Sex steroids and sleep: sleep disturbances in menopause

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INTRODUCTION

Sleeping problems and sleep disturbances are common. According to a French study 73% of 12,778 subjects had experienced sleeping problems during the previous month and 29% of them had sleeping problems continuously [22]. Women report sleep disturbances more often than men [6, 19, 22, 30]. The most important sleeping problem in women is insomnia, which typically manifests as difficulty of falling asleep, frequent awakenings or awakening too early from sleep in the morning [41]. After the age of 50 years moderate insomnia is reported by 25% of women and severe insomnia by 15% of women [22]. Other important causes for sleeping problems are nocturnal breathing disturbances, restless legs syndrome, psychophysiological insomnia and depressive symptoms. The epidemiological data to indicate the proportion of sleep disturbances linked to the menopause is lacking although it is certain that the cessation of ovarian endocrine function at menopause results in a wide range of changes in biological functions including sleep.

Hot flashes and sweating are considered specific to climacterium [39]. In addition to these symptoms sleeping difficulties also occur frequently [28]. Sleeping problems have a profound effect to the general well-being of a woman. Poor sleep reflects as daytime tiredness and impairment of daily activities. Hormone replacement therapy (HRT) has proven to be effective treatment to climacteric symptoms [35, 36]. A recent study indicates that HRT alleviates also sleeping problems [35].

In the sleep quality evaluation, two different aspects are to be taken into account: the subjective and the objective sleep quality. Subjective sleep disturbance is a self-reported complaint, whereas objective sleep disturbance means reduced sleep efficiency or abnormalities in sleep architecture, measured by polygraphic recording of the electroencephalogram (EEG), electrooculogram (EOG) and electromyogram (EMG). It is noteworthy that these two conditions do not always overlap, which sometimes makes management and treatment more difficult.

MENOPAUSAL SLEEP DISTURBANCES

Several symptoms occur during climacterium: vasomotor symptoms (hot flashes and sweating), other somatic symptoms (insomnia, headache, dizziness, palpitations, numbness, myalgia, vaginal and urinary tract symptoms) and mental symptoms (anxiety, depression, decline of libido, lack of concentration, and memory impairment) [10, 17, 31]. Vasomotor symptoms are observed in 68-85% of symptomatic menopausal women, whereas insomnia is present in 51-77% [1, 7, 10]. Although vasomotor symptoms correlate strongly with sleep complaints [35], insomnia may occur in the absence of vasomotor symptoms and can be the exclusive climacteric symptom.

After menopause part of the sleeping problems is due to sleep-disordered breathing. Although sleep apnoea occurs seldom in women (in 2.5%) [13], partial upper airway obstruction, which contributes to the hypoventilation and the degree of CO$_2$-increase, is common (in 17%) [34]. The symptoms of partial upper airway obstruction resemble those of obstructive sleep apnoea. The key symptom is excessive sleepiness. This predisposes the patient to life-threatening situations at work or traffic. Other common complaints are lack of energy, low initiation capacity, difficulties in concentration, poor memory, and low mental tolerance. Since progestins are potent respiratory stimuli [45], the decrease of the hormone levels may at least partly explain the increased incidence of partial or complete upper airway obstruction during sleep after menopause.

Restless legs is a common condition which is best described as unpleasant creeping sensations in the lower extremities that are temporarily extinguishable by moving the leg. The sensation worsens at rest and may disturb falling asleep or wake up after some hours of sleep. A pathophysiological substrate for the restless legs symptom is the occurrence of periodic limb movements
during sleep, the prevalence of which increases with age but not with menopause per se.

Menopausal insomnia may continue as psychophysiological insomnia through learning or behavioral mechanisms, if the sleeper’s bedroom has become associated with frustration and poor sleep during the menopausal period. Insomnia is a sensitive marker of psychological disturbance, correlating with depressive symptoms [14]. Early morning awakening is a typical depressive symptom.

**MENOPAUSAL SLEEP DISORDERS AND HORMONE REPLACEMENT THERAPY**

Oestrogen has effects on several neurotransmitters, including acetylcholine, serotonin, dopamine, noradrenaline and gamma-aminobutyric acid. These neurotransmitters are involved in regulation of sleep, memory, mental and motor functions. Oestrogen increases the synthesis of acetylcholine by increasing the amount of cholinesterase, the enzyme that synthesizes acetylcholine [4, 23]. It induces degradation of monoamine-oxidase, the enzyme catalyzing serotonin. This leads to decreased turnover of serotonin [5]. Oestrogen also regulates serotonin transport and binding in the brain [26, 32].

Oestrogen has both agonistic and antagonistic properties on the dopaminergic system. It upregulates the dopamine receptors [18] and interferes with catechol-O-methyltransferases activity, the enzyme that degrades dopamine [3]. Oestradiol has been suggested to promote dopamine uptake in cultured mesencephalic neurons [9]. On the other hand, oestrogen reduces dopamine concentration in the striatum [12] and prevents the overactivity of dopamine receptors [21].

Catechol-O-methyltransferases also degrades noradrenaline. Thus, by interfering with catechol-O-methyltransferase activity, oestrogen increases the amount of noradrenaline [3]. Oestrogen has various effects on gamma-aminobutyric acid. Oestrogen increases gamma-aminobutyric acid levels in certain brain areas, whereas in the other areas the gamma-aminobutyric acid levels remain unchanged during oestrogen treatment [24]. Although the precise nature of the oestrogen effect is not fully understood, changes in both the release and re-uptake of gamma-aminobutyric acid appears to be involved [15, 16]. In hippocampal neurons oestrogen increases dendritic spine density by reducing gamma-aminobutyric acid neurotransmission [29].

HRT can be considered as an effective treatment to control subjective complaints of menopausal insomnia [35]. In our studies with a prospective, placebo-controlled cross-over design, it facilitated falling asleep, decreased nocturnal restlessness and awakenings. Women reported less tiredness in the morning and during the daytime. The degree of improvement in vasomotor symptoms was an important predictor of the degree of improvement in sleep disturbance, providing further evidence for the link between these two complaints. However, a subgroup of postmenopausal women who reported insomnia in the absence of vasomotor symptoms, also markedly benefited from oestrogen [35].

All-night polygraphic sleep recording is used to measure the objective sleep quality. According to electrophysiological criteria, sleep is divided into NREM (non-rapid-eye-movement) and REM (rapid-eye-movement) sleep. Normal sleep architecture requires that these two main phases of sleep repeat four or five times throughout the night. The fraction of NREM sleep with most synchronized EEG waves is called slow wave sleep and is considered as the most restorative part. Frequent arousals may significantly disturb sleep architecture.

Only a few previous studies have evaluated the effect of ERT/HRT on sleep in women using all-night polysomnographic recordings. The lack of consistency between these studies has been attributed to differences in oestrogen preparations, to differences in the age or the symptomatology of subjects in the study samples and to differences of the type of menopause. Thomson and Oswald [47] showed sleep improvement after eight weeks’oestrogen substitution (piperezine oestrone sulfate 1.5 mg twice daily) compared to placebo in 34 perimenopausal women aged 45-55 years in a cross-sectional double-blind study. A decrease of wakefulness and awakenings as well as an increase of REM sleep from the baseline was observed in the oestrone group. The recruitment criteria included amenorrhea for at least three months and symptoms of insomnia, depression, anxiety, and hot flashes. Surprisingly, in that study oestrogen was not superior to placebo in alleviation of hot flashes, mood or anxiety.

A beneficial effect of oestrogen on objectively measured sleep was reported by Schiff and co-workers in a group of 16 postmenopausal women receiving conjugated oestrogen 0.625 mg daily [44]. Here again the trial was conducted as a double-blind cross-sectional, placebo-controlled study. Oestrogen shortened the sleep latency and increased the amount of REM sleep. The population was recruited from a menopause clinic. Half of the women had been naturally menopausal for 2 to 22 years whereas the other half had oophorectomy (2 — 10 years before). Ten of the women reported vasomotor symptoms. The age ranged from 31 to 65 years. As markers of biological activity of oestrogen, serum FSH decreased 31% and vasomotor symptoms al-
leviated. Later the same research group re-evaluated the results and reported that out of eight subjects with insomnia complaints, four women reported alleviation of insomnia during oestrogen treatment with decrease of sleep latency, whereas the other four women reported increased insomnia during oestrogen treatment accompanied with increase in sleep latency [40].

Erlik et al. [11] evaluated in a case-control study the relationship between nocturnal hot flashes and waking episodes among nine postmenopausal women with severe hot flashes. The control group consisted of five asymptomatic premenopausal women who were studied in follicular phase. In eight out of nine subjects the hot flashes preceded waking episodes. After the initial sleep study four symptomatic postmenopausal women were treated with a daily dose of 0.05 mg of ethinyl oestradiol for 30 days. Oestrogen significantly reduced hot flashes and waking episodes.

Pickett et co-workers [33] studied nine healthy postmenopausal women, age 46-57 years, who all had previously (2-13 years ago) undergone hysterectomy and bilateral oophorectomy. All women received conjugated oestrogen before the study (daily dose of 0.25-2.5 mg). The study was a prospective, randomized, placebo-controlled, cross-over study. None of the women reported sleeping problems or heavy snoring before the trial. In the trial all women received conjugated oestrogen 1.25 mg daily combined with medroxyprogesterone acetate 20 mg daily. Both the HRT and the placebo treatments were given seven days. The study also evaluated nocturnal breathing and HRT effects on breathing. HRT significantly improved nocturnal breathing, but in terms of a distribution of sleep stages or the frequency of stage changes, arousals or awakenings no effect on sleep quality was seen.

Purdie et al. [38] conducted a trial with 33 healthy postmenopausal women with a randomized, single-blind placebo-controlled study design. The main outcome measures included polysomnographic variables, Stanford sleepiness scale, Crown-Crisp experimental index, and scoring of vasomotor and cognitive failure symptoms. All women had climacteric vasomotor symptoms and sleep complaints. They had been amenorrheic for at least six months and their serum oestradiol levels were less than 150 pmol/L. The duration of the study was 12 weeks. Half of the participants received 0.625 mg conjugated equine oestrogen daily for a month, accompanied with progestagen norgestrel 0.15 mg during the days 17-28 of each cycle. Half of the participants received placebo. HRT alleviated climacteric symptoms and improved psychological well-being but did not have any effect on polysomnographically determined sleep quality.

In a pilot study of Scharf and colleagues [43] with seven postmenopausal women (prospective, single-blind, placebo-controlled), conjugated equine oestrogen, 0.625 mg/day over a four-week period, reduced the frequency of hot flashes and the number of hot flashes associated awakenings when comparing to placebo. It also improved sleep efficiency and reduced the rate of cyclic alternating patterns of sleep. All women were climacterically symptomatic, including both naturally and surgically postmenopausal women aged 45 to 60 years.

In another pilot study of five postmenopausal women with obstructive sleep apnoea syndrome [20] both 2 mg 17β-oestradiol alone for three to four weeks or combined with progestin for 12 days increased the total amount of REM sleep and decreased the number of waking episodes. The study was a prospective, cross-over study. All women were free of menopausal symptoms. In that study reduction of sleep apnoea was also observed.

In our own prospective, randomized, placebo-controlled, double-blind, cross-over study [36] with 62 postmenopausal women, the decrease of movement arousals was the only objective change during HRT. We used transdermal oestrogen (gel 2.5 g/day or patches 50 µg/day). In the two latest polysomnographic sleep studies, HRT has shown to be beneficial. Antonijevic and co-workers [2] reported in a prospective, crossover study with 11 postmenopausal women (oestrogen 50 µg/day or 100 µg/day + 0.25 mg norethisterone acetate transdermally) an increase in REM sleep and a reduction of the time awake during first two sleep cycles of the night. Montplaisir et al. [27] studied ten postmenopausal women (age range 45-65 years) in a randomized, two-group-treatment study (conjugated equine oestrogen 0.625 mg/day with either medroxyprogesterone acetate 5 mg/day or micronized progesterone (200 mg/day). In that study sleep efficiency improved in the group of oestrogen combined with micronized progesterone but not with medroxyprogesterone acetate. Neither of these two latest studies included placebo.

Progestins can also improve sleep quality, since they have been reported to have direct anesthetic and hypnotic properties. This can be due to their metabolites, which are potent barbiturate-like [25] or benzodiazepine-like [46] ligands of the gamma-aminobutyric acid receptors.

The treatment of choice of severe obstructive sleep apnea syndrome in postmenopausal women is nasal continuous positive airway pressure (CPAP). Weight reduction is effective and should be the primary target. The efficacy of either oestrogen or progesterone replacement therapies has been studied. Whereas there is only little if any improvement of nocturnal ventilation with oestrogen alone, [20, 37] high doses of medroxyprogesterone acetate (60 mg/day) have resulted in...
significant improvement of nocturnal ventilation [42]. Therefore, the role of respiratory stimulants in treatment of nocturnal ventilation in postmenopausal women is currently being re-evaluated.

CONCLUSIONS

Sleep disorders are common in menopausal transition. Although women compose more than half of the adult population, 85% of sleep studies have been conducted in men [8]. Sleep is an important determinant of quality of life and improving sleep is a challenge to our health care systems. Assessment of both subjective and objective sleep qualities is important, because menopausal insomnia and nocturnal breathing disorders are common in this population. In women with climacteric vasomotor symptoms, HRT can be considered as the first line therapy for insomnia. Also climacteric women whose insomnia is essentially accompanied with mental symptoms, benefit from HRT. There is some evidence that women with menopausal insomnia without connective subjective climacteric vasomotor symptoms could also benefit from HRT [35]. Sometimes HRT must be accompanied with antidepressants or hypnotics.

Although climacterium often causes or worsens sleep disturbances it should be remembered that part of the disturbances may just coincide with the menopausal period and are not of endocrine origin. Thus signs and symptoms that would normally trigger a full sleep evaluation in premenopausal woman should be taken as seriously in postmenopausal women and not dismiss them only as a normal part of menopause.

REFERENCES
