INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Review Article

Long-Term Melatonin Use: Benefits, Risks, And Clinical Implications

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ARTICLE INFO

Published: 18 Aug. 2026
Keywords:
melatonin, clinical, n-acetyl-5-methoxytryptamine, insulin, glucocorticoids.
DOI:
10.5281/zenodo.21988755

ABSTRACT

Melatonin is a natural hormone that plays a big role in controlling our sleep wake cycle. This review covers its mechanism, receptors, chemistry and biosynthesis, dosing, interactions, agonists, most common uses, how effective it really is, contraindications, toxicity and what we know about safety from recent studies along with patient counselling highlighting the role of clinical pharmacist. It works best and has the strongest backing for things like jet lag (especially when flying east across five or more time zones), sleep troubles from shift work and helping kids with autism or ADHD get to sleep. For older adults, the slow release version can make it a little easier to fall asleep at night. There's also recent evidence that it helps prevent migraines, calm nerves before surgery. Early research points to possible perks for brain conditions like alzheimer's or Parkinson's, as extra support during cancer treatment, and even for keeping blood pressure in check, but we still need bigger studies there. Taking it for just a short time is usually safe with hardly any side effects. That said, some new findings from 2025 have raised questions about heart risks if people use it for a year or longer, though nothing is proven yet. Supplement quality varies a lot on the shelves, so getting the dose and timing right matters. It stands out as a helpful and generally safer choice than regular sleeping pills for many sleep and rhythm problems, as long as it's used properly and not for too long.

INTRODUCTION

Melatonin (N-acetyl-5-methoxytryptamine) is an indoleamine derivative. In 1967, Sagan proposed that melatonin is synthesized within mitochondria and chloroplasts, based on the evolutionary origin of these organelles from ancestral bacteria such as *Rhodospirillum rubrum* and cyanobacteria[1]. It is identified broadly throughout the eukaryotes. It is a natural hormone that the body releases mainly at night, acting as a key signal for the sleep wake cycle. It is produced by the pineal gland in response to darkness, while exposure to light suppresses its release. This daily rhythm is coordinated by the suprachiasmatic nucleus, the

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

brain's internal clock, which receives information about light from the eyes and adjusts melatonin secretion accordingly. Through this mechanism, melatonin helps synchronize the body's internal rhythms with the external day–night cycle, supporting normal sleep, alertness, and overall circadian regulation[2]. In humans, circulating melatonin is typically less than 2 pg/mL (8 pM) during the daytime, while at night it increases to about 30 to 70 pg/mL (130 to 300 pm) [3]. In mammals, melatonin mainly acts through two high-affinity G protein–coupled receptors, MT1 and MT2. These receptors respond to very low hormone concentrations, usually around 1 nM or less. They are activated by normal nighttime melatonin levels and are believed to be responsible for most of the hormone's physiological actions[4].

1) Background and History

Melatonin is considered an evolutionarily ancient molecule, present since the earliest stages of life. Its original biological role is thought to have been protection against oxidative damage by scavenging free radicals[7]. Evidence suggests that melatonin first evolved in bacteria, as it has been detected in both α-proteobacteria and photosynthetic organisms[7]. It was first isolated and identified in 1958 by Aron Lerner and his colleagues from extracts of the bovine pineal gland. Since that discovery, extensive research has uncovered detailed knowledge about its synthesis, metabolism, circadian regulation, and wide range of physiological and pathophysiological roles, along with its interactions with multiple endocrine and neuroendocrine systems throughout the body[5]. Lerner reported only drowsiness after a self-administered 100 mg dose of melatonin. In the 1960s, light dark rhythms were thought to affect animals but not humans, until Lewy showed in 1981 that nighttime light suppresses melatonin in humans. This discovery advanced chronobiology, and later studies in the 1990s revealed melatonin's roles in immunity, tumor inhibition, antioxidant defense, and metabolic regulation[6]. Melatonin ingested through food can be absorbed into the bloodstream and is able to cross into the brain, where it can bind to melatonin-specific binding sites in mammals[8]. More phases of melatonin research are still in progress and focuses on its potential role as an antioxidant and scavenger molecule. Despite extensive investigation, this area is marked by a lack of general consensus within the scientific community[9]. Hundreds of studies have suggested that melatonin may serve as a therapeutic agent for a wide range of major diseases. These include cancers, obesity, Alzheimer's disease, Parkinson's disease, and several viral infections such as AIDS, Ebola, and COVID-19[10].

2) Chemistry and Biosynthesis

CHEMICAL AND MOLECULAR LEVEL

Melatonin's antioxidant activity is mainly driven by its indole ring, which readily interacts with reactive species due to high resonance stability [84]. The amide side chain, particularly the N–C=O group, is essential for scavenging secondary radicals and forming stable reaction products, while the methoxy group at C5 helps prevent pro-oxidant behavior. Although replacing the methoxy group with a hydroxyl group may enhance antioxidant activity in vitro, it reduces lipophilicity and increases pro-oxidant risk. As a result, melatonin shows superior antioxidant efficacy in vivo compared with its hydroxylated analogs. Mechanistically, melatonin neutralizes reactive species through electron or hydrogen donation and radical addition reactions [84].

Biosynthesis

Melatonin synthesis involves six enzymes: L-tryptophan decarboxylase (TDC), tryptamine 5-hydroxylase (T5H), serotonin N-acetyltransferase

(SNAT), acetylserotonin O-methyltransferase (ASMT), caffeic acid 3-O-methyltransferase (COMT), and a putative, yet unidentified, tryptophan hydroxylase (TPH) [85].

Plants: In plants, two main melatonin biosynthetic pathways have been proposed based on enzyme kinetics. Under normal growth, melatonin is formed via the tryptophan → tryptamine → serotonin → N-acetylserotonin pathway, while under high serotonin conditions (e.g., senescence), an alternative 5-methoxytryptamine route may operate. Conversion of tryptophan to serotonin has a much higher capacity than the final serotonin-to-melatonin steps, resulting in relatively low melatonin levels in plants [86].

Animals: The melatonin biosynthetic pathway in mammals was first identified by Axelrod and colleagues in 1960 and is now well established [87]. Subsequent research has expanded this classical pathway across all vertebrates and shown that it is also conserved in other animals, including insects [87, 88]. Tryptophan is first converted to 5-hydroxytryptophan by tryptophan hydroxylase (TPH). 5-Hydroxytryptophan is then decarboxylated to serotonin by aromatic L-amino acid decarboxylase (AADC). Serotonin is acetylated to N-acetylserotonin by arylalkylamine N-acetyltransferase (AANAT). Finally, N-acetylserotonin is methylated by acetylserotonin O-methyltransferase (ASMT) to form melatonin [85].

3) Mechanism of action

Melatonin has endocrine, autocrine, and paracrine actions, which are mostly receptor mediated [19]. Melatonin exerts its effects through several molecular pathways. The most thoroughly studied mechanism involves the activation of two types of membrane-specific receptors: high-affinity ML1 sites and low-affinity ML2 sites [11, 13].

Melatonin also functions as a powerful antioxidant, neutralizing excessive free radicals through its anti-excitatory and anti-inflammatory actions [12]. Beyond this protective role, it exerts a wide range of physiological effects, including antitumor (oncostatic) activity, sleep promotion, immune modulation, and regulation of reproductive function and pubertal timing. Melatonin has additionally been implicated in mood regulation and has shown potential benefits in transplantation settings due to its immunomodulatory and cytoprotective properties [12]. Besides this it show anti tumor activity [20]. It also increases the production of IL-2 by Th1 cells [14]. but, CGP 55644 (anantagonist of melatonin nuclear receptor) significantly inhibits IL- 2 production by Jurkat cells [15].

A recent review by Liu et al. highlighted species-dependent differences in receptor pharmacology, based on affinity studies showing fluctuations in ligand selectivity in vivo [18]. Experimental models using mice with targeted disruption of either Mel1a or Mel1b receptor subtypes, as well as double mutants, have provided valuable insights into the cellular mechanisms through which melatonin regulates circadian and photoperiodic rhythmicity [17]. Production of melatonin also occurs in plants, in which the pathway from tryptophan to melatonin differs a bit from that in animals [86]

4) Melatonin Related Receptors

Distribution of melatonin receptors are highly species-specific [16]. Melatonin receptors are distributed across multiple tissues, including the brain and retina; the cardiovascular system (cardiac ventricular wall, aorta, coronary and cerebral arteries); liver and gallbladder; gastrointestinal tract (duodenum, colon, cecum, appendix); skin; parotid gland; exocrine pancreas; kidneys (including fetal kidney); immune cells and

platelets; brown and white adipose tissue; epithelial cells of the prostate and breast; ovaries (granulosa cells); myometrium; and placenta [89].

Both MT1 and MT2 receptors mainly signal through inhibitory Gi/o proteins, leading to reduced adenylyl cyclase activity and lower intracellular cAMP levels [90]. Melatonin acts through several receptor systems with distinct locations and functions. The classical G-protein–coupled membrane receptors include MT1 (melatonin receptor type 1a) and MT2 (melatonin receptor type 1b), both expressed on the cell membrane and involved in circadian rhythm regulation, sleep, and endocrine signaling. A third subtype, MT1c, has been identified in fish, amphibians, and birds, but is absent in mammals [89]. In addition to these, melatonin binds to quinone reductase 2 (QR2), also referred to as the MT3 binding site, which is primarily a detoxification enzyme rather than a classical receptor. Melatonin also interacts with RZR/RORα (retinoid-related orphan nuclear receptors), allowing it to influence gene transcription by binding to transcription factors within the nucleus. Finally, GPR50, an X-linked melatonin-related orphan receptor, does not bind melatonin directly but modulates melatonin signaling by forming heterodimers with MT1, thereby influencing MT1 receptor function [89].

5) Melatonin Receptor Signal Transduction

MTNR1A (MT1) and MTNR1B (MT2) are G-protein–coupled melatonin receptors, while the third receptor is a quinone reductase (MT3), whose signaling remains poorly defined. MT1 and MT2 are mainly expressed in the CNS and regulate circadian rhythms, whereas the nuclear receptor RZR/ROR is widely expressed in peripheral tissues and mediates immunomodulatory, growth, and metabolic effects [91]. Upon receptor binding, melatonin activates Gi/o proteins, reducing cAMP and influencing second messengers such as Ca^{2+}, cGMP, DAG, and arachidonic acid. MT1 additionally activates PLC–PKC and ERK/MAPK pathways, modulates ion channels, and promotes vasoconstriction by inhibiting potassium channels. MT2 also inhibits cGMP formation and affects glucose metabolism by reducing GLUT4 expression. Beyond receptor signaling, melatonin binds calmodulin and acts as a potent antioxidant by scavenging free radicals [91].

Melatonin influences several key intracellular signaling pathways. It typically lowers intracellular cAMP levels by activating inhibitory Gi/o proteins that suppress adenylyl cyclase activity, a mechanism central to its effects on circadian rhythm regulation, sleep initiation, and hormonal control. In parallel, melatonin can reduce cGMP production by dampening nitric oxide synthesis and subsequent guanylate cyclase activation, an effect often linked to MT2 receptor signaling. Additionally, melatonin activates phospholipid signaling through Gq or Gβγ subunits, stimulating phospholipase C and leading to the generation of IP_3 and DAG. This results in increased intracellular calcium release and activation of protein kinase C, contributing to melatonin's diverse physiological actions.

6) Interaction With Other Neuroendocrine Systems

INSULIN

MT1 and MT2 receptors are expressed in pancreatic islets, where they regulate insulin secretion from β-cells and glucagon release from α-cells [77]. Disruption of melatonin receptor signaling, particularly involving MT2, has been linked to an increased risk of type 2 diabetes in genome-wide association studies. Because melatonin is secreted in a circadian manner, it likely exerts time-dependent control over glucose

regulation within the islet. Animal studies show an inverse relationship between melatonin and insulin secretion, suggesting a potential role in metabolic dysregulation [77].

Research Review: Melatonin administration significantly reduced GIP secretion in healthy humans during an oral glucose challenge, an effect also confirmed in perfused rat intestine models. In rats, melatonin additionally suppressed GLP-1 secretion. Despite reduced incretin levels, glucose-stimulated insulin secretion in humans remained unaffected [78].

GLUCOCORTICOIDS

Corticosterone peaks at the light–dark transition, while melatonin peaks at night [79]. Corticosterone enhances nocturnal melatonin synthesis by suppressing NFκB activity in the pineal gland, a process partly blocked by mifepristone. Thus, melatonin production is regulated not only by the central circadian clock but also by glucocorticoid signaling [79]. Cortisol is a key stress hormone that increases glucose availability, cardiovascular activity, and alertness via activation of the HPA axis. While beneficial acutely, chronically elevated cortisol can impair sleep, cause fatigue, and reduce concentration [80]. Melatonin normally counteracts cortisol by rising in the evening as cortisol declines, promoting sleep. Stress disrupts this balance, leading to elevated evening cortisol, delayed melatonin release, and fragmented sleep, creating a cycle of stress and sleep disturbance [80].

SEX HARMONES

Melatonin exerts complex, context-dependent effects on sex hormones that vary with species, dose, and physiological state [84]. It modulates the hypothalamic–pituitary–gonadal axis by inhibiting GnRH release, leading to reduced LH and FSH secretion and decreased sex hormone production. In men, this can lower testosterone levels, while in female rats melatonin reduces LH and estradiol but increases progesterone levels [84].

Research Review: In a randomized double-blind placebo-controlled trial, 240 postmenopausal women received either melatonin (3 mg) or placebo for 3 months [81]. Sexual function scores improved significantly in both groups, but the increase was markedly greater in the melatonin group. Differences between groups were significant across follow-up assessments ($P < 0.001$). These findings indicate that melatonin significantly improves sexual function in postmenopausal women [81]

Research review: Melatonin–beeswax pellets implanted near the suprachiasmatic nucleus reduced sexual receptivity in ovariectomized, estrogen-treated female rats compared with beeswax controls [82]. This suppression of lordosis behavior supports the antireproductive effects of melatonin. The findings suggest that some effects previously attributed to serotonergic mechanisms may instead involve melatonergic action [82].

7) Pharmacokinetics

One of the main limitations of melatonin as a dietary supplement is its low and highly variable bioavailability among individuals. Animal studies suggest that melatonin is mainly metabolized in the liver by CYP1A2 and CYP2C19 into 6-hydroxymelatonin, which is then sulfated to 6-sulfatoxymelatonin (6-SM), making up about 80% of melatonin metabolites [71]. Similar pathways have been observed in humans [42]. The 6-SM metabolite is inactive and excreted in urine [72]. This variability in bioavailability is thought to result from extensive first-pass liver metabolism, poor gut absorption, or a combination of both,

leading to unpredictable levels in the bloodstream and variable clinical effects [69].

Research Review: A systematic review of 22 studies with doses ranging from 0.3 to 100 mg, given orally or intravenously, showed wide differences in pharmacokinetics [70]. For oral immediate-release melatonin, Tmax was around 50 minutes and T1/2 about 45 minutes. Other parameters such as Cmax, AUC, clearance, and volume of distribution varied considerably. Oral bioavailability averaged roughly 15% and was influenced by age, caffeine, smoking, feeding status, oral contraceptives, and fluvoxamine. In critically ill patients, absorption was faster but elimination was impaired, emphasizing the considerable variability between individuals [70].

8) Dosing in Children

Most research on pediatric melatonin use has focused on children with comorbidities such as autism spectrum disorder (ASD) or attention-deficit/hyperactivity disorder (ADHD). These studies generally report improvements in sleep onset and total sleep duration in these populations. However, evidence supporting the use of US melatonin formulations in otherwise healthy children is very limited. Because dietary melatonin products in the United States are not strictly regulated and their composition and potency can vary widely, their use in healthy pediatric populations should be approached with caution. Clinicians are advised to consider melatonin only when non-pharmacological strategies, such as sleep hygiene and behavioral interventions, are insufficient, and if used, it should be at the lowest effective dose with close monitoring [72].

Melatonin also plays a critical role in fetal development. Studies have confirmed that maternal melatonin crosses into fetal circulation, suggesting it may help guide the maturation of the fetal circadian system. Despite this, the processes governing fetal circadian rhythm synchronization remain poorly understood [73]. Irregularities in maternal or placental melatonin production have been associated with adverse pregnancy outcomes, including an increased risk of spontaneous abortion, highlighting the importance of maintaining appropriate maternal melatonin levels during gestation [74]. In healthy children, melatonin is generally administered at doses of 0.5 to 5 mg, taken 30–60 minutes before bedtime. This timing helps synchronize sleep with the natural circadian rhythm and promotes sleep onset. Doses are typically started low and titrated according to response and tolerability, taking into account individual differences in pharmacokinetics and sensitivity [71].

10) Therapeutic Application

A) WELL ESTABLISHED USES

Jet Lag

Melatonin has proven to be a efficient and safer treatment for Jet lag [25]. Melatonin works really well to stop or ease jet lag, and using it now and then for a short time seems safe [22].

Research Review: This study checked if 5 mg daily melatonin could help ease jet lag in people who flew from London to eastern Australia (10 time zones east).In a double-blind setup, 14 people got melatonin and 17 got a placebo, with doses timed to promote sleep best [23].After arrival, researchers measured grip strength and ear temperature several times a day on alternate days, plus daily jet lag ratings (0-10 scale) and a questionnaire on tiredness, sleep, meals, and focus for the first week. Participants kept their normal busy work routines.Results from 13 people in each group showed body temperature rhythms partly shifted to local time by day 6, and grip strength varied by time of day—but melatonin made no

difference compared to placebo [23].Jet lag symptoms lingered, with tiredness and overall ratings still high on day 6, while concentration and some sleep issues improved faster. The melatonin group felt no better than placebo on irritability, focus, meals, sleep quality, or bowel habits [23], but however, it usually does work especially for eastward flights crossing 5+ time zones. Many large reviews (including Cochrane 2014 & 2022 updates) confirm it reduces jet lag symptoms by 1–2 days on average.

Research Review: This older study on 52 flight crew found that taking 5 mg melatonin after returning home (not before) helped reduce jet lag, sleep issues, and fatigue better than placebo or starting it early. Late starters recovered energy and alertness faster, while early starters felt worse overall than placebo [24], Studies (including big reviews from places like Cochrane and CDC) show melatonin really cuts down jet lag symptoms when taken right—usually 0.5-5 mg near bedtime in the new zone, starting on arrival day for a few nights.

Doctors should suggest it to adults who are flying across five or more time zones, especially when going east, and mainly if they've had jet lag before on similar trips. People flying across two to four time zones can try it too if they feel they need it [22].

Delayed Sleep-Wake Phase Disorder (DSWPD)

DSWPD is a sleep disorder involves habitual sleep–wake times that are delayed compared to conventional or socially acceptable sleep times [26]. Co-morbidities are associated with DSPD are attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) [27].

Research Review: This meta-analysis of nine randomized trials (91 adults, 226 children) found that melatonin significantly advanced endogenous melatonin onset by 1.18 hours and sleep onset by 0.67 hours compared with placebo [28]. Sleep-onset latency was reduced by 23.3 minutes, while wake-up time and total sleep duration showed no significant change. Overall, melatonin was effective in correcting circadian phase delay in patients with delayed sleep phase disorder [28].

Shift Work Sleep Disorder

Exogenous melatonin has been shown to improve sleep disturbances in shift-working healthcare personnel and is generally well tolerated with few adverse effects, supporting its potential use in this group [29]. However, existing studies show wide variability in dosing, formulation, and follow-up duration, often include small sample sizes, and are largely limited to younger participants, which restricts the strength and generalizability of the evidence [29].

Insomnia in Older Adults (Age 55+)

Insomnia is among the most common sleep disorders in older adults. It is characterized by difficulty falling asleep, problems staying asleep, or early morning awakenings with an inability to return to sleep, despite having adequate opportunity and suitable conditions for sleep. These nighttime symptoms are accompanied by daytime distress or impairment in functioning [30].

Given the limited number of safe treatment options for insomnia in older adults, current evidence suggests that melatonin and the melatonin receptor agonist ramelteon have moderate effectiveness in increasing total sleep time and shortening sleep latency [31]. Melatonin generally shows a good safety profile in older adults, but evidence on its long-term use remains limited. Several age-related factors may increase the risk of adverse effects, and these should be carefully considered when

melatonin is prescribed in this population [31,32]. In contrast to well-recognized safety concerns associated with benzodiazepines and nonbenzodiazepine hypnotics, melatonin and ramelteon appear to be safer and potentially effective alternatives for managing insomnia in older patients [31].

Sleep Disturbances in Children with Neurodevelopmental Disorders (e.g., Autism, ADHD)

Sleep disturbances are particularly common in neurodevelopmental disorders. Among individuals with autism spectrum disorder (ASD), a high proportion experience difficulty falling asleep (53%), restless sleep (40%), nighttime awakenings (34%), and problems waking up from sleep (32%) [33]. Similarly, sleep problems affect about 73.3% of patients with ADHD, ranging from mild disturbances (28.5%) to moderate or severe issues (44.8%), including frequent nighttime awakenings, delayed sleep onset, and circadian rhythm disruptions [34].

Research Review: The study successfully met its primary outcome. After 13 weeks of double-blind treatment, children receiving PedPRM slept substantially longer at night compared with those on placebo, with marked improvements in both total sleep time and sleep latency, without causing earlier morning awakenings [40]. A significantly higher proportion of participants achieved clinically meaningful improvements with PedPRM, resulting in a low number needed to treat. Overall sleep disturbance also showed a downward trend. PedPRM was generally well tolerated, with somnolence reported more often than with placebo, and the pediatric formulation was well accepted even among children with swallowing difficulties [40].

B) USES WITH MODERATE OR EMERGING EVIDENCES

Primary Insomnia

Melatonin decreases sleep onset latency, increases total sleep time and improves the overall sleep quality [41].

REM sleep Behavior Disorder

Rapid eye movement sleep behavior disorder (RBD) is a complex parasomnia that often coexists with other sleep disorders and may be influenced by their treatments, such as those used for narcolepsy with cataplexy [32].

Melatonin is an effective option for treating REM sleep behavior disorder and may act more directly on disease mechanisms than clonazepam. Although its exact mechanism is unclear, a possible role as a calmodulin antagonist has been suggested. In the absence of direct comparative trials, its good safety profile makes melatonin a suitable choice, especially for older patients with neurodegenerative disorders or polypharmacy [21].

Migrane Prevention

Melatonin demonstrates potential as a safe, well-tolerated, and affordable option for both the treatment and prevention of migraines, with some evidence of reducing migraine frequency [57].

Research Review: Seven studies including randomized trials and observational studies were analyzed. The results were mixed, with some showing melatonin effective for migraine prevention while others showed no difference from placebo or less effectiveness than amitriptyline [37]. Immediate-release melatonin 3 mg and agomelatine 25 mg showed promising results, and treatment duration of at least three months may be needed. Melatonin is generally

safe, though rare serious side effects have been reported. Overall, melatonin appears to be a promising option for migraine prophylaxis, but more high-quality studies are needed [37].

Agomelatine, a melatonin analog, also shows promising results. However, the optimal dosage, dose-dependent effects, and long-term safety of melatonin remain unclear. Further well-designed clinical trials are needed to confirm its efficacy and to explore agomelatine's role in migraine management [57].

C) INVESTIGATIONAL OR OFF LABEL USES

Neurodegenerative Disorders (e.g., Alzheimer's, Parkinson's)

Mild cognitive impairment (MCI) is characterized by deficits in memory, reasoning, or perception and is often considered an early stage in the progression to AD. Diagnosis can be supported by imaging evidence of amyloid-β plaques or tau fibers on PET scans [60]. A systematic review and meta-analysis of more than 22 randomized controlled trials demonstrated that melatonin supplementation significantly improved Mini-Mental State Examination scores in patients with mild AD [58]. These findings suggest that melatonin may be a promising adjuvant therapy for enhancing cognitive function in individuals with MCI associated with early AD.

Overall, melatonin appears to be a promising therapeutic agent in the battle against neurodegenerative diseases commonly found in older adults [42]. The compound's complex mechanisms, encompassing strong antioxidant capabilities, anti-inflammatory actions, and circadian rhythm regulation, establish it as a vital component in safeguarding brain health. Melatonin's capacity to remove free radicals and decrease oxidative stress holds particular importance, given that oxidative damage is a defining characteristic of neurodegenerative disorders [42].

Cancer as Adjuvant

Melatonin has been shown to act synergistically with chemotherapeutic agents by inhibiting angiogenesis, a process often unintentionally stimulated by chemotherapy itself. Adding melatonin can counteract this pro-angiogenic effect, which may help explain its anticancer properties and its ability to enhance tumor sensitivity to standard chemotherapy, even in resistant cancers [35]. Immunomodulating neurohormones normally regulate the release of hormones and cytokines by the endocrine system. Accordingly, as an immunomodulatory agent, MLT may be considered a palliative treatment for cachexia [40]. The effects of MLT on tumors can be classified as either cytostatic or cytotoxic. Cytotoxicity occurs exclusively at high MLT concentrations, and the type of cells and tumor determine the level of effectiveness. In this respect, MLT treatment levels may differ based on the type of cancer cell. Breast cancer cells, for example, are sensitive to low (nanomolecular) MLT concentrations, stopping their proliferation. Other cancer cells do not respond to low MLT levels, whilst high MLT levels can inhibit their proliferation, as observed in colon cancer cells and human prostate cancer cells. The absence of cytotoxicity is observed in all nontumor cells, even at high MLT levels. Due to this property, MLT can be used as an anti-tumor agent without causing damage to healthy cells [41].

Melatonin influences the expression and activity of multiple angiogenesis related factors that are altered during cancer treatment and has also been proposed as a radiosensitizer, strengthening the tumor suppressive effects of radiation therapy. Together, these actions highlight melatonin's role

in improving the effectiveness of anticancer treatments through antiangiogenic mechanisms [35].

High Blood Pressure

Oral melatonin has been proposed as a possible alternative therapy for hypertension. Among the 13 clinical trials identified, only three specifically evaluated the effects of melatonin. These trials were analyzed in detail, including their study design, participant numbers, clinical conditions, interventions, and outcome measures, to better understand the potential risks and benefits of melatonin in high arterial blood pressure. Overall, melatonin appears to have a blood pressure lowering effect, but further well designed studies are needed to clearly define its benefits, risks, and the mechanisms involved in blood pressure regulation [59].

A meta analysis of randomized controlled trials up to June 2021 assessed whether melatonin lowers blood pressure, improves sleep, and is well tolerated compared with placebo **[45].** Only four trials met inclusion criteria, and just one had a low risk of bias, with none reporting cardiovascular outcomes. Controlled release melatonin modestly reduced asleep systolic blood pressure by about 3.6 mm Hg, while effects on diastolic pressure were not statistically significant. Melatonin improved sleep quality and total sleep time and was generally safe, but overall evidence quality was low, highlighting the need for larger, well designed trials [45].

Obesity

Several studies have linked melatonin (MLT) deficiency to obesity and its complications [36,38]. Owing to its antioxidant and metabolic regulatory properties, MLT has been proposed as a therapeutic agent [36,38]. Mechanistically, MLT epigenetically modulates nuclear factor erythroid 2-related factor 2 and inhibits pro-inflammatory pathways such as NF-κB and NLRP3 [39]. Clinical and experimental evidence shows that MLT reduces adipocyte secretion of TNF-α and IL-6, increases high-density lipoprotein cholesterol, lowers visceral fat, and decreases plasma triglycerides, low-density lipoproteins, and very-low-density lipoprotein cholesterol [39].

11) Comparative effectiveness with other Chronobiotics

Chronobiotics are agents that influence the timing of the biological clock (circadian rhythms).

TASIMELTEON

Tasimelteon is a melatonin receptor agonist indicated for the treatment of non-24-hour sleep–wake disorder in blind individuals. Its use has been associated with a low incidence of serum enzyme elevations and has not been linked to clinically significant liver injury [63]. Tasimelteon remains the only medication authorized by the FDA in 2014 and the EMA in 2015 for treating non-24-hour sleep–wake rhythm disorder (Non-24), with orphan drug status [61].

It is a selective agonist of the melatonin MTNR1A and MTNR1B receptors and has been shown to reduce sleep-onset latency, improve sleep maintenance, and realign the circadian melatonin rhythm, supporting its potential use in circadian rhythm sleep disorders (CRSD) [64]. It has been suggested that tasimelteon, like agomelatine, may have potential therapeutic utility in the management of depression [62].

RAMELTEON

Research Review: Ramelteon is a potent melatonin receptor agonist with high affinity for MT1 and MT2 receptors, promoting sleep and supporting circadian rhythm regulation. It reaches peak plasma concentration in approximately 0.75 hours

[65]. Research was conducted by Nalaka S. Gooneratne, M.D., M.Sc,Philip Gehrman, Ph.D. ,Indira Gurubhagavatula, M.D. ,Erica Al-Shehabi, B.A. ,Elisabeth Marie, M.A.,Richard Schwab, M.D. , to evaluate the efficacy of ramelteon in managing insomnia among older adults beginning auto-titrating positive airway pressure (APAP) therapy for sleep apnea [66].

In a randomized, double-blind, placebo-controlled pilot trial involving 21 adults aged ≥60 years with obstructive sleep apnea and insomnia initiating APAP therapy, participants received ramelteon 8 mg or placebo for 4 weeks [66]. Ramelteon significantly reduced polysomnography-measured sleep onset latency compared with placebo, without affecting subjective sleep measures, AHI, sleep efficiency, or APAP adherence. The treatment was well tolerated, supporting ramelteon's potential role in managing insomnia in older adults with sleep apnea [66].

AGOMELATINE

Agomelatine acts as an antagonist at the postsynaptic serotonin 5-HT_2C receptor and as an agonist at melatonergic MT1 and MT2 receptors [68]. Through this dual mechanism, it modulates circadian rhythm regulation while enhancing monoaminergic neurotransmission, which is thought to contribute to its antidepressant effects. Agomelatine is approved for the treatment of major depressive disorder (MDD) and is particularly noted for improving sleep–wake disturbances associated with depression, with a generally favorable tolerability profile [68].

Research Review: A systematic review and meta-analysis of 10 randomized controlled trials evaluated the efficacy and safety of agomelatine in depressive disorder [67]. Agomelatine significantly improved HAMD-17 scores compared with placebo, with no significant difference in adverse events after accounting for heterogeneity. These findings support agomelatine as an effective and well-tolerated treatment option for depression [67].

Table 1

Agent	Mechanism	Main Use	Comparative Notes
Melatonin	Natural hormone	Sleep onset, circadian phase shift	Safe, low risk, modest effect
Tasimelteon	MT1/MT2 agonist	Non-24-hour sleep-wake disorder	Similar SOL effects to melatonin; possibly better on SE & TST
Ramelteon	MT1/MT2 agonist	Insomnia (sleep onset)	Modest benefits vs placebo; similar overall to melatonin
Agomelatine	MT1/MT2 agonist + 5-HT_2C antagonist	Depression + sleep issues	Beneficial for mood + sleep but liver risk

12) Drug Interactions

Melatonin is known to interact with more than 300 medications, especially alcohol and other drugs that cause drowsiness or dizziness, which can intensify these effects. When taken alongside blood thinners such as warfarin, melatonin may also raise the risk of bleeding [52]. It is metabolized by cytochrome P450 enzymes that also process many drugs commonly prescribed in older adults. The extent of drug–melatonin interactions varies, and only a limited number have been systematically studied [53].

Several selective serotonin reuptake inhibitors (SSRIs) can significantly alter melatonin levels.

Fluvoxamine, for example, increases maximum serum concentrations by 2.8- to 12 [49]. Citalopram alone does not appear to raise melatonin concentrations; however, when combined with proton-pump inhibitors (both CYP2C19 substrates), urinary melatonin metabolites double [50].

Melatonin may also reduce the efficacy of the calcium channel blocker nifedipine. In patients receiving 5 mg of melatonin daily for four weeks, systolic and diastolic blood pressure increased by 6.5 and 4.5 mmHg, respectively [55].

Melatonin should not be used alongside immunosuppressive drugs, as it can stimulate immune activity. Caution is advised when using melatonin in individuals with autoimmune diseases, liver or kidney impairment, hypertension, seizure disorders, or depression [54] . Its use in children and adolescents under 20 years should be carefully considered, since melatonin may interfere with pubertal development, cause menstrual irregularities, or trigger early puberty after discontinuation. Prolonged use may also suppress reproductive hormone secretion [54].

Co-administration of cannabinol (CBN) and melatonin may lead to a pharmacokinetic drug–drug interaction, as cannabinoids can inhibit drug-metabolizing enzymes. CBN has been shown to strongly inhibit CYP1A2, the primary enzyme responsible for melatonin metabolism [56]. Experimental findings indicate that CBN markedly suppresses CYP1A2-mediated melatonin metabolism, resulting in a substantial increase in melatonin exposure, with a four-fold rise in plasma levels observed in animal models [56].

Immediate-release melatonin acts for a short duration (about 3–4 hours), while prolonged-release formulations maintain effective levels across the night. Medications that inhibit CYP1A2 can reduce melatonin metabolism, and wide interindividual differences in bioavailability make dose adjustment important [51]. Melatonin appears generally safe for short-term use (up to three months), and available long-term data with pediatric prolonged-release melatonin show mainly mild effects such as fatigue, sleepiness, and occasional mood changes, without impacts on growth, BMI, pubertal development, tolerance, or withdrawal [51].

13) Contraindications

Although melatonin is generally well-tolerated, rare cases of angioedema have been reported in association with its use [43] [44]. Because melatonin is an endogenous hormone, adverse reactions may sometimes be linked to unregulated excipients present in certain supplement formulations [43] [44]. Clinicians should be cautious when prescribing melatonin to patients with autoimmune conditions, including rheumatoid arthritis or those who have undergone organ transplantation.

Melatonin has been shown to stimulate immune function by enhancing the production of interleukins (IL-1, IL-2, IL-6, IL-12), interferon-γ, helper T cells, cytotoxic T cells, and B- and T-cell precursors. However, the clinical relevance of these immunomodulatory effects remains uncertain [45].

14) Toxicity and Safety Profile of Melatonin

Melatonin exhibits remarkably low acute toxicity in both animal and human studies. Even at supraphysiological doses, adverse drug reactions are generally mild and may include headaches, rashes, gastritis, nightmares, or insomnia. Importantly, no lethal dose (LD50) has been established in animals, with studies reporting no fatalities even at doses as high as 800 mg/kg [48].

Preliminary human observations suggest that prolonged melatonin administration may negatively affect semen quality in healthy men, potentially through aromatase inhibition at the testicular level [46].

Recent public health data raise concerns about pediatric exposure. A morbidity and mortality report documented a sharp rise in annual pediatric melatonin overdose cases, increasing from approximately 8,000 in 2012 to more than 52,000 in 2021. Notably, 15% of affected children required hospitalization due to overdose complications [47].

15) Patient Counseling on Melatonin

Patient counseling is important for the safe use of melatonin, as it is easily available over the counter and often considered harmless. Patients should understand that melatonin mainly helps regulate the sleep wake cycle and works best for circadian rhythm disorders, not as a general sleeping pill. It should be taken regularly about 30–60 minutes before bedtime along with good sleep habits [93].

Patients should be advised to start with the lowest effective dose and avoid long-term use without medical supervision, especially in children and adolescents. Common side effects such as daytime sleepiness, headache, dizziness, and vivid dreams should be explained. They should avoid driving if they feel drowsy and should not take melatonin with alcohol due to increased CNS effects [41].

Extra caution is needed in patients with other illnesses or those taking multiple medicines. Patients should inform healthcare providers if they are using melatonin, particularly when taking antidepressants, anticoagulants, antiepileptics, or immunosuppressants. Melatonin should be avoided during pregnancy and breastfeeding unless prescribed, and patients should be advised to choose reliable, quality-controlled products [95].

16) Future Directions

High-dose melatonin use, especially in infants and vulnerable patients, should be limited as a precaution [10]. The safety profile at such levels remains largely unknown, and even moderate doses have not been thoroughly evaluated in humans. There is a significant need for clinical trials to better understand the long-term physiological effects of melatonin. Key aspects, including the signaling mechanisms of its receptors, their structures, and how they interact with the hormone, remain largely unexplored, offering numerous avenues for future research. A deeper understanding of these receptors and their signaling pathways could lead to the development of more effective therapies for a range of diseases and disorders. Given melatonin's regulatory influence on multiple physiological systems, it holds considerable promise as a therapeutic agent across diverse clinical applications. Assuming that a naturally occurring substance is automatically safe can be misleading and may pose risks, highlighting the importance of careful dosing and further safety studies [10].

CONCLUSION:

Melatonin is a naturally occurring hormone with a strong safety profile and very high LD_{50} in animal studies, meaning it has low toxicity even at high doses. In humans, side effects are generally mild and temporary, such as sleepiness during the day, headache, dizziness, or mild digestive discomfort. Clinically, melatonin is most commonly used for sleep and circadian rhythm disorders, including insomnia, jet lag, and shift work disorder, and it shows promise as an adjunct in mood or metabolic conditions. Its effects are largely mediated through MT1 and MT2 receptors, and selective agonists

like ramelteon and tasimelteon allow more targeted therapy.

Melatonin also interacts with several endocrine systems. It can influence the hypothalamic–pituitary gonadal axis, modulate insulin secretion from the pancreas, affect glucocorticoid rhythms, and play a role in leptin signaling. These interactions, together with individual differences in absorption and metabolism, mean that responses can vary from person to person. Long-term use appears well tolerated, but more studies are needed, especially in children, older adults, and patients with chronic illnesses.

Looking forward, research should aim to standardize formulations, better understand melatonin's hormonal crosstalk, and optimize dosing for different populations and conditions. Exploring its potential beyond sleep such as in metabolic, reproductive, and neuropsychiatric disorders—could help unlock its full therapeutic benefits while minimizing variability and side effects.

CONFLICT OF INTEREST:

The author declares that there is no conflict of interest.

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HOW TO CITE: Swaraj Mahanag*, Gauri Kshirsagar, Dr. Anand Khode, Long-Term Melatonin Use: Benefits, Risks, And Clinical Implications., Int. J. of Pharm. Sci., 2026, Vol 4, Issue 8, 2763-2783. https://doi.org/10.5281/zenodo.21988755