Complementary and Alternative Medicines Patients Are Talking About: Melatonin

Melatonin (N-acetyl-5-methoxytryptamine) is a hormone produced by the pineal gland in the brain in response to darkness. Melatonin is made available when tryptophan is converted to serotonin and then enzymatically converted to melatonin in the pineal gland. Serum levels are low during the day, with peak levels occurring from 2–4 am.

**Route of Administration**

Melatonin is extracted from the pineal gland of beef cattle or synthesized chemically from 5-methoxytryptamine. Synthetic melatonin is taken orally as a tablet, sublingually, as an intramuscular injection, or as an IV infusion.

**Dosing and Cost**

Dosing of melatonin varies from 5 mg daily for relief of jet lag to 75 mg daily for chronic insomnia (Natural Medicines Comprehensive Database, 2005). Clinical trial doses range from 10–40 mg daily. The monthly cost for a 3 mg daily dose is about $5, which is not covered by insurance.

**Indications**

Melatonin is marketed commercially for the relief of jet lag and insomnia. Other reported uses are for the treatment of tinnitus and cachexia, as oral contraception when combined with progestin, and for cancer treatment as combination therapy prior to or during interleukin-2 treatment. Melatonin also is believed to possess antioxidant properties (Thomson™ Micromedex, 2005).

**Regulation**

As a dietary supplement, defined by the Dietary Supplemental Health and Education Act of 1994, melatonin does not fall under postmarket regulation by the U.S. Food and Drug Administration (FDA). The FDA is responsible, however, for taking action against any unsafe products once reported.

**Safety and Efficacy**

Supplements with melatonin appear to have a good safety profile. Ten clinical trials from 1992–2003 involving the use of melatonin for the treatment of cancer or supportive care were included in a systematic review reporting that, despite differences in tumor type and dosing, melatonin diminished the risk of mortality at one year (Mills, Wu, Seely, & Guyatt, 2005). Conflicting evidence exists regarding whether melatonin protects against chemotherapy-induced toxicities (Cerea et al., 2003; Ghielmini et al., 1999; Persson, Glimelius, Ronnelid, & Nygren, 2005). Table 1 offers a summary of the studies.

**Interactions**

Because the metabolism of melatonin occurs via the liver enzyme cytochrome P450 1A2, drugs that alter the activity of 1A2 may increase or decrease the effects of melatonin supplements (Natural Standard, 2005). Common drugs that increase the side effects of melatonin are anastrozole, cimetidine, ciprofloxacin, and interferon. Common drugs that decrease the therapeutic effects of melatonin are insulin, nafcillin, omeprazole, and ritonavir. Increased daytime drowsiness is reported with concurrent use of zolpidem, lorazepam, codeine, and alcohol. Because long-term effects of melatonin have not been examined in women who are trying to conceive, pregnant, or nursing, caution is warranted.
Adverse Reactions

Melatonin generally is regarded as safe in recommended doses for short-term use. Common adverse effects include fatigue, dizziness, headaches, irritability, and sleepiness. Case reports of blood clotting abnormalities (particularly in patients taking warfarin), increased risk of seizure, and disorientation with overdose have been linked to melatonin (Natural Standard, 2005; Natural Medicines Comprehensive Database, 2005; Thomson Micromedex, 2005).

Clinical Trials

The effects of melatonin on chemotherapy-related side effects in patients with non-small cell lung cancer is being studied in an active clinical trial (Cancer Treatment Centers of America, 2005). Published results are not yet available from a randomized, multicenter, closed clinical trial determining the effect of melatonin as a radiosensitizer or radioprotectant in the clinical deterioration of patients with brain metastases (Protocol ID: RTOG BR-0119) (Physicians Data Query®, 2005).

Table 1. Clinical Efficacy Trials Involving Melatonin

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<th>AUTHOR</th>
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<td>Cerea et al., 2003</td>
<td>Summary of evidence surrounding the influence of concurrent administration of melatonin with various cytotoxic agents in the treatment of metastatic colorectal cancer</td>
<td>30 pretreated patients with metastatic colorectal cancer were randomized to receive irinotecan alone (125 mg/m twice a week for nine consecutive weeks) or irinotecan plus daily evening melatonin (20 mg per day). Patients were pretreated with a 5-fluorouracil-containing regimen.</td>
<td>The authors reported that partial responses were achieved in 2 of 16 patients who received irinotecan alone (5 of 16 had stable disease) and 5 of 14 patients who received irinotecan plus melatonin (7 of 14 had stable disease). The authors supported the belief that the efficacy of irinotecan may be enhanced by daily administration of melatonin.</td>
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<td>Ghielmini et al., 1999</td>
<td>Summary of evidence of efficacy of proposed myeloprotective effect of melatonin in patients with lung cancer</td>
<td>20 untreated patients with inoperable lung cancer were randomized to receive chemotherapy plus melatonin 40 mg or placebo for 21 days of either the first or second cycle. Chemotherapy included carboplatin (day 1) and etoposide (days 1–3) every four weeks.</td>
<td>The authors reported no significant difference in the multivariate factors (age, sex, diagnosis, stage, performance status, and cytotoxic agent doses) and melatonin and placebo or hematologic parameters (hemoglobin, platelets, neutrophils). The authors concluded that 40 mg of daily melatonin does not provide myelotoxic protection against carboplatin and etoposide.</td>
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<td>Mills et al., 2005</td>
<td>Systematic review of 10 randomized, controlled trials involving the use of melatonin for cancer treatment or supportive care and its impact on survival at one year</td>
<td>10 trials published from 1992–2003 met the review criteria for inclusion and involved 643 patients with solid tumors such as non-small cell lung cancer, breast cancer, renal cell carcinoma, glioblastoma, and malignant melanoma. Trials involved all ages, genders, and cancer stages, including the use of melatonin as sole or adjunct therapy. Trials involving animals and pharmacokinetics and those combining melatonin with nonstandard cytotoxic regimens were excluded. The melatonin dosage range was 10–40 mg daily at bedtime.</td>
<td>The authors reported that, despite differences in tumor type and dosing, melatonin diminished the risk of mortality at one year. No severe adverse events were reported, and melatonin was well tolerated in all trials. Of note, the trials were conducted in the same network of investigators and were unblinded in design. The authors recommended future blinded, long-term, independent studies to verify the results. Nonetheless, the authors agreed that melatonin has great potential for treating cancer based on the reduction in risk, low adverse events reported, and low associated cost.</td>
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<td>Persson et al., 2005</td>
<td>Summary of evidence of the efficacy of fish oil, melatonin, and/or dietary advice on cancer-related cachexia and biochemistry variables</td>
<td>Assessments of biochemistry, performance status, quality of life, and food intake were recorded for 24 patients with pretreated, advanced gastrointestinal cancer. Patients were randomized to receive fish oil (providing 4.9 g of eicosapentaenoic acid and 3.2 g of docosahexaenoic acid) or melatonin 18 mg per day for four weeks. For the next four weeks, all patients received fish oil and melatonin at stated doses. Markers for biochemistry (eicosapentaenoic, docosahexaenoic, arachidonic, and linoleic acids) and cytokines (tumor necrosis factor-α, interleukin-1β, and soluble interleukin-2, -6, and -8) were measured.</td>
<td>The authors reported that 5 of 13 patients in the fish oil (first four weeks) group showed either weight stabilization or weight gain versus 3 of 11 patients in the melatonin (first four weeks) group. In the next four weeks, weight stabilization or weight gain was noted in each group, with 8 of 13 patients in the (original) fish oil group and 7 of 13 in the (original) melatonin group. No statistically significant differences were reported in quality of life or survival between groups. The authors concluded that neither fish oil, melatonin, nor their combination produced a strong antica- chectic effect.</td>
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Future

Because of melatonin’s popularity and its demonstrated efficacy, it likely will continue to be marketed in single and combination products.

Key Patient Teaching Points

- Treatment decisions regarding melatonin should be made jointly between healthcare providers and patients with assessment of potential risks and drug interactions.
- Women who are trying to conceive or are pregnant or breastfeeding should consider avoiding melatonin until more clinical information is available.
- Melatonin should be avoided in patients with clotting abnormalities or those receiving warfarin.

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References


