Consider melatonin for migraine prevention

This affordable, over-the-counter hormone is as effective as amitriptyline, causes fewer adverse effects, and may have a surprising added benefit.

Evidence-based guidelines from the American Academy of Neurology and the American Headache Society state that antiepileptic drugs (divalproex sodium, sodium valproate, topiramate) and many beta-blockers (metoprolol, propranolol, timolol) are effective and should be recommended for migraine prevention (level A recommendation; based on ≥2 class I trials). Medications such as antidepressants (amitriptyline, venlafaxine) and other beta-blockers (atenolol, nadolol) are probably effective and can be considered (level B recommendation; based on one class I trial or 2 class II trials). However, adverse effects, such as somnolence, are listed as frequent with amitriptyline and occasional to frequent with topiramate.

Researchers have investigated melatonin before. But a 2010 double-blind, crossover, randomized controlled trial (RCT) of 46 patients with 2 to 7 migraine attacks per month found no significant difference in reduction of headache frequency with extended-release melatonin 2 mg taken one hour before bed compared to placebo over an 8-week period.

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Researchers have investigated melatonin before. But a 2010 double-blind, crossover, randomized controlled trial (RCT) of 46 patients with 2 to 7 migraine attacks per month found no significant difference in reduction of headache frequency with extended-release melatonin 2 mg taken one hour before bed compared to placebo over an 8-week period.
196 adults (ages 18-65 years) with chronic migraines. Eligible patients had a history of at least 3 migraine attacks or 4 migraine headache days per month. Patients were randomized to take identically-appearing melatonin 3 mg, amitriptyline 25 mg, or placebo nightly. The investigators appear to have concealed allocation adequately, and used double-blinding.

The primary outcome was the number of headache days per month, comparing baseline with the 4 weeks of treatment. Secondary endpoints included reduction in migraine intensity, duration, number of analgesics used, and percentage of patients with more than 50% reduction in migraine headache days.

Compared to placebo, headache days per month were reduced in both the melatonin group (6.2 days vs 4.6 days, respectively; mean difference [MD], -1.6; 95% confidence interval [CI], -2.4 to -0.9) and the amitriptyline group (6.2 days vs 5 days, respectively; MD, -1.1; 95% CI, -1.5 to -0.7) at 12 weeks, based on intention-to-treat analysis. Mean headache intensity (0-10 pain scale) was also lower at 12 weeks in the melatonin group (4.8 vs 3.6; MD, -1.2; 95% CI, -1.6 to -0.8) and in the amitriptyline group (4.8 vs 3.5; MD, -1.3; 95% CI, -1.7 to -0.9), when compared to placebo.

Headache duration (hours/month) at 12 weeks was reduced in both groups (amitriptyline MD, -4.4 hours; 95% CI, -5.1 to -3.9; melatonin MD, -4.8 hours; 95% CI, -5.7 to -3.9), as was the number of analgesics used (amitriptyline MD, -1; 95% CI, -1.5 to -0.5; melatonin MD, -1; 95% CI, -1.4 to -0.6) when compared to placebo. There was no significant difference between the melatonin and amitriptyline groups for these outcomes.

Patients taking melatonin were more likely to have a >50% improvement in headache frequency compared to amitriptyline (54% vs 39%; number needed to treat [NNT]=7; P<.05); melatonin worked much better than placebo (54% vs 20%; NNT=3; P<.01).

Adverse events were reported more often in the amitriptyline group than in the melatonin group (46 vs 16; P<.03) with daytime sleepiness being the most frequent complaint (41% of patients in the amitriptyline group vs 18% of the melatonin group; number needed to harm [NNH]=5). There was no significant difference in adverse events between melatonin and placebo (16 vs 17; P=not significant). Melatonin resulted in weight loss (mean, -0.14 kg), whereas those taking amitriptyline gained weight (+0.97 kg; P<.01).

**WHAT’S NEW**

**An effective migraine prevention alternative with minimal adverse effects**

Melatonin is an accessible and affordable option for preventing migraine headaches in chronic sufferers. The 3-mg dosing reduces headache frequency—both in terms of the number of migraine headache days per month and in terms of the percentage of patients with a >50% reduction in headache events—as well as headache intensity, with minimal adverse effects.

**CAVEATS**

**Product consistency, missing study data**

This trial used 3-mg dosing, so it is not clear if other doses are also effective. In addition, because melatonin is available over-the-counter, the quality/actual doses may be less well regulated, and thus, there may be a lack of consistency between brands. Unlike clinical practice, neither the amitriptyline nor the melatonin dose was titrated according to patient response or adverse effects. As a result, we are not sure of the actual lowest effective dose, or if greater effect (with continued minimal adverse effects) could be achieved with higher doses.

Lastly, 69% to 75% of patients in the treatment groups completed the 16-week trial, but the authors of the study reported using 3 different analytic techniques to estimate missing data. The primary outcome included 178 of 196 randomized patients (90.8%). For the primary endpoint, the authors treated all missing data as non-headache days. It is unclear how these missing data would affect the outcome, although an analysis like this would tend towards a null effect.

**An estimated 38% of patients with migraines are appropriate candidates for prophylactic therapy, but only 3% to 13% are taking preventive medications.**
CHALLENGES TO IMPLEMENTATION

Challenges are negligible

There are really no challenges to implementing this practice changer; melatonin is readily available over-the-counter and it is affordable.

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