FPIN's Clinical Inquiries

Melatonin to Treat Insomnia in Older Adults

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Clinical Question

How safe and effective are melatonin receptor agonists for treating insomnia in older adults?

Evidence-Based Answer

Melatonin preparations reduce sleep-onset latency, increase total sleep time, and slightly improve sleep efficiency. (Strength of Recommendation [SOR]: B, based on meta-analysis of primarily small randomized crossover trials.) Prolonged-release melatonin reduces sleep-onset latency in older adults and has rates of adverse effects similar to those of placebo. (SOR: B, based on randomized controlled trials [RCTs] from a single research team.) Ramelteon (Rozerem; a melatonin receptor agonist) also reduces sleep-onset latency and may increase total sleep time. (SOR: B, based on large RCTs from a single research team.) Ramelteon use is not associated with severe traumatic accidents (e.g., falls, head injuries, motor vehicle crashes). (SOR: B, based on a retrospective cohort study.)

Evidence Summary

MELATONIN

A systematic review and meta-analysis included 15 primarily randomized crossover trials (N = 284) using objective measures to assess the effect of melatonin on sleep.[1] Healthy young adults (six trials; n = 71) and adults older than 50 years (seven trials; n = 195) with insomnia comprised most of the participants. Eleven trials used oral immediate-release melatonin (0.1 to 80 mg nightly, with most patients receiving 1 to 5 mg nightly), and four used prolonged-release melatonin (0.5 to 2.5 mg nightly). Overall, melatonin treatment reduced sleep-onset latency (mean difference [MD] = –7.5 minutes; 95% CI, –9.9 to –5.2), increased total sleep time (MD = 12.8 minutes; 95% CI, 2.9 to 22.8), and improved sleep efficiency (MD = 2%; 95% CI, 0.2% to 4.2%) compared with placebo. Authors performed no subanalyses of older adults or various types of melatonin and did not address possible adverse effects. Most studies were crossover trials, enrolled fewer than 30 patients, and gave medication for two weeks or less.

Three industry-sponsored RCTs evaluated prolonged-release melatonin in older adults.[2-4] In the first study, researchers randomized 281 patients 65 to 80 years of age (mean age = 71 years) with primary insomnia to prolonged-release melatonin (2 mg nightly) or placebo for three weeks.[2] Researchers then re-randomized patients who were on placebo to prolonged-release melatonin or placebo for another 26 weeks. Melatonin reduced sleep-onset latency at three weeks (MD = –15.6 minutes; 95% CI, –25.3 to –6.0) and at 26 weeks (MD = –14.5 minutes; 95% CI, –21.4 to –7.7) compared with placebo. Adverse effects that were presumed to be drug related occurred in 6.1% of patients taking melatonin and 5.3% of those taking placebo (no *P* value given).

In the second study, researchers randomized 354 patients 55 to 80 years of age (mean age = 66 years) with primary insomnia to prolonged-release melatonin (2 mg nightly) or placebo for three weeks.[3] The primary outcome was a favorable response, defined as a 10% improvement on both the Leeds Sleep Evaluation Questionnaire "quality of sleep" and "behavior following wakefulness" scales. Treatment with melatonin doubled the odds of a favorable response (odds ratio = 1.97; 95% CI,

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1.14 to 3.41) and reduced sleep-onset latency (MD = –8.8 minutes; 95% CI, –16.7 to –1.0). Adverse effects occurred in 24% of patients taking melatonin and 21% of those taking placebo (no *P* value given).

In the third trial, the research group randomized 170 patients 55 to 93 years of age (mean age = 69 years) with primary insomnia to prolonged-release melatonin (2 mg nightly) or placebo for three weeks.[4] Prolonged-release melatonin improved sleep quality (MD = 22%; $P < .0001$) and morning alertness (MD = 16%; $P < .0001$) on the Leeds questionnaire compared with placebo. In a two-week posttreatment washout period, no withdrawal effects occurred.

RAMELTEON

Three industry-sponsored trials evaluated the melatonin receptor agonist, ramelteon, for treatment of insomnia in older adults. In the largest trial, researchers randomized 829 patients 64 to 93 years of age (mean age = 72 years) with primary insomnia (baseline sleep-onset latency of at least 45 minutes) to ramelteon in a dosage of 4 mg or 8 mg or placebo for five weeks, followed by a one-week washout period.[5] With 4-mg ramelteon, sleep-onset latency decreased at one week (MD = –8.3 minutes; $P = .008$) and five weeks (MD = –7.2 minutes; $P = .028$). With 8-mg ramelteon, sleep-onset latency also decreased at one week (MD = –8.3 minutes; $P = .008$) and five weeks (MD = –12.9 minutes; $P < .001$). There was a small increase in total sleep time at week 1 with 4 mg (MD = 10.7 minutes; $P = .004$), but not with 8 mg. Neither dose was significant at week 5. Presumed drug-related adverse effects occurred in 11% of patients taking 4-mg ramelteon, 5% of those taking 8-mg ramelteon, and 7% of those taking placebo (no *P* value given). A subgroup analysis of the study evaluated 8-mg ramelteon in 327 patients (mean age = 73 years) with subjective sleep-onset latency greater than 60 minutes.[6] The 8-mg ramelteon dose reduced subjective sleep-onset latency at one week (MD = –15.7 minutes; $P = .002$) and five weeks (MD = –20.3 minutes; $P < .001$). The most common adverse effects were dizziness (8.9% vs. 7.1% with placebo), dysgeusia (7% vs. 2.9% with placebo), and myalgias (6.4% vs. 3.5% with placebo). No *P* values were provided for adverse effect rates.

A crossover trial studied 100 patients 65 to 83 years of age (mean age = 71 years) with chronic primary insomnia who received ramelteon in a dosage of 4 mg or 8 mg or placebo for two nights each.[7] Between each treatment phase, patients had a washout period of five to 12 days. Sleep-onset latency decreased with 4 mg (MD = –9.7 minutes; $P < .001$) and 8 mg (MD = –7.7; $P = .005$) each compared with placebo. Total sleep time increased with 4 mg (MD = 9.0 minutes; $P = .036$) and 8 mg (MD = 11.6 minutes; $P = .007$) compared with placebo.

A retrospective cohort study reviewed records of 445,329 Medicare patients 65 years and older taking at least one medication to treat insomnia.[8] Researchers tallied severe accidents (e.g., falls, fractures, dislocations, head injuries, lacerations, motor vehicle crashes) after patients began taking a sleep medication. At three months, there were no severe accidents in patients taking ramelteon, but they did occur in patients taking long-acting benzodiazepines (0.40%), short-acting benzodiazepines (0.37%), nonbenzodiazepine Z-class drugs (0.28%), and sedating antidepressants (0.36%).

Recommendations from Others

According to the American Academy of Sleep Medicine (AASM) and the Choosing Wisely campaign, cognitive behavior therapy should be the primary treatment for chronic insomnia in adults.[9] The 2017 AASM guidelines gave a weak recommendation for 8-mg ramelteon for chronic sleep-onset insomnia not responsive to cognitive behavior therapy.[10] The AASM guidelines also gave a weak recommendation against the use of 2-mg melatonin, citing only small benefit in very low-quality trials.

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