

CLINICAL REVIEWS

Melatonin Use in Primary Care: Clinical Evidence, Safety Considerations, and Practical Guidance for Family Physicians

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Melatonin is one of the most widely used over-the-counter sleep aids in the United States. Patients frequently self-initiate therapy, often without clinician guidance regarding appropriate dosing, indications, safety, or potential drug interactions. This narrative review summarizes current clinical evidence regarding melatonin's pharmacology, efficacy across age groups, safety profile, adverse effects, drug interactions, long-term use, cardiovascular considerations, and the role of behavioral therapies for insomnia. Practical recommendations are provided to assist family physicians in counseling patients and making evidence-informed decisions regarding melatonin use.

Introduction

Sleep disturbances are among the most common complaints encountered in primary care. Melatonin, an endogenous hormone regulating circadian rhythms, is widely used as a nonprescription sleep aid. Its perceived safety and "natural" origin contribute to extensive unsupervised use. However, variability in product quality, uncertainty regarding dosing, potential interactions, and limited long-term data create challenges for clinicians. A structured understanding of melatonin's benefits and risks alongside evidence-based behavioral treatments for insomnia is essential for appropriate patient counseling.

Pharmacology and Mechanism of Action

Melatonin is synthesized in the pineal gland and secreted in response to darkness, signaling circadian night. It acts primarily through MT1 and MT2 receptors in the suprachiasmatic nucleus, facilitating sleep initiation and circadian phase regulation. Exogenous melatonin has chronobiotic effects, shifting circadian timing when administered appropriately relative to endogenous secretion. Immediate-release formulations primarily reduce sleep latency, whereas prolonged-release formulations may improve sleep maintenance.¹

Clinical Evidence for Efficacy

Evidence supports melatonin for circadian rhythm sleep-wake disorders, including delayed sleep phase disorder and jet lag. A clinical practice guideline reported modest reductions in sleep onset latency and improved sleep timing in these conditions.¹ Evidence for primary insomnia is mixed, with generally modest benefits compared with behavioral interventions. In older adults, prolonged-release formulations may improve sleep quality modestly.²

Pediatric use has increased, particularly among children with neurodevelopmental disorders. Studies suggest improvements in sleep onset and duration, although optimal dosing and long-term safety remain uncertain.³

Safety and Adverse Effects

Melatonin is generally well tolerated. Common adverse effects include daytime somnolence, headache, dizziness, and nausea. Systematic reviews report low rates of serious adverse events.⁴ Higher doses may increase sedation and impair psychomotor performance.⁵ Rare reports describe vivid dreams, mood changes, or hypotension.

Melatonin is marketed as a dietary supplement in the United States and is not subject to the same regulatory standards as prescription medications. Analyses of commercial products reveal substantial variability in labeled content and occasional contamination.²

Drug Interactions

Melatonin may interact with several medication classes through pharmacodynamic and pharmacokinetic mechanisms. Sedative effects may be potentiated when combined with central nervous system depressants, including benzodiazepines, opioids, or alcohol.⁶ Concomitant use with antidepressants or antipsychotics may increase sedation or alter circadian regulation.

Melatonin can influence platelet aggregation and may increase bleeding risk when used with anticoagulants or antiplatelet agents.⁷ Additionally, metabolism via cytochrome P450 enzymes suggests potential interactions with medications affecting CYP1A2 activity, such as fluvoxamine or certain antibiotics. Careful medication reconciliation is therefore essential when patients report melatonin use.

Special Populations

Children and Adolescents

Melatonin is commonly used for pediatric insomnia, especially in neurodevelopmental disorders. Short-term studies indicate effectiveness for sleep initiation; however, long-term safety data are limited. Concerns include potential effects on pubertal development due to hormonal interactions.³ Use should ideally occur under specialist guidance.

Pregnancy and Lactation

Data regarding safety in pregnancy and breastfeeding are insufficient. Current evidence does not support routine use outside research settings.⁸

Long-Term Use

Long-term safety data are limited but generally reassuring. Observational studies and pharmacovigilance analyses suggest low rates of serious adverse outcomes with chronic use, although controlled long-duration trials are lacking.^{9,10} Periodic reassessment of ongoing need is recommended, with emphasis on nonpharmacologic therapies for persistent insomnia.

Cardiovascular and Metabolic Considerations

Melatonin influences circadian regulation of blood pressure, glucose metabolism, and autonomic function. Some studies suggest modest nocturnal antihypertensive effects, whereas others raise concerns about potential arrhythmias or interactions with cardiovascular medications.¹¹ A large cohort study found no clear increase in major cardiovascular events among supplement users, although confounding factors limit interpretation.¹² Overall, evidence neither strongly supports nor contraindicates use in most cardiovascular patients, but caution is warranted in individuals with unstable cardiac conditions.

Supplement Quality and Regulation

Because melatonin products are sold as dietary supplements, manufacturing standards vary widely. Independent testing has demonstrated discrepancies between labeled and actual melatonin content and the presence of impurities.² Recommending products that undergo third-party quality testing may reduce risk.

Behavioral Therapy and Sleep Hygiene

Nonpharmacologic treatment remains the cornerstone of management for chronic insomnia. Current guidelines recommend cognitive behavioral therapy for insomnia (CBT-I) as the first-line treatment for persistent insomnia. CBT-I incorporates structured strategies to modify maladaptive sleep behaviors, regulate sleep–wake schedules, reduce physiologic and

cognitive arousal, and challenge dysfunctional beliefs about sleep. These interventions typically include stimulus control, sleep restriction therapy, relaxation techniques, and cognitive restructuring. Compared with pharmacologic treatments, CBT-I produces more durable improvements in sleep outcomes and is associated with fewer adverse effects.¹³

Basic sleep hygiene measures are also important adjuncts. These include maintaining consistent bedtimes and wake times, minimizing evening exposure to bright light and electronic screens, avoiding caffeine and heavy meals before bedtime, and optimizing the sleep environment for comfort and darkness. Pharmacologic therapies such as melatonin should generally be considered adjunctive to these behavioral approaches rather than replacements for them.

Clinical Application in Primary Care

In primary care settings, melatonin and melatonin-receptor agonists represent low-risk therapeutic options for older adults with sleep-onset insomnia. Evidence synthesized in *American Family Physician* demonstrates that both immediate-release and prolonged-release melatonin produce statistically significant but clinically modest improvements, reducing sleep-onset latency by approximately 7–15 minutes and increasing total sleep time by 10–13 minutes.¹⁴ Prolonged-release melatonin at a 2-mg nightly dose shows the most consistent benefit in adults over 55, with trials reporting improved sleep latency, better subjective sleep quality, and no increase in adverse effects compared with placebo.¹⁴ Ramelteon offers similar reductions in sleep-onset latency with a particularly favorable safety profile, including no observed increase in falls, fractures, or motor vehicle accidents in large Medicare cohort analyses.¹⁴ For primary care clinicians, these agents are best positioned as safe adjuncts for patients seeking non-sedating alternatives or those who are poor candidates for benzodiazepines or Z-drugs, while cognitive behavioral therapy for insomnia remains the recommended first-line intervention.

Conclusion

Melatonin can be a useful therapeutic option for selected sleep disorders, particularly circadian rhythm disturbances, but its widespread unsupervised use raises important safety and efficacy considerations. Primary care clinicians play a critical role in guiding appropriate dosing, identifying drug interactions, counseling special populations, and emphasizing evidence-based behavioral treatments for insomnia. Continued research is needed to clarify long-term safety, cardiovascular effects, and optimal clinical use.

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Table 1. Clinical Guidance for Melatonin Use in Primary Care

Clinical Situation	Typical Dose & Timing	Evidence of Benefit	Safety Considerations	Drug Interactions	Special Guidance
Circadian rhythm sleep-wake disorders (e.g., delayed sleep phase)	0.5–5 mg 1–3 h before desired bedtime	Moderate evidence for phase shifting and reduced sleep latency ¹	Generally well tolerated; monitor for morning sedation ⁴	CNS depressants ⁶ , CYP1A2 inhibitors ⁷	Most evidence-supported indication ¹
Jet lag	0.5–5 mg at destination bedtime for several nights	Moderate evidence for improving sleep and daytime alertness ¹	Short-term use considered safe ⁴	Sedatives, alcohol ⁶	Begin on arrival at destination ¹
Primary insomnia (adults)	1–5 mg 1–2 h before bedtime	Modest benefit compared with placebo ¹	May cause daytime drowsiness, dizziness ⁴	Antidepressants, antipsychotics, sedatives ⁶	Behavioral therapy preferred first-line ¹³
Older adults with sleep maintenance insomnia	1–2 mg prolonged-release formulation	Modest improvements in sleep quality ²	Increased fall risk if excessive sedation ⁴	Antihypertensives, sedatives ⁶	Start low, monitor closely ²
Pediatric insomnia (especially neurodevelopmental disorders)	0.5–3 mg initially; up to 5 mg in selected cases	Evidence for reduced sleep latency ³	Limited long-term safety data ³	Sedatives, stimulants ⁶	Use under specialist guidance ³
Pregnancy and lactation	Not routinely recommended	Insufficient evidence ⁸	Unknown fetal and neonatal effects ⁸	Unknown	Avoid unless specialist-directed ⁸
Long-term use	Lowest effective dose	Limited long-term controlled data ^{9,10}	Periodic reassessment advised ^{9,10}	Depends on concomitant medications	Emphasize behavioral therapies ¹³
Cardiovascular disease	Individualized	Unclear net benefit ^{11,12}	Possible effects on BP, heart rate ¹¹	Antihypertensives, anticoagulants ⁷	Use caution in unstable disease ¹¹
Patients on anticoagulants / antiplatelets	Avoid or monitor closely	No direct sleep benefit evidence	Possible increased bleeding risk ⁷	Warfarin, DOACs, aspirin ⁷	Consider alternatives ⁷
Concurrent CNS depressants	Reduce dose or avoid	Additive sedation risk ⁶	Impaired alertness, falls ⁶	Benzodiazepines, opioids, alcohol ⁶	Counsel regarding safety ⁶

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