary syndrome. JCEM 2008;93:3878–3884)

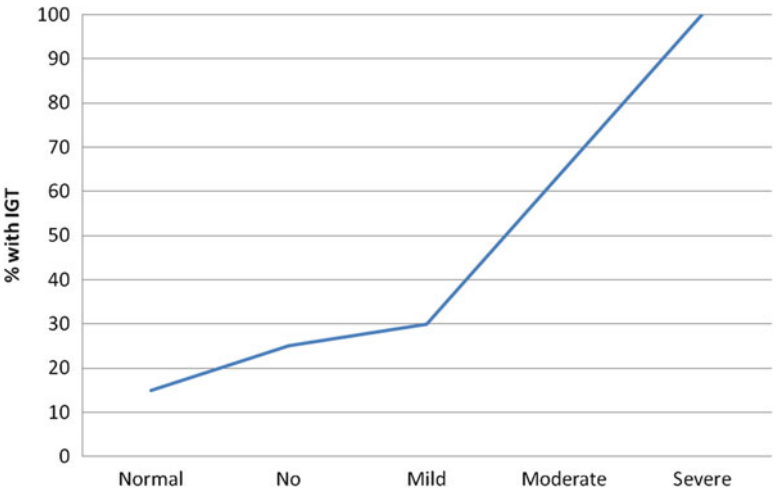

Fig. 11.10 Prevalence of IGT among normal (no PCOS, no OSA) and PCOS women with no, mild, moderate, and severe OSA (based on data from Tasali E, Van Cauter E, Hoffman L, Ehrmann DA. Impact of obstructive sleep apnea on insulin resistance and glucose tolerance in women with polycystic ovary syndrome. JCEM 2008;93:3878–3884)

OSA Treatment

Treatment for OSA is multifaceted. It can involve lifestyle changes, weight loss, mechanical assistance, and surgery, with possible roles being investigated for pharmacologic therapies. Treatment modalities may help not only SDB, but also associated visceral obesity, insulin resistance, and neuroendocrine abnormalities.

Lifestyle changes refer primarily to improving sleep hygiene, by avoiding possible triggers of airway collapsibility and sleep-related arousals [67]. These triggers include alcohol, sedatives, and supine positioning, although outcomes of avoiding these triggers have not been measured [67]. Longitudinal assessment of weight changes and SDB indicated that even a 5% reduction of body weight resulted in a significant (14%) reduction in OSA severity by AHI [19]. Weight reduction interventions do produce fairly good improvement in OSA in the short term (6–12 months), but weight maintenance is more difficult [68, 69]. Further, even for patients who maintain their weight loss in the long term, OSA may persist or recur [68, 69].

Nasal CPAP is the most commonly accepted mechanical treatment for OSA. CPAP prevents negative inspiratory pressure in the upper airway, and thus prevents pharyngeal collapse [70]. Use requires wearing a mask over the nose that is held in place with chin straps [6]. The level of positive pressure is determined with the PSG, as too little may be ineffective and too much may promote arousal, central sleep apnea, and even cardiac arrhythmias in susceptible patients [6]. Although the device effectively treats OSA in 80–90% of cases, patient compliance is often poor due to skin, eye, and nasal irritation.

Other forms of mechanical assistance include bilevel positive airway pressure, which provides different pressures during inspiration and expiration [6], and oral devices to modify the position of upper airway structures such as the tongue to improve airway collapsibility and muscle function [67].

Visceral body fat, as measured by computerized tomography, significantly decreased with CPAP treatment in a Japanese report of 12 mostly male overweight OSA patients treated with >6 months of CPAP without body weight changes [71]. These patients also had improvements in HDL and LDL cholesterol [71]. Insulin sensitivity as measured by hyperinsulinemic euglycemic clamp may, without BMI reduction, improve with CPAP in non-insulin diabetic patients with moderate-severe OSA [72], although this improvement was not seen in more recent study [73]. Glucose tolerance does not appear to improve with CPAP in the absence of BMI reduction, as variously measured by insulin, fasting glucose, HbA1c, or oral glucose tolerance testing [71–73].

CPAP seems to effect neuroendocrine changes, as well. OSA in men is associated with decreased serum secretion of insulin growth factor-1 (IGF-1), perhaps due to changes in slow wave sleep, as well as decreased SHBG and total testosterone [74]. In 43 obese men with OSA studied before and after 3 months of CPAP, IGF-I, total testosterone, and SHBG rose to normal levels without changes in body weight [74].

The most common surgical procedure to treat OSA is uvulopalatopharyngoplasty (UPPP), which removes the uvula, portions of the soft palate, and redundant pharyngeal tissue, but is only successful in 40–50% of cases [6]. UPPP works best with isolated upper pharyngeal pathology, but usually fails if the obstruction is at the tongue base [67]. Laser-assisted uvulopalatoplasty compares favorably to UPPP in terms of success but carries a higher risk of worsening the OSA if it fails [67]. Other options include midline glossectomy to trim an obstructive tongue, maxillary advancement, and procedures to correct craniofacial abnormalities [6].

Limited information is available regarding pharmacologic treatment of OSA. Estrogen alone or combined estrogen/progestin therapy has not been shown to be

effective in treating OSA in postmenopausal women [75]. Three weeks of etanercept, which blocks TNFα (alpha) and IL-6, significantly reduced daytime sleepiness and modestly reduced AHI in eight obese men in a randomized, double-blind, placebo-controlled, cross-over pilot study [56]. However, given that these cytokine elevations may be independent of OSA in PCOS [64], it is unclear whether etanercept would be effective as treatment in this population.

At present, only one study has reported on the cardiovascular impact of CPAP specifically in obese women with PCOS and OSA. Eight weeks of CPAP led to reduced norephinephrine secretion, a marker of sympathetic activation that is associated with cardiovascular disease, and improved insulin sensitivity even after controlling for BMI [76]. These improvements were observed in a dose-dependent manner, with a 7% increase in insulin sensitivity for each hour of CPAP [76].

Conclusion

The combination of OSA and PCOS begs for more study, both from a public health point of view and to understand their probable interrelated pathophysiology. Studies evaluating these conditions before and after treatment would be particularly valuable in this regard, as the majority of the literature focuses on men. Given that PCOS is so common, these patients represent an important opportunity to improve the screening, prevention, and treatment of sleep disorders and their sequelae in women.

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Chapter 12
Women and Excessive Daytime Sleepiness

Nidhi S. Undevia

Introduction

This chapter discusses excessive daytime sleepiness (EDS) due to primary sleep disorders other than Obstructive Sleep Apnea Syndrome (OSAS) and Restless Legs Syndrome (RLS) including Narcolepsy, Recurrent Hypersomnia, Idiopathic Hypersomnia, Behaviorally Induced Insufficient Sleep Syndrome as well as Hypersomnia Due to Medical condition and Hypersomnia Due to Drug or Substance.

Several studies over the years have demonstrated that sleep complaints in general, and EDS in particular, tend to be more prevalent among women. The 2007 Sleep in America poll of women age 40–60 years old found that 20% reported sleepiness that interfered with daily life [1]. There has been some evidence to suggest that this is, at least partly, due to women being more sleep deprived [2]. A study of Japanese workers demonstrated that women with a family to care for were more likely to suffer from EDS than those without a family to care for or those living alone, while having a family was protective against sleep deprivation in men [3]. This suggests that one of the causes of more prevalent insufficient sleep in women is more extensive work and homecare responsibilities [3]. However, having children did not increase the risk of hypersomnolence in a cross-sectional population study of 5,508 women in Sweden. This study found that 16.1% reported daytime hypersomnolence, that the risk of hypersomnolence decreased with increasing age and that anxiety and depression were highly related to hypersomnolence [4]. Women also nap less during the day than men do, despite having similar total sleep time at

Note: In the previous edition of this book, the chapter on this subject was authored by Hrayr Attarian, MD

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Table 12.1 Epworth sleepiness scale

0 = no chance of dozing 1 = slight chance of dozing 2 = moderate chance of dozing 3 = high chance of dozing	Score of 9 or higher indicative of sleepiness
Situation	*Chance of dozing*
Sitting and reading	0 1 2 3
Watching TV	0 1 2 3
Sitting inactive in a public place (e.g., a theater or a meeting)	0 1 2 3
As a passenger in a car for an hour without a break	0 1 2 3
Lying down to rest in the afternoon when circumstances permit	0 1 2 3
Sitting and talking to someone	0 1 2 3
Sitting quietly after a lunch without alcohol	0 1 2 3
In a car, while stopped for a few minutes in traffic	0 1 2 3

night and similar sleep efficiency [5], thus curtailing their total sleep time. Another variable that may partially contribute to the higher prevalence of excessive sleepiness in women is the under-diagnosis of most sleep disorders in women.

One of the tools most commonly used to screen for excessive sleepiness, and therefore sleep disorders, is the Epworth Sleepiness (ESS) Scale (Table 12.1). This is a simple, self-administered questionnaire, which is shown to provide a measurement of the subject's general level of daytime sleepiness. Patients rate the chances that they would doze off or fall asleep when in eight different situations commonly encountered in daily life [6]. One study demonstrated that using the ESS to detect subjective sleepiness is more likely to identify men with sleepiness. Since the ESS is more strongly related to other subjective measures in men, the ESS may be a more sensitive measure of subjective sleepiness in men than in women. Findings indicate that men and women answer questions on sleepiness differently [7]. A recent study of older black and white women found that the ESS was an internally consistent, valid measure of self-reported sleep problems in older women [8]. A third factor is hormonal changes and their impact on sleep in women. This gender difference in the prevalence of the EDS is not present among prepubertal children [9] and seems to be consistently reported in adults. Problems with sleep including hypersomnolence are common in perimenopausal and menopausal women and are associated with sleep disturbances due to hot flashes, sleep apnea, RLS, and depression. Several studies have found that women with severe premenstrual symptoms are sleepier than women with minimal symptoms [10, 11]. Menstrual-related hypersomnia is discussed in detail in this chapter with detailed descriptions of hormonal variables and their impact on sleep discussed in Chap. 5 of this book.

Prior to discussing specific disorders associated with hypersomnolence in women, a brief description of the different diagnostic tests used in sleep medicine is warranted, as they will be mentioned during the rest of this chapter and elsewhere in the book.

Diagnostic Tests

Polysomnogram

The polysomnogram (PSG) is a polygraph of EEG findings, eye movements, electromyography readings, oxygen saturation, limb movements, airflow, ECG, and chest and abdominal movements taken during sleep, usually for the entire night.

Multiple Sleep Latency Test

The Multiple Sleep Latency Test (MSLT) is a well-validated measurement of the tendency to fall asleep during normal waking hours. It consists of five testing periods performed at 2-h intervals throughout the day. A mean sleep latency of 8min or less is significant for hypersomnia and 10min or more is normal.

Maintenance of Wakefulness Test

The Maintenance of Wakefulness Test (MWT) determines the ability to remain awake while sitting in a quiet, darkened room. The test consists of four 40min trials conducted at 2h intervals commencing 1.5–3h after awakening from a night of sleep. A mean sleep latency of less than 19.4min is significant for hypersomnia [12, 13].

Primary Sleep Disorders Resulting in EDS

The primary sleep disorders, other than OSA and RLS, which result in symptoms of EDS include Narcolepsy, Recurrent Hypersomnia, Idiopathic Hypersomnia, Behaviorally Induced Insufficient Sleep Syndrome, Hypersomnia Due to Medical Condition, Hypersomnia due to Drug, or Substance and Hypersomnia Not Due to Substance or Known Physiological Condition. These conditions are listed in the Second Edition of the *International Classification of Sleep Disorders* (*ICSD-2*) under the category of "Hypersomnias of Central Origin Not Due to a Circadian Rhythm Sleep Disorder, Sleep-Related Breathing Disorder, or Other Cause of Disturbed Nocturnal Sleep" [14]. Each of these conditions will be discussed in this chapter.

Narcolepsy

Narcolepsy is a neurological disorder characterized by the tetrad of EDS, cataplexy, sleep paralysis, and hypnagogic/hypnapompic hallucinations. All four symptoms may not be present in a patient diagnosed with narcolepsy. Cataplexy is unique to narcolepsy while the other symptoms may occur in individuals who are severely sleep deprived. Men and women are both affected with a slight preponderance of males. Usually, it is of gradual onset, symptoms typically starting in the second or third decade of life. Case reports, however, exist of childhood onset, and some patients are not diagnosed until middle age [15, 16] Narcolepsy with cataplexy affects 1 in 2,000 individuals.

EDS is the sine qua non of narcolepsy. As with the sleepiness of other sleep disorders, the EDS of narcolepsy presents with an increased propensity to fall asleep, nod or doze easily in relaxed or sedentary situations, or a need to exert extra effort to avoid sleeping in these situations [17]. EDS of narcolepsy is not any different from that of other sleep disorders. The "sleep attacks" are not instantaneous lapses into sleep, as is often thought by the general public, but are similar to episodes of profound sleepiness experienced by those with marked sleep deprivation or other severe sleep disorders [17]. The duration of sleep attacks may vary from a few seconds to several minutes. Naps are characteristically refreshing in narcolepsy. Sleepiness is usually the first symptom to appear. Cataplexy, a unique feature of narcolepsy, is the partial or complete loss of bilateral muscle tone in response to strong emotion, typically anger or laughter. Reduced muscle tone may be minimal, occur in a few muscle groups, and cause minimal symptoms such as bilateral ptosis, head drooping, slurred speech, or dropping things from the hand. Or, it may be so severe that total body paralysis occurs, resulting in complete collapse. Awareness is preserved throughout the attack. Cataplectic events usually last from a few seconds to 2 or 3min but occasionally continue longer [17]. Respiratory and oculomotor muscles are not affected. Status cataplecticus is a rare manifestation of cataplexy characterized by prolonged cataplexy lasting hours. Cataplexy rarely precedes the onset of excessive sleepiness but may develop simultaneously with sleepiness or with a delay of 1–30 years. Hypnagogic (hypnapompic) hallucinations are vivid perceptual experiences that occur at sleep onset (hypnagogic) or at sleep offset (hypnapompic). These hallucinations are unpleasant and associated with feelings of fear of major threat and sometimes associated with a fear of dying. Sleep paralysis is a transient, generalized inability to move or to speak during the transition between sleep and wakefulness. The experiences are often frightening.

Disrupted nocturnal sleep with frequent awakenings is common, and patients may complain of insomnia. Other associated sleep-related problems include sleep disordered breathing, periodic limb movements, non-REM parasomnias, and REM sleep behavior disorder,

The Second Edition of the *International Classification of Sleep Disorders* (*ICSD-2*) divides narcolepsy into several types including Narcolepsy With Cataplexy, Narcolepsy

Table 12.2 Diagnostic criteria: narcolepsy with cataplexy

The patient has a complaint of excessive sleepiness occurring almost daily for at least 3 months
A definite history of cataplexy, defined as sudden and transient episodes of loss of muscle tone triggered by emotion is present
The diagnosis of narcolepsy with cataplexy should, whenever possible, be confirmed by nocturnal polysomnography followed by MSLT; the mean sleep latency on the MSLT is less than or equal to 8min and two or more SOREMPs are observed following sufficient nocturnal sleep (minimum 6h) during the night prior to the test. Alternatively, hypocretin-1 levels in the CSF are less than or equal to 110pg/mL or one-third of mean normal control values
The hypersomnia is not better explained by another sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder

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Table 12.3 Diagnostic criteria: narcolepsy without cataplexy

The patient has a complaint of excessive daytime sleepiness occurring almost daily for at least 3 months
Typical cataplexy is not present, although doubtful or atypical cataplexy-like episodes may be reported
The diagnosis of narcolepsy without cataplexy must be confirmed by nocturnal polysomnography followed by an MSLT. In narcolepsy without cataplexy, the mean sleep latency on the MSLT is less than nor equal to 8min and two or more SOREMPs are observed following sufficient nocturnal sleep (minimum 6h) during the night prior to the test
The hypersomnia is not better explained by another sleep disorder, medial or neurological disorder, mental disorder, medication use, or substance use disorder

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Without Cataplexy, Narcolepsy Due to Medical Condition and Narcolepsy, Unspecified [14]. The diagnosis of narcolepsy requires a complaint of EDS occurring almost daily for at least 3 months. The diagnosis should, whenever possible, be confirmed by nocturnal PSG followed by MSLT. The mean sleep onset latency on the MSLT is less than or equal to 8min, with two or more sleep onset REM periods observed. Alternatively, CSF hypocretin-1 levels may be used (Table 12.2). Narcolepsy with cataplexy is differentiated from narcolepsy without cataplexy by the presence of definite cataplexy (Tables 12.2 and 12.3). The cause of narcolepsy due to medical condition is a coexisting medical or neurological disorder. Disorders which have been associated with narcolepsy include tumors, sarcoidosis, multiple sclerosis, head trauma, myotonic dystrophy, Prader-Willi syndrome, Parkinson's disease, and multiple system atrophy.

Genetics/Pathophysiology

Many studies suggest a genetic influence to narcolepsy. Narcolepsy with cataplexy is closely associated with the human leukocyte antigen (HLA) subtypes HLA-DR1501 (DR15 or DR2), and HLA-DQB1-0602 (DQ) has been associated with narcolepsy. The most common HLA marker associated with narcolepsy with cataplexy is DQB1*0602 with a prevalence of 85–95%. In patients with narcolepsy without cataplexy, the HLA DQB1*O602 prevalence is also increased (about 40%). Polymorphisms in the tumor necrosis factor (TNF0 alpha and TNF receptor 2 genes) have also been implicated [18, 19]. Two hypothalamic peptides called hypocretin I and II, also called orexin A and B [20], are important in the pathophysiology of narcolepsy [21]. Narcolepsy in dogs is caused by a deletion in the hypocretin 2-receptor gene [22] whereas REM sleep episodes while awake and cataplexy are observed in hypocretin knockout mice [23]. In the hypothalamus of patients with narcolepsy, hypocretin-producing cells are reduced by 85–95% [24]. CSF content of hypocretin is undetectable in most patients with narcolepsy with cataplexy [25]. Serum levels, however, are normal, pointing to the brainloc.lity of the disorder. There are certain genetic forms of narcolepsy with cataplexy that do not depend on the hypocretin pathway and have patients have normal hypocretin levels in the CSF [26]. Another study found a loss of about a third of hypothalamic hypocretin containing cells in a patient with narcolepsy without cataplexy [27]. An autoimmune process may be responsible for the loss of the hypocretin neurons; however, antibodies of hypocretin and hypocretin receptors have not been found [28, 29]. Increased antistreptococcal antibodies have been reported in patients with recent onset of narcolepsy, suggesting that a streptococcal infection may be an inciting event triggering an autoimmune process [30].

Treatment

No cause-specific treatment is currently available for narcolepsy. The goal of treatment should include control of sleepiness and other sleep-related symptoms when present [31]. Nonpharmacologic management should be used in all patients including avoidance of sleep deprivation and good sleep hygiene. Short naps can help daytime alertness. Medications currently approved by the US Food and Drug Administration (FDA) for the treatment of narcolepsy include modafinil, armodafinil, sodium oxybate, amphetamines, and methylphenidate [31].

EDS had been treated with stimulants such as methylphenidate or dextroamphetamine but, more recently, modafinil and armodafinil have become the first-line treatment for most patients. Modafinil is a novel wake-promoting agent that is chemically and pharmacologically unique and distinct from the other stimulants. It has a low potential for abuse [32] and is a first-line therapy for EDS associated with narcolepsy and is recognized as standard patient care [33]. Modafinil is not a

dopamine receptor agonist [34, 35], and does not promote widespread activation of the central nervous system [36]. It promotes wakefulness through the selective modulation of hypothalamo-cortical pathways involved in the physiological regulation of sleep and wakefulness [37, 38]. The dose of modafinil is usually 200–400mg a day, but higher doses may be required in some patients [39]. Armodafinil is the dextro-enantiomer component of modafinil. It has similar therapeutic and side effect profile to modafinil but has a longer elimination half-life. Sodium oxybate is the sodium salt of gamma-hydroxy-butyrate (GHB) and is an endogenous substance in the brain that is an effective treatment of daytime sleepiness in narcolepsy. Sodium oxybate is GHB or γ-Hydroxy butyrate, a 4 carbon fatty acid that is found in mammalian hypothalamus, basal ganglia, and archicortex [40]. It has been used as an anesthetic for many years in Europe. Progress towards the development of a hypocretin antagonist for treatment of hypersomnolence has been slow, though an internasal hypocretin agonist holds promise [41, 42].

Most medications used for the treatment of cataplexy have REM sleep suppressant properties. Cataplexy has been traditionally treated with tricyclic antidepressants or fluoxetine. More recently, a specific medication, sodium oxybate has been approved for its treatment. There is evidence supporting the long-term efficacy of sodium oxybate for the treatment of cataplexy. In contrast with antidepressant drug therapy, there is no evidence of rebound cataplexy upon abrupt discontinuation of treatment [43] The dosage for cataplexy is 4.5–9g taken in two divided doses at night (one dose at bedtime and one dose in the middle of the major sleep period about 3h after the first dose). Sodium oxybate and the antidepressants have also been shown effective in treating the fragmentation of nighttime sleep, hypnic hallucinations, and the sleep paralysis associated with narcolepsy.

Recurrent Hypersomnia

Recurrent hypersomnia is characterized by recurrent episodes of hypersomnia often associated with other symptoms that typically last weeks or months apart. Episodes usually last a few days to several weeks and appear once to ten times a year. Sleep and general behavior must be normal between episodes. Kleine-Levin Syndrome (KLS) and Menstrual-Related Hypersomnia are two distinct clinical subtypes of recurrent hypersomnia (Table 12.4).

The male to female ratio in KLS is about 4:1. Behavioral abnormalities such as binge eating, hypersexuality, irritability, and aggressiveness may be present. The age of onset of KLS is usually in the second decade. A flu-like illness or an infection is occasionally reported immediately prior to the onset of the first episode, suggesting the involvement of an autoimmune disorder. HLA DQB1*02 has been found to be increased in patients with KLS, suggesting a genetic predisposition. Several familial cases of KLS have been reported [44–47]. CSF analysis is within normal limits, including levels of hypocretin-1 which is deficient in narcolepsy with cataplexy.

Table 12.4 Diagnostic criteria: recurrent hypersomnia (including Kleine-Levin Sydrome and menstrual-related hypersomnia)

The patient experiences recurrent episodes of excessive sleepiness of 2 days to 4 weeks duration
Episodes recur at least once a year
The patient has normal alertness, cognitive functioning and behavior between attacks
The hypersomnia is not better explained by another sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder

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Menstrual-related hypersomnia, a rarely described but distinct entity, is a periodic hypersomnia associated with the menstrual cycle. This is usually noted during the first few months after menarche. The EDS generally lasts 1–2 weeks after ovulation, with sudden resolution occurring at the time of menses. The first case in the medical literature discussing this distinct entity was published in 1975 by Billiard and colleagues. They described a 13-year-old girl with recurring episodes of periodic excessive sleepiness with each menstruation. During episodes of hypersomnia, the subject slept for an average time of 14h and 19min per 24h. They also showed a significantly reduced level of performance when evaluated by the Wilkinson Addition Test (a performance test in which the subject adds numbers for 1h which is often used, in addition with other tests, to measure the impact of sleep loss). Looking for hormonal abnormalities did not reveal any striking findings. Based on the close relationship between the episodes of hypersomnia and the end of menstruation, they suggested that progesterone may have a role in its pathogenesis. The hypersomnia in this case was successfully treated with oral contraceptives, thus blocking ovulation [48]. Pappy etal. followed another subject for 8 years with menstrual-related hypersomnia. Serial EEGs during the period of excessive sleepiness did not reveal any abnormalities. In this individual, events initially occurred at approximately 5–6 days after menstruation and later on occurred during ovulation. Again, hormonal abnormalities were not found, and oral contraception eliminated the events [49]. Sachs etal. also reported a case in 1982 of menstrual-related hypersomnia in a 16-year-old girl who was followed for 3 years after a hospital stay of 31 days. Neurologic and gynecological exams were normal, and serum levels of reproductive hormones were normal. CSF concentrations of homovanillic acid and 5-hydroxyindolacetic acid were lower in her hypersomnia phases compared to symptom-free phases. As in the previous two cases, sleep periods occurred only in connection with ovulation. Inhibition of ovulation with the oral contraceptive pill (OCP) led to a resolution of the hypersomnia. When treatment was discontinued, ovulation and periodic hypersomnia reoccurred regularly. Reinstitution of the OCP again controlled the symptoms. The recurrence of the sleepiness and ovulation when off OCPs and its resolution with the resumption of the pill were reproduced twice during the 3 years [50]. A case of an older woman (42 years old) with the same symptoms was reported in 1993 by Bamford. This subject's menstrual cycles stopped while taking metoclopramide, but

stopping them did not improve the EDS. The periods of EDS became more erratic. High serum prolactin levels were found to coincide with the subject's period of sleepiness. Unlike the previous cases, hormonal replacement therapy did not control the periods of somnolence. Low dose methylphenidate provided successful symptomatic relief [51]. All of these cases did not have any other medical or psychiatric symptoms associated with the EDS. Menstrual-related hypersomnia has also been reported during the luteal phase in some women with severe premenstrual symptoms as well as opposed to premenstrual insomnia during the same phase in women with mild premenstrual symptoms [52]. A recent case report describes a case of a male sibling with KLS and a sister with menstrual-related hypersomnia further supporting the hypothesis of a genetic predisposition [53].

Pathophysiology

Bamford postulated, based on the high prolactin levels coinciding with the episodes of somnolence, that it is likely that the pathophysiology of menstrual-related hypersomnia involves the dopaminergic and monoaminergic neurotransmitter systems. This has been also theorized to be the underlying cause of KLS, another disorder characterized by episodic hypersomnia. In well-documented cases, KLS brain imaging and MRI were normal. However, SPECT analysis has demonstrated hypoperfusion in the area of the hypothalamus during symptomatic periods which was reversed during the asymptomatic period [54–56].

Diagnosis

There is no established objective test to affirm the presence of KLS. In menstrual-related hypersomnia, MSLT and polysomnography (PSG), administered in a standardized fashion during and after the symptomatic period, usually make the diagnosis. PSG and the MSLT should be performed no earlier than the second night after the onset of a symptomatic episode and the following day to reveal maximal hypersomnolence, and more than 2 weeks after a symptomatic episode to represent the asymptomatic interval [57].

Treatment

The treatment for the recurrent hypersomnias includes stimulant and hormonal therapies (in the case of menstrual-related hypersomnia). Stimulants are usually given during the symptomatic phase, and the preferred stimulant, because of its favorable adverse effect profile and low risk of addiction, is modafinil. In KLS, stimulants have had an

effect, not on the reoccurrence, but on the duration of the symptomatic period. Medication has not been found to reduce the overall frequency of the relapses and has not changed symptoms during the initial days of the symptomatic phase [58]. Lithium may be effective for the treatment of KLS based on a small case series of five patients found that the duration of hypersomnia episodes was shorter and there were no behavioral symptoms during episodes treated with lithium [59].

Hormonal treatments such as OCPs and hormone replacement therapy have been shown to be effective for menstrual-related hypersomnia.

Idiopathic Hypersomnia

Idiopathic hypersomnia (IH) is a clinically heterogeneous entity that is not well delineated. Previously, two forms of the disorder were described: (1) a polysymptomatic form, characterized by EDS, nocturnal sleep of abnormally long duration, and signs of sleep drunkenness on awakening, and (2) a monosymptomatic form that manifests only by EDS [60]. The ICSD-2 distinguishes between idiopathic hypersomnia with long sleep time and idiopathic hypersomnia without long sleep time (Tables 12.5 and 12.6). IH is characterized by constant and severe excessive sleepiness. Naps are typically unrefreshing, and post-awakening confusion (sleep drunkenness) is often reported. Individuals often report difficulty waking up in the morning with use of special devices or procedures to wake up. In the case of IH with long sleep time, there is a prolonged major sleep episode (Table 12.5). Prevalence of IH is not known; however, the disorder appears to be less frequently diagnosed now than in the past, likely due to more stringent diagnostic criteria. The onset of IH typically occurs before 25 years of age and no sex predominance is apparent. The disorder is stable in severity and long lasting once established. Polysomnography must exclude

Table 12.5 Diagnostic criteria: idiopathic hypersomnia with long sleep time

The patient has a complaint of excessive daytime sleepiness occurring almost daily for at least 3 months
The patient has prolonged nocturnal sleep time (more than 10h) documented by interview, actigraphy, or sleep logs. Waking up in the morning or at the end of naps is almost always laborious
Nocturnal polysomnography has excluded other causes of daytime sleepiness
The polysomnogram demonstrates a short sleep latency and a major sleep period that is prolonged to more than 10h in duration
If an MSLT is performed following overnight polysomnography, a mean sleep latency of less than 8min is found and fewer than two SOREMPs are recorded. Mean sleep latency in idiopathic hypersomnia with long sleep time has been shown to be 6.2 ± 3.0min
The hypersomnia is not better explained by another sleep disorder, medical or neurological disorder, mental disorder, medication use or substance use disorder

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Table 12.6 Diagnostic criteria: idiopathic hypersomnia without long sleep time

The patient has a complaint of excessive daytime sleepiness occurring almost daily for at least 3 months
The patient has normal nocturnal sleep (greater than 6h but less than 10h), documented by interviews, actigraphy, or sleep logs
Nocturnal polysomnography has excluded other causes of daytime sleepiness
Polysomnography demonstrates a major sleep period that is normal in duration (greater than 6h but less than 10h)
An MSLT following overnight polysomnography demonstrates a mean sleep latency of less than 8min and fewer than two SOREMPs. Mean sleep latency in idiopathic hypersomnia has been shown to be 6.2 ± 3.0min
The hypersomnia is not better explained by another sleep disorder, medical or neurological disorder, mental disorder, medication use or substance use disorder

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other causes of daytime sleepiness, and an MSLT must demonstrate a mean sleep onset latency of less than 8min with fewer than two sleep onset REM periods.

Pathophysiology

Its pathophysiology is much less understood than that of narcolepsy due to the lack of animal models [61]. There have been reports that, unlike in narcolepsy, the levels of CSF hypocretin in patients with IH are normal to high [62]. The levels of CSF leptin, however, are low both in subjects with narcolepsy and those with IH [63].

Treatment

Modafinil, amphetamine, methamphetamine, and dextroamphetamine may be effective for treatment of daytime sleepiness due to IH [31]. In a study of 24 patients with narcolepsy and 18 patients with IH, modafinil improved the number of drowsy episodes [64].

Behaviorally Induced Insufficient Sleep Syndrome

Behaviorally induced insufficient sleep syndrome occurs when an individual, unintentionally, persistently fails to obtain the amount of sleep required to maintain normal levels of alertness and wakefulness. A positive response to increased sleep time is diagnostic of this disorder [14].

Hypersomnia Due to Medical Condition

The direct cause of hypersomnia due to medical condition is a coexisting medical or neurological disorder that produces hypersomnia. Cataplexy must not be present, and the patient should not meet criteria for a diagnosis of narcolepsy. Hypersomnia due to medical condition should only be diagnosed if the medical condition is judged to be directly causing the hypersomnia. Hypersomnia due to a psychiatric diagnosis, drugs, or medications are classified separately. Nocturnal sleep should be greater than 6h, and another sleep disorder such as sleep-related breathing disorder or periodic limb movement disorder should not be present. Clinical and pathologic subtypes include hypersomnia due to Parkinson's disease, posttraumatic hypersomnia, genetic disorders, brain tumors, infections or CNS lesions, endocrine disorders (particularly hypothyroidism), and hypersomnia secondary to toxic and metabolic conditions [14].

Hypersomnia Due to Drug or Substance

Hypersomnia due to drug or substance should be diagnosed in patients with excessive nocturnal sleep, daytime sleepiness or excessive napping that is believed to be secondary to substance use. This can be related to the withdrawal of stimulant medications, the use of sedative hypnotic drugs or the use of medications with drugs with a sedative effect. Sleep-related breathing disorders may be increased in patients using sedatives, and this should be ruled out [14]. A detailed discussion of all medications that can cause hypersomnia is beyond the scope of this chapter, but there are certain characteristics common to most of these medications and pharmacological agents. Most of these drugs tend to be highly lipophilic, and they affect dopaminergic, cholinergic, or histaminergic receptors. In addition to direct action, medications and drugs can cause EDS by disturbing sleep architecture and as a symptom of withdrawal. Table 12.7 outlines the different classes of medications associated with EDS.

Hypersomnia Not Due to Substance or Known Physiological Condition

In hypersomnia not due to substance or known physiological condition, excessive nocturnal sleep, daytime sleepiness, or excessive napping are reported. Patients are often intensely focused on their hypersomnia. Causative psychiatric conditions include mood disorders, conversion disorder, or other mental disorders [14]. Hypersomnia can be a symptom of depression especially in women. Khan etal. explored gender differences in the symptoms of major depression in male–female

Table 12.7 Different classes of medications associated with excessive daytime sleepiness (EDS)

Analgesics
Antiasthmatic agents
Anticonvulsants
Antidepressants
Antihistamines
Antihypertensives
Antiparkinsonian agents
Antipsychotic agents
Benzodiazepines
Antiemetics
Withdrawal from stimulants

twin pairs. Female twins reported experiencing significantly more fatigue, hypersomnia, and psychomotor retardation during the most severe major depressive episode, whereas male twins reported more insomnia and agitation [65]. In addition, depression is twofold more prevalent in women and depressive episodes more common in women with bipolar illness [66]. Given these factors, although a diagnosis of exclusion, depression should be relatively high on the differential diagnoses list for female patients complaining of fatigue and EDS. Patients complaining of psychiatric hypersomnia tend to have more disrupted sleep at night and on objective measures of daytime sleepiness tend to score in the normal range despite profound subjective sleepiness. This is in contrast to patients with primary hypersomnia who tend to have normal sleep at night and are profoundly sleepy both on objective and subjective measures of sleepiness [67].

Conclusion

EDS is a very prevalent problem in developed societies. Women tend to complain more of EDS than men. This prevalence may partially be due to greater sleep deprivation, hormonal factors, and the higher incidence of some primary and secondary sleep disorders in women.

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Chapter 13
Parasomnias from a Woman's Health Perspective

Cynthia L. Bodkin, Carlos H. Schenck, and Michael J. Howell

Introduction

Parasomnias are defined as undesirable physical events or experiences that occur during entry into sleep, within sleep, or during arousals from sleep [1]. Parasomnias encompass abnormal movements, behaviors, emotions, perceptions, dreaming, and autonomic nervous system functioning that can emerge in relation to any sleep stage at any time of the night. These disorders may result in injuries, sleep disruption, adverse health effects, and psychological or interpersonal distress affecting a person and his or her bed partner or roommate.

Parasomnias can occur at any age, including in utero (as described in the documentary *Sleep Runners: The Stories Behind Everyday Parasomnias* [2]). It is believed that the kicking of a fetus is a manifestation of "spontaneous motility patterns," that is, the most primitive form of motor activation—without concurrent inhibition—during primordial sleep [3]. This developmentally normal motor activity, when exaggerated in intensity and duration, could alter or disrupt the sleep of the bed partner, causing an insomnia or environmental sleep disorder in the mother induced by parasomnia behavior in her fetus [1].

In the previous edition of this book, Mark W. Mahowald, MD, was a coauthor of this chapter.

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Parasomnias are the dysfunctional nocturnal manifestation of basic drives or deepest instinctual urges. These central pattern generators can become inappropriately activated during sleep, often with bizarre, frightening, and harmful consequences. These drives, such as ambulation, feeding, sexual activity, as well as violent behaviors, can become pathologically engaged during sleep on a recurring basis.

Parasomnias can be categorized as primary parasomnias (disorders of sleep per se) or as secondary parasomnias (disorders of other organ systems that manifest themselves during sleep) [4, 5]. Primary parasomnias comprise 12 diagnostic categories across rapid eye movement (REM) and non-REM sleep [1]. This chapter focuses on parasomnias and their particular relevance to females.

Secondary parasomnias can be subdivided according to the organ system involved, such as central nervous system (seizures, headaches), cardiopulmonary system (cardiac arrhythmias, nocturnal angina pectoris, nocturnal asthma, etc.), and gastrointestinal system (gastroesophageal reflux, etc.). Also, various sleep disorders can trigger a secondary parasomnia, such as obstructive sleep apnea (OSA) which increases the homeostatic sleep drive through sleep fragmentation as well as can lead to sudden arousal precipitating a parasomnia episode. Other sleep/circadian rhythm disorders and sedating medications can be frequently associated with parasomnia behaviors.

During the past two decades, a growing body of work on the parasomnias has been published in peer-reviewed medical journals. As a result, our understanding of the pathophysiology of these fascinating behaviors has been expanded and deepened. New conditions have been identified, and known disorders are now recognized to occur more frequently, across a broader age group, and with more serious consequences than previously recognized. Furthermore, striking gender differences exist across many of the parasomnias, which is a theme that is emphasized in this chapter. A strong genetic basis has been identified for some of the parasomnias, and it is common for multiple parasomnias to be present within a family or, conversely, for one patient to be afflicted with multiple parasomnias. Finally, most parasomnias can be substantially if not fully controlled with specific therapies once the correct diagnosis is established.

This chapter will begin by outlining a practical method to clinically investigate parasomnias in women. Subsequently a review will be presented on the pathophysiology and management of individual parasomnias. These include the NREM parasomnias, which including sleepwalking, confusional arousals, and night terrors. Next, we will review REM parasomnias including REM sleep behavior disorder (RBD) and other forms of dream-enactment behavior as well as isolated sleep paralysis. Previously, RBD has been considered primarily a disorder of elderly men. We will extensively review two conditions that predominantly affect women but also defy current classification, sleep-related eating disorder (SRED) and sleep-related dissociative disorder. Interestingly, many cases of SRED may in fact actually be a non-motor manifestation of restless legs syndrome (RLS), a condition with a strong female predominance. Finally, we will conclude with a review of parasomnias during pregnancy.

Table 13.1 Parasomnias by gender predominance

	Female predominant	Gender neutral	Male predominant
NREM parasomnias		Sleep walking Confusional arousals Sleep terrors	Sexsomnia
REM parasomnias		Isolated sleep paralysis	REM sleep behavior disorder
Other or uncertain etiology	Sleep-related eating disorder Sleep-related dissociative disorder Pregnancy parasomnias Menstrual parasomnias		

After reading this chapter, the reader should be able to recognize that: (a) women are especially vulnerable to developing certain parasomnias; (b) women can be adversely affected by parasomnias that affect men equally; (c) women can be adversely affected by aggressive and violent parasomnias preferentially emerging in men; (d) parasomnias can emerge premenstrually in some susceptible women; and (e) parasomnias can pose various risks during pregnancy (Table 13.1).

Clinical Evaluation of Parasomnias

The proper clinical evaluation of parasomnias starts with a detailed history. The history should not only be obtained from the patient, but also the bed partner if available. Frequently, the bed partner provides the most valuable information and therefore should be encouraged to accompany the patient to the appointment. Specific screening questions (Table 13.2) can be asked at the visit or prior by questionnaire. Any "yes" answers could indicate an underlying parasomnia and should be further explored with follow-up questions. The patient should be urged to talk to family members to acquire their observations.

Questions regarding sleep habits and other provocative behaviors should be addressed (Table 13.3), as well as a detailed medical and psychiatric history, review of systems, past or current history of abuse (physical, sexual, verbal–emotional), and family medical history (including sleep difficulties). A psychiatric interview and screening psychological tests (e.g., Beck Depression and Anxiety Inventories, Minnesota Multiphasic Personality Inventory, Symptom Checklist-90, Dissociative Experiences Scale) are important when evaluating complex sleep-related behaviors [6].

The physical examination is generally normal in patients with primary parasomnias; however, abnormalities may signify a secondary parasomnia, most notably the presence of parkinsonism in the setting of RBD.

Table 13.2 Specific screening questions for parasomnias

Do you or your bed partner believe that you move your arms, legs, or body too much or have disturbing behaviors during sleep?
Do you move while dreaming, as if you are acting out the dream?
Have you ever hurt yourself or your bed partner while asleep?
Do you sleepwalk or have you had night terrors with shouting or screaming?
Do your legs feel restless and/or begin to twitch a lot or jump around when you are drowsy or sleepy?
Do you eat, drink, or have sex without full awareness during the night?
Do you ever wake up in the morning with food in your mouth, feeling bloated, having no desire to eat breakfast, or see a mess indicating that you prepared food at night?
Are you gaining weight inexplicably and wondering if it is from eating during the night?
Are you told that you engage in abnormal sexual behaviors with yourself or your bed partner during sleep, such as prolonged and/or violent masturbation, loud or objectionable sexual vocalizations, or (inappropriate) sexual contact with your bed partner?
Do your legs feel restless or uncomfortable and give you an urge to get up and walk around, making it difficult to fall asleep?
Do you have episodes of sudden muscle paralysis as you are falling asleep or waking up? Are these episodes sometimes accompanied by visual, auditory, or tactile hallucinations?
Do you have episodes of arising during the night after having fallen asleep in which you leave the house without remembering what you did?
Do you have loud and prolonged groaning during sleep that you may not be aware of, but which disturbs the sleep of others?
Do you have body rocking, head rolling, or head banging while being drowsy or during sleep?
Do you scratch yourself, bit your nails, or pull your hair during sleep without being aware of it?

Table 13.3 Sleep habits and behavior questions

What is your schedule for falling asleep and waking up?
Do you wake up rested or unrefreshed?
What is your pattern and timing for consuming alcohol and caffeine?
Describe the stresses in your life that interfere with your sleep
Do you have physical symptoms or a medical or psychiatric disorder that could be affecting your sleep?
What medications, including those over-the-counter, do you take?

Subsequently, a sleep study should be performed at an accredited sleep center that has experience with evaluating and treating parasomnias. It is strongly recommended that patients be evaluated by a sleep physician before a polysomnogram (PSG) is performed. Often a PSG is ordered before seeing the sleep clinician in order to "save time." However, PSGs are not homogenous, and various sub-investigations can be performed depending upon the clinical evaluation. In addition to standard PSG recording of eye movements (EOG), brain-wave activity (6 lead EEG), muscle tone (chin EMG), heart rhythm (EKG), and airflow with respiratory effort monitoring, parasomnia investigations may include 4-limb EMG, full audio–visual recording, and 32-lead EEG (seizure) montage.

NREM Sleep Parasomnias

Sleepwalking, Confusional Arousals, and Sleep Terrors

Clinical Findings

Sleepwalking and sleep terrors typically arise from the slow-wave stage of deep non-REM sleep (N3) [1]. Sleepwalking and sleep terrors primarily affect children, but adults can also be affected with an estimated adult prevalence of 4% [7].

Sleepwalking is characterized by complex, ambulating behaviors, such as leaving the bed, wandering about semi-purposely, carrying objects nonsensically from one place to another, and urinating in closets or into waste baskets. Alarmingly, sometimes these behaviors involved leaving the house and operating a motor vehicle. The patient will appear to be awake, frequently with nonsensical conversation, however have little to no recall of events in the morning [1].

Frenzied or aggressive behavior, the wielding of weapons (knives, guns, baseball bats), or the calm suspension of judgment (e.g., going out a bedroom window or wandering far outdoors on a winter's night) can result in inadvertent injury or death to oneself or others [6, 8, 9]. Sleepwalking episodes usually emerge 15–120 min after sleep onset, but they can occur throughout the entire sleep period in adults. The duration of each episode can vary widely, with the most prolonged episodes associated with sedative-hypnotic medications often prescribed in the setting of RLS [10]. Sleep terrors are characterized by sudden, loud, terrified screaming in a patient (typically a child) who is inconsolable. There is often increased autonomic activity manifested by pupil dilatation, tachycardia, tachypnea, and hyper-hidrosis [1]. Like sleepwalking, sleep terror episodes usually appear in the first half of the sleep period, although they can occur at any time of the night.

Compared to childhood sleepwalking, adults typically have some recall of the events and may describe dream mentation. During dramatic sleepwalking events, these dreams often involve a threat of imminent danger, such as a menacing intruder, a fire, or the ceiling collapsing. In these cases, the distinction between agitated sleepwalking and sleep terrors is often blurred, because terrified screaming can be noted; therefore, we often diagnose adults with mixed "sleepwalking/sleep terrors."

Typically there is greater interaction with the actual environment in sleepwalking compared to RBD, as sleepwalking episodes are usually more prolonged, and involve partial cortical arousal. This contrasts with RBD, where patients are still in REM sleep attending to an inner dialogue of dream mentation [1].

The prevalence of sleepwalking has been estimated to be as high as 17% in childhood (peaking at age 4–8 years), and recent data indicate a higher prevalence in adults (4–10%) than previously recognized [11, 12]. The prevalence of sleep terrors ranges from 1 to 6.5% in children and 2.3 to 2.6% across the 15- to 64-year age span, before dropping to 1% after age 65 [1, 13]. A familial–genetic basis for sleepwalking and sleep terrors is well established. Noninjurious sleepwalking has no

gender preference, but injurious sleepwalking is more male predominant. There is no distinct gender difference in sleep terrors.

Confusional arousals comprise another category of NREM parasomnia and represent partial manifestations of sleepwalking and sleep terrors [1]. Confusional arousals can last for variable intervals of time, including prolonged episodes with irritability and anger. Confusional arousals are especially common among children and adults younger than 35 years. Based on large population-based studies, the prevalence rate in children 3–13 years of age was 17.3% and in adults younger than 35 years of age is 2.9–6.9% [1, 14, 15].

Sleep inertia—or the inability to promptly and properly transition oneself between sleep to wakefulness—is the defining feature of confusional arousals. Predisposing factors include hereditary disposition as well as any condition that leads to an increase in homeostatic sleep drive such as sleep deprivation, shift work, or sedative medications. Confusional arousals are then precipitated by any sudden arousal such as from sleep-disordered breathing, periodic limb movement disorder, or environmental sleep disruption.

Sleep-related abnormal sexual behavior is a recognized variant of confusional arousal, with published reports referring to this phenomenon as "sleep sex," "sexsomnia," or "atypical sexual behavior during sleep" [1, 16–19]. Behaviors during sleep include loud sexual vocalizations, prolonged and/or violent masturbation, sexual molestation and assaults of minors or adults (including spouses), and initiation of sexual intercourse irrespective of the menstrual status of the bed partner (unlike during wakefulness). Some sexsomnia cases have also included other parasomnia activity, such as sleep-related eating and sleep-related driving. Although confusional arousals are reported equally in men and women, sexsomnia is reported more often in men. Women tend to be the sufferer more than men because of the adverse physical or mental consequences of the sexual act. Morning amnesia for the nocturnal sexual activity has been present in all reported cases, and PSG investigation usually documents evidence supporting the diagnosis of NREM parasomnia.

Finally, repetitive nocturnal scratching, nail-biting, and hair-pulling can be regarded as other variants of NREM parasomnias and can be so vigorous as to draw blood, resulting in multiple scabs, skin sores, and infections. At times, the focus of this repetitive scratching is the peri-anal region. Gender distribution appears to be equal. Treatment may consist of wearing gloves to bed (often wrapped in tape to make them more difficult to remove during sleep) as well as medications such as sedating antihistamines and benzodiazepines (BZDs) [20, 21].

Polysomnographic Findings in Sleepwalking, Sleep Terrors, and Confusional Arousal

Episodes of sleepwalking and sleep terrors arise abruptly during arousal from any stage of non-REM sleep but most commonly from slow-wave (N3). During an episode, the brain-wave activity (EEG) typically shows either the admixture of sleep and

wakefulness, or complete wakefulness. There is often an impressive dissociation—a major discordance—between a fully awake brain-wave pattern and the patients disoriented appearance and confused behavior [6, 22, 23].

The contemporary medical literature on adult sleepwalking and sleep terrors indicates that most cases are not causally associated with a psychological problem or a psychiatric disorder, although stress can play a promoting role. Nevertheless, at least half of adult patients with sleepwalking and sleep terrors have a history of depression and/or anxiety [15].

Treatment of Sleepwalking, Sleep Terrors, and Confusional Arousal

Fortunately, most NREM parasomnias are limited in duration and severity and thus most patients may be given reassurance regarding the benign nature of their condition. If treatment is necessary, management should be first directed at identifying and minimizing risk factors such as sleep deprivations, circadian misalignment, sedating medications, and comorbid sleep disorders, as well as maximizing the safety of the bedroom.

When sleepwalking is associated with use of sedative-hypnotics, it is of particular importance to carefully reconsider the diagnosis for which the medication was originally prescribed. In these cases, patients may not have insomnia (for which the sedating agent was prescribed) but rather another disorder that leads to sleep initiation difficulties such as RLS or a delayed circadian rhythm [10, 24, 25]. Removal of offending agents will typically resolve the abnormal nighttime behavior, particularly if another underlying condition is identified and treated [10, 25, 26].

The etiology of frequent cortical arousal in sleepwalkers is often related to other sleep disorders such as sleep apnea. Clinically symptomatic or severe comorbid conditions, such as OSA and RLS, should always be treated. A pivotal report from 2005 studied 60 chronic sleepwalking patients with PSG and followed them prospectively for a year after diagnosis. Of the 60 sleepwalking patients, a high number ($n=53$) were diagnosed as having sleep-disordered breathing. In the majority of cases, the SDB was mild, often not reaching the criteria for OSA, but instead indicated upper airway resistance syndrome (UARS), and the majority did not demonstrate daytime sleepiness. Only 3 patients dropped out of the study, while, of the remaining 50, all reported resolution of sleepwalking after treatment of SDB. Of those 50 patients, 42 patients reported compliance with nasal continuous positive airway pressure (nCPAP) while the remaining 8 patients described resolution of sleepwalking after upper airway surgical treatment. These dramatic results suggest that treatment of even mild, asymptomatic SDB may result in resolution of sleepwalking [27].

For patients with NREM parasomnias who are resistant to previously described interventions, a variety of different therapies have been reported. Pharmacological interventions include a variety of BZDs and antidepressant medications. Nonpharmacological interventions include scheduled awakenings and hypnotherapy.

Benzodiazepines

The most commonly reported pharmacological treatments for NREM parasomnias are various agents in the BZD class of sedative-hypnotics. BZDs act by increasing the chloride conductance through GABAa receptors [28]. BZDs reported to be effective for NREM parasomnias are typically categorized as either intermediate- or long-acting agents. The use of BZDs in the treatment of NREM parasomnias is seemingly paradoxical, as other sedative-hypnotics, such as benzodiazepine receptor agonists (BRAs), can induce amnestic nocturnal behavior [10].

One of the earliest reported pharmacological studies, a double-blind crossover trial of diazepam, reported mixed results. In this investigation, five adults with chronic sleepwalking were given either 10 mg of diazepam or placebo. They reported that diazepam administration resulted in resolution of sleepwalking events in some, but not all, subjects. There was no significant difference between placebo and treatment groups; however, this was a small study and it is uncertain whether other sleep phenomena, such as subtle sleep-disordered breathing, may have been present [29]. The most extensively studied agent in the treatment of NREM parasomnias is clonazepam. In 1989, a series was published of 61 patients with sleep-related injury who were treated with clonazepam. 83.6% of patients had a "rapid and sustained" response to clonazepam [6]. Later, the same investigators reported on an expanded series of 170 patients with mixed sleep disorders (69 with sleepwalking/night terrors) treated with BZDs, primarily clonazepam ($n=136$) [30]. The majority (86%) of patients with a variety of sleep disorders reported complete/nearly complete efficacy after a mean follow-up of 3.5 years. Importantly, the authors reported sustained efficacy with clonazepam with low risk of dosage tolerance. Further support for the use of clonazepam was noted in a small series of patients ($n=10$) with a history of sleepwalking, who were followed after a variety of treatments were initiated. PSG was used to confirm the NREM parasomnia, and clonazepam was initiated in six subjects. Sleepwalking was suppressed in five of six patients in whom it was tried [31]. Conversely, a more recent report claims that clonazepam failed to demonstrate sustained efficacy in five sleepwalking patients. This investigation carefully excluded even subtle sleep-disordered breathing or other associated mental illness. After 1 year, all patients treated with clonazepam dropped out of the study but reported persistence of sleepwalking [27].

Mood Altering Medications

Reports have suggested that agents with serotonergic actions, e.g., commonly prescribed SSRI antidepressants, may be effective in the treatment of NREM parasomnias, in particular sleep terrors, in some patients. However, as these investigations are limited to case reports or small case series, further investigations are necessary.

In 1994, a 30-year-old patient with a combination of sleep terrors and somnambulism was reported to be successfully treated with paroxetine [32]. The authors suggested that SSRIs may be uniquely effective for night terrors through serotonin

effects on terror centers in the brain stem. In particular, the periaquaductal grey matter in the midbrain has been implicated. Conversely, there has been a report of paroxetine inducing sleepwalking [33]. Further, one series of sleepwalking patients, who were closely screened for underlying mood or anxiety disorders, included eight patients who were treated for these conditions with either medications (SSRIs, Trazodone, or anxiolytics) and/or psychotherapy. After 1-year follow-up, all eight patients described a persistence of sleepwalking [27]. Clearly more research, in particular a randomized controlled trial, is needed.

Sexsomnia Treatment

Treatment of abnormal sleep-related sexual behaviors primarily consists of treating the underlying disorder, namely confusional arousals and sleepwalking: bedtime administration of clonazepam has been reported to be effective [17], as has CPAP therapy (if OSA is present, presumably enhancing the confusional arousal and/or sleepwalking with abnormal sexual behaviors). Also, the physician should consider referral of the patient and partner to a psychologist or psychiatrist for one of two reasons (or both): (a) to explore the marital/interpersonal relationship as a contributing factor to the sexual parasomnia and (b) to deal with the adverse consequences (personal and interpersonal) of the sexual parasomnia.

Hypnosis and Environmental Changes

Teaching a patient to practice self-hypnosis [34] or other relaxation techniques at bedtime can be effective in milder cases of adult or childhood sleepwalking and sleep terrors. A psychologist or other clinician can tailor the self-hypnosis and relaxation instructions to suit the individual needs and wishes of each affected person.

Environmental safety is a critical component in treating all cases of potentially injurious sleepwalking behavior. The patient should be advised to remove any bedside object or furniture that could be injurious either to them or to a bed partner. Removal of firearms is of paramount importance. Use of night-lights, motion sensors, door alarms, and other safety devices should always be considered.

REM Sleep Parasomnias

REM Sleep Behavior Disorders

REM sleep in mammals involves a highly energized state of brain activity and is frequently termed "paradoxical sleep" because of the nearly complete suppression

of muscle tone despite the high level of brain activity. This generalized muscle paralysis (REM-atonia) is one of the three defining features of mammalian REM sleep, besides REMs and an activated brain-wave (EEG) pattern virtually identical to the EEG of wakefulness.

The customary muscle atonia of REM sleep is lost in RBD and carries serious clinical consequences. The clinic hallmark of RBD is the acting out of dreams that are vivid, intense, action-packed, confrontational, and violent. These dream scenarios often involve being threatened or attacked by unfamiliar people, animals, or insects, and then fighting the attacker to protect oneself or a loved one from being harmed.

Clinical Findings

There is a distinct clinical profile in the longstanding (chronic) form of RBD [1, 35]. Chronic RBD has an older male predominance, with an average age of onset in the early 50s, and with males generally comprising more than 85% of patients [36–38]. Nevertheless, females and virtually all age groups can be identified with RBD with a mean age of onset in the 40s [39].

Dream-enacting behaviors (DEB) observed by the bed partners and documented during sleep lab monitoring in woman include the following: talking, yelling, swearing, crying, laughing, gesturing, grabbing, arm flailing, punching, kicking, sitting, thrashing, pelvis thrusting, jumping out of bed, falling out of bed, strangling bed partner, crawling, and running. Of female RBD cases reported, 60% were noted to have violent behaviors [39]. Before eventually seeking help at a sleep disorders center, patients with RBD often have had to protect themselves while sleeping and have resorted to such measures as retiring for the night to a sleeping bag, padded waterbed, barricade of pillows, or mattress placed on the floor or tying themselves to their beds or bedposts with belts, ropes, or dog leashes [40, 41].

The female bed partners of patients with RBD are often battered during violent dream-enacting behaviors, and their faces, arms, and torsos can become bruised. Not uncommonly, physicians and nurses question whether willful domestic abuse has taken place. Nevertheless, it is evident to these women that their bed partners are asleep and dreaming while they engage in their aggressive and violent nocturnal behavior. Furthermore, in many cases the women remain in bed with their significant other in order to protect them from hurting themselves. While there have been no reported cases of marital separation or divorce directly due to the dream-enactment behavior of RBD, there was one case of discord in a recently married young adult couple. The difficulties fortunately resolved once the RBD was controlled with appropriate treatment [42].

More than half of RBD cases are closely associated with brain disorders [35]. The brain disorders are predominantly neurodegenerative conditions (especially synucleinopathies such as Parkinson's disease and related conditions), but also narcolepsy, and stroke. In fact, RBD may be the first sign of a neurological disorder

whose other ("classic") manifestations may not emerge until several years or decades after the onset of RBD. For example, about two-thirds of men over the age of 50 years with RBD eventually developed Parkinson's disease (PD) or a related condition, such as multiple system atrophy or Lewy body dementia, at a mean interval of 13 years, but with the range extending from 2 to 29 years [43, 44]. In patients with RBD without a clear cause, their 12-year risk of developing a neurodegenerative disease is 52% [45]. Recent studies suggest RBD may not only be a marker for PD, but a marker for PD with cognitive dysfunction [46–50]. This is fascinating, and also ominous, in that a change in a person's nocturnal behavior can be the harbinger of a fulminate brain disorder decades from manifesting itself. Thus, routine neurological evaluations are indicated in the long-term management of RBD. The course of RBD is usually progressive; spontaneous remissions are very rare.

The prevalence of RBD is unknown, but is estimated to be 0.5% in the elderly population [1]. Although the majority of patients with RBD are male, it is possible, if not likely, that many female cases of RBD go unnoticed as they may have less violent DEB (a general trend in male–female comparisons), and thus have an attenuated form of the condition that remains mainly unnoticed, and thus does not require medical intervention. When consecutive patients with PD are screened for RBD with PSG, the incidence of RBD in women is less than, but comparable to, men (38% vs. 57%) [39].

There is also an acute toxic form of RBD that emerges during exposure to serotonergic agents. Certain antidepressant medications appear to be especially likely to cause or aggravate RBD, or its precursor, preclinical RBD (i.e., polysomnographic abnormalities without a clinical parasomnia history to date): selective serotonin reuptake inhibitors (fluoxetine [Prozac®, Eli Lilly, Indianapolis, IN], sertraline [Zoloft®, Pfizer, New York, NY], citalopram (Celexa®, Forest Laboratories, St. Louis, MS), venlafaxine (Effexor®, Pfizer, New York, NY), mirtazapine (Remeron®, Oss, The Netherlands)) and others, such as tricyclic antidepressants and monoamine oxidase inhibitors [51]. The behavioral and dream abnormalities in these cases of toxic RBD are virtually identical to those in chronic RBD; however, the age of onset is often young adulthood [52].

Diagnosis

The diagnosis requires formal sleep laboratory (i.e., polysomnographic) monitoring in conjunction with clinical evaluations. The diagnostic criteria for RBD include (a) increased muscle tone and/or increased muscle twitching during REM sleep, (b) abnormal behaviors documented during REM sleep and/or a history of injurious or disruptive sleep behaviors, and (c) absence of epileptic brainwave activity during REM sleep. It is suggested that arm EMG electrodes maybe more sensitive in picking up REM without atonia in women than leg EMG electrodes [53].

Treatment

RBD can be successfully controlled in about 90% of patients [36, 37]. Clonazepam is the treatment of choice, with the typical effective bedtime dose being 0.5–1.0 mg [30]. Clonazepam appears to suppress the abnormal phasic muscle twitching and behavioral release during REM sleep, rather than restore the normal muscle paralysis (REM atonia) of REM sleep [54]. More recently, the hormone melatonin (normally secreted by the pineal gland) administered at bedtime has been shown to be effective in RBD at doses ranging from 3 to 15 mg [35, 55]. The mechanism of therapeutic action for melatonin is unknown. Some patients with RBD seem to respond best to a combination of clonazepam and melatonin, especially those with (advanced) neurodegenerative disorders. It is important to note that RBD cannot be "cured" but is rather controlled—provided that the medication(s) is (are) taken faithfully every night. Therefore, people must be attentive and diligent in bringing their medication along during any trip, even a brief weekend trip, since any recurrence of RBD carries the risk of major injury to oneself or a bed partner.

Despite optimal medical management, some patients continue expressing potentially injurious nocturnal behaviors or are unable to tolerate sedating agents. A recent report suggests that these cases of treatment-resistant RBD may benefit from a customized bed alarm [56]. This therapy, studied in both men and women, utilizes a pressure-sensitive bed alarm in combination with a familiar voice, usually a family member, recorded into the alarm system. Then, when an RBD patient attempts to arise from the bed during an episode of DEB, they hear the familiar voice informing them they are having a dream and should lie back down. Finally, maximizing the safety of the sleeping environment should always be encouraged (e.g., keep sharp objects away from the bedside).

Other Parasomnias with Dream-Enacting Behaviors

RBD is not the only parasomnia associated with DEB [35]. It is therefore necessary for patients (and their bed partners) who complain of a dream-enacting disorder to have a careful interview with an experienced sleep clinician that is followed by overnight PSG monitoring at a sleep laboratory experienced with parasomnias. A history of DEB should not prompt the reflexive and premature diagnosis of RBD and its treatment. As already alluded to, various parasomnias other than RBD can manifest with attempted dream enactment, such as sleepwalking, sleep terrors, parasomnia overlap disorder, SRED, OSA, nocturnal seizures, rhythmic movement disorders, and somatic conditions.

We have reported on two cases of exclusively premenstrual sleep terrors and injurious sleepwalking [57]. The first case involved a 17-year-old female who presented with a 6-year history of exclusively premenstrual sleep terrors and sleepwalking,

associated with recurrent injury, which had begun 1 year after menarche. During the four nights preceding each menses, she would scream and run from her bed. There was no associated psychiatric history. A PSG study 3 days before the onset of menses confirmed the diagnosis of sleepwalking. Treatment with self-hypnosis practiced at bedtime was rapidly effective, with a benefit maintained for more than 2 years. The second case involved a 46-year-old female who had a 5-year history of sleep terrors and sleepwalking, with recurrent injury, which initially was not menstrually related, but commencing 8 months prior to referral she developed an exclusively premenstrual parasomnia. Treatment with hypnosis and clonazepam 0.25 mg was partially beneficial. Therefore, clinicians should inquire about any strong premenstrual association, or exacerbation, of sleepwalking or sleep terrors in their patients.

Recurrent Isolated Sleep Paralysis

Clinical Findings

Recurrent isolated sleep paralysis is the inability to move at sleep onset or upon wakening with preserved consciousness, breathing, and eye movements. There is typically a foreboding sense of terror, and hypnopompic or hypnagogic hallucinations can be associated with sleep paralysis [1]. Sleep paralysis (SP) is a dissociated state with REM atonia occurring during wakefulness and thus is considered an REM parasomnia. Duration usually is only seconds but can be extremely frightening to the patient. The episodes usually spontaneously resolve but can often be halted by external auditory or tactile stimulation. Sleep paralysis is commonly thought of as a symptom of narcolepsy, which is reviewed elsewhere in this book, but can occur in isolation especially in the setting of sleep deprivation or circadian misalignment.

The lifetime prevalence of sleep paralysis, based on a large systematic review, is estimated to be 7.6% of the general population, 28.3% of students, and 31.9% of psychiatric patients [58], with different rates among cultures and with Americans reporting a lower incidence [59]. Different patients will have various interpretations of the SP experience; however, there are striking cross-cultural parallels. Patients will often describe a paranormal or religious experience and various anecdotes including: "a dead body climbed on top of me," "the ghost pushes you down," and "the devil lay upon her and held her down" [60–62]. There are also reports of families with familial sleep paralysis [1].

Poor quality sleep, irregular sleep–wake cycles, chronic sleep deprivation, OSA, jet lag, and other sleep disorders are factors that contribute to SP [63–66]. There appears to be a relationship between mental health and SP, with anxiety disorders being the most common [63, 64, 67–70]. Sleeping in the supine position is also associated with PS, although this maybe secondary to arousals from sleep-disordered breathing [71].

Polysomnographic Findings

PSG during forced awakenings has demonstrated SP that occurs at sleep onset, REM with intrusions of alpha rhythm and/or persistence of muscle atonia into wakefulness [65].

Treatment

The vast majority of SP cases can be successfully treated by correcting any underlying sleep disorder as well as the optimizing the circadian timing and duration of sleep. Patients should also be reassured that SP does not typically represent an underlying neuropsychiatric condition. Only rarely are the episodes both resistant to conservative intervention and bothersome enough for patients to choose to take medication. In these circumstances, serotoninergic agents appear to have some benefit [72, 73].

Parasomnias Associated with OSA and Its Treatment

Parasomnias and OSA can interact in a number of adverse ways (Table 13.4) [1, 5]. It is therefore important to screen all parasomnia patients for possible OSA. Treating comorbid OSA not only addresses the symptoms of sleep-disordered breathing but often controls the nocturnal behavior without a need for medication.

Table 13.4 Interaction between parasomnias and OSA

OSA-induced arousals from REM sleep with dream-related complex or violent behaviors can resemble REM sleep behavior disorder: pseudo-RBD
OSA-induced confusional arousals from non-REM sleep can be associated with recurrent abnormal sexual behaviors (sexsomnia)
OSA-induced arousals from non-REM sleep with complex, agitated, or violent behaviors can resemble sleepwalking and/or sleep terrors
CPAP therapy of OSA may prompt a major slow-wave sleep “rebound” and the emergence of sleepwalking or sleep terrors
Untreated sleepwalking or sleep terrors, with recurrent sleep disruption, can undermine CPAP therapy of OSA, because of the repeated or prolonged removal of the CPAP mask
OSA-induced confusional arousals from non-REM or REM sleep can be associated with involuntary sleep-related eating disorder, which can eventually induce excessive weight gain, which, in turn, may aggravate the OSA
Sleep-related eating disorder can induce weight gain, which may then result in the clinical emergence of OSA
OSA may induce complex or violent epileptic seizures as a result of the brain insult resulting from hypoxia
OSA (with precipitous decrease of available oxygen) can induce nocturnal cerebral anoxic attacks punctuated by vigorous behaviors

Female-Predominant Parasomnias

Sleep-Related Eating Disorder

SRED is characterized by a disruption of the nocturnal fast with episodes of feeding after an arousal from sleep. This is in contrast to normal human physiology where nighttime is characterized by a period of fasting and energy homeostasis maintained through the sleep period by alterations in metabolism and appetite modulation [74].

Clinical Findings

The sleep-related eating episodes often occur in an involuntary, compulsive, or "out of control manner." Interestingly, patients often deny hunger but instead describe an inability to return to sleep without eating [75, 76]. Amnestic eating is associated with sedative-hypnotic medications, in particular the BRAs such as zolpidem [77, 78], and, in this regard, SRED resembles somnambulism. As such, SRED is recognized as a parasomnia (i.e., a behavioral disorder accompanying sleep) and frequently noted with other sleep disorders such as sleepwalking and OSA [1]. Recently, compelling evidence suggests that many cases of nocturnal eating may be a non-motor manifestation of RLS [24] (see section in this chapter on RLS and SRED).

SRED is a relentless, chronic condition. In the original description, over half (58%) described nocturnal eating at least once a night [79]. In another study, the majority of patients described a long history of involuntary nocturnal eating (mean duration 16 years), and nearly all reported eating on a nightly basis [76]. A substantial proportion (23%) describe eating greater than five times a night [75].

SRED is characterized by consumption of high caloric sometimes dangerous foods and by the occasional ingestion of nonfood substances. The most commonly consumed nocturnal foods are higher in carbohydrates and fats than daytime ingestions. Unconscious food preparation has resulted in injuries such as drinking excessively hot liquids, choking, burns, and lacerations. Furthermore, inedible and toxic substances have been consumed such as egg shells, coffee grounds, sunflower shells, buttered cigarettes, glue, and cleaning solutions. Finally, patients with food allergies have ingested substances that during the daytime they take extreme precautions to avoid [41, 80, 81].

Various medical consequences can occur from repeated nocturnal eating. Weight gain is commonly reported, and SRED may precipitate, or aggravate, diabetes mellitus, hyperlipidemia, hypercholesterolemia, hypertension, and OSA [41, 76, 81]. Patients with nocturnal eating are at increased risk for dental caries, as oral hygiene practices rarely follow feeding episodes [81], there is a nocturnal decline in salivary flow, and patients will often fall asleep with an oral food bolus. Finally, failure to exhibit control over nocturnal eating can be associated with secondary depressive disorders [76].

Table 13.5 Medications associated with SRED

Zolpidem-immediate release
Zolpidem-sustained release
Zopiclone
Zaleplon
Triazolam
Midazolam
Risperidone
Olanzapine

Complete or partial impaired consciousness was a defining criterion for SRED. In the original series of SRED cases, 84% (32/38) of patients claimed an impairment in awareness [79]. In another case series, 91% (21/23) of patients had incomplete consciousness and/or amnesia of the behavior [76]. Conversely, a subsequent report noted full awareness in all 26 patients after episodes of nocturnal eating in a sleep laboratory. Currently, reduced awareness and subsequent amnesia is not a required diagnostic criterion for SRED in the International Classification of Sleep Disorders, 2nd version [1].

The discrepancy in consciousness among SRED reports may be best explained by the use of sedating medications and comorbid sleepwalking disorders [75]. The first case reports of amnestic nocturnal eating were associated with sedative psychotropic medications (combination of chlorpromazine, amitriptyline, and methyprylon) as well as other parasomnias [81–83]. Moreover, the majority of patients in the original series were taking hypnotic medication or had a previous history of sleepwalking [79]. However, in a community survey of 92 subjects who admitted to nocturnal eating, only 18% reported at least partial unawareness and none of those who were fully aware had a history of sleepwalking. Conversely, if subjects did have a sleepwalking history, they were far more likely (73%) to be at least partially unaware of the behavior [84]. More definitively, all 26 patients with full consciousness during nocturnal eating episodes in a sleep laboratory were drug free and only one had a history of sleepwalking [75].

Amnestic nocturnal eating has continued to be associated with sedating psychotropic medications. SRED has been reported with triazolam, lithium, olanzapine, risperidone, zopiclone, and zaleplon (Table 13.5) [81, 85–88] as well as with zolpidem extended release formulation [89, 90]. The majority of drug cases are related to zolpidem, a BRA. A series of zolpidem-associated SRED followed in 2002. Five middle-aged patients were described; two of whom already had intermittent episodes of conscious nocturnal eating prior to starting zolpidem. All five patients were on various neuropsychiatric agents, and, interestingly, all had a history of RLS. Soon after initiating zolpidem, each patient described amnestic nocturnal eating that stopped with discontinuation [77]. Further, in a series of 1,235 patients at an outpatient psychiatry clinic, the combination of zolpidem and antidepressants posed the greatest risk for SRED.

Uncontrollable nocturnal eating is often reported after patients ingest greater than the maximum recommended dose of zolpidem (10 mg) [91–92]. Often, this occurs when, in a desperate attempt to initiate sleep, patients escalate their dose without a new prescription [93].

BRAs enhance GABA activity at central GABA A receptors, resulting in hypnotic phenomena such as sleep and amnesia [10, 94]. As hypnotic agents suppress executive function, it may be that zolpidem, by itself, does not activate SRED but instead disinhibits the behavior in a patient population at risk for nocturnal feeding. Patients with RLS demonstrate a greater tendency toward nocturnal eating [24, 25], and a substantial number of BRA-associated amnestic nocturnal eating cases have been reported in patients with RLS [24, 25, 77, 89, 95].

Epidemiological studies suggest that nocturnal eating (both dysfunctional and non-dysfunctional) and SRED (dysfunctional nocturnal eating alone) are common, particularly among patients with other sleep disorders. The most striking relationship is between RLS and SRED. In a survey of 53 RLS patients who presented to a sleep disorder center, 66% had frequent nocturnal eating and 45% had SRED [24]. These findings are similar to a survey of 100 RLS patients who demonstrated a 33% prevalence of SRED compared to normal population controls (1%) [25]. SRED is also frequently associated with other parasomnias. Three series have reported comorbid sleepwalking in 48–65% of patients with SRED [76, 79, 96]. Sleepwalking without eating may precede SRED, and then, once nocturnal eating develops, it often becomes the predominant sleepwalking behavior [79]. The majority (60–83%) of reported cases are female [75, 76, 79].

The Relationship Between SRED and RLS

A critical review of both the SRED and RLS literature suggests an intimate, possibly causal, relationship between these conditions. This conclusion is based upon similarities in epidemiology, polysomnographic phenomena, clinical course, and treatment response.

Like SRED, RLS has a higher prevalence in women [1, 97]. Further, medication-induced SRED is also more common in women [78, 92]. Similar to RLS, several features of SRED suggest an underlying dopamine dysfunction [98]. First, dopamine mediates impulsive behaviors such as motor restlessness, smoking, and binge eating [98, 99]. Second, a polysomnography (PSG) study of 35 SRED patients demonstrated that 77% had PSG confirmation of wakeful RLS and periodic limb movement during sleep [75]. Third, rhythmic masticatory muscle activity (RMMA) and bruxism, dopaminergic phenomena [75, 100] associated with RLS [101], are commonly seen in SRED [75, 81].

Intriguingly, the nocturnal feeding behavior of SRED closely resembles the motor activity of RLS. RLS is characterized by an underlying feeling (often poorly described) of discomfort in the lower extremities that compels the patient to move. Movement relieves the discomfort, and sleep is unable to be reinitiated until this urge is addressed [102]. In SRED, patients state that after an awakening from sleep they have a compulsion to eat (often without hunger) that interferes with sleep maintenance. Subsequently, once food is ingested the feeling abates and sleep may be reinitiated [1, 25, 81, 103]. In a survey of 33 patients with SRED and RLS, subjects whose nocturnal eating symptoms were under control were more likely to be

Table 13.6 The relationship between SRED and RLS

RLS has frequently been noted in cases of medication- and non-medication-induced SRED
Nocturnal eating is often described in patients with RLS, including Ekbom's original 1960 report
SRED is common in patients with RLS
The nocturnal eating in RLS is not merely "killing time" as patients with other causes of fragmented sleep, such as psychophysiological insomnia (PI), rarely break the nighttime fast
The compulsive nature of nocturnal eating in SRED is similar in character to the motor and other non-motor manifestations of RLS
Polysomnographic studies demonstrate PLMs, RMMA, and bruxism in SRED. These phenomena are frequently noted in RLS and like RLS are associated with dopaminergic dysfunction
The nocturnal eating and motor restlessness of RLS frequently arise, intensify, and subside in parallel
In several reports the underlying sleep fragmentation of drug-induced SRED was not caused by PI, but instead RLS, a common condition that is easily confused with (and treated as) PI
The rise of amnestic SRED reports parallels the rise of benzodiazepine receptor agonist use
The CNS actions of sedative-hypnotic medications (suppression of memory and judgment) unleash predisposed behaviors. Which in the case of RLS include inappropriate and amnestic ambulation with eating
The SRED is rarely noted when patients have been rigorously evaluated and cases with underlying motor restlessness excluded from hypnotic treatment
Early evidence suggests that dopaminergic treatments for RLS appear to improve, rather than exacerbate nocturnal eating and SRED

on these agents than subjects who continued to have nocturnal eating [25]. Further, a double-blind treatment trial of pramipexole for SRED demonstrated improved sleep and reduced nighttime activity [104].

Importantly, a substantial number of zolpidem-induced SRED cases occur in the setting of RLS [77, 89, 94, 105]. RLS is a condition distinct from, but often clinically mistaken for, PI. It is notable that SRED, sleepwalking, and other complex sleep behaviors are rare (1% or less) in zolpidem-treated PI patients when RLS has been carefully excluded [106–109]. In one compelling case of zolpidem-induced SRED with RLS, both motor restlessness and amnestic nocturnal eating resolved once zolpidem was stopped and RLS therapy began. The same authors subsequently reviewed ten other cases and noted that, in all eight cases of ZSRED in which RLS was considered, RLS was confirmed [94]. Thus, the mistreatment of RLS as PI may be a crucial underlying step in the pathogenesis of many amnestic SRED cases.

In conclusion, Table 13.6 summarizes the lines of evidence which suggest that SRED may be a non-motor manifestation of RLS and that mistreatment of RLS as PI is a crucial step in the pathogenesis of drug-induced SRED cases.

Treatment

The first goal in treating SRED is directed at controlling any underlying sleep disorder or discontinuing any medication (Table 13.6) that is suspected to be

causing or promoting the SRED. For example, in patients with SRED presumably induced by OSA, treatment of the OSA with nCPAP may also control abnormal nocturnal eating. Dopaminergics, opioids, and BZDs are agents typically employed in the treatment of RLS. Interestingly, SRED comorbid with sleepwalking can also be effectively treated with these agents. In one case series, eight sleepwalking patients with SRED were effectively treated with bromocriptine and/or clonazepam [26].

At this time, two classes of pharmacotherapies have been studied in SRED and appear to be potentially effective in the treatment of dysfunctional nocturnal eating. In particular, dopaminergics and the antiseizure medication topiramate have both demonstrated preliminary, yet promising, results.

Dopaminergic agents are effective in the treatment of SRED even in the absence of clinical motor restlessness. The original case series noted that either bedtime levodopa or bromocriptine was effective in eliminating nocturnal eating [26]. Recently, pramipexole, a dopamine agonist, was investigated in a small double-blind, placebo-controlled crossover trial. Pramipexole was well tolerated in all patients, including those without diagnosed RLS or PLMD. On pramipexole, subjects noted improved sleep, and reduced nighttime activity was documented with actigraphy. There was no improvement in the number or duration of awakenings [104]. The main side effects of dopamine agonist include sedation, orthostasis, and impulsive behaviors.

Early reports indicate that the antiseizure medication topiramate may be an effective therapy. An open label trial of topiramate in four patients with nocturnal eating demonstrated positive results. The agent was well tolerated, reports of nocturnal eating were diminished, and weight loss was noted in all four individuals over 8.5 months [110]. In another case series, 12 of 17 SRED patients treated with topiramate were treatment responsive [111]. Another review of 25 SRED patients on topiramate reported that 68% of SRED patients were treatment responders. Further, over 1 year, 28% of patients lost more than 10% of their body weight. Adverse events were high, however, and 41% of patients discontinued the medication [112]. The main side effects of topiramate include weight loss, paresthesias, renal calculus, cognitive dysfunction, and orthostasis.

Sleep-Related Dissociative Disorders

Clinical Findings

Sleep-related (or nocturnal) dissociative disorders (DDs) are complex nocturnal behaviors that emerge during well-established periods of wakefulness [1, 113]. Sleep-related DDs can emerge either immediately after a short transition from wakefulness to sleep or within several minutes after an awakening from any stage of sleep. This is different from sleepwalking or night terrors, which emerge immediately

during precipitous arousals from non-REM sleep. It is also very different from RBD, which emerges during REM sleep.

Nocturnal DDs comprise a sleep-related variant of DDs, which are defined in the fourth edition of the *Diagnostic and Statistical Manual of Psychiatric Disorders* (DSM-IV), published by the American Psychiatric Association, as follows: "The essential feature…is a disruption in the usually integrated functions of consciousness, memory, identity, or perception of the environment."

Of the five listed diagnostic categories contained within the DD section of DSM-IV, three categories to date have been documented with nocturnal DDs: dissociative identity disorder (formerly called multiple personality disorder), dissociative fugue, and dissociative disorder not otherwise specified.

Most patients with nocturnal DDs also have corresponding daytime DDs and also have past and/or current histories of physical and/or sexual abuse. Posttraumatic stress disorder, major mood disorders, severe anxiety disorders, multiple suicide attempts, self-mutilating behaviors, and repeated psychiatric hospitalizations are also common. Nevertheless, a nocturnal DD can at times (seemingly) occur in isolation, without a daytime component.

During the sleep period, patients with nocturnal dissociation can scream; walk or run around in a frenzied manner; and engage in self-mutilating behaviors (including genital and body slashing with a knife, burn oneself, bang head, pull hair) and other violent behaviors, including acts of violence—and attempted homicidal acts—toward the bed partner.

The episodes of nocturnal dissociation can be elaborate and last several minutes to an hour or longer and often involve behaviors that represent reenactments of previous physical or sexual abuse scenarios. This activity may occur with perceived dreaming, which is actually a dissociated wakeful memory of past abuse. Sexualized behavior (e.g., pelvic thrusting) can occur and be paired with defensive behavior (e.g., warding off or hitting an attacker) and with congruent verbalization (e.g., telling the attacker to stop or go away). Other dissociative episodes may occur as confusional states, with or without elaborate behaviors, which are not associated with perceived dreaming. A post assault headache can be reexperienced during nocturnal dissociation. One patient was reported with at least two episodes of nocturnal fugues in which she awakened from sleep and drove her car to an airport, where she purchased a ticket and flew to a distant city, where shortly after arrival she "came to" and realized she had just finished another dissociative episode [41, 113].

Nocturnal DDs are highly female-predominant. Age of onset ranges from childhood to early-mid adulthood. The course is usually chronic and severe, with episodes often occurring several times weekly or multiple times nightly. Complications include repeated injuries to oneself and/or one's bed partner while the person is in a dissociative state; this includes bruises, fractures, lacerations, and burn wounds. Skin and genital infections from self-mutilation can also occur. A past and/or current history of physical, sexual, or verbal–emotional abuse along with a severe and chronic history of psychiatric disorders constitute the major predisposing and precipitating factors [114].

Polysomnographic Findings

At least nine cases have been documented (four from our sleep center) involving episodes of nocturnal dissociation recorded during polysomnographic monitoring [113, 115]. EEG (brain-wave) wakefulness was maintained before, during, and after each episode.

Treatment

Specialized psychiatric treatments, both inpatient and outpatient, offer the best chance of helping severely afflicted patients. DDs are among the most difficult psychiatric disorders to control, and chronic, relapsing histories are common.

Parasomnias During Pregnancy

An epidemiological study has explored the relationship between pregnancy and parasomnias [116]. This investigation followed 325 mothers in Finland who completed five parasomnia-related questionnaires covering the 3 months before they became pregnant, each of the three trimesters of pregnancy, and the 3 months after delivering their babies. The questionnaires included structured questions on the presence of sleeptalking and sleepwalking (lumped together), sleep starts, hypnagogic hallucinations, sleep paralysis, nightmares, sleep bruxism, and nocturnal enuresis. A methodological strength of this study was the participation of a spouse or bed partner in helping answer the questionnaire in 93.5% of the cases. The main results were as follows: The total number of parasomnias declined during pregnancy, particularly in the primipara group compared to the multipara group, with the difference maintained until the third trimester. Sleep paralysis was the only parasomnia that increased during later pregnancy, even though it decreased during the first trimester.

At least two cases have been reported of either sleepwalking or sleep terrors becoming exacerbated during pregnancy [117, 118]. Also, pregnant women who have an active parasomnia with complex, vigorous, or violent behaviors, or who are sleeping with bed partners having an active parasomnia with aggression or violence, such as RBD or agitated sleepwalking/sleep terrors, are at risk for sleep-related injury, along with their unborn child [119]. One book on parasomnias containing more than 60 clinical stories told by patients and their families provides diverse examples of the hazards associated with pregnancy and active parasomnias, along with the dangers to nonpregnant women who have agitated sleepwalking and sleep terrors or who sleep with men who have RBD or agitated sleepwalking and sleep terrors [41]. Treatment of parasomnias during pregnancy has not been well studied. The FDA has assigned clonazepam to pregnancy category D. Therefore, it is generally recommended discontinuing clonazepam prior to pregnancy [120].

Conclusion

Parasomnias encompass an array of recurrent, peculiar, dangerous, and distressing behaviors and altered experiences that can adversely affect women in diverse ways. Fortunately, parasomnias are often scientifically explainable and are usually treatable. An experienced sleep disorders center, with the availability of sleep laboratory monitoring, is a valuable resource for the evaluation and treatment of parasomnias.

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Part IV
Pregnancy

Chapter 14
Gestational Restless Legs Syndrome

Mari Viola-Saltzman

Introduction

Restless legs syndrome (RLS) is characterized by limb akathisia that is maximal in the evening while at rest and transiently relieved by movement. The prevalence and severity of RLS increases with age. Women over the age of 65 years have a prevalence of 19%, while in nonpregnant woman under 30 years it is only 5% [1]. However, gestational RLS (gRLS) is strikingly common with approximately 25% of pregnant women affected. The association of RLS with pregnancy has been noted since the term was first coined by Ekbom in 1945. RLS is a clinical diagnosis and has four cardinal features, which have been reviewed in an earlier chapter of this book (see Chap. 8). Further details regarding diagnosis are well described by the International RLS Study Group [2, 3].

A sister condition to RLS is periodic limb movement disorder (PLMD). PLMD occurs during sleep and consists of episodes of flexion at the hips, knees, and feet lasting 0.5–5 s and recurring every 5–90 s [4]. These movements can lead to sleep fragmentation. Approximately 70% of persons with RLS have PLMD. Women with RLS experienced more PLMs before and after delivery than those without RLS [5, 6]. However, not everyone found to have PLMD on polysomnography (PSG) will have RLS [3].

Morbidity related to gRLS has not been well characterized. In a large cross-sectional questionnaire survey, Suzuki et al. found that women with gRLS report difficulty initiating sleep, difficulty maintaining sleep, early morning awakening, and excessive daytime somnolence. There was also a small but significant shortening of total sleep time [7]. The detrimental effects of RLS and/or PLMD combined

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with other sleep conditions common to pregnancy likely lead to considerable difficulties with daytime somnolence, mood, and quality of life.

Epidemiologic Considerations

The prevalence of RLS in the general population is 5–10% and increases with age [8]. Studies have reported an increased prevalence of RLS during pregnancy ranging from 11 to 34% [9–11]. The findings of these studies are presented in Table 14.1. Variations in the prevalence rate are in part explained by differences in case definition, assessment method, the month during pregnancy when symptoms were assessed, maternal age, and genetic inhomogeneities between study populations [9].

The most rigorous study on this topic was by Manconi et al. Of their sample of 642 consecutive pregnant women taken from an Italian obstetric clinic, 9.9% had preexisting RLS and 16.7% were incident cases. Nearly 15% of the group had RLS symptoms greater than 3 days per week. Small, but statistically significant factors associated with the development of gRLS were prior gRLS, maternal age, increased maternal weight prior to pregnancy, low hemoglobin, and mean corpuscular volume (MCV) [12].

There is a steady rise in RLS symptoms during pregnancy, exceeding 5% by the fifth gestational month. The peak incidence of RLS during pregnancy is in the sixth month and the condition is most severe during months 7 and 8. There is a rapid decline in RLS symptoms by 1 month postpartum. Goodman et al. noted a >50% decrease in gRLS by 1 week postdelivery. The illness may persist in a small subset of new onset RLS cases [7, 12–14]. RLS symptoms are significantly worse during pregnancy in those with preexisting RLS compared to those who did not have symptoms prior to pregnancy [15]. Among a study of Canadian families, Xiong et al. reported that women with pregnancy-related RLS symptoms had a much younger mean age at onset (20.7 vs. 32.6 years; $P<0.001$) and longer illness duration (mean 33.1 vs. 22.5 years; $P<0.001$) compared to women with pregnancy-unrelated RLS [16]. In a study of over 200 pregnant women, there was a fourfold increase in developing a chronic form of RLS in those who experienced it initially during pregnancy and a reappearance of RLS during subsequent pregnancies in almost 60% [17].

Table 14.1 A review of RLS prevalence during pregnancy. Studies initially identified by Manconi and Ferini-Strambi [9]

First author/country	Publication year	Sample	Prevalence (%)
Ekbom/Sweden	1945	486	11
Jolivet/France	1953	100	27
Ekbom/Sweden	1970	202	12
Goodman/England	1988	500	19
Hedman/Finland	2002	325	30
Suzuki/Japan	2003	16,528	20
Manconi/Italy	2004	606	26

Adapted with permission from Manconi et al. [12]

Etiology of RLS in Pregnancy

RLS is considered to be idiopathic if no secondary cause other than family history is identified. Thus far, two pedigrees of familial RLS have led to the identification of a different autosomal dominant gene in each family (Chap. 8). The presence of other gene loci related to RLS is suspected but their discovery awaits further study. Several environmental modifiers likely affect the penetrance, age of incidence, and severity of this syndrome.

A number of secondary causes of RLS have been identified including pregnancy. Women with a family history of RLS experience a worsening of symptoms during pregnancy far more often than those without (19% vs. 3%, respectively) [18]. The means by which the gravid state affects the incidence and severity of RLS is unclear.

A number of observations support the concept that RLS is due to or exacerbated by iron deficiency [19]. Some suggest that a disorder in the homeostasis of iron in the central nervous system (CNS) results in a decrease of dopamine production in the basal ganglia. In persons with RLS and normal systemic iron stores, an iron deficiency limited to the CNS has been suggested. This theory is supported by studies of the cerebrospinal fluid finding low ferritin and increased transferrin. In addition, low iron concentration of the substantia nigra and putamen has been found with magnetic resonance iron quantification studies and confirmed by autopsy. Reduction of the dopamine receptor D2 has been discovered with single-photon emission computed tomography (SPECT) and positron emission tomography (PET) imaging studies [20, 21].

Iron deficiency is common during pregnancy. An increased risk of gRLS in women with diminished iron stores (low ferritin and increased total iron binding capacity) has been reported. Further, iron supplementation is said to improve symptoms [4]. A recent study of women just prior to term observed a significant decrease in hemoglobin and MCV in women with gRLS relative to a control group [22]. Ferritin levels were not reported. No studies on CNS iron metabolism in gRLS are reported. The replenishment of iron stores during the postpartum period takes 3 months. The striking improvement in gRLS at delivery is therefore a difficult observation to reconcile given the iron deficiency hypothesis of gRLS.

It is tempting to attribute the occurrence of gRLS to the marked hormonal changes of pregnancy [22, 23]. Prolactin levels are greatly elevated during pregnancy. This hormone is noted to have anti-dopaminergic properties, providing a potential mechanism of gRLS. However, prolactin levels continue to be elevated in the postpartum period in woman who breastfeed. Estrogen and progesterone levels progressively rise during pregnancy and then dramatically fall at term. However, some women report a decrease in gRLS up to 2 weeks prior to delivery [13]. An improvement of symptoms prior to birth would argue against hormonal changes as the prime etiology. Further, there are no controlled studies suggesting a variation in RLS during the menstrual cycle when cyclic changes in estrogen and progesterone are also present. Regardless, a relationship between hormonal factors and gRLS remains intriguing.

Some authors suggest that gRLS is related to altered neuronal function due to a local pressure or a traction effect upon the proximal nerves and spinal cord. An alteration in a subcortical sensorimotor oscillator has been suggested. A number of cases of RLS have been described to occur coincident with or as a late feature of acute nerve and spinal cord injury. That a local affect on the thoracolumbar spinal cord or lumbosacral plexus might lead to an emergence of gRLS symptoms remains plausible [14].

The etiology of gRLS remains unknown. This ignorance is concerning in light of the increase in RLS later in life observed in multiparous women. Berger et al. recently revealed a startling correlation of RLS prevalence with parity. Nulliparous woman and men under the age of 64 had a similar prevalence of RLS. However, women with one child had a near doubling of RLS prevalence. There is an apparent dosage effect, with an increase in prevalence in women with three or more pregnancies. Also of interest is the finding that woman with gRLS are more likely to re-present with RLS later in life [24]. These observations support the idea that the gravid state exacerbates a latent predisposition to this syndrome and that this effect is long lasting.

Clinical Presentation of Gestational RLS

Those affected seldom present to the clinician volunteering that they have the cardinal symptoms of RLS. More often, a difficulty with initiating sleep or recurrent nocturnal awakenings are reported. There are a number of other conditions that can lead to limb discomfort and sleep fragmentation in the third trimester. These include insomnia, abdominal distension, gastroesophageal reflux, fetal movements, arthritis, low back pain, muscle cramps, nocturia, and peripheral neuropathy. The clinician will likely have to specifically ask questions probing for RLS features to make a diagnosis. Adherence to the cardinal features of RLS typically allows differentiation of mimickers of this diagnosis.

There is no confirmatory test needed to diagnose RLS. However, it is reasonable to exclude secondary causes in addition to pregnancy. Assessment for anemia, serum ferritin, and iron binding capacity should be obtained. Screening for diabetes and hypothyroidism is also a consideration. Bosco et al. suggest that even the prediabetic state (or those with an impaired glucose tolerance test) is associated with idiopathic RLS [25]. Renal insufficiency can also produce RLS, and checking a creatinine and blood urea nitrogen level can address this concern. The presence of intact sensation, strength, and deep tendon reflexes will help to exclude neuropathy.

Treatment Options for Gestational RLS

The concern of possible teratogenic effects of medications severely limits pharmacologic treatment options for RLS during pregnancy. Nearly all medications to treat RLS are US Food and Drug Administration (FDA) pregnancy category C or greater,

indicating fetal adverse effects in animal studies and a lack of human fetal outcome studies. Two exceptions are the category B agents pergolide and non-chronic use of oxycodone. However, the human data on pergolide during pregnancy are limited. There are also increasing reports of cardiac valvular fibrosis, a high incidence of side effects, and a likely negative effect on lactation with this agent. In addition, dopa-agonists suppress prolactin levels and may interfere with lactation. Narcotic use in pregnancy can lead to a neonatal withdrawal syndrome making oxycodone a difficult agent to use in this circumstance. There are no reports of a pregnancy occurring while using ropinirole (personal communication with GlaxoSmithKline, Inc., May 2005). The use of antiseizure agents (e.g., gabapentin or carbamazepine) may be associated with a number of side effects, including neonatal sedation and poor feeding. However, the often feared risk of spina bifida is not a concern when these agents are used in the third trimester of pregnancy, a time when gRLS symptoms are at their worst. If medication is considered in severe gRLS, use of the lowest possible dose and frequency is recommended.

Iron and folate supplementation have been shown to be efficacious [14, 26, 27]. Supplementation is suggested even if levels are not low. Earley recommends 325 mg of ferrous sulfate three times daily. Increased absorption occurs if iron is taken on an empty stomach and supplemented with 100 mg of vitamin C. Abdominal pain and constipation are common side effects. Folate supplementation is already present in prenatal multivitamins, with most containing 0.8 mg. An additional 1 mg twice daily could be considered. Intravenous magnesium sulfate administration was found to be effective in improving RLS symptoms in a 26-week pregnant woman with preterm labor [28].

A safer approach is to review medications and limit those known to exacerbate RLS, if possible. The leader among these agents is caffeine, which should be avoided in gRLS. Other medication categories known to exacerbate RLS are antiemetics, antihistamines, antipsychotics, neuroleptics, selective serotonin reuptake inhibitors, alcohol, and nicotine.

The complexities of medication use in the gravid state offer an excellent opportunity to maximize non-pharmacologic options. Although there are few studies to assess efficacy or degree of benefit, many authors have suggested exercise, including active stretching near bedtime, massage, and hot or cold baths. Mild-to-moderate exercise in the early evening, but not heavy exercise, has also been reported to be of benefit. Poor sleep hygiene, including sleep deprivation, can aggravate RLS. Review of sleep hygiene and education is likely to lead to at least partial symptom improvement.

It should be emphasized that many patients report a great sense of relief upon hearing that their symptom complex is not due to a psychiatric disorder of some progressive neurologic condition. Accurate diagnosis and patient counseling may confer significant relief to the patient. It is important to review with patients that those with moderate-to-severe RLS are, for all intents and purposes, chronically sleep deprived. If symptoms of excessive daytime sleepiness are present, a discussion about driving safety and safety related to operating heavy machinery should be considered. Daytime naps, particularly in the morning hours when RLS symptoms are at their minimum, may be a helpful short-term strategy.

Conclusion

gRLS is a common and often unrecognized symptom constellation that produces discomfort, sleep fragmentation, and daytime somnolence. The etiology of gRLS remains undetermined. When discovered, other conditions that can produce gRLS should be investigated, including diabetes, iron deficiency, hypothyroidism, renal insufficiency, and neuropathy. A number of pharmacologic therapies are available, though their use in pregnancy poses many obstacles. Iron and folate supplementation should be implemented. A review of concurrent medications and limiting agents that may exaggerate RLS can often produce improvement. Non-pharmacological strategies are the mainstay of treatment. Although most women will have resolution of RLS symptoms in the weeks immediately prior to or following birth, there is an increased risk of symptom recurrence with future pregnancies or later in life.

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Chapter 15
Evaluating Insomnia During Pregnancy and Postpartum

Mary K. Barger, Aaron B. Caughey, and Kathryn A. Lee

Introduction

The large majority of women (84%) complain of insomnia at least a few nights a week during pregnancy, and one of three pregnant women say they rarely or never get a good night's sleep [1]. By the third trimester of pregnancy, women have more disrupted sleep, less total sleep time, and snore more [2–4]. Reasons for poor sleep vary by trimester, but sleep problems begin early in the first trimester with complaints of urinary frequency as progesterone level rises and the glomerular filtration rate increases [5, 6]. Pregnant women who are obese are at higher risk for obstructive sleep apnea [7]. The hypoxia associated with obstructive sleep apnea may contribute to maternal hypertension, gestational diabetes, and fetal growth restriction [8]. Furthermore, those women with snoring and daytime sleepiness are at higher risk for developing preeclampsia [9]. Anemia associated with pregnancy places women at increased risk for restless legs syndrome, and insufficient amounts of sleep during the third trimester may place women at increased risk for longer labors and cesarean births [10].

Sleep continues to be disrupted for new mothers during the postpartum period, regardless of type of infant feeding, location of infant, or extent of support with

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infant care at night [11, 12]. Postpartum depression may be difficult to distinguish from chronic sleep deprivation. Chronic postpartum sleep loss places women and their families at risk for accidents if they are driving or caring for their infant while excessively sleepy. Sleep-deprived parents coping with a difficult infant may even place the infant at risk for physical abuse. This chapter reviews the expected changes in sleep that occur during pregnancy and postpartum, and highlights particular issues of concern to guide clinical assessment with the goal of minimizing risk for adverse maternal health outcomes associated with insomnia.

Insomnia During Pregnancy

In addition to feeling nauseous, early symptoms of pregnancy include fatigue and sleep disturbance. As early as the tenth week of pregnancy, 10–15% of women report disturbed sleep due to nausea, backaches, or urinary frequency [5, 13]. In the second trimester, fetal movements and heartburn may begin to disrupt sleep, but sleep and daytime fatigue and mood generally improve for most women once the nausea disappears and they adapt to the hormonal changes. In the third trimester, the majority of women (65–80%) report symptoms such as urinary frequency, backaches, shortness of breath, leg cramps, itchy skin, and vivid frightening dreams or nightmares that interfere with sleep [1, 5, 13]. The content of dreams may change over the course of pregnancy, but both women and their male partners recall more dreams and different themes as the pregnancy progresses [14]. This may be due to waking up more often, leading to a higher likelihood of dream recall. Women with a prior pregnancy loss often report disturbing dreams during their subsequent pregnancy, but these dreams have themes that do not differ from those of women experiencing their first pregnancy [15].

During the third trimester, most women report 2–3 awakenings during the night and about 7h of sleep, but some report sleeping as little as 3 or 4 h [2, 16, 17]. Older women (over 30 years of age) report less sleep than younger women, but this may be secondary to other children in the household [4]. Nulliparas are at higher risk than multiparas for sleep deprivation during pregnancy possibly because they have no prior experience with pregnancy. When multiparas become pregnant, they are more likely to spend extra time in bed at night and plan for extra sleep, regardless of whether or not they have other children who are sleeping through the night [18].

Pregnant women are unlikely to complain of difficulty falling asleep (initiation insomnia) because they have an accumulated sleep loss from their frequent awakenings during the night and falling asleep is not at all problematic. They are more likely to report maintenance insomnia due to discomfort or frequent urination. With more objective measures, such as wrist actigraphy or polysomnography, pregnant women sleep about 7h (30min less sleep than they self-report) and brief awakenings over the course of the night can reach a total of 45–60min [6, 10, 13]. Table 15.1 compares the common reasons for awakenings in the first and third trimesters.

Table 15.1 Reasons for nighttime awakenings during pregnancy (%)

	First trimester (2–14 week gestation)	Third trimester (28–42 week gestation)
Urination	51	47
Leg cramps	13	45
Joint pain	4	23
Heartburn (esophageal reflux)	33	51
Bed partner	9	12
Dreams/nightmares	3	5
Anxiety	3	1
Fetal movement	0	5

Table 15.2 Insomnia during pregnancy: clinical assessment points

Sleep loss of about 1h per night is typical during pregnancy due to frequent awakenings
Nulliparas are at higher risk of insufficient sleep when compared to multiparas
Complaint of initiation insomnia is rare during pregnancy and requires clinical evaluation for: (a) anxiety about labor and delivery, (b) marital discord, (c) depression, or (d) feeling unsafe
Women with initiation insomnia are not likely to experience excessive daytime sleepiness, but may well complain of daytime fatigue and depressed mood
Any complaint of initiation insomnia should include an evaluation for restless legs. These women are likely to experience excessive daytime sleepiness as well as daytime fatigue and depressed mood
Women with a prior history of initiation insomnia are likely to report improvement during pregnancy because of the soporific and relaxing effects of higher progesterone levels

Clinical Summary

Over the course of pregnancy, women gradually lose about 1h of sleep each night as a result of many brief awakenings. Nulliparas are more likely to continue habitual bedtime and waketime, while multiparas are more likely to extend time in bed by an hour. Complaints of maintenance insomnia are common, but complaints of initiation insomnia are rare during pregnancy and should be further evaluated for possible reasons such as anxiety and fears about labor and delivery, marital discord, or environmental factors. Any complaint about difficulty falling asleep should also include an evaluation for restless legs syndrome, as discussed in detail in the next section. Table 15.2 summarizes six key points for clinical assessment of pregnancy-related insomnia.

Leg Sensations That Disrupt Sleep

Across preconception, pregnancy, and postpartum periods, 27–36% of women report the sensation of jerking legs at sleep onset [13]. This seldom interferes with sleep maintenance. Sudden awakenings from sleep due to severe muscle cramps occur in only about 10% of women before and after pregnancy, but the prevalence increases to 45% by the third trimester [19]. Whether leg cramps are associated with periodic leg movements during sleep is not known, but women with a multiple gestation (twins or triplets) are more likely to have periodic leg movements during sleep than women with a singleton pregnancy [20]. Leg cramps in pregnancy may be decreased with increased intake of magnesium lactate or citrate in a dose of 350mg (15mmol) daily [21, 22].

Initiation insomnia during pregnancy is most likely due to restless leg syndrome (RLS) associated with iron deficiency anemia, a common condition of pregnancy. Lower serum ferritin and folate levels at preconception, even if they are within what are considered normal limits, are thought to contribute to this disorder [23, 24]. The incidence of RLS reaches its peak of 23–37% by the third trimester and typically resolves with the birth of the infant [4, 23, 25]. During the childbearing years, it does not appear to vary with age [26], but women with multiple gestations are more likely to experience both RLS and periodic leg movements during sleep [20]. The wide range in incidence may be associated either with varying criteria for threshold frequency of self-reports during a typical week or month or with parity since women are more likely to have RLS with increasing numbers of pregnancies [26, 27].

Many women are unlikely to talk to their health care provider about their restless legs, either because they do not want medication, they know it will disappear after delivery, or they feel clinicians will think they are crazy or neurotic. Some women, on the other hand, describe their symptoms as “pure torture” or “worse than delivering a 15-lb baby” and describe “worms crawling inside their veins” or “ants crawling up and down inside their legs.” Some are so tortured that they vow never to become pregnant again. RLS typically begins in the evening before bedtime. Momentary relief comes with standing and walking, but as soon as a woman reclines the sensation can reappear.

In addition to experiencing restless legs at bedtime, sleep onset is significantly delayed and mood is more depressed [23]. Women who experience RLS in one pregnancy are more likely to experience it with subsequent pregnancies, but it can be totally absent between pregnancies [4]. For severe cases of RLS, other potential contributing disorders such as thyroid disease, varicosities, and use of medications that aggravate the condition such as SSRIs, antihistamines, and antiemetics should be considered [28]. RLS is often treated with opioids or dopamine agonists that many women and clinicians are loathe to use during pregnancy or lactation (Table 15.3). More acceptable remedies for pregnant women include walking, leg massage, or warm baths. In addition, reducing caffeine intake and increasing intake of foods with iron and folate should be encouraged even prior to pregnancy. If these should fail, pramipexole is a dopamine agonist with an FDA Category B, although there are limited human data on its use in pregnancy [29].

Table 15.3 Medication risk in pregnancy and lactation

	FDA pregnancy risk categories					Hale lactation risk categories				
Medications	A	B	C	D	X	1	2	3	4	5
Antihistamines										
Diphenhydramine		x					x			
Doxylamine	x							x		
Hydroxyzine			x			x				
Antidepressants										
Amitriptyline			x				x			
Fluoxetine			x				x			
Imipramine				x			x			
Paroxetine			x				x			
Sertraline			x				x			
Trazodone			x				x			
Venlafaxine			x					x		
Dopaminergics										
Carbamazepine				x			x			
Carbidopa/Levodopa			x					x		
Pramipexole		x							x	
Hypnotics										
Alcohol (ethanol)				x				x		
Alprazolam				x				x		
Clonazepam				x				x		
Diazepam				x				x		
Eszopiclone				x				x		
Flurazepam					x			x		
Lorazepam				x				x		
Midazolam				x			x			
Secobarbital				x				x		
Temazepam					x			x		
Triazolam					x			x		
Zaleplon			x				x			
Zolpidem			x					x		
Opioids										
Codeine			x					x		
Meperidine		x					x			
Morphine			x					x		
Oxymorphone		x						x		
Stimulants										
Caffeine		x					x			
Dextroamphetamine			x					x		
Methamphetamine			x							x
Modafinil			x						x	

(continued)

Table 15.3 (continued)

FDA pregnancy categories
Category A: fetal harm is remote
Category B: no risk in animal studies, but no human studies; or risk in animals documented but no risk to fetus in controlled human studies
Category C: animal studies document adverse fetal effects, but no studies in women; or studies in women and animals not available
Category D: positive evidence of human fetal risk, but benefits in pregnancy may be acceptable despite the risk
Category X: studies demonstrate high risk to fetus; drug is contraindicated regardless of risk to mother

Hale lactation categories
L1 Safest: large number of breastfeeding mothers have used without observable infant harm
L2 Safer: limited number of breastfeeding women have used without increased adverse effects and/or evidence of infant risk is likely to be remote
L3 Moderately safe: no controlled studies in breastfeeding; risk of untoward effects possible or controlled studies show only minimal nonthreatening adverse effects
L4 Possibly hazardous: positive evidence of risk to infant or milk production but benefits to mother may be acceptable
L5 Contraindicated: studies in breastfeeding mothers document significant risk to infant
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Clinical Summary

Women who are planning a pregnancy should be advised to begin taking prenatal vitamins with iron and folate for more than concerns about preventing neural tube defects. Dietary foods enriched with folate, such as breads and cereals, should be encouraged. To promote absorption of iron and folate, women should also be advised to take adequate amounts of vitamin C and eliminate caffeine and alcohol. Pregnant women at risk for anemia and women in the low range of normal serum levels for ferritin and folate should be asked about unusual leg sensations they might be experiencing in the evening while trying to fall asleep. If they are experiencing excessive daytime sleepiness as a result of their RLS and initiation insomnia, referral to an accredited sleep disorders center should be considered.

Snoring and Obesity Risk Factors for Maintenance Insomnia

In addition to observable weight gain that takes place over the course of pregnancy, women also increase blood volume by 2–3L and overall body fluid volume by about 7L. Higher fluid volume and increased estrogen production from the placenta are likely to result in complaints of nasal congestion and swelling in the extremities [30]. Congestion, upper body weight gain, and snoring are common complaints during pregnancy. However, these factors can place some woman at higher risk for obstructive sleep apnea while at the same time place her fetus at risk for repeated hypoxia, placental insufficiency, and fetal growth restriction.

During pregnancy, shortness of breath (dyspnea) appears to result from increased respiratory drive which, in turn, leads to increased minute ventilation. Dyspnea is increasingly common during the last trimester, particularly when the gravid uterus reduces functional residual capacity. Women often find it more comfortable and easier to breathe when sleeping with the head elevated, which also helps with complaints of heartburn and sleep disturbance due to esophageal reflux. Oxygen saturation remains stable during sleep in non-obese women [7]. If a pregnant woman lies flat on her back, however, the gravid uterus can compress her vena cava (supine hypotensive syndrome), decreasing cardiac output and causing early airway closing during tidal breathing resulting in oxygen desaturation and risk of fetal hypoxemia due to uteroplacental insufficiency [31].

In addition to increased minute ventilation and dyspnea, 10–35% of women report a new onset of snoring during pregnancy, compared to less than 5% who snored before conception [4, 8, 32]. Snoring is at one end of the continuum of sleep-disordered breathing, while obstructive apneic events are at the more severe end of the continuum. Sleep-disordered breathing in pregnancy may be associated with a higher rate of fetal and newborn complications such as fetal growth restriction and low birth weight [8, 32, 33]. Recent studies also show that sleep-disordered breathing in pregnancy doubles or triples the risk of maternal gestational diabetes even after controlling for body mass index [8]. Because of the fragmented sleep associated with obstructive sleep apnea, daytime sleepiness is often apparent, and women should be cautioned against performing hazardous jobs or driving and advised to schedule nap time during the day.

Preeclampsia

Gestational hypertension, preeclampsia, hemolysis-elevated liver enzymes-low platelet count (HELLP) syndrome, and eclampsia comprise the spectrum of a disorder associated with endothelial cell dysfunction which occurs in about 3–10% of pregnancies, with the higher rate found in a prospective trial with clinical data available for diagnosis and the population limited to first-time mothers [34–36]. Besides being characterized by high blood pressure, this group of disorders is associated with narrowed upper airways and limited airflow during sleep, most likely due to mucosal and pharyngeal edema [37–39]. Preeclampsia is also associated with increased incidence of periodic leg movements during sleep. Women with preeclampsia may have significantly larger neck circumference compared to healthy pregnant women, and, depending on body mass index, between 75 and 85% of those with preeclampsia report snoring [9, 40]. Because preeclampsia is associated with restricted airflow, frequent arousals from sleep are common and women with this type of maintenance insomnia may complain more of excessive daytime sleepiness than arousals from snoring and apnea. They are likely to complain of sudden awakenings with sensations of choking, coughing, or suffocating.

Women who are overweight or obese are more likely to develop preeclampsia [34, 41]. Even if such women do not develop preeclampsia, they still experience

more frequent snoring, excessive daytime sleepiness, insomnia, shorter sleep duration, and poorer quality of sleep [2].

Clinical Summary

Snoring is a common phenomenon during pregnancy, but obstructive sleep apnea is rare. Women who complain of excessive daytime sleepiness in association with bed partner reports of snoring or apneic events need further evaluation to rule out obstructive sleep apnea. Women with excessive weight gain, or women with pre-eclampsia, are at higher risk for sleep-disordered breathing, and both mother and fetus can benefit from timely intervention, typically with nasal continuous positive airway pressure (CPAP), until the birth.

Nasal CPAP may improve sleep, reduce daytime sleepiness, and lower blood pressure in pregnant women with sleep-disordered breathing. For those who may be unresponsive to current treatment for preeclampsia, nasal CPAP may be a worthwhile intervention to explore in a further attempt to prolong gestation until the fetus is viable [40, 42]. Although CPAP may not change the time spent in deep sleep or REM sleep stages, it may reduce nocturnal hypoxic episodes, improve placental perfusion, and extend gestation closer to full term. CPAP does not appear to have any adverse effects on the mother or fetus [43, 44].

Labor and Delivery

It is well documented that sleep quality diminishes as pregnancy moves closer to term (40–42 weeks gestation). This may be partially explained by increasing levels of oxytocin at term which promote wakefulness [45]. Successful labor requires careful orchestration of proteins and hormones produced by the fetus, the placenta, and the mother, especially from the hypothalamic–pituitary axis. Disrupted sleep and/or sleep deprivation has an effect on important neurotransmitters known to affect labor such as dopamine, norepinephrine, and serotonin [46]. It also can affect a woman's ability to concentrate, problem-solve in unexpected situations, and interferes with interpersonal communication, all of which are needed by women to cope with pain in labor [47]. Lack of sleep also increases sensitivity to pain [47, 48]. In one study, women who slept less than 6h at night during the few weeks prior to delivery had a labor that was, on average, about 10h longer, and were 3.5 times more likely to have a cesarean delivery than women who slept more than 7h [10].

In the early stages of labor, when contractions do not seem to be regular and progressing, morphine sulfate has been given to provide therapeutic rest, with 85% of women awakening in active labor [49]. The amount of sleep prior to beginning labor and the sleep loss that occurs as a result of being in active labor during the night has more of an effect on early postpartum "baby blues" and emotional distress than the sleep loss that occurs during early postpartum recovery [50].

Table 15.4 Implications of sleep loss for labor and delivery: clinical assessment points

Sleep loss of about 1 h during the night is typical during the third trimester
Nulliparas who average less than 6 h per night are likely to have a length of labor that is 10 h greater than nulliparas who sleep more than 7 h per night
Nulliparas who average less than 6 h of sleep per night are more likely to have a cesarean birth than nulliparas who sleep more than 7 h per night
Labor contractions often improve after women awaken from pharmacotherapeutic-induced sleep

Fragmented sleep appears to also decrease nightly prolactin concentrations [45]. New evidence shows that prolactin promotes oxytocin and vasopressin release during labor. During a normal vaginal delivery, prolactin levels spike for 4–6h and then return to a normal circadian pattern [51]. Women who have emergency cesareans do not have the prolactin increase that normally occurs about 30min after the onset of breastfeeding during the first few days postpartum [51]. How these labor and delivery factors affect mother and infant sleep postpartum remains unknown. Table 15.4 summarizes four key points for clinical assessment of sleep for labor and delivery implications.

Postpartum Insomnia

Sleep disruption continues from the day of delivery through the first 3 months postpartum, and is particularly problematic for primiparas (74%) and for women after cesarean births (73%) compared to vaginal births (57%) [52]. After delivery and until the infant is sleeping through the night, a new mother's sleep is disrupted by infant care needs.

When new mothers have their infants in the same room on their first postpartum night after vaginal delivery, they have lower sleep efficiency (74 ± 16.6%) and shorter REM latency (70.8 ± 23.2min), but no differences in amount of deep sleep (stage 3 and 4) or REM sleep compared to healthy controls [53].

Sleep efficiency averages about 90% during healthy pregnancy. During the first few months of postpartum recovery, however, sleep efficiency falls to about 77% in novice mothers and about 84% in experienced mothers [18]. New first-time mothers in Japan often share a futon with their infant, and their sleep efficiency is more comparable to Caucasian multiparas [54]. Regardless of parity, deep sleep (stage 3–4) is increased and light sleep (stages 1 and 2) is decreased during the first three postpartum months [18, 55, 56]. Table 15.5 summarizes eight key points for clinical assessment of sleep associated with postpartum insomnia.

Lactation and Breastfeeding

Mothers' perceptions of their sleep quality do not appear to be associated with the type of infant feeding [57, 58]. Lactating women do have higher basal levels of prolactin and bursts of prolactin secretion at the onset of each breastfeeding event,

Table 15.5 Insomnia during postpartum: clinical assessment points

Pregnant women should discuss plans for infant sleeping arrangements
Women who experience more changes in their sleep from pregnancy to postpartum may be at higher risk for postpartum depression
Postpartum women should be assessed for sleep deprivation prior to assuming major depression
New parents should be cautioned that chronic sleep loss places them at increased risk for accidents and errors of omission, such as forgetting to get their infant out of a car left in the hot sun, or not following directions for mixing infant formula or infant medication dosages
Infant sleeping arrangements should be evaluated
Breastfeeding should be encouraged to promote mother's deep sleep stages
Exercise and light exposure should be emphasized for postpartum mothers
Mothers should be queried about their infant's temperament and any difficult infant temperament should be evaluated in relation to mother's and father's coping strategies and risk for infant abuse

regardless of when sleep occurs. Within 24h of weaning, prolactin levels return to low basal levels and to the circadian sleep-associated patterns found in healthy women [59, 60]. There is little difference in REM sleep, but lactating women have more deep sleep (stage 3–4), less light sleep (stages 1 and 2), and fewer arousals compared to non-lactating postpartum women [61]. There may be a gradual decrease in REM sleep for formula-feeding compared to breastfeeding mothers [62]. Using wrist actigraphy measure, mothers who breastfeed during the early postpartum months had about 45min more sleep per night than mothers with infants receiving formula [63].

Co-sleeping and Bed-Sharing During the Postpartum Period

Adult parents in western cultures such as the United States are likely to value independence and, beginning at birth, find it more desirable to have their infant sleep alone in a separate room and bed [64]. A variety of co-sleeping (sleeping together) practices exist throughout the world and range from mother and baby sharing the same bed (bed-sharing) to mother and baby sleeping in the same room (room-sharing). Advantages of bed-sharing include facilitating breastfeeding and maternal-infant bonding, despite concerns about risk of smothering the infant from heavy blankets or obese parents, or concerns about sudden infant death syndrome (SIDS) from a softer adult mattress surface [65]. Postpartum mothers may have more arousals when bed-sharing with their infant, but sleep efficiency does not appear to be affected when sleeping alone nights are compared to bed-sharing nights [66].

The prevalence of bed-sharing in the United States has been steadily increasing from 6 to 13% in the 1990s [67] to a current rate of 22% at 1 month postpartum, with only 13% continuing to bed-share by 6 months postpartum [68]. Recent data from a population-based sample in Florida indicated a rate of 46% bed-sharing for infants 2–6 months of age [69]. There are some reports that bed-sharing promotes

breastfeeding [68, 70], but the practice does not appear to be associated with breastfeeding, cultural values, or crowded households [71].

In a 2007 National Sleep Foundation poll of 1,000 women, 9% indicated that they sleep with a child in the bed [1]. Bed-sharing may be more common for young single mothers with lower incomes and less education, but in our own sample of relatively affluent new parents, about 40% reported bed-sharing during the first month after delivery regardless of ethnicity or education, and the practice of bed-sharing decreased to about 20% by 3 months postpartum [63, 72]. Only 7% of these couples indicated that they planned to bed-share after the baby was born, and, therefore, it is unlikely that many new parents are counseled about health risks of bed-sharing.

New mothers are less likely to return to work in the early weeks of postpartum recovery and, therefore, have the opportunity to nap during the daytime and lessen the effects of sleep loss at night due to infant care and fragmented sleep. New fathers, on the other hand, often return to work, but still experience substantial sleep loss during the night and have no opportunity for a scheduled nap during the day [3]. Both new mothers and new fathers should be assessed for excessive daytime sleepiness regardless of who is doing the primary infant care during the night.

Postpartum Depression

There is a 10–20% incidence of a major depressive episode at some point in a woman's life. It is about 10–20% during the childbearing years as well, but pharmacological treatment during pregnancy or lactation is of concern due to potential growth and development risks to the infant. In an Italian sample of primiparous women, over 30% were still complaining of sleep loss and fatigue at 15 months postpartum, and more than 50% were reporting depressive symptoms [73]. In a longitudinal study of women on the east coast of the United States, researchers excluded women who were depressed in the third trimester, and followed 37 women for 15 months postpartum [16]. Ten (26%) had significant depressive symptoms at 3–4 weeks postpartum, but only two women continued having depressive symptoms at 12–15 months postpartum. With self-report sleep diaries, their total sleep time changed very little over the course of the study, but the 10 depressed mothers had more total sleep time, with later rise times and longer naps during their third trimester; they also had more disrupted nighttime sleep, later rise times, and naps during the day when assessed at 3–4 weeks postpartum [16]. The new mothers at higher risk for postpartum depression may be the ones who experience more of a change in their sleep patterns between pregnancy and postpartum [3]. Regardless of the documented associations between sleep and mood, it may be difficult for new mothers, family members, or clinicians to distinguish signs and symptoms of chronic postpartum sleep deprivation from signs and symptoms of depression [74].

An earlier onset of the first REM period after falling asleep and more REM sleep during the night is often seen in adults with major depressive episodes. Compared to healthy new mothers, postpartum women with depressive symptoms have significantly shorter REM latency as well, but they also average 1h less total sleep and about 12% lower sleep efficiency [3]. With the substantial sleep loss associated with caring for a new infant, most mothers easily fall asleep once they turn out the light. Depressive symptoms were more strongly associated with fragmented sleep than with the infant's temperament when dyads were assessed at 3 months postpartum [75]. Particularly important hallmarks of postpartum depression include a new mother's complaint of not being able to fall asleep easily at bedtime (initiation insomnia) as well as a low serum prolactin level [76].

Non-pharmacological treatment options for women with postpartum depression can include late partial sleep deprivation, in which a new mother would sleep only until about 2:00 a.m. to limit her amount of REM sleep [77] or bright light therapy in the morning which may take up to 4 weeks to be effective [78]. Pharmacological treatment options for women with insomnia or postpartum depression are presented in Table 15.3 along with their associated risk to the fetus or newborn [79].

Difficult Infant Temperament and Maternal Insomnia

A new mother often measures success in her motherhood role by growth and developmental stages reached by her infant, particularly the point at which the infant begins to sleep through the night. Many first-time mothers have the misconception that "sleeping through the night" means continuous sleep from 8:00 pm to 8:00 am, whereas most clinicians interpret sleeping through the night as the point at which an infant no longer awakens in the middle of the night for a feeding that is just 2–4 h after the previous feeding. This point in time may fluctuate from night to night for many weeks before it becomes the infant's routine sleep pattern. That infant, however, may still be feeding late at night and again in the early morning hours, only allowing parents 5–6 h of uninterrupted sleep when they may require 7–8h to feel rested. At 1 year of age, 20–30% of infants continue to have disrupted sleep during the night [80]. Parents who report fussy, irritable "colicky" infant temperament also describe the infant as a poor sleeper.

Even when assessed in the newborn nursery after delivery, there is wide variation in infant sleep, depending on gestational age and birth weight, type of delivery, and type of feeding. First-born infants sleep less than infants born to multiparous mothers, and infants from cesarean births have more active sleep (REM) than infants delivered vaginally [80]. A newborn's sleep pattern does not appear to vary by gender, maternal age, or socioeconomic status.

Despite the wide variation in recorded sleep, newborns in the nursery still sleep more during the 12-h night (7:00 pm to 6:59 am) than during the 12-h day (7:00 am to 6:59 pm) [80], but there are many awakenings during the night that may or may

not require parental intervention. If the new mother or father is sensitive to sleep loss and not coping well, there is high risk for physical abuse of an infant who is difficult to settle at bedtime or during the night. Over time, this difficult infant temperament, in combination with chronic sleep loss and poor coping strategies, requires intervention and support from family and friends before the infant's safety and well-being are jeopardized.

Clinical Summary

Some women may deliberately plan to bed-share with their infant during the early postpartum period to foster closeness and facilitate breastfeeding. Still others may not plan to do so, but resort to bed-sharing as a trial-and-error strategy to obtain more sleep. Although a pregnant woman may not be planning to bed-share with her infant or may be reluctant to discuss this with their health care provider, all women should be advised of the pros and cons regarding bed-sharing with an infant, and fathers should participate in the discussion as well. New parents have a great many adjustments to make in their daytime activities and their nightly sleep patterns once the baby is born. Their depressive symptoms may be more a function of chronic sleep loss rather than maladjustment to parenthood. Increased sleep, which can be improved with such daytime activities as light exposure and exercise, may be more therapeutic in treating depressed mood than counseling, psychotherapy, or antidepressant medication. Careful clinical evaluation is needed, however, if new mothers or fathers are not coping well with their disrupted sleep patterns, since there may be increased risk of physical abuse of an infant. Table 15.5 summarizes eight key points for the clinical assessment of sleep associated with postpartum insomnia.

Summary

Sleep patterns may be disturbed by the tenth week of pregnancy or even earlier than recorded in most research studies, when complaints of urinary frequency and fatigue are first noticed. Compared to pre-pregnancy and pregnancy or compared to healthy controls, sleep efficiency is lowest during the first postpartum month, particularly for novice mothers compared to experienced mothers, but significant sleep loss is evident for all new parents. The major concern for postpartum women is sleep loss and resulting physical fatigue, negative mood, and cognitive impairment (Table 15.6). How this sleep loss affects women's health, relationships with family, or the health of new fathers has not been a focus of research or clinical practice. Interventions to improve sleep may be minimally invasive and inexpensive, and such treatments should be evaluated from a clinical and cost-effectiveness standpoint.

Table 15.6 Typical sleep changes during pregnancy and postpartum

	First trimester	Second trimester	Third trimester	Postpartum
Sleep changes	Fragmented sleep due to frequent urination	Sleep less fragmented	Sleep fragmented by	Sleep fragmented by infant feeding
			Frequent urination	
			Leg cramps	More fragmented sleep for first-time mothers than experienced mothers
		First onset of snoring	Heartburn	
			Nasal congestion	
			Irregular contractions	
			Shortness of breath	Longer wake episodes for breastfeeding mothers, but they may have more deep sleep than non-lactating mothers
			Breast tenderness	
			Carpal tunnel/joint pain	More opportunity to nap if not employed outside the home
	Less deep sleep (stages 3–4 SWS) compared to preconception	Less deep sleep	Less deep sleep	More deep sleep
Daytime symptoms	Fatigue/sleepiness	More energy	Increased fatigue/sleepiness	Fatigue/sleepiness
	Morning or evening nausea	Nasal congestion		
Clinical evaluation	Check serum iron and folate levels for risk of restless legs syndrome	Assess for sleep-disordered breathing	Assess for	Assess for
			Restless legs	Excessive daytime sleepiness
			Sleep-disordered breathing	Cognitive dysfunction
				Postpartum depression
			Ask about plans for infant sleeping arrangements	Ask about infant's sleep and parenting activities during the night

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Chapter 16
Sleep-Disordered Breathing and Pregnancy

Sunita Kumar and Helena Schotland

Introduction

Pregnancy is a period of profound physiologic change. During gestation, alterations in sleep and breathing are common. In some cases, these normal physiologic alterations may result in sleep-disordered breathing (SDB). The purpose of this chapter is to describe the normal physiologic changes seen in sleep and breathing during pregnancy, and discuss the pathologic implications of these alterations as they relate to snoring and obstructive sleep apnea (OSA).

Sleep Architecture and Quality in Normal Pregnancy

Estrogen and progesterone levels rise progressively during pregnancy with implications for sleep and wakefulness. Estrogen is known to reduce REM sleep [1–3], while progesterone has a sedating effect [4] and can increase NREM sleep [5]. The alterations in the sleep patterns of a pregnant woman are most notable in the first and third trimesters of pregnancy. During the first trimester, there is an increase in total sleep time and daytime somnolence, while the third trimester is characterized by a decrease in total sleep time and an increase in nocturnal awakenings [6–8].

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The etiology of these awakenings is multifactorial and may be due to fetal movements, urinary frequency, leg cramps, back pain, heartburn, or generalized discomfort [6–9].

Respiratory Changes During Pregnancy

During pregnancy, there are a variety of physical and hormonal factors that influence breathing. Some of these factors are detrimental and may predispose pregnant women to SDB, while other factors may be protective. The most obvious mechanical factor appreciated during pregnancy is the enlarging uterus, which alters intraabdominal pressure and leads to deformation of the diaphragm and intrathoracic structures. Spirometric studies reveal a progressive decrease in functional residual capacity (FRC) and expiratory reserve volume as term approaches [10–13]. These alterations can cause closing volume to be greater than FRC, resulting in shunting and hypoxemia [14]. The reduced FRC is also associated with reduced lung oxygen stores, which may have obvious implications in the setting of a nocturnal respiratory disturbance [15], such as OSA. A number of studies have demonstrated that oxygen saturation is reduced in normal late pregnancy [16–18]. This effect is magnified when a pregnant woman is in the supine position [16, 19]. Fortunately, pregnant women have a preference for sleeping in the lateral position [17, 20], which may improve oxygenation and protect them from SDB. Pregnancy is also a physiologic state in which body weight increases dramatically over a short time period. In nonpregnant individuals, weight gain is directly correlated with severity of SDB over time [21]. It is not known whether gestational weight gain is an independent risk factor for SDB during pregnancy, but some authors suggest that it may exacerbate SDB, especially among obese women [22].

In addition to physical alterations of pregnancy affecting respiratory mechanics, hormonal changes may also lead to detrimental mechanical alterations in the respiratory system. For example, the rising estrogen concentration during pregnancy leads to changes in airway mucosa such as hyperemia and mucosal edema [23]. This effect is most prominent during the third trimester when significant nasal obstruction occurs and snoring is observed. Forty-two percent of pregnant women at 36 weeks gestation complain of rhinitis and nasal congestion [24]. In addition to the changes seen in the nasopharynx, the oropharynx is also altered during pregnancy. A study of 242 pregnant women revealed an increase in Mallampati scores between 12 and 38 weeks' gestation [25]. Pregnant women also demonstrated decreased upper airway size measured by an acoustic reflection technique [26].

The hormonal alterations of pregnancy may be associated with mechanisms that protect the pregnant woman from SDB. The rising progesterone concentration of pregnancy is associated with hyperventilation due to enhanced respiratory center sensitivity to carbon dioxide [27, 28]. This augmented respiratory drive also increases the responsiveness of upper airway dilator muscles to chemical stimuli [29, 30], thus theoretically protecting against airway obstruction.

The myriad alterations of pregnancy are associated with profound changes in the respiratory system: some changes protect pregnant women from developing SDB while others predispose pregnant subjects to SDB. The remainder of this chapter will be devoted to the discussion of abnormal breathing during sleep, from snoring to OSA.

Snoring and Pregnancy

In nonpregnant women, the prevalence of habitual snoring is only 4% [31, 32]. This is in stark contrast to the prevalence of snoring in pregnant women, which ranges from 11 to 23% for self-reported habitual snoring [31–33] to 41 to 46% for any self-reported snoring during pregnancy [32, 34]. Since snoring is a marker for OSA, this increase in snoring during pregnancy has prompted further investigation.

Two questionnaire studies have demonstrated conflicting results regarding fetal outcomes in pregnant snorers. Loube et al. [31] found no significant difference in mean birth weight, APGAR scores, or complications in newborns of snorers compared with the newborns of non-snorers. In contrast, Franklin et al. [33] demonstrated that habitual snorers were more likely to have infants with lower APGAR scores and growth retardation than non-habitual snorers. In this study, witnessed apneas were observed in 11% of the habitual snorers compared with only 2% of the non-habitual snoring group, but confirmatory polysomnograms (PSGs) were not performed. Thus, it is not possible to definitively link adverse fetal outcomes to OSA on the basis of this study. A recent study demonstrated increased umbilical cord blood levels of nucleated red blood cells, erythropoietin, and interleukin-6 in a population of pregnant habitual snorers; however, there was no significant difference in birth weights, APGAR scores, or umbilical cord blood pH in the newborn infants of habitual snorers vs. non-snorers [35].

Habitual snoring during pregnancy may have adverse effects on the health of the mother [32, 33] as well as the fetus. In addition to their findings of adverse fetal outcomes in habitual snorers, Franklin et al. [33] also reported a link between habitual snoring and pregnancy-induced hypertension. There was also an association between habitual snoring and preeclampsia in this study, although it did not reach statistical significance.

OSA and Pregnancy

Although OSA is a common disorder (affecting an estimated 2% of women) [36] and pregnancy is a common occurrence, the prevalence of OSA in pregnancy has not been studied extensively. Several investigators have performed polysomnographic studies in small groups of pregnant women [37, 38]. The medical literature

regarding OSA in pregnancy has largely been limited to single case reports [39–47] and several small series of patients [48–50]. See Table 16.1. The largest reported study was conducted in 267 pregnant women [32]. In this study, all 267 women underwent nocturnal polygraphic monitoring including an Edentrace® (Puritan Bennett, Boulder, CO) system. None of these subjects had an AHI greater than 5 events per hour at 6-months gestation. During the second portion of this study, 26 women were selected for polysomnography. Thirteen of these women were in the abnormal breathing group, which consisted of chronic, loud snorers or women with significant (≥5%) oxygen desaturation on initial ambulatory recording. At full polysomnography, none of these 26 subjects had an AHI greater than 5 events per hour; however, the women in the abnormal breathing group had signs of increased upper airway resistance, manifested by either crescendo respiratory effort or abnormal sustained effort [32].

Habitual and loud snoring has been used as surrogate measures in several studies for the presence of SDB among pregnant women to assess the relation of SDB with maternal and fetal outcomes. Other studies have relied on screening questionnaires without polysomnographic confirmation. However, a recent study noted that the Berlin's questionnaire had poor sensitivity and specificity, 35 and 63.8%, respectively, in detecting OSA among pregnant women [51]. Likewise, in another study where PSG was done in pregnant women who snored, OSA was diagnosed in 4 out of 35 snorers or 11.4% [52].

OSA and Hypertensive Disorders of Pregnancy

The other notable finding in the 33 pregnancies described in Table 16.1 is the increase in pregnancy-induced hypertension. Pregnancy-induced hypertension is associated with increased maternal and fetal morbidity and mortality [53]. It is characterized by hypertension after 20 weeks gestation with or without proteinuria (≥300 mg in 24 h) that regresses following delivery [53]. Pregnancy-induced hypertension may be classified into three types: gestational hypertension (5–9% of pregnancies), preeclampsia (5–7% of pregnancies in nulliparous women), and eclampsia (<1% of pregnancies) [54–57]. Several large studies in the general population have demonstrated that SDB is an independent predictor for the development of hypertension [58, 59]. The relationship between OSA and pregnancy-induced hypertension is not as well described (Table 16.2). Using an acoustic reflection method, Izci et al. [60] demonstrated that the upper airways of 37 women with preeclampsia were narrower than that of nonpregnant controls. Not surprisingly, inspiratory flow limitation during overnight polygraphic monitoring was also seen in 15 subjects with preeclampsia compared with normal pregnant and nonpregnant women [61]. However, none of these subjects with preeclampsia had OSA. In a study from Sweden, approximately 500 women filled out a questionnaire about snoring, witnessed apnea, and daytime fatigue on the day of delivery. The study showed that 14% of snoring women developed hypertension compared with 6% of non-snorers

Table 16.1 Medical literature regarding OSA in pregnancy

Authors	Year	*N*	Polysomnography or other study/observation	Associated conditions	Treatment	Fetal outcomes
Joel-Cohen and Schoenfeld [48]	1978	3	Clinical observations Patient 1: 20–60 s apneas Patient 2: 70–80 s apneas Patient 3: 40 s apneas	None in all 3 subjects	None in all 3 subjects	Patient 1: 2,810 g infant APGAR 5/7 Patient 2: 2,740 g infant APGAR 5/8 Patient 3: 2,680 g infant APGAR 6/8
Conti et al. [39]	1988	1	History of central and obstructive apneas on prior PSG	Gestational hypertension	None	2,730 g infant "Good" APGAR
Hastie et al. [40]	1989	1	Apnea/hypopnea index 19.7 per hour Oxygen saturation nadir 84%	Gestational diabetes mellitus	Tracheostomy at 22 weeks gestation	2,840 g infant APGAR 10/10
Kowall et al. [41]	1989	1	Apnea/hypopnea index 78.6 per hour Oxygen saturation nadir 74%	Polyhydramnios Preeclampsia	CPAP at 36 weeks gestation	Infant large for gestational age
Schoenfeld et al. [49]	1989	8	Clinical observations Snoring and nocturnal arousals in all 8 subjects	None	None in all 8 subjects	Mean newborn weight 1,780 g
Sherer et al. [42]	1991	1	PSG after delivery Apnea index 144 per hour Oxygen saturation nadir 63%	Diabetes mellitus, Preeclampsia Balanced chromosomal translocation	None during pregnancy	2,780 g infant APGAR 8/9
Charbonneau et al. [43]	1991	1	Apnea hypopnea index 159 per hour Oxygen saturation nadir 40%	Gestational diabetes mellitus	CPAP and oxygen at 36 weeks	2,680 g infant (<10th percentile), polycythemia

(continued)

Table 16.1 (continued)

Authors	Year	*N*	Polysomnography or other study/observation	Associated conditions	Treatment	Fetal outcomes
Lefcourt et al. [44]	1996	1	PSG after delivery 817 apneas and hypopneas total Oxygen saturation nadir <50%	Preeclampsia	None during pregnancy	2,300 g infant APGAR 9/9
Lewis et al. [45]	1998	1	Nocturnal oximetry with desaturation nadir of 70%	Pulmonary hypertension	CPAP and oxygen at 29 weeks gestation	3,055 g infant
Brain et al. [46]	2001	1 subject with 2 pregnancies	Apnea hypopnea index 30 per hour Oxygen saturation nadir 20%	Pregnancy 1: gestational hypertension Pregnancy 2: treated hypertension 1+ proteinuria	Pregnancy 1: no treatment Pregnancy 2: CPAP throughout pregnancy	Pregnancy 1: intrauterine fetal demise at 23 weeks; Fetal weight <10th percentile for gestational age Pregnancy 2: 3,250 g infant APGAR 6/8
Roush and Bell [47]	2004	1	PSG after delivery Apnea hypopnea index 160 per hour	Preeclampsia Fetal heart rate decelerations	None during pregnancy	1,700 kg infant APGAR 8/9
Guilleminault et al. [50]	2004	12	Apnea hypopnea index 9–31 per hour Oxygen saturation nadir 81–86%	Gestational hypertension in 1 subject	CPAP throughout pregnancy in 7 subjects; CPAP initiated between 8 and 13 weeks gestation in 5 subjects	All infants healthy All APGAR >8

Table 16.2 Studies investigating sleep-disordered breathing and pregnancy-induced hypertension and preeclampsia

Author	Year	Number of patients	Study design/methods	Results/conclusions
Higgins et al. [76]	2011	4,074 pregnant women 490 nonpregnant women	All subjects completed Berlin's questionnaire. Demographic information infant weight and APGAR scores maternal complications noted	Pregnant women more likely to have positive Berlin's questionnaire. Latter associated with increased OR of preeclampsia and decreased infant weight
Ayrim et al. [77]	2011	200 pregnant women 200 nonpregnant women	Prospective study. All subjects completed a questionnaire. Neck Circumference and Epworth sleepiness scale score was also noted	Only 5 out of 200 pregnant women reported habitual snoring and 1 reported witnessed apnea. No association between snoring and PIH and fetal outcome
Bourjeily et al. [67]	2010	1,000	Cross sectional study of randomly selected immediate postpartum women using multivariable apnea prediction index	Increased likelihood of PIH and preeclampsia in those at risk for SDB (adjusted OR 2.3, 95% CI 1.4–4). GDM and unplanned caesarian deliveries were also higher
Ursavas et al. [78]	2008	469 pregnant women 200 age matched controls	Subjects completed a questionnaire. Record review for maternal complications	Snoring higher in pregnant than nonpregnant women. 20 and 10.9% pregnant women with snoring had preeclampsia and PIH compared to 11 and 5.8% of non-snorers ($9p=0.045$)
Pérez-Chada et al. [79]	2007	469 pregnant women 208 age matched nonpregnant women	Questionnaires, record review	Snoring associated with PIH and preeclampsia with combined OR of 1.86 (CI 1.16–2.84) independent of age, BMI before pregnancy, weight gain during pregnancy, and neck circumference
Poyares et al. [63]	2007	16 pregnant women with hypertension and snoring (9 women in control group and 7 in the treatment arm)	Randomized control study comparing nasal CPAP treatment with standard prenatal care	CPAP therapy added to prenatal care during early pregnancy improved blood pressure control without need for escalating antihypertensive medication doses. However, infant outcomes were similar in the two groups

(continued)

Table 16.2 (continued)

Author	Year	Number of patients	Study design/methods	Results/conclusions
Izci et al. [80]	2005	167 healthy and 82 preeclamptic women in the third trimester of pregnancy and 160 nonpregnant women	Subjects and their partners completed a sleep questionnaire. Height, weight, neck circumferences, and blood pressure were recorded for all	Thirty-two percent of control, 55% of pregnant, and 85% of preeclamptic women snored ($p<0.001$), but pre-pregnancy snoring rates (preeclamptic = 36%, healthy pregnant women = 27%) were similar to those in nonpregnant women (32%) ($p>0.7$)
Connolly et al. [61]	2001	Fifteen females with preeclampsia were compared to 15 females from each of the three trimesters of pregnancy, as well as to 15 matched nonpregnant control females (total study population, 75 subjects)	Overnight monitoring of respiration, oxygen saturation, and blood pressure (BP)	No group had evidence of a clinically significant sleep apnea syndrome, but patients with preeclampsia spent substantially more time (31 ± 8.4% of sleep period time, mean ± SD) with evidence of inspiratory flow limitation compared to 15.5 ± 2.3% in third trimester subjects and <5% in the other three groups ($p=0.001$). In the majority of preeclamptics, the pattern of flow limitation was of prolonged episodes lasting several minutes without associated oxygen desaturation. As expected, systolic and diastolic BPs were significantly higher in the preeclamptic group ($p<0.001$)

PIH pregnancy-induced hypertension; *GDM* gestational diabetes mellitus; *SDB* sleep-disordered breathing; *OR* odds ratio; *CI* confidence interval

($p<0.01$). Prevalence of preeclampsia, likewise, was significantly greater in the snorers than non-snorers. In addition, infants born to snoring mothers were more likely to have low APGAR scores and birth weight. Habitual snoring was independently predictive of hypertension (odds ratio 2.03) and growth retardation (OR, 3.45) [33]. This study is limited by the absence of polysomnographic confirmation of OSA. Subsequently, in a study from Montreal, Canada, 17 pregnant females with gestational HTN underwent polysomnographic evaluation. These were then compared with a matched control group without HTN. An apnea-hypopneas index of 15 per hour and above was taken as the diagnostic threshold for diagnosis of OSA. This study found a higher AHI in the gestational HTN group compared to normotensive pregnant women: 38.6 ± 36.7 events per hour vs. 18.2 ± 12.2 events per hour, respectively. The unadjusted odds ratio for the presence of OSA in women with gestational HTN was 5.6. After adjusting for maternal age, pre-pregnancy BMI, gestational age, and prior pregnancies, the odds were even higher at 7.5 [62].

Other studies that suggest an association between gestational HTN and preeclampsia with OSA include those where initiation of continuous positive airway pressure (CPAP) led to reduction in blood pressure measurements. In one study, 11 women with preeclampsia underwent two consecutive sleep studies with simultaneous beat-to-beat blood pressure monitoring. Sleep architecture was similar on the two study nights. Sleep-induced partial upper airway flow limitation occurred in all patients in the initial study. Autosetting nasal CPAP applied at a mean maximal pressure of 6 ± 1 cm H_2O eliminated flow limitation throughout sleep on the treatment night. Investigators showed that the blood pressure was markedly reduced on the treatment night [$(128 \pm 3)/(73 \pm 3)$] when compared with the initial nontreatment study night [$(146 \pm 6)/(92 \pm 4)$], $p=(0.007)/(0.002)$. The study authors concluded that partial upper airway obstruction during sleep in women with preeclampsia was associated with increments in blood pressure, which can be eliminated with the use of nasal CPAP [8]. However, there is a paucity of studies looking at the impact of treatment of OSA with CPAP on fetal outcomes [50, 63]. In a small study of 12 pregnant women with preeclampsia risk factors, Guilleminault et al. reported that treatment with CPAP did not prevent adverse fetal outcomes, even though it successfully resolved the obstructive events [50].

OSA and Gestational Diabetes

OSA has been associated with the risk of developing glucose intolerance in general population irrespective of the presence of obesity and family history [64]. Studies examining the relation between OSA and glucose intolerance in pregnancy show similar results [65, 66]. In a study of 169 pregnant women, increased likelihood of gestational diabetes mellitus (GDM) was found in women with increased SDB risk (odds ratio 3.0 [95% CI 1.2–7.4]). Other risk factors included short sleep duration [65]. In a cross sectional study of 1,000 postpartum women, symptoms of SDB were associated with a higher likelihood of pregnancy-induced hypertension

and preeclampsia (adjusted OR 2.3, 95% CI 1.4–4.0), gestational diabetes (adjusted OR 2.1, 95% CI 1.3–3.4), and unplanned Caesarean deliveries (adjusted OR 2.1, 95% CI 1.4–3.2) after multivariable regression analysis [67]. In another cohort of 1,290 women, information about sleep duration and snoring during early pregnancy was collected. After adjusting for maternal age and race/ethnicity, GDM risk was increased among women sleeping ≤4 h compared with those sleeping 9 h per night (RR = 5.56; 95% CI 1.31–23.69). The corresponding RR for lean women (<25 kg/m^2) was 3.23 (95% CI 0.34–30.41) and 9.83 (95% CI 1.12–86.32) for overweight women (≥25 kg/m^2). Overall, snoring was associated with a 1.86-fold increased risk of GDM (RR = 1.86; 95% CI 0.88–3.94). The risk of GDM was particularly elevated among overweight women who snored. Compared with lean women who did not snore, those who were overweight and snored had a 6.9-fold increased risk of GDM (95% CI 2.87–16.6). These preliminary findings suggest associations of short sleep duration and snoring with glucose intolerance and GDM [68]. Though consistent with studies of men and nonpregnant women, larger studies that include objective measures of sleep duration, quality, and apnea are needed to obtain more precise estimates of observed associations.

The mechanistic pathways responsible for the development of hypertension and glucose intolerance in pregnancy are less well understood. However, it is hypothesized that, similar to the nonpregnant subjects with sleep apnea, obstructive events are associated with increasing sympathetic activation and release of oxidative stress markers which might be causative.

OSA in Pregnancy and Fetal Outcome

When the 33 pregnancies in Table 16.1 are further evaluated, one factor that stands out is the lower mean infant birth weight for mothers with untreated OSA (2,440 ± 431 g) compared with mothers who received some form of therapy for their OSA (2,956 ± 216 g). This may be confounded by varying amounts of GDM and preeclampsia (conditions which can affect birth weight) in the treatment and nontreatment groups. The obvious concern in the nontreatment group is that the hypoxemia associated with OSA leads to placental ischemia, resulting in infants that are small for their gestational age. Pregnant animals exposed to chronic or intermittent prolonged hypoxemia have demonstrated fetal growth restriction [69–71]. In humans, there is an association between maternal hypoxemia and fetal growth restriction in women with parenchymal lung disease and in women living at high altitude [72].

Studies have looked at the association between pregnancy-related OSA and fetal growth retardation as well as the effect of maternal hypoxia on fetal heart rate. The data on association of SDB with fetal growth retardation are controversial, with some studies showing adverse outcomes in association with habitual snoring and others showing no relation. As noted previously in the study by Franklin et al. [33], the presence of habitual snoring was associated with risk of growth retardation.

However, in a recent study of 246 low risk women comparing chronic (those with snoring prior to pregnancy) and new onset (those with snoring that developed during pregnancy) snorers with regard to fetal outcome, there was no significant difference in fetal growth. These investigators concluded that in pregnant women with no apparent risk factors maternal snoring does not affect fetal growth. No differences in maternal characteristics or fetal outcome were found between chronic snorers and new-onset snorers [73]. However, the drawback of this study and others using snoring as a surrogate for the presence of OSA is that the study group is likely to include pregnant women without evidence of OSA on a PSG, thereby "diluting" the impact of OSA on the final outcome measures.

Studies where the diagnosis of OSA is confirmed with PSG are few and limited by small numbers. In a study by Sahin et al. [74], women with self-reported snoring underwent a sleep study as well as non-stress test (NST) to assess the impact of maternal desaturation on fetal heart rate. These investigators noted OSA in 4 (11.4%) of the 35 pregnant women who underwent PSG. Three (75%) had fetal heart decelerations accompanying maternal desaturation. The neonates of women diagnosed with OSA had lower mean APGAR scores and birth weights compared with neonates of women without OSA. Three neonates from the women diagnosed with OSA were admitted to the newborn healthcare unit. Conflicting results were reported in another study where OSA-related desaturation was not associated with fetal heart rate abnormalities [51].

Influence of Pregnancy on OSA

Symptoms of SDB increase during pregnancy. Excessive daytime somnolence was highly prevalent even early in pregnancy and became increasingly common as pregnancy progressed [52]. Pregnancy worsens the severity of OSA both in terms of AHI and degree of desaturation. This is explained by previously described changes in upper airway diameter and reduced FRC in pregnant compared to nonpregnant women. In a cohort of ten patients with previously diagnosed OSA, Edwards et al. showed that the AHI in non-rapid eye movement sleep increased to 63 ± 15 per hour during pregnancy from 18 ± 4 per hour. In REM sleep, the AHI increased to 64 ± 11 per hour from 22 ± 4 per hour. Oxygen saturation nadir increased from $86 \pm 2\%$ antenatally to $91 \pm 1\%$ in the postnatal period [75]. These findings suggest that there is worsening of OSA severity as pregnancy progresses.

Management of OSA During Pregnancy

Thus far, there is no consensus regarding how to screen and whom to screen for OSA during pregnancy. It may be more appropriate to develop screening parameters once the prevalence of OSA in pregnancy and in conditions such as

pregnancy-induced hypertension has been established. Once OSA has been diagnosed in pregnancy, treatment is indicated. In the group of patients described in Table 16.1, the methods of treatment included CPAP therapy ± oxygen and tracheostomy. The advantage of CPAP therapy is that it is noninvasive and can be instituted rapidly. It was also shown to be a safe and effective treatment for OSA in pregnancy [41, 43, 45, 46, 50, 63]. There may be a role for an auto-titrating CPAP device as pregnant patients continue to gain weight during the gestational period and studies show worsening of AHI during pregnancy compared to prenatal AHI [75]. In the era of CPAP therapy, the need for tracheostomy is, thankfully, rare. The use of an oral appliance may also be appropriate for mild-to-moderate OSA; however, there are no studies at this time looking at their efficacy. Surgical treatment options (such as uvulopalatopharyngoplasty) for OSA are problematic for pregnant patients given the risks of anesthesia and the suboptimal efficacy of various surgical interventions.

Conclusion

SDB is very prevalent among pregnant women. It is associated with several adverse maternal and fetal outcomes. Physicians should therefore have a high level of suspicion and should actively look for signs of SDB including snoring and daytime fatigue. Overnight PSG should be considered for diagnosis. Role of ambulatory sleep studies in this population is not known at this time, but likely should be similar to that in men and nonpregnant women where there is a good correlation with attended PSGs. Additional research is needed to determine the prevalence of SDB among pregnant women with polysomnographic confirmation of the diagnosis. This will help us understand better the association between SDB in pregnancy and adverse maternal and fetal outcomes. In addition to this, the change in severity of OSA as pregnancy progresses needs further study. Treatment with CPAP should be considered in those diagnosed with OSA. Role of other treatment options, such as oral appliance, needs additional investigation as CPAP intolerance could be high in this group due to high prevalence of rhinitis. More studies examining the effect of treatment of SDB in pregnancy on maternal and fetal outcomes are needed.

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Part V
Menopause

Chapter 17
Restless Legs Syndrome and Menopause

Mari Viola-Saltzman

Introduction

There is no known pathophysiologic link and little in the literature written about the association between menopause and restless legs syndrome (RLS). Since the cellular mechanisms explaining the causality of RLS are unknown, much of the literature has focused on the numerous associations between RLS and other disorders. RLS is known to occur in middle-to-late aged individuals, having a higher prevalence in women. Following this line of logic, it would raise the question of whether there is a relationship between RLS and menopause. A questionnaire-based survey performed by Ghorayeb et al. revealed that 69% of patients reported worsening of restless leg symptoms following menopause [1].

Restless Legs Syndrome

Symptoms of RLS were described first in 1672 by Sir Thomas Willis [2], and in 1945 Karl Ekbom described the symptom complex [3]. RLS is a sensorimotor disorder characterized by an urge for leg movement, often accompanied by an uncomfortable sensation deep within the legs, and leg movement relieves the discomfort. RLS can be an idiopathic condition or occurs secondary to another disorder. Most commonly,

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RLS is associated with iron deficiency or dysfunctional iron states [4–7]. Additionally, dopaminergic dysfunctional states are associated with RLS [8]. Improvement in symptoms can be achieved with pro-dopaminergic medications [8, 9] and worsened with dopaminergic antagonists [8, 10]. Other medications such as selective serotonin reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, glucocorticoids, antipsychotics, antihistamines, calcium channel blockers, and caffeine are also known to exacerbate or cause symptoms of RLS [11]. Numerous other medical disorders are associated with RLS, including peripheral neuropathies [12], uremia [2, 5, 13], myelopathy [14], diabetes [5, 7, 13, 15], rheumatoid arthritis [7], hyperthyroidism [5, 13], hypoparathyroidism [13], and myocardial infarction not explained by age, sex, or diabetes [5]. The symptoms of RLS have a circadian rhythm in which they are worse in the evening and at bedtime. RLS is associated with pregnancy, especially in those with a positive family history and/or who are multiparous [5]. In addition, psychosocial disturbances are associated with increased reports of RLS, including those with lower income [15], poor mental health [15, 16], psychiatric disease such as depression [13], decreased general health [15, 17], lack of exercise [15], and less education [5]. Lastly, genetics play a strong role in RLS. Estimates of inherited RLS range from 0.33 to 65% [13]. Some investigators have reported autosomal dominance with variable penetrance [5, 18, 19].

Menopause

Menopause is defined as 1 year following cessation of menstrual periods. However, hormonal changes begin 7–10 years before the final menses with decreases in estradiol and disinhibin and increasing levels of follicular stimulating hormone (FSH) and lutenizing hormone (LH). Circulating estrogens change from estradiol to estrone and there are only minimal reductions of testosterone levels. Ovarian follicular loss accelerates logarithmically (3–6 times) during the decade prior to menopause [20].

Hormonal Influences in Menopause May Aggravate RLS

Estrogen

In general, estrogens are thought to be neuroprotective and act through genomic mechanisms modulating synthesis, release, and metabolism of many neuropeptides and neurotransmitters [21, 22]. Estrogen leads to neuronal repair and assists neuronal survival [23]. It has multiple effects on neuronal function and modulates the expression of several neurotransmitters. Estrogen increases the synthesis of acetylcholine, delays the turnover of serotonin, and regulates serotonin transport and

binding in the brain [21]. It also upregulates noradrenaline, but GABA is largely unaffected [23]. Estrogen causes increased turnover of brainstem norepinephrine, increases norepinephrine activity in the brain [20, 24] due to decreasing monoamine oxidase activity [25], and could then indirectly interfere with dopamine transmission [24]. It also has other mixed effects on norepinephrine [25].

Estrogen has both agonistic and antagonistic effects on the dopaminergic system. Long exposure to estrogen increases dopamine uptake site density in the nigrostriatal dopamine system [21]. Estrogen upregulates and increases the number of dopamine receptors [23]. Therefore, RLS symptoms may worsen during menopause due to this reduced estrogen state causing a lower number of dopamine receptors.

Estrogen also interferes with catechol-*O*-methyl transferase (COMT), an enzyme that degrades dopamine [21]. Another theory that might explain RLS symptoms worsening in menopause may be related to decreased COMT interference allowing increased COMT degradation of dopamine and, consequently, reduced amounts of central dopamine.

However, in pregnancy, RLS peaks in the third trimester at the time when there are rising levels of progesterone, prolactin, and estrogen [5, 20, 26]. There may then be another effect increasing RLS in pregnancy.

Melatonin

Both RLS and melatonin have a circadian rhythm. Decreases in total melatonin are not associated, per se, with menopause. However, postmenopausal women with insomnia generally have been shown to have lower melatonin levels than their cohorts. Additionally, estrogen may have a reciprocal melatonin supportive function. Both tamoxifen, an antiestrogen, and oophorectomy cause decreases in melatonin [25].

Age-related decrease in melatonin secretion in humans is widely documented [22] but has recently been challenged by investigators who, after controlling for confounding variables, showed no difference in levels of melatonin over the life span. These investigators showed that most healthy older adults have plasma melatonin comparable to those of young adults [27]. Therefore, decreasing levels of melatonin associated with decreasing levels of estrogen may not be a true association or provide a menopausal correlation/causality of RLS symptoms.

Further challenges to the prevailing theory of decreased melatonin and menopause were performed by Fernandez et al. who examined 77 healthy women ages 30–75. After measuring urine and serum melatonin levels and serum FSH, they showed that urinary melatonin was negatively associated with serum FSH during perimenopause with the sharpest decline in nocturnal excretion of melatonin far before menopause. In fact, age 30–39 had the highest amount of melatonin secretion compared to age groups of 40 years and above. Serum FSH rose sharply to high levels before age 50 and remained high thereafter. Their findings illustrate that the decrease in melatonin precedes increase in FSH far before menopause [28].

Preexisting RLS May Become More Evident During Menopause

Eichling's review paper on menopause and sleep disorders states that there is no direct correlation between RLS and menopause [25]. However, as with other authors, it suggests that with the onset of menopause-associated sleep disruption, a preexisting sleep disorder, such as RLS, may become more evident. Several etiologies for menopausal-related sleep disruption include hot flashes, mood disorders (depression and anxiety), psychophysiologic insomnia, and increased incidence of sleep disordered breathing. In support of this theory, Moline showed there is an increased prevalence of insomnia in postmenopausal women (44–61%) compared to premenopausal women (33–36%). Subjectively, postmenopausal women were less satisfied with their sleep than premenopausal women. However, polysomnography showed an increased total sleep time and amount of slow wave sleep and decreased wake time after sleep onset in the postmenopausal women [20].

Hormone replacement therapy has been shown to be an effective treatment for overall menopausal sleep quality [29–33]. However, in a randomized, double-masked, placebo-controlled, crossover trial of postmenopausal women with periodic limb movements, estrogen replacement therapy did not alter the incidence or intensity of nocturnal periodic limb movements [23]. In addition, Wesström et al. found no relationship between restless legs complaints and the use of hormone replacement therapy in the postmenopausal state [34].

Conclusion

Little is known about the physiological mechanisms underlying RLS, and there is paucity in the literature about what role, if any, menopause may contribute to RLS. Evidence from recent studies suggests that RLS is a chronic disorder resulting from complex metabolic dysfunction involving the subcortical central and possible peripheral nervous system often involving iron acquisition/regulation, dopaminergic and opiatergic pathways and influenced by genetic, circadian, psychosocial, medical disorders, and likely other changes associated with aging. If menopause is contributing to the influence of those hormonal changes of aging, perhaps loss of some neuroprotective effect of gonadal steroids on these iron acquisition and regulation of dopaminergic and opiatergic pathways, it would join numerous other medical- and aging-related conditions that contribute to aggravating the chronic underlying condition. In addition, RLS as a preexisting condition may become more evident in patients whose sleep is disrupted due to other sleep-disrupting conditions of middle-to-late age, especially menopause.

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Chapter 18
Insomnia During Menopause: Sleep Laboratory Studies on Insomnia Associated with Postmenopausal Syndrome and Hormone Replacement Therapy

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Introduction

Sleep disturbance is a prevalent health problem [1–3] that increases with age and occurs more frequently in women than in men [2, 4–6]. In women, insomnia increases particularly as women approach and pass through menopause [7–10].

Insomnia in postmenopausal women is one of the most common symptoms in menopause and is part of the climacteric syndrome [11, 12]. It also may occur in association with hormonal changes [13, 14]; on the other hand, women, especially after menopause, are more likely to suffer from psychiatric disorders, such as major depression and anxiety disorders, which are also correlated with insomnia [5]. Organic sleep disorders such as sleep-disordered breathing (SDB) resulting from a decrease in sex hormones in menopause may play an important role as well [15]. Other frequent insomnia comorbidities include restless legs syndrome (RLS) and periodic leg movements during sleep (PLMS), whose prevalence also increases with age is [16].

Subjective sleep disturbance and fatigue are among the most frequent complaints of perimenopausal women [3, 6, 17–19]. Owens and Mathews [5] reported that as many as 42% of the 521 postmenopausal women in their study had sleep

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disturbances, which were significantly increased in the transition from the pre- to the postmenopausal status in women who chose not to use hormone replacement therapy (HRT). However, there is little literature on the objective sleep quality (i.e., polysomnography) of postmenopausal syndrome patients compared with normal controls.

Moe [20] reported longer sleep latencies, increased nocturnal awakenings, and sleep fragmentation as well as decreased slow-wave sleep (SWS). A 24-h polysomnographic study showed that 10% of the accumulated sleep time of postmenopausal women was recorded out of bed and their sleep was observed shortly after arousal from bed in the morning, which indicated daytime tiredness [20, 21]. Not all studies of sleep in middle-aged women, however, found a significant impact of the menopausal status on sleep quality [22, 23].

The sleep changes in postmenopausal women have been partially attributed to the change of the sex steroid hormone profile, which can affect sleep either directly or through an effect on body temperature (hot flushes), circadian rhythm changes, or stress reactivity [9, 11]. Murphy and Campbell [24] and Ballinger [25] inferred that insomnia is a result of hormonal changes because their surveys showed that its incidence rose as the estrogen levels fell during this period. The polysomnographic effects of HRT have been studied for a long time. Thompson and Oswald [26] observed a reduction in wakefulness, a decrease in the number of awakenings, and an increase in rapid eye-movement (REM) sleep during 8 weeks of estrogen treatment when compared with baseline measures, whereas untreated control patients did not show any improvement. In a crossover study, Schiff et al. [27] found a significantly shorter sleep-onset time and more REM sleep during treatment with estradiol compared with placebo. Erlik et al. [28] reported that postmenopausal women treated with estrogen had fewer hot flushes associated with wakefulness per night than untreated women. Recently, it was observed that estrogen replacement therapy restored the normal sleep electroencephalogram (EEG) as it enhanced REM sleep and decreased time awake during the first sleep cycles [29]. The normal decrease in SWS and delta activity from the first to the second sleep cycle was also restored by estrogen. On the other hand, Purdie et al. [30] found an improvement in menopausal symptoms under combined estrogen–progesterone therapy, with an improvement of psychological well-being but not parameters of sleep quality. Polo-Kantola et al. [31] observed that estrogen effectively alleviated hot flushes, sweating, and sleep complaints and improved subjective sleep quality by reducing the total frequency of arousals, but did not affect any changes in sleep architecture. Although estrogen was found to enhance REM sleep [27], progesterone and its metabolite pregnanolone showed a marked sedating effect with a significant increase in non-REM sleep [32]. Moreover, pregnenolone, a precursor of progesterone, enhanced SWS and reduced EEG activity in high-frequency bands [33].

Steroid receptors have been discovered in a number of brain areas that are also involved in sleep regulation, i.e., the cortex, hippocampus, hypothalamus, amygdala, basal forebrain, midbrain raphe nuclei, pituitary gland, locus coeruleus, and cerebellum. At least two estrogen receptors, ERα and ERβ, are involved as well. Estrogen action is based on slowly initiated but long-lasting nuclear (genomic)

mechanisms and faster but shorter-acting nonnuclear mechanisms. Sleep steroids also influence the neurotransmitters that play a role in sleep regulation, i.e., the cholinergic, serotonergic, dopaminergic, and adrenergic neurotransmitter systems, as well as the glutamate, gamma-amino butyric acid, opiate, and vasopressin systems. Insulin-like growth factor 1, transforming growth factor alpha, cyclic aminophosphatase, protein kinase activators, and various other neurotransmitters can also activate estrogen and progesterone receptors. Within the central nervous system (CNS), estrogen may restore circadian hormones, i.e., growth hormone (GH), prolactin (PRL), cortisol, and melatonin [4, 34].

The aims of our study were to investigate the differences in sleep and awakening between untreated insomniac postmenopausal syndrome patients and normal controls as well as to compare the effects of continuous combined administration of 2 mg estradiol valerate plus 3 mg dienogest (Climodien® (Bayer Schering Pharma, Berlin, Germany) 2/3; regimen A) with those of estradiol valerate alone and placebo in a first double-blind, controlled phase. This was followed by an open-label phase, in which all patients were treated with a combination of 2 mg estradiol valerate plus 2 mg dienogest (Climodien 2/2; regimen A*), to allow a stratified comparison of the 2/2 mg preparation (A*) vs. placebo or vs. the 2/3 mg preparation (A).

The progestogen chosen for the present study, dienogest (17-α-cyanomethyl-17-β-hydroxy-estra-4,9(10)-dien-3-one), is a synthetic 19-norprogestin devised for oral HRT of natural or postsurgical menopause, as well as for prophylaxis of osteoporosis and cardiovascular diseases in postmenopausal women. The fixed combination of 2 mg of natural estradiol valerate and 2 or 3 mg dienogest is intended for continuous use over 28 days (i.e., without hormonal pause) to produce amenorrhea (Kliogest® (Novo Nordisk, Sorgenfri, Denmark) principle). This preparation is especially suited for patients who do not tolerate monthly bleeding caused by progestin withdrawal, especially for women at a later stage of menopause. Compared with other progestins of its structural class (19-nandrolone derivatives), dienogest has special pharmacodynamic and pharmacokinetic features:

1. Marked endometrium efficacy
2. Lack of interaction between steroid hormone-binding globulin and corticosteroid-binding globulin
3. High bioavailability resulting from high intestinal absorption and short plasma half-life (5–10 h) after oral administration
4. Marked antiandrogenicity
5. Antiproliferative effects
6. Metabolic neutrality
7. Good tolerance and safety profile, including lack of liver metabolic alterations
8. Low toxicity in acute and chronic toxicity tests
9. Lack of teratogenic, embryotoxic, or postnatal developmental effects [34]

Finally, at a biochemical level, dienogest does not influence the cytochrome P-450 system [34].

Dienogest has usually been analyzed in a dosage of 2 mg, in combination with ethinylestradiol (0.03 mg) (available in Germany as the contraceptive Valette®,

Bayer Schering Pharma, Berlin, Germany). The frequency of menstrual bleeding disorders is extremely low (4.5%), placing this estrogen–progestogen combination at the highest levels of tolerability among internationally used combined contraceptives.

Methods

Study Design and Patients

Sleep quality and daytime functioning of 55 insomniac postmenopausal patients was investigated in a double-blind, placebo-controlled, comparative, randomized, three-arm trial phase. The three arms were regimen A consisting of Climodien 2/3 (estradiol valerate 2 mg + the progestogen dienogest 3 mg), regimen EV (estradiol valerate 2 mg) and regimen P (placebo). The blinded phase was followed by an open-label phase in which all patients received regimen A* which was Climodien 2/2 (estradiol valerate 2 mg + dienogest 2 mg). Forty-nine women (16, 17, and 16, respectively, per arm) between 46 and 67 years of age (mean 58, 58, and 56 years, respectively) with the diagnosis of insomnia related to postmenopausal syndrome were included in the analysis of the double-blind phase. Pretreatment data of 49 patients (mean age 58 ± 5 years) were compared with those of 22 normal age-matched controls (mean age 57 ± 7 years). Forty-five patients (13, 17, and 15 valid patients) completed the open-label phase. The double-blind and open-label phases each lasted 2 months. The women enrolled in the study took one tablet daily at the same time of day (7 p.m.).

Inclusion criteria were as follows:

- A sleep complaint characterized primarily by difficulty falling asleep, maintaining sleep or nonrestorative sleep, which occurred at least three times per week for at least 1 month
- The prevailing sleep disorder was serious enough to require clinical attention
- The sleep disorder was not likely to be a direct physiological consequence of a medical condition (i.e., menopausal syndrome)
- The disorder could not be better explained by another psychological disorder (e.g., adaptive disorder with the cause of stress being a severe physical disease)
- The disorder did not satisfy the criteria for sleep apnea or narcolepsy
- The sleep disorders caused clinically significant distress or a disturbance in social, professional, or other important fields
- The state of menopause was confirmed by at least 24 months of amenorrhea and estradiol levels <55 pg/mL or follicle-stimulating hormone (FSH) >19 mU/mL
- Kupperman index >15 [35]

Exclusion criteria have been described in detail elsewhere [36].

The study protocol was approved by the Ethics Committee of the Medical Faculty of the University of Vienna and the General Hospital of the City of Vienna. Each patient was informed about the study, and a written consent was obtained. The study was performed in accordance with the ethical principles of the Declaration of Helsinki, as revised by the World Medical Assembly in Tokyo and Venice, as well as with the EC Guideline of Good Clinical Practice.

Evaluations were carried out at baseline as well as at the end of the 2-month double-blind and 2-month open-label phases, respectively (each time after one adaptation night). Thus, each patient spent six nights in the sleep lab. Normal controls were recorded for two nights (adaptation and baseline nights).

Evaluation of Objective Sleep Quality

Polysomnographic all-night recordings were obtained between approx 10:30 p.m. (lights out) and 6 a.m. (buzzer or alarm clock). Data were recorded by means of a 16-channel polygraph (Jaeger Sleep Lab 1000P) including three EEG channels (C4-A1, CZ-O2, and C3-A2) according to the 10/20 system, two electrooculogram channels (left/right), submental myogram and tibialis anterior electromyogram from both legs, nasal and oral airflow, movement of the chest and abdomen, snoring, transcutaneous oxygen saturation, and pulse rate (CRITICARE Pulse Oxymeter 504).

Evaluation of Subjective Sleep and Awakening Quality

After the morning toilet, the patients completed the Self-Assessment of Sleep and Awakening Quality Scale (SSA) [37]. Thymopsychic is variables (concerned with mood, drive, affectivity, etc) included subjective well-being in the evening and morning, based on the Von Zerssen BF-S Scale [38], as well as drive, mood, affectivity, and drowsiness in the morning, measured by means of 100-mm visual-analog scales. The Pittsburgh Sleep Quality Index [39] was evaluated as well.

Evaluation of Objective Awakening Quality (Psychometry)

Noopsychic (intellectual reformance) tests included the Grünberger Alphabetical Cancellation Test (Alphabetischer Durchstreichtest=AD) for quantification of attention (AD/total score), concentration (AD/E%, errors in percentage of the total score), and attention variability (AD/SV; difference between extreme scores) [40], the Numerical Memory Test [40], as well as the Grünberger Fine Motor Activity Test

(right and left hand) for evaluation of changes in psychomotor activity and drive [40]. Reaction time, reaction time variability (ms), and errors of omission and inclusion were determined by the computer-assisted reaction time apparatus.

Statistics and Sample Size Determination

The statistical analysis was carried out at the Department of Psychiatry, University of Vienna, using the SPSS software package (SPSS Inc., Chicago, IL; version 8.0.0) under Windows NT, based on descriptive data analysis [41] with one confirmatory statement on wakefulness during the total sleep period. The analysis included all variables studied in the clinical trial and was based on data grouped by treatment and trial times. The predetermined null hypothesis for the confirmatory statement was there is no difference between Climodien, estradiol valerate, and placebo in regard to wakefulness during the total sleep period (maximum error probability = 0.05). Alpha-adjustment by Bonferroni-Holm led to individual error probabilities of $p(1) < 0.0166$, $p(2) < 0.025$, and $p(3) < 0.05$. All other variables were tested descriptively.

Normal distribution was tested by means of the Kolmogorov Smirnov test. If in no cases the null hypothesis of normal distribution was rejected at alpha = 0.10, *t*-tests were used. In the case of a violation of the assumption of normal distribution, a nonparametric Wilcoxon test was used for intragroup comparison and a Mann–Whitney *U*-test for intergroup comparison. The present findings are based on a per-protocol analysis.

The sample size of 17 valid cases per arm was calculated on the basis of a placebo-controlled study carried out with piperazine estrone sulfate in perimenopausal women by Thompson and Oswald [26]. The size of the random sample was determined for the change in nocturnal waking times.

Results

Baseline Differences in Sleep and Awakening Quality between Insomniac Postmenopausal Syndrome Patients and Normal Controls

Baseline data of 49 drug-free insomniac postmenopausal syndrome patients (mean age 58 ± 5 years) were compared with those of 22 age- and gender-matched normal controls (mean age 57 ± 7 years). Figure 18.1 depicts the sleep profiles of an individual patient and an age- and gender-matched healthy control. Table 18.1 shows the means and standard deviations of the total groups of patients and normal

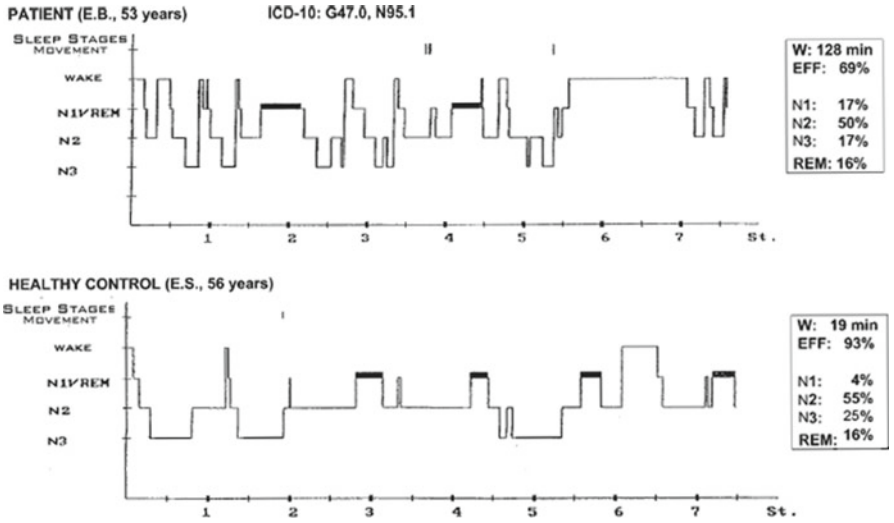

Fig. 18.1 Sleep profile of an insomniac postmenopausal syndrome patient compared with that of an age- and sex-matched healthy control. Time is shown in the abscissa; sleep stages are depicted in the ordinate. W = nocturnal wake time; EFF = sleep efficiency (sleep time in percentage of time in bed); N1 = first stage of NREM sleep; N2 = second stage of NREM sleep; N3 = third stage of NREM sleep; REM = rapid eye-movement sleep

Table 18.1 Insomnia related to postmenopausal syndrome: differences from normal controls in objective sleep variables

Variables	Patients ($N=49$; age 58 ± 5)	Controls ($N=22$; age 57 ± 7)
Sleep initiation + maintenance		
Latency to N1 (min) ↓	16 ± 15	10 ± 9
Latency to N2 (min) ↓	24 ± 17*	13 ± 9
Wake within TSP (min) ↓	52 ± 32	41 ± 20
Wake before buzzer (min) ↓	6 ± 23**	5 ± 9
Total sleep period (min) ↑	429 ± 26**	464 ± 19
Total sleep time (min) ↑	375 ± 40**	420 ± 24
Sleep efficiency (%) ↑	83 ± 9*	88 ± 5
Sleep architecture		
N1 (%)	11 ± 5*	9 ± 3
N2 (%)	49 ± 8*	54 ± 9
N3 (%)	21 ± 8	16 ± 8
REM (%)	20 ± 6	22 ± 6
Movement time (min)	2 ± 2	1 ± 1
REM latency (min)	91 ± 55	82 ± 40
Apnea–hypopnea index (*n*/hours of sleep)	7 ± 11	3 ± 5

↓↑ Direction of improvement

The data are presented as means ± SD; *$p<0.05$; **$p<0.01$ vs. controls (Mann–Whitney *U*-test)

N1 first stage of NREM sleep; *N2* second stage of NREM sleep; *N3* third stage of NREM sleep also known as slow-wave sleep; *TSP* total sleep period; *REM* rapid eye-movement sleep

Table 18.2 Insomnia related to postmenopausal syndrome: differences from normal controls in subjective sleep/awakening quality, thymopsychic, and noopsychic variables

Variables	Patients ($N=49$; age 58 ± 5)	Controls ($N=22$; age 57 ± 7)
Subjective sleep/awakening quality		
Pittsburgh Sleep Quality Index (score) ↓	11 ± 5**	4 ± 1
SSA 1—sleep quality (score) ↓	16 ± 5**	10 ± 2
SSA 2—awakening quality (score) ↓	16 ± 5	11 ± 2
SSA 3—somatic complaints (score) ↓	7 ± 2*	6 ± 1
SSA 4—(total score) ↓	39 ± 9**	27 ± 4
Thymopsyche		
Well-being evening (score) ↓	18 ± 12**	9 ± 8
Well-being morning (score) ↓	15 ± 10**	7 ± 6
Drive (mm) ↓	40 ± 25*	24 ± 17
Mood (mm) ↑	65 ± 23	76 ± 11
Affectivity (mm) ↑	71 ± 21	81 ± 9
Drowsiness (mm) ↓	41 ± 29*	22 ± 16
Noopsyche		
Attention (score) ↑	526 ± 117	502 ± 113
Concentration (% errors) ↓	5 ± 4	4 ± 3
Attention variability (score) ↓	15 ± 6	14 ± 5
Numerical memory (N) ↑	5 ± 2**	6 ± 1
Fine motor activity right ↑	34 ± 9**	36 ± 13
Fine motor activity left ↑	27 ± 8	30 ± 10
Fine motor activity right + left ↑	61 ± 15	66 ± 22
Reaction time (RT) (ms) ↓	616 ± 94*	536 ± 107
RT variability (ms) ↓	123 ± 37	100 ± 41
RT errors/commission (N) ↓	6 ± 4	4 ± 4
RT errors/omission (N) ↓	2 ± 3*	1 ± 1

↑↓ Direction of improvement

The data are presented as means ± SD; *$p<0.05$; **$p<0.01$ vs. controls (Mann–Whitney U-test)

controls together with the statistically significant intergroup differences (Mann–Whitney U-test). The patients exhibited slight but statistically significant deviations from the norm concerning sleep initiation and maintenance as well as sleep architecture (Table 18.1), with increased latency to N2 (early insomnia) and wakefulness before the buzzer (late insomnia), a shortened sleep period and total sleep time, as well as reduced sleep efficiency. Regarding sleep architecture, N1 was increased, whereas N2 was decreased. No differences between patients and controls were observed in regard to N3, dream sleep, movement time, REM latency, or the apnea–hypopnea index (AHI).

Subjective sleep quality was reduced (Table 18.2), as revealed by both the Pittsburgh Sleep Quality Index and the SSA. The latter also showed increased is somatic complaints in the morning. Feeling of well-being in the evening and morning and drive in the morning were reduced, whereas drowsiness was increased. Numerical memory, reaction time, and reaction time performance were worse compared to healthy controls.

HRT and Sleep Initiation and Maintenance

The primary efficacy variable wakefulness during the total sleep period showed a decrease by 18 min on Climodien, 15 min on estradiol, and 4 min on placebo. None of the changes, however, reached the level of statistical significance ($p<0.05$, Wilcoxon and Mann Whitney *U*-Test, respectively) both among groups and as compared to baseline. In the subsequent open-label phase, when all patients received Climodien 2/2, those treated in the double-blind phase with Climodien 2/3 improved further on Climodien 2/2, whereas the former estradiol and placebo groups showed an increase in wakefulness during the 2 months of treatment with Climodien 2/2 (Table 18.3). These findings also failed to reach the level of statistical significance.

Latency to sleep onset (NA) showed a nonsignificant shortening in all three arms (Table 18.3). In the open-label phase, Climodien 2/2 induced a significant lengthening of sleep latency in patients before treated with placebo ($p<0.05$, Wilcoxon test). The difference between these two treatments was significant ($p<0.05$, Wilcoxon test). Moreover, the estradiol group showed a latency increase under Climodien 2/2 that differed significantly from the shortening observed compared with baseline in the double-blind phase ($p<0.05$).

Latency to stage N2 is showed a significant shortening after 2 months of estradiol ($p<0.05$), which differed significantly from the lengthening under Climodien 2/2 in the following open-label phase. There were no significant findings in the Climodien 3/2 and placebo groups.

Wake before the alarm (measuring late insomnia) showed neither significant changes compared to baseline nor significant intergroup differences. The same was true for the number of awakenings.

The total sleep period demonstrated a decrease under Climodien 2/2 in the open-label phase, which differed significantly from the increase under the preceding Climodien 2/3 treatment ($p<0.05$). Moreover, compared with placebo, Climodien 2/2 significantly decreased the total time in bed.

Total sleep time and sleep efficiency increased after Climodien 2/3 and estradiol, whereas they remained unchanged under placebo. The changes, however, did not reach the level of statistical significance. In the former placebo group, 2 months of treatment with Climodien 2/2 resulted in a nonsignificant decrease in sleep efficiency.

HRT and Sleep Architecture

The percentages of stages N1, N2, N3, and REM did not show any significant changes or any intergroup differences (Table 18.4).

Movement time, REM latency, and stage shifts did not exhibit any significant changes.

Table 18.3 Sleep initiation and maintenance in insomniac postmenopausal syndrome patients before and after 2 months of Climodien A (2 mg estradiol valerate (EV) + 3 mg dienogest (DNG)) or 2 mg EV alone or placebo as well as after subsequent 2-month therapy with Climodien A* (2 mg EV + 2 mg DNG)

Variable	Night	Climodien A ($N=16$)	Estradiol B ($N=17$)	Placebo C ($N=16$)	Intergroup difference *$p<0.05$; **$p<0.01$; U-test
Latency to N1 (min)	Pre	21 ± 17	15 ± 14	10 ± 8	
	2MoDRUG	18 ± 18	10 ± 10	9 ± 7	
	+2MoA*	17 ± 15	18 ± 23[e]	19 ± 18[c,e]	
Latency to N2 (min)	Pre	27 ± 17	25 ± 18	17 ± 11	
	2MoDRUG	28 ± 22	15 ± 10[a]	18 ± 19	
	+2MoA*	23 ± 16	22 ± 14[e]	26 ± 18	
Wake/TSP (min)	Pre	59 ± 43	47 ± 28	48 ± 28	
	2MoDRUG	41 ± 24	32 ± 23	44 ± 32	
	+2MoA*	34 ± 27	37 ± 23	52 ± 46	
Wake/before buzzer (min)	pre	7 ± 15	13 ± 37	0 ± 1	
	2MoDRUG	8 ± 19	10 ± 17	2 ± 6	
	+2MoA*	12 ± 22	3 ± 11	6 ± 13	
Number of awakenings (*N*/TSP)	Pre	9 ± 5	9 ± 4	10 ± 6	
	2MoDRUG	8 ± 3	9 ± 4	10 ± 6	
	+2MoA*	7 ± 3	9 ± 4	8 ± 5	
Total sleep period (TSP) (min)	Pre	422 ± 20	424 ± 37	442 ± 11	Pre: A:C**; B:C*
	2MoDRUG	426 ± 24	435 ± 26	441 ± 12	
	+2MoA*	421 ± 23[e]	435 ± 20	427 ± 20[c]	
Total sleep time (TST) (min)	Pre	362 ± 51	375 ± 35	392 ± 35	
	2MoDRUG	384 ± 31	402 ± 29	395 ± 37	
	+2MoA*	386 ± 36	396 ± 29	374 ± 47	
SE TST/TIB (%)	Pre	80 ± 11	83 ± 7	87 ± 7	
	2MoDRUG	85 ± 7	88 ± 6	87 ± 8	
	+2MoA*	86 ± 8	88 ± 6	83 ± 10	

2MoDRUG double-blind phase (active drug arm); *2MoA** open-label phase
[a]$p<0.05$, [b]$p<0.01$ change vs. pre, Wilcoxon
[c]$p<0.05$, [d]$p<0.01$ change vs. 2MoDRUG, Wilcoxon
[e]$p<0.05$, [f]$p<0.01$ difference (second to first period), Wilcoxon

HRT and Respiratory Events and Snoring

The apnea index showed a significant improvement under Climodien 2/3 ($p<0.05$), although the index had a priori been within normal limits, as specified by the protocol (Table 18.5). Climodien 2/3 was in this respect significantly superior to placebo ($p<0.05$, U-Test).

Table 18.4 Sleep architecture in insomniac postmenopausal syndrome patients before and after 2 months of Climodien A (2 mg estradiol valerate (EV) + 3 mg dienogest (DNG)) or 2 mg EV alone or placebo as well as after subsequent 2-month therapy with Climodien A* (2 mg EV + 2 mg DNG)

Variable	Night	Climodien A ($N=16$)	Estradiol B ($N=17$)	Placebo C ($N=16$)
Stage N1 (%)	Pre	11 ± 6	11 ± 5	11 ± 6
	2MoDRUG	11 ± 5	10 ± 4	10 ± 4
	+2MoA*	11 ± 3	11 ± 6	10 ± 4
Stage N2 (%)	Pre	50 ± 6	48 ± 10	50 ± 8
	2MoDRUG	53 ± 7	50 ± 6	54 ± 5
	+2MoA*	53 ± 5	53 ± 8	50 ± 9
Stage N3 (%)	Pre	20 ± 7	21 ± 9	20 ± 6
	2MoDRUG	17 ± 8	21 ± 6	18 ± 6
	+2MoA*	14 ± 7	18 ± 8	19 ± 7
Stage REM (%)	Pre	19 ± 6	21 ± 6	19 ± 6
	2MoDRUG	19 ± 6	19 ± 5	19 ± 4
	+2MoA*	21 ± 4	18 ± 3	20 ± 5
Movement time (min)	Pre	1 ± 1	2 ± 1	2 ± 2
	2MoDRUG	2 ± 1	1 ± 1	2 ± 2
	+2MoA*	2 ± 1	1 ± 1	2 ± 2
REM latency (min)	Pre	97 ± 59	79 ± 50	89 ± 40
	2MoDRUG	72 ± 35	70 ± 34	94 ± 38
	+2MoA*	68 ± 31	72 ± 42	89 ± 45
Stage shifts	Pre	61 ± 13	62 ± 10	68 ± 18
	2MoDRUG	61 ± 9	65 ± 15	65 ± 18
	+2MoA*	60 ± 11	64 ± 11	59 ± 15

2MoDRUG double-blind phase (active drug arm); *2MoA** open-label phase
[a]$p<0.05$, [b]$p<0.01$ change vs. pre, Wilcoxon
[c]$p<0.05$, [d]$p<0.01$ change vs. 2MoDRUG, Wilcoxon
[e]$p<0.05$, [f]$p<0.01$ difference (second to first period), Wilcoxon

The AHI also improved significantly under Climodien 2/3 ($p<0.05$), whereas with placebo no changes were observed, with intergroup differences reaching the level of statistical significance. In the open-label phase under Climodien 2/2, the AHI increased again in the Climodien 2/3 group, whereas in the group that had been treated with placebo it decreased (although nonsignificantly). Nevertheless, the AHIs in all three groups were within normal limits, which is in agreement with the selection criteria excluding patients with sleep apnea syndrome.

The desaturation index also showed a nonsignificant improvement under Climodien 2/2, as did minimum O_2 levels. The average O_2 desaturation decreased minimally under estradiol and increased minimally under placebo, with a significant difference between the different trends.

The snoring index improved significantly under Climodien 2/2 compared with the value after 2 months of Climodien 2/3 (Table 18.6).

Table 18.5 Respiratory variables in insomniac postmenopausal syndrome patients before and after 2 months of Climodien A (2 mg estradiol valerate (EV) + 3 mg dienogest (DNG)) or 2 mg EV alone or placebo as well as after subsequent 2-month therapy with Climodien A* (2 mg EV + 2 mg DNG)

Variable	Night	Climodien A ($N=16$)	Estradiol B ($N=17$)	Placebo C ($N=16$)	Intergroup difference $*p<0.05$; $**p<0.01$; U-test
Apneas total #	Pre	15 ± 25	20 ± 41	16 ± 36	
	2MoDRUG	8 ± 12	9 ± 13	8 ± 8	
	+2MoA*	10 ± 16	9 ± 13	5 ± 6	
Apneas #/hours of sleep	Pre	2 ± 4	3 ± 7	2 ± 6	
	2MoDRUG	1 ± 2[a]	1 ± 2	1 ± 1	2MoDRUG-Pre: A:C*
	+2MoA*	2 ± 2	1 ± 2	1 ± 1	
Apneas + hypopneas total #	Pre	51 ± 58	38 ± 71	33 ± 75	
	2MoDRUG	16 ± 21[a]	23 ± 43	32 ± 40	2MoDRUG-Pre: A:C*
	+2MoA*	46 ± 87	24 ± 34	16 ± 17	
Apneas + hypopneas #/hours of sleep	Pre	8 ± 9	6 ± 12	5 ± 12	
	2MoDRUG	3 ± 3[a]	4 ± 7	5 ± 6	2MoDRUG-Pre: A:C*
	+2MoA*	7 ± 12	4 ± 6	3 ± 3	
Desaturations total #	Pre	29 ± 34	40 ± 50	64 ± 97	
	2MoDRUG	35 ± 58	25 ± 40	30 ± 56	
	+2MoA*	26 ± 47	17 ± 35	23 ± 38	
Desaturations #/hours of sleep	Pre	5 ± 6	7 ± 9	10 ± 15	
	2MoDRUG	6 ± 9	4 ± 6	5 ± 8	
	+2MoA*	4 ± 8	3 ± 6	4 ± 6	
Minimum O_2	Pre	88 ± 4	73 ± 18	85 ± 8	Pre: A:B**;B:C*
	2MoDRUG	87 ± 7	77 ± 20	86 ± 10	
	+2MoA*	88 ± 5	86 ± 8	89 ± 6	
Average low O_2	Pre	91 ± 1	90 ± 2	90 ± 3	
	2MoDRUG	91 ± 5	89 ± 5	91 ± 2	2MoDRUG-Pre: B:C*
	+2MoA*	91 ± 2	88 ± 8	91 ± 3	

2MoDRUG double-blind phase (active drug arm); *2MoA** open-label phase
[a]$p<0.05$, [b]$p<0.01$ change vs. pre, Wilcoxon
[c]$p<0.05$, [d]$p<0.01$ change vs. 2MoDRUG, Wilcoxon
[e]$p<0.05$, [f]$p<0.01$ difference (second to first period), Wilcoxon

HRT and Periodic Leg Movements

The number of periodic leg movements per hour of total time in bed showed a nonsignificant decrease after Climodien 3/2 and estradiol, but a nonsignificant increase after placebo (Table 18.6). The changes remained nonsignificant in the open-label phase.

Table 18.6 Snoring and periodic leg movements in insomniac postmenopausal syndrome patients before and after 2 months of Climodien A (2 mg estradiol valerate (EV) + 3 mg dienogest (DNG)) or 2 mg EV alone or placebo as well as after subsequent 2-month therapy with Climodien A* (2 mg EV + 2 mg DNG)

Variable	Night	Climodien A ($N=16$)	Estradiol B ($N=17$)	Placebo C ($N=16$)	Intergroup difference *$p<0.05$; **$p<0.01$; U-test
Snoring events total #	Pre	340 ± 369	113 ± 203	321 ± 312	Pre: A:B*; B:C*
	2MoDRUG	371 ± 360	200 ± 293	296 ± 403	
	+2MoA*	226 ± 260[c]	225 ± 212	223 ± 217	
Snoring events #/ hours of sleep	Pre	59 ± 65	20 ± 40	50 ± 48	Pre: A:B*; B:C*
	2MoDRUG	59 ± 56	31 ± 48	45 ± 60	
	+2MoA*	35 ± 40[c]	34 ± 33	37 ± 38	
Periodic leg movements #/hours of time in bed	Pre	21 ± 21	18 ± 18	13 ± 15	
	2MoDRUG	14 ± 8	15 ± 11	19 ± 25	
	+2MoA*	15 ± 17	14 ± 12	23 ± 36	

2MoDRUG double-blind phase (active drug arm); *2MoA** open-label phase
[a]$p<0.05$, [b]$p<0.01$ change vs. pre, Wilcoxon
[c]$p<0.05$, [d]$p<0.01$ change vs. 2 MoDRUG, Wilcoxon
[e]$p<0.05$, [f]$p<0.01$ difference (second to first period), Wilcoxon

HRT and Subjective Sleep and Awakening Quality

Subjective sleep quality, evaluated by SSA, improved significantly under Climodien 3/2 and estradiol, but not under placebo (Table 18.7). The changes induced by the active drugs were significantly suggests to those under placebo. In the open-label phase with Climodien 2/2, sleep quality improved further in the Climodien 3/2 group (significantly) ($p<0.05$, Wilcoxon), and estradiol group (nonsignificantly), whereas there was a further nonsignificant deterioration in the placebo group.

Awakening quality improved nonsignificantly under Climodien 3/2 and Climodien 2/2, whereas no changes occurred in the estradiol or placebo groups. Similar results were obtained for somatic complaints.

Thus, the total SSA score improved most pronouncedly with Climodien 3/2, followed by estradiol, while there was a slight deterioration with placebo, although the findings did not reach the level of statistical significance. The same results were obtained for the open-label phase.

The Pittsburgh Sleep Quality Index improved significantly with all three compounds compared with baseline. In the open-label phase, Climodien 2/2 improved the index significantly compared with the preceding placebo treatment.

Well-being in the evening and morning did not yield any significant results. The same was true for morning drive, mood, affectivity, and drowsiness (Table 18.8).

Table 18.7 Subjective sleep and awakening quality (SSA) in insomniac postmenopausal syndrome patients before and after 2 months of Climodien A (2 mg estradiol valerate (EV) + 3 mg dienogest (DNG)) or 2 mg EV alone or placebo as well as after subsequent 2-month therapy with Climodien A* (2 mg EV + 2 mg DNG)

Variable	Night	Climodien A ($N=16$)	Estradiol B ($N=17$)	Placebo C ($N=16$)	Intergroup difference *$p<0.05$; **$p<0.01$; U-test
Sleep quality (SSA-1) ↓	Pre	17 ± 4	17 ± 5	13 ± 3	Pre: A:C**; B:C*
	2MoDRUG	14 ± 5[a]	14 ± 5[a]	14 ± 5	2MoDRUG-Pre: A:C**; B:C*
	+2MoA*	13 ± 5[c]	13 ± 3	15 ± 4	
Awakening quality (SSA-2) ↓	Pre	16 ± 5	15 ± 5	15 ± 4	
	2MoDRUG	15 ± 5	15 ± 6	15 ± 4	
	+2MoA*	13 ± 3	15 ± 4	15 ± 3	
Somatic complaints (SSA-3) ↓	Pre	7 ± 2	7 ± 2	6 ± 1	
	2MoDRUG	7 ± 2	7 ± 2	6 ± 2	
	+2MoA*	6 ± 1	7 ± 2	6 ± 1	
Total score (SSA) ↓	Pre	40 ± 8	39 ± 11	34 ± 7	Pre: A:C*
	2MoDRUG	35 ± 11	36 ± 11	35 ± 9	
	+2MoA*	31 ± 7	34 ± 6	35 ± 6	
Pittsburgh sleep quality index (PSQI)	Pre	11 ± 4	13 ± 3	11 ± 4	
	2MoDRUG	8 ± 4[a]	10 ± 4[b]	9 ± 3[a]	
	+2MoA*	8 ± 2	10 ± 4[e]	7 ± 3[c]	

↓↑ direction of improvement
2MoDRUG double-blind phase (active drug arm); *2MoA** open-label phase
[a]$p<0.05$, [b]$p<0.01$ change vs. pre, Wilcoxon
[c]$p<0.05$, [d]$p<0.01$ change vs. 2MoDRUG, Wilcoxon
[e]$p<0.05$, [f]$p<0.01$ change difference (second to first period), Wilcoxon

HRT and Objective Awakening Quality (Psychometry)

Intellectual and Mnestic (Memory-Related) Performance

Attention did not improve significantly with Climodien 3/2, estradiol, or placebo (Table 18.9).

In the open-label phase, it improved in the former Climodien 3/2 and estradiol groups ($p<0.05$), but remained unchanged in the placebo group. Concentration and attention variability showed no significant improvements.

Numerical memory improved significantly under Climodien 2/3 compared with baseline ($p<0.05$), whereas there were no significant changes in the estradiol or placebo groups (Table 18.9). Under Climodien 2/2, mnestic performance did not decline in the former Climodien group, whereas it improved in the estradiol group and remained unchanged in the placebo group.

Table 18.8 Morning/evening thymopsychic findings in insomniac postmenopausal syndrome patients before and after 2 months of Climodien A (2 mg estradiol valerate (EV) + 3 mg dienogest (DNG)) or 2 mg EV alone or placebo as well as after subsequent 2-month therapy with Climodien A* (2 mg EV + 2 mg DNG)

Variable	Night	Climodien A ($N=16$)	Estradiol B ($N=17$)	Placebo C ($N=16$)	Intergroup difference *$p<0.05$; **$p<0.01$; U-test
Well-being evening ↓	Pre	20 ± 14	14 ± 12	19 ± 11	
	2MoDRUG	15 ± 10	8 ± 7	17 ± 12	
	+2MoA*	12 ± 10	8 ± 9	12 ± 10	
Well-being morning ↓	Pre	16 ± 10	12 ± 10	16 ± 12	
	2MoDRUG	17 ± 15	10 ± 10	17 ± 14	
	+2MoA*	9 ± 8	9 ± 10	13 ± 9	
Drive (ASES-1) morning ↓	Pre	39 ± 23	30 ± 24	50 ± 25	Pre: B:C*
	2MoDRUG	44 ± 35	32 ± 23	53 ± 31	
	+2MoA*	36 ± 21	39 ± 32	41 ± 24	
Mood (ASES-2) morning ↑	Pre	65 ± 19	76 ± 20	57 ± 28	Pre: B:C*
	2MoDRUG	67 ± 24	76 ± 12	56 ± 29	
	+2MoA*	71 ± 24	78 ± 17	64 ± 20	
Affectivity (ASES-3) morning ↑	Pre	69 ± 22	79 ± 16	60 ± 28	
	2MoDRUG	64 ± 34	72 ± 20	57 ± 29	
	+2MoA*	73 ± 22	79 ± 19	65 ± 16	
Drowsiness (ASES-4) morning ↓	Pre	45 ± 28	38 ± 33	39 ± 27	
	2MoDRUG	43 ± 37	39 ± 30	52 ± 27	
	+2MoA*	45 ± 31	45 ± 36	45 ± 26	

↓↑ direction of improvement
2MoDRUG double-blind phase (active drug arm); *2MoA** open-label phase
[a]$p<0.05$, [d]$p<0.01$ change vs. pre, Wilcoxon
[c]$p<0.05$, [d]$p<0.01$ change vs. 2MoDRUG, Wilcoxon
[e]$p<0.05$, [f]$p<0.01$ difference (second to first period), Wilcoxon

Psychomotor Performance

Fine motor activity of the right hand improved under Climodien 2/3 and estradiol, with the changes after the latter reaching the level of statistical significance ($p<0.01$, Wilcoxon test); under placebo there were no changes (Table 18.10). Under open-label treatment with Climodien 2/2, there was a further improvement in the former Climodien and placebo groups, whereas a nonsignificant decrease occurred in the estradiol group.

Fine motor activity of the left hand showed similar findings, which did not reach the level of statistical significance. Reaction time and reaction time variability did not show any significant changes. However, in regard to the quality of reaction time performance measured by errors of commission, there was a significant improvement

Table 18.9 Morning intellectual and mnestic performance in insomniac postmenopausal syndrome patients before and after 2 months of Climodien A (2 mg estradiol valerate (EV) + 3 mg dienogest (DNG)) or 2 mg EV alone or placebo as well as after subsequent 2-month therapy with Climodien A* (2 mg EV + 2 mg DNG)

Variable	Night	Climodien A ($N=16$)	Estradiol B ($N=17$)	Placebo C ($N=16$)
Attention (AD/total score) ↑	Pre	538 ± 124	492 ± 110	537 ± 122
	2MoDRUG	549 ± 110	511 ± 85	566 ± 108
	+2MoA*	558 ± 105	535 ± 95	564 ± 132[e]
Concentration (AD/errors (%)) ↓	Pre	4 ± 3	4 ± 3	6 ± 5
	2MoDRUG	4 ± 3	4 ± 5	5 ± 4
	+2MoA*	4 ± 3	4 ± 4	5 ± 3
Attention variability (AD/SV) ↓	Pre	13 ± 3	16 ± 7	14 ± 7
	2MoDRUG	14 ± 3	15 ± 6	17 ± 8
	+2MoA*	15 ± 3	13 ± 2	13 ± 5
Numerical memory (number) ↑	Pre	5 ± 2	5 ± 2	4 ± 1
	2MoDRUG	6 ± 2[a]	4 ± 1	5 ± 2
	+2MoA*	5 ± 2	5 ± 2	5 ± 2

↓↑ direction of improvement
AD; Alphabetical Cancellation Test; *SV* attention variability; *2MoDRUG* double-blind phase (active drug arm); *2MoA** open-label phase
[a]$p<0.05$, [b]$p<0.01$ change vs. pre, Wilcoxon
[c]$p<0.05$, [d]$p<0.01$ change vs. 2MoDRUG, Wilcoxon
[e]$p<0.05$, [f]$p<0.01$ difference (second to first period), Wilcoxon

after 2 months of Climodien 2/3 and estradiol, as well as after placebo ($p<0.01$), with no further significant changes during the open-label phase. Errors of omission did not yield any significant results.

Psychophysiological Measures

Critical flicker frequency did not change significantly. Muscular strength of the right fingers improved significantly only upon estradiol valerate treatment ($p<0.01$); muscular strength of the left fingers did not change significantly. Muscular strength of the right hand decreased significantly ($p<0.01$) after 2 months of Climodien 2/3 (which was also significantly different from placebo; $p<0.05$), but increased significantly ($p<0.05$) after 2 months of Climodien 2/2 (also in comparison with placebo; $p<0.05$). The positive effects induced by Climodien 2/2 differed significantly ($p<0.05$) from those observed after Climodien 2/3. Muscular strength of the left hand decreased slightly under Climodien 2/3, whereas it increased after estradiol valerate and placebo. The differences between the drugs reached statistical significance ($p<0.05$).

Systolic and diastolic blood pressure and pulse rate did not change significantly. The morning pulse rate increased after 2 months of therapy with Climodien 2/2 in comparison with estradiol valerate ($p<0.05$).

Table 18.10 Morning psychomotor performance in insomniac postmenopausal syndrome patients before and after 2 months of Climodien A (2 mg estradiol valerate (EV) + 3 mg dienogest (DNG)) or 2 mg EV alone or placebo as well as after subsequent 2-month therapy with Climodien A* (2 mg EV + 2 mg DNG)

Variable	Night	Climodien A ($N=16$)	Estradiol B ($N=16$)	Placebo C ($N=16$)
Fine motor activity (right) ↑	Pre	36 ± 10	32 ± 8	34 ± 8
	2MoDRUG	37 ± 9	35 ± 8[b]	34 ± 10
	+2MoA*	42 ± 10	34 ± 10	36 ± 9
Fine motor activity (left) ↑	Pre	27 ± 8	26 ± 7	26 ± 7
	2MoDRUG	30 ± 11	25 ± 7	27 ± 9
	+2MoA*	33 ± 11	27 ± 8	30 ± 9
Fine motor activity (right + left) ↑	Pre	62 ± 17	58 ± 14	60 ± 14
	2MoDRUG	68 ± 20	61 ± 14	61 ± 18
	+2MoA*	75 ± 20	61 ± 17	67 ± 18
Reaction time (RT) (ms) ↓	Pre	617 ± 104	608 ± 96	624 ± 87
	2MoDRUG	623 ± 82	620 ± 100	654 ± 86
	+2MoA*	637 ± 77	594 ± 75	614 ± 79
RT variability (ms) ↓	Pre	134 ± 32	142 ± 40	120 ± 37
	2MoDRUG	102 ± 30	120 ± 31	124 ± 29
	+2MoA*	98 ± 32	106 ± 36	115 ± 28
RT errors of commission	Pre	6 ± 4	5 ± 5	6 ± 5
	2MoDRUG	3 ± 3[b]	4 ± 2[b]	3 ± 2[b]
	+2MoA*	2 ± 2	2 ± 2	4 ± 7
RT errors of omission ↓	Pre	2 ± 3	2 ± 3	1 ± 1
	2MoDRUG	1 ± 1	1 ± 1	1 ± 1
	+2MoA*	1 ± 1	0 ± 1	0 ± 1

↓↑ direction of improvement
2MoDRUG double-blind phase (active drug arm); *2MoA** open-label phase
[a]$p<0.05$, [b]$p<0.01$ change vs. Pre, Wilcoxon
[c]$p<0.05$, [d]$p<0.01$ change vs. 2MoDRUG, Wilcoxon
[e]$p<0.05$, [f]$p<0.01$ difference (second to first period), Wilcoxon

Discussion

Our polysomnographic investigations concerning the differences between patients with insomnia resulting from a postmenopausal syndrome and normal controls demonstrated a significant deterioration of sleep initiation and maintenance as well as increased stage N1 and decreased stage N2 in patients, whereas N3 and REM stages showed no differences compared with controls. These findings are in agreement with the literature on sleep disorders in the menopause [17, 42–44]. Some authors interpret the changes in terms of an aging effect, because sleep disturbances increase with increasing age in both sexes [45–47]. Indeed, sleep architecture changes significantly with the aging process: total sleep time, N3 (S3+S4 classified according to Rechtschaffen and Kales [48]), and REM stages decrease, whereas no culral wakefulness and N1 increase [49, 50]. Thus, our sleep findings in postmenopausal patients

do not merely reflect an enhanced aging process; they also differ from those obtained in other sleep disorders. Insomnia related to depression, for instance, shows shortened REM latency and increased REM density in addition to reduced N3 [51–54]; insomnia resulting from generalized anxiety disorder and panic disorder [55–57] exhibits predominantly decreased N2 and increased N3, whereas organic insomnia (e.g., consequent to sleep apnea [58] and RLS [59, 60] or periodic limb movement disorder (PLMD) [61]) shows different sleep architecture patterns.

Our double-blind, placebo-controlled sleep laboratory investigations with Climodien 2/3 (a new combination of estradiol valerate 2 mg + the progestogen dienogest 3 mg) vs. estradiol valerate 2 mg alone in patients with insomnia related to a postmenopausal syndrome showed a moderate improvement in the primary efficacy variable wakefulness during the total sleep period after 2-month treatment with both Climodien 2/3 and estradiol compared with baseline, whereas for placebo only minimal changes were observed. Although our findings were in agreement with those obtained by Thompson and Oswald [26] concerning the beneficial effect of estrogen therapy (piperazine estrone sulfate 1.5 mg twice a day given orally over 8 weeks) in perimenopausal women, neither the changes compared with pre-drug treatment nor the differences between the changes in the three groups reached the level of statistical significance. In the subsequent open-label phase, patients on Climodien 2/2 (estradiol valerate 2 mg + dienogest 2 mg) improved further, whereas those who had been in the estradiol and placebo groups showed an increase in wakefulness. However, our findings did not reach the level of statistical significance. Similarly, Purdie et al. [30] reported a nonsignificant reduction in vasomotor symptoms associated with awakening with the use of 0.625 mg of conjugated equine estrogen with progestogen morgestral 0.15, taken by postmenopausal women for 12 days per 28-day cycle. Recently, estrogen administered by skin patch was found to reduce time awake during the just two sleep cycles to 12 ± 5 in postmenopausal women vs. 20 ± 6 min in nontreated women [29].

Interesting and partly significant findings were obtained regarding secondary efficacy variables. Concerning sleep initiation, latency to N1 sleep showed a nonsignificant shortening after all three compounds. Schiff et al. [27] also found a significantly shorter sleep-onset time with estradiol than with placebo. In the open-label phase, Climodien 2/2 induced a significant lengthening in patients who had before been treated with placebo or with estradiol. In regard to sleep maintenance, an increase in the total sleep period was induced by Climodien 2/3, which differed significantly from the decrease under the subsequent Climodien 2/2 treatment. Moreover, as compared with placebo treatment, Climodien 2/2 significantly decreased the total sleep period. Thus, the dienogest dosage seems to play an important role, with 3 mg showing more sleep-promoting properties than 2 mg. Investigating differential effects of two regimens of estrogen–progesterone replacement therapy on the nocturnal sleep of postmenopausal women, Montplaisir et al. [62] found increased sleep efficiency after 6-month therapy with oral micronized progesterone, but not with medroxyprogesterone acetate.

Concerning sleep architecture, we observed no changes with Climodien 2/2 compared with the preceding 2 months of estradiol therapy. This was partially in

agreement with the results of other studies that reported no change in sleep architecture with HRT [30, 63]. Investigating HRT with 0.625 mg conjugated equine estrogens in combination with 0.15 mg cyclic norgestrel taken for 12 days per 28-day cycle, Purdie et al. [30] did not find improved polysomnographic parameters of sleep quality. On the other hand, Thompson and Oswald [26] observed a reduction in wakefulness, a decrease in the number of awakenings, and an increase in REM sleep during 8 weeks of estrogen treatment. However, judging the severity of insomnia by wakefulness, it seems that our patients suffered from more severe insomnia, with a wakefulness of almost 1 h and 9–10 awakenings compared with a wakefulness during the total sleep period of 25–40 min and 4–5 awakenings in Thompson and Oswald's patients. On the other hand, the latter were more symptomatic than the 33 healthy postmenopausal women of Purdie's group, who showed a wakefulness of only 10–20 min. Thus, the data suggest that a moderately ill group may benefit most from HRT, while in more severe cases psychopharmacological agents should be used because, although hormones are subtly sleep-promoting, they are not sleeping pills.

The most interesting findings with Climodien occurred in respiratory variables. The apnea index and the AHI showed a significant improvement under Climodien compared with baseline, although the indices had a priori been within normal limits, as required by the protocol. It is noteworthy that, in improving respiratory variables during sleep, Climodien was significantly superior to placebo. This confirms the previous findings of Pickett et al. [64], who described a reduced number of apneas and hypopneas in healthy postmenopausal women after 7 days of combined progestogen (medroxyprogesterone acetate 20 mg three times a day) and estrogen (conjugated equine estrogens, Premarin, 1.25 mg twice a day). As progesterone is decreased in postmenopausal women and is known to be a ventilatory stimulant [65], it has been considered the protective substance in SDB. However, Block et al. [66] reported that in contrast to natural progesterone, a synthetic progestogen administered to postmenopausal women reduced the duration of hypopneas, but not the number of episodes of SDB. Several authors reported that progestogen had limited effects in men with SDB [67–71]. Thus, progestogen alone obviously cannot develop a protective effect in the absence of estrogen, because estrogen is required to induce progesterone receptors [72]. Brodeur et al. [73] pointed out that the effects of progesterone might be enhanced by the presence of estrogen.

In a pilot study to test the efficacy of estrogen in sleep apnea syndrome, Keefe et al. [74] noticed an improvement within 1 month of initiating therapy with 17β-estradiol alone or in combination with medroxyprogesterone acetate. The respiratory distress index decreased by 25%; the addition of progestogen reduced the sleep apnea syndrome to 50%.

In our study, snoring was reduced by Climodien 2/2 as compared with Climodien 2/3, which reveals that in this regard 2 mg of dienogest are more effective than 3 mg. Further studies should be conducted to determine whether postmenopausal women with snoring and/or sleep-related breathing disorders such as obstructive snoring and obstructive sleep apnea could benefit from Climodien. As the results of our study are consistent with the view that female hormones provide protection

against SDB, non-gender-specific variants of female hormones for men suffering from sleep-related breathing disorders may be developed. Recent epidemiological studies in Austria showed that 37% of men and 19% of women snored, whereas 10% of men and 7% of women reported apneas [75]. In both males and females there was a substantial age-related increase in snoring and apneas: 54% of men and 34% of women over the age of 50 years snored, whereas 15% of men and 12% of women showed apneas. Snoring and sleep-related breathing disorders lead to abnormalities in sleep architecture and changes in brain function [58, 76, 77]. Moreover, nocturnal respiratory and arousal events are correlated with daytime vigilance decrements [58]. Apneas are associated with an increase in morbidity related to cardiovascular and cerebrovascular diseases [78], changes of cerebral hemodynamics [79], and neuropsychological dysfunction [80, 81]. In a recent study on the prevalence of SDB, Bixler et al. [82] pointed out that the menopause is a significant risk factor for sleep apnea in women and that hormone replacement appears to be associated with a reduced risk. On the other hand, concerning the association of hypertension and sleep-related breathing disorders, neither sex nor the menopause changed this relationship [83]. In view of the relative paucity of data concerning periodic leg movements and drugs, it is noteworthy that, in contrast to placebo, both Climodien and estradiol tended to attenuate periodic leg movements.

Subjective sleep quality, evaluated by means of the SSA, demonstrated a significant improvement after Climodien and estradiol compared with baseline, with the drug-induced changes being significantly different from the minimal alterations induced by placebo. Thus, the daily ratings of subjective sleep quality seem to be superior to a global rating over a longer period of time; in contrast to the SSA, the Pittsburgh Sleep Quality Index showed no differences between HRT and placebo. Our SSA ratings, performed daily, confirm previous clinical observations of a beneficial influence of estrogen therapy on sleep in postmenopausal women [84]. Erlik et al. [28] reported that estrogen induced a significant reduction in both hot flushes and waking episodes, whereas Crown and Crisp [85] found that only sleep-onset time was sensitive to HRT. In contrast, Purdie et al. [30] found no changes in objective or subjective parameters of sleep quality in healthy postmenopausal women during HRT, whereas psychological well-being showed a significant improvement (HRT: 0.625 mg conjugated equine estrogens with 0.15 mg cyclic norgestrel taken for 12 days per 28-day cycle over a study period of 12 weeks). In a 1-year, seven-center trial, 1-month treatment with HRT was found to have a long-term beneficial effect on sleep as assessed by the Sleep Dysfunction Scale [86].

Concerning awakening quality, somatic complaints, and thymopsychic variables in the morning, no significant findings were obtained. Thompson and Oswald's group [26] did not observe any differences compared with placebo in regard to mood, whereas the healthy postmenopausal women in Purdie et al.'s study [30] showed a significant improvement in free-floating anxiety, somatic anxiety, and depression compared with placebo-treated controls.

Concerning noopsychic variables, numerical memory improved significantly after Climodien compared with pretreatment, whereas after estradiol fine motor activity increased significantly. Errors of commission in the reaction time task

improved with all three compounds, which may have been due to a training effect. The observed improvement in numerical memory under Climodien is obviously a result of the increased availability of cognitive information-processing resources, objectified by the P300 amplitude. To our knowledge, our data on noopsychic performance after HRT are the first obtained in the morning after all-night sleep recordings. They are also in agreement with the improvement in vigilance, measured by EEG mapping [87], cognition, measured by event-related potentials [88], and mental performance, evaluated during mid-morning hours [89].

The lack of significant findings in psychophysiological measures reflects the excellent tolerability of all compounds given.

Conclusion

The estrogen–progestogen combination containing estradiol valerate and dienogest (Climodien, Lafamme®, Bayer Schering Pharma, Berlin, Germany) significantly improved subjective sleep quality and sleep-related breathing disorders, but had only a slight effect on objective sleep quality and subjective thymopsychic variables. However, the differences between untreated patients and normal controls at baseline were slight, but statistically significant. It may be speculated that the greater improvement in subjective compared to objective sleep variables may be the result of a halo effect based on an improvement of the postmenopausal syndrome itself, including vegetative disturbances as well as thymopsychic alterations. Psychometric tests revealed that both an estrogen–progestogen combination and estrogen alone induced a significant improvement in somatic complaints and trait anxiety, whereas state anxiety was more pronouncedly reduced by the combination drug than by estrogen alone [89]. Vigilance [53] and cognition [88] also produced a more pronounced improvement under the combination drug than under estrogen alone, although both preparations were superior to placebo. Thus, the addition of the progestogen dienogest to estrogen did not attenuate the effect of the latter, but augmented it, which was also seen for some variables of the present study.

The daytime effects of both HRT preparations seem to be superior to the nighttime effects, which is not surprising, as we have shown in circadian rhythm studies that estradiol, luteinizing hormone, and FSH blood levels are higher during the day than at night [90, 91].

Concerning noopsychic performance, numerical memory was significantly improved, whereas fine motor activity was ameliorated with estradiol valerate. Improvements in noopsychic performance were found to have their neurophysiological correlate in a shortening of latency and an augmentation of amplitudes of the cognitive event-related potentials [88]. Finally, the mild improvement in sleep with HRT was complemented by a marked vigilance improvement during the day, objectified by computer-assisted EEG-mapping techniques [87]. Vigilance improvement is in turn a sine qua non for the aforementioned improvement in cognition and psychometric performance.

In conclusion, the use of HRT may be helpful in the treatment of insomnia during menopause, provided that the risk-benefit ratio is carefully evaluated [16].

Of course also during the menopause, the targeted treatment of individual sleep disorders, such as sleep-related breathing disorders or nocturnal movement disorders, as well as the therapy of nonorganic insomnia related to different mental disorders in the sense of a key-lock principle, is of essential importance [92]. Moreover, as in all chronic sleep disorders, sleep hygiene and sleep education (e.g., cognitive behavioral therapy for insomnia = CBT-I) also play an important role [93].

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Chapter 19
Practical Approach for the Diagnosis and Management of Insomnia During Menopausal Transition

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Introduction

Sleep problems are one of the key symptoms of menopausal transition. Fifty to eighty percent of peri- and postmenopausal women report to suffer from them [1]. Insomnia diagnosis requires perceived difficulties in initiating or maintaining sleep or nonrestorative sleep despite adequate opportunity for sleep. Patient must also have daytime functional impairments resulting from nocturnal sleep disturbance [2]. Possible causes of insomnia in midlife women consist of four major categories: (1) menopausal insomnia (often related to climacteric vasomotor symptoms); (2) primary (psychophysiologic) insomnia; (3) secondary insomnia due to primary sleep disorders, mental or medical disorders, or aging; and (4) insomnia induced by behavioral, environmental, or psychosocial factors (Fig. 19.1).

The subset of women with vasomotor symptoms has more sleep complaints and higher risk of insomnia and depression. Sleep misperception is common: the subjectively experienced sleep quality may be poor even when the objectively measured sleep is within reference range [3, 4]. Insomnia at menopause is often

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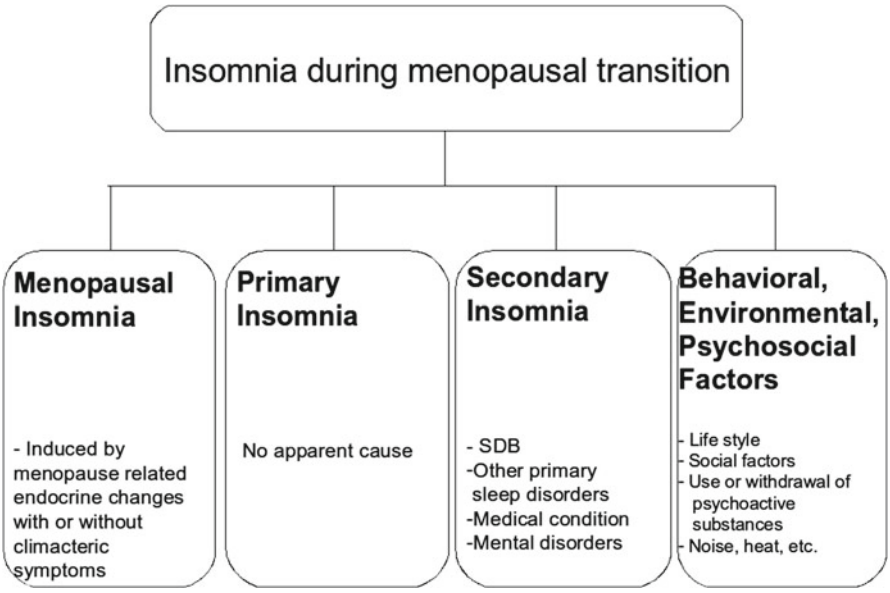

Fig. 19.1 Possible causes of menopausal insomnia. *SDB* sleep-disordered breathing

multifactorial. Sleep-disordered breathing (SDB) increases markedly after menopause due to weight gain and hormonal changes [5, 6]. Since SDB is generally considered as a condition of middle-aged obese men with excessive sleepiness, it is under-recognized in peri- or postmenopausal women complaining of insomnia. Sleep complaints should not be readily associated with vasomotor symptoms or depression without considering SDB. Menopausal sleep disruption can aggravate other preexisting sleep disorders including the restless legs syndrome (RLS) or circadian disorders. Fibromyalgia (FM) has gender, age, and probably hormonal associations [7]. Sleep complaints with associated objective findings in sleep recordings are common in FM. In pre- and postmenopausal women, mental health problems are a major predisposing factor for various sleep complaints [8]. Comorbidities without direct link with menopause as well as stressful life events coinciding with the menopausal transition should also be considered when exploring the etiology of insomnia in middle-aged women.

Menopausal insomnia is still underdiagnosed or misdiagnosed. Proper diagnosis is a prerequisite for proper treatment. The details of the history (Table 19.1) obtained at the interview with the patient and, if possible, with a family member should be supplemented by a physical examination (Table 19.2). The exact nature of the symptoms and the sequence of their appearance should be recorded. Details of the onset of complaints and any progression should be elicited. Sleep diaries are of value in patients with insomnia. These are usually completed for 2 weeks. The patient should record all episodes of sleep during day or night and

Table 19.1 Issues to be covered when taking a history of a patient with menopausal insomnia

Sleep
Duration and type of insomnia symptoms; what happened when the symptoms appeared
Sleep duration during work days and leisure days
Sleep schedule
SDB symptoms
RLS symptoms
Symptoms of other primary sleep disorders
Family history of sleep disorders
Other issues interfering with sleep (noise, pets, children, bed partner)
The attitudes of the patient to insomnia
Vasomotor symptoms
Hot flashes
Night sweats (if sweating only during night, consider SDB; menopausal sweating usually occurs also during the daytime)
Behavioral, environmental, and psychosocial factors
Working hours, shift-work, crossing time zones frequently, profession
Family, pets
Stress
Cigarette smoking, alcohol and caffeine consumption, recreational drugs
Comorbidities and their medication
Weight changes
Medical and psychiatric illnesses
Nocturnal pain, breathing problems, nocturia
Medication affecting sleep, withdrawal of drugs

Table 19.2 Physical examination in a patient with menopausal insomnia

General
Features of depression, anxiety, other mental disorders
Weight, abdominal obesity, enlarged collar size (risk factor especially for SDB)
Blood pressure (hypertension is a risk factor for SDB)
Craniofacial features
Nose (nasal stuffiness predisposing to SDB)
Pharynx (enlarged tongue and tonsils and pharyngeal obstruction suggesting SDB)
Retro- or micrognathia (predisposing to SDB)
Gynecological, neurological, or cardiorespiratory system
If the clinical picture suggests that these systems may be implicated in the sleep disorder

report any other relevant events such as consumption of caffeinated drinks or alcohol, cigarette smoking, meals, and exercise. Self-assessment scales can be used to supplement history taking. An overnight sleep study in a sleep laboratory or at home may be needed to confirm or exclude SDB as a cause of insomnia. Effective behavioral, pharmacological, and other treatment options (Fig. 19.2) are available to improve quality of life and possibly prevent comorbid conditions.

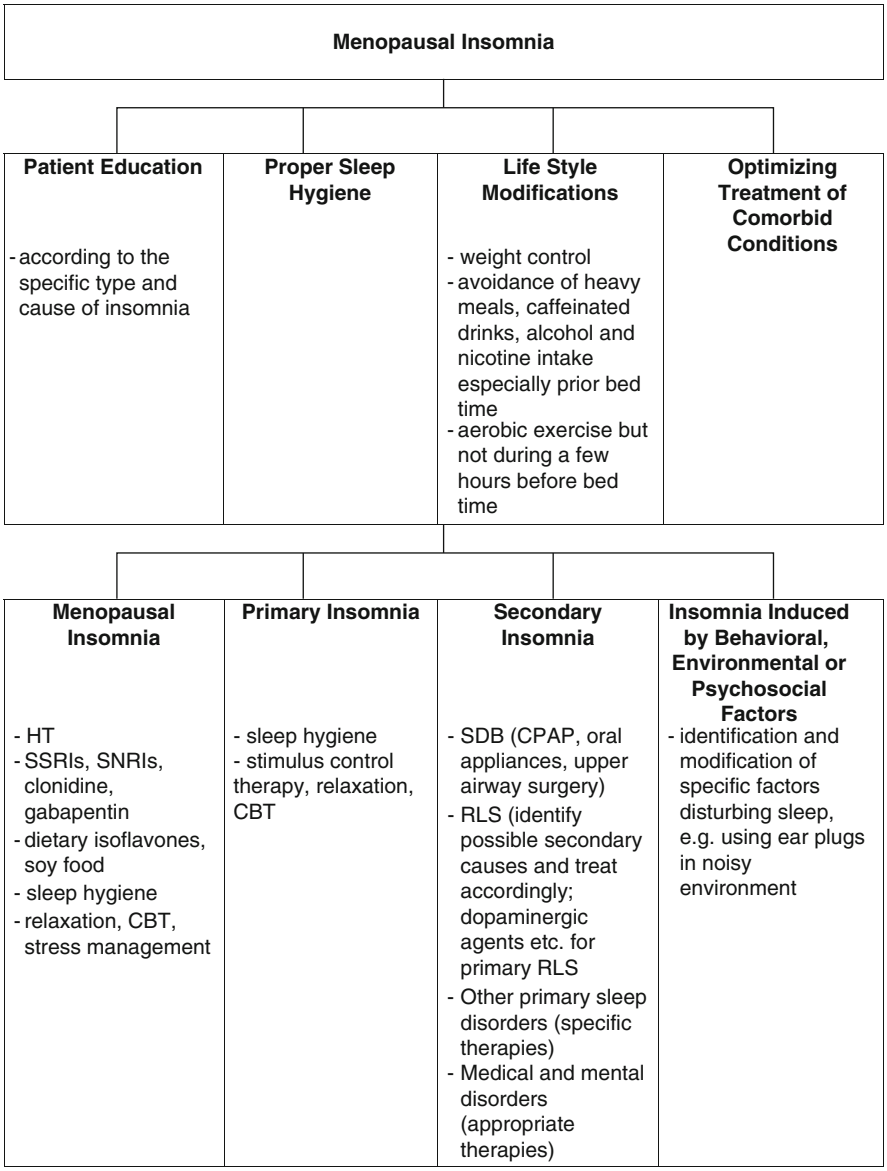

Fig. 19.2 Management of menopausal insomnia

Characteristics of the Climacterium

The menopause is the time point of cessation of menstrual cycles caused by reduced secretion of ovarian hormones estrogen and progesterone. The average age of menopause is 51–52 years with the range of 45–55 years [9]. Perimenopause is the period of time immediately before and after the menopause. The menopause can be diagnosed retrospectively after 12 months of permanent amenorrhea, and the succeeding time is called postmenopause [10]. The climacterium covers the perimenopause and the part of postmenopausal period, indicating the course of time when a woman passes through a transition from the reproductive stage to postmenopausal years, the era when climacteric symptoms occur.

During climacterium, women suffer from several symptoms with wide variation in severity. Vasomotor instability and hot flashes and sweating are the most typical symptoms with the feature of thermoregulatory events: peripheral vasodilatation especially in the upper body and around the face and the chest is usually followed by sweating, causing evaporative cooling [11]. Using core temperature measurements, it has been shown that temperature threshold for sweating is lower and shivering threshold higher in vasomotorically symptomatic postmenopausal women compared to asymptomatic women [12, 13]. The symptoms are supposed to be mediated through the preoptic area of the anterior hypothalamus. It has been hypothesized that adrenalin concentrations in the hypothalamus decrease with declining estrogen production, enhancing release of noradrenaline and serotonin [12, 14–16]. In spite of these findings, there is a lack of comprehensive understanding of reasons for variability in symptom frequency and response. Approximately 75% of postmenopausal women and 40% of perimenopausal women experience vasomotor symptoms [17]. Similar to severity, the duration of symptoms alters among individuals. On average, the occurrence of vasomotor symptoms is 1–2 years, but about 25% of women report them for 5 years and 9% suffer from them practically the entire time after menopause [18, 19].

Climacteric women often report several additional symptoms, both physical and mental. However, apart from vasomotor symptoms, only vaginal dryness has consistently been associated with menopause. Indeed, vaginal dryness as well as nocturia and other urinary tract symptoms are estrogen dependent and clearly deteriorate after menopause, normally with some years' delay [20]. Of other common symptoms, palpitations may occur during the daytime and at night and are closely related to vasomotor symptoms as an additional mark of autonomic nervous system dysfunction [20]. Dizziness, deterioration in postural balance, headache, numbness, muscle and joint pain, dry eyes and mouth, and decreased skin elasticity also occur and are often related to menopause, although they do not correlate to the reduced estrogen levels [20]. Mental symptoms such as anxiety, depression, lack of concentration, memory impairment, or decline of libido occur, and these symptoms may even exceed the severity of vasomotor symptoms. Furthermore, sleep problems are common, arising either solely or more typically in relation to other climacteric symptoms [21]. After menopause, 50–80% of women report mental symptoms and sleep problems [17, 22].

Climacterium and Sleep

Clinicians acknowledge the increase of sleep problems at menopausal transition. Although the reasons for sleep problems are often complex, there is a strong support that menopause or menopause-related symptoms are linked with increasing sleep problems. Between ages 50 and 64, 25% of women report sleep problems, of which 15% categorize them as severe [23]. In a survey with 100 menopause clinic patients, nearly 80% suffered from insomnia and over 90% from fatigue. Awakening too early in the morning or intermittent sleep was the most typical complaints [24].

Sleep quality often decreases already during the perimenopausal period. Many studies have demonstrated the increase of sleep problems in the menopausal transition [3, 25–28]. Compared to premenopausal women, odds ratios for sleep problems in perimenopausal women have been found to be 1.3–1.5 [26, 27]. In postmenopausal women, odds ratios from 1.5 to even 3.4 have been reported [25, 26]. The Survey of Women's Health Across the Nation (SWAN) with over 12,600 women with multiethnic origin reported odds ratios for trouble sleeping of 1.2 for naturally postmenopausal, 1.6 for surgically postmenopausal, and 1.3 for perimenopausal compared to premenopausal women [27]. In the Wisconsin Sleep Cohort study with over 580 women, peri- and postmenopausal women were more dissatisfied with their sleep quality compared to premenopausal women [3]. Baker et al. found that perimenopausal women had more frequent and longer arousals resulting in less sleep compared to premenopausal women. Further, in perimenopausal women symptoms of poor mood were more prevalent and they were associated with sleep disturbances [28].

The clinical importance of sleep disturbances is more pronounced if they are associated with daytime sleepiness or impaired daytime performance. In a study with detailed insomnia and sleepiness questions, postmenopausal women (aged 59–71) had higher insomnia scores compared to either premenopausal (aged 45–51) or young women (aged 20–26) [29]. Furthermore, the scores of premenopausal women were higher than those in young women. However, no differences in sleepiness scores were found between the three groups [29]. In a study of over 1,100 women, menopause was associated with sleep problems such as difficulty initiating sleep and sleep fragmentation [30]. Furthermore, higher anxiety scores were related to all sleep problems except for early morning awakening and excessive daytime sleepiness. In a study with over 3,000 women, difficulty falling asleep and staying asleep increased through menopausal transition, but early morning awakening decreased from late perimenopause to postmenopause [31].

All studies, however, have not supported the menopause-related increase in sleep problems. In our own large cohort study with over 3,400 women, various sleep problem subtypes and daytime consequences were evaluated with a detailed questionnaire in five age groups between 41 and 55 years [8]. All kind of sleep problems were common in all age groups, and the older (and obviously postmenopausal) women did not report them more often than their younger (and obviously premenopausal) counterparts. On the contrary, the only difference between the five age groups was the higher frequency of morning tiredness in the youngest age group

(41–42 years) compared to the others [8]. The most important factor correlating with all subtypes of sleep complaints was preexisting mental health problem. In other words, although menopause certainly affects sleep quality and in many women is associated with sleep deterioration, the causes for sleep problems are often multifactorial, thus explaining their high frequency in midlife.

Climacterically symptomatic women often report sleep problems. Those with vasomotor symptoms typically have perspiration or palpitation after falling asleep, interfering with sleep continuity, or sweating causing frequent awakenings [17, 27, 32]. In clinical practice, one often witnesses that a climacteric woman with no previous sleep difficulties explains how she wakes up "soaking so that she has to change their nightdress or bed clothes" or that she frequently wakes up spontaneously or her sleep is terminated too early in the morning. Several studies have strengthened this relationship between self-reported climacteric symptoms and self-reported sleep problems [17, 27, 32, 33]. A study with over 5,000 women found a conclusive correlation between sleep problems and vasomotor symptoms [17]. In another study with 12,600 women (SWAN), an odds ratio for sleep problems in women with climacteric symptoms was 2.0 compared to asymptomatic women [27]. In a subsequent study of SWAN with over 3,000 women, compared to asymptomatic women odds ratios of various sleep problems in women with moderate vasomotor symptoms were 1.9 for trouble falling asleep, 1.7 for awakenings during the night, and 1.7 for waking up too early. Odds ratios for women with severe vasomotor symptoms were 5.3, 4.9, and 3.9, respectively [31]. Other studies have also shown both climacteric symptoms and mood symptoms to have a strong association with sleep problems [32, 34].

Despite these well-established clinical observations, the studies that utilize objective measurements have not found as robust an association between vascular changes and sleep disturbances. A study that measured skin conductance along with surveying for subjective vasomotor symptoms, sleep quality and duration, and psychological symptoms found a correlation between subjective hot flashes and sleep problems but neither was associated with objective hot flashes (by skin conductance) during sleep [35]. Data about the relationship between objectively measured sleep quality (polysomnography (PSG), actigraphy, or quantitative analysis of electroencephalogram (EEG)) and climacteric symptoms are even more incongruent. When relying on subjective sensations of vasomotor symptoms, more time in bed and longer rapid eye movement sleep (REM-sleep) latency [33] have been found in symptomatic women compared to asymptomatic women, although studies with no differences have also been published [3, 32, 36]. Few PSG studies have been carried out with objective measures of vasomotor symptoms (skin conductance or core body temperature). In a study by Freedman and colleagues, vasomotor symptoms caused nocturnal awakenings, increased sleep stage changes, and lowered sleep efficiency, but on the other hand symptomatic women had more Stage N3 (slow-wave sleep, SWS) than asymptomatic women [37]. Subsequently, in another study comparing symptomatic postmenopausal women with asymptomatic or premenopausal women, no association with symptoms and PSG findings

was shown after carefully controlling for confounding factors (like sleep disorders, physical and mental diseases, drug use, obesity, and smoking) [38], and, in a subsequent study, hot flashes reduced sleep quality, causing arousals and awakenings in the first half but not in the second half of the night [39].

Female Sex Steroids and Sleep

Female sex steroid receptors are found in various brain areas, like in the cerebral cortex, hippocampus, hypothalamus, amygdala, basal forebrain, midbrain raphe nuclei, pituitary gland, locus coruleus, and cerebellum [40–42], areas which participate also in sleep regulation [43]. In the brain, sex steroids, especially estrogen, increase blood circulation and therefore diminish oxidative stress. Estrogen also increases excitability of neurons and activation of intracellular signaling pathways, as well as modulation of proteins and protection against neuronal damage [40]. Sex steroids contribute to several neurotransmitter actions, for instance to cholinergic-, serotonergic-, dopaminergic-, and noradrenergic systems [44]. It probably involves glutamate-, gamma-amino-butyric acid (GABA)-, opiate-, and vasopressin-systems as well as insulin-like growth factor-1 (IGF-1), transforming growth factor-alpha (TGF-α), protein kinase activators, and various other neurotransmitters actions as well [45]. All these neurotransmitters are also important for sleep [43]. Therefore, the disturbance in their secretion in connection with menopausal changes in female sex steroid levels may contribute to sleep problems.

Although central nervous system (CNS)-related circadian hormones, like growth hormone (GH), prolactin (PRL), cortisol, or melatonin, are mainly age-dependent, menopause and reduced sex steroid levels may contribute to the alterations [45]. After menopause, diurnal GH and PRL levels decrease [46–49] whereas cortisol levels increase [50] or remain unaffected [49]. Unopposed estrogen therapy (ET) increases serum GH levels [51–53], but results on the effects with combined hormone therapy (HT) are inconsistent [47, 49, 54, 55]. ET alone or combined with progestogens has been found to elevate serum PRL [49, 56]. Studies on the effect of HT on cortisol levels are conflicting [49, 57, 58].

Estrogen and Sleep

Replacing low hormone levels with hormone therapy (HT) offers a practical tool to investigate whether sleep problems during menopause are hormone dependent or just coincide with menopausal period. HT, either unopposed estrogen (ET) [22, 59] or combined estrogen-progesterone therapy (EPT) [60, 61], has been shown to be an effective treatment for menopausal sleep problems. Controlled clinical trials have shown an improvement in subjective sleep quality during menopause by HT [17, 22, 59–66]. The results have been beneficial regardless of dose [22, 59, 62, 63],

administration route [59–62], or duration [22, 60, 62] of the treatment. Our own study, which distinguished the effect of estrogen on various subjective sleep problems, found an unquestionable advantage in sleep quality [59]. The trial was a prospective, randomized, placebo-controlled, cross-over study with both vasomotorically symptomatic and asymptomatic postmenopausal women. Estrogen facilitated falling asleep and decreased nocturnal restlessness and awakenings, decreased tiredness in the morning and during the daytime, and improved the general sleep quality. Although the degree of improvement in vasomotor symptoms was an important predictor for the degree of improvement in sleep disturbance, the vasomotorically asymptomatic women with sleep symptoms also benefit from estrogen [59]. The Women's Health Initiative (WHI) study, which evaluated the long-term effects of HT on the quality of life in asymptomatic or mildly symptomatic postmenopausal women, found an improvement of sleep quality after 1 year's follow-up compared to placebo [61]. In that study, however, only the overall sleep quality was determined without detailed estimates. In the two more recent prospective placebo-controlled studies, HT improved sleep quality measured by Women's Health Questionnaire (WHQ) [65, 66].

At least two main mechanisms may explain the favorable effects of HT on sleep quality. First, female sex steroids have potent direct CNS effects in brain areas responsible for sleep regulation [44]. Second, sleep problems in menopause could be consequences of other climacteric symptoms, especially vasomotor symptoms. Thus, the alleviation or abolishment of these symptoms should also greatly assist patients with their sleep problems [59, 60].

Despite the results that subjective sleep studies have been convincing and in line with clinical experience, the inconsistent findings using objective measurements of sleep quality have muddled the opinion on HT in the management of menopausal sleep problems. HT has been shown to increase REM sleep [67–69], to decrease stage 1 sleep [70], and to reduce awakenings [67, 71–74] and nocturnal wakefulness during the entire night [67, 75] or in the first sleep cycle [69]. In addition, a shortening in sleep latency [68, 76], an improvement in sleep efficiency [70, 72, 75], and a reduction of the rate of cyclic alternating patterns of sleep [72] have also been reported. According to some studies, HT has no effects on PSG sleep measures or the findings have been minor [77–80]. Further, in an observational study without a placebo group, the postmenopausal HT users had worse sleep quality compared to nonusers, since they had less SWS, more stage 1 sleep, and their sleep was more fragmented [3].

The definite conclusions on the effect of HT on objectively measured sleep quality are impossible to draw, since there are remarkable differences in study designs, subject enrollment procedures, treatment forms, doses, and durations between the trials. Some studies have enrolled both peri- and postmenopausal women without hormone level measurements [67] or both naturally and surgically menopausal women [68]. This has led to a wide age range or differences in biological circumstances and clinical symptoms [81]. In observational studies, self-selection of HT [3, 75] has presumably caused some bias. In controlled studies, the follow-up time has been short, from 4 weeks to 7 months, and thus the long-term effects of HT are

lacking. The incongruence in objective sleep studies calls in question the PSG techniques. Sleep laboratory studies are needed to exclude possible underlying sleep disorders such as sleep apnea, narcolepsy, or sleep movement disorders, but in clinical practice evaluation of subjective sleep quality by questionnaires is generally sufficient to diagnose insomnia. And, last but not least, PSG changes seem to be more age- than hormone-dependent, since in a recent PSG study sleep measures were similar between pre- and postmenopausal women with various hormonal states but differed significantly when compared to young women [29].

Progestogens and Sleep

Progesterone has sedative, benzodiazepine-like agonistic effects on $GABA_A$ receptor [82]. The sedative effects on sleep appear to be mediated via the conversion of progesterone to its major metabolite, allopregnanolone [83]. However, the effects of progesterone on sleep are controversial. Premenstrual syndrome occurs during the luteal phase of the menstrual cycle, when progesterone levels are increased. Furthermore, premenstrual syndrome presents with hypersomnolence in some and with insomnia in others.

Scarce data are available on the effects of progestogen monotherapy on sleep in postmenopausal women. In two small placebo-controlled, non-randomized studies, a 3-week administration of medroxyprogesterone acetate, a progesterone derivative, did not affect objective or subjective sleep quality in postmenopausal women with SDB [84] or in end-stage stable chronic obstructive pulmonary disease (COPD) [85]. In a double-blind, randomized, placebo-controlled study of 8 healthy postmenopausal women without vasomotor symptoms or sleep complaints, a 3-week progesterone therapy had no effect on undisturbed sleep but restored normal sleep when sleep was disturbed [86]. Progestogens are also powerful respiratory stimulants [84, 87–89] but little is known about their effects in women with SDB [84, 90].

Diagnosis and Treatment of Insomnia during Menopausal Transition

Menopausal Insomnia

The etiology of menopausal sleep problems is often complex, which challenges the management. In women with climacteric vasomotor symptoms, the first line treatment is HT, as it has been shown to be the most effective therapy for reducing vasomotor symptoms and related sleep problems [17, 22, 59–61, 63]. Randomized controlled trials indicate that, compared to placebo, estrogen reduces the frequency of hot flashes by 77% [91]. In addition, HT often reduces sleep problems associated

with climacteric mood symptoms [59]. Also, vasomotorically asymptomatic women have reported alleviation of sleep problems during HT [59]. The window for initiation of HT is crucial: the treatment should be started when entering menopause, not long thereafter. The lowest effective doses should be used and the consideration of the treatment made annually [92]. The mammography examination with at least two dimensions should be performed every year and women should be encouraged to self-palpate their breasts. If no symptom relief has been achieved in a few months, further medical examinations are necessary. In women over 60, the risks outweigh the benefits [93] and thus initiation of HT is not recommended.

At present, the principal indication to prescribe HT is alleviation of climacteric symptoms, especially vasomotor symptoms [92]. Observational as well as controlled clinical trials have shown the protection against osteoporosis and bone fractures during HT [93, 94]. In general, the most important risks during HT are increase of cardiovascular disease, stroke, venous thromboembolism, and breast cancer [95]. The effect on cardiovascular system is controversial: a cardioprotective action of HT has been suggested when initiated at menopause [96], although all data do not support this hypothesis [97] and, furthermore, initiation several years after menopause can have reverse effects [93]. The hazard ratio for coronary heart disease is highest during the first year of use, but declines in follow-up [93, 95]. Instead, the risk for venous thromboembolism remains unchanged during HT [93]. The risk for breast cancer is dependent on the duration of the treatment and regimen type (EPT or ET) [93, 95, 98]. Furthermore, the adverse effects of HT seem to be dependent, to a certain extent, on the route of administration: oral HT increases cardiovascular risk and risk for venous thromboembolism and breast cancer [99]. As complications due to HT are associated with higher doses and longer duration of treatment and with its use in older women [92], counseling before initiating therapy should be done in addition to keeping the duration of treatment as short as possible and at the lowest effective dose [92]. In addition, there is some evidence that the transdermal route of administration is safer than the oral one [99].

In addition to conventional HT, tissue selective estrogenic activity regulator (STEAR) tibolone alleviates climacteric symptoms, especially vasomotor symptoms and sleep problems [100, 101]. As the adverse effects and safety profile are similar to conventional HT, the same contraindications also apply to tibolone.

For those vasomotorically symptomatic women who choose to abstain from HT or in whom the use of HT may be contraindicated, treatments which directly affect thermoregulatory mechanisms, such as medications that affect adrenergic, serotonergic, and dopaminergic systems, may be tried [15, 102]. Antidepressants such as paroxetine [102] and venlafaxine reduce hot flashes, while fluoxetine and citalopram are less effective [103]. The most typical side effects are nausea, dry mouth, drowsiness, insomnia, or somnolence. Antidopaminergic drug veralipride can cause mastodynia and galactorrhea, and the selective monoamine oxidase-A inhibitor moclobemide can cause severe somnolence. In most of these cases, medications should be discontinued as the side effects outweigh the benefits [103]. In clinical practice, paroxetine and venlafaxine are most commonly used. The fact that paroxetine and venlafaxine improve hot flashes earlier than they impact mood suggests

Table 19.3 Principles of sleep hygiene (controlling of behavioral and environmental factors that precede sleep and may interfere with sleep)

Go to bed only when you are sleepy. This reduces the time you are awake in bed. If you can't fall asleep within 20 min, get up and do something boring until you feel sleepy. Do not expose yourself to bright light while you are up
Do not take naps. This will ensure you are tired at bedtime. If you just cannot make it through the day without a nap, sleep less than 1 h, before 3 p.m.
Get up and go to bed at the same time every day
Refrain from exercise at least 4 h before bedtime. Regular exercise is good for sleep but not prior to bedtime
Develop sleep rituals: These rituals prepare your body to slow down and sleep
Only use your bed for sleeping and sex
Avoid caffeine, nicotine, and alcohol at least 4–6 h before bedtime
Have a light snack before bedtime
Make sure that your bed is comfortable and bedroom quiet, dark, and its temperature comfortable
Use sunlight to set your biological clock in the morning

that the mechanism of action is different from the antidepressant action [102]. Their effect on menopausal insomnia, however, remains unclear.

Clonidine, an α_2 adrenergic agonist [15, 103], has shown to decrease climacteric symptoms according to some studies but not according to others [103]. Its adverse effects include dry mouth, insomnia, and drowsiness; interestingly, no impact on blood pressure control has been reported [103]. The GABA analog anticonvulsive gabapentin has also shown to reduce vasomotor symptoms [15]. In a meta-analysis, the frequency and severity of hot flashes were reduced 20–30% with gabapentin (daily doses ranged from 900 to 2,400 mg) compared to placebo, but the adverse events of dizziness, unsteadiness, fatigue, and somnolence were more common with the active drug [104]. With all these treatments the benefits must always be weighed against possible side effects.

Bellergal, a combination of ergotamine, phenobarbital, and levorotatory alkaloids, is used as an alternative treatment for hot flashes despite the fact there is no evidence for its efficacy. Side effects include dry mouth, dizziness, and sleepiness [105]. Some women report a beneficial effect of phytoestrogens (red clover isoflavones, which contain genistein, daidzein, formononetin, biochanin or soy isoflavones) on hot flashes [106]. Placebo-controlled trials, however, do not support the efficacy of red clover isoflavone and display conflicting results regarding the efficacy of soy isoflavone. Even though their side effects are similar to that of placebo, true safety data on these drugs are lacking [103]. Some women may benefit from sedative-hypnotic medications, which should be used for short periods under close supervision.

Good sleep hygiene is the cornerstone for good quality sleep (Table 19.3). The bedroom should be dark, quiet, comfortable, and often cool. Avoidance of daytime naps, caffeinated beverages (tea, coffee, some soft drinks, and herbal drinks), smoking, alcohol, and exercise close to bedtime is important [107], especially with older individuals.

Some women benefit from relaxation or cognitive behavioral therapies (CBTs). Further, stress management, naturopathic care, massage therapy, and energy therapy have been used as alternative treatments for climacteric symptoms [108] and thus can be considered also in the management of menopausal sleep problems, although standardization of doses and forms or controlled studies about their efficacy are not available.

Primary Insomnia

According to sleep surveys, women report more sleep problems than men across all age groups [23, 109–111]. The factors contributing to these differences, however, are not clear. Although there are several reasons for insomnia, it may also occur as a primary disorder unrelated to underlying medical or psychiatric diseases [112]. Primary insomnia is often further divided into psychophysiological insomnia, idiopathic insomnia, and paradoxical insomnia [112]. Typically, the patients have long-standing sleep problems, sometimes dating back to childhood, and in idiopathic insomnia at least the symptoms are quite resistant to treatments.

During menopause, primary insomnia may coexist with insomnia due to climacteric symptoms. The two conditions may lead to worse sleep disturbances than ever before and it may be the first time that the patient seeks medical attention for it. HT relieves symptoms to some extent and is often used as adjunct therapy. Some patients respond to tricyclic antidepressants, neuroleptics, and sedative-hypnotics [112]. Good sleep hygiene is essential. Stimulus control therapy, relaxation training, and CBT have been shown to be effective in individual cases [113]. A systematic review that included 37 treatment studies showed that CBT and other behavioral interventions (stimulus control therapy, relaxation, paradoxical intention, and sleep restriction) improved sleep quality [114], and their beneficial effects were sustained over time. In addition, the chronic use of sedative-hypnotics decreased. There failed to be, however, a clinically significant reduction in morbidity, especially in daytime fatigue.

Secondary Insomnia

Causes for secondary insomnia include primary sleep disorders such as SDB and restless leg syndrome (RLS), medical conditions, mental disorders, medication side effects, and aging. In many cases, two or more underlying causes of insomnia can be identified.

Sleep-Disordered Breathing

SDB comprises a wide array of sleep-breathing disorders from primary snoring to classical sleep apnea. Frequently, it is used as a synonym for obstructive sleep apnea

syndrome (OSAS), a condition characterized by partial or total periodical collapses of the upper airway during sleep. Most although not all community-based and clinic-based cross-sectional studies show increased prevalence estimates of sleep apnea after menopause, the prevalence being comparable to that of men [5, 6, 115–118]. When diagnosing female SDB, two specific issues have to be considered. First, clinical presentation of SDB differs from the "classical" clinical picture of OSAS. The gender differences in clinical presentation may result in underdiagnosis or misdiagnosis of SDB in women [119–121]. Second, apnea-hypopnea index (AHI, i.e., the sum of apneic and hypopneic episodes per hour of sleep) required to cause symptoms in women is lower than in men; therefore women are symptomatic at lower AHIs [122]. These facts have implications for treatment as well.

The classical clinical picture of OSAS includes complaints of loud snoring, breathing pauses during sleep, waking up with gasping or choking, and excessive daytime sleepiness. Women tend to report snoring less frequently than men even within similar AHI ranges [115, 123, 124] and are less likely to report their own nocturnal apneas while reporting more frequently that of their bed partners' [115, 119, 124]. Male SDB patients express sleepiness whereas females tend to use words like fatigue, lack of energy, or tiredness [125, 126]. Women with SDB may complain more frequently of morning headaches [123, 125, 127]. In addition, hypothyroidism, a condition that may induce SDB, is more prevalent in women than in men [128].

Compared to men, women with SDB are more likely to have an initial complaint of insomnia or depression [124, 127, 129]. Guilleminault and colleagues observed that 80% of 394 postmenopausal women with chronic insomnia had sleep apnea [129]. PSG recordings confirmed insomnia in 68% of 38 normal weight postmenopausal women complaining of insomnia and revealed sleep apnea in 50%, periodic leg movements during sleep (PLMS) in 7.8%, and bruxism in 2.6% of the subjects [130]. PLMS in women with SDB seem to be more common than in men, with SDB possibly leading to more insomnia [124]. Difficulties falling asleep, awakenings during the night, nocturia, dry mouth in the morning, nightmares, and night sweats are more common among female than male SDB patients [124, 127]. The consequences of subsequently occurring insomnia and OSAS appear to be additive, with patients who suffer both conditions experiencing greater daytime impairment, including psychiatric distress [131], sleepiness [132], and slower reaction times [133, 134], compared to patients with only one disorder. Patients with both disorders also have greater neurocognitive and functional impairment, and are sleepier than patients with sleep apnea alone [132]. Depressive mood and depression are highly prevalent among patients with SDB and may contribute to symptoms of insomnia. Females with SDB present with these symptoms and are treated for depression more often than males, and women with severe SDB have higher depression scores compared to those with milder SDB [123, 124, 127, 135].

SDB is diagnosed by patient history (Table 19.1), physical examination (Table 19.2), and PSG, which remains the gold standard. Conventional PSG includes electroencephalography (EEG), electro-oculography (EOG), and electromyography (EMG) and therefore allows sleep staging. Sensors for detecting respiratory effort, airflow, and oxygen saturation are needed to define the AHI and the

oxygen desaturation index (ODI, i.e., the number of oxygen saturation dips per hour of sleep). The more cost-effective cardiorespiratory polygraphy (EEG not included) is frequently used, especially in the northern European countries, and in most cases, when combined with history and physical exam, is adequate to diagnose SDB [136, 137].

The AHI is commonly used to describe the severity of SDB. An AHI of less than five per hour of sleep is usually considered normal. In women, the AHI grossly underestimates the clinical severity of SDB. High frequency of symptoms with low AHI suggests that women have other factors contributing to their symptoms [122]. We have shown that partial upper airway obstruction is far more common than "conventional" sleep apnea. Out of 62 "healthy" postmenopausal women, 17% had significant amount of partial upper airway obstruction during sleep [138]. In a clinic-based population, 50% of breathing abnormalities were due to obstructive non-periodic breathing, i.e., partial upper airway obstruction, which results in low AHI [139]. Especially in women, it is of great importance not to look at only AHI when defining the clinical severity of SDB. The clinical severity of SDB has to be specified with two components: objective PSG findings (AHI plus flow limitation) and subjective daytime sleepiness with functional disability. According to the American Academy of Sleep Medicine Task Force severity criteria, the rating should be based on the most severe component of these two [140]. Symptomatic women with low (even with lower than five) AHI should be considered for a CPAP trial [141].

Patients with mild SDB, i.e., asymptomatic patients with low AHI, have poor adherence to nasal continuous positive airway pressure (CPAP) therapy [142, 143]. Partial upper airway obstruction is often misclassified as mild SDB because of low AHI [144], but patients with significant percentage of partial obstruction during sleep frequently complain of excessive daytime sleepiness and morning headaches in particular. Their symptoms usually respond well to nasal CPAP therapy, and their long-term adherence to CPAP is compatible with that of patients with conventional OSAS [119]. Women are more likely to require lower levels of CPAP support than men even after adjusting for the severity of OSAS defined by AHI [145].

All types of insomnia are more frequent in women than in men. Sleep maintenance insomnia complaints predict poor CPAP adherence [146]. Therefore, it is of importance to pay attention to patients with SDB and insomnia and, in addition to nasal CPAP therapy, consider behavioral and pharmacological treatment alternatives for insomnia.

A number of hormones, including female sex steroids, have been suggested to play a role in SDB [128]. In a cohort of 53 women, higher AHI was associated with lower levels of estradiol, progesterone, and 17-OH-progesterone, when adjusted for BMI, age, phase of the menstrual cycle, and postmenopausal status [147]. The cross-sectional study design, however, does not allow for drawing conclusions on causality.

High lipid solubility enables circulating sex steroids to easily cross the blood-brain barrier [148]. Sex steroids act directly or via central neuromodulatory systems [148] but also peripherally by contributing to upper airway patency [149]. Sex steroids influence neuromodulatory serotonergic neurons [44, 148], which are essentially

involved in the neural control of breathing [150]. Treatment with estrogen and/or progesterone can upregulate 5-hydroxytryptamine (5-HT) levels [151]. In humans, estrogen influences 5-HT synthesis and 5-HT_{2A} receptor binding in a gender-specific manner [152–154]. Serotonin also increases excitation of the upper airway and phrenic motoneurons [155, 156].

Progesterone is a powerful respiratory stimulant, acting via central and peripheral chemoreceptors [87, 88, 155, 156]. In healthy women, upper airway resistance is lower during the luteal (high progesterone levels) than the follicular phase of the menstrual cycle both during wakefulness and sleep [157]. Coadministration of estrogen and progesterone enhances progestin-induced ventilatory effects [158, 159], although contradictory findings have been reported [160]. The enhancement of ventilatory effects by combination therapy is likely to be associated with estrogen-induced upregulation of progesterone receptors [161].

Weight control and nasal CPAP therapy form the basis for treatment of SDB. Some patients benefit from oral appliances or different types of surgical interventions. In patients with persistent complaints of insomnia, behavioral and pharmacological therapies for insomnia should be added on. Postmenopausal HT might prevent or alleviate SDB, but the effect size is modest. The current body of data does not allow us to give any recommendations for using HT to prevent or treat SDB. In a cohort study, the prevalence estimates of sleep apnea in postmenopausal nonusers of HT were compatible with those in men, whereas in HT users they were compatible with those in premenopausal women [5]. Combination therapy with estrogen plus progesterone was not superior to unopposed ET. Short-term administration of progesterone alone [84, 162], unopposed estrogen [138, 163], or combination therapy [164, 165] has induced significant but clinically insufficient improvement of SDB.

Other Primary Sleep Disorders

RLS is characterized by the urge to move and unpleasant sensations in legs. These symptoms begin or worsen at rest, especially in the evening and at night. Symptoms are partially or completely relieved by movement. RLS affects women twice as often as men, the gender difference being explained mostly by parity [166]. About 80% of those with RLS have PLMS and about 35% of those with PLMS have RLS. The prevalence of PLMS is thought to be 30% between the ages of 50 and 65 years, and 45% in the population over the age of 65 [43]. During midlife, RLS occurs more frequently in women with vasomotor symptoms but is not related to postmenopausal state or HT use [167].

RLS is strongly linked to insomnia [168]. PLMS, urge to move, and abnormal sensations in legs prevent falling asleep, and cause brief arousals or prolonged awakenings during the night. Diagnosis is based on history and does not require a PSG for diagnosis. Secondary causes (see Chap. 17) of RLS have to be ruled out.

In general, pharmacological treatment should be limited to individuals who meet the diagnostic criteria of RLS, and especially to those who suffer from insomnia and/or excessive sleepiness due to RLS. Estrogen has been suggested to have antidopaminergic action, and therefore could play a role in RLS and PLMS. However, the role of female sex hormones in the etiology and treatment of RLS is unclear. Two small RCTs of HT in postmenopausal women showed that estrogen plus progesterone [74] but not unopposed estrogen therapy [169] had an effect on frequency of PLMS. According to the guidelines of the American Academy of Sleep Medicine, dopaminergic agents are the first-line therapy, followed by opioids, anticonvulsants, and benzodiazepines [170]. Current treatment guidelines also suggest nonpharmacologic interventions, such as sleep hygiene (Table 19.3), CBT, exercise and exposure to light, and avoidance of alcohol, caffeine, and heavy meals in the evening [171]. Treatment of RLS is described in more detail in Chaps. 8, 14 and 17.

Medical Disorders

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

Nocturnal and early morning headaches (frequently linked with partial upper airway obstruction during sleep or respiratory failure), neurological diseases such as neuromuscular diseases, Alzheimer's and Parkinson's disease, cancer, asthma, COPD, gastroesophageal reflux, hypertension, nocturnal angina and heart failure, musculoskeletal disorders, nocturia, obesity, hypothyroidism, and chronic pain syndromes including fibromyalgia are frequently revealed as contributing factors in sleep problems.

It is well established that patients with COPD have poor sleep quality not only during acute exacerbations of the disease but also during the stable phases. Despite often having very short and fragmented sleep, however (Fig. 19.3), these patients lack excessive daytime sleepiness [85]. Treatment with benzodiazepine derivatives should be avoided because of the risks of ventilatory depression, carbon dioxide retention, and addiction. Antidepressive agents help COPD patients with insomnia related to depression. Hypercapnic patients may benefit from nocturnal noninvasive ventilation [172]. CBT is unlikely to benefit insomnia related to nocturnal respiratory impairment but might be beneficial for anxiety or depression induced components of insomnia [173].

Nocturia means need for voiding twice or more often at night. It is often underdiagnosed. Nocturia may sometimes disrupt sleep more than vasomotor symptoms in postmenopausal women. In the National Sleep Foundation's 2007 Sleep in

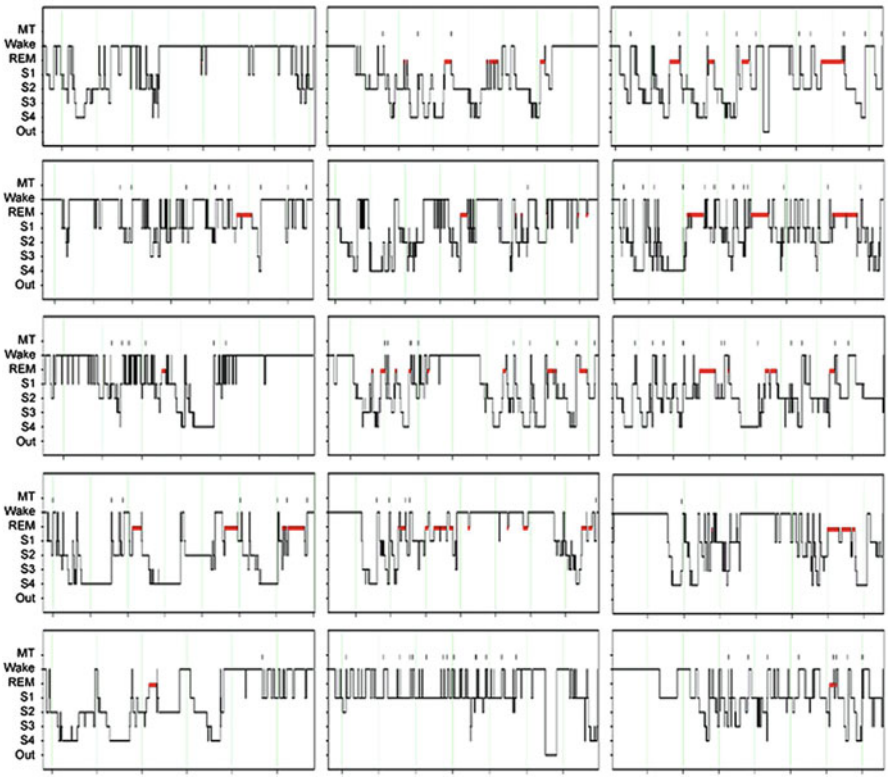

Fig. 19.3 Hypnograms of the 15 postmenopausal women with end-stage stable COPD. Their mean total sleep time is 4 h 41 min and sleep structure is markedly destroyed. MT, movement time; REM, rapid eye movement sleep; S1 and S2, sleep stages 1 and 2 (light sleep); S3 and S4, sleep stages 3 and 4 (slow-wave sleep, deep sleep). (Reproduced with permission from Saaresranta T, Irjala K, Aittokallio T, Polo O. Sleep quality, daytime sleepiness and fasting insulin levels in women with chronic obstructive pulmonary disease. Respir Med 2005;99:856–863)

America poll, approximately 20% of the community-dwelling 40–60 year-old women reported nocturnal awakening related to needing to go to the bathroom [174]. Not only diuretics, estrogen depletion, changes in the structure and position of the uterus, and structures related to it, but also SDB, has to be taken into account in the differential diagnostics of possible underlying causes of this troublesome disorder.

Fibromyalgia (FM) is a poorly understood, chronic disorder characterized by non-articular, widespread musculoskeletal pain. It affects 2% of the population and is seven times more frequent in women than in men [7]. The time of onset or the increase in intensity of FM symptoms often coincides with perimenopausal or postmenopausal period, suggesting that the endocrine changes at menopause may play a role in the pathophysiology of FM [175, 176]. The "core" symptoms include multifocal pain, fatigue, insomnia, cognitive/memory problems, and psychological distress.

Disturbed sleep, including sleep onset or sleep maintenance insomnia or persistent nonrestorative sleep, are especially distressing to FM patients [7, 177–180].

Some but not all studies have suggested misalignment of the phase of the circadian pacemaker. Circadian pacemaker influences both melatonin secretion and activity of the hypothalamic–pituitary–adrenal (HPA) axis. Studies comparing FM patients with healthy controls have shown normal [181], decreased [182], or increased [183] melatonin levels in FM patients. A blunted rise in ACTH has been reported in women with FM during a hypoglycemic-hyperinsulinemic clamp performed in the morning [184] and a delayed rise in ACTH in response to infused interleukin-6 [185]. Some, but not all, studies have shown blunting of the normal diurnal cortisol rhythm, with elevated evening cortisol levels in FM [184, 186, 187]. One study done under the constant routine conditions did not find any difference between the women with fibromyalgia and controls in the circadian amplitude or phase of rhythms of melatonin, cortisol, and core body temperature [188].

There are associated, although not specific, findings in PSG recordings. Three distinct patterns of alpha sleep activity have been detected in FM [189]. Phasic alpha simultaneously with delta activity is found in 50% of FM patients, tonic alpha continuously through NREM sleep in 20% of patients, and low alpha activity in the remaining 30% of patients compared to low alpha detected in 84% of healthy controls [189]. All patients with phasic alpha, 58% of those with low alpha, and 12% of patients with tonic alpha reported poor perceived sleep. Patients with phasic alpha also showed lower sleep efficiency and shorter total sleep time. FM patients have increased CNS levels of the nociceptive neuropeptide substance P and lower serotonin levels resulting in a lower pain threshold to normal stimuli. High substance P and low serotonin have significant potential to affect sleep and mood. Treatment of sleep itself seems to improve, if not resolve, FM.

Sedating antidepressants, zolpidem tartrate, and sodium oxybate have shown a short-term efficacy for treating FM-associated fatigue and insomnia but the beneficial effects often decrease over time [190–193]. Pregabalin, duloxetine, and milnacipran have been successfully used for FM [194]. Pregabalin is a GABA analog which binds to the alpha-2-delta subunit of calcium ion channels. Duloxetine and milnacipran is serotonin-norepinephrine reuptake inhibitors (SNRIs). Duloxetine inhibits serotonin reuptake markedly more than norepinephrine reuptake, whereas milnacipran inhibits norepinephrine reuptake more than serotonin reuptake [194]. A meta-analysis of 11 RCTs with a total of 6,388 subjects compared the benefits and side effects of duloxetine, milnacipran, and pregabalin in FM patients [195]. All three drugs were superior to placebo except for the following symptoms: duloxetine for fatigue, milnacipran for sleep disturbances, and pregabalin for depressed mood. Duloxetine and pregabalin were superior to milnacipran for pain and sleep disturbance. Milnacipran and pregabalin were superior to duloxetine for fatigue. The numbers needed to harm (NNHs) for discontinuation due to adverse effects were 14.9 for duloxetine, and 7.6 for both milnacipran and pregabalin [195]. Based on that indirect comparison of these three drugs, pregabalin might be the first choice in patients with insomnia due to FM. Administration of melatonin as mono-

therapy or in combination showed promising results for pain and sleep in a recent RCT in FM [196] but the data of its long-term efficacy are lacking.

Non-pharmacological approaches such as exercise, education, and CBT have positive impact in FM, but these therapies are underutilized in usual clinical practice [197]. CBT has shown promising responses in the treatment of FM-related chronic insomnia [198]. In a randomized clinical trial of 42 FM patients with chronic insomnia sleep logs showed that CBT-treated patients achieved almost a 50% decrease in their nocturnal wake time compared to 20% with sleep hygiene instructions and 3.5% with usual care. Actigraphic findings were in line with sleep log findings [198]. However, a recent systematic review of the efficacy of CBT in FM was not able to show any positive effects of CBT on fatigue or sleep in FM [199].

Mental Disorders

A large body of literature agrees that mental disorders and mood symptoms, like depression and anxiety, are connected with sleep problems [111, 200–203]. Depressive patients typically suffer from sleep problems [201–203], which in turn often may worsen depression [204]. On the other hand, chronic insomniacs often become depressed [205]. Depressed patients have been shown to have disturbances in sleep continuity and reduced SWS. Furthermore, there are REM sleep abnormalities including shortened REM latency and increased REM density. It has been suggested that the complementary interaction between REM and non-REM sleep is unbalanced in depression [206].

Women report mood symptoms, like depression, anxiety, and lack of initiative, more often than men [207, 208]. Several factors, such as psychosocial vulnerability, excessive stress, and somatic diseases, may explain the gender differences [209]. However, mood symptoms are also related to the female reproductive cycle, as they are frequently reported in connection with premenstrual tension syndrome, postpartum depression, or climacteric depression [205, 210]. Therefore, the influence of female sex hormones seems to be important. Especially in menopausal transition, a lowered estrogen level may cause or contribute to depression either directly by biochemical effects on the brain or indirectly via climacteric symptoms such as hot flashes, sweating, or sleep problems [34, 204, 211]. Although HT has shown to have an antidepressant effect [212, 213] and does alleviate climacteric depressive symptoms [204], in depressed patients it is recommended as an adjunct therapy [214].

Depressive and anxiety symptoms are frequent during climacterium: they are reported in up to 70–90% of symptomatic women [17]. According to some studies, their prevalence increases from early menopause to late menopause [74]. Sleep problems, especially difficulties falling asleep and early morning awakenings, are subtle markers of mood symptoms [28, 215] and thus can be the first signs of depressed mood.

In middle-aged and older women, sleep problems have been associated with psychiatric disorders and mood symptoms. Hollander et al. showed that poor sleep was associated with higher anxiety and depression levels in over 400 middle-aged women [216]. Freedman et al. found in a sample of 102 peri- and postmenopausal women that high anxiety scores predicted low subjective sleep quality [217]. In our own study with more than 3,400 middle-aged women, mental health problems were the most significant predisposing factor for various sleep problems [8]. In another cohort with 850 middle-aged women, psychiatric symptoms were strongly associated with sleep problems, like difficulty falling asleep, nocturnal awakenings, early morning awakenings, as well as daytime consequences, like sleepiness in the morning and daytime, tendency of falling asleep at work and during leisure time, frequency of daytime naps, and consumption of sleeping pills (Polo-Kantola, unpublished). These results strongly suggest the importance of the impact of mental health on sleep in women. Therefore, when managing sleep problems, a careful assessment and treatment of psychiatric conditions is also essential.

Aging

Aging has deleterious effects on sleep length and quality through neuronal loss and atrophy, neurotransmitter defects, and decreasing cerebral blood flow [218]. Physiologic changes in the timing of the circadian clock easily affect sleep in midlife women. Circadian clock is advancing with age resulting in early morning awakening. This may be misperceived as insomnia or a symptom of depression. It also becomes more and more difficult to adjust to shift-work leading to aggravation of shift-work-related insomnia.

The symptoms of shift-work disorder can be treated using behavioral and pharmacological therapies. Current treatment guidelines suggest nonpharmacologic interventions, such as sleep hygiene (Table 19.3), exercise, and exposure to light [219]. In addition, medications that contain melatonin or caffeine may benefit some patients. The use of these therapies can significantly improve sleep, performance, and quality of life for patients with shift-work disorder.

Insomnia Induced by Behavioral, Environmental, or Psychosocial Factors

Modern 7/24 lifestyle has a negative impact on sleep especially during such vulnerable periods in a woman's life span as menopausal transition and the postmenopause. Poor sleep hygiene (i.e., irregular sleep-wake schedule, insufficient sleep), voluntary sleep restriction (i.e., staying up late or rising early to meet work or social demands), and environmental disturbances (i.e., snoring bed partner, pets, sleeping

with television or cell phone on, public lightning, noisy neighbors, traffic noise) may contribute to insomnia.

Noise and pets may be a more frequent cause of sleep disruption than usually thought and may predispose to insomnia. In the National Sleep Foundation's 2007 Sleep in America poll, 90.9% of community-dwelling 40–60 year-old female respondents reported nocturnal awakening and attributed these awakenings to the following: noise (40.1%), needing to go to the bathroom (20.1%), pets (18.7%), pain or discomfort (10.5%), and spouse or bed partner (7.9%). The frequency of noise or pets as a cause of sleep disruption is quite high when compared to the well-known "sleep disrupters" during menopause transition, i.e., hot flashes and night sweats, which were reported by 53.8% of respondents [174].

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

Conclusion

Menopausal women frequently report unsatisfactory sleep. Persistent insomnia in a midlife woman is not a single entity but comprises a wide spectrum of conditions, which may arise from a combination of predisposing, precipitating, and perpetuating factors. Etiologies other than menopause should also be considered and investigated. An individual woman's insomnia may be multifactorial. Comprehensive history (Table 19.1) and appropriate physical examination (Table 19.2) combined with specific diagnostic tools such as PSG or cardiorespiratory polygraphy form the basis for correct diagnosis and successful therapeutic interventions. Treatment options for menopause-associated insomnia include HT, hypnotic agents, and behavioral interventions as well as specifically targeted medication for depression, anxiety or other psychiatric disorders, or RLS or appropriate treatment for SDB (Fig. 19.2). Optimization of treatment of medical conditions has to be considered. Effective therapies are available to treat insomnia of different etiologies in midlife women (Fig. 19.2). Once a specific diagnosis is made, an affected woman deserves appropriate treatment because marked improvements in quality of life and health outcomes can be achieved.

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Chapter 20
Obstructive Sleep Apnea and Menopause

Grace W. Pien and Sigrid C. Veasey

Introduction

A growing body of work supports the concept that menopause is a risk factor for obstructive sleep apnea (OSA). These observations come from clinical and population data examining the relationship between menopausal status and sleep-disordered breathing, studies examining the clinical characteristics of disease in premenopausal and postmenopausal women, and laboratory studies seeking to understand what changes occur to place postmenopausal risk at increased risk for sleep apnea. This chapter will review what is known about the increased prevalence of OSA among postmenopausal women, how menopausal status affects the presentation of sleep-disordered breathing, and the mechanisms that may underlie the development of sleep apnea among postmenopausal women.

Menopause as a Risk Factor for Sleep Apnea

Initial reports of the obstructive sleep apnea syndrome described a striking predominance of disease among men relative to women, with estimated male:female ratios between 8 and 10:1 [1, 2]. These ratios, however, did not represent general populations. The first study sampled 30 asymptomatic men and 19 women, finding sleep apnea in 20 of the 30 males and very rare events in 3 of the 19 females. In the second study,

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the ratio of sleep apnea syndrome in males vs. females was determined using a sleep clinic population. The finding of very few premenopausal women with sleep apnea in these initial studies prompted a comparison of pre- and postmenopausal women [3]. This study found far more frequent OSA with more significant desaturations in postmenopausal compared to premenopausal women [3]. Thus, these earlier studies suggested that there might be both gender and menopause effects on the prevalence of sleep apnea.

It was not until 1993, however, that data from the Wisconsin Sleep Cohort Study (WSCS) were published revealing a more accurate prevalence for sleep apnea across several age groups and both genders. In this landmark general population study, undiagnosed sleep-disordered breathing was widely prevalent among both men and women (9% and 4%, respectively, when defined by ≥5 apnea or hypopnea episodes per hour of sleep) [4]. When restricted to individuals with both sleep-disordered breathing and excessive daytime somnolence, 2% of women and 4% of men between ages 30 and 60 were affected. Thus, the ratio of sleep apnea prevalence in males v. females is high, but not as disproportionate as initially thought. Although Young et al. did not report information about menopausal status, the prevalence of an apnea–hypopnea index (AHI) ≥5 events/hour of sleep among women between ages 30 and 39 was 6.5%. In women 50–60 years of age, the prevalence was 16%, suggesting that sleep-disordered breathing is more common in postmenopausal women. However, the prevalence of sleep-disordered breathing increases sharply among men in the same age groups, from 17 to 31% [4]. Thus, this study was unable to distinguish an age effect on sleep-disordered breathing prevalence from a menopause effect.

Subsequent longitudinal data from women enrolled in the WSCS have more clearly demonstrated that the menopausal transition increases the risk of sleep-disordered breathing [5]. Compared to premenopausal women, the odds ratios for developing an AHI of 5 or more events/hour increased to 1.66 for perimenopausal and to 2.82 for postmenopausal women. Increased risks for sleep-disordered breathing persisted after adjustment for potential confounding factors including age, body habitus, and smoking, so that at nearly every age between 32 and 53 years and at every BMI level, SDB prevalence was higher for perimenopausal and postmenopausal women compared to premenopausal women. Furthermore, the odds of having sleep-disordered breathing increased with the duration of the postmenopausal state.

The association between menopausal status and sleep-disordered breathing has also been examined in a community-based random sample of 1,000 women between 20 and 100 years of age from southern Pennsylvania [6]. The prevalence of OSA, defined as an AHI of ≥10 events/hour and clinical symptoms of daytime sleepiness, hypertension, or other cardiovascular complications, was 0.6% among premenopausal women compared to 1.9% among postmenopausal women (i.e., a threefold relative risk for postmenopausal women). When defined solely by AHI criteria (≥15 events/hour), the difference in prevalence was even more pronounced, rising from 0.6% of premenopausal women to 3.9% of postmenopausal women. Interestingly, the prevalence of OSA in postmenopausal women was very similar to the prevalence of sleep apnea in age-matched men [6].

Studies in diverse populations from Iceland, Italy, Spain, and Hong Kong have offered additional evidence for menopause as a risk factor for OSA [7–10]. Together, these studies demonstrate that menopause is a strong risk factor for OSA in women.

Hormone Replacement Therapy and Sleep-Disordered Breathing

The increased risk of sleep apnea among postmenopausal women suggests that lower levels of reproductive hormones adversely affect respiration during sleep and raises the possibility that HRT may reduce this risk. Indeed, lower levels of estradiol and progesterone levels have been observed among women of varying ages with OSA [11]. A number of mechanistic studies, discussed later in this chapter, have addressed potential pathways. Several epidemiologic studies have also examined whether the likelihood of having sleep apnea is reduced among users of replacement hormones. It is important to understand that in the studies described, women were not randomized to HRT.

In the southern Pennsylvania cohort previously described, postmenopausal women were categorized by HRT use and compared to premenopausal women [6]. Among postmenopausal women currently using HRT, the prevalence of sleep apnea (AHI ≥10 and clinical symptoms) was similar to that of premenopausal women (0.5% in postmenopausal women on HRT vs. 0.6% in premenopausal women). In contrast, the prevalence of sleep apnea among postmenopausal women not using HRT was significantly higher (2.7%). This difference could not be explained by obesity. In fact, women using HRT were twice as likely to be obese. Using an AHI criteria of >15, postmenopausal women not using replacement hormones were more than four times more likely to have sleep apnea than premenopausal women; postmenopausal women using HRT did not differ significantly from premenopausal women. The majority of subjects using hormones reported that they were taking estrogen-alone therapy rather than combination estrogen–progesterone therapy.

Among perimenopausal and postmenopausal subjects in the WSCS, 17–20% reported current HRT use [5]. Users of hormonal therapy were slightly less likely to have sleep-disordered breathing compared to peri- and postmenopausal non-HRT users, but this finding was not statistically significant. The investigators also looked for but did not find a long-term modifying effect that might reduce the likelihood of developing sleep-disordered breathing after cessation of replacement hormones.

Data from the Sleep Heart Health Study, a large epidemiologic study of the cardiovascular effects of sleep apnea, have also been used to examine the relationship between the use of replacement hormones and sleep-disordered breathing [12]. As menopausal status was not recorded at the time of polysomnography, analyses were restricted to women age 50 and older. Hormone users comprised 32% of the sample and had approximately half the prevalence of sleep-disordered breathing (defined as an AHI ≥15 events/hour) compared to nonusers, an association that persisted after adjustment for age and body mass index (BMI) (adjusted odds ratio 0.55). The protective effect of HRT was strongest among women 50–60 years of

age; it attenuated with age so that women between ages 70 and over had the least protective effect from HRT. However, the effect of replacement hormones appeared to be similar regardless of whether women used estrogen alone or an estrogen–progesterone combination.

Collectively, these data demonstrate that menopause increases the risk of sleep-disordered breathing and that HRT may attenuate this risk. The question of whether hormonal therapy may be used to prevent the development of sleep apnea across the menopausal transition has been raised, but has not been answered with clinical trials [13]. Recent results from the Women's Health Initiative, a primary preve ntion trial of HRT, demonstrated an increased rate of adverse cardiovascular outcomes among women taking estrogen and progestin [14]. These findings make a large-scale trial of HRT for the treatment of sleep apnea unlikely. In fact, the WHI study findings appear to have had a substantial impact on women's use of hormonal therapy: 58% of postmenopausal women in a New Zealand population surveyed 6 months after release of the study results reported having stopped their replacement hormones [15]. Whether a detectable increase in the overall prevalence of sleep apnea among postmenopausal women will occur due to widespread cessation of HRT remains to be seen.

Impact of the Menopausal Transition on Clinical Characteristics of Sleep-Disordered Breathing

A number of gender differences in the clinical characteristics of OSA have been described. These include differences in disease severity, apnea characteristics, distribution of SDB events during sleep, and clinical presentation. Evidence that some of these characteristics may likewise be affected by menopausal status will be reviewed here.

Sleep Apnea Severity

In the Sleep Heart Health Study, mean AHI was observed to be higher among men than women [16]. Even when matched by age and BMI, women with sleep apnea have fewer sleep-disordered breathing events compared to men [17]. In comparing sleep apnea severity on the basis of menopausal status, conflicting reports exist, with data drawn mostly from clinical rather than population-based samples. An early report from Guilleminault et al. reported higher mean AHIs among premenopausal than postmenopausal women with OSA [2]. However, other authors have observed either no difference in mean AHI between premenopausal and postmenopausal women with OSA [18], or more severe disease in postmenopausal women [19, 20]. These studies have often been limited by selection bias and lack of adjustment for confounding variables such as age and BMI.

Initial data from the WSCS showed that although sleep-disordered breathing (AHI ≥5 events/hour) was more common among women between 50 to 60 years of age than younger women (ages 30–40 and 40–50), the prevalence of more severe disease (AHI ≥10 or ≥15 events/hour) was similar in all groups [4]. More recent data from this study, using careful classification of menopausal status, demonstrate that whether defined by an AHI of ≥5 or ≥15, the prevalence of sleep-disordered breathing approximately triples among peri- and postmenopausal women compared to premenopausal women [5]. The latter report may suggest that, after taking menopausal status into account, disease severity is similar in premenopausal and postmenopausal women with OSA.

Sleep-Disordered Breathing Characteristics

Compared to men, women with sleep-disordered breathing have been observed to have a higher proportion of hypopneas than apneas, and to have shorter events associated with less severe oxyhemoglobin desaturation [17, 18, 21]. Differences in the characteristics of sleep-disordered breathing events by menopausal status have also been examined in a number of studies. Block et al. examined apnea and hypopnea frequency, duration, and associated desaturation among premenopausal women, postmenopausal women and men [3]. Compared to premenopausal women, postmenopausal women had more frequent events that were longer in duration and more likely to be associated with oxyhemoglobin desaturations less than 90% [3]. When postmenopausal women were compared to men over the age of 50, there were no significant differences in apnea frequency or events associated with oxyhemoglobin desaturation. In contrast, premenopausal women were significantly less likely to have such events than men <50 years of age.

Another study compared nocturnal breathing abnormalities in a clinical population of premenopausal and postmenopausal women referred for overnight sleep studies [22]. Static charge-sensitive bed technology was utilized to detect sleep-disordered breathing, including prolonged episodes of increased respiratory resistance not meeting usual definitions for apneas and hypopneas. Postmenopausal women experienced abnormalities in nocturnal breathing over a significantly larger proportion of the night compared to premenopausal women (68.1% vs. 35.8%, $p<0.001$). Rates of sleep-disordered breathing were slightly higher among postmenopausal women, a finding of borderline significance.

A third study examined a clinical sample of 485 women with sleep apnea and observed more sleep-disordered breathing events among postmenopausal than premenopausal women. However, postmenopausal women were also more likely to be overweight [23]. Two studies that used age as a surrogate marker for menopausal status, which may lead to misclassification bias, have failed to observe differences in the duration of sleep-disordered breathing events and oxyhemoglobin desaturation [18, 21].

In women, sleep-disordered breathing events have been observed to be more frequently concentrated during REM compared to non-REM sleep [17, 24]. Tantrakul and Guilleminault observed a significantly higher REM AHI among postmenopausal women compared to premenopausal women with OSA [23]. However, whether a greater percentage of all sleep-disordered breathing events occur during REM sleep in pre- or postmenopausal women has not been examined.

Clinical Presentation of Sleep-Disordered Breathing

Although symptoms of OSA clearly differ between women and men, less is known about whether the menopausal transition affects the clinical presentation of sleep apnea. Women referred for laboratory evaluation of sleep apnea are as likely as men to report sleepiness and snoring, snorting, gasping, or apneas when asked about these symptoms [25, 26]. However, compared to men, women with sleep apnea are more likely to complain primarily of insomnia and to have a history of depression or hypothyroidism [26]. In one sample, 67% of postmenopausal women with chronic insomnia without excessive daytime sleepiness were found to have sleep apnea (AHI ≥5) [27]. Snoring and extended nocturnal awakenings have also been observed to be significantly more common among postmenopausal women referred for polysomnography and found to have OSA, compared to their premenopausal counterparts [23]. Studies of gender differences in reporting sleep-disordered breathing symptoms have not compared pre- and postmenopausal women [25, 26, 28]. However, the persistence of gender differences in analyses by age-specific strata [25] may suggest that clinical symptoms are likely to be similar regardless of menopausal status.

Given the increased risk of sleep-disordered breathing conferred by menopause, the possibility of a relationship between menopausal vasomotor symptoms and sleep-disordered breathing has been explored [29]. Although nocturnal breathing abnormalities were common among postmenopausal women, vasomotor symptoms (hot flashes) did not predict the occurrence or severity of sleep-disordered breathing [29].

In summary, it is clear that differences between women and men exist in the clinical characteristics of sleep-disordered breathing. Less is known about effects of menopausal status on the clinical presentation of OSA. A small body of work suggests that clinical disease severity in women is similar regardless of menopausal status. However, compared to premenopausal women, apneas and hypopneas in postmenopausal women may more closely resemble the longer, more severe breathing events observed in men. Women with sleep-disordered breathing are more likely than men to complain primarily of insomnia or to have complaints aside from somnolence and apneic symptoms that may obscure the diagnosis. Further studies are needed to determine whether the clinical presentation of disease changes after menopause.

Mechanisms by Which Aging and Menopause May Predispose to the Development or Progression of Obstructive Sleep Apnea

Numerous clinical and animal model studies have explored potential mechanisms by which premenopausal women are relatively protected from OSA and why menopause may predispose to increase risk of sleep-disordered breathing. This section examines the potential mechanisms underlying menopause as a risk for sleep apnea and reviews this body of literature. Menopausal transition changes in reproductive hormone levels, weight, body fat redistribution, respiratory drive, ventilatory stability, and upper airway mechanics will be considered. It is hoped that an improved understanding of what is known and of the mechanisms through which menopause contributes to the progression and development of sleep apnea will unveil areas in need of further study and will ultimately lead to novel therapies to prevent and treat OSA in women across all ages.

Effects of Acutely Reducing Estrogen on Obstructive Sleep-Disordered Breathing

To test the relative importance of estrogen and/or progesterone in preventing OSA, D'Ambrosio et al. performed overnight polysomnographies in 12 healthy young adult females (mean body mass index <21 kg/m^2) before and after administration of leuprolide acetate [30]. 17 ß-estradiol levels were effectively reduced with leuprolide administration in all subjects with a mean reduction of 70%, and women reported increased snoring. However, there were no differences in objective measures of snoring, arousal indices, or obstructive breathing events. These findings suggest that acute reduction in estrogen levels is not sufficient to induce sleep apnea in lean otherwise healthy females. It will still be important to repeat this study in obese females without and with mild sleep apnea to determine if acute reductions in estrogen levels can affect the prevalence or severity of sleep-disordered breathing.

Despite increasing prevalences for both OSA and breast cancer, the effects of other estrogen blockade therapies such as tamoxifen on obstructive sleep-disordered breathing have not been reported. Tamoxifen may worsen OSA in at least the subset of premenopausal women with some propensity towards pharyngeal collapse in sleep. This issue should be advanced. If tamoxifen were found to worsen sleep apnea, this would impact upon treatment decisions in select cases of breast cancer and would suggest the need for improved screening for sleep apnea in persons in whom the drug is indicated. At the same time, examining the acute and chronic effects of estrogen blockade in individuals with mild OSA would also provide insight into the role intrinsic estrogen plays in upper airway collapsibility and sleep-disordered breathing.

Hormonal Replacement Therapy Effects on Obstructive Sleep-Disordered Breathing

Both estrogen and progesterone enhance ventilatory responses to carbon dioxide and oxygen levels, and, thus, both estrogen and progesterone have the potential to partly offset the sleep state-dependent reductions in ventilatory drive that are believed to underlie the pathogenesis of OSA [31]. Several studies have examined the effects of progesterone and/or estrogen replacement therapy on OSA in postmenopausal women. One week of medroxyprogesterone and premarin therapy in nine women with mild sleep apnea and previous bilateral ovariectomy and hysterectomy resulted in significant reductions in obstructive events [32]. Two smaller studies also identified reductions in apnea frequency with estrogen and progesterone supplementation [33, 34]. A study of six postmenopausal women found a reduction in the respiratory disturbance index from 25 to 12 events/hour with estrogen therapy alone [35]. In this study, the authors suggested that supplementation with progesterone was of no additional benefit and may have worsened the apnea frequency in a subset of the subjects [35]. A larger, randomized placebo-controlled trial also supports a positive effect of estrogen and progesterone (as estradiol valerate with the gestagen dienogest) on the AHI [36]. In this study, 51 postmenopausal women showed an overall improvement in AHI on combined therapy but not while taking estrogen alone. However, a similar number of studies have shown contradictory findings. Two small studies demonstrated no significant effects on sleep-disordered breathing frequency while using either estrogen alone therapy or estrogen and progesterone therapy in subjects with moderate-severe OSA [37, 38]. In a larger ($n=62$) randomized controlled crossover trial, estrogen therapy had minimal effects on sleep apnea or upper airways resistance syndrome in postmenopausal women [39]. In a more recent prospective trial, 62 women underwent baseline polysomnography and were then allowed to choose for themselves the use of hormonal replacement therapy; polysomnography in those using and not using HRT was repeated after 5 years [40]. Women who elected to use replacement therapy had improved nocturnal oxygenation, and, although the frequency of obstructive sleep-disordered breathing events did not improve, the women using HRT had less oxyhemoglobin desaturation with events. A potential confounder in this study was that women using HRT were, as a group, significantly leaner. The possibility that the difference in weight explains the improved oxygenation cannot be excluded. Future trials are needed to determine whether oxygenation improves in weight-matched women using HRT and whether sleepiness and cognitive function improve with HRT.

Overall, whether discrepancies in the effects of hormonal replacement therapies are due to underpowered studies, differences in drugs and doses, severity of apnea, age effects, or physical differences is not known. It is quite likely that sample sizes are inadequate to detect small but important reductions in apnea–hypopnea indices. However, in light of the absence of a large positive effect of hormonal replacement therapy on sleep apnea in postmenopausal women and the increasingly recognized adverse effects of HRT [41], hormonal replacement therapy for the treatment of obstructive sleep-disordered breathing events in postmenopausal women cannot be justified at present.

Estrogen and progesterone are not the only hormones that change across menopause. Menopause is associated also with declining levels of circulating testosterone [42]. In contrast to the potentially protective effects of estrogen and perhaps progesterone on OSA, testosterone has been implicated in the pathogenesis of OSA in men [43]. Testosterone supplementation in women has been shown to raise the hypocapneic ventilatory threshold, an effect that increases respiratory instability and, thus, could increase sleep apnea [44]. Therefore, use of androgen supplementation in postmenopausal women may exacerbate sleep apnea. In contrast, age-related declines in androgens would be expected to counter to some degree the climacteric increase in OSA.

Menopause is associated also with increased leptin levels, but only in females who gain weight [45, 46]. Leptin has significant stimulatory effects on ventilation and ventilatory responses to hypercapnia and hypoxia. Females have higher levels of leptin than men when matched for BMI, raising the possibility that leptin levels in females protect them in part from sleep apnea [47]. Complicating the interpretation of changes in leptin levels and their effects on respiration are bidirectional alterations in leptin resistance or reduced leptin responsiveness that may accompany the change in leptin level. Thus, an observed increase in leptin levels does not necessarily signify an increase in leptin activity. Clearly, further studies are needed to determine whether increased leptin signaling in postmenopausal women could improve obstructive sleep-disordered breathing.

In summary, hormonal changes are very likely to contribute to the development and/or progression of OSA in women across the menopausal transition. To really advance this hypothesis, a large-scale prospective study is needed to monitor sleep-disordered breathing in women across the menopause transition. To best determine exactly how hormonal changes in menopause contribute to sleep-disordered breathing requires following hormonal changes in parallel with sleep-disordered breathing changes across menopause, while also addressing the nonhormonal potential menopausal risk factors delineated next in this chapter.

Ventilatory Responsiveness Is Altered with Menopause

There are several unique characteristics of respiratory drive and responsiveness to respiratory challenges that may protect premenopausal women from sleep state-dependent respiratory instability. Presently, it is not known if gender differences in ventilatory responsiveness are explained completely by sex hormone signaling in the brain, whether there are secondary (long-term) hormonal changes and/or whether gender differences are independent of hormone differences. Progesterone has a clear stimulatory effect on central ventilatory drive and has been shown to enhance the respiratory response to acute hypoxia in waking [48]. There is some evidence that subtle physiological changes in hormonal levels are sufficient to alter respiratory responsiveness. Following a voluntary hyperventilation effort, ventilation does not abruptly return to normal but slowly declines. In premenopausal females, there is menstrual cycle variation in this post-hyperventilation ventilatory decline, such that ventilation remains elevated for

longer after a hyperventilation episode during the luteal phase than the follicular phase [49]. This raises the possibility of a novel way through which progesterone might stabilize ventilation during sleep after a sigh or deep breath. However, the rates of decline in ventilatory responses to acute hypoxia and to hypercarbia (the respiratory changes one expects in sleep apnea) do not vary with gender or with menstrual phase [50]. Other groups have looked at the absolute minute ventilation response to hypoxia and hypercarbia [51, 52]. The small sample sizes in these technically challenging clinical studies cannot exclude small (<30%) differences across gender.

In contrast to the above responses to acute single exposure to hypoxia and hypercarbia, there may be gender differences in responses to episodic hypoxia and hypercapnia, changes that more closely mimic what is seen in sleep apnea [52]. Specifically, males have a larger ventilatory response to hypercarbia in the presence of episodic hypoxia than females [52]. The significance of the greater ventilatory response upon arousal in males is that males develop more significant hypocapnia and are therefore likely to lower carbon dioxide levels to below the apnea threshold, thereby promoting ventilatory instability. Presently, it is not known whether this stabilizing response in premenopausal females diminishes or is attenuated across the development of menopause. It would also be of interest to examine this response before and after estrogen blockade in premenopausal females. The hypercapneic ventilatory response varies with estrogen and progesterone status, with substantial augmentation in the response with HRT. Recently, Preston et al. determined that postmenopausal reductions in the hypercapneic response are largely a consequence of reduced central chemosensitivity [53]. Impaired central chemosensitivity could contribute to longer and more severe apneas in postmenopausal women.

An equally compelling gender difference that may influence respiratory stability in sleep has been reported by Jordan and McEvoy [54]. They found that the cardiorespiratory responses to arousal from NREM sleep were far more pronounced in males than in premenopausal females. Men had higher initial increases in ventilation with arousal, and then, upon resumption of sleep, men showed more ventilatory suppression. This would clearly promote sleep state respiratory instability. Cardiovascular responses were measured as well. The amplitude of the finger pulse was larger in males upon arousal (either spontaneous or elicited), raising the possibility that sympathetic drive in response to arousal changes more in males, relative to premenopausal females. Subsequently, determinants of the apnea threshold have been examined in men and pre- and postmenopausal women [55]. Differences among the groups in end-tidal carbon dioxide levels were not observed during stable breathing in non-REM sleep. However, the magnitude of the change in end-tidal carbon dioxide levels needed to induce central apnea was larger for premenopausal women compared to postmenopausal women or men. Postmenopausal women were reevaluated after receiving HRT with oral medroxyprogesterone acetate and conjugated equine estrogen for 30 days. On HRT, end-tidal carbon dioxide levels during stable breathing decreased, and the magnitude of the change in end-tidal carbon dioxide need to induce central apnea increased significantly compared to baseline. This study suggests that estradiol and progestins affect the apnea threshold and control of breathing during non-REM sleep. It will now be important to

determine if the amplitude of ventilatory and/or cardiovascular responses predicts sleep-disordered breathing in women, and if this response changes across menopause with the progression of OSA. We must also determine if this gender difference can be explained by increased sympathetic drive in males, relative to females, because this may offer a potential pharmacotherapeutic avenue to reduce the progression of sleep-disordered breathing across menopause.

Nasal occlusion in sleep serves as a model of precipitating or increasing the frequency of obstructive sleep-disordered events. Carskadon et al. compared the responses of premenopausal, perimenopausal, and postmenopausal women to nasal occlusion events in sleep [56]. There was no main effect of menopausal status on the frequency or severity of apnea and hypopnea events or on the oxygen nadirs for events. This would suggest that changes in hormone levels across menopause are not a major contributor to the increased prevalence of OSA with menopause. In contrast, the key variables for the development of apneas and hypopneas precipitated by nasal occlusion were BMI, neck circumference, and mandibular-hyoid distance [56].

In summary, the gender differences identified to date that might protect premenopausal females from OSA are less hyperpnea after episodic hypoxia in females and more stable respiratory effort in NREM sleep in response to hypercarbia and arousals. It would be of considerable interest to test the effect of acute and longer-term estrogen blockade on these gender differences to determine the role played by hormone activity.

Obesity and Fat Redistribution with Menopause

Obesity and neck circumference are both well-established independent risk factors for OSA, and obesity increases with aging. A recent follow-up report in the Study of Women's Health Across the Nation (SWAN) with over 3,000 racially and ethnically diverse women followed across the menopausal transition found that menopause overall was not associated with significant weight gain or an increase in abdominal girth [57]. Weight over 3 years of observation increased by 3%, and waist circumference also increased by just 3%, whether women remained premenopausal, shifted into the menopause transition or completed menopause [57]. There was variability in weight gain across women in each group, such that it would be of interest to compare the risk of sleep apnea in women who did gain weight across menopause with those who did not gain weight. At the same time, it would be of considerable interest to determine if sleep apnea may occur across menopause without weight gain in some females.

Upper Airway Anatomy and Mechanics

Gender differences between men and premenopausal women have been described that may contribute to the increased prevalence and severity of sleep apnea in men. In males, the longer upper airway may contribute to increased collapsibility [58]. A separate study, however, found no difference in collapsibility between normal

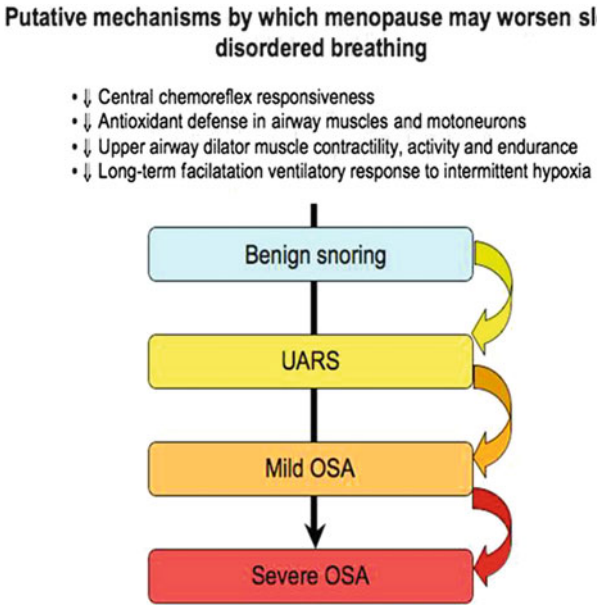

Fig. 20.1 Potential mechanisms by which reduced estrogen and progesterone may worsen obstructive sleep apnea (OSA) in females with increased collapsibility of the upper airway. Composite results from recent studies demonstrate that loss of estrogen and/or progesterone can have profound physiological effects (listed above) that could potentially worsen breathing during sleep in individuals with some upper airway collapsibility, shifting them from snoring to upper airway resistance syndrome (UARS), mild OSA, or possibly severe OSA. Causes of obstructive sleep apnea are multifactorial, and it is likely that menopausal state by itself does not cause obstructive sleep apnea but rather may shift the severity of disease as shown above through one or more of the proposed mechanisms. Epidemiological studies described here suggest that the larger menopause shift may occur from upper airways resistance syndrome to mild obstructive sleep apnea

males and females [59]. Moreover, the airway size is smaller in females [60]. The increased collapsibility in males may be a consequence of the increased neck circumference in males [61]. Yet neck circumference alone and neck circumference normalized to height explain less than 25% of the gender predisposition to OSA. There are also soft tissue gender differences that may predispose to OSA. The lateral fad pads are larger in males [62], but the relative role of this particular anatomical feature has not been differentiated from neck circumference. Whether any of these anatomical risk factors for OSA are modified across the menopause transition or in parallel to the development of OSA requires studying women across the menopausal transition.

Estrogen may have several important effects on upper airway dilator muscle function, as summarized in Fig. 20.1. Recent studies using a rat model of surgically induced menopause have found that estrogen improves genioglossus strength and reduces muscle fatigability [63, 64]. Intriguingly, estrogen may have estrogen

receptor-independent protective effects against hypoxic injury, including augmentation of the ERK/AKT pathways [65], although 17 ß-estradiol enhances genioglossus contractility through an estrogen receptor-dependent mechanism [66].

Conclusion

The prevalence of OSA increases with menopause. While this was established over two decades ago, the mechanisms by which sleep apnea worsens with menopause remain unclear and studies are needed to identify mechanisms. It is likely that estrogen and progesterone have complex effects on ventilatory control and muscle function. In addition, there are likely additional important state-dependent ventilatory response patterns and potentially changes in upper airway collapsibility which may or may not relate directly to hormonal changes. Future studies will be most insightful if cohorts of women are followed completely from well before the menopause transition to well into menopause, examining hormonal, weight, ventilatory, and upper airway dynamics in parallel with sleep studies to best identify important factors contributing to the increased risk of sleep apnea in menopause.

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