



# An integrated approach to diagnosing and managing sleep disorders in menopausal women



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## ABSTRACT

Sleep disorders increase in prevalence during the menopausal transition and they constitute a complex phenomenon. Insomnia, the main sleep disorder, can be a primary disorder or it can be secondary to hot flashes (HF), mood disorders, psychosocial factors, medical conditions, and other sleep disturbances, such as obstructive sleep apnoea (OSA) or restless legs syndrome (RLS). Menopausal women complaining of persistent sleep disorders should be referred to a sleep specialist for comprehensive sleep management because unrecognized and untreated sleep disorders can have dramatic health-related consequences. Women suffering from insomnia related to vasomotor symptoms (VMS) can be treated with hormone replacement therapy (HRT). Primary insomnia will be preferentially improved with cognitive behavioural therapy (CBT-I) or with non-benzodiazepine hypnotics or melatonin. CBT-I is a highly efficacious treatment for postmenopausal women with insomnia. Using antidepressants to treat sleep disruption in the absence of depression is not recommended; instead, the United States Food and Drug Administration (FDA) approved paroxetine as the first non-hormonal treatment for HF. Sleep disorders in menopausal women should not be underestimated. It is necessary to diagnose the specific causal disorder and then to provide treatment to improve sleep quality and quality of life.

## 1. Introduction

Menopause is characterized by the onset of vasomotor symptoms (VMS) and genitourinary syndrome of menopause (GSM) and it often features changes in mood, sleep patterns, memory and body shape. The Study of Women's Health Across the Nation (SWAN) showed that in the premenopausal age group the prevalence of sleep disturbance ranges from 16% to 42%, in perimenopausal women from 39% to 47%, and in postmenopausal women from 35% to 60% [1]. Sleep disorders among menopausal women have been linked to several factors: normal physiological changes associated with aging, menopause-related symptoms, stress, mood symptoms (depression or anxiety), and chronic health problems [2] (Fig. 1). Poor sleep quality is related to vasomotor and other physical menopausal symptoms [3]. Insomnia, the main sleep disturbance, can be a primary disorder or it can be secondary to HF, mood disorders, psychosocial factors, medical conditions, and other sleep disorders, such as obstructive sleep apnoea (OSA) or restless legs syndrome (RLS). It is mandatory to identify the various morbidities and comorbidities of menopausal women and the interplay of these factors, and to assess their impact on sleep.

## 2. Methods

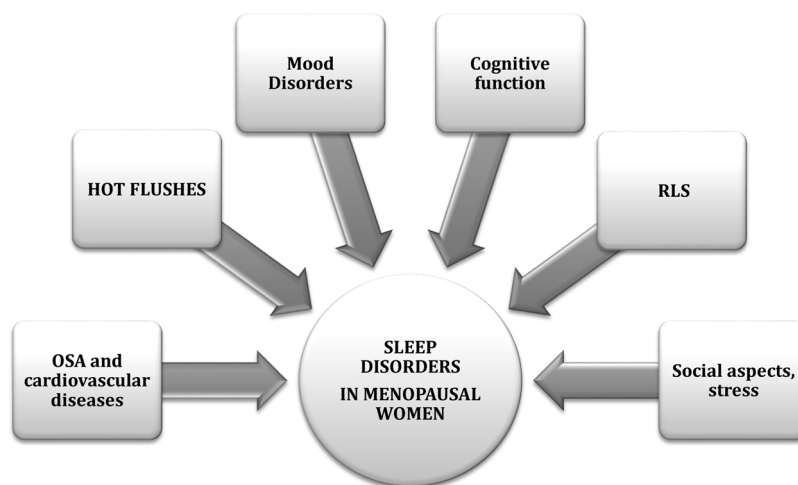
This narrative review of the literature focuses on the diagnosis and management of sleep disorders in menopausal women. To identify eligible studies, the main search was conducted in the electronic database PubMed, covering the period from conception until April 2019 and using the following terms: Hormone replacement therapy, Insomnia, Menopause, Sleep disorders, Vasomotor symptoms. The main search was completed independently by three authors.

## 3. Menopausal women and sleep disorders

Sleep disorders in menopausal women have been ascribed to several factors: normal physiological changes of aging, menopause-related symptoms, stress, mood symptoms (such as depression and anxiety), and chronic health issues. Besides these biological and chronobiological factors, socioeconomic, psychosocial and cultural factors may also play a mediating role between the sleep and menopause [4]. In menopause transition and in post-menopause, insomnia (primary or secondary) is much more frequent than intrinsic sleep disorders such as OSA and RLS. The majority of sleep complaints will be related to secondary insomnia (66–77% of insomnia-related sleep complaints) [5]. The sleep disorders

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**Fig. 1.** Sleep disturbance and menopause-related symptoms. Many factors are associated with sleep disturbances in the context of the menopausal transition and several factors may also worsen sleep quality. OSA: Obstructive sleep apnea; RLS: Restless legs syndrome.

cause significant distress and impairment in social, occupational, educational, academic and behavioural spheres and reduce overall quality of life (QoL) [6].

#### 4. Diagnosing sleep disorders in menopausal women

The essential diagnostic tool for insomnia is a clinical interview: it can reveal medical and psychiatric conditions, social history, and other menopausal complaints (HF, night sweats, incontinence, diminished libido, vaginal dryness, depressed mood), current life situation (including urinary problems, endocrine diseases, use of neuroactive medications, cigarettes, alcohol, caffeinated drinks, work stress) [7].

The diagnostic method considered the gold standard for sleep disorders is polysomnography (PSG), but it has some limitations due to the inability to evaluate quality of sleep and the impact of a sleep disorder on daily activities. Patients generally fill out a pre-study questionnaire before undergoing PSG [8]. The aims of the questionnaire are: to create a standardized measure of sleep quality; to provide a tool to distinguish good versus poor sleep quality; to create a measure of sleep quality that is user-friendly for patients and clinicians and that provides a clinical tool to assess a list of sleep disturbances that affect sleep quality [9].

The Insomnia Severity Index (ISI), Athens Insomnia Scale (AIS) and Pittsburgh Quality of Sleep Index (PSQI) are the scales most frequently used to study sleep disorders in menopause. The last does not relate specifically to insomnia. The major causes proposed to explain the poor quality of sleep are: sleep disruption, associated with HF, sleep apnoea, mood disorder and inadequate sleep hygiene [10].

#### 5. Management of sleep disorders in menopausal women

According to recent guidelines, insomnia can be treated with psychological therapy, pharmacological therapy, or a combination of both [11].

##### 5.1. Cognitive behavioural treatment for insomnia (CBT-I)

Cognitive-behavioural therapy for insomnia (CBT-I) is the first-line treatment for chronic insomnia in adults [11]. CBT-I is a structured, skill-focused psychotherapy that consists of cognitive therapy (challenging irrational/distorted beliefs about sleep); behavioural strategies (sleep restriction, stimulus control therapy, relaxation techniques) and education about sleep hygiene. The techniques of cognitive behavioural therapy have been applied to menopausal symptoms. CBT-I is a multicomponent behavioural intervention targeting multiple menopausal symptoms [10].

##### 5.2. Hormone replacement therapy (HRT)

There are several clinical trials and review studies on the treatment of menopausal sleep disturbance. There is wide heterogeneity in the studies, both in the various formulations used and in the women enrolled in the trial. HRT theoretically can improve both VMS and chronic insomnia because lowers estrogen levels, which are associated with VMS in perimenopause, and VMS are strongly associated with chronic insomnia. Estrogen therapy, with or without progesterone, is known to be beneficial in treating menopause-related symptoms and in improving QoL in postmenopausal women [12]. Estrogen therapy improves the quality of sleep by decreasing HF and the frequent night-time awakenings. Oral progesterone has a sedative effect probably through a GABA-agonistic action: it reduces wakefulness without impeding daytime function [13]. HRT theoretically improves subjective sleep quality by reducing night-time awakening and sleep latency.

Bazedoxifene/conjugate estrogen (Bza/Ce) is a novel tissue-selective estrogen complex (TSEC) and has been evaluated and compared with the placebo in a randomized, double-blind, placebo-controlled trial in the Selective Estrogens, Menopause And Response to Therapy (SMART) trials. Compared with placebo, Bza 20 mg/CE 0.45 and 0.625 mg produced significant decreases in HF frequency and severity, and an improvement in health-related quality of life and sleep parameters at 3 months [14].

##### 5.3. Non-hormonal pharmacological options

Non-hormonal pharmacological options include benzodiazepines (BZ), benzodiazepine receptor agonists, antidepressants, antipsychotics and melatonin. Classic non-benzodiazepine hypnotic therapy includes zopiclone or eszopiclone. These drugs are efficient in promoting sleep initiation and maintenance. Eszopiclone has been shown to reduce the perception of HF [15].

The mechanisms of action of antidepressants in insomnia include blocking wake-promoting neurotransmitters (acetylcholine, histamine, norepinephrine, serotonin, and dopamine) for sleep enhancement. Some antidepressants and mood stabilizers (venlafaxine, gabapentin) may ameliorate mood and VMS but may aggravate insomnia. Several studies were conducted with escitalopram (an SSRI): Freeman et al. showed the effect of escitalopram on insomnia symptoms and subjective sleep quality in healthy menopausal women with HF [16].

Recently, paroxetine (an SSRI) received approval by the US FDA to treat moderate to severe menopause-related hot flashes: paroxetine is the first non-hormonal treatment for hot flashes approved by the FDA.

Other sedating antidepressants have been evaluated as treatments

for menopause-related insomnia, such as trazodone and mirtazapine, but they are not FDA approved for the treatment of insomnia without comorbid depression [10]. Mirtazapine improves menopause-related depression that is unresponsive to HRT [17]. In a 2-week single-blind placebo run-in phase, followed by an 8-week open-label flexible-dose trial with quetiapine in a group of 40 perimenopausal women with major depressive disorder and chronic insomnia, quetiapine improved subjective reports of sleep quality and VMS. Antidepressants are generally not advised for routine use in menopause-related insomnia without depression [12].

The pineal hormone melatonin plays a central role in the regulation of the circadian sleep/wake cycle and mood, and its endogenous secretion decreases with age. Women treated with melatonin reported a considerable improvement in mood disturbances and in depression [18]. Attention has been focused on the development of ramelteon, a melatonin receptor (MT1 and MT2) agonist. A single open-label trial of 20 perimenopausal women with insomnia showed improvement in sleep diaries with a nightly dose of ramelteon 8 mg for 4 weeks [19]. Melatonergic compounds could be useful in the treatment of insomnia in menopausal patients [18].

#### 5.4. Healthy lifestyle

Healthier behaviour can mitigate menopausal symptoms and improve sleep quality. Sleep hygiene education is a common insomnia-focused treatment. It should cover limiting daytime naps, ensuring adequate exposure to natural light, a regular relaxing bedtime routine, and the avoidance of stimulants such as caffeine and nicotine close to bedtime [10]. A healthy lifestyle should include high-intensity exercise: high levels of physical activity are associated with significant improvement in sleep diaries, PSQI scores, and PSG measures of sleep efficiency, as well as decreased arousal index [12]. If patients report symptoms consistent with SDB, OSA, RLS, or other sleep disorders, a referral to a sleep specialist is recommended.

## 6. Conclusions

Good sleep quality is required for both good health and quality of life. HRT is one of the recommended treatments to relieve menopausal symptoms, which in turn can improve the quality of sleep and also quality of life. Other medications, including benzodiazepines, benzodiazepine receptor agonists, antidepressants, antipsychotics and melatonin, have demonstrated mixed benefits for sleep in menopause. CBTI is the non-pharmacological insomnia treatment most commonly administered by sleep specialists but CBTI for menopausal insomnia has only recently been investigated. Sleep disorders in menopausal women should not be underestimated. It is necessary to diagnose the specific causal disorder and then to provide a treatment to improve sleep quality and quality of life.

#### 6.1. Practice points

Sleep disorders increase in prevalence during the menopausal transition and they are related to vasomotor and other physical menopausal symptoms.

Women suffering from sleep disturbances related to vasomotor symptoms can be treated with hormone replacement therapy.

Menopausal women complaining of persistent sleep disorders should be referred to a sleep specialist for comprehensive sleep management.

#### 6.2. Research agenda

Future studies are needed to focus on the definition and management of sleep disorders in menopause, to identify more standardized interventions and to conduct wide-scale randomized trials of the more

promising therapies.

## Contributors

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