Melatonin in Health and Disease

Amy Fitzpatrick, M.S., R.D.

Melatonin, a hormone manufactured primarily by the pineal gland in the brain, is involved in various physiologic functions, such as coordination of circadian rhythms, sleep regulation, immune function, tumor-growth inhibition, blood-pressure regulation, modulation of cognitive function, and free-radical scavenging.

While researchers have primarily focused on the effects of melatonin supplementation and its ability to synchronize the body's daily biorhythms and promote more restful sleep, emerging research has also explored potential benefits of melatonin's antioxidant activity as well as its effect on immune, brain, cardiovascular and gastrointestinal (GI) health. This review provides a summary of relevant research in these key areas.

Background

Although melatonin was first identified in 1958, the exact functions of this hormone are still poorly understood.[1] Most of the scientific research has focused on melatonin's involvement in the synchronization of hormone secretion and the circadian rhythm. Dubbed "the hormone of darkness," because darkness stimulates melatonin secretion and light suppresses melatonin activity,[2] this hormone is involved in the body's internal 24-hour timekeeping system, which plays an important role in helping people fall asleep and wake up.

Melatonin has been available as a dietary supplement for more than a decade and is primarily used to promote sleep. Commercially available melatonin was initially isolated from the pineal glands of beef cattle but is now chemically synthesized; the latter is the preferred form in order to reduce the potential for contamination.

Benefits

The most well-studied uses of melatonin in humans are for the manipulation of the circadian clock and as a sleep aid.[3–5] Normal melatonin cycles are disrupted when a person is exposed to excessive light in the evening or to too little light during the daytime. For example, traveling across time zones, shift work, and blindness can all disrupt melatonin cycles.[6–9] Furthermore, some individuals appear to produce low levels of melatonin, for which melatonin supplementation may be beneficial.[10–13]

Recent studies also suggest that melatonin may have antioxidant properties,[14,15] influence immunity,[16–18] exert neuroprotective effects and have a beneficial impact on cognition in the elderly.[19,20] The effects of melatonin on the cardiovascular system[21] and its role in GI health have also been studied.[22,23]

Biochemistry

Melatonin (N-acetyl-5-methoxytryptamine) is produced primarily in the pineal gland and, to a lesser extent, in the retina, bone marrow, GI tract, and lymphocytes.[24] Melatonin is also produced by plants, with the highest amounts found in rice, barley, sweet corn, and oats.[25]

The essential amino acid L-tryptophan is a precursor of melatonin synthesis. In this process, L-tryptophan is converted to 5-hydroxytryptophan (5-HTP), which, in turn, is converted to 5-hydroxytryptamine (serotonin).[26] Serotonin is finally converted to melatonin in a two-step process, of which, one of these is increased by darkness[27] and inhibited by light.[28,29]

The endogenous rhythm of melatonin secretion is generated by the suprachiasmatic nucleus (SCN), a bundle of neurons and fibers in the hypothalamus. This nerve cluster takes its name from its location, which is just above (supra) the optic chiasm, a major junction for nerves transmitting information about light from the eyes.

The approach of dusk each day prompts the SCN, or the body's master clock, to signal the nearby pineal gland to produce melatonin. Therefore, the SCN is entrained by the light–dark cycle and acts as a pacemaker to regulate the circadian rhythms in the body including temperature, cortisol levels, melatonin rhythm, and sleep propensity.[30] The daily rhythm in melatonin production and release is evidenced by the fact that nocturnal melatonin levels reach 10 times those found during the day (60–200 pg/mL versus 3–10 pg/mL, respectively).[31,32]

Pharmacokinetics

Research studies indicate that there is a large individual variation in the bioavailability of oral melatonin, with a range of 8–56 percent reported in the literature.[33–35] Orally administered melatonin is absorbed from the small intestine and is transported to the liver where it undergoes extensive and rapid first-pass metabolism.[36] After a typical oral dosage, an average of 30–60 percent of the melatonin is metabolized rapidly by this first-pass effect.[37] Melatonin is metabolized in the liver and then the majority of its metabolite (i.e., 6-sulfatoxymelatonin) is excreted in the urine.

Nonmetabolized melatonin is transported via the systemic circulation to various tissues in the body. The serum half-life of melatonin is approximately 30–60 minutes.[34,38] Ingestion of melatonin at 0.1–0.3 mg results in an increase in plasma melatonin to a level that is within the normal range for endogenous melatonin.[39]

Impact of Age or Disease on Melatonin Levels

Many studies have suggested that the magnitude of the nocturnal melatonin peak declines with age.[10,40–49] However, other researchers have not found an association between age and melatonin decline.[50–53] Interestingly, evidence does suggest that there are variations in nocturnal melatonin secretions among healthy individuals that are not explained by age, gender, height, or weight—which could suggest a genetic role in the production and utilization of this hormone.[54]

In individuals considered to be "high secretors," peak nighttime melatonin levels range from 54–75 pg/mL; "low secretors" typically have peak nighttime levels in the range of 18–40 pg/mL. This theory could explain why age-related sleep problems can be corrected in some individuals by increasing circulating melatonin to "youthful" levels; yet, some elderly subjects with low melatonin levels continue to experience normal sleep.

Melatonin levels appear to decrease in a variety of disease states (e.g., coronary-artery disease, type 2 diabetes, and Alzheimer's disease);[55–59] however, the hormone's exact role in the etiology and pathophysiology of these conditions is unknown. It is also common to find altered melatonin rhythms in some individuals with insomnia.[39,60,61]

Physiologic Effects and Mechanisms of Action

Sleep-Inducing

The basic mechanisms by which melatonin produces sleepiness in humans is unclear, although several hypotheses have been proposed. The mechanisms appear to involve a shift in the endogenous circadian pacemaker and its rhythm, a reduction in core body temperature, direct action on somnogenic (i.e., sleep-promoting) structures of the brain, and/or inhibiting the wake-promoting signal emanating from the circadian pacemaker.

Melatonin receptors have been identified in the human SCN and cerebellar cortex, and animal studies suggest that the phase-shifting effects of melatonin are mediated by these receptors.[3] The hypnotic and sedative effect of melatonin is thought to be related to the ability of melatonin to potentiate the effects of gamma-aminobutyric acid (GABA) via direct interaction with GABA receptors.[62]

Although more research is necessary to understand the physiologic mechanisms of melatonin better, current research suggests that melatonin may: (1) induce sleep when the body's natural drive to sleep is insufficient (e.g., a low melatonin level)[13]; (2) inhibit the drive for wakefulness emanating from the circadian pacemaker[3]; and (3) induce phase shifts in the circadian clock so that sleep propensity occurs at a new, desired time.[63]

Antioxidant

Melatonin's antioxidant properties were discovered in 1993. Since then, a vast amount of research in vitro and in vivo indicates that melatonin plays a vital role in the body's defense against free radicals.[64–68]

In vivo melatonin has consistently been found to be highly efficient in limiting peroxidation of lipids (i.e., breakdown of lipid cellular membranes by free radicals).[69] For instance, results from a preliminary study involving postmenopausal women indicate that taking 6 mg of melatonin per day may reduce the oxidation of low-density lipoprotein (LDL) cholesterol in the blood.[15]

Furthermore, individuals who underwent cardiopulmonary bypass surgery and were treated with melatonin prior to the surgery had a reduction in lipid peroxidation and improvements in red blood cell membrane rigidity (i.e., decreased cellular membrane fluidity).[70]

Melatonin, which is a lipid-soluble compound, has been reported to have twice the antioxidant power of vitamin E, and four times more than vitamin C and glutathione in preliminary in vitro research.[67] When compared under conditions of high oxidative stress in vivo, melatonin has been reported to be superior to vitamins C and E for reducing oxidative damage.[69] Animal research indicates that a diet rich in walnuts, a good source of melatonin, can increase blood levels of melatonin, which correlate with an improved antioxidative capacity of the blood.[71]

The potential importance of the antioxidant protection of melatonin is based on its ability to function via multiple mechanisms. Not only does melatonin have a direct antioxidant effect by neutralizing a variety of free radicals (i.e., hydroxyl and peroxyl radicals, singlet oxygen and nitric oxide [NO]), but it may also act indirectly by stimulating the activity of endogenous antioxidant enzymes such as superoxide dismutase, glutathione peroxidase, glutathione reductase, and catalase.[69]

Furthermore, melatonin may have the potential to downregulate pro-oxidant enzymes such as NO synthases and lipoxygenases, and the electron donation by melatonin during its direct free-radical–scavenging effects appears to form additional protective metabolites.[72]

Other potential actions include melatonin's ability to augment the activities of other antioxidants, its protection of antioxidative enzymes from oxidative damage, and the hormone's ability to increase the efficiency of mitochondrial electron-transport chain (ETC) thereby lowering electron leakage and reducing free-radical generation.[69]

Immunomodulation

The ability of melatonin to influence immunity has been extensively investigated in vitro and in vivo. Laboratory studies reveal that melatonin can activate T-helper (Th) cells, which stimulate the production and release of other important immune-system components such as interleukin-2, γ–interferon, and opioid peptides.[73,74] Melatonin also stimulates natural-killer cell, monocyte, and macrophage production, and is believed to affect immune function primarily via the immune-opioid network, via cyclic adenosine 3′,5′-cyclic monophosphate (cyclic cAMP) signal transduction, and via regulating intracellular glutathione levels.[75]

Dietary supplementation, using melatonin, has been shown to arrest the attenuated immune responses associated with aging.[75,*] Depressed circadian biosynthesis of melatonin has also been linked to inhibition of cellular and humoral (i.e., blood or body fluid) responses in mice.[76]

The significance of melatonin's effect on the immune system is demonstrated by the abundance of in vitro and in vivo research that suggests that melatonin administration can influence nonspecific humoral and cellular immune responses as well as cellular proliferation and immune-mediator production.[75,77] Melatonin's actions in several immune pathologies—including infection, inflammation, and autoimmunity—together with the relationships among melatonin, immunity, and cancer have recently been highlighted.[78]

Clinical and Research Applications

Modulation of the Circadian Rhythm

The body naturally secretes melatonin to act as a time signal for daily and annual biologic rhythms, such as sleep and hormone patterns. This primary function of melatonin has led researchers to investigate the impact of melatonin supplementation on the body's circadian rhythm.[3,5]

Melatonin receptors have been identified in the SCN. Animal studies have shown that melatonin can shift the rhythmic nerve-cell activity at certain circadian times, providing evidence that melatonin has direct effects on the internal body clock.[79] Oral administration of melatonin, in humans, has been shown to shift circadian rhythms according to a phase–response curve.[80]

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Administration of melatonin during the daytime, when the body's production of melatonin is low, leads to an increased tendency to sleep[81–84] and shifts in the timing of the endogenous rhythm of melatonin.[85–87] For instance, timed chronic administration of melatonin to individuals who are blind and in whom circadian rhythms are not synchronized to the external light–dark cycle, can resynchronize these rhythms to the 24-hour day.[88]

Circadian adaptation to jet travel across many time zones or to night-shift work requires that circadian rhythms phase-shift to reentrain to the new light–dark and sleep–wake cycle. There is currently a great deal of interest in whether properly timed melatonin administration can facilitate circadian phase-shifting in these situations.

Some, but not all,[89,90] researchers say that melatonin supplementation may be beneficial for individuals who need circadian rhythm-shifting, such as shift workers and travelers who have jet lag.[91–95] Yet others indicate that melatonin may provide a modest benefit for relief of the daytime-fatigue and the sleep-disturbance aspects of jet lag,[96,97] and can significantly enhance total sleep times and adaptation to shift work in night-shift workers.[98]

Not all studies report phase-shifting effects possibly because of melatonin not being administered at the correct circadian time.[99,100] According to one review of the literature, melatonin treatment for jet lag is most effective for people who have crossed multiple time zones, which significantly offsets the circadian rhythm.[91]

Interesting new research has led some investigators to conclude that individuals who took melatonin slept significantly longer than the study's placebo group but this effect was noted only in periods of sleep that occurred during the volunteers' biologic day—that is, when their bodies were not producing natural melatonin.[101]

On average, the melatonin users slept 83 percent of the time they spent in bed compared with 77 percent in the placebo group. The researchers indicate that this improvement in sleep efficiency translates to an extra half an hour of sleep. The study was designed to desynchronize the volunteers' sleep–wake cycle; therefore, individuals were monitored in a controlled setting during strict 20-hour cycles of sleep and wakefulness similar to the off-hour sleep–wake cycle that shift workers and jet-lagged travelers experience.

A similar sleep protocol of strict sleep–wake cycles in a prolonged controlled setting suggests that continuous melatonin supplementation during the early evening, when melatonin levels are lower, eventually leads to improvements in sleep during extended sleep opportunities throughout the following day.[3]

Addressing Sleep Disorders

Although melatonin does seem to work, in part, by shifting or resetting the biologic clock, the hormone also has direct sedative effects. Based on this mechanism, melatonin has been tried for treating sleep disorders of various types, with some positive results.

Insomnia, literally the "inability to sleep," has various etiologies and is the most common sleep disorder. Some researchers have reported that melatonin can improve the subjective quality of sleep in people who have insomnia but may not improve objective measures such as the time it takes to fall asleep (sleep latency) or total sleep time.[89,102]

For instance, melatonin has been shown to improve sleep efficiency or quality of sleep in elderly people who have insomnia compared with similar patients on placebo; however, effects on total sleep time, number of awakenings, latency to sleep onset, and latency to REM sleep were unaffected by melatonin supplementation.[13]

Although some researchers have reported that melatonin can hasten the onset of sleep, increase total sleep time, and improve sleep efficiency while reducing wakefulness,[84,103] the evidence suggests that the sleep-enhancing effect is modest, with improvements of only 2–3 percent.[103]

* For more information on melatonin and aging, see the section on melatonin on pages 270-271 in the article by Chris D. Meletis, N.D., with Nieske Zabriskie, N.D., in this issue.

The effect of melatonin on patients with secondary sleep disorders, or sleep problems associated with neurologic or other disorders has yet to be confirmed. Some researchers have reported a small improvement in sleep efficiency in individuals who have secondary sleep disorders, but the clinical significance of these findings has been questioned.[89,90]

The sleep-promoting effects of melatonin appear to extend to individuals with sleep–wake disorders such as delayed sleep-phase syndrome (DSPS),[104,105] a condition in which individuals find it impossible to fall asleep until early morning. Melatonin, taken in the evening, can advance sleep and circadian phasing in patients with DSPS.[106] Other researchers have reported similar findings that suggest that melatonin decreased sleep onset latency in people with DSPS, with the magnitude of this effect being clinically significant.[90]

Normal Sleepers

The potential for melatonin to promote sleep appears to extend to normal sleepers, both young and old alike. While much of the research has evaluated melatonin administration for improving sleep quality in elderly patients,[11,107] research also suggests that young, healthy individuals may also benefit from taking melatonin.[108,109] Although some researchers have reported improvements in sleep latency and sleep efficiency in normal sleepers using melatonin, the magnitude and clinical significance of this effect has been questioned.[90]

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While most people who take melatonin supplements prefer to augment the body's natural production of melatonin at night to help improve their natural sleeping patterns, administration of melatonin during the daytime, when the body's production of the hormone is low, has been reported to promote sleep.[81,82] Unlike some sleep-inducing medications, melatonin, when used appropriately, appears to improve sleep without impairing memory and performance upon wakening.[110,111]

Cancer

The specific mechanisms of action involved in melatonin's potential anticarcinogenic effect are currently unknown, but are most likely the result of the hormone's immunomodulatory, antiproliferative, and antioxidant properties. These effects may also involve modulation of the endocrine system and/or the direct anticancer action of melatonin.[112]

For example, melatonin can reduce levels of insulin-like growth factor 1 (IGF-1) and prolactin (PRL), which have roles in breast cancer and in prostate-cell proliferation.[113] Melatonin may also make an impact on tumor cells by controlling genes that contribute to production of cancer and by inducing cancer-cell apoptosis.[114] Melatonin decreases the spread of certain cancer-cell types; this antiangiogenic effect has been documented in patients who have cancer.[115]

Animal studies have shown that melatonin can inhibit a number of indirect chemical mutagens. For instance, melatonin inhibited the development of spontaneous and induced mammary carcinogenesis in rodents; and induced colon, uterine cervix, soft-tissue, lung, and hepatocarcinogenesis in various animal models.[116] The biochemical and molecular mechanisms of melatonin's anticancer action have been reviewed.[114]

Melatonin has also been used with conventional anticancer therapy in several clinical studies.[117–123] For the most part, these studies have focused on individuals with advanced-stage cancer and examined the effect of melatonin with regard to slowing the progression of disease and/or decreasing the side-effects of conventional anticancer therapy.

Cognitive Health

Once formed, melatonin diffuses out into the capillary blood and cerebrospinal fluid and can readily cross the blood–brain barrier.[69] Interestingly, melatonin levels in brain tissue are reportedly higher than in other tissues in the body.[124] Recent in vitro[125–127] and animal[128] findings have indicated that melatonin, as an antioxidant, produced pronounced neuroprotective effects against β-amyloid peptide, one of the specific underlying causes of Alzheimer's disease.

Other researchers have found that melatonin may exert neuroprotective effects via prevention of nerve-cell death, maintenance of energy, and oxygen metabolism in highly stressed cells, and via rescuing neurons that are highly vulnerable to the overexcitation that occurs in some genetically susceptible people.[124]

Melatonin's ability to cross the blood–brain barrier, coupled with the hormone's antioxidant and neuroprotective properties, suggests that it may be of benefit in improving the quality of life in individuals with dementia, Alzheimer's disease, and other neurodegenerative disorders. Interestingly, decreased nocturnal melatonin levels have been shown to correlate with the severity of mental impairment of patients who have dementia, and disturbed circadian rhythms are considered to be related to the cognitive performance of elderly people and patients with Alzheimer's disease.[124,129,130]

Preliminary human research suggests that melatonin may play a role in supporting cognitive functions, such as verbal learning in elderly people.[19,20] However, recent reviews suggest that there is insufficient evidence to support the effectiveness of melatonin for managing the cognitive decline of dementia.[131] In patients with Alzheimer's disease, both open and controlled studies have found a significant decrease of cognitive deterioration when these patients are treated with melatonin.[66,124]

Gastrointestinal Health

Melatonin is involved in regulation of GI motility and is thought to be potentially beneficial for patients who have irritable bowel syndrome (IBS) by decreasing gut hypersensitivity.

Tell Your Patients

Interactions Between Melatonin and Drugs, Supplements, and/or Foods

Interactions with drugs

Anyone taking medication should be encouraged to speak to a physician before taking melatonin. The following drugs may interact with it:

- Aspirin and ibuprofen (large amounts)—can decrease melatonin secretion[a]
- Beta-blockers—may lead to decreased melatonin secretion[b]
- Calcium channel blockers—melatonin may impair their antihypertensive efficacy[c]
- Mood-altering drugs—melatonin taken with fluvoxamine (selective-serotonin-reuptake-inhibitor antidepressant) or sedating/antipsychotic drugs, such as haloperidol, phenothiazines (chlorpromazine), and benzodiazepines (diazepam) appears to reduce melatonin metabolism[d]
- Warfarin—there have been isolated case reports of minor bleeding and decreased prothrombin activity in people taking melatonin with warfarin (mechanism of this interaction is unknown but, theoretically, melatonin might increase the effect of anticoagulant or antiplatelet drugs)
- Sedatives—melatonin with any products with sedative effects (e.g., alcohol, benzodiazapines, codeine, antihistamines, sleeping medication, etc.) might lead to additive sedation.

Interactions with foods and/or supplements

At this time there are no well-known interactions between melatonin and certain foods. However, caution is warranted when combining melatonin with other dietary supplements that may cause sedation (e.g., 5-hydroxytryptophan [5-HTP], *Valeriana officinalis* [valerian], *Humulus lupulus* [hops], *Piper methysticum* [kava]), as this combination might enhance therapeutic and adverse effects.

[a]Murphy PJ, Myers BL, Badia P. Nonsteroidal anti-inflammatory drugs alter body temperature and suppress melatonin in humans. Physiol Behav 1996;59:133–139; [b]From ref. 50; [c]Lusardi P, Piazza E, Fogari R. Cardiovascular effects of melatonin in hypertensive patients well controlled by nifedipine: A 24-hour study. Br J Clin Pharmacol 2000;49:423–427; [d]From ref. 39.

Some evidence suggests that melatonin can increase the rectal pain threshold in patients with IBS when they are measured by rectal manometry.[23]

Preliminary evidence suggests that patients with IBS, who also complain of poor sleep, have decreased symptoms of IBS-related abdominal pain after taking 3 mg of melatonin at bedtime for 2 weeks. But melatonin does not seem to influence stool frequency or consistency; decrease bloating; or affect mood, sleep, or overall quality of life in these individuals.[22,23]

Cardiovascular Health

Individuals with coronary heart disease have a low melatonin-production rate, especially those with higher risk of cardiac infarction and/or sudden death; and patients with hypertension have lower melatonin levels than do those with normal blood pressure.[132]

Several clinical trials have documented the ability of melatonin to lower blood pressure.[133–135]

A variety of mechanisms have been suggested to explain melatonin's ability to regulate blood pressure. The SCN influences the autonomic nervous system output to the cardiovascular system; therefore, researchers propose that restoration of proper functioning of the SCN in patients with hypertension could improve the autonomic regulation of blood pressure.[21]

Other mechanisms, such as decreasing the level of catecholamines (e.g., hormones such as adrenaline, which can play a role in increasing blood pressure) or relaxing the smooth muscle in the aorta wall have also been proposed.[132]

Recommended Dosage

The optimal dosage of melatonin has not been established. In general, 0.5 mg is understood as the cutoff between a "high physiologic" and "low pharmacologic" dose; however, even at this level many people can experience an elevation of melatonin

Table 1. Recommended Dosages of Melatonin

Indication	Dosage
Jet lag	5 mg of melatonin given on preflight and flight days, followed by 5 mg/day at bedtime at the final destination for the next 3 days.[a]
Sleep	0.3–0.5 mg of melatonin is usually effective as a sleep aid[b] when taken in the evening one-half hour to 1 hour before bedtime.[c] Doses ranging from 1 to 5 mg have also been used successfully.
Antioxidant	More studies are needed to determine the effective dosage; however, preliminary research suggests 0.5–6 mg/day may work.[d–f]
Cardiovascular	Acute administration of 1–2.5 mg of melatonin has been shown to lower blood pressure in hypertensive[g] and healthy men,[h] young women on birth control pills,[i] and postmenopausal women on hormone replacement therapy.[j]
Cognitive function	In elderly adults with mild cognitive impairment, a benefit was noted with 6 mg of melatonin over a 10-day period.[k] Benefits were also found in adults with Alzheimer's type dementia with a 3-mg dose over a 4-week period.[l]

[a]From refs. 92 & 93; [b]National Nutritional Food Association. NNFA updates melatonin position [statement by the National Nutritional Food Association]. January 22, 1996. Online document at: www.melatonin.com/melatonin-nnfa.php Accessed November 14, 2006; [c]From ref. 39; [d]From ref. 15; [e]Tan DX, Reiter RJ, Chen LD, et al. Both physiological and pharmacological levels of melatonin reduce DNA adduct formation by the carcinogen safrole. Carcinogenesis 1994;15:215–218; [f]Benot S, Goberna R, Reiter RJ, et al. Physiologic levels of melatonin contribute to the antioxidant capacity of human serum. J Pineal Res 1999;27:59–64; [g]From ref. 21; [h]Arangino S, Cagnacci A, Angiolucci M, et al. Effects of melatonin on vascular reactivity, catecholamine levels and blood pressure in healthy men. Am J Cardiol 1999;83:1417–1419; [i]From ref. 133; [j]Cagnacci A, Arangino S, Angiolucci M, et al. Effect of exogenous melatonin on vascular reactivity and nitric oxide in postmenopausal women: Role of hormone replacement therapy. Clin Endocrinol 2001;54:261–266; [k]Jean-Louis G, von Gizycki H, Zizi F. Melatonin effects on sleep, mood, and cognition in elderly with mild cognitive impairment. J Pineal Res 1998;25:177–183; [l]From ref. 20.

blood levels into the pharmacologic range—with much depending on a formulation's rate of release (i.e., slow versus quick release).[136] The dose of melatonin sold as dietary supplements is typically between 1 and 3 mg, which produces peak levels that are at least 10 times physiologic concentrations. (See Table 1.)

Safety

Melatonin is likely to be safe for occasional use. Significant side-effects of short-term melatonin treatment are believed to be uncommon. A safety study showed that melatonin at a dose of 10 mg per day produced no toxic effects when given to 40 healthy males for a period of 28 days.[137] In a study of low-dose cumulative toxicity in rats, extensive chemical and histopathologic investigation revealed little toxicity for melatonin at 3 dose levels over 28 days.[39]

Currently, the safety of melatonin when used in the long term, over months and years, remains unclear. Patients should be told that long-term use of melatonin should be supervised by a health care provider.

Melatonin is naturally produced in the body in amounts that are much lower than those typically used in dietary supplements—that is, the body produces approximately 0.1 mg of melatonin per day; amounts provided in supplement form are typically in the range of 1–3 mg per day or 10–30 times the amount normally produced by the body.

The time at which melatonin is given is important. Limited studies suggest that giving melatonin to shift workers should be done only under controlled conditions and that taking it at the wrong time can actually impair job performance.[138]

Side-Effects

According to a preliminary safety review of melatonin developed by the Institute of Medicine, the primary adverse events associated with melatonin intake include drowsiness, fatigue, headache, confusion/agitation, depression, and alterations in the levels of other hormones.[39] These effects were most evident with large doses of melatonin (5 mg to 1 g per day). Fewer adverse effects were seen with lower intakes (0.5–1 mg per day).

Although rare, there was also evidence that melatonin in doses of 10 mg per day or less may cause adverse events in the cardiovascular (i.e., hypertension), GI (i.e., autoimmune hepatitis, constipation), and central nervous (i.e., seizures, nightmares) systems. Melatonin supplementation has been reported to increase the severity of symptoms of depressive disorders. (See boxes entitled Contraindications for Melatonin and Tell Your Patients: Interactions Between Melatonin and Drugs, Supplement, and/or Foods.)

Discussion

Differing conclusions regarding the sleep-promoting effects of melatonin may be the result of the heterogeneous nature of the scientific literature.

Contraindications for Melatonin

Tell patients not to take melatonin except under medical advice if they have[a]:

- Asthma
- Autoimmune disorders (including systemic lupus erythematosus)
- Depression
- Diabetes or other endocrine disorders
- Serious illness
- Schizophrenia
- Seizures.

Other situations requiring medical advice include:

- Pregnancy and lactation or trying to conceive (large doses of melatonin [300 mg] have been shown to inhibit ovulation)[b]
- Driving or operating hazardous machinery.[c]

[a]National Nutritional Food Association. NNFA updates melatonin position [statement by the National Nutritional Food Association]. January 22, 1996. Online document at: www.melatonin.com/melatonin-nnfa.php Accessed November 14, 2006; [b]Voordouw BC, Euser R, Verdonk RE, et al. Melatonin and melatonin-progestin combinations alter pituitary-ovarian function in women and can inhibit ovulation. J Clin Endocrinol Metab 1992;74:108–117; [c]Suhner A, Schlagenhauf P, Tschopp A, et al. Impact of melatonin on driving performance. J Travel Med 1998;5:7–13.

For instance, a broad range of doses used, the differing categories of subjects tested (normal subjects, patients with insomnia, elderly people, etc.), the varying times of administration (daytime versus night-time), acute versus chronic intake, varied sleep protocols, and assessment tools, and the type of melatonin supplement used (fast versus time-release) make it difficult to draw firm conclusions about the clinical significance of melatonin supplementation.

Discrepancies between findings of different investigators can also be attributed to the interindividual variation in melatonin levels in people of the same age group.

Furthermore, the etiology of sleep problems may provide some clues as to whether melatonin will improve sleep effectively in certain patient populations.

For instance, melatonin appears to reduce sleep-onset latency to a greater extent in people with DSPS than in people with insomnia.[139] Individuals with DSPS are distinguished from those with insomnia by the presence of a circadian abnormality. Based on these findings, melatonin seems to function by resetting the endogenous circadian pacemaker rather than acting on the somnogenic structures of the brain in individuals with DSPS. In the case of insomnia, the etiology is so diverse that it makes it difficult to draw definitive conclusions about how melatonin may improve sleep efficiency other than acting as a sedative.

The emerging research about the antioxidant benefits of melatonin is exciting; however, it is important to note that scientists have yet to recommend taking melatonin specifically for this purpose. The relative importance of the direct and indirect antioxidative processes of melatonin in reducing tissue damage in vivo requires further investigation. Furthermore, some researchers have questioned the long-term safety of using the high doses that may be necessary to achieve antioxidant effects.[140] Additional

clinical trials are necessary to understand the efficacy and safety of melatonin as a cellular protector better.

Although melatonin's ability to modulate immunity is intriguing, the research at this point is too preliminary to recommend melatonin as a supplement for promoting immune health. Well-controlled research studies in humans are necessary to understand the potential benefit of melatonin for immunity fully and to determine which age groups of people, if any, can benefit from taking melatonin for this purpose.

While melatonin as an adjunct tool to standard cancer therapy has been quite promising, this research is also considered to be preliminary and must be interpreted with caution. Larger, well-controlled studies are needed to support this use of melatonin. It is strongly recommended that individuals with cancer be urged to seek professional medical guidance before beginning a melatonin supplementation regimen, given that a complete understanding of melatonin's benefits and safety is not known in this patient population.

The preliminary findings in the scientific literature in regard to melatonin's neuroprotective and cognitive-enhancing abilities are encouraging; however, many questions remain unanswered. Whether melatonin has value for preventing or treating dementia or Alzheimer's disease—affecting disease initiation or progression—and the specific mechanisms of action remains to be answered in future studies.

The role of melatonin in enhancing GI and cardiovascular health is intriguing, but further studies are needed to clarify the exact mechanisms involved, and if the benefits already observed in humans are clinically significant. □

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Amy Fitzpatrick M.S., R.D., is a corporate nutritionist and complementary medicine and nutrition research consultant with Natural Health Solutions, in Kingsport, TN.

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