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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.

PRACTICE CHANGER

Recommend nightly melatonin 3 mg to your patients with chronic migraines, as it appears to be as effective as amitriptyline in reducing headaches and causes fewer adverse effects.

STRENGTH OF RECOMMENDATION

B: Based on a single, good quality randomized controlled trial.

Gonçalves AL, Martini Ferreira A, Ribeiro RT, et al. Randomised clinical trial comparing melatonin 3 mg, amitriptyline 25 mg and placebo for migraine prevention. *J Neurol Neurosurg Psychiatry*. 2016;87:1127-1132.[1]

ILLUSTRATIVE CASE

A 32-year-old woman comes to your office for help with her recurrent migraines, which she's had since her early 20s. She is otherwise healthy and active. She is frustrated over the frequency of her migraines and the debilitation they cause. She has tried prophylactic medications in the past, but stopped taking them because of the adverse effects. What do you recommend for treatment?

Daily preventive medication can be helpful for chronic migraine sufferers whose headaches have a significant impact on their lives and who have a goal of reducing headache frequency or severity, disability, and/or avoiding acute headache medication escalation.[2] An estimated 38% of patients with migraines are appropriate candidates for prophylactic therapy, but only 3% to 13% are taking preventive medications.[3]

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).[2] 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).[2] However, adverse effects, such as somnolence, are listed as frequent with amitriptyline and occasional to frequent with topiramate.[4]

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.[5]

STUDY SUMMARY

Melatonin tops amitriptyline in >50% improvement in headache frequency

This RCT conducted in Brazil compared the effectiveness of melatonin to amitriptyline and placebo for migraine prevention in

INSTANT POLL

Do you ever prescribe melatonin for the prevention of migraines in chronic migraine sufferers?

☐ Yes
☐ No

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196 adults (ages 18-65 years) with chronic migraines.[1] 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.

CONTINUED

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. JFP

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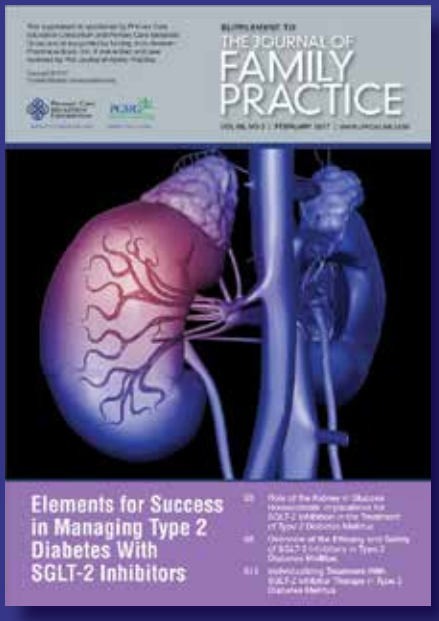

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