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Sleep and sleep disorders in the menopausal transition

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INTRODUCTION

Sleep disturbances increase in prevalence during the menopausal transition, with the most common complaint being nighttime awakenings.^{1, 2} Sleep disturbances impact health-related quality of life, work productivity, and healthcare utilization,³ and can have long-term effects on health and wellbeing across several years of the menopausal transition. Here, we aim to provide an overview of sleep disturbances in the context of the menopausal transition, considering self-reported and objectively measured indicators of sleep. We also consider factors that could mediate sleep disturbance, including female sex steroids, vasomotor

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symptoms (e.g. hot flashes and sweating), aging, and stressful life events. Finally, we provide an overview of potential treatment options and their efficacy and highlight the need for further research. Understanding the causes, as well as effective preventative and treatment strategies for menopausal sleep disturbances, is essential for better health, quality of life, and work ability.

DEFINITION AND PHYSIOLOGY OF MENOPAUSE

Menopause (defined as the time of the final menstrual period) is a natural process in normal female aging, resulting from depletion of ovarian follicles, and occurs at a median age of 51 years,⁴ with the menopausal transition usually starting at about 47 years.⁵ The Stages of Reproductive Aging Workshop (STRAW +10) standardizes the division of a woman's late reproductive life, broadly grouping women into three categories (reproductive, menopausal transition, and post-menopause) further subdivided, according to menstrual cycle length and regularity.⁶ Peri-menopause encompasses the menopausal transition and the first year after the final menstrual period. The term "climacteric" may also be used to describe peri-menopause and the part of the post-menopausal period in which climacteric symptoms occur.

Ovarian function begins to deteriorate, and function of the hypothalamic-pituitary-ovarian axis begins to change, several years before menopause. These endocrinological changes typically occur gradually and are not linear. Levels of follicle stimulating hormone (FSH) rise overall, and are typically >25 IU/L in the late menopausal transition. In association with the fluctuation and gradual decline in estrogen (typically estradiol) across the menopausal transition, menopausal symptoms emerge and include vasomotor symptoms (hot flashes and sweating), sleep disturbances, and mood symptoms (Table 1).

SLEEP QUALITY DURING THE MENOPAUSAL TRANSITION

Self-reported sleep quality

Among menopausal symptoms, sleep disturbances are one of the most bothersome symptoms, and are reported by 40–60% of menopausal women.⁷ There is convincing evidence from several cross-sectional⁸⁻¹² and longitudinal¹³⁻¹⁶ studies that the prevalence of perceived sleep disturbances increases in the menopausal transition, even after controlling for age. A recent meta-analysis of cross-sectional data from 24 studies reported higher odds of experiencing sleep disturbance in peri-menopause (1.60), post-menopause (1.67), and surgical menopause (2.17) relative to women who are pre-menopausal.¹⁷

The most common sleep-related complaint is nighttime awakenings.^{8, 11, 14, 16} In their seven-year follow-up of 3045 women, the Study of Women's Health Across the Nation (SWAN) reported an increase in odds ratios (OR) for difficulty staying asleep across the menopausal transition after adjusting for demographics and health-related factors.¹⁴ ORs also increased for difficulty falling asleep across the transition, but decreased for early morning awakening from late peri-menopause to post-menopause. While the majority of studies examined associations between sleep and menopausal stages based on bleeding patterns, some studies have investigated the association between follicle stimulating

hormone (FSH) concentrations and self-reported sleep.^{14, 16} Increasing FSH was associated with greater odds of waking up several times, whereas decreasing estrogen (E₂) was associated with higher odds of difficulty falling and staying asleep in SWAN.¹⁴

Polysomnographic (PSG) studies

Even though the evidence for declining self-reported sleep quality across the menopausal transition is strong, polysomnographic (PSG) studies have generally not found a corresponding negative change in sleep architecture. PSG-derived measures of sleep do not necessarily reflect self-report sleep quality ratings¹⁸ and psychological state may influence sleep quality judgments by affecting the sleep appraisal process rather than sleep itself.¹⁹ Also, most PSG studies have been cross-sectional and included small samples, with few exceptions.^{12, 20} Further, studies have varied in methodology including definitions of menopausal stages, age ranges, assessment of the presence of sleep disorders like obstructive sleep apnea, and inclusion of an adaptation night, leading to contradictory results and challenges when trying to make study comparisons.

Some studies have found no differences in sleep architecture between pre- and post-menopausal women,²¹⁻²³ while a few studies have reported more slow wave sleep (SWS) in peri- and post-menopausal women than pre-menopausal women.^{12, 20, 24} More SWS could be interpreted as reflecting a better sleep pattern, on the one hand, but alternatively could reflect a recovery response to sleep deprivation; further studies are needed to better understand potential changes in SWS post-menopause. Post-menopausal women had a higher apnea-hypopnea index (AHI) and lower arterial oxyhemoglobin saturation (SaO₂).²⁰ Finally, SWAN investigators found no differences in PSG measures according to menopausal status.²¹ However, late peri-menopausal and post-menopausal women had more high frequency beta EEG activity, suggesting greater cortical hyperarousal, during sleep than pre-menopausal and early peri-menopausal women, an effect partially explained by higher frequency of self-report hot flashes.²¹

A limited number of studies have investigated the association between FSH, as an endocrine marker of transitioning menopause, with PSG measures. SWAN investigators found that a more rapid rate of FSH change over the previous few years was associated with higher amount of SWS and longer total sleep time (TST) during a subsequent sleep study.²⁵ Another cross-sectional study of women mostly in the early menopausal transition (aged 43–52 years) without sleep complaints found that higher FSH concentrations were associated with more wakefulness after sleep onset (WASO), awakenings, and arousals, after adjusting for age and BMI.²⁶ However, in women with menopausal insomnia, PSG measures did not correlate with FSH and instead were associated with anxiety and depression symptoms.²⁶ In a small study that evaluated associations of sleep and hypothalamic-pituitary-ovarian (HPO) axis hormones in a group of pre- and post-menopausal women with diagnoses of depression, FSH level was positively associated with WASO and negatively associated with SWS.²⁷

In the only longitudinal study of changes in PSG measures across the menopausal transition, Lampio and colleagues²⁴ studied 60 midlife women at a pre-menopausal baseline visit and again, six years later. At follow-up, women had less TST and more WASO after adjusting for vasomotor symptoms, BMI, and mood (See Figure 1 showing the PSG changes in a

representative participant). These changes in sleep were linked with advancing age rather than increased FSH levels. Increasing FSH was associated with a greater proportion of SWS (although not with slow wave EEG activity), which the authors propose as reflecting an adaptive change to counteract the age-related sleep fragmentation.²⁴

In summary, PSG studies have shown few consistent effects of menopausal stage on sleep architecture independent of age. All but one study were cross-sectional and therefore unable to track changes in sleep across the transition, and few studies have used more complex indicators of sleep disruption, like quantitative EEG analysis. Given between-women variability in hormone trajectories, speed of transitioning menopause, and life experiences as they transition menopause, all of which can interact with sleep, further longitudinal studies are needed in midlife women to establish if PSG measures fluctuate in association with the changing hormone environment in the menopausal transition. Also, as discussed next, subgroups of women might be more susceptible to sleep disturbances, particularly women with severe vasomotor symptoms or insomnia disorder.

VASOMOTOR SYMPTOMS (HOT FLASHES AND SWEATING) AND SLEEP DISTURBANCE

Vasomotor symptoms, an umbrella term used to describe hot flashes and sweating, affect up to 80% of women during menopause transition.²⁸ Data from SWAN show a median duration for vasomotor symptoms of 7.4 years²⁹ but the temporal pattern based on symptom onset and persistence varies,^{30, 31} with symptoms persisting more than 10 years in some women.^{29, 32}

The precise mechanism of vasomotor symptoms is poorly understood, but is hypothesized to result from disturbance of the temperature-regulating system in the hypothalamus, triggered by a decline in E_2 .²⁸ Vasomotor symptoms may occur at any time, and usually begin with sensations of heat or warmth in the upper body, associated with peripheral vasodilation, sweating, and elevated skin blood flow.³³ Vasomotor symptoms are proposed to be triggered by small elevations in core body temperature acting within a narrowed thermoneutral zone.³³ The duration of a flash usually ranges from one to five minutes, but some flashes last up to 60 minutes.^{28, 33}

Self-reported vasomotor symptoms are consistently associated with poorer self-reported sleep quality and chronic insomnia.^{10, 14, 34, 35} Longitudinal SWAN data show that women with moderate-severe hot flashes are almost three times more likely to report frequent nocturnal awakenings compared to women without hot flashes.³⁶ Studies that investigated relationships between reported vasomotor symptoms and objectively measured sleep (with actigraphy or PSG) have produced conflicting results, with early studies showing no relationship^{12, 22} and more recent studies finding an association between hot flashes and disrupted sleep.³⁷⁻³⁹

Vasomotor symptoms can be measured objectively using sternal skin conductance.⁴⁰ Objectively detected vasomotor symptoms have been linked to sleep disruption in some,^{37, 38, 41, 42} but not all studies.^{22, 39, 43} Differences between studies might relate to the

classification of hot flashes in association with awakenings,³⁷ as well as between-women variability in the impact of hot flashes on sleep. In an experimental model of new-onset hot flashes in young pre-menopausal women treated with a gonadotropin-releasing hormone agonist that simulates menopause, hot flashes were linked with more PSG awakenings, more WASO, and more Stage 1 sleep.⁴⁴ Thus, these data provide support for a link between hot flashes and disturbed sleep. In an analysis of the overall impact of hot flashes on sleep architecture, de Zambotti and colleagues reported that wake time attributed to hot flashes was responsible for, on average, 27% of objective WASO, although there was wide variability in hot flash impact between women.³⁷ They also reported that an awakening occurred coincident with the majority (69%) of hot flashes.

In summary, while not all hot flashes are associated with disturbed sleep, they are a strong correlate of poor sleep, and many nocturnal hot flash events are closely linked with periods of PSG-wake. The strong overlap in timing between hot flash onset and awakenings suggests that these events may be driven by a common mechanism within the central nervous system in response to fluctuating estrogen levels, although sweating triggered by a hot flash may still contribute to, or extend, the interval of waking.³⁷ Nocturnal hot flashes are an important component of sleep disturbance during midlife, particularly in women with severe sleep difficulties that qualifies them for insomnia disorder, as discussed later. However, not all women who have menopause-related sleep problems complain of hot flashes⁴¹ and it is important to consider other factors that could disturb sleep, including the presence of sleep-disordered breathing (SDB), mood disturbances, medical conditions, and socioeconomic factors (See Figure 2). Importantly, several of these factors may interact with each other, making it challenging to determine the primary cause of sleep disturbance.

DEPRESSION AND SLEEP DISTURBANCE IN MENOPAUSAL TRANSITION

Risk for depression increases during the menopausal transition, independently of other factors.⁴⁵⁻⁴⁸ In SWAN, women were two to four times more likely to develop major depressive disorder in menopausal transition and early post-menopause compared to pre-menopause, after adjusting for confounding factors.⁴⁶ It is hypothesized that fluctuation and an eventual drop in estrogen is responsible for impaired mood^{49, 50} and women vulnerable to developing mood symptoms during other reproductive transitions (e.g. pre-menstrual phase of the menstrual cycle or postpartum) are at greater risk for developing depressive symptoms in menopausal transition.⁵¹

There is a bi-directional relationship between mood and sleep disturbances.^{52, 53} The relationship between depressive symptoms and subjective sleep disturbances has also been documented in women in the menopausal transition.⁵⁴⁻⁵⁶ In a longitudinal analysis of 309 women transitioning menopause, Avis and colleagues reported that depressive symptoms were unrelated to menopausal status or annual change in E₂, but were associated with hot flashes and sleep disturbance.⁵⁷ Further, in a longitudinal analysis of SWAN data, Bromberger and colleagues found that the presence of subjective sleep problems at baseline was a significant predictor of persistent/recurrent major depressive disorder at follow-up.⁵⁸

Researchers have also investigated the association of sleep architecture with depressive symptoms, although findings are conflicting. In one study, more depressive symptoms were associated with lower sleep efficiency and shorter TST in peri-menopausal women, and with a higher percentage of REM sleep in post-menopausal women.⁵⁶ In contrast, a substudy of SWAN found that mood symptoms were not independently related to sleep architecture; anxiety symptoms were related to longer sleep onset latency and lower sleep efficiency; however, this was found only in women who also reported vasomotor symptoms.⁵⁹

The “domino theory,” which predicts that vasomotor symptoms lead to insomnia, which then leads to the development of mood symptoms,⁶⁰ currently has only partial support.¹ Recent data showed that hot flashes and depressive symptoms were associated with different sleep disturbance patterns; hot flashes being uniquely associated with frequent awakenings and depression uniquely associated with difficulty falling asleep and waking up earlier than desired.⁶¹ Further, an intervention study of peri-menopausal women with depressive symptoms found that, in adjusted models, improvement in depression was predicted by improved sleep and increasing E₂, but not by reduction of vasomotor symptoms.⁶² Therefore, the causal directionality between these factors in relation to the decline in ovarian function in the approach to menopause still needs to be clarified.

SLEEP DISORDERS IN THE MENOPAUSAL TRANSITION

Insomnia Disorder

While epidemiological studies show a clear increase in poor sleep quality as women enter menopause, the severity and persistence of poor sleep, as well as the extent of impairment in daytime function, varies between women. Insomnia disorder is the most severe clinical manifestation of recurrent and chronic perceived poor sleep (difficulty falling asleep and staying asleep despite adequate opportunity to sleep), occurring three or more times per week and causing significant distress and daytime consequences. In the context of menopause, classic clinical features of insomnia such as rumination, anxiety, and generalized hyperarousal^{63, 64} overlap with aspects of insomnia specific to menopause, such as vasomotor symptoms.

Based on a structured phone interview of almost 1000 women, Ohayon and colleagues reported that 26% of peri-menopausal women qualified for a DSM-IV diagnosis of insomnia, with difficulty maintaining sleep the most common symptom.³⁵ The likelihood of having chronic insomnia symptoms increased with the severity of hot flashes.³⁵ Other factors that are associated with increased risk for insomnia disorder in the context of the menopausal transition include personality factors such as neuroticism, past depression, a history of severe premenstrual symptoms, and chronic stress.⁶⁵⁻⁶⁷

There are limited data on PSG measures for insomnia disorder in the menopausal transition. One study found significant objective sleep disruption, with shorter TST, more WASO, and poorer sleep efficiency; the disruption matching subjective reports of poor sleep quality in this group relative to women without insomnia who were also in menopausal transition.⁶⁸ In fact, almost 50% of the insomnia group had short sleep duration (<6 hours). These data matched sleep diary data collected over a 2-week period.⁶⁸ Women with insomnia were

more likely to have objectively measured hot flashes, and the presence of hot flashes predicted the number of PSG-awakenings per hour of sleep.⁶⁸ While data were only available from one study, findings suggest that in cases of severe subjective sleep disturbance qualifying for insomnia disorder, there is PSG evidence of poor sleep that is partly attributed to the impact of hot flashes.

In another study Xu and colleagues⁶⁹ compared subjective and PSG measures in pre-, peri/post-menopausal women with insomnia. While subjective measures of sleep disturbance and depression were similar between groups, peri/post-menopausal women had a longer PSG-defined total wake time and lower sleep efficiency, suggesting that PSG measures of sleep quality are impacted to a greater extent in peri/post-menopausal than in pre-menopausal women with insomnia. The presence of hot flashes was not evaluated in this study.

The links between insomnia disorder and adverse mental and physical conditions, including depression and cardiovascular disease, are well established,⁷⁰ and insomnia combined with short sleep duration is proposed as the most biologically severe phenotype of the disorder.⁷¹ It is unclear if insomnia disorder that develops in the context of the menopausal transition has a similar impact on long-term health compared with insomnia that develops in other circumstances, and how comorbid features, such as hot flashes or depression, might interact with sleep difficulties to contribute to impairment. Emerging data show an association between menopausal insomnia and unfavorable nocturnal blood pressure⁷² and heart rate⁷³ profiles, however, the causes and long-term consequences of this altered blood pressure profile remain to be determined.

Primary Sleep Disorders and Other Medical Disorders

Sleep disturbances may arise during the menopausal transition and post-menopause in association with primary sleep disorders, such as SDB, restless legs syndrome (RLS), and periodic limb movement disorder (PLMD).^{2, 74}

Sleep disordered breathing

SDB is characterized by snoring, upper airway obstruction, inspiratory flow limitation, and excessive daytime sleepiness.⁷⁵ An apnea hypopnea index (AHI) of five or more per hour of sleep is usually considered abnormal and indicates SDB.⁷⁵ The prevalence of SDB is higher in men than in women before menopause,⁷⁶ however, the prevalence increases in women following menopausal transition.⁷⁷⁻⁸¹

In the Wisconsin Sleep Cohort, post-menopausal women were 2.6 times more likely to have an AHI ≥ 5 per hour and 3.5 times more likely to have an AHI ≥ 15 per hour, compared with pre-menopausal women, after adjusting for confounding factors (age, BMI, and smoking).⁸⁰ In the recent longitudinal analyses of that dataset, AHI increased from pre-menopause to peri- and post-menopause, independent of age and changes in body habitus, although these factors were also associated with AHI.⁷⁷ The greater prevalence of SDB after menopause might be due in part to loss of protective effects of female reproductive steroid hormones, especially progesterone,^{80, 81} as well as changes in fat distribution after menopause.⁷⁸

The clinical picture of SDB in women usually differs from that of men. Women are more symptomatic with lower AHI compared to men, and they have more prolonged partial upper airway obstruction, and report insomnia as a symptom of SDB more frequently.^{82, 83} Of importance, patients with SDB and insomnia-like symptoms have higher burden of cardiovascular, pulmonary and psychiatric comorbidity compared to patients with traditional sleepy phenotype despite less severe SDB in terms of AHI.⁸³ Further, patients with SDB and insomnia symptoms have lower adherence to continuous positive airway pressure treatment^{83, 84} and may benefit from concomitant cognitive behavioral therapy for insomnia (CBT-I).⁸⁵ Perhaps as a consequence of these differences in clinical presentation, women with SDB are more often underdiagnosed, as well as undertreated compared to men.⁸⁶

Restless legs syndrome (RLS) and periodic limb movement disorder (PLMD)

The prevalence of RLS and PLMD increases with age, and RLS is more common in women.⁸⁷ Freedman and colleagues found periodic limb movements and apneas to be the best predictors for poorer sleep efficiency in peri- and post-menopausal women reporting sleep disturbances.⁴³ However, in a group of asymptomatic post-menopausal women, the incidence of periodic limb movements was unrelated to E₂ or FSH levels,⁸⁸ suggesting that the increase in prevalence of RLS and PLMD after menopause may be related more to aging than to hormonal changes.

Other medical disorders and use of medications

In addition to primary sleep disorders, other medical disorders, as well as use of medications, become more common with advancing age and may affect sleep in midlife women.⁸⁹⁻⁹¹ In one of the few prospective studies assessing predictors for menopausal sleep disturbances, medical diseases and use of prescribed medication predicted future sleep disturbances.⁹² In another prospective study depressive symptoms, personal crises, use of medications affecting the CNS and perceived impaired general health already five years before menopause predicted various sleep disturbances in menopausal transition.⁶⁷

DEMOGRAPHIC AND PSYCHO-SOCIAL FACTORS AND SLEEP IN MENOPAUSAL TRANSITION

Women face multiple challenges and personal life stressors in midlife, including changing family roles, loss of significant others, changes and increasing demands at work, and health concerns and worries about retiring and getting old.⁹³ Peri-menopausal women have higher levels of psychological distress compared to pre-menopausal women⁹⁴ and employment, depressed mood, and poor perceived health are among the most significant factors causing stress in midlife women.⁹⁵ Life stressors and experiencing stress could contribute to sleep disturbances.^{93, 96, 97} Indeed, perceived stress and poor perceived health have been associated with sleep disturbances in midlife women.^{16, 90} Further, Hall and colleagues⁶⁶ found that midlife women with more chronic stress exposure over a 9-year period had greater PSG-assessed WASO and were more likely to have insomnia at follow-up than participants with moderate stress exposure.

A limited number of studies have investigated the relationship between work stresses specifically and menopausal symptoms including sleep disturbances. An Australian study of 476 peri- and post-menopausal women working in the higher education sector found that higher supervisor support, being employed on a full-time basis, and having control over workplace temperature were independently associated with lower menopausal symptom reporting.⁹⁸ This study did not specifically assess sleep disturbances. However, there is good evidence that job strain and high work demands are associated with increased prevalence of sleep disturbances in the general population.⁹⁹⁻¹⁰¹ A recent Finnish prospective study with over 24,000 participants (82% women, mean age 44 years) showed that the disappearance of job strain was associated with lower odds of insomnia symptoms.¹⁰¹ In addition, according to a sleep diary study, post-menopausal women had worse sleep than pre-menopausal women during working days, but few differences during leisure days, showing an existing coping mechanism of work stress after menopause and the necessity of enough rest.¹⁰²

Some socioeconomic factors are protective against the development of sleep disturbances in the menopausal transition; higher educational level,³⁴ lower financial strain,¹⁰³ and satisfactory marriage^{104, 105} are all associated with less sleep disturbance. Further, the prevalence of menopausal sleep disturbance is influenced by race and ethnicity: Caucasian women have higher rates while Hispanic women have lower rates of sleep disturbance.¹⁴

There is a bi-directional relationship between psychosocial factors and menopausal symptoms, including sleep disturbance. Just as psychological distress, stressors, and poor health can lead to sleep disturbances, sleep disturbances can also lead to poorer health and quality of life, depressed mood, and reduced work productivity. For example, in a study of 131 Egyptian teachers in the menopausal transition (aged 46–59 years), the most important menopausal symptoms that affected their work capacity and performance were tiredness (83%) and sleep disturbances (64%).¹⁰⁶ A larger study of 961 midlife women found that insomnia symptoms were the most problematic menopausal symptoms to affect daily life and working performance.¹⁰⁷

Recent studies have demonstrated that the presence of menopausal symptoms increases health care utilization and costs, as well as sick leave days.^{3, 108-110} In one study that assessed the burden of menopausal sleep disturbances on societal costs, Bolge and colleagues concluded that menopausal chronic insomnia, characterized by nighttime awakenings, was linked with increased health care utilization and associated costs, decreased work productivity, and decreased health-related quality of life after adjustment for demographics and comorbidity.³

MANAGEMENT OF SLEEP DISTURBANCES IN THE CONTEXT OF MENOPAUSE

As discussed in the above sections, there are potentially multiple, and sometimes overlapping, causes of sleep disturbances in midlife women as they approach and pass menopause. For some women, the sleep disturbances may be transient and without associated distress and therefore not require active treatment. However, others may experience severe sleep disturbances with a significant impact on functioning and quality of

life, necessitating treatment. In some cases, combined treatments may be required, such as for women who have depression in addition to severe vasomotor symptoms and sleep problems.

During evaluation of sleep problems with a sleep history assessment¹¹¹ or sleep diary,¹¹² women should be questioned about the timing of sleep difficulties in relation to menopausal symptoms, changes in bleeding patterns, and presence and severity of menopausal symptoms like hot flashes and night sweats, in addition to screening for sleep breathing and movement disorders. Treatment options include hormone therapy (HT), non-hormonal pharmacological medications, non-pharmacological and self-management strategies.

Cognitive-behavioral treatment of insomnia

Cognitive-behavioral treatment of insomnia (CBT-I) is considered the primary intervention for patients with chronic insomnia,¹¹³ and is superior to sleep medication alone in the long-term.¹¹⁴ CBT-I has recently been evaluated for insomnia during the menopausal transition in a randomized clinical trial of peri- and post-menopausal women with insomnia symptoms as well as daily hot flashes.¹¹⁵ Compared to a menopause education control condition, 8-weeks of CBT-I led to a greater reduction in insomnia symptoms, with improvements maintained at 6 months post-treatment.¹¹⁵ Preliminary data from an open trial of CBT-I in women with menopausal sleep problems also indicated a reduction in insomnia (and depression) symptoms post-treatment.¹¹⁶ While further trials are needed, initial findings provide support for effectiveness of CBT-I in women with insomnia during the menopausal transition.

Other non-pharmacological approaches for treating menopausal insomnia, including acupuncture, yoga, massage, exercise and nutritional supplements containing soy isoflavones have been tried, with mixed effects (reviewed in Attarian, 2015).

Hormone Therapy (HT) and Sleep

HT, comprised of estrogen combined with progestin, or estrogen alone for women with a history of hysterectomy, is the most effective treatment for menopausal symptoms.¹¹⁷ HT has other beneficial effects, including prevention of bone loss and osteoporosis-related fractures.^{118, 119} However, HT may also have negative effects. Oral (but not transdermal) administration of HT increases the risk for venous thromboembolism.^{118, 120} In addition, there is a slightly elevated risk for breast cancer that seems to be primarily, but not exclusively, related to the progestin used in combined therapy.^{118, 121, 122} According to current opinion, therefore, the indications and possible contraindications (e.g. history of breast or gynecological cancer, venous thromboembolism, or severe cardiovascular diseases) should be evaluated before initiating HT. HT should be considered when the balance of potential benefits and risks is favorable for a woman¹²³ at the lowest effective dose, using transdermal administration when appropriate. The duration should be individualized based on duration of menopausal symptoms, age, and possible risk factors.¹¹⁸

Several studies have evaluated the effect of HT on sleep, however, findings are mixed and difficult to compare, given the heterogeneity in study populations, tools to evaluate sleep, and various HT preparations (formulation, dose and type of administration). According to a recent meta-analysis, HT modestly improves subjectively evaluated sleep disturbance.¹²⁴ In

most studies, improved sleep quality has co-occurred with improvement in vasomotor symptom.¹²⁴⁻¹²⁸ However, there are also data on enhanced sleep quality with HT without the report of vasomotor symptoms.¹²⁶ PSG studies examining the effect of HT on sleep architecture in menopausal women share the same problems with study design as the studies evaluating subjective sleep quality and HT. Those studies are rare, and their results are conflicting. Some studies have observed positive changes in sleep architecture with HT,¹²⁹⁻¹³² mainly decreasing WASO, although other studies found no improvement.¹³³⁻¹³⁵

In cases where HT is contra-indicated or not preferred, non-hormonal pharmacological options for treating hot flashes and associated insomnia symptoms are available.¹³⁶ Low-dose selective serotonin/serotonin norepinephrine reuptake inhibitors reduce hot flashes to some extent and modestly reduce insomnia symptoms in women with hot flashes,¹³⁷⁻¹³⁹ although the adverse-effect profiles of these medications need to be carefully considered before use. Evidence from a single trial shows that gabapentin improves sleep quality in peri-menopausal women with hot flashes and insomnia.¹⁴⁰

CONCLUSION

Sleep difficulties increase as women approach menopause. For some women, sleep problems are severe and thus impact daytime functioning and quality of life, having long-term consequences for mental and physical health. Menopausal vasomotor symptoms typically interfere with sleep, and are strongly associated with self-reports of sleep disturbances as well as PSG-measured wakefulness. However, when evaluating the causes of sleep disturbance during menopause other factors directly related to the menopausal transition (e.g., instability/changes in the hormone environment with progressive decreases in estradiol and increases in FSH) and factors coincident with the transition (e.g., SDB or movement disorders, mood disturbance, presence of medical conditions, or life stressors) also need to be considered. Given the presence of unique sleep-disruptive factors (e.g., hot flashes) and the multifactorial nature of sleep difficulties in women approaching menopause, often with many interacting factors, treatment options need to be tailored to the individual woman.

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KEY POINTS

1. There is an increase in self-reported sleep disturbance, particularly nocturnal awakenings, across the menopausal transition. Symptoms are bothersome and impact quality of life, health, and productivity.
2. Vasomotor symptoms, both self-reported and measured hot flashes and sweating, are critical symptoms associated with disrupted sleep in the menopausal transition.
3. Associations between menopausal stage and/or hormone levels and polysomnographic (PSG) measures are less consistent and further longitudinal studies are required.
4. Sleep disturbances may arise during the menopausal transition in association with primary sleep disorders (e.g. sleep-disordered breathing). Women with sleep complaints should be evaluated and appropriately treated.
5. Effective management strategies for menopausal sleep disturbances include hormone therapy, other pharmacological treatments (e.g. gabapentin), and cognitive behavioral therapy for insomnia.

SYNOPSIS

The menopausal transition is associated with an increase in insomnia symptoms, especially difficulty staying asleep, which negatively impacts quality of life. Vasomotor symptoms are a key component of sleep disruption. Findings from polysomnographic studies are less consistent in showing disrupted sleep in the menopausal transition independent of aging; further prospective studies are needed. Hormone therapy alleviates subjective sleep disturbances, particularly if vasomotor symptoms are present. However, due to contraindications, other options, including cognitive behavioral therapy for insomnia, should be considered. Further work is needed to develop preventive and treatment strategies for alleviating sleep disturbances to ensure better health, quality of life, and productivity in midlife women.

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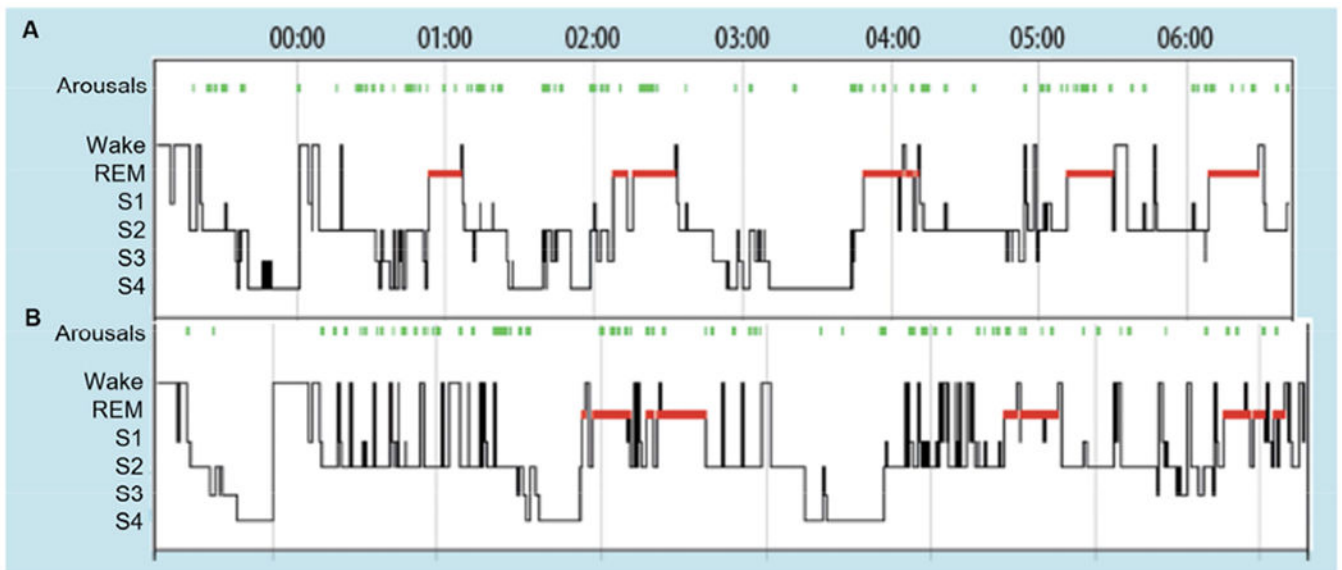


Figure 1:

Hypnograms derived from the polysomnograms of one representative participant during her premenopausal baseline visit (A) and at a follow-up visit 6 years later (B), when she was peri-menopausal. Data from Lampio L, Polo-Kantola P, Himanen SL, et al. Sleep during menopausal transition: A six-year follow-up. *Sleep*. 2017.

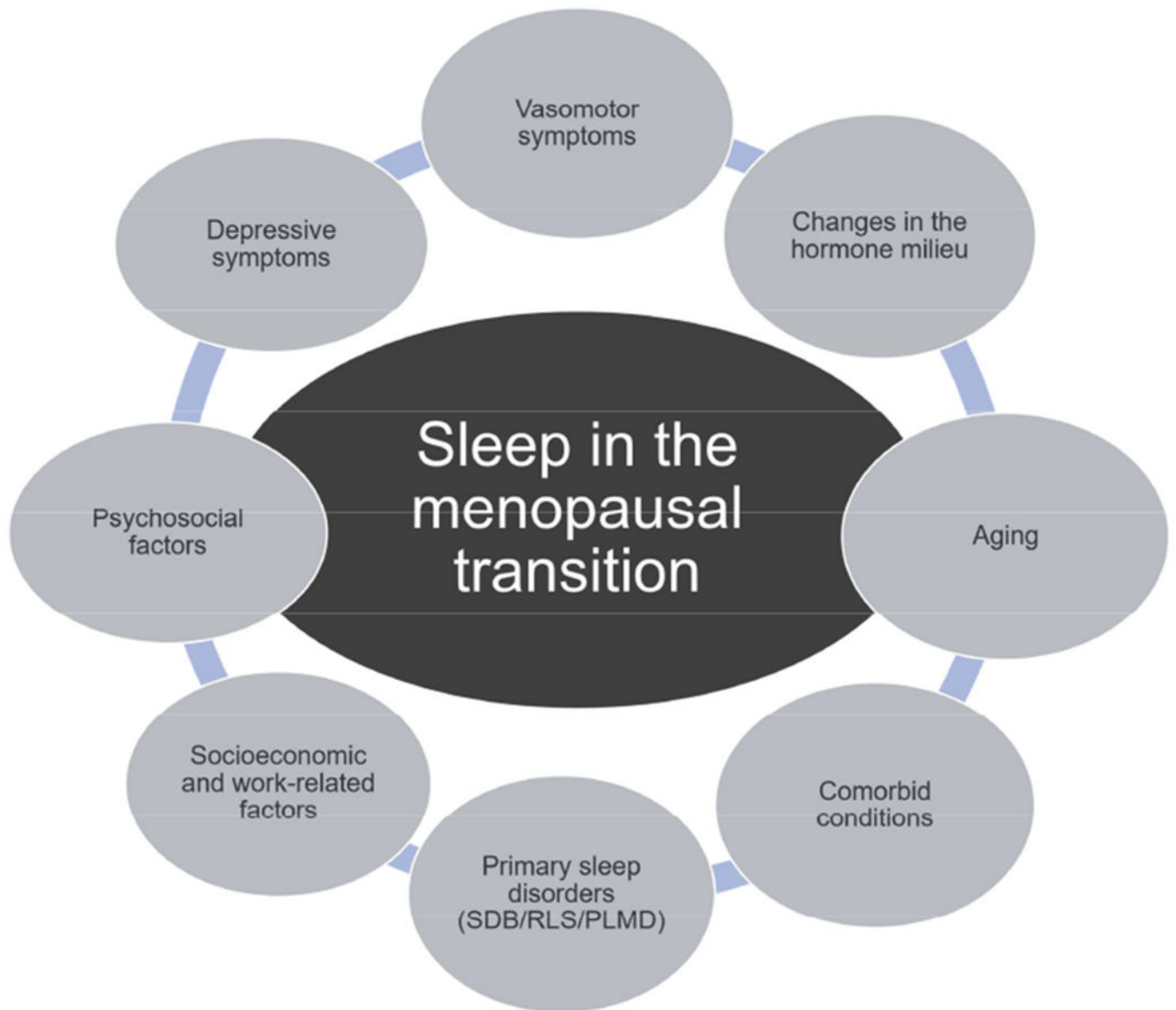


Figure 2. Many factors are associated with sleep disturbances in the context of the menopausal transition. Some factors may also interact to worsen sleep quality. SDB, sleep-disordered breathing; PLMD, periodic limb movement disorder; RLS, restless legs syndrome.

Table 1.

Typical menopausal symptoms and their prevalence in midlife women

Symptom	Prevalence (%)
Hot flashes and/or night sweats	36 – 87
Sleep problems	40 – 60
Mood symptoms	15 – 78
Weight gain	60 – 70
Muscle and/or joint pain	48 – 72
Palpitation	44 – 50
Headache	32 – 71
Memory impairment	41 – 44
Genitourinary symptoms	25 – 30
Sexual dysfunction	20 – 30

Data from references 7, 28, 41, 141-145

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