



Physiology and clinical use of melatonin

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INTRODUCTION — Melatonin, like thyroxine or insulin, is a hormone, produced in the pineal gland from the amino acid tryptophan, and secreted into the blood and cerebrospinal fluid. It conveys signals to distant organs, principally the brain, and affects the synthesis of second messengers and, ultimately, sleep and circadian rhythms. However unlike most other hormones, melatonin's use is not regulated ~~as a drug~~ in many countries. (See '[Regulatory issues](#)' below.)

This topic review will discuss melatonin's history; current knowledge of its synthesis and metabolism; the physiologic regulation of plasma melatonin concentrations; the known effects of endogenous and exogenous (oral) melatonin in humans; and the melatonin analogs currently approved for use.

HISTORY — The human pineal gland is an important structure that transmits signals to the brain and other organs by secreting its unique hormone, melatonin. However this concept is only a few decades old. For most of the twentieth century, the pineal was generally dismissed as a "vestige," a "third eye" in certain lower vertebrates, the cells of which, in humans, died and became calcified early in life. Tumors of the pineal gland were known sometimes to be associated with a reproductive disorder, precocious puberty, especially in boys, and some scientists attributed this phenomenon to the destruction of functioning pineal tissue. However the majority concluded that the accelerated sexual maturation was simply a nonspecific consequence of increased intracranial pressure.

In 1917, the modern history of the pineal gland began with the discovery that cow pineals contained a compound that could lighten the skin of frogs [1]. The physiological significance of this relationship seemed obscure, as bovine pineal extracts had no effect on pigmentation in bovines (nor humans), and frog pineals lacked detectable skin-lightening ability. However the finding did indicate that the pineal contained a compound with at least some biological activity, and it provided a way for identifying the active compound, using assays based on the ability of sequentially-purified pineal extracts to aggregate the melanin granules in the frog's pigment cells. In 1958, one study identified that compound's chemical structure as 5-methoxy-N-acetyltryptamine and named it melatonin [2].

In the prior decade, scientists had made four seemingly-unrelated discoveries that became coherent, once melatonin was identified and could be tested. These included:

- The demonstration that surgical removal of the rat's pineal accelerated the growth of the ovaries, while administration of bovine pineal extracts had the opposite effect [3]
- The observation that housing rats in a continuously-lit environment decreased the weights of their pineals [4]
- The discovery that, though the pineal gland originates embryologically as part of the brain, it loses most or all of its CNS connections by birth, and instead receives its innervation from peripheral sympathetic nerves [5]
- The demonstration that pinealectomy, or prolonged light exposure, or both procedures, accelerate the growth of the ovaries to an equal extent, and that

the effects of the two treatments are blocked by giving the animals pineal extracts [6].

Between 1963 and 1964, it was shown that melatonin was a hormone in rats; that it was the gonad-inhibiting substance previously described in pineal extracts; and that its synthesis in the pineal gland was suppressed when rats were exposed continuously to light, the light acting not directly, as on a "third eye," but indirectly, via the animal's eyes and sympathetic nerves [7-9]. The chemical that mediates the sympathetic nervous signals was subsequently shown to be norepinephrine, which stimulates beta-receptors and thereby increases pineal production of cyclic-AMP [10-12]. The rates at which the rats' pineal synthesizes serotonin and melatonin were soon shown to vary with circadian rhythms, and the melatonin rhythm was ultimately found to be generated by intrinsic circadian signals emanating from the suprachiasmatic nucleus of the brain, which were controlled primarily by the light dark-cycle [13-15].

Finally, in 1975, it was discovered that melatonin production in humans, like that in all other mammals studied, exhibits a pronounced circadian rhythm such that nocturnal plasma melatonin concentrations are at least 10-fold higher than daytime concentrations [16]. Moreover, this rhythm is truly circadian, and not simply a response to the environmental light-dark cycle. This was illustrated in a study of subjects who underwent a 12-hour phase shift in the light/dark cycle (dark between 11 am and 7 pm instead of the customary 11 pm to 7 am); five to seven days were needed for their melatonin rhythms to re-entrain [17].

The view thus became canonized that the pineal is a "neuroendocrine transducer" which tells all mammals when it is dark outside by raising their plasma melatonin concentrations [18]. The uses to which the body puts this information vary considerably among species. In diurnal, but not nocturnal animals, melatonin promotes sleep onset and maintenance. In animals that breed seasonally, melatonin influences the choice of breeding season (ie, Spring or Fall). In humans, although there is evidence that endogenous melatonin may have an effect on puberty [19], no reproductive effects of exogenous melatonin have been clearly demonstrated [20].

Much subsequent pineal research has concerned the human brain's responses to melatonin rhythms. The most compelling evidence now available supports two roles for melatonin in humans: the involvement of nocturnal melatonin secretion in initiating and maintaining sleep, and control by the day/night melatonin rhythm of the timing of other 24-hour rhythms. (See '[Circadian rhythm](#)' below.)

Melatonin's effect on sleep underlies most of its current use as a drug and the development of melatonin analogs as new drugs [21,22]. Some additional possible benefits of melatonin supplementation or melatonin analogs have been proposed (eg, as an antioxidant, or to slow aging, or to suppress cancer growth or to treat depression). However compelling evidence to support these effects is limited.

Evidence is even more limited for labeling melatonin as a "dietary supplement" (which is what it is considered to be by the United States Food and Drug Administration). For melatonin to earn this appellation, it would have to be shown that at least some of the melatonin molecules in human plasma derive from food sources, and that "supplementary" exogenous melatonin simply adds to what the foods provide. But there is no satisfactory evidence, based on contemporary analytic techniques that any available foods contain more than trace amounts of melatonin,

and no evidence at all that eating any food elevates human plasma melatonin concentrations. Despite its lack of overt toxicity, melatonin is a **hormone**, and should be labeled and regulated as such.

Regulatory issues — ~~Although melatonin is a hormone, and its safety has not been definitively established, m~~Melatonin products are regulated differently in many countries [23]:

- In the United States, melatonin falls under the Food and Drug Administration's Dietary Health and Education Act as a "dietary supplement". It can be purchased in any dosage without a prescription.
- ~~In the European Union, melatonin is considered a medicine or hormone and is available only by prescription. In the European Union, melatonin has very recently been evaluated by an official regulatory agency, the European Food Safety Authority (EFSA) for use in reducing sleep latency, the time it takes for normal sleepers or people with insomnia to fall asleep (at bedtime or after a nocturnal awakening)[103]. Based on the evidence provided in all three of the statistically-valid published meta-analyses [61;104-105], the agency concluded that there exists "...a cause and effect relationship between the consumption of melatonin and a reduction of sleep onset latency..." and that up to "...1 mg of melatonin should be consumed close to bedtime." [103]~~
- In Canada, melatonin is included in the Natural Health Products Directorate of Health Canada, and is available for sale, once preparations meet the licensing, manufacturing, labeling, and safety standards.
- In Australia, melatonin is an unregistered product under the Therapeutic Goods administration. With a prescription, it can be imported for use under the Personal Import Scheme.

Of note is that in situations where the sale of melatonin is not regulated, ~~as a drug,~~ enormous doses can be sold, and preparations may contain additives that have their own pharmacological actions and potential side effects. Occasional claims to the contrary notwithstanding, apparently all of the melatonin sold in the United States is of synthetic origin.

MELATONIN SYNTHESIS AND METABOLISM

Synthesis — Almost all of the melatonin formed in mammals is synthesized within the pineal gland from the essential amino acid tryptophan ([figure 1](#)) [10]. Small amounts of melatonin have also been found in the retina, Harderian gland, and enterochromaffin cells of the gut, however there is little evidence that extrapineal sources contribute significantly to human plasma melatonin concentrations. Since the pineal lies outside the blood brain barrier, tryptophan's uptake by the pineal, in contrast to its uptake into the brain, is not subject to competition from other circulating neutral amino acids, and thus is unaffected by diet composition. The tryptophan is first 5-hydroxylated (by the enzyme tryptophan hydroxylase) and then

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decarboxylated (by the enzyme aromatic L-amino acid decarboxylase) to form 5-hydroxytryptamine, or serotonin ([figure 1](#)) [[10](#)].

During daylight hours, the serotonin in pinealocytes tends to be stored, and unavailable to enzymes (monoamine oxidase and the melatonin-forming enzymes) that would otherwise act on it. With the onset of darkness, postganglionic sympathetic outflow to the pineal increases and the consequent release of norepinephrine onto pinealocytes causes stored serotonin to become accessible for intracellular metabolism. At the same time the norepinephrine activates the enzymes, especially serotonin-N-acetyltransferase (SNAT) [[24](#)], but also hydroxyindole-O-methyltransferase (HIOMT) [[8,25](#)], that convert serotonin to melatonin. Consequently, pineal melatonin levels rise many-fold [[14](#)]. Pineal levels of the corresponding deaminated and O-methylated metabolite of serotonin, 5-methoxytryptophol, also rise [[26](#)], even though formation of this compound is independent of SNAT. This suggests that the daily rhythm in pineal SNAT activity is not the cause of the rhythm in melatonin synthesis, as has sometimes been proposed.

The melatonin then diffuses out of the pineal gland and into the blood stream and cerebrospinal fluid [[27](#)], rapidly raising its plasma concentrations from about 2 to 10 pg/ml to 100 to 200 pg/ml [[16](#)]. Melatonin is highly lipid-soluble, because both of the ionizable groups in serotonin, the hydroxyl and the amine, have been blocked by its O-methylation and N-acetylation. Thus it diffuses freely across cell membranes, including those of the blood-brain-barrier [[28](#)], and travels in the blood largely bound to albumin [[29](#)].

Metabolism — Most of the melatonin in the circulation is inactivated in the liver, where it is first oxidized to 6-OH-melatonin by a P450-dependent microsomal oxidase and then largely conjugated to sulfate or glucuronide before being excreted into the urine or feces [[30](#)]. About 2 to 3 percent of the circulating melatonin is excreted unchanged into the urine or the saliva, enabling measurements of urinary or salivary melatonin to be used as rough estimates of plasma melatonin concentrations. Salivary melatonin levels apparently correspond to those of the 25 to 30 percent of blood melatonin that is not bound to albumin.

Melatonin receptors — Studies using radioactively-labeled melatonin have identified three probable melatonin receptors, two of which have been cloned using human sources [[31](#)]. These macromolecules are concentrated, respectively, within the suprachiasmatic nucleus of the hypothalamus, the pars tuberalis of the pituitary, and cardiac blood vessels (MT1); the retina and hippocampus (MT2); and in kidney, brain, and various peripheral organs (MT3). Their affinities for melatonin are enhanced in the presence of several G-proteins.

Activation of the MT1 and MT2 receptors by melatonin suppresses cAMP production, but can also stimulate phospholipase C and various ion channels. The MT2 receptor also mediates melatonin's ability to inhibit hippocampal long-term potentiation in brain slices [[32](#)]. The MT3 site shares 95 percent homology with a detoxifying enzyme, quinone reductase 2; its effects on specific signal transduction pathways await identification. Because of melatonin's unusual lipid-solubility, its receptors could be located intracellularly, in contrast to the plasma membrane receptors characteristic of neurotransmitters; indeed, a nuclear binding site has been

identified. The MT1 receptors in the SCN allow melatonin to inhibit the firing of SCN neurons during the nighttime, an action that might contribute to melatonin's sleep-promoting effects. The SCN's MT2 receptors apparently mediate melatonin's effects on the SCN's own circadian rhythms.

Melatonin's MT1 and MT2 receptors are highly susceptible to "desensitization," their activity decreasing markedly after exposure to supranormal concentrations of the hormone [33,34]. This bears on the prolonged use of high melatonin doses to promote sleep, particularly in older people with difficulty remaining asleep during the night who might inadvertently purchase excessively large doses of the hormone.

Circadian rhythm — In all mammals examined thus far, melatonin secretion manifests a similar circadian rhythm, with plasma and urine concentrations low during daylight, ascending after the onset of darkness, peaking in the middle of the night between 11 pm and 3 am, and then falling sharply before the time of light onset [16]. It should be noted that high nocturnal plasma melatonin concentrations are characteristic of both diurnally-active species (like humans), in which the high levels promote sleep onset and maintenance, and nocturnally-active ones (like rats), in which melatonin has no obvious relationship to sleep.

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While this rhythm normally is tightly entrained to the environmental light cycle, it does persist when people are placed for a few days in a dark room [35], and, as described above, does not immediately phase-shift when the light schedule is altered [17], indicating that it is not simply generated by the light-dark cycle but also by cyclic endogenous signals, probably arising in the SCN. Signals originating in the retina or the SCN reach the pineal via a retinohypothalamic tract, the superior cervical ganglia, and postganglionic sympathetic fibers that re-enter the cranial cavity [9,36].

In certain fish, birds, and reptiles, pineal glands also contain true photoreceptors, and denervated (or even cultured) glands can sustain circadian rhythms in melatonin synthesis which can be entrained by the light-dark cycle. In contrast, light has no known direct effects on pineal melatonin synthesis in humans and other mammals.

PLASMA MELATONIN CONCENTRATIONS — Plasma melatonin concentration reflects:

- The amount secreted by the pineal gland (and, conceivably, the other organs described above)
- The influx of melatonin into tissues when its plasma concentrations are high and efflux from them when plasma concentrations are low
- Its destruction in the liver
- Its secretion into such body fluids as urine and saliva

Usually, the principal factor affecting plasma melatonin concentration is its rate of secretion, which varies with the circadian rhythm and with age (see '[Circadian rhythm](#)' above and '[Age](#)' below).

Effect of diet — Now, at a time when melatonin is also generally available as a dietary supplement, plasma concentrations can also reflect consumption of the exogenous compound. Available evidence does not support the view that humans derive any of their plasma melatonin from foods. Several laboratories have described a compound in dietary fruits or vegetables (eg, tomato [37-39]) that they concluded was melatonin. But in only one of these studies was the identity of the melatonin unambiguously confirmed by gas chromatography-mass spectrometry, and in that study, the melatonin concentrations were very low (<20 ng/kg of fruit), and were thought to represent contamination [39]. Of perhaps greater relevance, it has never been reported that feeding any amount of any food to humans can raise plasma melatonin concentrations.

Age — Melatonin secretion by the human pineal varies markedly with age. Melatonin secretion starts during the third or fourth months of life, coincident with the consolidation of sleeping at nighttime [40]. It then increases rapidly, causing nocturnal melatonin concentrations to peak at ages 1 to 3 years, then decline slightly to a plateau that persists throughout early adulthood (figure 2).

Nocturnal melatonin secretion then starts a marked, continuing decline in most people, with peak nocturnal concentrations in 70-year-olds being only a quarter or less of what they are in young adults (figure 2) [19,41]. This decline may reflect the progressive, age-related calcification of the pineal gland and its resulting loss of secretory tissue. Obviously, one strategy in using supplemental melatonin is to administer it to older people in doses just sufficient to compensate for this age-related decline.

Effects of drugs — Nocturnal melatonin concentrations can also be affected by drugs that interfere with the transmission of neurotransmitter signals to pineal cells (like propranolol, a beta-blocking agent [42]), or those that inhibit melatonin's metabolism (like 8-methoxypsoralen [43]), and by a few drugs that lack clear links to melatonin's synthesis or metabolism (eg, caffeine [44], ethanol [45,46]).

Nocturnal melatonin secretion is also suppressed by exposure to environmental lighting, even by a relatively dim 100 to 200 lux when pupils are dilated [35,47,48].

High dose melatonin — The first person to examine the physiological or behavioral effects of exogenous melatonin was the person who discovered it, Aaron Lerner, who reported giving himself 200 mg intravenously per day for five consecutive days [49]. He described feeling "relaxed." Neither Lerner nor the investigators who subsequently gave it (in doses of 10 mg to 6.6 g) to 96 other subjects prior to 1977 measured its effects on plasma melatonin concentrations [49]. However since most gave doses in excess of 1 g, it can be assumed that the increases in plasma melatonin were massive. When one trial administered 80 mg doses to two male volunteers in 1987, plasma concentrations increased by more than 1000-fold, and serum prolactin levels rose significantly [50], an effect not observed with more physiologic melatonin doses.

In 1993, one study examined the effects of 10, 20, 40, or 80 mg melatonin on various behavioral indices (auditory vigilance; self-reported fatigue, confusion, and sleepiness; reaction times), body temperature, and plasma melatonin

concentrations. All of the doses tested produced similar and significant changes in the behavioral assays; ~~a reduction in reduced~~ body temperature; ~~and a~~ raised plasma melatonin concentrations to at least 5000 pg/ml, well beyond the normal nocturnal range of 100 to 200 pg/ml [51].

Physiologic dose melatonin — The study described above [51], was repeated using much lower doses (0.1 to 10 mg orally) [52]. They found that oral doses as low as 0.1 to 0.3 mg caused dose-related decreases in sleep latency and increases in sleep duration and self-reported sleepiness and fatigue, but without reducing body temperature or elevating plasma melatonin concentrations beyond their normal nocturnal range (figure 3) [52]. This suggested that nocturnal melatonin secretion, which produces plasma melatonin concentrations similar to those seen after the 0.3 mg dose, does have a physiologic effect on sleep. It also identified the dosage range that clinicians and investigators need to use if they want to examine melatonin's physiologic effects.

Melatonin bioavailability — There is considerable person-to-person variability in the bioavailability of melatonin. In one study using single 80 mg doses, there were 25-fold variations in AUCs (areas under the curve) for the five subjects studied [53]. In another, using 0.5 mg oral doses, peak plasma melatonin concentrations among the four subjects varied from 480 to 9200 ng/L [54]. Melatonin's bioavailability was relatively poor, 10 to 56 percent, which the authors attributed to person-to-person differences in first-pass hepatic extraction. Perhaps reflecting such differences in hepatic function, older subjects in another study given a 0.3 mg oral dose of melatonin were found to exhibit considerably greater increments in plasma melatonin concentrations, with correspondingly greater variability, than young adults receiving that dose [55].

These findings all suggest that while a 0.3 mg dose given to young subjects during the daytime, or to older insomniacs at night, can, on average, produce normal nocturnal plasma melatonin concentrations, some individuals may need slightly more, or significantly less melatonin to attain this effect.

The pharmacokinetic properties of any oral dosage of melatonin can also vary widely based upon the lipid-solubility of the inert ingredients that accompany it. A preparation containing corn oil plus 0.05 mg melatonin elevated plasma melatonin concentrations to as high a peak (from 4 to 118 pg/ml) [56], though for a shorter period, as one containing 0.3 mg melatonin plus microcrystalline cellulose (15 to 105 pg/ml) [52].

CLINICAL EFFECTS OF EXOGENOUS MELATONIN — Because melatonin is available as a dietary supplement and is relatively nontoxic, physicians, researchers, and even consumers are able to administer or consume doses that elevate its plasma concentrations to hundreds or even thousands of times those that occur normally [50,57]. Even the 1 to 10 mg doses most commonly marketed raise plasma concentrations to 3 to 60 times their normal peak values [52].

Not surprisingly, such supraphysiologic concentrations of melatonin produce numerous biological effects, including daytime sleepiness; impaired mental and physical performance [58]; hypothermia [56]; and hyperprolactinemia [50]. However, the demonstration that pharmacologic doses of melatonin produce a given

biological effect in no way implies that this effect also occurs normally, at nighttime plasma melatonin concentrations, nor that the age-related decline in plasma melatonin concentrations results in opposite effects. As an example, melatonin concentrations hundreds or thousands times normal can inhibit the aggregation of A-beta peptides to form amyloid in vitro [59]. However, the normal nocturnal rise in plasma melatonin has no demonstrable effects on APP metabolism, and there is no evidence whatsoever that the age-related decline in plasma melatonin is an independent risk factor for Alzheimer disease.

Exogenous melatonin administration appears to have two effects like those occurring physiologically with nocturnal melatonin secretion; the promotion of sleep onset and maintenance [52,60-77,104-105], and the phase-shifting of circadian rhythms, including the rhythm in melatonin itself [78]. Both have been shown to be produced by physiologic doses (ie, 0.1 to 0.3 mg for sleep and 0.3 to 0.5 mg for phase-shifting, doses which raise daytime plasma melatonin levels into the normal nocturnal range observed in young adults).

Sleep — Melatonin can directly affect parameters of sleep itself, decreasing sleep latency, increasing sleep efficiency, and increasing total sleep time. The hormone can also affect sleep indirectly, acting via the mechanisms that control circadian rhythms to change the phasing of the sleep rhythm.

A 1997 review of melatonin and sleep included 24 studies, almost all of which described sedation, fatigue, decreased alertness, increased reaction time, shortened sleep latency (ie, number of minutes needed to fall asleep), increased sleep efficiency (ie, percent of the total sleep period actually spent sleeping), and/or increased total sleep time.

A meta-analysis published in 2005 included 17 studies involving 284 subjects [61]. In this meta-analysis, melatonin administration was found to cause:

- A significant decrease in sleep latency (by four minutes; 95% CI 2.5-5.4).
- A significant increase in sleep efficiency (2.2 percent, 95% CI 0.2 to 4.2)
- A significant increase in total sleep duration (12.8 minutes; 95% CI 2.9 to 22.8).

The 17 studies included in this meta-analysis were far more heterogeneous than those in meta-analyses of drugs already approved for treating specific indications at specific dosages, reflecting melatonin's anomalous status as an unregulated dietary supplement. Subjects received doses ranging from 0.1 mg to 80 mg, for one day to two months, and included those who slept normally, or suffered from insomnia caused by age-related impairments in sleep efficiency or by time-zone shifts, or was secondary to Alzheimer disease or schizophrenia. Since, as an example, age-related insomnia has little effect on sleep latency while the insomnia of "jet-lag" principally affects this parameter, it's almost surprising that significant results were obtained. Melatonin would not be expected to decrease sleep latency among older subjects, in whom latency was already normal, nor to increase sleep efficiency among time-zone-shifted younger people who had little difficulty sleeping through the night.

~~Two additional meta-analyses have confirmed that oral melatonin significantly reduces sleep latency in normal individuals and those with insomnia [104, 105].~~

Another meta-analysis ~~of melatonin's sleep-promoting effect, published more recently [79], which~~ included only studies involving patients with secondary insomnia (related to an underlying neurologic or psychiatric disease: six trials involving 97 participants) or with insomnia resulting from sleep restriction (such as jet lag and shiftwork [80]; ~~nine trials involving 427 subjects~~). It concluded that melatonin ~~was is~~ ineffective in these ~~particular~~ disorders, ~~that analysis excluded numerous relevant studies in which melatonin had been found to be effective [80], and However,~~ almost all of the studies ~~that it did cite~~d used very high melatonin doses which were probably sufficient to desensitize melatonin's receptors. Moreover, ~~the this~~ meta-analysis did demonstrate a statistically significant improvement in sleep efficiency, even though it excluded the patients (those with age-related insomnia), in whom decreased sleep efficiency most often tends to be a problem. The improvement was comparable (1.9 percent) to that produced by ramelteon (2.5 percent), a hypnotic melatonin analog studied in a homogeneous clinical trial [81].

Experimental paradigms — The effects of exogenous melatonin on sleep have been examined under three types of experimental conditions in relation to the onset or offset of endogenous melatonin secretion:

- In some studies the hormone was administered during the daily light period, such that blood melatonin concentrations would be transiently elevated, but would then return to baseline before the initiation of nocturnal melatonin secretion. Such experiments were used to demonstrate that melatonin can decrease sleep latency when given at any time in the afternoon or evening; hence this effect is independent of the hormone's action on the mechanisms that generate circadian rhythms (since no treatment can immediately shift the phase of a circadian rhythm by 8 to 10 hours) [52].
- In others, the hormone was also given during the light period, but close enough to the onset of darkness so that melatonin concentrations would still be elevated when nocturnal melatonin secretion started [70,72]. The period during which plasma melatonin concentrations were continuously elevated would thus be prolonged. Such experiments modeled the use of melatonin to decrease sleep latency and maintain continuous sleep, as an example, among shift-workers or in eastbound world travelers who had to start going to bed earlier.
- In a third paradigm, the hormone was given at the end of the light period to older insomniacs with low nighttime plasma melatonin concentrations [75]. The intent was to prolong the portion of the night during which plasma melatonin concentrations would be elevated to the same range as those of non-insomniac young adults.

In all of these situations, exogenous melatonin decreased sleep latency when it was elevated, and, when tested, increased sleep duration and sleep efficiency. A 0.3 mg dose was either as effective as, or more effective than, higher doses [70,72,75], particularly when the hormone was administered for several days. Unlike the higher doses, this low dose had no effect on body temperature, affirming that, while pharmacologic doses can cause hypothermia, melatonin's ability to promote sleep is not mediated by such a change, as had been suggested [56].

Sleep architecture — The hormone had no consistent effect on sleep architecture, neither increasing nor decreasing the portion of the sleep period during which subjects exhibited REM. Its effects were different from those usually associated with hypnotic drugs, since after melatonin, subjects could readily keep from falling asleep if they so chose, and their cognitive abilities the morning after receiving the hormone were unchanged or improved [[70,72](#)].

Insomnia — In one study using 30 subjects who were 50 years old or older with or without clinically-significant insomnia (ie, sleep efficiencies of 70 to 80 percent in the insomniacs versus 92 percent in controls), and who received each of four randomized doses of melatonin (0, 0.1, 0.3, or 3.0 mg) orally for a week, with one-week washout periods, the following results were seen [[75](#)]:

- Melatonin produced significant improvements in sleep efficiency (particularly during the middle portion of the nocturnal sleep period) ([figure 4](#)) in patients with insomnia. The 0.3 mg dose produced the greatest effect ([figure 5](#)).
- In patients with insomnia, no effects were seen in total sleep time, latency to sleep onset (not abnormal in this population), REM sleep, or percent time spent in any of the sleep stages. However, no improvement would be expected in sleep latency in these patients as their problem ~~is~~was with waking up during the night (sleep efficiency), not with falling asleep (sleep latency).
- In patients without insomnia, no effects on any sleep parameters were seen.
- Dose-related increases in plasma melatonin concentrations were observed. The 0.3 mg dose resulted in peak concentrations in the normal nocturnal young adult range.
- 10 hours after administration of the 0.1 and 0.3 mg doses, plasma melatonin concentrations were no different than those for placebo. However, in the 3 mg group, melatonin concentrations remained significantly elevated for much of the following day ([figure 6](#)). The 3 mg dose (but not the 0.1 or 0.3 mg doses) also resulted in hypothermia ([figure 7](#)).

The effects of melatonin agonists for insomnia are reviewed in detail separately. (See "[Treatment of insomnia](#)".)

Melatonin agonists — A synthetic melatonin agonist, ramelteon, thought to activate MT1 and MT2 melatonin receptors selectively, is available in the United States (as a non-scheduled drug) for the treatment of chronic insomnia, but not in the European Union, where it was denied approval. No data are available that directly compare the efficacies and toxicities of this compound with those of the much lower recommended dose (0.3 mg) of melatonin. The use of melatonin agonists for the treatment of insomnia is discussed separately. (See "[Treatment of insomnia](#)", [section on 'Melatonin agonists'](#).)

A second melatonin agonist, tasimelteon (VEC-162) [[22](#)], may be a promising option for improving sleep latency and sleep maintenance in individuals with jet-lag disorder or in those who have sleep problems due to starting work at very early hours. It

appears to reduce sleep onset latency and to reset the circadian plasma melatonin rhythm. (See "[Jet lag](#)", [section on 'Melatonin agonists'](#).)

Circadian rhythms

Phase-shifting — The ability of exogenous melatonin to synchronize and to shift the phases of various human circadian rhythms is generally accepted. In studies of healthy volunteers, 0.5 mg of pure melatonin [78], or 0.05 mg of melatonin in corn oil (which causes earlier peaks in, and the more rapid disappearance of, elevated plasma melatonin concentrations) was able to advance the onset of nocturnal melatonin secretion when administered at 5 PM, and larger doses caused greater phase advances [56]. In addition, melatonin was able to shift the core body temperature rhythm, however, a statistically significant effect was found only with doses \geq 0.5 mg. These doses increased plasma melatonin concentrations well above the upper limits of normal (>1327 pg/ml) [56].

As described above, melatonin can also control the timing of the sleep and sleepiness rhythms, an effect readily demonstrated among blind individuals with free-running melatonin and sleep rhythms [82], but also among sighted individuals [66,83]. Moreover, physiologic doses (0.3 mg) entrain a variety of otherwise free-running rhythms in blind individuals [84].

Jet lag — Melatonin's ability to phase-shift circadian rhythms underlies its common use to prevent or treat "jet lag," particularly that associated with eastbound travel [80]. The role of melatonin therapy for prevention of jet lag is discussed in detail elsewhere. (See "[Jet lag](#)", [section on 'Exogenous melatonin'](#).)

Antioxidant — It has been suggested that melatonin is a potent antioxidant [85,86], and that melatonin supplements may protect against such age-related diseases as atherosclerosis, cancer, and Alzheimer disease [59,87-91]. None of these proposed uses has been tested in a controlled clinical trial nor has any been approved for use. Most studies have not provided plasma melatonin data, and most have not compared melatonin's effects to those of known antioxidants [92,93].

It has usually been possible to demonstrate antioxidant or free radical scavenger effects of melatonin in vitro [57,85], however such studies generally have required melatonin concentrations 1000 to 100,000 times those ever occurring in vivo [57]. Similarly, while high doses of melatonin (10 to 450 mg/kg body weight parenterally) have sometimes elicited antioxidant effects in experimental animals in vivo [94], neither their long-term safety nor their effects on the animals' melatonin concentrations have been characterized. In humans, such megadoses might ultimately impair sleep or various circadian rhythms, perhaps by desensitizing melatonin receptors [33].

Only one study has described careful dose-response experiments on the ability of melatonin to protect against auto-oxidation, and has compared melatonin with known antioxidants [57]. That study examined the cell-mediated (by human macrophages) and cell-free (by copper sulfate) oxidation of low density lipoproteins (LDL), a process believed to contribute to atherosclerosis. Melatonin did exhibit weak

antioxidant activity, but only at 10,000- to 100,000-fold physiologic concentrations. In contrast, a vitamin E preparation (alpha-tocopherol) was 50- to 100-fold more potent than melatonin, and was effective at physiologic concentrations. Similarly, vitamin C (ascorbic acid) and tryptophan, melatonin's indolic circulating precursor, were significantly more potent than melatonin, and were active at physiologic concentrations. Thus, melatonin appears to have at best, very weak antioxidant activity, but only at extremely supraphysiologic concentrations.

Dementia — As noted above, plasma melatonin concentrations decline with age. In patients with dementia, melatonin levels may decline to an even greater extent than in normal aging. However, melatonin does not appear to have a beneficial effect on cognition in patients with dementia. The effect of melatonin on noncognitive symptoms such as sleep and agitation is unclear. (See "[Treatment of behavioral symptoms related to dementia](#)", section on 'Other agents'.) [One paper suggests that if demented patients are to be treated with melatonin they should also be exposed to supplemental light to block any adverse effects on mood \[106\].](#)

Other effects

Nocturnal blood pressure — While sleeping at night, the blood pressure normally falls by approximately 15 percent from daytime values. Patients in whom this reduction does not occur are considered to have nocturnal hypertension, which has been associated with an excess risk of cardiovascular disease. (See "[Ambulatory blood pressure monitoring and white coat hypertension in adults](#)", section on 'Nocturnal blood pressure and nondippers'.)

Two observations suggest the melatonin plays a role in nocturnal blood pressure regulation:

- The normal nighttime surge in serum melatonin concentration may be blunted in patients with nocturnal hypertension [95].
- Melatonin administration appears to lower blood pressure, particularly at night [96-99].

In a randomized trial, 38 men with treated hypertension and confirmed nocturnal hypertension (mean nighttime systolic BP >125 mmHg) were assigned to receive controlled-release melatonin (2 mg) or placebo two hours before bedtime for four weeks [99]. Significant reductions in nocturnal systolic and diastolic blood pressures (mean 6/3 mmHg) were observed in the melatonin, but not the placebo group. The effect on blood pressure could not be explained by a change in sleep quality.

A significant fall in nocturnal blood pressure was also noted in a smaller randomized trial in which melatonin had no effect on daytime blood pressure [98].

In summary, exogenous melatonin may have a modest effect on nocturnal blood pressure. However, we do not currently recommend its use for this indication since there are no data showing improved outcomes.

Antiaging — Some investigators suggest, based on small studies in laboratory rodents, that melatonin "maintains juvenile conditions" and is a "geroprotector" [[100,101](#)]. There is no evidence that melatonin has any "antiaging" effects in humans.

Adverse effects — Despite the fact that melatonin is an unregulated drug in many countries, and is often used in excessive doses, there does not appear to be a major pattern of side effects. One report described a search for reports of adverse effects with melatonin over 35 years [[102](#)]. In those that described adverse effects, pharmacologic doses had been used (1 to 36 mg).

In the absence of governmental regulation, companies are able to sell melatonin at dosages that are many times those needed for promoting sleep or shifting rhythms, or for restoring normal nocturnal plasma melatonin levels in older people. These dosages can elevate plasma melatonin to levels thousands of times greater than ever occur normally, and produce mild but not-benign side-effects, like hypothermia and "hangovers." Paradoxically, they also may, through receptor desensitization, exacerbate the insomnia that the consumer was trying to treat.

SUMMARY AND RECOMMENDATIONS — Melatonin is synthesized at nighttime in the human pineal gland, and released into the blood and the cerebrospinal fluid. It acts on the brains of humans and other diurnally-active mammals to promote sleep, and also influences the phasing of sleep and various other circadian rhythms. During the daytime, plasma melatonin concentrations are low; at nighttime, they rise by 10- to ~~100~~30-fold or more in young adults, but by considerably less in older people, who may have frequent nocturnal awakenings as a consequence.

Recommendations for the clinical use of exogenous melatonin are presented here:

Sleep

- For individuals with age-related insomnia (problems with sleep efficiency), we suggest melatonin therapy ([Grade 2B](#)).

For most adults, we suggest a starting dose of melatonin 0.3 mg (or 0.2 mg in patients weighing less than 120 lbs/54.5 kg) ([Grade 2C](#)). If after a week, the patient is not waking up less frequently and falling back asleep faster during the night, we usually double the dose. If the patient responds initially, but stops responding as well after a few weeks, we suggest taking a "drug holiday", followed by starting again at the same dose.

Jet lag

- Jet lag recommendations are found separately. (See "[Jet lag](#)".)

Cognitive impairment

- For patients with cognitive impairment associated with dementia, we suggest **not** using melatonin treatment ([Grade 2B](#)). (See ['Dementia'](#) above.)

Other

- Because of reports of adverse events possibly related to melatonin in patients with seizure disorders or in those taking warfarin or other oral anticoagulants, we suggest not using melatonin ([Grade 2C](#)).
- In the absence of safety and efficacy data in children, we suggest not using melatonin ([Grade 2C](#)). (See ['Jet lag'](#) above.)

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New or Modified Reference

Please fill out the area below for any new references to include in this document.

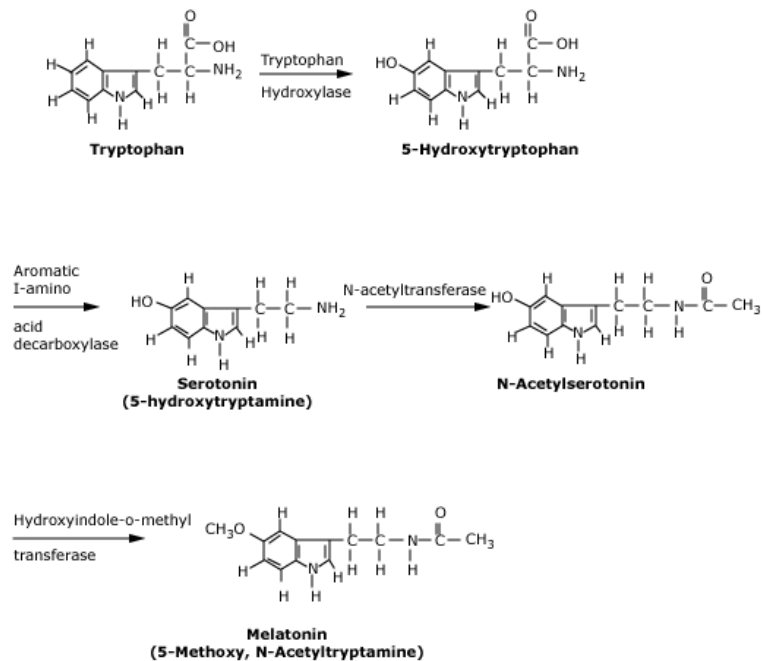
<p>103. European Food Safety Authority. Scientific Opinion of the substantiation of a health claim related to melatonin and reduction of sleep onset latency (ID 1698, 1790, 4080) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. <i>EFSA Journal</i>, 2011; 9(6):2241.</p> <p>104. Buscemi N, V, 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.</p>
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Graphics

figure 1

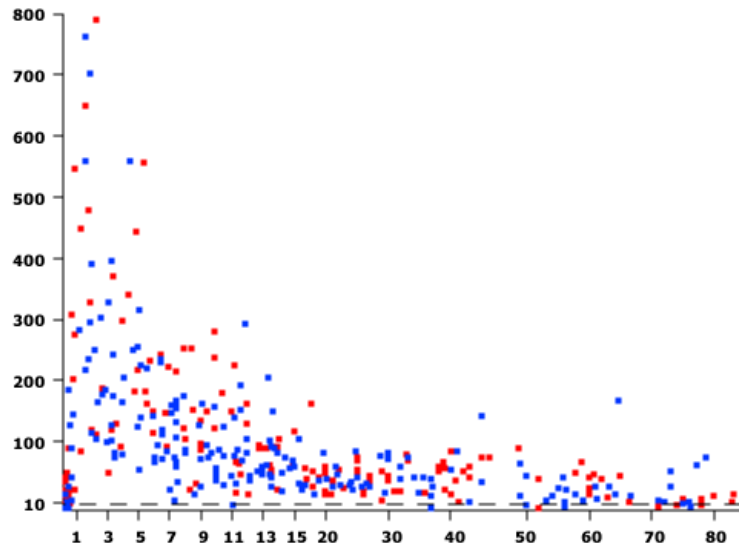
Metabolism of tryptophan to melatonin in the pineal gland



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figure 2

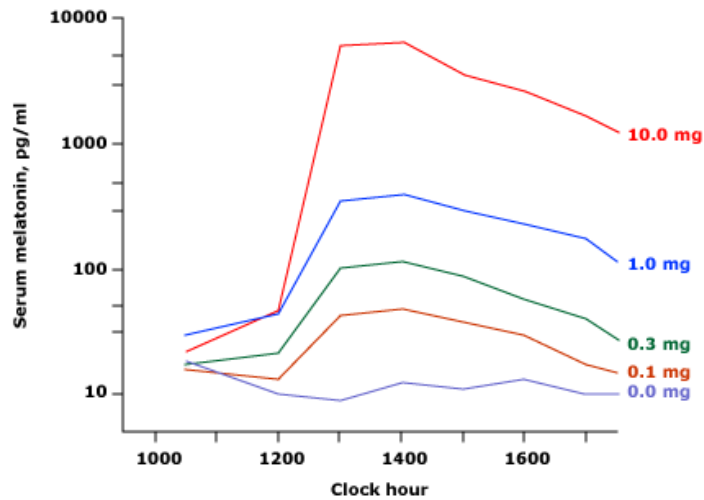
Nighttime peak serum melatonin levels in subjects of different ages, years



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figure 3

Mean serum melatonin profiles

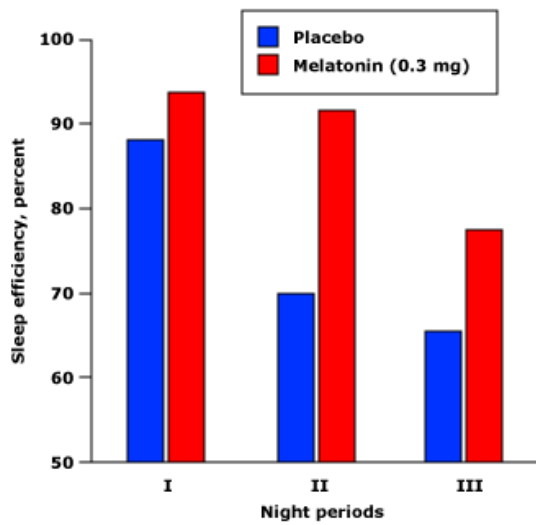


Mean serum melatonin profiles of 20 subjects sampled at intervals after ingesting 0.1, 0.3, 1.0, and 10 mg of melatonin or placebo at 11:45 am.

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figure 4

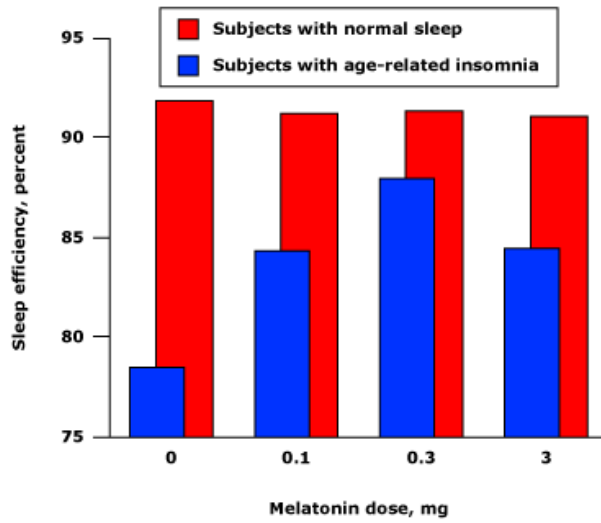
Sleep efficiency in insomniacs during three consecutive parts (I, II, and III) of the night, following placebo or melatonin (0.3 mg) treatment



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figure 5

Sleep efficiency in subjects with normal sleep and age-related insomnia



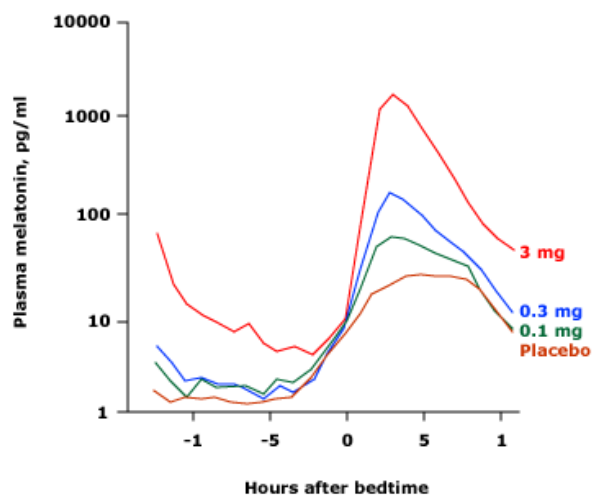
Red: subjects with normal sleep.

Blue: subjects with age-related insomnia.

Data from: Zhdanova, IV, Wurtman, RJ, Regan, MM, Taylor, JA, et al. Melatonin treatment for age-related insomnia. *J Clin Endocrinol Metab* 2001; 86:4727.

figure 6

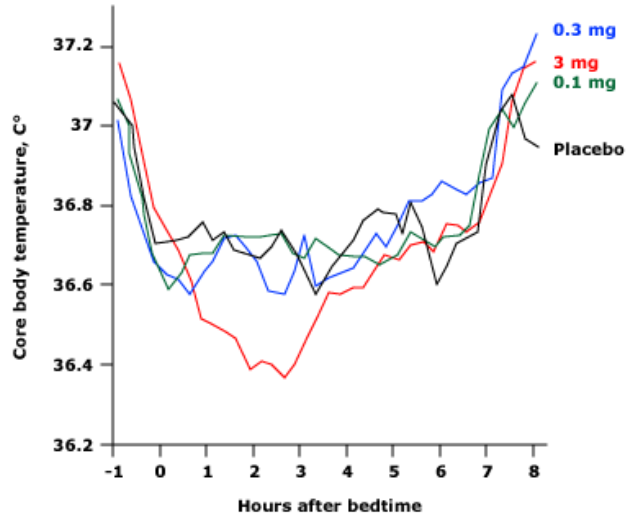
Mean group (n=30) plasma melatonin profiles after melatonin or placebo treatment 30 min before bedtime



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figure 7

Core body temperature profiles following melatonin or placebo treatment



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