

## Use of Melatonin to Promote Sleep in Older People

Richard J Wurtman

*Cecil H Green Distinguished Professor Emeritus, Department of Brain and Cognitive Sciences,  
Massachusetts Institute of Technology, Cambridge, Massachusetts, US*

### 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 ageing. 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 ageing 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; hypoprolactinaemia; morning grogginess) and ultimately desensitising melatonin receptors in the brain. The reasons why 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, ageing, sleep, nocturnal awakenings, sleep latency, melatonin receptors, gamma-aminobutyric acid (GABA) receptors, hypothermia, hyperprolactinaemia

**Disclosure:** Richard J Wurtman is a member of staff at the Massachusetts Institute of Technology (MIT). MIT holds patents on the use of melatonin to promote and sustain sleep. Dr Wurtman receives royalties from these patents, all of which are donated back to the MIT. All of the research in Dr Wurtman's laboratory described in this article has been supported exclusively by the US National Institutes of Health.

**Received:** 8 May 2012 **Accepted:** 22 May 2012 **Citation:** *European Neurological Review*, 2012;7(2):90–1 DOI:10.17925/ENR.2012.07.02.90

**Correspondence:** Richard J Wurtman, Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, 77 Mass Ave, Bldg 46-5009, Cambridge, MA 02139, US. E: dick@mit.edu

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.<sup>1</sup> It concluded that the evidence from all three of the statistically valid published meta-analyses<sup>2,3,4</sup> 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..."<sup>1</sup> 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 colour of amphibians, and shown in 1963 to be a hormone<sup>5</sup> which the pineal gland synthesises when mammals are exposed to darkness.<sup>5</sup> In 1975, our laboratory reported that blood melatonin levels in humans also are about tenfold higher during the hours of darkness than in daytime.<sup>6</sup> 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.<sup>7</sup>

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,<sup>5</sup> 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.<sup>5,8</sup> In 1982, it had been demonstrated that nocturnal plasma melatonin levels in most humans decline with ageing<sup>9</sup> – 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,<sup>8</sup> 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 asleep<sup>8</sup> 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 physiological sleep-promoting doses, for example,

hypothermia;<sup>7,8</sup> hyperprolactinemia; and 'morning grogginess'.<sup>5</sup> Moreover, the markedly-elevated melatonin levels can also desensitise the brain receptors on which melatonin must act to promote sleep,<sup>10</sup> 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 physiological 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 over-the-counter 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 synthesise 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 ageing 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. ■

1. European Food Safety Authority, Scientific Opinion on the substantiation of a health claim related to melatonin and reduction of sleep onset latency (ID 1698, 1790, 4080) pursuant to Article 13(1) of Regulation (EC) No 1924/2006, *EFSA Journal*, 2011;9(6):2241.
2. Buscemi N, Vandermeer B, Pandaya R, et al., *Melatonin for Treatment of Sleep Disorders. Summary, Evidence Report/Technology Assessment No. 108* (Prepared by the University of Alberta Evidence-based Practice Center under Contract No. 290-02-0023) AHRQ Publication No. 05-E002-1, Agency for Healthcare Research and Quality, Rockville, 2004. Available at: [www.ahrq.gov/downloads/pub/evidence/pdf/melatonin/melatonin.pdf](http://www.ahrq.gov/downloads/pub/evidence/pdf/melatonin/melatonin.pdf) (accessed 15 May 2012).
3. Buscemi N, Vandermeer B, Hooten N, et al., The efficacy and safety of exogenous melatonin for primary sleep disorders: a meta-analysis, *J Gen Int Med*, 2005;20:1151–8.
4. Brzezinski A, Vangel MG, Wurtman RJ, et al., Effects of exogenous melatonin on sleep: a meta-analysis, *Sleep Med Rev*, 2005;9:41–50.
5. Wurtman RJ, Melatonin. In: Coates P, Blackman M, Cragg G, et al. (eds), *Encyclopedia of Dietary Supplements*, Marcel Dekker, Inc, 2005;457–66.
6. Lynch HJ, Wurtman RJ, Moskowitz MA, et al., Daily rhythm in human urinary melatonin, *Science*, 1975;187:169–71.
7. Dollins AB, Zhdanova IV, Wurtman RJ, et al., Effect of inducing nocturnal serum melatonin concentrations in daytime on sleep, mood, body temperature, and performance, *Proc Natl Acad Sci*, 1994;91:1824–8.
8. Zhdanova IV, Wurtman RJ, Regan MM, et al., Melatonin treatment for age-related insomnia, *J Clin Endocrinol Metab*, 2001;86(10):4727–30.
9. Iguchi H, Kato KL, Ibayashi H, Age-dependent reduction in serum melatonin concentrations in healthy human subjects, *J Clin Endocrinol Metab*, 1982;55:27–9.
10. Gerdin MJ, Masana MI, Rivera-Bermudez MA, Melatonin desensitizes endogenous MT2 melatonin receptors in the rat suprachiasmatic nucleus: relevance for defining the periods of sensitivity of the mammalian circadian clock to melatonin, *FASEB J*, 2004;18:1646–56.