

FAST FACTS AND CONCEPTS #306
THE ROLE OF MELATONIN IN PALLIATIVE CARE

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Background Melatonin is a naturally occurring hormone classified as a dietary supplement in the United States (US) (1). It can be purchased over the counter (OTC) without a prescription and therefore is unregulated by the FDA. Many clinicians who care for seriously ill patients are asked about the use of melatonin to regulate the circadian rhythm and treat insomnia. This *Fast Fact* will focus on melatonin's pharmacology and its potential uses in the adult palliative care population, while acknowledging the emerging evidence for the pediatric population (2).

Pharmacology Melatonin is an endogenous metabolite of tryptophan and serotonin, released cyclically from the pineal gland according to the body's circadian rhythm. Plasma levels increase during the evening hours to encourage sleep onset and maintenance (3). Research suggests oral doses of 5 mg produce blood levels 25 times higher than normal but do not appear to alter endogenous production (4). When taken orally melatonin is rapidly absorbed; bioavailability ranges from 10-56% (5). This range may be due to extensive first pass metabolism, or variations between manufactured formulations. Due to its high lipophilicity, melatonin crosses the blood brain barrier quickly; onset and peak concentration are within 50 minutes and 2 ½ hours respectively (6). It is excreted quickly with a terminal half-life of only ~45 minutes; however, its duration of action is felt to be equal to four elimination half-lives (or about 3-5 hours) by most experts (7).

Dosing Melatonin is available in 1 mg, 3 mg, 5 mg and 10 mg immediate-release, and 3 mg and 5 mg controlled-release oral tablets. A prolonged-released 2 mg formulation is commercially available outside of the US. A typical starting dose is 1 mg once daily, with a more conservative dose of 0.5 mg in geriatric patients. Melatonin should be administered within 1 hour of bedtime to supplement the body's endogenous nocturnal surge. Due to its extensive hepatic metabolism, lower doses should be used in liver failure, although specific recommendations have not been published (5).

Research Data There is insufficient evidence to support the use of melatonin for primary insomnia disorders in adults or in insomnia related to moderate to severe dementia. However, data in the adult population suggests that short term use of melatonin (less than three months) may be effective in delayed sleep phase syndrome, where a person's sleep is delayed by 2 or more hours beyond the conventional bedtime (8-10). Similar results have been replicated in children and infants via exposure to melatonin in breast milk (2). Melatonin has been examined as an adjuvant to chemotherapy due to its antioxidant and immunomodulatory effects, but its role as an oncologic adjuvant needs further research and is not standard of care (11-12). An emerging role of great interest is in the prevention and management of delirium for adults. Case reports have shown success in treating severe post-operative delirium refractory to antipsychotics or benzodiazepines (13). One randomized, double-blinded, placebo-controlled study concluded that melatonin 0.5 mg/day was associated with a lower risk of delirium in hospitalized elderly patients (14). Additionally ramelteon, a melatonin receptor agonist, demonstrated similar benefit in a small randomized, placebo-controlled study preventing delirium among hospitalized elderly patients (15). Although evidence is promising, more research is needed to establish the role of both melatonin and ramelteon for the prevention and management of delirium.

Adverse Drug Reactions and Cautions Melatonin is relatively nontoxic in appropriate doses when used short term (4). The most common side effects are excess sedation and somnolence (4). Caution should be exhibited in the post organ transplant population as melatonin's immune-boosting effects could increase the risk of graft rejection though more research is needed (16).

Cost Due to its OTC status in the US, melatonin is rather inexpensive but is usually not covered by most private insurances or Medicare. Prices for over the counter melatonin range approximately from \$5-15 for a ninety count bottle.

Summary Melatonin is a naturally occurring hormone that has limited benefit in treatment of primary sleep disorders, but may have a potential benefit for the prevention and management of delirium. Given its low cost and lack of side effects, while it cannot be recommended, it should not be discouraged.

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