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Efficacy and safety of melatonin for migraine prophylaxis in adults: an umbrella review of network meta-analyses

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Introduction
Migraine is a prevalent and disabling neurological disorder. Although several preventive therapies are currently recommended, their use is often limited by adverse effects and poor adherence. Melatonin has emerged as an accepted prophylactic option due to its favorable safety profile and its role in circadian rhythm regulation and CGRP modulation. This umbrella review synthesized the highest level of evidence regarding the efficacy and safety of oral melatonin for migraine prevention in adults.

Objective
To evaluate the efficacy and safety of oral melatonin for migraine prophylaxis in adults.

Methods
An umbrella review was conducted according to PRISMA guidelines and registered in PROSPERO (CRD420026384791). Searches were performed in PubMed, Embase, Web of Science, Cochrane Library, and SciELO using the terms ("Migraine Disorders" OR migraine) AND melatonin AND ("systematic review" OR "meta-analysis"). Systematic reviews, conventional meta-analyses, and network meta-analyses involving adults aged 18–65 years with episodic or chronic migraine receiving oral melatonin were included. The main formulations analyzed were immediate-release (IR) melatonin 3 mg and prolonged-release (PR) melatonin 2 mg. Comparators included placebo, topiramate, valproate, propranolol, amitriptyline, valsartan, and cinnarizine. Outcomes comprised monthly migraine frequency, ≥50% responder rate, pain intensity, attack duration, safety, and treatment discontinuation. Methodological quality was assessed using AMSTAR 2 and risk of bias using the Cochrane Risk of Bias tool.

Results
Thirty-six studies were identified, and 16 reviews met the eligibility criteria. The proportion of primary studies with low risk of bias ranged from 41% to 57.2%. Melatonin was superior to placebo in reducing monthly migraine frequency (MR 0.65; 95% CI 0.54–0.80; I^2=0%). Melatonin 3 mg IR reduced headache days by 1.71 days/month (95% CI −3.27 to −0.14; p<0.05). Although valsartan (MR 0.35; 95% CI 0.23–0.53) and topiramate (MR 0.45; 95% CI 0.35–0.57) demonstrated greater efficacy, they showed poorer tolerability. For the ≥50% responder rate, melatonin 3 mg IR achieved OR 4.19 (95% CI 1.46–12.00;I^2=72.7%), outperforming topiramate (OR 2.50). Sensitivity analyses reduced heterogeneity to I^2=50.7% after excluding studies with follow-up shorter than 16 weeks. Melatonin also reduced attack duration (MD −4.98 h; 95% CI −9.30 to −0.67; p=0.02) and pain intensity (MR 0.66). Safety outcomes favored melatonin, with adverse-event rates comparable to placebo (RR≈1.0), whereas topiramate (RR 1.43), valproate (RR 2.09), amitriptyline (RR 2.12), and cinnarizine (RR 2.27) were associated with more adverse events and treatment discontinuation. In SUCRA multicriteria analysis, melatonin 3 mg IR showed the best efficacy–tolerability balance (Value Preference score 0.102).

Conclusion
Melatonin 3 mg IR showed efficacy, tolerability and safety in migraine prevention, representing a valuable alternative or adjunct to conventional prophylactic therapies overall.

Keywords:
Migraine prevention
Calcitonin gene-related peptide (CGRP)
Melatonin
Network meta-analysis

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