

## Low Doses of Melatonin Promote Sleep Onset and Maintenance in Older People—An Update

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### Abstract

Plasma melatonin levels in young adults are about 10-fold higher during the night than during daylight hours, and these high levels promote both the onset of sleep at bedtime and the speedy resumption of sleep after premature nocturnal awakenings. With aging, melatonin's nocturnal secretion from the pineal gland declines, as do plasma melatonin levels, total sleep time, and sleep efficiency. A very small dose (0.3 mg) of melatonin is usually sufficient to restore nighttime plasma melatonin levels to those characteristic of young people, and to accelerate the resumption of sleep after premature awakenings. The much larger doses that are marketed can produce side effects that are not observed when the melatonin in the plasma derives solely from its secretion by the pineal. Very high doses may also desensitize melatonin's receptors in the brain, subsequently diminishing melatonin's efficacy in promoting sleep. This article updates an earlier summary (Richard J Wurtman, Use of melatonin to promote sleep in older people, *US Neurology*, 2012;8(1):10–1) of melatonin's utility in promoting sleep among older people.

### Keywords

Melatonin, sleep, insomnia, desensitization, melatonin receptors, FDA

**Disclosure:** Richard J Wurtman has been a short-term consultant to several companies that required advice as to the correct melatonin dose to put in their products: Dreamerz, Healthy Directions, and Nature's Bounty, but no longer has formal relations with any of them. Similarly, Massachusetts Institute of Technology (MIT) formerly owned US patents on his discoveries relating melatonin dose to sleep; however, these patents have all expired. All of his melatonin research has been fully and exclusively supported by the US National Institutes of Health.

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Many older people purchase the hormone melatonin and consume it orally, each evening, to promote the onset of sleep at bedtime and, particularly, the resumption of sleep after premature nocturnal awakenings. This need for exogenous melatonin to supplement that secreted from the aging pineal arises from the gland's progressive, age-related calcification, which decreases the number of active pineal cells, causing parallel reductions in melatonin's synthesis and secretion.<sup>1–3</sup> In younger people, plasma melatonin levels generally are about 8–10 pcg/ml during the daytime hours when little melatonin is secreted, quickly rise to 100–200 pcg/ml with the onset of darkness, and remain at around that level until daybreak. With aging, plasma melatonin levels may be slightly lower during the daylight hours, however, nighttime levels are markedly reduced, usually rising only to 20–50 pcg/ml.<sup>4</sup> A single bedtime dose of 0.2–0.5 mg of melatonin will restore nighttime levels to those of younger people for several hours;<sup>4,5</sup> however, this dosage is not stocked in most pharmacies, so patients usually have little choice but to take the much higher doses (e.g. 3–10 mg) that are available. As discussed below, the very high doses may actually exacerbate insomnia in some people, by desensitizing the melatonin receptors on the brain neurons that mediate the hormone's sleep-promoting effects. Moreover such doses may

also produce side effects (hypothermia,<sup>4</sup> hyperprolactinemia,<sup>6</sup> morning grogginess<sup>5</sup>), which rarely, if ever, occur with endogenous melatonin secretion. Even with access to low melatonin dosages, it is still difficult, using melatonin supplements, for older people to reproduce the normal 'square-wave' pattern of plasma melatonin levels observed in younger people, i.e. the sudden, 10-fold-or-greater rise around 9–11 PM and the similar fall around daybreak. Doses that are high enough to produce satisfactory elevations in nocturnal plasma levels throughout the night usually cause plasma levels initially to peak well beyond their normal range, thus risking desensitization of the melatonin receptors. Some possible strategies for obviating this problem were described previously (Richard J Wurtman, use of melatonin to promote sleep in older people, *US Neurology*, 2012;8(1):10–1) and additional ones are discussed below.

### Regulatory Considerations in the Availability of Oral Melatonin

Although 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, as would be obligatory for hypnotic drugs or for other hormones, such as estrogens or thyroxine.

This is because, from a regulatory standpoint, orally-administered melatonin is classified not as a drug or hormone but as a ‘dietary supplement’—even though no food has been compellingly shown to contain more than trace amounts of authentic melatonin, nor has consumption of any food been shown by gas-chromatography-mass-spectroscopy to elevate plasma melatonin levels. And, 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 effects on normal people, and do not promote the supplements 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).

Recently the first official regulatory body—the European Food Safety Authority (EFSA)—evaluated the available evidence that melatonin can reduce the time it takes for normal sleepers and patients with insomnia to fall asleep.<sup>7</sup> It concluded that the evidence from all three of the statistically valid meta-analyses that have been published<sup>8–10</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>7</sup> (Individual publications demonstrated that a lower dose—0.3–0.5 mg—was as effective as 1.0 mg, however, too few such articles existed to enable a meta-analysis<sup>10</sup>). This recommendation can also help American physicians in dealing with patients’ questions about melatonin’s safety, and about which of the doses currently marketed is best for them. However, as described below, most Americans have little or no access to the low doses of melatonin recommended in the EFSA report and the meta-analyses because, due to absent FDA regulation, most stores stock melatonin only in doses as much as three to 30 times greater.

### Melatonin, Melatonin Receptors, and Sleep

Melatonin, a derivative of the circulating amino acid tryptophan, was discovered by Aaron Lerner in 1958, based on its ability to lighten the skin color of amphibians, *in vitro*. We then showed, in 1963, that melatonin functions as a hormone in mammals,<sup>1</sup> which the pineal gland produces and secretes when the animals are exposed to darkness.<sup>1,11</sup> In 1975 our laboratory further showed that blood melatonin levels in humans are also about tenfold higher during the hours of darkness than in daytime.<sup>11</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 *i.v.*); 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.<sup>5</sup> Peak effects were observed after surprisingly low doses (0.3–1.0 mg), which elevated plasma melatonin to the same levels (100–200 pcg/ml) as those normally occurring in young people at nighttime.<sup>5</sup>

Melatonin has two well-established physiologic effects in humans—promotion of sleep and entrainment of circadian rhythms. Both are mediated by its activation of two specific melatonin receptors, known as MT1 and MT2, on the surface of brain neurons that are concentrated within the suprachiasmatic nucleus, (which is also known to control sleep and circadian rhythms). The melatonin receptors differ from those for the neurotransmitter gamma-aminobutyric acid (GABA) 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 REM sleep nor, in general, affect the distribution of sleep stages.<sup>14</sup> Exposure to melatonin can cause the prolonged desensitization of both of its receptors: MT1 receptors require supraphysiologic melatonin concentrations to become internalized<sup>12,13</sup>—and thus unresponsive—but the MT2 receptor transiently becomes desensitized even after exposure to the melatonin concentrations occurring normally at nighttime.<sup>14</sup> It can be speculated that MT2 receptor desensitization provides a feedback mechanism that limits the neural effects of nighttime melatonin concentrations, and that too-high doses of supplemental melatonin will desensitize both MT1 and MT2 receptors, thereby paralyzing any contribution of the melatonin system to sleep until normal receptor sensitivity has been restored.<sup>13,15</sup>

### Melatonin and the Insomnia Associated with Aging

In 1982 it had been demonstrated that nocturnal plasma melatonin levels in most humans decline with aging<sup>2</sup>—a probable consequence of the still-unexplained tendency of the human pineal to calcify. Since this decline was known to coincide with a common age-related sleep problem, *i.e.* frequent nocturnal awakenings followed by difficulty in falling back asleep,<sup>4</sup> we investigated whether giving older people melatonin at bedtime, as a ‘hormone replacement therapy’ (*i.e.* 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, which raise plasma melatonin levels to the range that normally occurs nocturnally in young people) was found to help the patients to remain asleep or readily fall back asleep<sup>4</sup> throughout most of the night.

These observations, which have been widely confirmed, led to oral melatonin’s widespread use for promoting and sustaining sleep, particularly among older people. However, for the most part, patients have not been able to use the lowest fully effective doses, because only substantially higher doses have been commercially available to them. Such doses, which raise plasma melatonin to levels many times higher than those in younger people, produce side effects not observed at the lower, more physiologic sleep-promoting doses, for example, hypothermia,<sup>14</sup> hyperprolactinemia,<sup>6</sup> and morning grogginess.<sup>5</sup> As described above, the markedly elevated melatonin levels also can desensitize the MT1 and MT2 receptors in brain on which melatonin acts<sup>12–14</sup> *e.g.* to promote sleep, quite possibly causing some users to become refractory to the beneficial effects of the melatonin they take<sup>4</sup> or their own pineal glands secrete.

### Using Available Melatonin Preparations to Treat the Insomnia of Aging

We may wonder why it is that physiologic doses of melatonin—which elevate its plasma levels within their normal range in younger people—

remain generally unavailable, while very much larger, pharmacologic doses are ubiquitous in health-food stores and over-the-counter sections of pharmacies. Probably for several reasons, foremost of which is that the FDA does not set allowable replacement-doses of the hormone for the older people with insomnia who are deficient in it. But also because users may believe that if taking some of a drug or hormone 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 fails to produce signs of overt toxicity even at megadoses. Or perhaps because the decrease in melatonin-receptor-sensitivity that very large doses produce<sup>12–14</sup> ultimately protects patients from consequences of their continued administration. Another factor may involve melatonin's patent status: When the Massachusetts Institute of Technology first patented melatonin's use to promote sleep it was assumed that the hormone would be regulated as a drug, and the FDA would not allow doses greater than maximally effective ones (0.3–1.0 mg) to be marketed. In that circumstance it would not have appeared necessary to patent larger doses. Consequently, neither FDA regulations nor university-held patents constrained purveyors of melatonin from selling whatever dose above 1 mg that they might desire. In any event, the patents on melatonin-for-sleep have now expired, so the hormone's patent status should no longer be a factor diminishing the availability of low-dose preparations.

How, then, should health professionals advise patients who wish to use

melatonin to decrease or at least shorten nocturnal awakenings, but are unable to find low-dose preparations? Such people might consider purchasing 1.0 mg pills, and taking half of one nightly, at bedtime, and the other half, if needed, if they find themselves awake at 3 or 4 AM. Or they might try one of the sustained-release melatonin preparations generally available, which purportedly provide a high enough total dose (e.g. 1.0 or 2.0 mg<sup>16,17</sup>) to elevate plasma melatonin for most of the night, but probably not so much as would produce desensitizing peak levels. Or one of the new melatonin preparations, available on the internet, that provides within a single capsule both a melatonin solution containing an immediately available 0.3 mg, and a resin that slowly releases an additional 0.3–0.6 mg later in the night.

Few data are available on the plasma melatonin curves produced by such preparations, nor about how well these plasma curves correlate with sleep efficiency and sleep time. It should be noted that the bioavailability and pharmacokinetics of oral melatonin differ slightly between younger (29.5 years) and older adults (60 years).<sup>18</sup> As discussed above, young subjects exhibit significantly higher peak endogenous serum melatonin levels than older subjects, with greater inter-individual variability; however, older subjects exhibit higher and somewhat more variable serum levels after a 0.3 mg oral dose than younger ones. Hence, some older subjects might, for long-term daily use, actually require doses even lower than 0.3 mg.<sup>18</sup> ■

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