

## Should Melatonin Be Used as a Sleeping Aid for Elderly People?

### THE “PRO” SIDE

Sales of exogenous melatonin, a hormone that regulates the circadian rhythm, have increased significantly over the past few years.<sup>1</sup> In the United States, the most recent National Health Interview Survey showed that the overall use of melatonin among adults more than doubled between 2007 and 2012, to an estimated 3.1 million users.<sup>2</sup> Research has shown that endogenous melatonin levels decline with age, thereby providing the rationale to use melatonin supplements for sleep.<sup>1</sup> However, before considering this treatment, it is critical to determine the situations in which it may be effective and safe. More importantly, pharmacists should be aware of the situations where it has not been proven effective and therefore should not be recommended.

For chronic insomnia, melatonin has a statistically significant but relatively small effect on sleep latency, with a mean reduction of 9 min relative to placebo (95% confidence interval [CI] 2–15 min).<sup>3</sup> The effect on total sleep time or sleep quality is generally considered small or nonsignificant.<sup>3</sup> The practice guideline of the American Academy of Sleep Medicine (AASM) suggests ramelteon (a melatonin receptor agonist that is not available in Canada) as a treatment for sleep-onset insomnia, since its benefits marginally outweigh its harms, with limited to no consistent evidence of adverse events in excess of placebo (mean difference on sleep latency relative to placebo 10 min, 95% CI 6–13 min).<sup>3</sup> The AASM guideline does not recommend melatonin for insomnia in adults, because the quality of the evidence is lower, but it does report mixed evidence suggesting a possible greater improvement in sleep latency in the subpopulation of older adults (mean difference in sleep latency relative to placebo 16 min, 95% CI 6–25 min).<sup>3</sup> Given the positive effect on sleep latency and a good tolerance profile in 2 large trials involving older adults,<sup>4,5</sup> the British Association for Psychopharmacology consensus statement recommends prolonged-release melatonin as a first-line option for older patients when a hypnotic is indicated.<sup>6</sup> However, more data are required for very elderly people, given that the mean age of patients in these studies was below 70 years.<sup>4,5</sup>

Although the effect of melatonin on typical insomnia is mild, it may be useful for other types of sleep disorders, including rapid eye movement sleep behaviour disorder, which is commonly associated with synucleinopathies such as Parkinson disease or Lewy body

dementia. In these settings, melatonin is considered the preferred pharmacological option for elderly patients.<sup>7</sup> It is also an option for patients who are blind and suffer from non-24-hour sleep-wake rhythm disorder, given evidence supporting circadian entrainment.<sup>8</sup>

While melatonin may be useful in the aforementioned clinical settings, it is also worthwhile to highlight situations where its effectiveness has not been demonstrated. For example, melatonin should not be substituted for a proper tapering regimen for benzodiazepine cessation. A meta-analysis of 6 tapering trials found no significant effect of melatonin on the odds of successful benzodiazepine discontinuation (odds ratio 0.72, 95% CI 0.21–2.41).<sup>9</sup> However, there was significant heterogeneity among the included studies, with inconsistent effects, and the authors reiterated the need for larger and higher-quality trials.<sup>9</sup>

Caution should also be applied in the use of melatonin for patients with dementia. Although Wang and others,<sup>10</sup> in a meta-analysis published in 2017, reported that melatonin may improve nocturnal sleep time in patients with dementia, a Cochrane review published the previous year found no evidence that melatonin affected any major sleep outcomes in this population.<sup>11</sup> Reassuringly, no detrimental effect on cognition or activities of daily living was detected.<sup>11</sup>

Melatonin is generally well tolerated, and it has a low potential for abuse and no significant withdrawal effects.<sup>12,13</sup> However, side effects may include residual daytime sedation, irritability, restlessness, abnormal dreams, anxiety, nausea, and diarrhea.<sup>12,13</sup> Although melatonin is usually considered safer than benzodiazepines, an increased fracture risk has recently been reported with this drug, and caution should be advised for elderly patients at risk for falls.<sup>14</sup>

Melatonin is only one option in the armamentarium of sleep solutions for older adults. On the extremely harmful end of the spectrum are benzodiazepines, the so-called Z-drugs (nonbenzodiazepines), trazodone, quetiapine, and over-the-counter antihistamines, many of which are used off-label. Almost 17% of 85-year-olds take benzodiazepines, despite questionable clinical benefit.<sup>15</sup> Benzodiazepines reduce sleep-onset latency by 4.2 min and modestly increase total sleep duration, but the latter effect tends to wear off after 4 weeks.<sup>16</sup> Benzodiazepines are associated with significant adverse effects, such as cognitive decline, delirium, falls, fractures, and dependence.<sup>17,18</sup> The Z-drugs, including zopiclone and zolpidem, are not safer alternatives to benzodiazepines because they are also associated with a significant risk of adverse events, such as delirium, falls, and fractures, with minimal improvement in sleep latency and duration.<sup>17</sup> Among over-the-counter medications, antihistamines

such as diphenhydramine were identified as the most frequently used nonprescription products for sleep in a subset of older adults<sup>19</sup>; however, these drugs should be avoided for this purpose because tolerance develops when they are used as hypnotics, and they carry strong anticholinergic properties.<sup>17</sup>

Given the paucity of hypnotics that are safe for use by elderly patients, should melatonin be considered a legitimate alternative? Certainly the effect of melatonin on sleep, as demonstrated in clinical studies, remains of questionable clinical significance. However, when balancing the risks of insomnia itself, including impaired daytime functioning, cognitive impairment, falls, reduced quality of life, and increased mortality, and the known risks associated with benzodiazepines and Z-drugs, some may consider melatonin to be a reasonable alternative when nonpharmacological therapies have failed.<sup>12</sup> In Europe, Clay and others<sup>20</sup> reported that campaigns to reduce the use of benzodiazepines and derivatives were less successful when not associated with availability and sales uptake of melatonin.

Indeed, melatonin is already used by many patients as an over-the-counter product and, in this context, pharmacists should encourage appropriate use. For this purpose, identification of drug-induced insomnia is essential, to prevent medication cascades.<sup>12</sup> Sleep patterns should be assessed to differentiate pathological insomnia from normal age-related sleep changes and to establish realistic sleep expectations.<sup>12</sup> Patients should also be referred for appropriate medical assessment, because comorbidities contributing to insomnia (e.g., pain, heart failure, obstructive sleep apnea, restless leg syndrome) are frequent among elderly patients.<sup>12</sup> As first-line therapy for insomnia, cognitive behavioural therapy should be recommended,<sup>12,16</sup> and various online resources are available to pharmacists who wish to support patients in this area (e.g., the noncommercial Canadian websites <https://mysleepwell.ca> and <https://deprescribing.org/>).<sup>16</sup> Subsequently, education for patients about the documented marginal efficacy and potential adverse effects of melatonin (as well as other prescription and nonprescription sedatives) may help them in making an informed choice.

If a trial of melatonin is considered, experts recommend low doses (as low as 0.3 mg up to 2 mg) given 1 h before bedtime.<sup>1,13</sup> In fact, many of the large studies involving older patients with insomnia used a 2-mg dose.<sup>3</sup> Also, maximum concentrations reached with exogenous melatonin are higher in older than in younger adults, and higher doses increase the risk of prolonged supraphysiological blood levels and possible side effects on the following day.<sup>1</sup> Products licensed by Health Canada (identified by a Natural Product Number) should be selected. Appropriate monitoring should be instituted, and melatonin should be stopped if either significant adverse effects occur or lack of efficacy is noted, to avoid unnecessary polypharmacy.

Melatonin use is not a panacea for insomnia experienced by elderly patients. Efficacy remains marginal, and more data from very elderly and fragile patients are required to assess efficacy and safety at low doses. However, melatonin could be useful in specific clinical situations and might help to avoid the use of other hypnotic agents,

given its comparatively favourable side effect profile.<sup>13</sup> Moreover, considering its widespread use, pharmacists are well placed to promote the rational and appropriate use of melatonin.

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## THE “CON” SIDE

Aging is associated with changes, both qualitative and quantitative, in relation to sleep pattern and distribution.<sup>1</sup> The definition of an “elderly person”, as used in this article, is based on the chronological age of 65 years.<sup>2</sup> Elderly people have difficulty falling and staying asleep because of frequent awakenings. With aging, total sleep time decreases, sleep onset is delayed, and nap time increases, along with an increase in awakenings and arousals. The quality of sleep declines, and sleep becomes more fragmented with daytime naps.<sup>3</sup> A meta-analysis of 65 studies, representing 3577 healthy individuals aged 5 to 105 years, identified age-related changes by recording sleep patterns across the human lifespan. The authors reported that the total amount of sleep declined with age, with a loss of about 10 min per decade of life.<sup>4</sup>

Sleep architecture also changes with aging. Normal sleep is divided into rapid eye movement (REM) sleep and non-rapid eye movement (NREM) sleep, the latter consisting of 3 stages: N1 (formerly known as stage 1), N2 (stage 2), and N3 (stages 3 and 4).<sup>3</sup> With age, the proportion of total sleep that is REM sleep decreases; however, this decline appears subtle. An increase in N1 and N2 sleep, which results in waking up several times during the night, is described as sleep fragmentation. A decrease in N3 sleep with slow wave sleep is reported, and there are fewer sleep cycles throughout the night. Elderly people spend more time in the lighter phases of sleep (N1 and N2) than in the deep phase (N3).<sup>1,3,4</sup> Physiologic changes in circadian rhythm with aging help to explain why elderly patients often go to bed earlier and wake up earlier, which affects the quality and duration of their sleep.<sup>3</sup>

Sleep architecture may differ between men and women. Results from a meta-analysis suggested that men’s sleep patterns are more affected by age than women’s.<sup>4</sup> The same meta-analysis reported that men have less total sleep time, with a lower percentage in N3 and

REM sleep and a higher percentage in N2 sleep, relative to women.<sup>4</sup> Conversely, women have more sleep latencies than men. These findings may be important, given that women frequently self-report shorter and lower-quality sleep than men.<sup>5</sup> This difference between men and women in the perception of sleep problems is often presented as a reason why hypnotics are prescribed more frequently for women than for men.<sup>6</sup> Overall, the sex-based difference in sleep architecture remains to be elucidated.

Melatonin (*N*-acetyl-5-methoxytryptamine), a hormone released by the pineal gland, binds to the MT1 and MT2 receptors and regulates circadian rhythm.<sup>7</sup> Its production is controlled by light, whereby levels of serum melatonin increase during the evening hours, reaching peak concentration between 0200 and 0400, and are suppressed by light, with low concentrations occurring during daytime.<sup>1,3,4,7</sup> Studies have shown that melatonin level declines with age, which may increase conditions related to circadian rhythm, such as sleep disorders.<sup>1,3,4</sup>

Melatonin is often prescribed to treat insomnia in older patients. It is absorbed rapidly, reaching peak plasma concentration 60 min after oral administration, with a half-life of 35 to 61 min.<sup>8</sup> Bioavailability is about 15% (range 9% to 33%), with extensive first-pass metabolism. A small amount (5%) is excreted unchanged by the kidney.<sup>8</sup> Melatonin is extensively metabolized primarily by the cytochrome P450 1A2 isoenzyme, with minimal contributions by CYP2C9 and CYP2C19 isozymes.<sup>8</sup> In a cohort study involving 5 male volunteers, coadministration of fluvoxamine 50 mg and melatonin 5 mg increased the maximum serum concentration of melatonin by a factor of 12 and the area under the concentration–time curve of melatonin by a factor of 17.<sup>9</sup>

Erland and Saxena<sup>10</sup> analyzed 31 commonly available melatonin supplements purchased from local grocery stores and pharmacies in Guelph, Ontario. The products consisted of 16 different brands in various formulations, such as liquid, tablet, and capsule. The authors found that the melatonin content ranged from –83% to +478% of the label claim. Furthermore, lot-to-lot variability within the same product varied by as much as 465%.<sup>10</sup> Sublingual and tablet products had the least variability, and liquid formulations had the greatest variability. Furthermore, 8 (26%) of the 31 supplements tested were contaminated with the indoleamine serotonin.<sup>10</sup>

Melatonin administered orally has been reported to imitate endogenous melatonin by shifting the circadian clock earlier, thus promoting sleep onset and morning awakening. Numerous studies of the effects of melatonin on sleep in elderly patients have been published,<sup>11,12</sup> but their results have been inconsistent because of a lack of high-quality randomized controlled trials. Results from these studies have shown no overall improvement in objective measures of sleep, with a lack of significant effect on sleep time, sleep latency, number of awakenings, and sleep efficiency.<sup>11,12</sup> Safety concerns, especially among elderly patients, are residual daytime drowsiness, tiredness upon rising, and increased sleep disruption.<sup>11,12</sup>

A 2016 Cochrane systematic review evaluated melatonin’s

clinical effect on sleep and its side effects in persons with dementia.<sup>13</sup> Only randomized placebo-controlled trials, including crossover trials, were included in the review. Two studies (with a total of 184 patients) met the inclusion criteria. The primary outcomes were total nocturnal sleep time (mean difference 10.68 min, 95% CI -16.22 to 37.59) and ratio of daytime sleep to night-time sleep (mean difference -0.13, 95% CI -0.29 to 0.03). In this systematic review, the authors reported that a dose of up to 10 mg of melatonin did not improve sleep outcome measures over an 8- to 10-week period in patients with Alzheimer disease and sleep disturbance. They also reported no effect of melatonin on cognition or activities of daily living, and no serious side effects.<sup>13</sup>

In 2016, the Agence nationale de sécurité du médicament et des produits de santé (France) published a summary list of 200 side effects associated with the use of melatonin, reported between 1985 and 2016.<sup>14</sup> These reported side effects included neurological disorders (43%), such as syncope, headache, and convulsion; psychiatric disorders (24%), such as anxiety and depression; skin disorders (19%), such as rashes and maculopapular rashes; and digestive problems (19%), such as constipation, acute pancreatitis, and nausea.<sup>14</sup>

Factors causing insomnia in elderly patients should be ruled out. Treatment for chronic medical conditions, such as congestive heart failure, chronic obstructive pulmonary disease, Parkinson disease, depression, dementia, and pain, should be instituted and optimized. Numerous medications and other substances, such as caffeine, decongestants, corticosteroids, diuretics, nicotine, selective serotonin reuptake inhibitors, theophylline, thyroid hormone, and alcohol, can contribute to (or cause) insomnia.<sup>15</sup> Patients' use of these medications and substances should be carefully evaluated on a regular basis.

Cognitive behavioural therapy for insomnia is a nonpharmacological approach that has been shown to improve sleep hygiene. It is based on various elements of sleep hygiene and behaviour modification, such as restricting the amount of time in bed, reducing external stimuli, promoting relaxation through meditation, limiting caffeine and alcohol intake, and avoiding daytime napping and exercise close to bedtime. Randomized controlled trials involving older patients have found that these interventions can achieve long-term improvements in sleep and reductions in hypnotic use by older patients.<sup>15</sup>

In summary, the quality of the evidence for using melatonin to treat insomnia in elderly patients is weak. Furthermore, some clinically significant side effects have been reported with its use in this population. In Canada, melatonin can be obtained as an over-the-counter supplement and in health food stores; hence, adverse effects are likely under-reported. As alternatives to melatonin therapy, factors that may contribute to insomnia should be reduced and nonpharmacological treatments suggested to the patient, along with cognitive behavioural interventions. Patients should also be educated about changes in sleep pattern with aging. Pharmacists can play an important role in providing this information.

As a final comment, we perhaps need to reconsider the time at which elderly patients are put to bed in some nursing homes and

other long-term care settings in Canada. Anecdotal information indicates that it is not uncommon for elderly patients to be in bed by 1900. If you were 85 years old and put to bed by early evening, wouldn't you be awake at midnight, asking for a hypnotic or sedative? Ultimately, we need to meet the needs of our patients, not those of the nursing home.

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