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Insomnia and menopause: a narrative review on mechanisms and treatments

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ABSTRACT

The menopausal transition is associated with an increased frequency of sleep disturbances. Insomnia represents one of the most reported symptoms by menopausal women. According to its pathogenetic model (3-P Model), different predisposing factors (i.e. a persistent condition of past insomnia and aging per se) increase the risk of insomnia during menopause. Moreover, multiple precipitating and perpetuating factors should favor its occurrence across menopause, including hormonal changes, menopausal transition stage symptoms (i.e. hot flashes, night sweats), mood disorders, poor health and pain, other sleep disorders and circadian modifications. Thus, insomnia management implies a careful evaluation of the psychological and somatic symptoms of the individual menopausal woman by a multidisciplinary team. Therapeutic strategies encompass different drugs but also behavioral interventions. Indeed, cognitive behavioral therapy represents the first-line treatment of insomnia in the general population, regardless of the presence of mood disorders and/or vasomotor symptoms (VMS). Different antidepressants seem to improve sleep disturbances. However, when VMS are present, menopausal hormone therapy should be considered in the treatment of related insomnia taking into account the risk–benefit profile. Finally, given its good tolerability, safety, and efficacy on multiple sleep and daytime parameters, prolonged-released melatonin should represent a first-line drug in women aged ≥ 55 years.

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Introduction

Current evidence suggests that neurophysiological phenomena occurring during sleep fulfill different functions. Indeed, sleep is essential for multiple cerebral processes, such as learning and memory consolidation, but contributes also to metabolic and hormonal regulations. Sleep differs between men and women, probably related to gender differences in hormone secretion. Women report consistently worse sleep quality over the entire life span with some ‘vulnerable periods’ related to specific female conditions, such as menstrual cycle, pregnancy, and menopause^{1,2}.

The aim of this narrative review is to summarize up-to-date theories regarding the pathogenic mechanisms of sleep difficulties during menopause. Indeed, an in-depth knowledge of those factors affecting sleep across the transition and beyond might be also essential to efficiently target sleep disorder management. Finally, in the last part we also review the main therapeutic options for insomnia during menopause, providing an algorithm to help the clinician selecting the more appropriate pharmacological or behavioral treatment strategy.

Method

A literature search for studies (January 1980–January 2020) focusing on sleep disturbances during menopause published in the National Library of Medicine (Medline Database, Google Scholar, and Scopus) was performed using the search terms ‘menopause’ and ‘sleep disturbances/disorders’ or ‘insomnia’. We considered studies investigating: the prevalence of sleep disorders in menopausal transition; the pathogenetic mechanisms at the basis of the association between menopause and insomnia; and the therapeutic options for insomnia during menopause. Exclusion criteria were: language other than English; unavailable full-length texts; dissertations; and correspondence. Two of us (C.C. and R.E.N.) extracted the data independently.

Insomnia: definition and epidemiology

Insomnia represents a persistent difficulty of falling asleep and maintaining sleep, which occurs even if every condition for a good sleep is settled, resulting in daytime impairment. Insomnia is considered ‘chronic’ when it occurs for at least three nights a week for three consecutive months³. In its

chronic form, insomnia causes clinically significant social, occupational, and behavioral distress⁴. Daytime symptoms include fatigue, sleepiness, mood disturbances, alterations of memory functions and attention, and accidents. Recent evidence revealed an association of insomnia with cardiovascular diseases like hypertension, cardiovascular disease, diabetes, and increased risk of mortality⁵.

Epidemiologically, insomnia is a very common health problem. Large cohorts from various countries reported a wide range of prevalence. Regional and cultural differences and heterogeneity of assessment tools contribute to the large prevalence variation. In 2006, a population-based study found that 6–33% were affected by insomnia⁶.

Different studies suggest that women complain more frequently of insomnia than men do². Moreover, insomnia increases with age⁶. Insomnia seems to be common for women across different stages of the reproductive lifespan and varies during the menstrual cycle, suggesting that fluctuations of sexual hormones play a crucial role in several sleep disorders^{7,8}.

Insomnia across the menopause

Sleep alterations represent a key symptom of menopause transition⁷. Many biological and chronobiological factors, such as physiological alterations associated with aging, menopausal symptoms (e.g. vasomotor symptoms [VMS]), poor health perception, mood symptoms, and comorbid chronic health issues (low back pain, musculoskeletal disorders, and osteoarthritis)⁹, together with socioeconomic, psychosocial, and race/ethnic factors¹⁰ are involved. However, an independent correlation between menopausal stages and sleep disturbance, beyond the effects of aging and other confounders, is evident⁸. Insomnia is the most frequent sleep disorder during menopause as compared with the prevalence of obstructive sleep apnea (16–20%) or restless leg syndrome (20–24%)^{11–16} (Table 1).

In a multiethnic survey (the Study of Women's Health Across the Nation [SWAN]) following women for 10 years across the menopause, insomnia was present in 46–48% of menopausal women versus 38% of premenopausal women^{17,18}. Another large survey conducted in a Latin American population confirmed that the prevalence of insomnia increases with female age and menopausal stages¹⁹.

The main predictive factor for insomnia during menopause is the premenopausal sleep condition: a persistent condition of past insomnia is strongly related to future sleep disturbances^{20,21}. Regarding insomnia subtypes, a disorder of sleep maintenance is the most frequently reported, with different awakenings and non-restorative sleep^{22–24}. As in the general population, insomnia at menopause is associated with multiple adverse effects such as poor health-related quality of life, decreased work productivity, and increased healthcare utilization²⁵ but also with higher prevalence of anxiety, depression, and cardiovascular diseases^{26–28}.

Insomnia and menopause: pathophysiologic links

Mechanisms causing insomnia in menopausal women are multifactorial and involve hormonal changes, transition-stage symptoms (e.g. hot flashes [HFs], night sweats), and mood disorders as well as some factors coincident with midlife and being older, such as stress²⁵, obesity²⁹, poor health, and increased incidence of other sleep disorders^{16,23}.

Hormonal changes

Many studies reported an effect of sexual hormones on sleep^{30–34}. Progesterone exerts anxiolytic and sedative properties, stimulating benzodiazepine receptors favoring non-rapid eye movement sleep. Estrogens seem to decrease sleep latency and the number of awakenings³⁴. Indeed, low estrogen levels have been found to be associated with a greater severity of awakenings²⁶. Moreover, they regulate the time of lowest body temperature during the night, as demonstrated by the evidence that stopping estrogen therapy leads to a shift forward of the aforementioned time and changes the depth of the temperature drop³⁵. Finally, little is known about the effect of androgens on sleep. A cross-sectional observational study showed a positive association of dehydroepiandrosterone sulfate with wake after sleep onset in a general population of women³⁶. Other findings on the relationship between steroid hormone levels and sleep difficulties in menopause showed an association between follicle stimulating hormone, estradiol changes, and estradiol to total testosterone ratio and poor sleep quality across the transition and in the late reproductive stage³⁷.

Despite intensive research, a correlation between polysomnographic features, menopausal stages, and hormonal levels is not clearly demonstrated. This may be due to the presence of multiple influencing factors, including a high variability of their measurements across the menopausal phases. This makes the isolation of hormone influence challenging. For instance, in women with insomnia during menopause, no relationship between follicle stimulating hormone and wake after sleep onset (a common sleep alteration in this population) has been shown³².

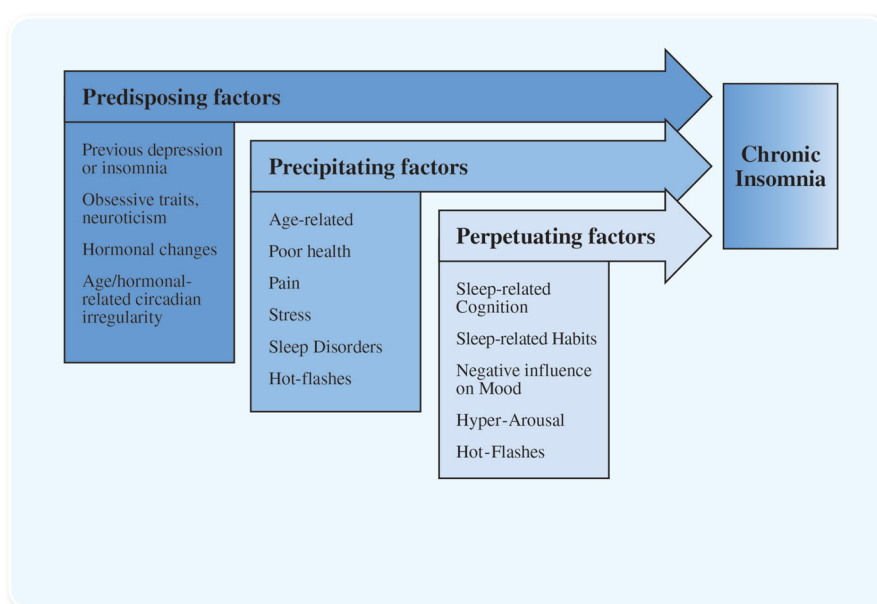
Hot flashes

HFs are common symptoms of impending menopause (reported by up to 80% of women³⁸) and are considered an important source of sleep disturbance^{39,40}. The presence of HFs has been consistently associated with poorer self-reported sleep quality, suggesting a possible link between HFs and nocturnal awakenings^{17,41}. Data regarding the grade of interference between VMS and sleep in menopausal women are discordant; differences might be related to how HFs were classified in term of intensity and interference with sleep continuity. Campbell and Murphy⁴² reported symptoms of insomnia in 29% of menopausal women with HFs. They found that high body core temperature prior to and during sleep was significantly correlated with poorer sleep efficiency and higher luteinizing hormone levels even in women

Table 1. Prevalence, physiopathology, symptoms, and treatments of other sleep disorders in menopause.

Sleep disorder	Prevalence (%)	Physiopathology	Signs/symptoms	Treatment
Obstructive sleep apnea	16–20	Loss of protective effects of female hormones (progesterone) Weight gain and changes in fat distribution	Obesity Snoring and witness apneas Dry mouth Choking Nocturia Nocturnal sweating Daytime sleepiness Morning or nocturnal headache	Weight loss CPAP
RLS/PLM	20–24	Aging Unknown role of female hormones (usually, high estrogen levels increase the risk of RLS)	An urge to move the legs, usually accompanied by unpleasant sensations in the legs. These symptoms must: <ul style="list-style-type: none"> • Begin or worsen during periods of rest or inactivity • Be partially or totally relieved by movement • Occur exclusively or predominantly in the evening or night 	Dopamine agonists Gabapentin, pregabalin

CPAP, continuous positive air pressure; PLM, periodic leg movements; RLS, restless leg syndrome.

**Figure 1.** Model of insomnia in perimenopause (3-P Model).

without VMS. More recently, it has been found that almost 80% of HFs interfered with sleep⁴³. Longitudinal data have shown that women with moderate-to-severe HFs present a higher risk of frequent nocturnal awakenings in comparison to women without HFs¹³. Bothersome HFs, but not HFs alone, seem to be associated with sleep difficulties⁸. A recent protocol demonstrated that an objective increase of HFs is most common during early sleep and wake, typically preceding or occurring simultaneously with wake episodes, and that the number of HFs reported at night correlates with worsening of sleep disturbance indices⁴⁴. Finally, treatment of HFs using menopausal hormone therapy (MHT) seems to improve sleep quality^{11,45}.

Mood disorders

The association between menopause, mood disorders, and insomnia is widely reported. Depression represents a risk factor for poor sleep²¹ and menopausal women are at increased

risk of developing a major depressive episode, especially when HFs are present⁹. In accordance with the 'domino effect theory', sleep is disturbed by HFs or other menopause-related factors, and multiple arousals permit the development of intrusive anxious thoughts several times during the night (also exacerbated by pre-existing anxiety or depression). In turn, waking up repeatedly offers plenty of opportunities for presenting anxiety throughout the night. Finally, sleep fragmentation may contribute to daytime mood symptoms. In this context, insomnia follows sleep disruption and depression follows insomnia within a vicious circle⁴⁶ (Figure 1).

Circadian modifications

The sleep/wake alternation is regulated by two biological mechanisms, the circadian and the homeostatic processes⁴⁷. While the homeostatic system regulates sleep intensity, the circadian clock controls sleep timing. This latter process is

driven by an endogenous pacemaker located in the hypothalamic suprachiasmatic nuclei. The suprachiasmatic nuclei is normally entrained by different stimuli that signal the time of day; light is the most important stimulus in mammals. The pineal gland is the nucleus where melatonin is synthesized, according to the light level; thus, the absence of light represents the principal stimulus for melatonin secretion. Melatonin exerts beneficial effects on sleep through its soporific and synchronizing effects on circadian rhythms. Recent findings demonstrated that this hormone plays an important role also in the modulation of mood, immune functions, carcinogenesis, and reproduction⁴⁸.

Aging is typically associated with both alteration of the circadian system and a decrease in melatonin secretion, which are two strongly connected conditions. Limited data suggest that differences in circadian regulation (advanced circadian phase) in postmenopausal women could contribute to sleep difficulties, particularly a more fragmented sleep or early morning awakening⁴⁹. Animal models also suggest that alterations of reproductive hormone secretion may alter circadian rhythmicity⁵⁰, although many knowledge gaps remain. Circadian processes are critical to both sleep/wake and mood regulation. Consistent with findings in general populations, sleep/wake rhythms alterations are correlated with both higher anxiety and the presence of depression in menopausal women^{51,52}.

Together with the sharp decrease of estrogen levels during menopause, even the gradual reduction of melatonin levels seems to play a role in developing insomnia. Indeed, these hormonal changes can eventually bring sleep disturbances and decreased quality of life in menopausal women⁵³. Toffol *et al.* demonstrated that postmenopausal women had lower night-time serum melatonin concentrations than perimenopausal women⁵¹. Interestingly, a transient peak was observed at the time of full-blown menopause, where women can feel a transient improvement in sleep quality in spite of low estrogen levels⁹. Following this time period, melatonin secretion continues to decrease, sometimes to the extent that the woman experiences an advanced sleep phase syndrome.

Some authors proposed that the complex interaction between melatonin and gonadal hormonal milieu relies on the influence of sex steroids on the effects of melatonin rather than on its own levels⁵⁴. Acute melatonin administration reduces body temperature, glucose tolerance, and insulin sensitivity, increases thyroid stimulating hormone, and stimulates luteinizing hormone. Sex steroid changes related to the menstrual cycle modulate most of these effects, but at menopause they are less active⁵⁴. Melatonin may favor sleep by peripheral vasodilating and thermoregulatory actions. These effects are modulated by sex steroids and are probably reduced in postmenopausal women⁵⁴, facilitating the development of insomnia. Moreover, the change in melatonin level induces important alterations in the biological function of almost every organ⁵⁵ with potential implications in sleep quality.

Finally, numerous recent studies recognize sleep disorders and sleep/wake rhythm disturbances as risk factors for

dementia development, through different mechanisms. Indeed, the circadian system seems to play a role for the clearance of several proteins also involved in the pathogenesis of several forms of dementia. Epidemiological studies revealed that the risk of dementia is higher in women, given the modulatory role of sex steroids on cognition^{34,56}. Therefore, the loss of ovarian hormones during menopause could act on cognitive reserve both directly and indirectly through an increase of sleep disorders, accelerating cognitive decline⁵⁷.

Management of insomnia during menopause

In menopausal women, insomnia should be a primary disorder or can occur as a secondary condition underlying other sleep disorders. It is therefore mandatory to first exclude or treat these disorders before starting a specific treatment. Recently, a position statement by the Italian Association of Sleep Medicine was published to provide evidence-based advice on the management of postmenopausal sleep disorders⁵⁸. Indeed, during evaluation of sleep problems, clinicians – using sleep history assessment or specific questionnaires – should investigate the timing of sleep difficulties in relation to menopausal symptoms, changes in bleeding patterns, and the presence of menopausal disturbances, but also the occurrence of symptoms suggestive for obstructive sleep apnea or movement disorders⁵⁸ (Table 1).

Insomnia is usually diagnosed through clinical evaluation and a polysomnographic study is generally not recommended. However, in the non-responder insomniac patient, or if other sleep disorders are supposed, polysomnography is suggested⁵⁹.

In general, the identification of patients with higher risk of insomnia is important in order to provide primary (i.e. education on stress management) and secondary (i.e. modify sleep-related behaviors) prevention countermeasures. Similarly, in menopausal transition, women at risk of developing insomnia (i.e. history of severe premenstrual syndrome and neurotic personality style) might benefit from the same preventative interventions^{60,61}.

According to the European guideline for the diagnosis and treatment of insomnia, the first-line treatment for chronic insomnia in adults of any age in the general population is represented by cognitive behavioral therapy for insomnia (CBT-I). A pharmacological intervention can be proposed when CBT-I is not effective or unavailable⁶².

Table 2 summarizes the most relevant RCT studies focused on management of insomnia during menopause.

Cognitive behavioral treatment

CBT-I represents a multicomponent treatment targeting cognitive and behavioral factors contributing to insomnia. Its efficacy in the general population is well known from multiple controlled trials⁶³.

Two studies belong to the Menopause Strategies Finding Lasting Answers for Symptoms and Health research network (MsFLASH). The first trial⁶⁴ was a randomized controlled trial

Table 2. Randomized controlled trials on insomnia treatment in menopausal women.

Insomnia treatment	Study	Population	Interventions	Sleep outcomes	Results
CBT-I	McCurry <i>et al.</i> ⁶⁴	106 perimenopausal or postmenopausal women	CBT-I, telephone-delivered menopause education	ISI, PSQI	CBT-I improves self-reported insomnia symptoms and VMS
	Guthrie <i>et al.</i> ⁶⁵	546 perimenopausal and postmenopausal women	CBT-I, escitalopram, yoga, aerobic exercise, omega-3 fatty acids, oral E2, venlafaxine	ISI, PSQI	CBT-I produced the greatest reduction in ISI. Effects on ISI were similar for exercise and venlafaxine; small decreases in ISI were observed with escitalopram, yoga, and E2. The largest reduction in PSQI was with CBT-I. PSQI decreases were significantly better than control with escitalopram, exercise, yoga, estradiol, and venlafaxine. Omega-3 supplements did not improve insomnia symptoms
	Drake <i>et al.</i> ⁶⁶	150 postmenopausal women	CBT-I, sleep hygiene education, sleep restriction therapy	ISI, sleep diaries	CBT-I and sleep restriction resulted in more effective insomnia treatment. CBT-I was superior to sleep restriction in improving sleep maintenance
MHT	Hays <i>et al.</i> ⁶⁸	16,608 postmenopausal women	0.625 mg CEE + 2.5 mg MPA versus placebo	WHIIRS	CEE + MPA was associated with a statistically significant but small and not clinically meaningful benefit in terms of sleep disturbance. Among women aged 50–54 years with VMS, CEE + MPA improved VMS and resulted in a small benefit in terms of sleep disturbance
	Saletu-Zyhlarz <i>et al.</i> ⁶⁹	51 postmenopausal women	2 mg EV + 3 mg DNG versus 2 mg EV versus placebo	PSG parameters and PSQI	EV + DNG significantly improved subjective sleep quality and marginally improved variables concerning objective sleep and awakening quality
	Sherman <i>et al.</i> ⁷⁰	246 postmenopausal women with heart disease	0.625 mg CEE versus CEE + 2.5 mg/day MPA versus placebo	WHIIRS	MHT was not significantly associated with more favorable outcomes for any health-related quality of life
	Heinrich and Wolf ⁷¹	51 hysterectomized women	2 mg EV versus EV + 100 mg MP versus placebo	ADSK Sleep item + Sleep item from Menopausal Index (combined)	EV or EV + MP treatment had no effect on mood, well-being, menopausal symptoms, sleep quality, and depressive symptoms
	Savolainen-Peltonen <i>et al.</i> ⁷⁴	150 postmenopausal women (half of women with severe VMS, half of symptom free)	Transdermal 1 mg E2 versus oral E2 2 mg with or without 5 mg MPA versus placebo	WHQ sleep item	In women with baseline VMS, MHT significantly improved the scores for sleep
	Cintron <i>et al.</i> ⁷⁵	727 perimenopausal or postmenopausal women	Oral CEE versus transdermal E2 plus MP (200 mg) versus placebo	PSQI	Sleep quality improved with both MHT formulations
	LeBlanc <i>et al.</i> ⁷⁶	37 postmenopausal women	2 mg E2	OHSU SL sleep diary	Women receiving E2 had greater improvements in menopausal symptoms and sleep
	Antidepressants	Ensrud <i>et al.</i> ⁸⁸	205 perimenopausal and postmenopausal women with VMS	Escitalopram (10–20 mg/day) versus placebo	ISI, PSQI
DeFronzo <i>et al.</i> ⁸⁹		25 menopausal women	Escitalopram (10–20 mg flexibly dosed) versus placebo	PSQI	Escitalopram induced a decrease in both VMS frequency and severity and an improvement in dysphoria, anxiety, quality of life, and sleep
Davari-Tanha <i>et al.</i> ⁹⁰		20 postmenopausal women	Venlafaxine (75 mg/day) versus citalopram (20 mg/day) versus placebo	PSQI	Citalopram and venlafaxine are equally more effective than placebo in reducing sleep disturbance and severity of VMS. Citalopram is more effective in reducing frequency of VMS than venlafaxine. Venlafaxine is more effective than citalopram in treatment of depression

(continued)

Table 2. Continued.

Insomnia treatment	Study	Population	Interventions	Sleep outcomes	Results
	Suvanto-Luukkonen <i>et al.</i> ⁹¹	150 postmenopausal women	Fluoxetine (10–30 mg/day) versus citalopram (10–30 mg/day) versus placebo	Patient reports	Insomnia improved significantly only in the citalopram group; VMS did not improve in any of the three groups
BDZ and Z-drugs	Dorsey <i>et al.</i> ¹¹⁰	141 perimenopausal or postmenopausal women	Zolpidem (10 mg/day) versus placebo	Diary-based sleep parameters and GSDS	Zolpidem induced an increase in TST, a decrease in WASO and number of awakenings, and an improvement in sleep-related difficulty with daytime functioning
	Soares <i>et al.</i> ¹¹¹	410 perimenopausal or early postmenopausal women	Eszopiclone (3 mg/day) versus placebo	Physician global assessments of menopause, GCS, MADRS, and SDS	Eszopiclone provided significant improvements in sleep and positively impacted mood, quality of life, and menopause-related symptoms
	Joffe <i>et al.</i> ¹¹²	46 perimenopausal and postmenopausal women	Eszopiclone (3 mg/day) versus placebo	ISI and diary-based sleep parameters	Eszopiclone reduced ISI scores and improved all sleep parameters, depressive symptoms, anxiety symptoms, quality of life, and night-time but not daytime VMS
Gabapentin	Yurcheshen <i>et al.</i> ¹¹⁹	59 perimenopausal women with VMS	Gabapentin (300 mg three times daily) versus placebo	PSQI	Gabapentin induced an improvement in the sleep quality factor score, in the sleep efficiency factor score, and in the global PSQI score

ADSK, German version of Center for Epidemiological Studies Depression Scale; BDZ, benzodiazepine; CBT-I, cognitive behavior treatment for insomnia; CEE, conjugated equine estrogen; DNG, dienogest; E2, estradiol; EV, estradiol valerate; GCS, Greene Climacteric Scale; GSDS, General Sleep Disturbance Scale; ISI, Insomnia Severity Index; MADRS, Montgomery Asberg Depression Rating Scale; MHT, menopausal hormone therapy; MP, micronized progesterone; MPA, medroxyprogesterone acetate; OHSU SL, Oregon Health and Science University Sleep Laboratory; PSG, polysomnography; PSQI, Pittsburgh Sleep Quality Index; SDS, Sheehan Disability Scale; TST, total sleep time; VMS, vasomotor symptoms; WASO, wake time after sleep onset; WHIIRS, Women's Health Initiative Insomnia Rating Scale; WHQ, Women's Health Questionnaire.

(RCT) of a telephone CBT-I intervention versus telephone-delivered menopause education. In this study, CBT-I resulted in significant improvements in self-reported insomnia symptoms, sleep quality, sleep latency, wake time after sleep onset, and sleep efficiency compared to the educational protocol. Moreover, CBT-I reduced self-reported HFs interference more than the educational protocol. A second research trial⁶⁵ compared the results of several RCTs on the effects of different interventions on insomnia and VMS in women with a comparably severity of both insomnia and VMS. They analyzed 546 perimenopausal women included in different trials and found that telephone-delivered CBT-I was more effective for reducing moderate-to-severe insomnia symptoms in women with HFs than other commonly used pharmacologic or lifestyle modification options. If CBT-I is unavailable, exercise and the antidepressant venlafaxine may produce moderate improvements in sleep quality⁶⁵.

A recent controlled trial⁶⁶ evaluated 150 postmenopausal insomniac women treated with sleep hygiene education versus sleep restriction therapy (SRT) versus CBT-I. SRT requires patients to limit the amount of time they spend in bed to an amount equal to their average total sleep time. This intentional limitation of the time in bed produces a mild sleep deprivation which leads to faster sleep onset and a deeper sleep. A final result of SRT is also a reduction in the negative beliefs and attitudes associated with sleep. CBT-I and SRT were more effective in insomnia treatment compared to sleep hygiene education. Although the response to CBT-I and SRT were similar overall, CBT-I was superior to SRT in

improving sleep maintenance, a common perimenopausal problem.

Menopausal hormone therapy

MHT has long been considered an effective treatment for sleep disturbances in menopausal women^{67–76}. However, a recent meta-analysis reported an improvement in quality of life with MHT only in patients with VMS⁷³. Indeed, MHT may act by improving other symptoms disturbing sleep across menopause. Estrogens may have an antidepressant effect, by the norepinephrine and histamine pathways, and a direct action on sleep and body thermoregulation^{33,35,77,78}. Progesterone has a direct sedative function, stimulating the benzodiazepine receptors, with a consequent increase in the production of the γ -aminobutyric acid receptors during non-rapid eye movement sleep. Moreover, it may have an anxiolytic effect as a γ -aminobutyric acid agonist, even though the exact mechanism is unclear^{33,77}. It is likely that different progestogens, depending on their metabolites, may exert specific effects on sleep. Indeed, a recent review showed that oral micronized progesterone is particularly effective for both treating VMS and improving sleep, highlighting its safety in menopausal women⁷⁹. When prescribing MHT with the aim of relieving insomnia, it should be evaluated how much the benefits outweigh the risks of MHT exposure^{80–83}. Recent data showed that transdermal estradiol associated with micronized progesterone did not increase the risk for stroke or other thromboembolic events. Thus, transdermal

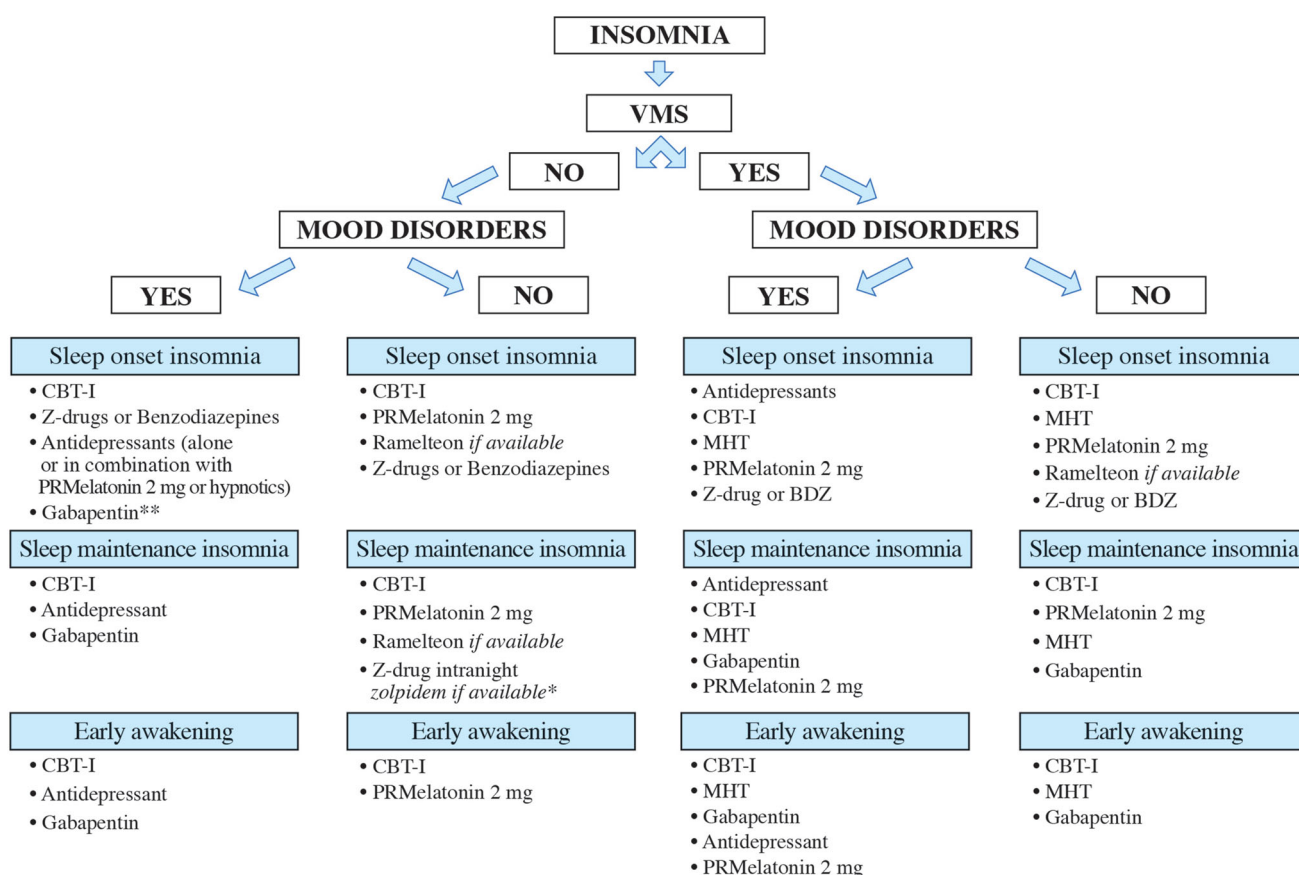


Figure 2. Proposal for a practical algorithm to treat insomnia in menopausal women. Our proposed algorithm was based on available randomized controlled trials on treatment conducted in menopausal women (see Table 2) and on recent insomnia treatment guidelines in menopausal women⁵⁸ and in the general population^{103,104}. *Antidepressant off label, trazodone, may be effective. **If non-responder, consider MHT (refers to menopause experts). BDZ, benzodiazepines; CBT-I, cognitive behavioral therapy for insomnia; MHT, menopausal hormone therapy; PRMelatonin, prolonged-release melatonin; VMS, vasomotor symptoms.

treatment seems to be the safest type of MHT when risk of venous thromboembolism is considered⁸⁴. The only increased risk of MHT in postmenopausal women with increasing duration is breast cancer. In 2014, a meta-analysis reviewed studies analyzing isoflavone properties on HFs and other menopausal-related symptoms, showing that these alternative therapies are not effective on HFs but exert some beneficial effects on sleep disturbances⁸⁵.

Antidepressants

The most popular prescriptive treatments for VMS other than MHT in menopausal women affected by insomnia are antidepressants, especially in women with contraindications to hormonal treatments⁸⁶. Escitalopram is effective, especially in the case of comorbid depression⁸⁷. In particular, a large RCT showed that escitalopram at 10–20 mg/day compared with placebo reduced insomnia symptoms and improved subjective sleep quality in 205 perimenopausal and postmenopausal women with HFs⁸⁸. Another single-blind, placebo-controlled study found an improvement in mood, sleep parameters, VMS, and overall quality of life with escitalopram (10–20 mg)⁸⁹. A RCT showed that citalopram and venlafaxine are equally more effective than placebo in reducing sleep disturbances and severity of HFs. Specifically, citalopram seems to be more effective in reducing HFs, whereas

venlafaxine is more effective in the treatment of postmenopausal depression⁹⁰. Another RCT compared the efficacy of fluoxetine and citalopram versus placebo. Sleep outcomes were assessed only by patient reports. Insomnia improved significantly only in the citalopram group, whereas VMS did not improve in any of the three groups⁹¹. A small case series of 11 menopausal women with insomnia showed that treatment with mirtazapine alone or associated with prolonged-release melatonin (PRM) significantly improved the subjective quality of sleep. The majority of women reported weight gain following mirtazapine intake; interestingly, weight decreased following mirtazapine withdrawal and PRM intake⁹². Further studies are needed to evaluate the efficacy of other new antidepressants with potential efficacy on both VMS and insomnia. For instance, two RCTs on esmirtazapine, the (S)-(+)-enantiomer of mirtazapine, found that this drug reduced the frequency and severity of moderate-to-severe VMS associated with menopause and was generally well tolerated⁹³. However, since these studies were conducted, the company discontinued further development of esmirtazapine.

Melatonin

Previous studies have shown that melatonin treatment may improve both subjective sleep problems and mood

disturbances in postmenopausal women with insomnia. Treatment with melatonin had a mild hypnotic effect and did not provoke hangover symptoms in the morning^{94–96}.

In the last years, a PRM formulation (2 mg) has been approved for primary insomnia characterized by poor quality of sleep in people aged ≥ 55 years^{97,98}. It represents the only licensed medication containing melatonin and its prolonged release formulation mimics the internal melatonin secretion profile by releasing melatonin gradually. Such a formulation has been shown to preserve sleep structure⁹⁹ without withdrawal effects¹⁰⁰, in the absence of negative impacts on psychomotor functions, memory recall, and postural stability in older adults^{101,102}.

PRM (2 mg) has shown efficacy in multiple sleep and daytime parameters in patients aged 55–80 years, including improvements in sleep quality, morning alertness, and quality of life, as well as sleep latency; these improvements were maintained or enhanced over the 6-month period⁹⁷. Most safety concerns with use of hypnotics do not occur with PRM (2 mg). Thus, also in accordance with the updated 'British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders'¹⁰³, the recent Italian consensus recommendations for the evaluation and management of insomnia in clinical practice suggested that PRM 2 mg should be the preferred choice in subjects aged > 55 years in light of its efficacy and limited side effects¹⁰⁴. Given as a first-line prescription daily for 13 weeks, PRM (2 mg) has the potential to avoid long-term, hazardous use of hypnotics, without causing rebound effects. Moreover, as discussed above, during menopausal transition, decreased melatonin secretion and alteration of the circadian oscillator system play a pivotal role in inducing sleep-disturbing symptoms and impairing sleep regulation¹⁰⁵.

Therefore, in spite of the lack of RCT available in menopause, PRM (2 mg) seems to be a valuable treatment option for menopausal women and represents a safe alternative to benzodiazepine or Z-drugs¹⁰⁶, given its good tolerability and no safety concerns on concomitant therapy with antihypertensive, antidiabetic, lipid-lowering, or anti-inflammatory drugs¹⁰⁰.

Another melatonin drug agonist, the MT1 and MT2 melatonergic receptor agonist ramelteon, has been shown to be effective in improving objective sleep alterations in insomnia patients¹⁰⁷. Its safety has been demonstrated in long-term studies^{108,109}.

Benzodiazepine and Z-drugs

A short-term treatment (2–4 weeks) with short-acting benzodiazepines (triazolam, brotizolam) or Z-drugs (zolpidem, zopiclone, zaleplon) may be an efficacious approach^{11,62}. In the general population, a buffered zolpidem sublingual formulation is approved to be taken in the middle of the night by patients with early awakening insomnia and at least 4 h of bedtime remaining. RCTs in menopause women are only available for Z-drugs. Zolpidem has been shown to increase reported total sleep time and decrease the wake time after

sleep onset and number of awakenings in perimenopausal or postmenopausal women, without causing tolerance¹¹⁰. Similarly, eszopiclone resulted effective in the treatment of both insomnia and VMS in two RCTs^{111,112}.

Both benzodiazepines and Z-drugs are effective in facilitating sleep onset but should be used with caution considering adverse health associations in long-term users. Their side effects include postural instability and falls during nocturnal awakenings, cognitive impairment, tolerance, rebound insomnia upon discontinuation, car accidents, and abuse¹¹³. However, it is unclear how much of the impact of sedative hypnotics is specific for menopausal insomnia¹¹³. The health outcome of the increased risk of falls may be more serious at advanced age because older women display a greater vulnerability to fracture¹⁰². Indeed, different meta-analyses showed that the use of benzodiazepines¹¹⁴ or Z-drugs¹¹⁵ is associated with a significant increase in fracture risk. Moreover, benzodiazepine use is a major osteoporosis risk factor in women 50–65 years of age, second only to low calcium intake¹¹⁶. On the other hand, progesterone may potentiate the behavioral effects of benzodiazepines and may contribute to benzodiazepine use and abuse among women¹¹⁷.

Gabapentin

Gabapentin has been proposed as an alternative or associative treatment in menopausal insomnia. In doses of 300–900 mg, gabapentin seems to reduce symptoms of HFs by 66%¹¹⁸. In particular, a RCT showed a significant improvement of sleep quality in patients treated with gabapentin 300 mg three times daily in a cohort of perimenopausal women with HFs and chronic insomnia¹¹⁹. Recently, a positive effect of this drug was demonstrated on 'LUNA', a syndrome associating low estradiol levels and night-time awakening, with or without HFs. In this case series, gabapentin induced a reduction in sleep latency, an increase of slow wave sleep and rapid eye movement sleep, and a longer sleep time¹²⁰. Gabapentin may induce side effects such as motor incoordination, drowsiness, and fluid retention.

Conclusion

Insomnia represents one of the most frequent symptoms of menopause. Hormonal changes can be responsible for insomnia across menopause transition and beyond, but the high prevalence of this sleep disorder is likely to be influenced by psychological changes or by alterations in other regulatory systems (i.e. circadian rhythm) often co-occurring in relation to the aging process. To date, there are no universal guidelines for insomnia treatment during menopause but when a hypnotic is indicated, PRM (2 mg) should be tried first, considering its good tolerability, safety, and efficacy on multiple sleep and daytime parameters. However, we believe that a careful evaluation of the psychological and somatic symptoms of the patient by a multidisciplinary team is essential to drive a more adequate therapeutic approach, taking

into account the domino effect of menopausal syndrome (Figure 2).

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