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Evaluation and Management of Sleep Disturbance During the Menopause Transition

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Abstract

Sleep disturbances in midlife women are common and have been associated with the menopause transition itself, symptoms of hot flashes, anxiety and depressive disorders, aging, primary sleep disorders (i.e., obstructive sleep apnea, periodic limb movement disorder), comorbid medical conditions and medications, as well as with psychosocial and behavioral factors. Because there are several common sources of sleep problems in midlife women, the cause of an individual woman's sleep disturbance may be multifactorial. Effective behavioral and pharmacological therapies are available to treat sleep disturbances of different etiologies. This review provides an overview of different types of sleep disturbance occurring in midlife women and presents data supporting the use of hormone therapy, hypnotic agents, and behavioral strategies to treat sleep problems in this population. The review aims to equip clinicians evaluating menopause-age women with the knowledge and evaluation tools to diagnose, engage sleep experts where appropriate, and treat sleep disturbance in this population. Sleep disorders in midlife women should be treated because substantial improvements in quality of life and health outcomes are achievable.

Introduction

Sleep complaints increase dramatically in women during midlife,^[1] suggesting a potential association between sleep disturbance and the menopause transition. In the 2005 National Institutes of Health State-of-the-Science Conference panel report on menopause-related symptoms,^[2] sleep disturbance was identified as a key symptom of the menopause transition. Nocturnal hot flashes have been hypothesized to be a primary source of menopause-associated sleep disturbance. However, other contributors to sleep disruption must also be considered in midlife women who report sleeping problems. Common etiologies of persistent sleep disturbance in this population include hot flashes, age-related factors, primary sleep disorders, and psychiatric illness.^[3] Additional nonpathological causes of sleep disruption may result from psychosocial, behavioral, and stress-related factors.

This review provides an overview of different types of sleep disturbance occurring in midlife women. Sleep-related concerns associated with (1) vasomotor symptoms; (2) depressive and anxiety symptoms; (3) primary sleep disorders, and (4) aging and medical illness are described. Data supporting these common sources of sleep disturbance during the menopause transition, as well as other nonpathological contributors, are reviewed. Throughout the article, differences between perceived and objectively measured sleep are discussed. The review aims to equip clinicians evaluating menopause-age women with the knowledge and evaluation tools to diagnose, engage sleep experts where appropriate, and treat sleep disturbance in midlife women.

Terminology and Definitions

The term *sleep disturbance* describes subjectively perceived sleep problems that do not necessarily meet criteria for a clinical disorder but are bothersome to the individual. In

contrast, insomnia is a clinically defined disorder that is diagnosed when an individual reports a constellation of symptoms that meets criteria for an insomnia syndrome.^[4] The insomnia diagnosis requires a report of difficulty initiating sleep, maintaining sleep, or experiencing nonrestorative sleep, despite adequate opportunity for sleep. Daytime functional impairments resulting from nocturnal sleep disturbance must also be reported.^[4] Insomniacs commonly describe excessive daytime sleepiness and/or fatigue that co-occurs with their diminished ability to sleep at night. A diagnosis of insomnia does not require that sleep disturbance be documented objectively.^[5] In fact, when polysomnography (PSG) is conducted, abnormalities may or may not be detected and, even if documented, may not correspond to the clinical complaints.^[5] Thus PSG is not recommended routinely to diagnose insomnia.^[6] Nevertheless, PSG can sometimes be useful in insomnia patients—especially those who fail to respond to treatment—because it has the potential to reveal an occult sleep disorder that was not suspected based on history and physical examination when the initial diagnosis of insomnia was made.^[7]

Another common sleep disorder that does not require a PSG for diagnosis is restless legs syndrome (RLS). RLS is a sleep disorder characterized by an urge to move the legs during periods of rest or inactivity.^[4] By definition, RLS symptoms have a circadian pattern with increasing severity at night. RLS is considered a sleep disorder because deliberate limb movements initiated to provide relief from RLS discomfort delay the onset of sleep. Individuals with RLS frequently report sleep-onset insomnia and subsequent daytime sleepiness and fatigue.

In contrast to insomnia and RLS, other primary sleep disorders (e.g., sleep apnea and periodic limb movement disorder [PLMD]) are diagnosed using objective measurements of sleep. Conventional PSG detects sleep stages (rapid eye movement [REM], non-REM light [stage 1 and 2, also called N1 and N2], and non-REM deep sleep [stage 3 and 4, also called N3]) by measuring brain activity using electroencephalography (EEG) combined with electro-oculography and electromyography to measure eye movements and muscle activity, respectively.^[8,9] Respiratory effort and airflow indicators and pulse oximetry are used concurrently to diagnose sleep-disordered breathing, most commonly obstructive sleep apnea (OSA), which is defined by repetitive episodes of complete (apnea) or partial (hypopnea) airway obstruction that are associated with transient oxygen desaturations and short arousals from sleep. Multiple arousals related to airway obstruction throughout the night lead to snoring and sleep fragmentation, which can result in sleepiness, lethargy, and mood disturbances during the daytime.^[4] A PSG evaluation for OSA should be considered when individuals report snoring together with awakenings from sleep, unrefreshing sleep, and/or daytime sleepiness.

A diagnosis of PLMD should be considered when an individual reports awakenings and kicking during the night, restless sleeping, and daytime fatigue. PLMD is diagnosed based on repetitive, stereotyped limb movements (PLMs) that last up to several seconds and lead to fragmentation of and repeated awakenings from sleep, which results in daytime sleepiness and fatigue. However, PLMs are considered pathological only if they occur frequently at night and produce arousals from sleep. The pathophysiology of PLMD is unknown, but it frequently co-occurs with RLS, REM behavior disorder, or narcolepsy. Up to 80% of patients with RLS also have PLMD, and 30% of individuals with PLMD also have RLS.^[10] Secondary, reversible causes of PLMs, including antidepressant medication use and OSA, also exist. In contrast to RLS, PLMD is a disorder associated with awakenings after sleep is initiated, and PLMD requires a PSG to establish the diagnosis.

Actigraphy is an alternate technology to PSG that is used to document rest and activity states. The device is worn like a wristwatch and measures activity counts with an

accelerometer. Sleep and wakefulness are estimated from the activity counts using algorithms that were developed by correlating patterns of movement with EEG-based determination of sleep. Actigraphy provides an estimate of sleep time, sleep onset, sleep offset, and sleep efficiency and also detects sleep disturbance associated with increased movement. It does not measure sleep architecture, however, and the accrued data are not fully concordant with those procured by PSG.^[11–16] Although actigraphy cannot be used to make a diagnosis of sleep apnea or PLMD, it offers advantages over PSG for measuring sleep disturbance and insomnia, including the capacity to monitor sleep behavior over multiple nights and the ability to measure sleep in an individual's usual sleeping environment.

Association between Sleep Disturbance and the Menopause Transition

In contrast to men, sleep complaints increase dramatically during midlife in women, with the prevalence increasing from ~12 to 40% in women during the late 40s and early 50s,^[1] consistent with the typical age of the menopause transition. Epidemiological studies indicate that women are more likely to report sleeping problems as they transition from late reproductive age into the perimenopause.^[17–21] In epidemiological studies documenting the presence of an insomnia syndrome, peri- and early postmenopausal women are more likely to meet criteria for an insomnia disorder than older reproductive-age women (26% versus 13%).^[22] These results highlight the vulnerability to perceived sleep disturbance and insomnia during the menopause transition.

However, in contrast to the perceived sleep disturbance associated with the menopause transition, studies examining differences in objectively measured sleep patterns using PSG have not found clear evidence that peri- and postmenopausal women have worse measured sleep than premenopausal women.^[18,23,24] In one large epidemiological study that found comparable PSG sleep among women in different menopause status groups,^[18] postmenopausal women obtained an average of 14 minutes more sleep per night than premenopausal women and had slightly more deep sleep (16% versus 13%).^[18] These differences are consistent with better PSG sleep in the postmenopausal group, but, in light of the higher rate of subjective sleep complaints in this sample of postmenopausal women, these PSG findings may represent a compensatory response to other unmeasured sleep differences.

Although the absence of abnormalities in PSG-measured sleep in perimenopausal women might appear inconsistent with the perceived sleep disturbance reported during the menopause transition, it is notable that perceived and objectively defined sleep measures capture different parameters of sleep and frequently do not coincide among women with vasomotor symptoms^[25] or in individuals with sleep disorders such as OSA.^[26] Individuals reporting insomnia frequently do not have abnormalities on PSG,^[5] and, in older adults, significant sleep abnormalities can be seen on PSG among individuals who do not identify themselves as having a sleep problem.^[27]

Changing levels of sex hormones across the menstrual cycle and through the menopause transition have been associated with differences in perceived sleep quality and objectively measured sleep patterns.^[20,28–31] lists findings from studies reporting associations between reproductive hormone levels and sleep in women during the menopause transition. Taken together, results of these studies suggest that decreases in estradiol and increases in follicle-stimulating hormone, progesterone, and testosterone may adversely modulate sleep-wake behaviors and contribute to the heightened risk for sleep disturbance and insomnia in women undergoing the menopause transition.

Factors Associated with Perceived and Measured Sleep Disturbance in Women during the Menopause Transition

Several clinical characteristics have been associated with sleep complaints in peri- and postmenopausal women (). Studies investigating sources of perceived and PSG-measured sleep disturbance in midlife women who report sleep problems have found a variety of associated factors.^[3,21,32,33] The specific conditions associated with sleep disturbance vary depending on the particular sleep parameter investigated. Psychological symptoms and hot flashes are associated most strongly with perceived sleep disturbance, whereas OSA and PLMD are associated with objective abnormalities in PSG-measured sleep. Such studies suggest that midlife women with sleep problems are a heterogeneous group. Given the wide range of potential sleep problems, it is expected that sleep disturbance during midlife is multifactorial and that several sleep-disrupting causes may co-occur even within an individual woman. The challenge of making attributions of sleep disturbance to specific health conditions is made even more complicated by age-related increases in sleep that can be difficult to disentangle.

Sleep Disturbance and Hot Flashes

Nighttime hot flashes, or night sweats, are almost universal in women with daytime hot flashes. When hot flashes persist during the night, they frequently, but not universally, awaken a woman from sleep, although not every nocturnal hot flash is associated with an awakening. Women with hot flashes may also experience nocturnal awakenings that are unrelated to a vasomotor event. Hot flashes occur in 60 to 80% of women during the menopause transition^[34] and persist for 4 to 5 years on average.^[35,36] Because of their prevalence, nocturnal hot flashes are thought to be a common source of sleep disturbance in midlife women.

Multiple large epidemiological studies have concluded that, although hot flashes are associated with reduced sleep quality, including unrefreshing sleep and repeated brief awakenings from sleep, they are unlikely contributors to problems with falling asleep at the beginning of the night.^[3,18–20,29,31,33,37,38] Hot flashes/night sweats correlate with the severity of insomnia symptoms^[39] and are associated with a greater likelihood of an insomnia diagnosis (28.5% versus 10.5%).^[22] For women with severe hot flashes, 81.3% report poor sleep quality, and 43.8% meet criteria for chronic insomnia.^[22]

Despite the strong association between hot flashes and insomnia, only limited and contradictory evidence supports an association between hot flashes and objectively measured sleep disturbance.^[18,23,24,37–42] Although perceived hot flashes correlate with poor perceived sleep quality, studies measuring hot flashes objectively have not linked hot flashes to perceived sleep disturbance.^[43] Similarly, perceived hot flashes were not associated with differences in PSG parameters of sleep in a large epidemiological study,^[18] and a smaller study found reduced sleep efficiency and longer REM latency in women reporting hot flashes.^[24] However, when sleep was measured using actigraphy, hot flashes were associated with selected components of sleep disruption (i.e., greater nighttime wakefulness and more wake episodes).^[39]

When hot flashes are measured objectively, data bearing on the relationship to objectively measured sleep are conflicting ().^[37,42,44–46] These studies compared cross-sectional PSG-measured sleep parameters in symptomatic midlife women with those observed in women without objectively measured hot flashes. Results from these studies are inconsistent, with four identifying a deleterious effect^[37,40–42] and one showing no effect of hot flashes on sleep.^[38] The contradictory results of these studies may result from small sample sizes,

cross-sectional designs, and varying eligibility criteria and analytic approaches. Four studies of postmenopausal women did not require sleep complaints for eligibility,^[38,40–42] and another study of breast cancer patients with insomnia did not require hot flashes for eligibility.^[37] Additional studies are clearly needed to better elucidate and isolate the impact of hot flashes on objective parameters of sleep.

Although the absence of a clear-cut association between hot flashes and objectively measured sleep appears to contradict the strong association between perceived hot flashes and subjective sleep disturbance, these sleep parameters measure different components of sleep that may not necessarily be overlapping. In addition, although PSG is the gold standard for screening and quantifying sleep disturbance, PSG is typically conducted in the laboratory for 1 to 3 nights, potentially providing insufficient sampling to adequately capture sleep disturbance related to hot flashes. Supporting this notion is the observation of night-to-night variability in the severity of other disorders that disrupt sleep such as OSA^[47] and insomnia.^[48,49] Future investigations may inform which component of objectively measured sleep predicts the perception of poor sleep quality in women with hot flashes.

Data on the mechanism by which hot flashes may disrupt sleep are limited and controversial.^[2] Hot flashes can be documented objectively during the nighttime even in the absence of an awakening, indicating that not all hot flashes are equally disruptive to nocturnal sleep.^[40] The likelihood of waking up in association with a hot flash may vary in part with the sleep stage in which the hot flash occurs, with a greater likelihood of awakening during sleep periods composed of less REM sleep.^[45]

Changes in core body temperature (T_C) produced by hot flashes may be another mechanism through which hot flashes produce sleep disruption. Thermoregulation is tightly coupled to sleep, and some have hypothesized that an inability to dissipate heat at night reflects a hyperaroused state that may lead to insomnia.^[50] Hot flashes are commonly preceded by a transient increase in T_C .^[51] At hot flash onset, sternal sweating occurs, which dissipates heat and results in a decline in T_C , sometimes transiently below baseline T_C levels. Although it has been hypothesized that fluctuations in T_C precipitate an awakening, data indicating that awakenings are equally likely to precede or follow a nocturnal hot flash suggest that the T_C increase frequently preceding a flash may not necessarily be responsible for inducing an awakening.^[38] However, it is plausible that the central nervous system changes that likely precede both the fluctuation in T_C and the perception of a hot flash may be responsible for precipitating an awakening.

Overall, T_C is lower among women with hot flashes throughout the day and night,^[51] suggesting a disruption of the typical circadian temperature rhythm. Results of these preliminary studies are at odds with other investigations indicating that higher T_C during sleep is associated with worse PSG-measured sleep.^[52,53] A potential link between thermoregulation, hot flashes, and sleep disruption warrants further investigation to determine the precise mechanism underlying these interrelated physiological processes.

Sleep Disturbance, Anxiety, and Depressive Symptoms

In addition to hot flashes, higher levels of depressive^[20,21,29,33] and anxiety^[3,21,29] symptoms have been associated with a perception of worse sleep quality in midlife women. Such studies have not specifically distinguished whether women with depressive and/or anxiety symptoms meet criteria for a psychiatric disorder. Other studies confirm that even mild psychological distress is linked to worse sleep quality.^[26]

Psychiatric disorders including major depression, dysthymia, generalized anxiety disorder, panic disorder, and other mood and anxiety disorders all have sleep disruption (perceived

and objectively measured) as a common symptom component.^[54,55] Because women are at increased risk for experiencing a major depressive episode during the perimenopause,^[56,57] sleep disturbance during midlife may be a marker of a clinically significant mood disorder that warrants further evaluation. Moreover, because hot flashes are strongly associated with depression symptoms^[58,59] and women with hot flashes are more likely to develop a major depressive episode,^[56] sleep problems may result from both hot flashes and depression in women who have multiple concurrent symptoms. Midlife women who have depression in addition to hot flashes and sleep disruption report worse sleep quality and objectively measured sleep than those without depression,^[60] suggesting that depression and hot flashes may have an additive effect on sleep disturbance.

To confound matters, women with a prior history of depression are more likely to report hot flashes^[61] and may develop sleep disturbance because of hot flashes when they are not depressed. Another potential temporal pattern is that sleep disturbance resulting from hot flashes may also increase the risk of subsequent depression.^[62,63] Indeed, disrupted sleep has been shown to precede the onset^[64] and recurrence^[65] of depression in other populations.

Like depression, anxiety correlates strongly with insomnia. This link has been established for specific anxiety disorders, including panic disorder,^[66] generalized anxiety disorder,^[67] social phobia,^[68] and posttraumatic stress disorder.^[69] In addition, trouble sleeping is associated with mild anxiety symptoms, presenting as higher levels of stress, tension, and self-consciousness.^[21] Moreover, like depressive symptoms, anxiety also correlates with and commonly precedes the onset of hot flashes during the menopause transition,^[70,71] raising the possibility that sleep disturbance may result from anxiety, hot flashes, or both. Because anxiety and depressive symptoms commonly, but not uniformly, co-occur, it can be difficult to disentangle the individual contributions of these psychological symptoms. Thus, in evaluating women who report sleep disturbance during the menopause transition, anxiety disorders, depressive disorders, and hot flashes should all be considered as potential contributing factors that may act independently or jointly to disrupt sleep.

Primary Sleep Disorders

Primary sleep disorders such as OSA, RLS, and PLMD are common in midlife women and contribute to complaints of disturbed sleep in this population.

The overall prevalence of OSA is estimated at 9% in women, but this prevalence increases as women transition into midlife, with the prevalence increasing from 6.5% to 8.7% to 16% in women in their 30s, 40s, and 50s, respectively.^[72] Several physiological changes that occur in midlife women converge to increase OSA in this population. For instance, OSA risk rises both with age and with increasing body mass index (BMI).^[73] Studies that have examined OSA specifically in midlife women suggest that body weight is a stronger predictor of OSA than is menopausal status per se,^[74–77] and thus women who experience excessive weight gain in midlife may experience more disrupted sleep and sleep-disordered breathing.^[78] Nonetheless, when controlling for age and BMI, OSA is more common among postmenopausal women than premenopausal women, suggesting that the menopause transition is also a factor in the development of OSA.^[72–79]

Evidence suggests that sleep-disordered breathing is underdiagnosed in women,^[72,80,81] perhaps due to gender bias^[81] or differing symptom presentations between men and women.^[82,83] Compared with men with OSA, women with OSA are more likely to have an initial complaint of insomnia or depression.^[83] It is incumbent on clinicians treating sleep disturbances in midlife women not to overlook symptoms suggestive of sleep-disordered breathing and to refer such patients for PSG given the medical risks associated with OSA

including coronary artery disease,^[84] hypertension,^[85] stroke,^[86] depression,^[87] and death.^[88]

RLS is another common sleep disorder that disrupts sleep in midlife women. Although RLS affects ~10% of the population, the disorder is twice as common in women as men,^[89] and the risk of RLS in women increases with age and parity.^[90] During midlife, RLS occurs more frequently in women with vasomotor symptoms, but this disorder has not been linked with menopausal status or hormone therapy.^[91] The pathophysiology involves iron metabolism and dopaminergic neurotransmission primarily,^[92,93] but secondary causes (e.g., thyroid disease, antidepressant medication use) also exist. A possible etiologic role of reproductive hormones in RLS is suggested by an association between RLS and increased endogenous estradiol levels in pregnant women.^[94] Because RLS increases with aging and secondary causes that are common in midlife women, a clinical history for RLS symptoms should be obtained when problems initiating sleep are reported.

PLMD is another primary sleep disorder that increases in prevalence with age and is common among menopausal women.^[95] Because PLMs may result from the use of antidepressant medications and sleep-disordered breathing, both of which are common in midlife women, secondary causes of PLMs should be considered because they may play a role in the high prevalence of PLMD in this population.

Although a role for estrogen in the etiology of PLMD has been suggested by increased PLMs during pregnancy,^[96] the role of sex hormones in PLMD has not been well defined in women undergoing the menopausal transition. Two small randomized controlled trials of hormone therapy in postmenopausal women showed that estrogen plus progesterone,^[97] but not estrogen alone,^[95] decreased PLMs. The link between reproductive hormones and PLMD is unclear, and further study of the roles of estrogen and progesterone in the etiology and treatment of PLMs is needed.

Age-related Sleep Changes and Medical Conditions

Although perceived sleep disturbance in midlife women is associated with the menopausal transition, sleep complaints in this population also correlate with age-related sleep changes and with medical conditions that increase during midlife.^[98] Common conditions that may affect sleep that increase with age include obesity,^[99] cancer,^[100] gastroesophageal reflux,^[101] urinary incontinence and nocturnal micturition,^[77,102–104] thyroid dysfunction,^[105] chronic pain syndromes,^[106] and fibromyalgia.^[107] As women age, increased use of neuroactive medications may also contribute to sleep difficulties.

Behavioral and Psychosocial Factors

Other common causes of sleep disturbances in midlife women that may contribute to significant sleep disruption include poor sleep hygiene (i.e., irregular sleep-wake schedule, excessive napping, insufficient sleep), decreased sleep due to volitional factors (i.e., staying up late or rising early by choice or to meet work or social obligations), and environmental disturbances (e.g., snoring bed partner, sleeping with lights, television, cell phone on).

Psychosocial factors may also contribute to sleep disturbances. Disturbed sleep in midlife women has been linked to marital dissatisfaction,^[108] and women in midlife are often sandwiched between the time-consuming demands of caring for their children and their aging parents. Therefore, although hot flashes, medical conditions, psychiatric illness, sleep disorders, and medications may be etiological in sleep disturbance, behavioral and psychosocial factors are important in the differential diagnoses for the midlife woman reporting nonrestorative sleep, sleep disruption, and/or daytime fatigue.^[77]

Management Strategies for Sleep Disturbances during the Menopause Transition

Randomized placebo-controlled trials have demonstrated the efficacy of hormone therapy (HT) and hypnotic agents for treatment of sleep disturbance occurring in women during the perimenopause and early postmenopause. In this section, we summarize results of randomized controlled trials (RCTs) comparing HT and hypnotic therapies to placebo in the management of sleep disorders in perimenopausal and postmenopausal women. Also discussed briefly are nonpharmacological behavioral interventions that have been studied widely for the management of insomnia (i.e., cognitive behavioral therapy, sleep hygiene), albeit not specifically in the context of reproductive aging.

Beyond the scope of this review is a discussion of other commonly used sleeping aids for sleep disruption, including benzodiazepines, trazodone, melatonin, melatonin agonists, diphenhydramine, and other over-the-counter treatments. Many of these are effective hypnotics, but none have been studied specifically in women with sleep disturbances related to the menopause transition.

Estrogen and Progestin Therapy

The effect of HT on sleep has been studied widely in postmenopausal women (and). The vast majority of RCTs comparing HT to placebo have found that HT improves perceived sleep quality and self-reported sleeping problems more than placebo,^[97,109–122] although several others did not find an advantage of HT over placebo ().^[123,124]

Results of studies using PSG to measure HT effects on sleep parameters objectively have been mixed (), with some reporting improvement in selected components of sleep^[97,117,118,121,122,125,126] and others describing either no effect^[76,95,122] or even deleterious effects of interventions on isolated components of PSG-measured sleep.^[122,127] Overall, most of the studies involving PSG measures showed small but favorable effects of HT on sleep. The most consistent findings are less fragmentation of sleep, with a reduction in wakefulness and arousals. These decreases in PSG-measured sleep fragmentation are consistent with subjective reports of improved sleep quality with HT. However, the positive effects of HT on sleep as measured by PSG were small in some studies, which may limit the clinical significance of these findings. Inconsistencies between study results relating to selected PSG-measured sleep parameters are difficult to interpret in part because of small sample sizes and due to variability in measurement approaches and outcome variables. Additional studies are thus needed to gain a better understanding of the effects of HT on PSG-measured sleep in women during and after the menopause transition.

Analyses of the effects of HT on sleep have commonly been conducted as part of larger investigations of multiple quality-of-life domains and primarily in women who do not have a specific sleep complaint, although some^[112,115,119,120,128] required hot flashes for eligibility. Although no sleep complaint was required, it is notable that improved sleep was reported and/or measured by PSG among study populations of predominantly asymptomatic women. However, some studies found that the beneficial effects were small and potentially not clinically meaningful. Finally, several RCTs reported that HT had a more marked effect on sleep either among women with hot flashes or for those with sleep disturbances associated with hot flashes,^[112–114] suggesting that sleeping problems co-occurring with nocturnal hot flashes are most amenable to treatment with HT.^[116]

Most studies administered combined estrogen and progestin therapy, making it difficult to distinguish the beneficial effects of estrogen from that of the coadministered progestin.^[97,109,110,112–115,117–121,124,125,127] However, beneficial effects on sleep were also

seen in studies using estrogen alone^[95,111,122,126,129,130] or progestin alone,^[121,128] suggesting that estrogen and progestins may have independent therapeutic effects on sleep. Greater benefit of natural progesterone over medroxyprogesterone on perceived sleep quality and on selected PSG-based sleep parameters has been shown in preliminary studies comparing HT preparations composed of different progestins.^[117,119]

Data are limited on the effect of HT on sleeping problems among women with primary sleep disorders (). Studies in postmenopausal women who have a clinical diagnosis of insomnia show better perceived sleep quality and a trend toward improvement of PSG-measured sleep parameters with HT.^[118,125] Results of a few studies investigating the effects of hormone therapy in postmenopausal women suggest that HT may ameliorate apnea symptoms in women without a formal diagnosis of OSA.^[97,118,125,130] Studies examining effects of HT on PLMs in women without a PLMD disorder have not shown worsening of PLMs,^[95,97] which is important in light of the suggested deleterious role of estrogen in younger women with PLMD.^[96]

The mechanisms through which estrogen and progestin therapies may improve sleep are not known. Estrogen itself may have a direct sleep effect by increasing homeostatic drive for sleep;^[131] however the specific mechanisms through which these effects may occur have not been described in humans. Studies in rodents suggest that the effect of estradiol on sleep/wake cycles may be explained by a reduction in prostaglandin synthesis in the ventrolateral preoptic nucleus of the hypothalamus.^[132] Alternatively, for women with co-occurring hot flashes, estrogen therapy may improve sleep disturbance as an indirect consequence of its salutary effects on nocturnal hot flashes.^[116]

Progestins are known to exert a direct sleep induction or hypnotic effect mediated through gamma-aminobutyric acid-active metabolites.^[133] Progestins are also a potent respiratory stimulant that decrease the number of apnea episodes in men,^[134] but little is known about effects of progestins in women with OSA.

Non-benzodiazepine Sedative-hypnotics

The non-benzodiazepines zolpidem and eszopiclone have been shown to be more effective than placebo in the treatment of insomnia in peri- and early postmenopausal women.^[135–137] Studies show that these hypnotic agents improve sleep in women who have difficulty initiating^[135,136] and/or maintaining sleep.^[136,137] Participants in these studies typically had hot flashes that co-occurred with their sleep disturbance and developed in concert with the onset of hot flashes. In addition to treating insomnia symptoms, use of eszopiclone reduced the number of perceived hot flashes occurring at night, but not during the daytime, suggesting that women sleep through their nocturnal vasomotor symptoms, rather than the agent having a direct effect on hot flashes.^[136]

Sleep Hygiene and Cognitive Behavioral Therapy for Insomnia

Insomnia and milder forms of sleep disturbance may respond well to nonpharmacological treatment such as sleep hygiene approaches and cognitive behavioral therapy for insomnia. Sleep hygiene involves targeted behavioral modification approaches that can be taught in the office, reviewed on multiple online resources such as www.sleepfoundation.org, and implemented at home. Sleep hygiene addresses commonsense health practices such as exercise, diet, cigarette smoking, alcohol use, as well as environmental factors including light, noise, and temperature exposure that may interfere with sleep.^[138] Other components of good sleep hygiene include ritualized bedtime routines and strategies to avoid frustration with not being able to initiate sleep or return to sleep after an awakening.

Cognitive behavioral therapy for insomnia (CBT-I) is a structured short-term psychotherapy intervention conducted by a licensed psychologist or behavioral medicine practitioner. CBT-I identifies the psychological and behavioral factors that play a role in an individual's insomnia. Components include stimulus control, sleep hygiene, sleep restriction, paradoxical intention, relaxation training, and reframing of negative/false beliefs about sleep and insomnia. CBT-I works by modifying faulty beliefs, expectations, and attributions about sleep and insomnia. RCTs of CBT-I show benefit in 70 to 80% of individuals with primary insomnia.^[138] Multiple well-controlled trials have documented the sustained efficacy of CBT-I up to 6 months after a course of treatment is completed.^[139–141] Some studies suggest that CBT-I is more efficacious than hypnotic medications,^[141] whereas others report superior outcomes when CBT-I is combined with a hypnotic medication.^[139] Although CBT has been shown to be highly effective for treating primary insomnia, including in midlife women, its benefit for sleep disturbances related specifically to menopause have yet to be studied.

Discussion

Sleep disturbance becomes more common in women during midlife and is specifically associated with the menopause transition, with worse perceived sleep quality reported by peri- and early postmenopausal women than by similarly aged premenopausal women. Although hot flashes are linked to perceived sleep problems, their association to PSG-measured sleep remains unclear, and other common medical conditions, mental health problems, age-related factors, and primary sleep disorders also correlate strongly with sleep problems in this population. Evaluation of midlife women with sleep complaints should involve consideration of these potential causes of sleep disruption, including the possibility that different sleep problems may co-occur. Persistent sleep disturbance and insomnia may arise from a combination of predisposing, precipitating, and perpetuating factors.^[142] Therefore, women who report sleep problems during the menopause transition may be predisposed to develop new-onset sleep disturbance from hot flashes and other sleep-disrupting factors.^[143]

Treatment considerations for women with menopause-associated sleep disturbance include use of hormone therapy, hypnotic agents, and behavioral interventions. In addition, concurrent therapy may be required to target co-occurring symptoms of hot flashes, depression, and anxiety, where present. In some individuals, the constellation of co-occurring symptoms may be the primary determinant for treatment. For example, women with prominent hot flashes may be treated optimally with HT, which is likely to suppress both sleep and vasomotor symptoms.^[116] Those with concurrent hot flashes who are unable to take HT can be treated with a combination of therapies targeting both sleep disturbance and hot flashes. Alternatively, hypnotic treatments can be used alone, especially if vasomotor symptoms are not particularly bothersome or if hot flashes are primarily nocturnal, in which case treatments targeting sleep can be used to help women sleep through hot flashes, rather than directly suppress hot flashes.^[136] Widely used nonhormonal pharmacological treatments for hot flashes include serotonergic antidepressants (i.e., selective serotonin reuptake inhibitor [SSRI], selective noradrenergic reuptake inhibitor [SNRI]) and selected antidepressants (i.e., gabapentin, pregabalin).^[144,145] In some cases, use of the SSRI/SNRI to treat hot flashes may also improve sleep disturbance, thereby eliminating the need for hypnotic treatments.^[146] However, other studies suggest that augmentation of SNRI/SSRI with the hypnotic agent zolpidem improves sleep and quality-of-life relative to use of the SNRI/SSRI alone in women with hot flashes and associated sleep disturbance.^[147] In this common scenario of co-occurring hot flashes and sleep disturbance, the need to prioritize targeting insomnia symptoms with a specific hypnotic therapy likely varies according to the degree of sleep impairment resulting from hot flashes.

However, combined treatments should be considered because concurrent therapy may be required to optimize well-being.

Analogous to the approach used to target co-occurring hot flashes in women with sleep disturbance, combined treatments may also be required for women who have sleep problems concurrent with depression and anxiety disorders. Women with persistent sleep disruption should be evaluated for such psychiatric illnesses and referred for treatment where appropriate. Similarly, women whose sleep problems are part of a primary sleep disorder, such as OSA, RLS, or PLMD, should be referred for specific therapies targeting treatments for these disorders.

Conclusions

In summary, sleep difficulties in midlife women are common and have been associated with the menopause transition itself, symptoms of hot flashes, anxiety and depressive disorders, aging, primary sleep disorders, comorbid medical conditions and medications, as well as with psychosocial and behavioral factors. Clinicians should be aware of the prevalence of sleep disturbance and sleep disorders in this population and refer women for evaluation if a sleep disorder is suspected, particularly in light of the morbidity and mortality associated with sleep apnea. Effective behavioral and pharmacological therapies are available to treat sleep disturbances of different etiologies, and once a specific diagnosis is made, affected women should be treated because substantial improvements in quality of life and health outcomes are achievable. There are several common sources of sleep problems in midlife women, and an individual woman's sleep disturbance may be multifactorial. Careful evaluation of the nature of the sleep disturbance will help identify the underlying causes and determine priorities for evaluation and treatment.

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Table 1

Association between Reproductive Hormones and Sleep Quality and Patterns in Midlife Women

Study	Findings	Population	Design
Clark et al ^[28]	No association	23 women (age 40–55)	Cross-sectional study with FSH and 7-night sleep diary
Hollander et al ^[29]	Reduction in E2 levels associated with reduction in sleep quality	536 older premenopausal women (age 37–49) in POA Study (half white, half African American)	Two-year longitudinal study with sleep questionnaire (St. Mary's Hospital Sleep Questionnaire) and serum E2, FSH, LH, T, and DHEAS completed every 8 months
Kravitz et al ^[20]	1. Increased progesterone metabolite levels associated with increased trouble sleeping in perimenopausal women 2. Increased FSH associated with increased trouble sleeping in premenopausal women	630 multiracial pre- or early perimenopausal women (age 43–53) in the SWAN Daily Hormone Study	Daily urinary LH, FSH, and E2 and progesterone metabolite levels and concurrent daily sleep symptom questionnaire during one menstrual cycle
Kravitz et al ^[31]	1. Decreasing estradiol levels in women with trouble falling and staying asleep 2. Increasing FSH in women with trouble staying asleep	3045 multiracial pre- or early perimenopausal women (age 42–52) in SWAN	Longitudinal study with serum E2 and FSH concurrent with sleep symptom questionnaire completed annually for 8 years
Pien et al ^[33]	1. Decreasing inhibin B 2. No association with changes with E2, FSH, LH, T, and DHEAS	□	Eight-year longitudinal study with sleep questionnaire (St. Mary's Hospital Sleep Questionnaire) and serum inhibin B, E2, FSH, LH, T, and DHEAS completed every 8 months
Sowers et al ^[30]	1. More rapidly increasing FSH associated with: a. Longer sleep duration b. Higher delta sleep % c. Less favorable self-reported sleep quality (PSQI) 2. Higher T and lower E2/T ratio associated with greater sleep continuity (lower WASO)	365 multiracial peri- and postmenopausal women (median age 52, IQR 3) in SWAN	Cross-sectional study involving three consecutive PSG following seven prior annual serum FSH

FSH, follicle-stimulating hormone; E2, estradiol; POA, Penn Ovarian Aging Study; LH, luteinizing hormone; T, testosterone; DHEAS, dehydroepiandrosterone sulfate; SWAN, Study of Women's Health across the Nation; PSQI, Pittsburgh Sleep Quality Index; WASO, wake time after sleep onset; IQR, interquartile range; PSG, polysomnography.

Table 2

Factors Associated with Sleep Complaints during and after the Menopause Transition

Type	Detail
Vasomotor symptoms	Hot flashes and/or night sweats ^[3,18–20,29,31,33,37,38,43]
Hormone dynamics	↓ Estradiol ^[29,31] ↑ Follicle-stimulating hormone ^[20,30,31] ↑ Testosterone ^[30] ↑ Progesterone ^[20] ↓ Inhibin B ^[33]
Primary sleep disorders	Obstructive sleep apnea ^[3,18] Periodic limb movement disorder ^[3,29] Restless legs syndrome ^[91]
Mental health symptoms	Anxiety symptoms ^[3,21,29] Depressive symptoms ^[20,21,29,33]
Medical problems	Obesity ^[99] Gastroesophageal reflux disease ^[101] Cancer ^[100] Thyroid dysfunction ^[105] Chronic pain ^[140] Fibromyalgia ^[107] Hypertension ^[21]
Lifestyle factors	Caffeine consumption ^[29]
Psychosocial factors	Higher levels of stress, tension, and public self-consciousness ^[21]

Sleep Disturbance and Hot Flashes

Table 3

Effect of Objectively Measured Hot Flashes on Objectively Measured Sleep

□	Freedman and Roehrs, 2004 ^[46]	Woodward and Freedman, 1994 ^[42]	Savard et al, 2004 ^[37]	Freedman and Roehrs, 2006 ^[45]	Erlik et al, 1981 ^[40]
No. of women with hot flashes	12	12	24	18	9
Objectively measured sleep in women with versus without hot flashes	No differences	1. ↓Sleep efficiency 2. ↑Awakenings 3. ↑% stage 3 4. ↓% stage 4	1. ↓sleep efficiency 2. ↑% wake time 3. ↓% stage 2 4. ↑REM latency	1. ↑ awakenings 2. ↑ arousals in first half of night 3. No other differences	↑ Awakenings
Relationship of individual hot flashes to individual awakenings	Awakenings were not more likely to precede than follow a hot flash	□	↑ time awake in 10 minutes surrounding hot flash compared with 10-minute sleep periods when no hot flash	Hot flashes more likely to precede awakening in first half of night and to follow awakening in second half of night	45/47 (96%) of individual hot flashes were associated with an awakening

REM, rapid eye movement (sleep).

Table 4

Double-Blind Randomized Placebo-Controlled Trials Showing Effect of Estrogen and/or Progestin Therapy on Perceived Sleep Quality

Author	Study Population	Sample Size	Hormone Preparation	Duration	Treatment Measure	Results ^{*,†}
Perceived sleep measures						
Welton et al ^[109]	Postmenopausal 50–69 years No sleep complaints	3721	Continuous combined CEE 0.625 mg/day bMPA 2.5/5.0 mg/day versus placebo	Median of 10 years	WHQ (includes three items that address sleep)	HT >placebo
Diem et al ^[123]	Postmenopausal 60–80 years No sleep complaint required	417	E2 0.014 mg/day patch versus placebo	2 years	Likert scale (includes one item that addresses sleep)	HT = placebo
Nielsen et al ^[110]	Postmenopausal 40–65 years No sleep complaint required	335	Intranasal E2 150 or 300 µg/day +cyclic- dosed OMP 200 mg/ day (if intact uterus)	2 years	WHQ (includes two items that address sleep)	HT >placebo
Heinrich and Wolf ^[124]	Postmenopausal 58–75 years No sleep complaint required	35	Oral E2 2 mg/day +OMP 100 mg/day versus oral E2 2 mg/ day versus placebo	24 weeks	Perceived sleep problems (two items)	HT = placebo
Levine et al ^[120]	Postmenopausal 40–70 years Trial 1: No symptoms Trial 2: 8 VMS/day	Trial 1: 474 Trial 2: 205	Trial 1: Continuous combined transdermal E2 50 µg/day +NE 140-, 250-, or 400-µg/ day patch versus E2 50 µg/day patch alone Trial 2: Continuous combined transdermal E2 50 µg/day +NE 140-, 250-, or 400 µg/ day patch versus placebo	Trial 1: 52 weeks Trial 2: 12 weeks	WHI Insomnia Rating Scale (WHIIRS)	Trial 1: All HT preparations >baseline E2 +NE =E2 alone Trial 2: All HT preparations >placebo → Improvement correlated with reduction in VMS
Gambacciani et al ^[119]	Postmenopausal 45–55 years Menopause- related symptoms (VMS, insomnia, anxiety, and/or mood swings) required	60	CEE 0.3 mg/day +MPA 2.5 mg/day versus CEE 0.3 mg/day +OMP 100 mg/day versus calcium carbonate 1000 mg/day as control	12 weeks	Visual Analog Scale of perceived sleep problems	Both HT preparations >calcium control CEE/ OMP >CEE/ MPA
Brunner et al ^[111]	Postmenopausal 50–79 years No sleep complaint required	10,739 (subgroup = 1189)	Continuous combined CEE 0.625 mg/day versus placebo	1 year (3 years for subgroup)	WHI Insomnia Rating Scale (five items)	HT >placebo (at 1 year) HT = placebo (at 3 years)
Schürmann et al ^[112]	Postmenopausal 45–65 years Reporting VMS but no sleep complaint required	225	Continuous combined E2 1 mg/day +DRSP 1 mg/day versus E2 1 mg/day +DRSP 2 mg/day versus E2 1 mg/day +DRSP 3 mg/day versus placebo	16 weeks	Daily diary rating	All HT preparations >placebo
Vestergaard et al ^[113]	Peri- and postmenopausal 45–58 years No sleep complaint required	1006	Continuous oral E2 1– 2 mg/day (and cyclic NE 1 mg/day if intact uterus) versus no treatment (i.e., no placebo was used)	5 years	Modified Greene Climacteric scale (including items that address sleep related and unrelated to VMS)	Both HT preparations >no treatment (sleeping problems related to VMS) Both

Author	Study Population	Sample Size	Hormone Preparation	Duration	Treatment Measure	Results ^{*,†}
						HT preparations = no treatment (sleeping problems unrelated to VMS)
Hays et al ^[114]	Postmenopausal 50–79 years No sleep complaint required	16,608 (subgroup = 1511)	Continuous combined CEE 0.625 mg/day +MPA 2.5 mg/day versus placebo	1 year (3 years for subgroup)	WHI Insomnia Rating Scale (five items addressing sleep)	HT >placebo (at 1 year) HT = placebo (at 3 year) HT >placebo (subgroup with VMS at 3yrs)
Gambacciani et al ^[115]	Postmenopausal Mean age 54 years No sleep complaint required	50	Continuous combined oral E2 1 mg/day +NE 0.5 mg/day versus calcium-vitamin control group	12 weeks	WHQ (includes three items that address sleep)	HT >placebo
Polo-Kantola et al, ^[129]	Postmenopausal 47–65 years No sleep complaint required	63	Age <56 years: E2 gel 2.5 g/day versus placebo Age ≥56 years: E2 patch 50 µg/day versus placebo	Crossover trial: 3 months per arm	Visual Analog Scales (eight sleep complaints)	E2 >placebo (<56 years) E2 >placebo (≥56 years)

CEE, conjugated equine estradiol; WHQ, Women's Health Questionnaire; HT, hormone therapy (estrogen combined with a progestin); MPA, medroxyprogesterone acetate; E2, 17-β-estradiol; OMP, oral micronized progesterone; VMS, vasomotor symptoms; NE, norethindrone; DRSP, drospirenone; WHI, Women's Health Initiative.

* Effect of first treatment was greater than the effect of second treatment when '>' used.

† Effect of first treatment was not different than the effect of second treatment when '=' used.

Table 5

Double-Blind Randomized Trials Showing Effect of Estrogen and/or Progestin Therapy on Sleep Parameters Measured Objectively with Polysomnography and Perceived Sleep Quality

Author	Study Population	Sample Size	Hormone Preparation	Duration	Treatment Measure	Results ^{*,†}
Studies using PSG without sleep disorder measures						
Kalleinen et al. ^[127]	Premenopausal: 45–51 years Postmenopausal: 58–70 years No sleep complaint required	35 (17 pre-, 18 post)	Premenopausal: Oral E2 2 mg/day (days 1–16) +oral NE 1 mg/day (days 17–29) versus placebo Postmenopausal: Continuous combined oral E2 2 mg/day +oral NE 0.7 mg/day versus placebo	6 months	PSG	Placebo >HT (↑ awakenings from stage 1 sleep) on PSG for premenopausal women Placebo >HT (↑ total awakenings, ↓ slow wave activity in NREM) on PSG for premenopausal women HT =placebo (total sleep time, sleep efficiency, sleep stages) on PSG (although mean differences favored placebo) for both pre-and postmenopausal women
Schüssler et al. ^[121]	Postmenopausal 54–70 years No sleep complaint required	10	OMP 300 mg/day ×21 days versus placebo	Crossover trial: 8 weeks per treatment arm	PSG including spectral analysis; perceived sleep problems	OMP >placebo (↓ wakefulness, ↑ REM during the first third of the night on PSG) OMP =placebo (on spectral power and perceived sleep quality)
Montplaisir et al. ^[117]	Postmenopausal 45–65 years No sleep complaint required	21	CEE 0.625 mg/day (days 25–30) +MPA 5 mg/day or OMP 200 mg/day (days 12–25) (no placebo arm)	6 months	PSG; perceived sleep problems	CEE +OMP improved PSG-sleep of ↑ sleep efficiency, ↓ wake time after sleep onset (versus baseline) CEE +MPA: No effect on PSG-measured sleep (versus baseline) Both HT preparation ↓ perceived sleep problems (versus baseline)
Antonijevic et al. ^[126]	Postmenopausal 46–62 years No sleep complaint required	11	Transdermal patch E2 50 mg/day versus no patch	2 weeks	PSG	E2 >no treatment group (↓ wakefulness, ↑ REM, ↑ deep sleep)

Author	Study Population	Sample Size	Hormone Preparation	Duration	Treatment Measure	Results ^{*,†}
Polo-Kantola et al ^[122]	Postmenopausal 47–65 years No sleep complaint required	62	Age <56 years: E2 gel 2.5 g/day versus placebo Age ≥56 years: E2 patch 50 mg/day versus placebo	Crossover trial: 3 months per treatment arm	PSG; perceived sleep problems	E2 >placebo (↓frequency of movement arousals on PSG) Placebo >E2 (↑ EEG arousals in stage 1 sleep on PSG) E2 =placebo (sleep time, sleep stages, and sleep efficiency on PSG) E2 >placebo (perceived sleep problems)
PSG with sleep disorder measures						
Hachul et al ^[97]	Postmenopausal 50–65 years No sleep complaint required	33	Phase 1: CEE 0.625 mg/day versus placebo Phase 2: Cyclic MPA 5 mg/day (days 15–28) added to treatment used during phase 1	24 weeks (two 12-week phases)	PSG; Epworth Sleepiness Scale; perceived sleep	PSG: MPA (±CEE) improved sleep by ↓ number of arousals (versus baseline) apnea; subjective Addition of MPA to CEE reduced PLMs sleep quality (versus CEE alone) Subjective: CEE alone ↓ perceived sleep apnea (versus baseline) MPA alone >placebo (↓snoring and perceived sleep apnea)
Polo-Kantola et al ^[130]	Postmenopausal 47–65 years No sleep complaint required	62	Age <56 years: E2 gel 2.5 g/day versus placebo Age ≥56 years: E2 patch 50 mg/day versus placebo	Crossover trial: 3 months per treatment arm	Respiration for apnea ^c	E2 >placebo (↓one type of obstructive breathing pattern) E2 =placebo (on arterial oxyhemoglobin saturation component of respiration)
Saletu ^[118]	Postmenopausal 46–67 years	49	Oral E2 2 mg/day versus E2	2 months	PSG; perceived sleep quality (20 items)	E2 (±dienogest) >placebo (nonsignificant trend in sleep efficiency on PSG) E2 (±dienogest) >placebo (perceived sleep quality) E2 +dienogest >placebo sleep apnea E2 alone improved apnea (non significant trend) on PSG

Author	Study Population	Sample Size	Hormone Preparation	Duration	Treatment Measure	Results ^{*,†}
	Diagnosis of insomnia related to menopause					(versus baseline)
Saletu-Zyhlarz et al ^[125]	Postmenopausal 46–67 years Insomnia diagnosis	49	Oral E2 2 mg/day +dienogest 3 mg versus E2 2 mg/day alone	2 months	PSG; PSQI; perceived sleep quality (20 items)	Both HT preparation =placebo (sleep stages on PSG) E2 alone improved versus placebo time to stage 2 sleep on PSG (versus baseline) E2 +dienogest improved apnea (versus baseline) Sleep quality E2 ±dienogest improved (versus baseline)
Polo-Kantola et al ^[95]	Postmenopausal 47–65 years No sleep complaint required (although PLMs observed in 46% of women at baseline)	62	Age <56 years: E2 gel 2.5 g/day versus placebo Age ≥56 years: E2 patch 50 µg/day versus placebo	Crossover trial: 3 months per treatment arm	PLMs [‡]	E2 = placebo (on PLMs)
Block et al ^[28]	Postmenopausal mean age 50 years Reporting VMS No sleep complaint required	21	MPA 30 mg/day versus placebo	1 month	PSG	No effect of MPA (sleep apnea parameters)

^{*}Effect of first treatment was greater than the effect of second treatment when '>' used.

[†]Effect of first treatment was not different than the effect of second treatment when '=' used.

[‡]Nonstandard measurement. PSG, polysomnography; E2, 17-β-estradiol; NE, norethindrone; HT, hormone therapy (estrogen combined with a progestin); NREM, nonrapid eye movement (sleep); OMP, oral micronized progesterone; REM, rapid eye movement (sleep); CEE, conjugated equine estradiol; MPA, medroxyprogesterone acetate; EEG, electroencephalogram; PLMs, periodic limb movements; PSQI, Pittsburgh Sleep Quality Index; VMS, vasomotor symptoms.