



Sleep disturbances in menopausal women: Aetiology and practical aspects



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ABSTRACT

Sleep deteriorates with age. The menopause is often a turning point for women's sleep, as complaints of insomnia increase significantly thereafter. Insomnia can occur as a secondary disorder to hot flashes, mood disorders, medical conditions, psychosocial factors, underlying intrinsic sleep disorders, such as obstructive sleep apnoea (OSA) or restless legs syndrome (RLS), or it can be a primary disorder. Since unrecognized OSA can have dramatic health-related consequences, menopausal women complaining of persisting sleep disturbances suggesting primary insomnia or intrinsic sleep disorders should be referred to a sleep specialist for a comprehensive sleep assessment.

Patients suffering from primary insomnia will be preferentially treated with non-benzodiazepine hypnotics or melatonin, or with cognitive behavioural therapy.

Insomnia related to vasomotor symptoms can be improved with hormone replacement therapy. Gabapentin and isoflavones have also shown efficacy in small series but their precise role has yet to be established.

In patients suffering from OSA, non-pharmacological therapy will be applied: continuous positive airway pressure or an oral appliance, according to the severity of the disorder.

In the case of RLS, triggering factors must be avoided; dopaminergic agonists are the first-line treatment for moderate to severe disease.

In conclusion, persisting sleep complaints should be addressed in menopausal women, in order to correctly diagnose the specific causal disorder and to prescribe treatments that have been shown to improve sleep quality, quality of life and long-term health status.

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1. Introduction

Sleep is a physiological state which deteriorates with age: there is a progressive decrease in both quantity and quality – sleep disruption, less slow-wave sleep (SWS) and less rapid eye movement (REM) sleep. In parallel, complaints of insomnia increase, and are more frequent in women, whose sleep quality, however, remains better than that of men. Insomnia affects 19–50% of patients seen in primary care or specialist clinics [1]. Around the menopause, secondary to hormonal changes, sleep disturbances frequently occur or worsen and can be related to several associated disorders. In middle-aged women, insomnia (primary or secondary) is much more frequent than intrinsic sleep disorders such as obstructive sleep apnoea (OSA) or restless legs syndrome (RLS). The majority

of sleep complaints reported to the family doctor will be related to secondary insomnia (66–77% of insomnia-related sleep complaints), provoked by physical problems (bladder problems, low back pain, musculoskeletal disorders, osteoarthritis, cancer, etc.), psychosocial factors (money worries, bereavement, mid-life crisis, children, divorce, ill-health, unemployment, etc.), medications or poor sleep hygiene (e.g. alcohol intake) [1,2]. Some of these complaints can be resolved by treating the underlying disorder or by sleep hygiene tips; nonetheless, additional treatment for the insomnia is often required [1,2]. Menopausal women complaining of persisting sleep disturbances suggesting primary insomnia or intrinsic sleep disorders should be referred to a sleep specialist for a comprehensive sleep assessment.

1.1. Insomnia

Insomnia is defined as difficulty in getting to sleep or in maintaining sleep, or the feeling that sleep is non-restorative, despite sufficient opportunity for sleep [3]. This pathology has long-term

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health consequences (depression, hypertension). It can be either a primary disorder or secondary disorder, associated with a comorbid state (i.e. a physical or mental disease) [3].

The menopause is often a turning point for women's sleep. In the SWAN study [4], 12,603 peri- or post-menopausal women were followed for 10 years. Insomnia was present in 46–48% of menopausal women versus 38% of pre-menopausal women. In another large series, sleep complaints in menopausal women were frequently associated with hot flashes (HF) or mood disorders such as anxiety or depression [5].

1.1.1. Primary insomnia

Primary insomnia is declared when any specific aetiology has been excluded. The problem must have lasted at least one month. It is often caused by worries, life events and professional stress, but frequently persists even if the initial trigger no longer applies. In such cases, classic non-benzodiazepine hypnotic therapy can be indicated, such as **zopiclone** or **eszopiclone**. These drugs are efficient in promoting sleep initiation and maintenance [5]. Eszopiclone has been shown to reduce the perception of HF [6].

Melatonin is another effective drug. Endogenous melatonin levels decrease with normal ageing, but a transient peak is observed at the time of menopause due to low oestrogen levels. Women can feel, in parallel with this, a transient improvement in sleep quality. Following this, secretion continues to decrease, sometimes to the extent that the woman experiences an advanced sleep phase syndrome. Treatment with prolonged-release melatonin has been shown to improve sleep latency and sleep quality in patients older than 55 years who are suffering from primary insomnia [7].

Cognitive behavioural therapy is a non-pharmacological psychotherapeutic intervention that employs sleep restriction, stimulus control, sleep hygiene education and cognitive therapy. There is a growing evidence base in support of this technique for primary or co-morbid insomnia; it avoids pharmacological side-effects and has long-term efficacy [8].

1.1.2. Vasomotor symptoms

Seventy-five per cent of menopausal women suffer from HF, leading to night sweats and increased night body temperature, which is responsible for impaired sleep quality. It has been demonstrated that night-time awakenings precede HF. As a consequence, insomnia is present in 29% of menopausal suffering from HF vs 11% in those who do not suffer from HF [9].

Menopausal hormone therapy (MHT) improves subjective sleep quality, as shown by polysomnography (PSG), an objective sleep assessment, with reduced night-time awakening, reduced sleep latency and an increased proportion of SWS, especially in menopausal women experiencing HF [10]. However, MHT cannot be prescribed to all patients, and therefore research has focused on alternative treatments.

A recent meta-analysis [11] has shown that **isoflavones** (soy extracts) are not efficient on HF but work well for menopausal women with sleep disturbances. Hachul et al. allocated a group of 38 women to either 80 mg isoflavones daily or a placebo daily for 4 months. Sleep efficiency was improved on PSG in the treated group: 78–84% versus 78–81% in the placebo group. Sleep complaints decreased from 90% to 37% in treated group versus 95% to 63% in the placebo group [12]. These findings have to be confirmed in further studies.

Gabapentin has also shown efficacy on HF [13]. Recently, a positive effect of this drug was demonstrated on 'LUNA' [14], a syndrome associating low oestradiol levels and night-time awakening, with or without HF. In this case series, gabapentin induced a reduction in sleep latency, an increase in the proportion of sleep spent in SWS and REM sleep, and a longer sleep time.

Table 1

Causal factors of obstructive sleep apnea syndrome.

Characteristics	Risk factors
Sex	Male
Age	Ageing
Habitus	Obesity, android > gynoid
Race	African > Caucasian
Cranio-facial anatomy	Retrognathia, micrognathia, tonsillar hypertrophy, septal deviation
Endocrine disorders	Acromegaly, hypothyroidism
Fluid retention	Heart failure, end-stage renal disease
Drugs	Tobacco, alcohol, benzodiazepines

1.1.3. Mood disorders

During the peri-menopausal period, women are at increased risk of developing a major depressive episode, especially if they suffer from HF. Depression is associated with sleep disturbances (insomnia, frequent awakening, or waking early) and must be treated specifically. Anxiety disorder is also very common in menopausal women experiencing insomnia.

1.1.4. Medical conditions

All medical conditions can induce short-term and long-term insomnia [3]. Low back pain, musculoskeletal disorders and osteoarthritis are very common causes of discomfort and poor sleep.

1.2. Obstructive sleep apnoea

OSA is characterized by the presence of repeated episodes of upper airway collapse (apnoea or hypopnoea) during sleep. Predominant risk factors are increasing age, male sex and (android) obesity, which explain the striking increase in prevalence over the last decades: 13% of men and 6% of women now suffer from the disease [15]. Other causes are outlined in Table 1.

Menopausal women have a 2.6- to 3.5-fold greater chance of developing the syndrome compared with pre-menopausal women [16]. Physiological factors explaining this increased prevalence include weight gain, fat distribution changes due to increased testosterone production and a decreased level of circulating female gonadal hormones.

Night-time apnoea and hypopnoea result in sleep quality deterioration due to intermittent hypoxaemia, arousals and both REM sleep and SWS reduction. Affected patients complain of daytime sleepiness and insomnia and from numerous other symptoms (snoring, gasping, choking, memory impairment) leading to an impaired quality of life. Untreated OSA is an independent risk factor for the development of cardiovascular disease, including hypertension, coronary artery disease, arrhythmias, congestive cardiac failure and stroke, leading to an increased mortality in the absence of treatment [17].

In the presence of signs and symptoms suggestive of OSA, a complete sleep recording (PSG) is required to confirm the diagnosis and establish the severity of the disorder (Table 2).

Treatment of OSA is based on long-term multidisciplinary management. The best strategy is chosen for each individual patient,

Table 2

Classification of severity of obstructive sleep apnea syndrome (OSA).

Severity of OSA	Apnea-hypopnea index
Mild	5–14
Moderate	15–29
Severe	>30

Apnea-hypopnea index refers to the number of obstructive sleep events (apnea + hypopnea) observed per hour of sleep during a polysomnographic recording.

Table 3
Treatment of restless legs syndrome.

Restless legs syndrome treatment		
1. Treat iron shortage		
2. Avoid aggravating factors (coffee, nicotine, caffeine, alcohol, antidepressants and anti-hypertensive drugs. . .)		
3. Drugs, in case of moderate to severe persistent symptoms		
<i>First line treatment</i>	Dopamin agonists	Pramipexole, ropinirole, rotigotine
<i>Alternatives</i>	α -2-delta Ca^{++} channel ligand	Gabapentin, pregabalin
<i>Other agents</i>		Levodopa, benzodiazepines, opioids

depending on the severity of the OSA, the patient's habitus and upper airway anatomy. Weight loss is mandatory. Continuous positive airway pressure (CPAP) and oral appliances (OA) are the first-choice options to treat OSA in adults. CPAP is the most clinically effective option in moderate to severe OSA, while CPAP and OA appear to be equally effective treatment options in mild to moderate OSA [18].

CPAP has been proven to increase survival rates in patients with severe disease, to improve sleep quality and health-related quality of life, and to decrease cardiovascular events such as stroke and myocardial infarction [17].

1.3. Restless legs syndrome

RLS is twice as prevalent in women as men. Some 5–10% of the population is affected. The disorder is idiopathic or can be associated with iron deficiency, renal failure, hypothyroidism and diabetes, among other problems.

Its occurrence is increased in women during pregnancy (due to iron metabolism dysfunction and high oestrogen levels) and at around 50–60 years in both genders. There is no data to suggest that hormonal changes are responsible for this increased prevalence: as the disorder is associated with high oestrogen levels in pregnancy, one would rather expect a lower prevalence among post-menopausal women. Menopausal women affected previously by RLS describe a worsening of severity of RLS after menopause, regardless of the use of MHT [19].

Symptoms are mainly unpleasant sensations in the legs associated with an irresistible urge to move, and occur during the evening or at bedtime. Around 80% of RLS patients exhibit periodic limb movements during sleep, leading potentially to impaired sleep quality, sleep disruption, difficulties in sleep initiation and diurnal fatigue and sleepiness. Quality of life is reduced by RLS.

The diagnosis and assessment of the severity of the disorder are based on symptoms but can be confirmed by PSG.

For treatment, the first step is to avoid triggering factors such as coffee, nicotine, caffeine, alcohol, antidepressants and antihypertensive drugs. **Iron** replacement is mandatory in case of deficiency. Specific drugs can be prescribed for people with moderate to severe RLS. **Dopaminergic agonists** are the recommended first-line treatment [20] but there are also alternatives (see Table 3) [21]. **Gabapentin**, for instance, is an efficient second-line treatment. Compared with placebo, symptoms decrease and sleep quality improves on PSG [22].

This is an excellent alternative for RLS treatment in menopausal women, as suggested by its efficacy on HF and LUNA in patients for whom MHT is contra-indicated [13,14].

2. Conclusion

Sleep disorders are frequent in menopausal women. They can be primary, or provoked by hot flashes, mood disorders, medical conditions, psychosocial factors or intrinsic sleep disorders such as OSA or RLS. The priority is to diagnose OSA correctly, since untreated OSA has dramatic health-related consequences. However, where

they have persistent sleep problems suggesting primary insomnia or intrinsic sleep disorders, menopausal women should be offered specific management by sleep specialists, since effective treatments are available.

Practice points

- Sleep complaints seem to be increasing among menopausal women and must be specifically addressed.
- Aetiological factors include insomnia (primary or secondary), OSA and RLS.
- The prevalence of OSA is increasing among menopausal women due to weight gain and hormonal changes and must be recognized, since the consequences of untreated OSA are dramatic.
- There are effective pharmacological and non-pharmacological treatments for sleep disturbances, regardless of their aetiology.

Research agenda

- The effect of MHT on objective sleep parameters should be studied further.
- The precise role of isoflavones in insomnia related to vasomotor symptoms has yet to be established.
- Future research needs to focus on the use of gabapentin for the treatment of insomnia related to vasomotor symptoms.
- We need to address the pathophysiological mechanism responsible for the worsening of RLS in menopausal women.

Contributors

The author, Dr Marie Bruyneel, is the unique contributor of this manuscript.

Competing interest

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