

Use of Melatonin to Promote Sleep in Older People

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Abstract

Many older Americans purchase the hormone melatonin and take it orally, nightly, to promote sleep onset and to help them fall back asleep after the frequent nocturnal awakenings associated with aging. This need for exogenous melatonin reflects the fact that the progressive calcification of the human pineal diminishes the organ's ability to secrete its hormone, so that instead of plasma melatonin levels rising normally by 10-fold or more around bedtime the rise may be only by twofold, or even less. The quantity of melatonin that most aging people need to restore nocturnal plasma melatonin levels to what they are in youth—and, concurrently, to promote sleep—is tiny, only about 0.2–0.5 mg. However, this dosage is generally unavailable, so patients may take doses 10-fold greater, or more, producing side-effects (e.g., hypothermia; hypoprolactinemia; morning grogginess) and ultimately desensitizing melatonin receptors in the brain. The reasons that low-dose melatonin is generally unavailable are described and a strategy is proposed for enabling patients to consume the correct dosage even when preparations containing that dosage cannot be obtained.

Keywords

Melatonin, calcified pineal, aging, sleep, nocturnal awakenings, sleep latency, melatonin receptors, GABA receptors, hypothermia, hyperprolactinemia

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Although very large numbers of older Americans purchase the hormone melatonin and take it nightly to promote and sustain sleep, the US Food and Drug Administration (FDA) does not require that consumers be provided with guidelines concerning its proper dosage nor information about its generally minor side-effects, both of which are obligatory for hypnotic drugs.

This reflects the fact that, from a regulatory standpoint, exogenous melatonin is classified not as a drug but as a 'dietary supplement'—even though it remains to be proved that any food actually contains more than trace amounts of real melatonin, or that consumption of any food actually elevates plasma melatonin levels. By virtue of the Dietary Supplement Health and Education Act of 1994, dietary supplements are regulated as though they are foods (which do not require prior FDA approval), rather than as drugs, so long as their marketers make only 'structure or function claims' relating to their effects on normal people, and do not promote them for treating disease states. Supplements are not subject to the safety and efficacy testing requirements imposed on drugs, and the FDA may take action against their sale only after they have been shown to be unsafe (which, fortunately, has not been the case for melatonin).

Very recently an official regulatory body—the European Food Safety Authority (EFSA)—has evaluated the available evidence that melatonin

can reduce the time it takes for normal sleepers and patients with insomnia to fall asleep.¹ It concluded that the evidence from all three of the statistically valid published meta-analyses^{2,3,4} affirms "a cause and effect relationship... between the consumption of melatonin and [a] reduction of sleep onset latency...", and that "... 1 mg of melatonin should be consumed close to bedtime..."¹ Such recommendations usually win approval by the European Commission and its member states, a process that generally requires about six months. This recommendation should also help American physicians in dealing with patients' questions about melatonin's safety, and deciding which of the doses currently marketed is best for them. However, as described below, most Americans have little or no access to the low, maximally effective melatonin doses recommended in the EFSA report and the meta-analyses (not more than 1 mg) because, absent FDA regulation, most stores stock melatonin only in doses as much as ten- to thirty times greater.

Melatonin, a derivative of the circulating amino acid tryptophan, was discovered by Aaron Lerner in 1959 based on its ability to lighten the skin color of amphibians, and shown in 1963 to be a hormone⁵ which the pineal gland synthesizes when mammals are exposed to darkness.⁵ In 1975, our laboratory reported that blood melatonin levels in humans also are about tenfold higher during the hours of darkness than in daytime.⁶ This finding was interpreted as suggesting that the hormone might have

something to do with sleep in humans and other diurnally-active animals; Lerner had, in fact, described feeling 'relaxed' after self-administering a very large dose of melatonin (200 mg intravenously). However the hormone's possible relationship to sleep was not systematically explored until the 1990s, when it was found that giving single melatonin doses to normal young subjects during the daytime caused dose-related, parallel increases in sleepiness, sleep, and plasma melatonin levels. Peak effects were observed after surprisingly low doses (0.3–1.0 mg), which elevated plasma melatonin to levels (100–200 pcg/ml) normally occurring in young people at night-time.⁷

Melatonin's two well-established physiological effects—promotion of sleep and entrainment of circadian rhythms—are both mediated by two specific receptor proteins in the brain,⁵ and not by the gamma-aminobutyric acid (GABA) receptors through which most hypnotic agents act. This difference probably explains why, unlike the GABA-agonist drugs, which are true 'sleeping pills', melatonin does not suppress rapid eye movement (REM) sleep nor, in general, affect the distribution of sleep stages.^{5,8} In 1982, it had been demonstrated that nocturnal plasma melatonin levels in most humans decline with aging,⁹—a probable consequence of the still-unexplained tendency of the human pineal to calcify. Since this decline coincides with a very common age-related sleep problem, i.e., frequent nocturnal awakenings followed by difficulty in falling back asleep,⁸ we investigated whether giving older people melatonin at bedtime, as a 'hormone replacement therapy' (that is, providing them with a dose sufficient to restore nocturnal plasma levels to those of young adults) would also suppress nocturnal awakenings and shorten the time needed to resume sleeping. Again, the melatonin doses now recommended by the EFSA (0.3–1.0 mg) raised plasma melatonin levels in aged insomniacs to those occurring nocturnally in young people, and also helped the patients to remain asleep or readily fall back asleep⁸ throughout most of the night.

These widely confirmed observations have led to the widespread application of melatonin for promoting and sustaining sleep in older people. However, for the most part patients have not been able to use the lowest fully effective doses because the only doses that are commercially available have been substantially higher. Such doses, which raise plasma melatonin to levels many times greater than those of younger

people, produce side-effects not observed at the lower, more physiologic sleep-promoting doses, for example hypothermia;^{7,8} hyperprolactinemia; and 'morning grogginess'.⁵ Moreover, the markedly-elevated melatonin levels can also desensitize the brain receptors on which melatonin must act to promote sleep,¹⁰ probably causing some users to become refractory to the beneficial effects of exogenous melatonin or even to the melatonin their own pineal glands secrete.

Why are physiologic doses of melatonin—those which elevate its plasma levels within their normal range—generally unavailable, while very much larger doses are ubiquitous in health-food stores and the OTC sections of American pharmacies? Probably for several reasons, foremost of which is that the FDA does not set allowable doses, but also because users may believe that if taking some of a drug is good, then taking more must be better; or because melatonin is so inexpensive to synthesize that even a 10 mg pill costs its manufacturer little more than one containing 0.3 mg; or because the hormone causes little overt toxicity even at megadoses; or perhaps because the decrease in melatonin-receptor-sensitivity that very large doses produce ultimately protects patients from consequences of their continued administration. Another factor may involve melatonin's patent status: when the Massachusetts Institute of Technology (MIT) first patented melatonin's use to promote sleep it was assumed that the hormone would be regulated by the FDA as a drug; hence doses greater than maximally-effective ones (0.3–1.0 mg) would not be allowed for sale, making it unnecessary to include such doses in the patent. Consequently, nothing now constrains a purveyor of melatonin from selling any dose above 1 mg that it wishes to sell, without having to obtain a license or pay a royalty. This probably has not led to great savings by the marketers or great losses to the inventor, since all of these inventor's royalties are routinely returned to MIT. However, it has had the unintended consequence of helping to make low-dose melatonin almost unavailable.

What then, should physicians tell aging patients who wish to use melatonin to decrease or at least shorten nocturnal awakenings, but are unable to find low-dose preparations? I advise such people to purchase 1.0 mg pills, and take half of one nightly, at bedtime, and the other half, if needed, if they find themselves awake at 3 or 4 am. If after a week of treatment this dosage regimen has not helped, I suggest they try taking the entire 1.0 mg at bedtime, as the EFSA now recommends. ■

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