



## **Flight Crews Cautioned About Unsupervised Melatonin Use**

*Despite claims about its effectiveness in inducing sleep and producing other health benefits, it is still not known whether long-term melatonin use can result in side effects.*

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Melatonin, a natural hormone that has been associated with the onset of sleep, is receiving increasing attention from researchers, and among the public its use as a sleep aid is now widespread.

Flight crew and cabin crew members, especially those who fly long-haul and international routes, are frequently exposed to potential sleep disturbances and circadian rhythm disruptions because of duty-time and scheduling factors. Melatonin is said not only to be a safe, gentle and natural means of inducing sleep, but to cut recovery time from jet lag in half.

But despite claims about its effectiveness, pilots should be extremely cautious in regard to melatonin use. A flight crew member should not use melatonin without first consulting his or her aviation medical specialist.

Dr. Jerry Hordinsky, a physician at the U.S. Federal Aviation Administration's (FAA's) Civil Aeromedical Institute in Oklahoma City, Oklahoma, U.S., said that the FAA is not conducting direct research into melatonin use and that the agency has no official position on its use. "The FAA does not yet have sufficient information from ongoing studies to officially recommend (or not recommend) its use to pilots and crew," Hordinsky said. "The evidence is not in yet."<sup>1</sup>

The primary arguments for caution in the use of melatonin center around the lack of long-term controlled studies in

humans and melatonin's lack of U.S. Food and Drug Administration (FDA) regulation — and, therefore, absence of an approval process in the United States. Hordinsky said that the consensus among aviation medical specialists now "is to recommend against pilots taking melatonin because the research is not sufficiently mature yet to say what you should take."

In the United States, melatonin is sold as a "food supplement." The FDA does not consider melatonin a drug and therefore does not regulate its manufacture and sale. Because the FDA does not test the efficacy of melatonin, the buyer must trust the manufacturer with respect to dosage and purity claims. The U.K. Medicines Control Agency, however, has classified melatonin as a "medicinal product," available only by prescription.<sup>2</sup> Over-the-counter sale of melatonin has also been banned by the Swiss, German, Belgian and other European food and drug regulatory authorities, according to Stefanie Geiser, a spokeswoman for European Advisory Services, a Brussels-based consulting firm specializing in European health policy.<sup>3</sup>

Melatonin is a natural hormone that evolved in certain amphibian vertebrate animals. It causes specific cells in the skin to contract in dark environments.<sup>4</sup> Associated with these changes is a decrease in body activity and the gradual onset of sleep. The sensory mechanism involved is triggered through the eyes: as the environment darkens, the eyes send signals

through the optic nerve to the pineal gland in the brain. The pineal gland, in response, secretes the hormone melatonin, which is circulated throughout the body in the bloodstream. Lerner et al. discovered the chemical formula for melatonin and named it, reportedly because they derived it in the laboratory from serotonin and it affected melanin (pigment)-containing cells.<sup>5</sup>

Bovine (cow) pineal glands are processed as one source of melatonin,<sup>6</sup> and chemically synthesized melatonin sources are also available.<sup>7</sup> Health-food stores and over-the-counter sections of many pharmacies carry these products. Researchers say that synthetic forms of the product are less likely to be contaminated.

Trademarked melatonin products are marketed by a variety of manufacturers. A variety of dosages is available, but most formulations provide 1.0 milligram to 3.0 milligrams per tablet (10 times the amount used in several melatonin studies).

Claims for melatonin's usefulness and effectiveness are often extravagant.<sup>8</sup> Proponents of melatonin use say that, besides its sleep-inducing and circadian rhythm-normalizing properties, the hormone has anti-aging effects; boosts the immune system; and helps prevent heart disease, Alzheimer's disease, Parkinson's disease, diabetes and cataracts.<sup>7</sup> Other researchers, however, caution that the effects of long-term melatonin use are not known.

There is strong evidence that melatonin and sleep are closely associated in humans. Rigorous studies conducted by reputable scientists are providing data suggesting that a single, low dose (0.1 milligram to 0.3 milligram) of melatonin, taken orally, can help the early onset of natural, refreshing sleep.

Researchers at Harvard University and the Massachusetts Institute of Technology (MIT) have used advanced, objective sleep measurement techniques to study the sleep-inducing effects of melatonin.<sup>6</sup> In these studies, the effects of low doses (0.3 milligram) of melatonin, taken orally, were measured against the effects of a placebo. The investigators found that in most subjects there was a clear distinction between the effects of melatonin and the placebo. "All melatonin doses tested significantly increased sleep duration, as well as self-reported sleepiness and fatigue, relative to placebo," the Harvard/MIT study said.

The study said that sleep onset was faster with the melatonin, and hangover effects the next morning, as assessed by mood and performance tests, did not occur. In addition, rapid eye movement (REM)-cycle sleep, considered to be an important component of refreshing sleep, was not suppressed, as often happens with over-the-counter and prescribed sleep medications and with alcohol.

Additional studies by the Harvard/MIT researchers showed that a 0.1-milligram oral dose of melatonin, taken two or three hours before bedtime, has similar effects to the 0.3-milligram dose.<sup>9</sup> Melatonin, like many hormones, operates at very low blood levels, and, accordingly, a small oral supplement to the normal circulating level seems to boost its sleep-inducing effect, the researchers said.

Most prescription and over-the-counter sleep-inducing medications have, to varying degrees, adverse side effects, including suppression of REM-cycle sleep and other adverse hangover effects. But studies in the clinical literature on low doses of melatonin have documented no such adverse side effects. These results support the concept that oral melatonin in low doses may be a useful treatment for insomnia.

Studies performed to date have revealed no toxic effects of melatonin and few side effects. In their book *Melatonin*, Reiter and Robinson said that "melatonin is one of the least toxic substances known. People have taken as much as 6 grams of the substance in carefully monitored studies with no signs of toxicity. The only consistent side effect of high doses has been drowsiness and a slower reaction time."<sup>7</sup>

But Reiter and Robinson also pointed out that "a substance can have little or no toxicity ... and still produce negative effects in some people or under some circumstances. In fact, melatonin's very *assets* could turn into liabilities. Consider melatonin's wonderful sleep-enhancing effect. It could prove a decided liability if you were foolish enough to take a high dose of melatonin before driving a car or operating a dangerous piece of machinery."

Reiter and Robinson added that "... although melatonin has been tested on humans in hundreds of studies, it has not been administered in the large-scale, carefully controlled studies necessary to determine its ultimate safety. People who choose to take melatonin at the present time are facing some unknown risks.

"Another reason to be cautious about taking melatonin is that there is great biological diversity among human beings. Melatonin has not been administered to enough people or for a long enough period of time to rule out the possibility that some people may react atypically to the hormone. In fact it is possible that some diseases and conditions might be *exacerbated* by melatonin. Another note of caution is that there is always a possibility of contamination during the manufacture of any drug or food supplement, especially when it is not being regulated by the FDA. A substance with no known toxicity in its pure form could cause a negative reaction if mingled with toxic impurities."

Many physicians and researchers believe that the efficacy of melatonin must be determined on an individual basis by the

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person experiencing sleep problems. Some people taking melatonin report it has little or no effect on their sleeplessness. Others are convinced that a small amount of oral melatonin taken in accordance with the manufacturer's recommendations does help induce sleep. Nevertheless, some persons have reported that the higher doses (3.0 milligrams, for example) seemed to produce excessively vivid dreams and even nightmares.

If melatonin is found to help induce sleep for a flight crew member (after consultation with an aviation medical specialist), he or she must not take it prior to reporting for flight duty, driving or operating machinery. It should not be necessary to continue taking melatonin daily once relief from insomnia is obtained. The substance can be taken on an as-needed basis, one or two hours prior to bedtime.

Those considering using melatonin should keep in mind that serious sleep difficulty can have many causes, and to rule out any of these causes requires a sleep-laboratory assessment. Sleep apnea, cigarette smoking, alcohol abuse, sedative drug abuse, depression and other factors can cause insomnia. Thus, these factors should be ruled out or dealt with directly before melatonin is used.

Physicians and researchers have cautioned the following people not to take melatonin or to take it only under close medical supervision: People taking steroid drugs such as cortisone and dexamethasone; pregnant women; women wanting to conceive; nursing mothers; people with severe mental illness or severe allergies; people with autoimmune diseases or immune system cancers such as lymphoma and leukemia and normal children of all ages (most children have naturally high levels of melatonin).

Joan Garrett, a registered nurse and president of MedAire Inc., said that even though "it is believed that controlled oral administration of melatonin can alleviate symptoms of jet-lag and fatigue ... until quality of manufacturing is regulated, consumers should avoid self-medication with over-the-counter formulations of melatonin, no matter how enthusiastically the media portray its benefits."

Garrett said that to promote it for use by flight crews at this time "would go beyond the boundaries of good conscience."<sup>10</sup>

As further research on melatonin is conducted and prior studies are replicated, melatonin will probably become more widely used on an as-needed basis by those who occasionally find that obtaining sufficient restful sleep is difficult because of jet lag, shift-work schedules, or other reasons.

But for now, flight crew members would do well to follow a conservative course and refrain from taking melatonin. "In five years, we should know a great deal more about the possible

benefits and risks of taking the hormone, especially in regard to treating insomnia, biological rhythm disorders and cancer, which are the most active areas of research at this time," according to Reiter and Robinson.♦

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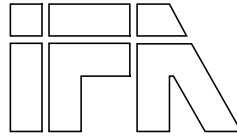
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