

Melatonin's Benefits and Risks as a Therapy for Sleep Disturbances in the Elderly: Current Insights

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Abstract: Aging is accompanied by circadian changes, including disruptive alterations in the sleep/wake cycle, as well as the beginning of low-degree inflammation (“inflammaging”), a scenario that leads to several chronic illnesses, including cancer, and metabolic, cardiovascular, and neurological dysfunctions. As a result, any effective approach to healthy aging must consider both the correction of circadian disturbance and the control of low-grade inflammation. One of the most important prerequisites for healthy aging is the preservation of robust circadian rhythmicity (particularly of the sleep/wake cycle). Sleep disturbance disrupts various activities in the central nervous system, including waste molecule elimination. Melatonin is a chemical with extraordinary phylogenetic conservation found in all known aerobic creatures whose alteration plays an important role in sleep changes with aging. Every day, the late afternoon/nocturnal surge in pineal melatonin helps to synchronize both the central circadian pacemaker found in the hypothalamic suprachiasmatic nuclei (SCN) and a plethora of peripheral cellular circadian clocks. Melatonin is an example of an endogenous chronobiotic substance that can influence the timing and amplitude of circadian rhythms. Moreover, melatonin is also an excellent anti-inflammatory agent, buffering free radicals, down-regulating proinflammatory cytokines, and reducing insulin resistance, among other things. We present both scientific and clinical evidence that melatonin is a safe drug for treating sleep disturbances in the elderly.

Keywords: melatonin, sleep, elderly, safety, neurodegeneration

Introduction

The basic pathophysiological causes of aging include numerous interconnected processes, notable circadian desynchronization, and a low degree inflammation (“inflammaging”).^{1,2} In this context, maintaining a sleep/wake cycle that is regular is important for the promotion of health in the elderly. The fundamental circadian rhythm in the body is the sleep/wakefulness pattern. According to the current consensus on its physiological control, it is governed by two components: a circadian (24-hour) one and a homeostatic one.³

Melatonin, a chemical that is conserved so consistently phylogenetically that it is found in all known aerobic phyla, is a vital component of the circadian component that governs the sleep schedule. Melatonin is the prototypical molecule that affects the circadian system (ie, chronobiotics).^{4,5} In both normal and blind patients, the circadian rhythm in pineal melatonin production and secretion as a hormone into the circulation is strongly related to the sleep rhythm.⁶ The onset of night-time melatonin release occurs approximately 2 hours before an individual's habitual bedtime and has been shown to correspond with the onset of evening tiredness. Several studies have established a linkage between plasma melatonin levels to the physiological control of circadian processes that govern sleep proclivity.^{7,8}

In humans, the pineal gland is the most obvious source of circulating melatonin, and a decrease in plasma melatonin is one of the hallmarks of aging.⁹ The hormone melatonin is robustly cytoprotective with substantial antioxidant, anti-inflammatory, and immunoregulating action in addition to its role as a primary coordinator of circadian rhythmicity.¹⁰ As a result, melatonin administration as therapy may effectively manage the low degree inflammation found in aging. This review focuses on the advantages and disadvantages of utilizing melatonin to treat sleep disturbances in the elderly.

Aging and Sleep

Sleep is a reversible behavioral condition characterized by diminished perception leading to disengagement from and unresponsiveness to the environment.¹¹ As noted above, getting the sleep that is both sufficient and of good quality daily is one of the cornerstones of healthy aging. The precise quantity of sleep required for good human health, on the other hand, varies significantly across and among individuals.

Sleep and aging are inextricably linked bidirectionally. Insufficient sleep, both in terms of duration and quality, can be harmful to one's health and, as a result, contribute to the aging process. Sleep difficulties, on the other hand, frequently worsen with age due to the flattening and mistimed circadian rhythms (for example, melatonin production), and also the sleep-disturbing effects of age-related ailments and diseases.¹²

Norms for sleep characteristics were established in a representative population sample of 100 healthy volunteers aged 19 to 77 years old using overnight polysomnography (PSG).¹³ Healthy people's overall sleep length, the amount of time spent in each sleep stage, and the prevalence of sleep-disrupting events all altered as they got older. Specifically, sleep efficiency dropped from 87% to around 80% in senior people, with a reciprocal rise in sleep onset latency (SOL), the proportion of time spent in light sleep stages N1 and N2 (non-rapid eye movement, NREM), and waking after sleep onset (WASO). When compared to younger people, the elderly had a drop-in total sleep time (TST) from around 413 minutes to about 378 minutes. The frequency of apnea or hypopnea episodes per hour, as well as the apnea-hypopnea index (AHI), was higher in older participants. Notably, decreased oxygenation, as seen in sleep apnea, is known to be linked to an increased risk of cardiovascular disease.¹³ Reduced slow wave sleep (NREM deep sleep; Stage N3) and REM sleep were also age-related decrements. The elderly exhibited lower levels of NREM and REM sleep, as well as lower levels of delta activity, according to EEG spectral power assessments of polysomnographic data.¹⁴ In essence, as people become older, their sleep experiences become more fragmented, which encourages compensatory behaviors like taking more daytime naps.

Sleep has long been thought to be solely a central nervous system (CNS) phenomenon. It is a distinct physiological programmatic state from waking, consisting of two very different homeostatic states of all organs and systems, namely NREM and REM sleep. It's as if we have three distinct bodies (wakefulness, slow wave sleep, and REM sleep) that must all work together to keep us healthy.¹⁵ A 76-year-old man who sleeps 8 hours a day has spent 50 years in wakefulness, 20 years in slow-wave sleep, and 6 years in REM sleep. However, given that living in our modern 24/7 society has resulted in a 25% drop-in sleep hours over the last 40 years, the above equation now equates to around 56 years of waking, 15 years of slow-wave sleep, and 5 years of REM sleep. As a result, we live in a sleep-deprived society where the sympathetic catabolic configuration of alertness surpasses the parasympathetic anabolic configuration of NREM sleep.¹⁵ In the aged, this decrease in slow-wave sleep contributes to the imbalance of sleep, which leads to clear inflammaging promotion and other health repercussions, such as obesity, high blood pressure, diabetes, and neurodegenerative disorders.¹⁶

Furthermore, there is growing evidence that sleep problems such as insomnia and obstructive sleep apnea become more common as people become older. According to an epidemiological study, more than half of persons over the age of 65 suffer from some sort of persistent sleep-related ailment.¹⁷

Several studies have found that sleep disturbance contributes significantly to neuropathology. Sleep deprivation¹⁸ elevated cerebrospinal fluid (CSF) levels of amyloid β ($A\beta$)₁₋₄₂ in healthy individuals. Furthermore, an animal study found a link between $A\beta$ and alertness, with infusions of the wakefulness-related neuropeptide orexin increasing $A\beta$ levels while an orexin antagonist, almorexant, lowered $A\beta$ levels.¹⁹ As a result, while these findings do not yet permit a firm conclusion on the impact of sleep deprivation on the development of Alzheimer's disease (AD) per se, the link between $A\beta$ and being awake during sleep time should be taken very seriously.

Indeed, the reduction of NREM sleep is critical for the removal of brain waste. This is dependent on a process that significantly contributes to brain recovery processes: an active, lymphatic-like movement occurring in the extracellular space of the brain, driven by perivascular astrocytes (which are highly enriched in aquaporin-4) and changes in the vascular lumen ("glymphatic" system²⁰). This exchange of solutes between the CSF and the interstitial fluid occurs primarily during NREM sleep, when the cerebral interstitial space expands by more than 60%, allowing CSF and interstitial fluid movement in the brain parenchyma.²¹ The aging human brain likely suffers from impairment of this

process. Various neurological illness states, such as stroke, traumatic brain injury, and AD, have thus been explained in terms of glymphatic dysfunction.²²

It is of great interest that melatonin, a potent antioxidant, and neuroprotective substance, is secreted directly from the pineal into the third ventricle in both animals and man, from which it diffuses widely into brain tissue.²³ There is evidence that melatonin is in higher concentrations than in blood and that in the brain it is capable of removing toxins such as A β from the central nervous system to protect against cognitive decline.²⁴

Melatonin (*N*-acetyl-5-methoxytryptamine) contains two functional groups that result in its specificity and amphiphilicity ie, the 5-methoxy group and the N-acetyl side chain.²⁵ Although the metabolic machinery to produce melatonin is found in a wide range of tissues circulating melatonin is derived from the pineal gland. The body's master clock located in the hypothalamic suprachiasmatic nuclei (SCN) regulates melatonin production in the pineal. Once released into the blood, approximately 70% of melatonin is bound to albumin,²⁶ while the rest diffuses easily into the surrounding tissues. Melatonin has a biexponential half-life in the blood, with a first distribution half-life of 2 minutes and the second half-life of roughly 20 minutes.⁹ In a single pass, the liver removes 92–97% of melatonin from circulation.²⁷ Melatonin is metabolized in the liver by cytochrome P450 monooxygenases (isoenzymes CYP1A1, CYP1A2, and to a lesser degree CYP1B1) and with sulphate conjugation is then excreted as 6-sulphatoxymelatonin. Melatonin is also demethylated by CYP1A2 and, to a lesser extent, CYP2C19 to its precursor N-acetylserotonin. The brain contains specialized melatonin deacetylases as well as less specific aryl acylamidases.²⁷

About one-third of total melatonin metabolism in the brain is attributable to oxidative pyrrole-ring breakage to *N*¹-acetyl-*N*²-formyl-5-methoxykynuramine (AFMK), which is then deformylated to *N*¹-acetyl-5-methoxykynuramine (AMK) by arylamine formamidase or heme peroxidase.²⁸ Other oxidative catabolites produced include 2-hydroxymelatonin and cyclic 3-hydroxymelatonin. AFMK and AMK interact with reactive oxygen and nitrogen acting as antioxidants. Melatonin synthesis has been documented in mitochondria resulting in a high concentration in immediate juxtaposition to those reactive oxygen species.²⁹ Melatonin and its endogenous metabolites protect mitochondrial electron flow via this mechanism.³⁰

In humans, two Gi-protein-coupled membrane melatonin receptors have currently been identified.³¹ In terms of amino acid sequence, the MT1 receptor sequence is 60% like the MT2 receptor. Furthermore, a third receptor (GPR50) has 45% of the amino acid sequence with MT1 and MT2 although it does not bind melatonin.

The SCN, choroid plexus, cerebellum and prefrontal cortex, hippocampus, nucleus accumbens, basal ganglia, substantia nigra, ventral tegmental region, and retinal horizontal, amacrine, and ganglion cells have all been established as containing MT1 and MT2 receptors.³² MT1 receptors are abundant in the human SCN, especially in neurons that contain vasopressin. In contrast, the MT2 receptors are found in the SCN of many animals and when present is particularly critical for circadian phase-shifting.³³

Pineal melatonin is an essential coordinator for circadian rhythm. Melatonin is a “signal” from the biological clock and responds to SCN activation. Therefore, melatonin cycle timing reveals both the phase of the body clock (ie, internal clock time relative to external clock time) and amplitude. In the late afternoon, melatonin decreases the wakefulness-promotion by SCN, inducing sleep.³⁴ Melatonin, on the other hand, is a chemical signal of the night: the longer the night, the longer the length of its release. Melatonin secretion is a temporal cue for seasonal rhythms in most mammalian species.³⁵

Melatonin synthesis, and hence its CSF and blood levels, are circadian and tightly linked with the ambient light/dark cycle. Indeed, in all mammalian species, the circadian pineal synthesis of melatonin is confined to the dark phase of the light/dark cycle. It is worth noting that melatonin is always generated at night, regardless of the species' day routine of activity/rest, demonstrating a strong link with the external photoperiod. Furthermore, melatonin is synthesized at night but only when there is no light in the surroundings.

Light during the night, notably in the blue range, activates specialized retinal melanopsin-containing retinal ganglion cells that travel via the retinohypothalamic tract to the SCN to inhibit ultimately pineal sympathetic norepinephrine release and, as a result, decrease or abolish melatonin production.³⁶

The effects of the internal zeitgeber melatonin on the circadian clock are time-dependent, much as but opposite to, the effects of the external zeitgeber light. Melatonin given to rats daily can change the phase of the circadian clock, and

a similar effect could explain the influence of melatonin on sleep in humans. An important clinical example provided indirect support for such a physiological involvement: clinical trials on blind patients (who have free-running circadian rhythms) were successfully synchronized by treatment with melatonin.⁵ The revelation that the phase response curve for melatonin is opposite (ie, around 180 degrees out of phase) to that of light offers more concrete evidence for this notion.³⁷

As previously stated, circulating melatonin in animals and humans is virtually all obtained from the pineal. Additionally, melatonin is generated locally in most cells, tissues, and organs, including lymphocytes, bone marrow, the thymus, the gastrointestinal system, the skin, and the eyes, where it can have an autocrine or paracrine role.³⁸ Indeed, there is now compelling evidence that melatonin is synthesized in every animal cell with mitochondria.³⁹ Melatonin engages in a variety of physiological tasks in both animals and humans, not only indicating the length of the night but also improving the removal of free radicals and immunological responses, as well as having both anti-inflammatory and cytoprotective actions.⁴⁰

Melatonin and Sleep

Not only should an ideal hypnotic reduce sleep onset latency, but it should also boost total sleep time and sleep efficiency. Furthermore, the ideal hypnotic medicine should not have undesirable side effects such as impaired memory, cognition, next psychomotor slowdown, day hangover symptoms, or the possibility of misuse. Many of these conditions are satisfied by melatonin, as evidenced by various consensus declarations and meta-analysis articles.^{8,41–46}

Melatonin is a potent chronobiotic with mild hypnotic properties. Daily dosages of 2–5 mg melatonin, timed to advance the phase of the internal clock through interaction with MT1 receptors in the SCN, sustain circadian rhythm synchronization to a 24-h cycle in sighted people who live in situations that are prone to produce a free-running rhythm.³⁷ Melatonin synchronizes a person's rhythm after a brief time of free running. By administering melatonin to blind subjects with free-running rhythms, researchers were able to stabilize or entrain, the sleep/wake cycle to 24 hours, resulting in improved sleep and mood.⁵ In recent month-long crossover research, 24 healthy older individuals were given a placebo for two weeks and then either 0.3 mg or 5 mg of melatonin 30 minutes before going to bed. The 5 mg melatonin dosage considerably boosted sleep efficiency throughout both biological day and night, mostly by extending the duration of Stage 2 non-REM sleep and somewhat reducing awakenings.⁴⁷

Melatonin therapy helps to minimize variance in sleep start time in normal aged adults and dementia patients with disrupted synchronization of the sleep/wake cycle. Melatonin's phase-shifting effects are also adequate to explain its efficacy as a therapy for circadian-related sleep disorders such as jet lag and delayed phase sleep syndrome.^{48,49}

Melatonin and BZD Use in Insomniacs

Insomnia is a relatively prevalent illness that is typically related to medical and psychological problems. In the United States, the overall economic cost of insomnia has been estimated to reach up to \$107.5 billion per year.⁵⁰ According to epidemiological findings, 12–20% of people over the age of 65 suffer from insomnia, and up to 40% are dissatisfied with their sleep or have difficulty beginning or sustaining sleep. Epidemiological studies on the elderly have found a link between insomnia, particularly with decreased or fragmented sleep, and an increased risk of accidents and falls.⁵¹

It is not unexpected, then, that the elderly take hypnotics more often, with 30 to 40% of the elderly using BZD and related Z medications to improve their sleep. However, adverse effects of hypnotics are more prevalent in the elderly due both to increased sensitivity of the aging neurological system as well as to decreasing amounts of serum albumin, the major protein binding the medication in the circulation. As a result, hypnotic medicines operate differently and less predictably in older persons compared to their younger counterparts.⁵²

Elderly individuals are frequently treated either for longer periods or with larger dosages of hypnotic medicines BZD/Z drugs than is indicated. Such failure to adapt individual dosing to the pharmacokinetic and pharmacodynamic changes caused by aging and/ or concomitant medical issues can make therapy more difficult and even dangerous. As a result, chronic and widespread use of BZD/Z medicines has become a significant public health issue, prompting attempts to decrease their prescribing, particularly in Europe.⁵³

Most studies recommend avoiding the long-acting BZD as well as using hypnotics for the shortest time that is feasible in elderly patients, usually no more than 2–3 weeks. The most obvious technique is to taper the medicine; sudden discontinuation is only appropriate if a very major side effect occurs during therapy. There is no strong data to recommend the best rate of tapering, with timetables ranging from 4 weeks to many months. However, because they become dependent, most patients continued to take BZD or medicines for extended periods.

The discovery that following pinealectomy (Px), brain GABA concentration rose and was counteracted by melatonin was the first evidence of a possible link between pineal and brain GABAergic neurons.⁵⁴ Melatonin's inhibitory function was shown in Px-induced seizures in gerbils⁵⁵ and kindled seizures in rats.⁵⁶ Melatonin has a definitive anticonvulsant impact when administered alone to adult rats, hamsters, guinea pigs, cats, and baboons while in mice it enhances the anticonvulsant activity of phenobarbital and carbamazepine against electroshock-induced seizures.^{57,58} Its anticonvulsant impact has been linked to both MT1 and MT2 receptors.^{59–62} and comparable anti-seizure actions have been reported with the MT1/MT2 agonist ramelteon.⁶³ Melatonergic drugs' anti-excitatory effects are also linked to their anxiolytic, antihyperalgesic, and antinociceptive properties.^{64–66}

CNS synapses using GABA as an inhibitory transmitter are targets for pineal melatonin activity.⁶⁷ Melatonin improves GABA binding by GABA_A receptors in vitro and in vivo, and allosterically blocks the binding of caged convulsants to GABA-gated chloride channels in the rat brain.⁶⁸ Moreover melatonin competes for diazepam binding sites with micromolar affinity in rat, human, and bovine brain membranes, implying a direct interaction at the level of the BZD binding pocket, which is situated at the subunit interface of the GABA_A receptor complex.

In vivo electrophysiological investigations in the mammalian brain have shown that nanomolar melatonin concentrations enhance GABAergic regulation of neuronal activity.⁶⁹ Electrophysiological investigations in vitro have revealed that the MT1 receptor is linked to increased GABAergic activity in hypothalamic slices, but that the MT2 receptor is tied to the reverse effect in hippocampal slices.⁷⁰ Consistent with the MT1 receptor subtype's relatively high expression, melatonin's principal function in the rat SCN is to suppress neuronal activity.⁷¹ Melatonin was shown to increase GABA-induced currents and GABAergic micro inhibitory postsynaptic currents in cultured rat hippocampus neurons, an action that was reduced by the BZD receptor antagonist flumazenil.⁷²

European health authorities are gradually instituting rules and making suggestions to minimize the use of BZD and BZD-like Z medicines. Despite national guidelines and recommendations, however, the efforts have usually not been successful, and the use of these medications has increased. The more obvious technique for reducing chronic BZD usage is the reduction of doses; rapid discontinuation is only acceptable if a major side effect arises during therapy. There is no clear data on the best rate of change, and timeframes for tapering extend from 4 weeks to many months.

Melatonin has been proposed for usage in BZD/Z drug withdrawal. Since the initial documented series of elderly patients with decreased BZD intake following melatonin therapy was reported in 1997,⁷³ there have been publications both supporting^{74–79} and refuting it.^{80–82} Recent conflicting meta-analyses and systematic reviews continue this contention.^{83,84}

According to a study that examined and evaluated both the impact of anti-BZD/Z-drug campaigns and the availability of melatonin pharmacotherapy on BZD and Z-drug consumption in several European countries, such campaigns failed when they were not also associated with the availability of melatonin on the market.⁵³ Reimbursement for melatonin supported higher penetration rates and lower sales for BZD/Z-drugs in this pharmacoepidemiologic investigation.

Melatonin and Sleep in Neurodegenerative Disorders

Sleep disruptions have been linked to memory and cognitive impairment in cross-sectional research.^{85,86} A substantial disturbance of circadian timing occurs in AD, as evidenced by changes in several biological rhythms such as body temperature, glucocorticoids, and/or plasma melatonin. Internal body rhythm desynchronization is prominent in AD patients. "Sundowning", a chronobiological dysfunction reported in AD, is one such developing symptom.⁸⁷ Sundowning symptoms include disordered thinking, a reduced ability to pay attention to external stimuli, agitation, wandering, and perceptual and emotional abnormalities, all of which manifest in the late afternoon or early evening. Strong light exposure and timed melatonin delivery at specific circadian times relieved sundowning symptoms and improved sleep-wake patterns in AD disease patients.^{88,89}

Even in the preclinical stages of AD, when patients have no cognitive impairment, CSF melatonin levels fall, indicating that CSF melatonin reduction may be an early cause and marker for Alzheimer's disease.⁹⁰ Although it is unknown whether melatonin deficiency is a result or a cause of neurodegeneration, it is clear that melatonin deficiency exacerbates the illness, and that early circadian disruption may be an important deficit to consider and correct. Melatonin levels differ significantly between those with moderate cognitive impairment (MCI) and AD⁹¹ such that there is a negative connection between the neuropsychological evaluation of dementia and melatonin levels. Thus, low melatonin equated to more cognitive impairment.

MCI is diagnosed in those who have an objective and demonstrable impairment in cognitive processes but who are still able to perform daily tasks. Estimates of yearly conversion rates to dementia vary between studies but can reach as high as 10–15%, with MCI constituting a clinically essential stage for detecting and treating patients at risk.⁹² It has been established that the degeneration process in the AD brain begins 20–30 years before the disease's clinical presentation. Plaques and the burden of tangles rise during this period, and the first symptom only develops once a particular level is reached. Several meta-analyses demonstrate that melatonin treatment improves sleep in MCI patients.^{93–95} Furthermore, both melatonin and melatonergic agonists are useful in the treatment of delirium, an acute condition of mental disorientation that can lead to a variety of negative consequences in elderly patients in critical care units.⁹⁶

An examination of published data on the use of melatonin in the early stages of cognitive decline revealed that taking melatonin every night before retiring improves sleep quality and cognitive performance at this stage of the disease.^{93,97} In one of the authors' laboratories, a retrospective analysis of 25 patients with MCI who had received a daily dose of 3–9 mg of melatonin along with their usual medication in the previous three years was carried out.⁷⁹ Melatonin-treated patients improved cognitive and emotional function, as well as sleep/wake cycle quality, as compared to an untreated group. Another study included 96 outpatients with mild cognitive impairment, 61 of whom had been taking 3–24 mg of melatonin daily for 15 to 60 months.⁹⁸ Melatonin-treated patients performed much better on several cognitive tests. They also had decreased Beck Depression Inventory ratings, which coincided with improvements in sleep and wakefulness.

Motor symptoms in Parkinson's disease occur only after roughly 3/4 of the dopaminergic cells in the substantia nigra pars compacta are destroyed. However, non-motor symptoms, such as REM sleep behavior disorder (RBD), may occur years before the start of frank Parkinson's disease and as such may be an indicator of a poor prognosis. RBD is a parasomnia characterized by dream-related vocalizations and/or complicated motor actions due to REM sleep muscle atonia.⁹⁹ It affects roughly 1% of normal individuals, compared to 20% to 50% of those with Parkinson's disease. The research implies that RBD may be a prodrome to synucleinopathies such as Parkinson's disease. Most RBD patients, particularly males over 50, will progress to α -synucleinopathy, with a typical conversion gap of 10 years from the time of RBD start.¹⁰⁰

A daily dose of 3–12 mg of melatonin at bedtime is useful in the treatment of RBD and may stop the progression of Parkinson's disease.^{99,101} Polysomnography in RBD patients treated with melatonin revealed substantial reductions in the number of R epochs without atony and movement duration during REM sleep, in contrast to the persistence of muscular tone in R sleep shown in clonazepam patients. Based on these findings, a clinical consensus suggested using melatonin in RBD.¹⁰² More high-quality research, however, is required.¹⁰³

In recent research, 171 individuals who took 2 mg of melatonin daily were assessed using a specific RBD questionnaire.¹⁰⁴ RBD symptom intensity decreased gradually over the first four weeks of therapy with melatonin and remained stable for up to 0.6–21.7 years. RBD symptoms gradually resurfaced after only 1–3 months of treatment. RBD symptoms remained in the absence of melatonin and did not fade over time.¹⁰⁴

Based on the significant conversion rate of idiopathic RBD to Parkinson's, several consensus statements have been claimed for the application of neuroprotective medicines in RBD. The rate of conversion to synucleinopathy is particularly high in RBD patients treated with clonazepam.¹⁰⁰ Although similar data for RBD patients treated with melatonin are not yet available, a case report merits consideration.¹⁰⁵ A 72-year-old male RBD patient treated with 2 mg slow-release melatonin daily showed an increase in dopamine transporter density (as measured by dopamine transporter scintigraphy) over time. The clinical and electrophysiologic indications of RBD vanished after 6 months of progressive recovery. While the examination prior to melatonin therapy revealed clear evidence of Parkinson's disease, the

examination two years later was deemed suspect, with no signs of Parkinson's disease present four years later. Melatonin may play a neuroprotective effect in synucleinopathy, according to these findings.¹⁰⁵

Safety for the Clinical Use of Melatonin

Melatonin is surprisingly non-toxic, with a high level of safety. The lethal dose 50 (LD50) of melatonin for intraperitoneal injection in rats (1168 mg/kg) and mice (1131 mg/kg) could not be attained following oral administration of melatonin (tested up to 3200 mg/kg in rats) or subcutaneous injection of melatonin (tested up to 1600 mg/kg in rats and mice).¹⁰⁶ Unlike many other compounds, the Merck Index (<https://www.rsc.org/merck-index>) does not include an LD50 for this chemical, and the Merck Safety data sheet specifies an LD50 of >3.2 g/kg for a single oral dosage in rats, indicating that it is not poisonous. Melatonin's extraordinary absence of toxicity in humans up to 100 mg has been demonstrated in dosage escalation trials.^{107,108} Large dosages of melatonin have been used in a variety of illnesses with no negative consequences; in people, melatonin has a high safety profile and is generally well tolerated (see ref.¹⁰⁹). According to a recent study, the number of US individuals aged 65 and over who have used melatonin in the last month has increased threefold over the last two decades.¹¹⁰

Melatonin is available as a medicament in both controlled-release and immediate-release formulations. For chronobiotic effects and sleep induction, immediate-release melatonin is the more effective formulation. Melatonin is very widely accessible as an over-the-counter dietary supplement in various countries, and as a food additive in the United States, where an estimated 3.1 million individuals (1.3% of US adults) consume it daily.¹¹¹ The manufacturing quality and bioavailability of melatonin and the potential contaminants differ widely in these unlicensed melatonin preparations.^{112,113} As a result, although melatonin does not have significant toxicity at the provided levels, it is as yet impossible to make more comprehensive conclusions about melatonin's potential undesirable side effects and especially those after long-term use.

A report on melatonin prescription stated that it was prescribed in 82% of communities in data obtained from 250 randomly chosen assisted living communities among 5777 inhabitants across seven states in the United States and weighted to an estimated 4043 communities and 152,719 people.¹¹⁴ Prescriptions were more likely in facilities that had a registered nurse or licensed practical nurse on staff and whose health care supervisor was more supportive of non-pharmacologic approaches.

Adverse effects in melatonin clinical trials for primary or secondary sleep disorders were typically few, mild to moderate in intensity, and either self-limiting or resolved promptly after treatment discontinuation. In a systematic review and meta-analysis of the therapeutic effect of exogenous melatonin on depressive symptoms, 8 out of 19 studies discussed adverse events associated with melatonin administration (eg, headache, daytime sleepiness, dizziness, poor sleep, insomnia, a fuzzy feeling, altered bowel habits, and tachycardia), with six reporting data on adverse events.¹¹⁵ The average rate of adverse events was 16.41% in the melatonin group and 14.73% in the placebo group. In this set of trials, a meta-analysis revealed no significant difference in adverse events between the melatonin and placebo groups.¹¹⁵

A comprehensive study of the negative consequences of oral melatonin supplementation has been conducted.¹¹⁶ 26 of the 50 publications revealed no statistically significant adverse events, whereas 24 reported at least one statistically significant adverse event. Adverse effects were typically small, brief, and readily handled, with tiredness, mood, or psychomotor and neurocognitive function being the most often reported. A few studies reported adverse effects including endocrine (eg, reproductive parameters, glucose metabolism) and cardiovascular (eg, blood pressure, heart rate) function, which appear to be regulated by dosage, dose timing, and possible interactions with antihypertensive medications.¹¹⁶

A search of the literature was done to find randomized, placebo-controlled trials (RCTs) of exogenous melatonin used to treat primary or secondary sleep disturbances.¹¹⁷ The adverse effects that were most reported in the 37 RCTs identified were daytime drowsiness (1.66%), headache (0.74%), other sleep-related adverse effects (0.74%), dizziness (0.74%), and hypothermia (0.62%). There were very few severe or clinically significant occurrences. Agitation, weariness, mood fluctuations, nightmares, skin discomfort, and palpitations were among them. Most adverse effects disappeared spontaneously after a few days with no melatonin modification, or promptly upon drug discontinuation. The authors stated that the lack of data from long-term RCTs restricts their findings on the safety of continuous melatonin treatment over lengthy periods.¹¹⁷

Another meta-analysis includes RCTs on high-dose melatonin (>10 mg) in human adults over the age of 30.¹¹⁸ The number of adverse events, significant adverse events, and withdrawals owing to adverse events were the outcomes studied. There was no mention of the existence or absence of harmful effects in 29 studies (37%). Melatonin did not produce a noticeable increase in significant adverse events or withdrawals in the four trials that fulfilled the pre-specified low risk of bias criteria, although it did appear to raise the likelihood of adverse events such as sleepiness, headache, and dizziness.¹¹⁸

Uncontrolled melatonin usage in children has been noted as a growing health issue in the melatonin literature.¹¹⁹ Between 2012 and 2021, the yearly number of pediatric melatonin ingestions climbed by 530%, with a total of 260,435 ingestions recorded. Pediatric hospitalizations and bad outcomes rose as well, owing mostly to a rise in inadvertent melatonin ingestions in children aged 5 years. Increased usage of over-the-counter melatonin (particularly when consumed like candy) may put youngsters at risk of harmful effects.¹¹⁹

Concluding Remarks

Melatonin is a pleiotropic chemical agent with numerous cellular and systemic functions. Its anti-oxidant, anti-inflammatory, anticoagulopathic, and endothelium-protective properties are just a few examples. As far as sleep is concerned, melatonin is not meant for all types of sleep disorders but has a limited scope in adults and children. For example, melatonin is effective in treating circadian desynchronization (eg, delayed sleep phase syndrome in children; advanced sleep phase syndrome and old-age insomnia in the elderly, and shift work disorders and transitory jetlag disorder).^{120–122} Additionally, other studies point to the fact that melatonin is useful in psychiatric and neurological (eg, autism, neurodegenerative diseases) dysfunctions.^{43,123,124}

Melatonin clinical research has expanded beyond therapy of sleep problems into a variety of additional possible applications as our understanding of its physiological activities grows. Aside from the neurodegenerative diseases mentioned above, applications include cardiovascular disorders, cancer adjuvant treatment, side effects of conventional cancer treatments, treatment of liver diseases and injuries, fertility support, post-surgical recovery, gastrointestinal disorders, and many more. To minimize adverse effects and maximize possible advantages in future therapeutic applications, the intricacy of melatonin's interaction with the complete range of human physiological systems must be thoroughly elucidated.

Aging is accompanied by circadian changes, such as a disturbed sleep/wake cycle, as well as the emergence of low-degree inflammation (“inflammaging”), a scenario that leads to several chronic illnesses, including cancer, metabolic, cardiovascular, and neurological disorders. As a result, any effective approach to healthy aging must consider both the repair of circadian disturbance and the regulation of low-grade inflammation. Melatonin combines two features for use in human medicine: chronobiotic and cytoprotection through reducing low-grade inflammation. Melatonin is found in almost every cell of the human body, in far higher concentrations than that seen in blood drawn from the pineal gland. To change intracellular melatonin levels, dosages substantially greater than those used as a chronobiotic are required. Melatonin's remarkable evolutionary conservation strongly implies that its cytoprotective actions are important for cell function. This area is gaining more scientific attention.

In the meanwhile, the toxicity of long-term melatonin usage should be investigated. Several potentially helpful effects of melatonin, such as those in neurodegenerative illnesses or metabolic syndrome, require substantial doses of melatonin to become visible in animal experiments. Melatonin is very widely accessible as an over-the-counter dietary supplement in various countries, and as a food additive in the United States. However, the manufacturing quality and bioavailability of melatonin and the potential contaminants differ widely in these unlicensed melatonin preparations. Indeed, melatonin has come under close scientific scrutiny over the years due to its widespread use as a dietary supplement, the numerous media hypes, and frenzies, as well as its cult status and unsubstantiated therapeutic claims. Melatonin, for instance, has been called the “elixir of life”, the “hormone of darkness”, the “Princess Diana drug”, the “Dracula hormone”, “sleep hormone”, “nature's sleeping aid”, and “cure all pill.”¹²⁵ But extensive studies on melatonin over the years have shed light on its many potential functions (what it is good for), going beyond what was anticipated in terms of its ability to safeguard human health and well-being. Melatonin is generally safe in adults and children in short- (few weeks) and medium-term use (<18 months). Despite this, there are disagreements and issues with melatonin's quality, efficacy, and safety profile. In other words, there are “unknown unknowns” and “known unknowns”. Some of the causes have been briefly discussed here.

Melatonin is recognised as a natural food supplement or nutraceutical in most nations. This explains why, when, where, and how melatonin is deficient. Long-term studies on animals show that melatonin affects the reproductive axis (eg, delay of sexual maturation). Until now, there are no long-term safety data for humans (>6 months to >2 years of treatment). The fact that melatonin is typically not considered a drug, creates more issues. Over the years, for instance, some members of the public believe that melatonin is a well-liked and widely accessible over-the-counter (OTC) “cure-all pill” that does not require a prescription. This increases abuse potential. Many businesses produce and market melatonin due to its enormous commercial potential and laxer regulatory requirements. There have been reports of contaminants and dosage inconsistencies. This in turn will affect the products’ effectiveness and safety.

The immunological aspects of melatonin are not fully understood⁴⁰. Additional issues include the lack of long-term safety data, the claimed vs actual content of melatonin formulations, presence of impurities and potential contaminations, an ignorance of melatonin-drug interactions, and inter-individual variation in melatonin response.^{113,126–129}

Finally, one must realise that melatonin by itself is not responsible for this. When looking at the history of pharmaceuticals as a whole, it becomes clear that many drugs came to light because of impurities, poisoning, or dangerous side effects. For instance, thalidomide (“phocomelia”), paracetamol (poisoning), and tryptophan (eosinophilia myalgia syndrome), to name a few. This does not render the drugs ineffective. This applies to formulations with melatonin as well. Physicians and patients should carefully and continuously evaluate any products or molecules when there is a lack of supporting evidence. A prudent use or judicial prescription based on ethical principles, therapeutic evidence, and guidelines could prevent future complications. In this regard, melatonin usage needs to be made more widely known to both medical professionals and the general public. This would dispel many of the myths surrounding melatonin.

Disclosure

The authors report no conflicts of interest in this work.

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