ORIGINAL ARTICLE

Sleep Science

# Sleep, Melatonin, and the Menopausal Transition: What Are the Links?

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Received: August 15, 2016; Accepted: December 28, 2016.

DOI: 10.5935/1984-0063.20170003

**ABSTRACT**

The pineal hormone Melatonin plays an important role in the regulation of the circadian sleep/wake cycle, mood, and perhaps immune functions, carcinogensis and reproduction. The human circadian rhythm of melatonin release from the pineal gland is tightly synchronized with the habitual hours of sleep. Peri- and postmenopausal women often complain of difficulties initiating and/or maintaining sleep, with frequent nocturnal and early morning awakenings. In this review we discuss the pathophysiology of melatonin function as it relates to sleep disorders in menopausal women, highlighting the potential use of exogenous melatonin during the menopausal transition and beyond.

**Keywords:** Sleep; Melatonin; Aging; Circadian rhythm; Hormones; Gender; Menopause.

## INTRODUCTION

Insomnia is a major complaint among menopausal and postmenopausal women, presumably due to decreased levels of estrogen, and possibly melatonin. As a woman approaches menopause the levels of estrogen sharply decrease. Melatonin serum levels also decrease, but in a more gradual course.

At the menopausal transition, insomnia is part of the typical menopausal symptoms (e.g. hot flashes, vaginal dryness, sexual dysfunction, mood disturbances, anxiety and restlessness). These symptoms coexsist with the decrease in reproductive hormones and melatonin. These hormonal changes seem to affect sleep directly. A decline in the levels of these hormones in menopausal and postmenopausal women and the complex interaction among these hormones can significantly contribute to sleep problems, poor concentration, fatigue and decreased quality of life[1-3].

During menopausal transition, vasomotor symptoms (i.e. hot flashes, night sweats, palpitations) are typically experienced and cause sleep disturbances, but gradualy disappear thereafter in most women. In others, menopausal transition and the postmenopausal phase are periods during which comorbitidies develop, which are associated with stronger reductions in melatonin and more persistent sleep difficulties. An adequate consideration of the hormonal changes, especially those concerning melatonin, requires a distinction among three subtypes of menopause-associated sleep disorders[4], and also an understanding of the differences to changes that generally occur in the course of senescence including males[5]. The three kinds of sleep disorders in menopause[4] may be characterized as (1) insomnia with concurrent or developing depression, (2) sleep-disordered breathing, and (3) sleep disturbances in fibromyalgia. They strongly differ concerning the association with other symptoms, but all might be related to melatonin levels, as will be discussed below.

## MELATONIN RHYTHM AND ITS CONTROL BY THE CENTRAL CIRCADIAN PACEMAKER

The suprachiasmatic nucleus (SCN), which resides in the anterior hypothalamus, acts as a central circadian pacemaker. It regulates the circadian timing, including the sleep/wake rhythm in humans, via the sympathetic and parasympathetic nervous systems[6-8]. In mammals, the pineal gland is steered by the SCN through a neuronal pathway, which finally activates melatonin synthesis by norepinephrine released from postganglionic sympathetic fibers, an action that is modulated by several other neurotransmitters[9].

Light turns off the secretion of melatonin by the pineal gland[10-12]. This relationship has two different aspects. On the one hand, light/dark and dark/light transitions determine the phasing of the circadian pacemaker via mechanisms of resetting, but, on the other hand, light at night can directly and immediately suppress melatonin secretion in terms of a so-called photic turn-off mechanism[13,14], which is not equivalent to phase shifting. However, in cell biological terms, the circadian decrease and the direct photic shut-off are mechanistically similar with regard to downregulation of the rate-limiting enzyme of melatonin synthesis, aralkylamine *N*-acetyltransferase (AANAT)[9,15].

In the absence of light and in the appropriate circadian phase, the pineal gland is no longer inhibited and starts secreting melatonin. Notably, the rise in melatonin may be blunted in the case of a dysphased circadian rhythm. From the pineal gland, melatonin is secreted (by passive diffusion) into the blood stream and also, via the pineal recess, into the third ventricle of the brain. In humans, melatonin synthesis occurs in the pineal gland and through the blood stream is distributed all over the body tissues[16,17].

Because of its amphiphilicity, melatonin is believed to enter all cells[9]. This has also been regarded as an explanation for its capability of crossing the blood brain barrier, although additional mechanisms are important for intra- and extracellular brain levels, such as uptake via the choroid plexus and direct secretion via the pineal recess[9,17-19], as well as local biosynthesis, such as in the cerebellum[20].

It should be briefly mentioned that by orders of magnitude, higher quantities of melatonin are formed outside the pineal gland, but that these extrapineal sources contribute poorly to the circulating levels[17,21]. This retention may challenge the statements on free diffusibility of melatonin, but perhaps, may be explained by intracellular sequestration[22]. Nevertheless, melatonin retention by other organs, at least in mammals, leads to the consequence that the pineal gland is privileged as a mediator of the signal "darkness."

The circadian system controls countless physiological and cell biological functions. This system exhibits a remarkable complexity and is not only described by the actions of the SCN, but rather composed of numerous central and peripheral oscillators, which gradually differ in their dependence on the SCN, including some almost autonomous oscillators[23]. Although pineal melatonin secretion largely depends on the SCN, other oscillators are also relevant to melatonin in terms of its targets. There are two membrane-bound, high-affinity melatonin (MT) receptors, $MT_1$ and $MT_2$, which are expressed in numerous cell types[17].

Both of them can be found in the SCN of most mammals. However, in humans, $MT_1$ is, at least, prevailing, whereas $MT_2$ is poorly expressed and, perhaps, absent in many SCN neurons[17]. Despite this difference between human and non-human SCN expression of $MT_2$, drug development has frequently overlooked the prevalence of $MT_1$ in the human SCN. Melatonin effects on the SCN receptors have been utilized in the treatment of disorders such as shift work, jet lag and other circadian rhythm sleep/wake disorders, as well as chronic insomnia in the setting of menopause[24].

## HUMAN AGING AND MELATONIN SECRETION

Aging is typically associated with both impairments of the circadian system and decreases in melatonin secretion[5,25-29]. As outlined in these reviews, the changes are interindividually

highly variable. Functional impairments in the circadian system seem to be associated with decreased circadian amplitudes, which may not be clinically diagnosed at first glance, but can be the causes of sleep disturbances and nocturia, in addition to the alterations that are perceived by a high percentage of people within the population.

The earlier, often subclinical changes in circadian system and melatonin secretion typically develop around midlife and have to be distinguished from later deteriorations that occur in the course of neurodegeneration within the SCN and cause disruption of internal circadian phase relationships. These include loss of precise phasing and stronger reductions of melatonin, alterations that are more strongly pronounced in neurodegenerative diseases such as Alzheimer's disease[5,28,30].

The interindividual variability concerning decreased melatonin levels is, at least, partially explained by effects of numerous diseases and disorders on melatonin formation and secretion, as summarized elsewhere[5,29]. These comprise some psychiatric disorders, pain- and stress-associated pathologies, heart diseases, diabetes type 2, and forms of cancer. Notably, these changes in melatonin are also observed in some symptoms linked to menopause.

Regarding the first subtype of menopause-related sleep disturbances that is associated with depression, it should be noted that some subtypes of depression, including bipolar disorder (BP), lead to decreases in melatonin[31,32]. Reduced levels and atypical secretion patterns of melatonin have been also observed in obstructive sleep apnea syndrome (OSAS)[33,34] and chronic obstructive pulmonary disease (COPD)[35], findings that may indicate a possible relationship to the second type of sleep-disordered breathing.

Relatively strong evidence for decreases in melatonin as well as abnormal secretion patterns exists in fibromyalgia[5,32,36,37]. Although these results were not generally obtained under specific conditions of menopause transition, they may be taken as a hint for a relationship between reduced melatonin and respective menopause symptoms. In fact, reductions in melatonin levels from peri- to postmenopausal stages have been described[38,39].

In this context, it is, however, important to remain aware of the complexity of the circadian machinery, including its influence on pineal melatonin secretion and the feedback of melatonin to the SCN. Disorders and diseases mentioned in this paragraph, such as BP, OSAS, COPD and fibromyalgia are all associated with circadian disturbances, which, on the one hand, lead to altered melatonin patterns and levels and, on the other hand, can cause sleep disturbances, either directly via changes in SCN function or indirectly via melatonin deficiencies.

Additionally, inflammatory responses can be favored by deviations in both the circadian system and melatonin, which is an immune modulatory agent[17,28,40]. This may be also assumed for cases of menopause with relevant pathological symptoms, as has been shown especially for fibromyalgia and BP[32]. In these illnesses, enhanced levels of inflammatory mediators, oxidative and nitrosative stress, and indications of mitochondrial malfunction were observed. These deviations were suggested to cause an increased tryptophan catabolism via indoleamine 2,3-dioxygenase, which consumes this precursor of serotonin and melatonin and might explain losses in melatonin as well as neurological symptoms and circadian impairments[32].

Associated changes in melatonin levels and circadian phasing are, in fact, not uncommon in aging and can be traced by determining respective markers. The dim light melatonin onset (DLMO) and minimum core body temperature (cBT min) are important circadian markers[41]. DLMO, the onset of melatonin secretion under dim light conditions, is the single most accurate marker for assessing the circadian pacemaker. With the nocturnal rise of the melatonin level, the cBT decreases, changes that are involved in the regulation of the sleep/wake cycle. cBT min is also known as circadian time 0 and represents an important therapeutic target for circadian rhythms sleep disorders (CRSDs).

The age-related changes in DLMO and cBT min are correlated with sleep disturbances in old age. One study compared the sleep of younger, premenopausal women with that of postmenopausal individuals with and without insomnia[42]. Differences mainly appeared between good and poor sleepers. While the DMLO was not substantially changed in postmenopausal good sleepers, it was delayed by about 50 minutes in the poor sleepers, who also showed smaller evening increases and lower levels of melatonin. Moreover, older poor sleepers exhibited a shortened phase angle between DLMO and sleep onset, but a longer one between cBT peak and sleep onset[42].

These results indicate that it is not the menopause per se that causes the circadian and melatonin-related deviations, but that a subpopulation develops during menopause a risk for pathological changes as described, perhaps on the basis of pre-existing pathologies or other risk factors. However, it should be noted that investigating older, postmenopausal individuals does not provide insights into the changes during menopausal transition and its related discomfort.

## A BRIEF LOOK AT MELATONIN'S PLEIOTROPY AND CONSEQUENCES THEREOF

Changes in melatonin levels can cause a plethora of effects, because the pineal hormone acts as an orchestrating regulator of numerous physiological and cell biological functions, not only via the circadian system, but also by direct stimulatory and inhibitory effects in practically every organ (for a comprehensive review, see ref.[17]).

In the context of aging[5,28,43], the following functions have been mentioned as being particularly relevant: promotion of sleep, modulation of the immune system, prevention of neuronal overexcitation and dampening of microglia activation, analgesic, antinociceptive and anxiolytic effects, support of bone mineralization, participation in metabolic control mechanisms and nutrient sensing, support of mitochondrial function and integrity, and antioxidative protection. With regard to these numerous actions, reductions in melatonin levels can be

expected to have many disfavorable consequences to an aging individual. However, a major point to be clarified concerns the level below which these deficiencies become clinically relevant.

The role of melatonin in the immune system and the deviations caused by its decline are complicated by two facts. First, melatonin acts both as an immune-stimulatory regulator, which includes proinflammatory and pro-oxidant effects, and as an anti-iflammatory and antioxidant agent[17,28,44]. The proinflammatory actions can result in aggravations of rheumatic diseases. However, in most aging organs including the brain, the anti-inflammatory effects of melatonin have been observed to prevail[28,40]. Second, the age-related changes in the immune system are not mainly a consequence of reduced melatonin, as discussed in other publications[43,45]. In the human, the antioxidant actions of melatonin should not be mainly seen under the aspect of free-radical scavenging, but alsoby upregulation of antioxidant enzymes[17,28,40,46].

## GONADAL HORMONES, MELATONIN, VASOMOTOR SYMPTOMS AND SLEEP IN PERIMENOPAUSE, POSTMENOPAUSE

Vasomotor symptoms commonly include a feeling of intense heat, with sweating and tachycardia, which usually lasts minutes to half an hour. A decline of estrogen blood levels is thought to be the causative factor. These vasomotor symptoms usually accompanied menstrual irregularities in premenopausal and postmenopausal women[47-51]. These hormonal irregularities and sleep disturbances are more common in perimenopausal women than premenopausal or late postmenopausal women[50,52]. Vasomotor symptoms are a major causative factors in sleep disturbances in perimenopausal women and also contribute to dysphoria in insomniac patients.

Sex-hormones fluctuations are typical to the perimenopausal period. This hormonal fluctuation is mainly responsible for menstrual irregularities, vasomotor symptoms, sleep disturbances, sexual disfunction and depressive symptoms during the menopausal transition and beyond. Melatonin is known most for its beneficial effects on sleep through its resynchronization of circadian rhythms to align more with the light/dark cycle in middle aged to elderly patients without harmful side effects, making it a safe alternative for use in an aging population.

Melatonin levels decrease (especially at nighttime) with age, particularly during the peri-menopausal period. This observation has led some to speculate that melatonin may play a role in the menopausal transition. Although melatonin probably doesn't play any role in vasomotor symptoms, it could improve symptoms related to perimenopause such as mood and wellbeing[53].

Melatonin has also a positive effect on bone density and strength perhaps through synchronization of bone turnover. Therefore, the lack of melatonin may play a role in the development of postmenopausal osteoporosis. in support of this, peri-menopausal women taking 3 mg melatonin nightly for 6 months showed improvement in markers of bone turnover (decreased bone resorption, increased bone formation) resembling the bone turnover of young pre-menopausal women[54].

## THE POSSIBLE HEALTH CONSEQUENSES OF DECREASED MELATONIN LEVELS AT MENOPAUSE

There are several possible health effects of decreased melatonin levels in postmenopausal women that are not directrly related to sleep effects but should be noted in the context of postmenopausal health. Theses include:

### Breast Cancer

It has been suggested that decreased melatonin levels are associated with increased risk of breast cancer[55,56]. Night shift work reportedly increases the risk of estrogen-related breast cancer, possibly due to melatonin suppression in people working at night[57]. In vitro, melatonin counteracts the proliferation of cancer cells, which indicates an oncostatic role[58,59-61]. Urinary 6-sulfatoxymelatonin level (metabolite of melatonin) is reportedly decreased in postmenopausal women with breast cancer[62,63].

### Endometrial cancer

It has been reported that melatonin might have an oncostatic effect on endometrial cancer[64-66,67]. In Ishikawa cells, an established, estrogen receptor–positive endometrial adenocarcinoma cell line, melatonin inhibits the proliferation by signaling via the $MT_2$ receptor[68].

## TREATMENT OF INSOMNIA IN POSTMENOPAUSAL WOMEN

Postmenopausal women usually complain of difficulty in falling asleep as well as awakenings in the middle of the night and early in the morning. Although these sleep complaints in menopause can be multifactorial (poor sleep hygiene, depression, primary sleep disorders, sleep-disordered breathing, fibromyalgia), decreased melatonin secretion and the disturbance of the circadian oscillator system are also of substantial relevance, both with regard to the sleep-disturbing symptoms and to the direct impairment of sleep regulation.

These sleep problems have been treated by hormone supplementation with melatonin, by improving sleep hygiene, hormone replacement therapy with combinations of estrogen and gestagens, and using other interventions for treating advanced age diseases such as hypertension, diabetes, osteoarthritis, pain management, etc.[69]. However, it is important to remain aware of the differences between women in the postmenopausal phase and those passing menopausal transition. In the latter case, the reasons for sleep disturbances are different and typically associated with changes in vasomotor activity, which cause discomfort, such as from hot flashes, but disappear in time and are not of particular relevance in other insomnia-

associated symptoms such as depression or fibromyalgia.

These associated symptoms, in particular, fibromyalgia, can be treated by melatonin[70-72]. However, the options for treating the transient, menopause transition–associated sleep disturbances, as far as they are not accompanied by depression, breathing symptoms or fibromyalgia, should be seen differently. Although melatonin can reliably reduce sleep-onset difficulties[5], the most recommendable and well-established treatment is that of hormone-substitution therapy with estradiol and progesterone, a combination that has several advantages over combinations with other, synthetic progestins and is particularly effective in suppressing vasomotor symptoms and their related sleep disturbances that are typical for the transition phase[73].

Regarding nocturnal awakenings during menopausal transition, easily applicable preparations of gonadosteroids as gels or transdermal pads can be successfully used as alternatives to oral administration[74]. As far as difficulties with falling asleep are concerned, the general efficacy of melatonin in reducing sleep onset latency[5], which acts already at doses below 1 mg[75], would be helpful and may be used in addition to gonadosteroid replacement. The aspect of supporting sleep onset, in addition to the suppression of vasomotor symptoms, should be seen in the background of general sleep peculiarities of women, in whom fluctuations of reproductive hormones influence sleep also under premenopausal conditions, such as within the menstrual cycle or during pregnancy[76].

## TREATMENT OF MENOPAUSAL INSOMNIA USING MELATONIN

In humans, the circadian rhythm of melatonin released from the pineal gland is highly synchronized with the habitual hours of sleep[16,77,78]. The daily onset of melatonin secretion is well correlated with the onset of the steepest increase in nocturnal sleepiness ("*sleep gate*")[79,80]. The endogenous secretion of melatonin decreases with aging across genders[81] and, among women, menopause is associated with a significant reduction of melatonin levels[82,83].

However, these reductions are poorly described by mean values, since moderate decreases in women who are free of complicating sleep-disturbing symptoms have to be distinguished from stronger decreases in those who suffer from depression, breathing problems or fibromyalgia. Exogenous melatonin reportedly induces drowsiness and sleep, and may ameliorate sleep disturbances, including the nocturnal awakenings associated with old age[84].

However, in terms of a balanced view, one has to admit that improvements of sleep maintenance, even though they may be statistically demonstrable, often remain quantitatively rather moderate[5], again with a high interindividual variability. This poorer outcome concerning sleep maintenance strongly contrasts with the relatively reliable reduction of sleep onset latency.

To improve sleep quality in postmenopausal women, a fixed wake cycle with adequate sleep hours is necessary. Women treated with melatonin reported a considerable improvement in mood disturbances and in depression[85,86]. Melatonin treatment of insomniac postmenopausal women showed, as compared to a placebo, an improvement in sleep problems[87].

However, these findings from a long-term study were based on subjective measures, which frequently indicate stronger ameliorations than objective data from polysomnography. Treating with melatonin does not cause a hangover in the morning and results in a relatively mild hypnotic effect as compared to other sleep-inducing agents[88]. In total, the exogenous melatonin administration has a beneficial effect in the management of insomnia, including sleep disturbances with jet leg[2].

Existing studies on the hypnotic efficacy of melatonin have been highly heterogeneous with regard to inclusion and exclusion criteria, methods adopted to evaluate insomnia, doses of the medication, and routes of administration. In addition to this complexity, there continues to be considerable controversy over the meaning of the discrepancies that sometimes exist between subjective and objective measures of good and bad sleep[89].

Thus, attention has been focused either on the development of more potent melatonin analogs with prolonged effects and/or higher receptor affinity, or on the design of prolonged-release melatonin preparations[90,91]. The $MT_1$ and $MT_2$ melatonergic receptor agonist ramelteon[92,93] was found to be effective in increasing total sleep time (TST) and sleep efficiency (SE), as well as in reducing sleep onset latency (SOL) in insomnia patients[94]. The safety of ramelteon has been demonstrated in long-term studies of six months[95] or one year[96].

The melatonergic antidepressant agomelatine, displaying a potent $MT_1$ and $MT_2$ melatonergic agonism and a relatively weak serotonin $5HT_{2C}$ receptor antagonism[97,98], was found to be effective in the treatment of insomnia comorbid with depression[99,100]. However, treatment with agomelatine requires particular caution and surveillance because of a risk of hepatotoxicity that exists, at least, in a subpopulation of patients[101]. With regard to menopausal comorbidities, one study reported that agomelatine slightly improved symptoms of depression and fibromyalgia, but did not ameliorate sleep quality[101]. Other melatonergic compounds are currently under development[102].

As a general impression, melatonergic compounds could be useful in the treatment of insomnia in peri- and postmenopausal patients**.** However, the superiority of synthetic drugs over the natural, particularly well-tolerable hormone melatonin may be questioned. Although ramelteon seems to exert somewhat stronger effects than melatonin in extending sleep time, its relative improvement in sleep maintenance in insomniacs is still rather moderate[26]. With regard to the much higher recommended doses of the synthetic drugs, compared to melatonin, the therapeutic gain may be questioned, since melatonin is already effective at rather low doses in promoting sleep onset [75].

## MELATONIN DOSES

There is a significant heterogeneity in the studies regarding the optimal dose of exogenous melatonin or melatonin agonists for induction and maitenense of sleep[103,104]. It has been suggested that low doses (0.3-1.0 mg) are the most effective dose[79,81]. Others report that a melatonin daily doses of 0.5¬–5 mg are effective. The administration of more than a 5 mg is probably ineffective. It has been suggested that in people with metabolic syndrome, the melatonin dose could be higher, as much as 50 mg¬–100 mg per day[105] but there is not enough evidence to support this assumption.

## DRUG INTERACTIONS WITH MELATONIN

Abnormal melatonin blood levels characteristic of circadian disruption are found in human alcoholics[103]. The mechanism by which alcohol affects melatonin secretion is yet unclear. Melatonin increases the effects of antidepressant medications, for example desipramine and fluoxetine (Prozac)[104]. Melatonin can increase the risk of bleeding if administered with Coumadin (warfarin)[105]. The melatonin level can be lowered by non-steroidal anti-inflammatory drugs (NSAIDs); for example, ibuprofen can lower the level of melatonin[106]. Melatonin enhances the effects of metformin and other antidiabetic medicines[107].

## CONCLUSION

The data presented above indicate that decreased endogenous melatonin levels might contribute to the common complaint of sleep disturbances during the menopausal transition and beyond. The data also indicate that exogenous melatonin or melatonin analogues miat improve sleep quality in these women. Focus on the associations among sleep disturbances, the menopausal transition, postmenopausal comorbidities, and the declining levels of melatonin and gonadosteroids reveals differences between early menopausal transition and later phases.

In early transition, the decreases in sex-hormones that are accompanied by vasomotor symptoms may be most easily treated by a moderate estradiol/progesterone substitution therapy. However, difficulties with falling asleep can be reliably alleviated by low doses of melatonin. The sleep problems in later phases are characterized by comorbidities such as depression, deviations in breathing, or fibromyalgia, and progressively by processes of aging.

These changes are typically associated with further decreases in melatonin levels and also by deteriorations in the circadian system, which in turn aggravate the comorbid symptoms. Notably, sleep problems do not only appear to be a consequence of depression but also of prodromal and causal importance to this complex disease. Some types of depression, such as BP, seasonal affective disorder (SAD) and, presumably, subtypes of major depression, are associated with deviations in the circadian system and, not rarely, reductions of melatonin[23,29]. Therefore, treatment with melatonin appears to be a reasonable option, not only for substituting the deficiencies of the pineal hormone, but also to stimulate and improve the circadian system[29].

While there is obviously a need for continued research, there are effective behavioral and pharmacological therapies available to treat sleep disturbances at this time in a woman's life.

The data presented above clearly indicate that exogenous melatonin and some of its analogs promote sleep. However, there is inconsistency and discrepancy among the large number of reports regarding the degree of efficacy and the clinical significance of these effects. Hence, prolonged released melatonin preparations and synthetic melatonin agonists were introduced and have shown promising results in treating insomnia. Further investigations by randomized controlled studies to evaluate the efficacy of these interventions in peri- and postmenopausal women are required and highly desirable.

### Acknowledgement and Funding

This work is supported by the following funding agencies: R25-HL105444 and R25-HL116378 (NHLBI); R01-MD007716 (NIMHD) to GJL. However, the funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

### Disclosure Statement

The authors have read the journal's policy and have the following potential conflicts: This study was not an industry-supported study. S.R. Pandi-Perumal is a stockholder and the President and Chief Executive Officer of Somnogen Canada Inc., a Canadian Corporation. This does not alter his adherence to all the journal policies. He declares that he has no competing interests that might be perceived to influence the content of this article. All remaining authors declare that they have no proprietary, financial, professional, nor any other personal interest of any nature or kind in any product or services and/or company that could be construed or considered to be a potential conflict of interest that might have influenced the views expressed in this manuscript.

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