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MELATONIN USE FOR THE MANAGEMENT OF SLEEP DISTURBANCES IN OLDER ADULTS

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Abstract

Sleep disturbances are common among older adults, with approximately 50% reporting sleep difficulty at least a few nights per week. Frequently prescribed sedative-hypnotics such as benzodiazepines (BZDs) pose high risk of adverse events and hence safer alternatives are necessary. Melatonin regulates the brain's endogenous clock and it is the only human hormone available as a natural product in Canada. Clinical practice guidelines recommend against the use of melatonin for insomnia but do not stratify recommendations based on age, frailty or comorbidity. This article reviews the evidence for and efficacy of melatonin use specifically for older adults with insomnia symptoms. Melatonin demonstrates modest improvements in sleep parameters and has a low side effect profile and minimal drug-drug interactions. The available evidence is limited by small sample sizes, heterogeneity in dosage and formulation, with few older adult-specific studies. Based on the overall assessment of risk and potential benefit, despite lack of support from guidelines, melatonin seems to be a reasonable first-line option for the treatment of insomnia in older adults, especially those with frailty syndromes or multi-morbidity. In this article the evidence is presented to allow readers to decide for themselves.

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Key words:
Sleep, insomnia, melatonin, dementia

Key Points

- Melatonin is an endogenous hormone that plays an important role in promoting and maintaining sleep through regulation of circadian rhythms.
- The production of melatonin declines significantly with age and the dysregulation of melatonin secretion is even more pronounced in patients with dementia.
- The current evidence for use of melatonin has limitations. Melatonin use is associated with modest improvement in sleep parameters, a favourable side effect profile and minimal drug interactions; consequently, despite not being supported by guidelines, the evidence suggests it may be a reasonable first-line option for the treatment of sleep disturbance in older adults.
- We recommend a maximum dose of 3 mg melatonin prescribed daily an hour prior to bedtime for a 3-4 week trial.

Clinical Case

An 82-year-old functionally independent woman living in the community is being assessed in an outpatient clinic for recurrent falls. She has a history of coronary artery disease, diabetes, osteoporosis, and hypothyroidism. She mentions that she is finding it increasingly difficult to sleep at night and she feels tired the next day, which limits her activities. She is asking about a medication to help with sleep. She has heard that some sleep medications could further increase her risk of falling and she is wondering if there are any safer alternatives.

Introduction

Sleep disturbances, including difficulty initiating or maintaining sleep, are common among older adults, with approximately 50% of older adults in community settings reporting sleep difficulty at least a few nights per week[1,2]. The etiology of sleep disorders can be primary or secondary. Primary sleep disorders include insomnia, central disorders of hypersomnolence (narcolepsy), parasomnias, and sleep-related movement or breathing disorders that are not attributable to other conditions[3] (see Table 1 in "Insomnia in the Elderly: Update on Assessment and Management"). In contrast, secondary sleep disorders can be attributed to underlying medical or psychiatric conditions, such as heart failure, depression, or anxiety disorders as well as to medications (see Tables 1 and 2 in "Approach to Insomnia in the Elderly: Practice Considerations in Primary Care for Complex Patients"). Thus, older adults are especially prone to sleep disturbances due to the higher rates of comorbidity and use of multiple medications[4,5]. The first step in the evaluation of insomnia symptoms should be a comprehensive clinical history to consider potentially contributing medications or treatable medical, psychiatric, or lifestyle factors. Appropriate management of underlying health conditions associated with poor sleep, such as depression or heart failure, is important prior to considering pharmacotherapy. If insomnia symptoms persist despite management of overlapping conditions, non-pharmacological interventions should be considered first, as outlined in Table 3 in "Insomnia in the Elderly: Update on Assessment and Management".

Common pharmacological interventions include BDZs, nonbenzodiazepine receptor agonists (Z-drugs), trazodone, and tricyclic antidepressants, as well as non-prescription medications such as melatonin[6]. The American Academy of Sleep Medicine (AASM - www.ncbi.nlm.nih.gov/pmc/articles/PMC5263087/) recommends the use of various BDZs and Z-drugs for adults with chronic primary insomnia with no special considerations for age, comorbidities, or frailty[7]. A major concern is that BDZs and Z-drugs have been shown to significantly increase the risk of adverse events in older adults (up to five-fold), including falls and fractures[8,9], cognitive and psychomotor slowing[10], and drug dependence, including tolerance and withdrawal[6,11]. The efficacy and risks of these medications as well as the non-pharmacological approaches to insomnia management are reviewed in "Approach to Insomnia in the Elderly: Practice Considerations in Primary Care for Complex Patients" and "Insomnia in the Elderly: Update on Assessment and Management". Given the high risk of adverse events from these prescription sleep aids, along with the relative safety and/or efficacy of melatonin, we believe the evidence for melatonin use for insomnia symptoms in older adults warrants further review.

This article will review the evidence for and efficacy of melatonin for sleep management in older adults. We will focus on the use of melatonin for insomnia symptoms and will not be assessing use in other sleep disorders such as obstructive sleep apnea and rapid eye movement sleep behaviour disorder. We will also provide guidance regarding optimal dosage, possible side effects, and use of melatonin for sleep in the setting of dementia.

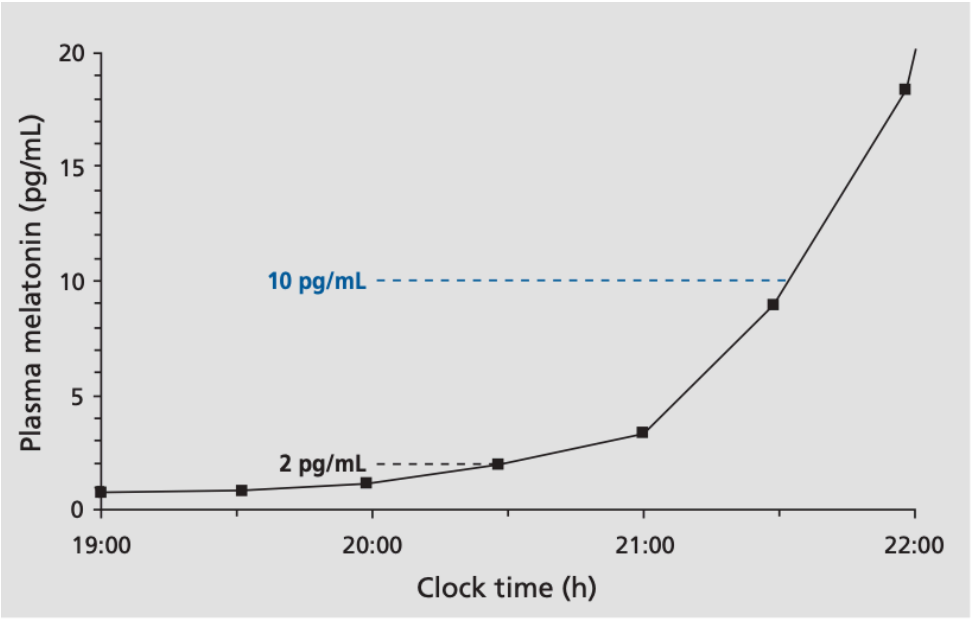
Sleep Disturbance and Aging

According to the National Sleep Foundation (see https://www.sleepfoundation.org/press-release/national-sleep-foundation-recommends-new-sleep-times) the current sleep recommendation for older adults is 7-8 hours daily, similar to the 7-9 hours recommended for younger adults[12]. While the requirement for sleep does not drastically change with age, one's ability to initiate or maintain sleep is typically reduced[13]. Sleep follows a daily circadian rhythm, modulated by diurnal patterns of key neurotransmitters and endocrine hormones involved in sleep and wakefulness. The two distinct types of sleep are rapid eye-movement (REM) and non-REM (NREM), with NREM sleep divided further into stages N1-N3. Upon sleep initiation, there is rapid descent to deeper sleep (stage N3), followed by cycling between the two types of sleep every 60-90 minutes[14]. Age-related changes in these sleep patterns have been well characterized. These include shifts in circadian rhythm (i.e. sleeping and waking up earlier), increased **sleep onset latency** (i.e. time to transition from wakefulness to a light NREM sleep stage) and decreased overall **sleep time** and **sleep efficiency / efficacy** (i.e. percent of time bedtime spent asleep)[13].

Melatonin for Insomnia Symptoms

Melatonin, naturally produced by the pineal gland in humans, is a hormone regulated by the hypothalamic suprachiasmatic nucleus (SCN), the brain's endogenous clock. Its synthesis is activated during the dark phases of the night and inhibited by light (Figure 1), thus following a circadian rhythm[15]. Melatonin seems to play an important role in initially promoting sleep and then helping to maintain it, possibly through potentiating the activity of melatonin receptors in the SCN[15]. Currently, it is the only human hormone whose synthetic preparations are available in Canada without a prescription[16]. Exogenous melatonin may have modest soporific effects, and functions to promote physiological sleep through SCN receptor activity on sleep-wake cycles[15] and homeostatic effects such as reduced core body temperature[17]. The endogenous production of melatonin appears to decline significantly with age[18], and reduction is more pronounced in patients suffering from chronic medical conditions, such as diabetes[19,20]. Thus, it has been postulated that exogenous melatonin may be an effective sleep aid in older adults, particularly those with multiple comorbidities.

Figure 1[21]: ***Rise in melatonin levels at Dim Light Melatonin Onset (DLMO). DLMO is defined as the time at which melatonin levels start to rise above a certain threshold, usually between 2-10 pg/ml (shown at hours 20:30 and 21:30).***



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Melatonin has been widely studied, with numerous randomized controlled trials (RCTs) and other trials evaluating its effect on sleep parameters. The most comprehensive meta-analysis comparing melatonin to placebo in individuals with primary sleep disorders included 19 RCTs and was published in 2013 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3656905/)[22]. There was a statistically significant reduction in sleep onset latency and total sleep time by seven minutes and eight minutes, respectively, based on objective and subjective measures combined[22]. However, the meta-analysis did not stratify primary study results by age. In eight of the 19 studies, the majority of patients included were over the age of 55, and one study stratified analysis by age groups. Despite large heterogeneity, many of these studies consistently reported statistically significant improvement in subjective sleep quality with prolonged-release melatonin intake[23-27], with inconsistent improvements in other sleep parameters[23,26,28-30]. Melatonin also maintained or improved effect with longer durations of use[24,30] (up to six months[28]) without negative impacts on physiologic sleep architecture in older adults[27]. While there were modest improvements in the sleep parameters, the effect sizes did not meet clinical significance thresholds (see Table 1). Additionally, observed effects of melatonin suggested at best half the efficacy of BDZs and Z-drugs. Importantly, no significant side effects were noted and there was no evidence of tolerance with long-term use[22]. A previous meta-analysis in 2005 of 17 RCTs demonstrated similar results but also noted an increase in sleep efficiency by 2.2%[31]. In comparison, the AASM conducted a meta-analysis of 3 RCTs (patients >55 years of age) and found that the absolute mean differences in sleep onset latency was 8.9 minutes lower and total sleep time was 2.2 minutes higher in melatonin groups compared to placebo. However, due to the low quality of evidence, the AASM recommended against the use of melatonin in chronic insomnia[7]. The most recent systematic review of sleep medications in older adults concluded there was no clear beneficial impact of melatonin after review of 10 studies[32]. The meta-analyses and systematic review were all limited by low quality of evidence and heterogeneity between the primary studies. As well, while most of the studies reviewed the efficacy of melatonin in patients with primary insomnia, it is difficult to determine how comprehensively these patients were evaluated for comorbid

conditions affecting sleep. This makes it even more challenging to apply existing evidence to patients in the real world, who are more likely to have overlapping conditions compared to trial patients.

Table 1. Summary Table of Meta-Analyses

	Clinical Significance Thresholds†		Melatonin[22]		BDZ[33]		Z-Drugs[33]		Ramelteon[34]	
	O	S	O	S	O	S	O	S	O	S
Sleep Onset Latency (-mins)	10	20	5.5*	10.7*	10.0*	19.6*	12.8*	17.0*	9.4	4.3*
Total Sleep Time (mins)	20	30	0.33	11.9*	32.8*	52.6	11.4*	31.4*	7.3	3.2

O=objective, S=subjective *indicates statistical significance

†2017 Clinical Practice Guidelines, American Academy of Sleep Medicine (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5263087/)

The efficacy of melatonin to help discontinue BDZs has also been explored in various trials, though more evidence is required to draw firm conclusions. Two trials from 1999 (adults) and 2009 (older adults) found significantly higher BDZ discontinuation rates among the melatonin treatment groups compared to placebo in BDZ users (64-78% vs 25%, respectively)[24,35]. The most recent meta-analysis of 6 trials in this area showed no significant benefit (OR 0.72, 95% CI 0.21-2.41, p=0.59) although confidence intervals were wide and there was like insufficient power to draw meaningful conclusions[36]. Notably, these studies were of low quality and the authors felt that the role of melatonin in improving BDZ discontinuation should not be ruled out[36].

Melatonin for Sleep Disturbance in Dementia

The dysregulation of melatonin secretion and deterioration of circadian rhythms is more pronounced in patients with dementia[37]. It is likely a multifactorial process, mediated by neurodegeneration causing pathologic changes in retinal and SCN receptors[38,39], and environmental influences such as decreased exposure to natural light[40]. A 2015 meta-analysis of seven RCTs evaluating the role of melatonin in patients with dementia showed a statistically significant increase in sleep efficacy by 2.2% and total sleep time by 24 minutes[41]. A 2017 meta-analysis, which included most of the same RCTs, also noted significant increase in total nighttime sleep duration but no difference in daytime sleep duration[42]. Both studies noted variable melatonin dosage, among other factors, leading to heterogeneity among the primary studies. A separate 2016 systematic review and meta-analysis, which included only four higher quality RCTs with minimal heterogeneity did not find significant differences in total sleep or other sleep parameters in individuals with Alzheimer's dementia and dementia in general, though there was a trend towards improved sleep parameters[43]. Overall, the current evidence for melatonin use in patients with dementia is insufficient to make recommendations for or against its use. However, the data published to date do not seem to suggest a dramatically different effect in older people with dementia compared to cognitively intact elders.

Melatonin: Dosage, Timing, and Side Effects

Doses ranging from 0.1-50 mg/kg of exogenous melatonin have been studied and it is clear that efficacy is both dose- and time-of-day dependent[44]. A 2014 systematic review of 14 studies (nine RCTs) evaluated the optimal doses of administered melatonin for adults over the age of 55 by measuring subsequent elevation of endogenous melatonin[44]. High doses resulted in sustained supra-physiological elevation of melatonin into the next day, which could theoretically cause unintended effects such as daytime drowsiness. Time of administration was also important with physiological levels of melatonin best restored if given prior to the onset of natural melatonin elevation (i.e. early evening). The review concluded that low doses (**0.3 to 1-2 mg approximately one hour before bedtime**) are effective in reaching significant concentrations of melatonin in older adults[44]. It is important to note that these concentrations were laboratory parameters and were not linked to clinical outcomes such as sleep quality or efficiency.

Another important consideration regarding the appropriate dose of melatonin is the brand, supplement type, and batch[45,46]. A Canadian study found that melatonin content varied significantly across these domains, with both higher and lower levels of melatonin found compared to labelled claims. This presents an additional challenge when it comes to reviewing the evidence and combining primary studies to make conclusions about efficacy. For example, prolonged and regular release melatonin may have clinically important differences with respect to onset of action, duration of therapy, and side effects. Based on the results of primary studies, prolonged-release melatonin shows more promising results with respect to sleep parameters[23-27], though there were no head-to-head comparisons between the two formulations. Given the heterogeneity of melatonin content across brands, the prolonged release formulations studied in trials may be different than what is available to Canadian consumers. This makes it very difficult to make any recommendation regarding the release preparation of melatonin. In addition, it highlights a need for more accurate labelling of dose and contents even when substances are considered to be “natural products”.

Potential Side Effects and Drug Interactions of Melatonin

The side effect profile of melatonin is relatively benign, and it is generally well-tolerated among older adults during short- and intermediate- term use[3,47]. Thus far, melatonin studies have not been sufficient in follow up length to be able to evaluate adverse events in the case of long-term use. Some studies have noted mild adverse effects such as headaches[47,48], dizziness[47], nausea[47,48], and sleepiness[47] with minimal or non-significant differences between treatment and placebo groups[47,48]. Other less likely side effects may include reduced blood pressure[49], vivid dreams[48], transient depressive symptoms with daytime administration[50], and abdominal cramps at higher doses[51]. Though melatonin is relatively safe, it is important to note that serotonin was found in multiple formulations of Canadian products, which could potentially lead to more serious side effects such as serotonin syndrome when combined with other agents[45].

Melatonin may have some minor medication interactions to keep in mind. There have been isolated case reports of increased effect of the anticoagulant drug warfarin (Coumadin)[52,53]. As well, there is some evidence that melatonin can increase seizure activity in children, possibly by inhibiting the effects of anticonvulsants[53,54], though this effect has not been seen in adults. It has also been suggested in animal studies that melatonin reduces the effectiveness of antihypertensive drugs, though this lacks clinical evidence in humans[55]. In general, melatonin is safe and well tolerated with minimal drug-to-drug interactions.

A Note on Ramelteon

Ramelteon, a selective melatonin receptor agonist, has a comparable safety profile to melatonin. Ramelteon has demonstrated a statistically significant improvement in sleep latency and improved total sleep time and sleep efficiency when evaluated using polysomnography[56]. Though not available in Canada, it has more consistently shown improvement in sleep parameters across all ages, including older adults[6,34]. A 2014 meta-analysis of 13 RCTs of Ramelteon studying adults of all ages found significantly reduced sleep onset latency by four minutes, increased sleep efficiency by 4.4%, and a trend toward increases in total sleep time[34]. Of the 13 studies, three studies recruited only older adult patients. If Ramelteon becomes available in Canada, it may be a favourable first-line option for older adults who have increased susceptibility to adverse outcomes of other medications. The AASM recommends the use of Ramelteon as the studies are of higher quality than melatonin

trials and have measured sleep parameters more rigorously[7]. However, similar to melatonin, the sleep parameter effects of Ramelteon have not yet met clinical significance (see Table 1).

Return to Clinical Case

A thorough history and physical exam should be conducted, specifically considering treatable underlying conditions such as obstructive sleep apnea and depression. This patient is presenting with recurrent falls, which limits pharmacotherapy options since many of the options (e.g. BZDs, Z-drugs, trazodone, and TCAs) are known to be associated with increased falls in older adults. If education around sleep hygiene has been provided and cognitive behavioural therapy is either unavailable or ineffective, given the evidence for modest improvements in sleep parameters and the low side effect profile, it would be reasonable to consider a trial of melatonin in this case. We recommend a maximum dose of 3 mg prescribed daily approximately 60 minutes prior to bedtime for a 3-4 week trial. We recommend that readers weigh the above evidence given guidelines do not recommend melatonin and use clinical judgment to decide for themselves.

Conclusion

In the most recent clinical practice guidelines, both the AASM and the US Department of Veterans Affairs recommend AGAINST the use of melatonin for the treatment of primary chronic insomnia[7,57]. As is often the case in clinical practice guidelines, the authors did not stratify recommendations based on age or frailty. We advise interpreting these recommendations with caution and taking a “first do no harm” approach when offering treatment for sleep disturbances in older adults. This aligns with Choosing Wisely guidelines from both Canadian[58] and American[59] Geriatrics Societies, which suggest NOT using BZDs or other sedative-hypnotics in older adults as a first choice for insomnia.

Certainly the current evidence for the use of melatonin has significant limitations, including small sample sizes, heterogeneity of dose and sleep efficacy outcomes, and few older adult-specific studies. Many studies focused on the treatment of primary sleep disorders, whereas older adults often present with overlapping conditions. However, given the modest improvement in sleep parameters, low side effect profile, and minimal drug to drug interactions, we believe that melatonin remains a reasonable first-line option for the treatment of sleep disturbances in older adults with frailty syndromes and multi-morbidity after addressing causes and considering non-pharmacological approaches (for more information see “Approach to Insomnia in the Elderly: Practice Considerations in Primary Care for Complex Patients” and “Insomnia in the Elderly: Update on Assessment and Management”).

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