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# Non-trivial uses of melatonin: Its effects on sleep, jet lag, obesity, migraine, and gastrointestinal disorders

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**ABSTRACT**

**Introduction and aim of the study:** Melatonin consumption is steadily increasing. In this literature review, the authors intended to introduce the latest scientific evidence on the influence of the sleep hormone not only on the quality of time spent in bed and jet lag, but also to consider possible other positive impacts. Its eventual effects on headaches, gastrointestinal complaints, or obesity were analyzed.

**Materials and methods:** The authors searched the scientific literature utilizing search engines such as Science Direct, Cochrane, PubMed, Google Scholar, and UpToDate. The literature review focused on the association of melatonin with issues such as sleep, migraines, GERD, IBS, and jet lag.

**Results**: Most of the articles reviewed in this study highlighted the positive effects of melatonin supplementation on sleep problems and jet lag. Furthermore, many studies report that it likewise has a beneficial impact on conditions not directly related to sleep, such as obesity, GERD, IBS, or migraine. Nevertheless, the articles emphasize the need for further research to establish treatment protocols and to select an optimal dose.

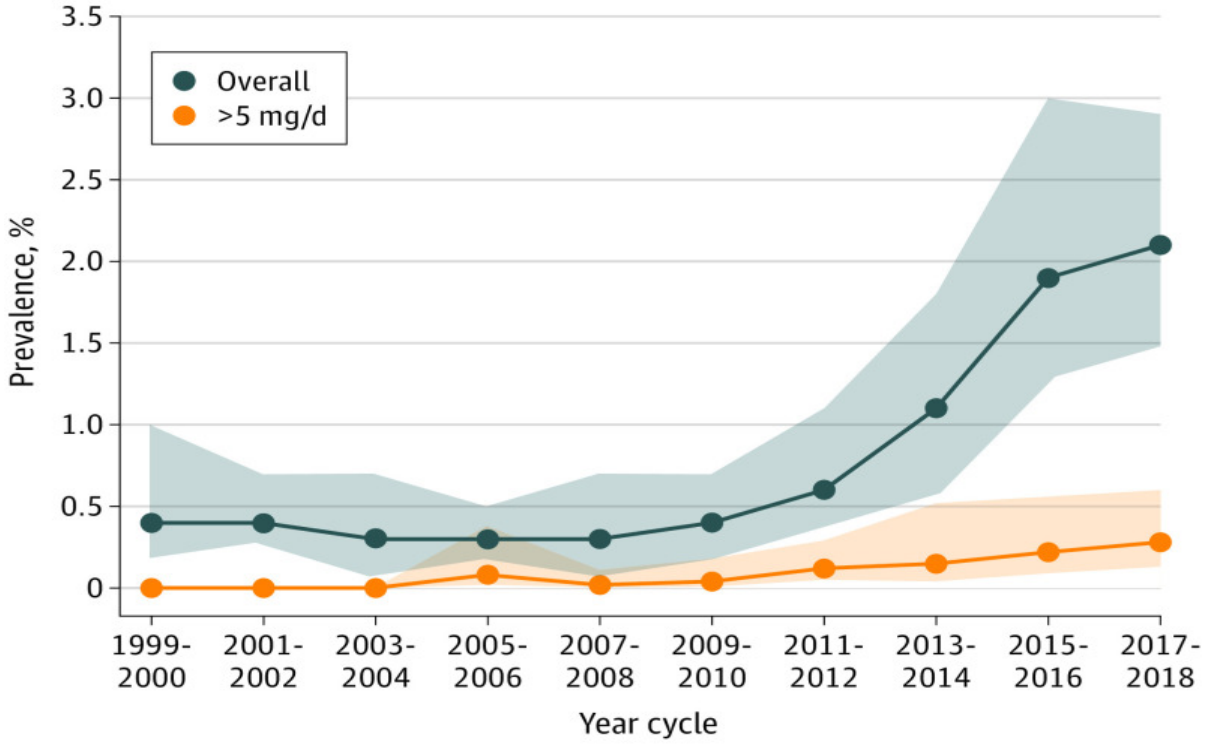
**Keywords**: melatonin, indoleamines, sleep, obesity, shift work, jet lag, safety, migraine, GERD, IBS,

## INTRODUCTION

Melatonin (N-acetyl-5-methoxytryptamine) is a versatile substance belonging to the endogenous indoleamines. (1) It occurs endogenously in both animals and plants. The human body obtains it from exogenous sources, i.e., diet, and produces it independently. Endogenous production occurs from the amino acid tryptophan in the pineal gland and enterochromaffin cells in the gut. Interestingly, 400 times more of it is in the intestines than in the pineal gland. (2) Daily melatonin secretion in the pineal gland averages between 0.1 and 0.9 mg. (3,4) The hormone has also been detected in the trachea, retina, lens, thyroid, cochlea, skin, brain, liver, kidney, spleen, pancreas, thymus, and reproductive tissues, (3) as well as in all body fluids: cerebrospinal fluid, saliva, feces, bile, amniotic fluid, urine, semen, synovial fluid, and breast milk. (5–7)

Circadian generators in the brain regulate the concentration of this substance in the body during the day. (8) This substance acts as a circadian rhythm indicator in the central nervous system. (9) It is also attributed to the role of a darkness indicator, as its production is induced by darkness sensed by the eye's retina. (4) Exposure to light reduces indoleamine production, and this also applies to artificial light, which reduces melatonin levels and increases the risk of disease. (3,4)

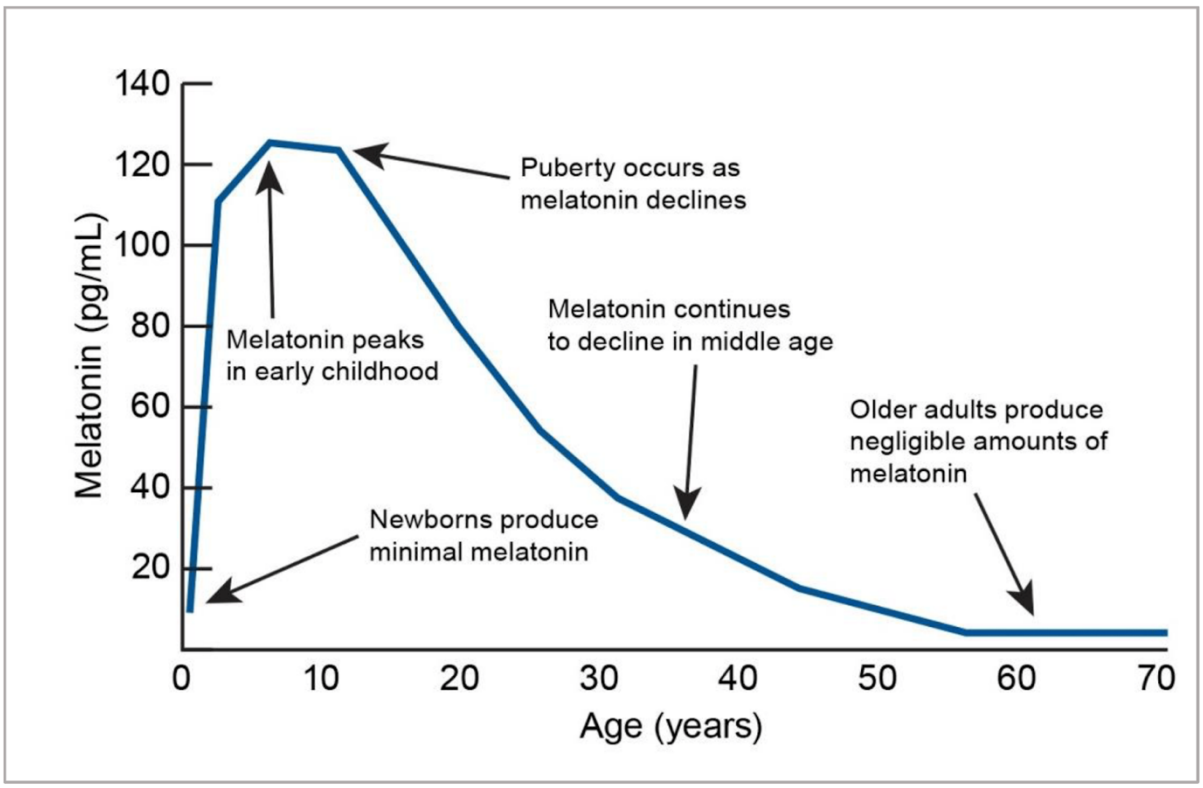
Due to the possible wide range of uses of melatonin, interest in its supplementation in people with sleep disorders or in improving immunity, is very high. A study by Hartstein et. al found that in 2022, as many as 19% of children and adolescents in the United States (US) are taking these substances, when in 2017, the percentage was only 1.3%. (10) A study by Li et al. among US adults showed an increase in melatonin intake from 0.4 percent in 1999- 2000 to 2.1 percent in 2017-2018. Trends were seen in both genders and across all age groups. There was also an increase in the frequency of intake of this substance above 5mg/d. Results are presented in graph 1. (11)




Graph 1

Incidence of general melatonin administration and administration at doses higher than 5 mg per day in adults in the US. (11)

The amount of melatonin produced in humans changes with age. Infants do not produce their melatonin until around 3 months of age, (12) and their natural source is breast milk. (13) Subsequently, its levels in the body increase with puberty and reach a plateau at puberty, followed by a gradual decline from the late twenties to the fifties. (14,15)




Graph 2

Fluctuations in melatonin levels with age. (14)

Studies have shown that calcification of the pineal gland, which has the highest calcification rate among all organs and tissues of the human body, may also be responsible for reducing hormone secretion, (7) disease, (16) diet, (4) medication, (17) lifestyle (17) and exposure to bright light at night (18) may also have a significant impact on melatonin levels.

In their comprehensive review study, Minich et al. compared melatonin and its role in the human body to vitamin D, as it is a highly interesting compound with broad applications and pleiotropic activity. It has potent antioxidant activity and the ability to inhibit inflammation, cross the blood-brain barrier, and interact with the gut microbiome, so it can have a significant impact on the occurrence of systemic diseases. Disorders of its function can cause "darkness deficiency". (19)

In this review article, we will evaluate the existing evidence for the effects of melatonin on directly related issues such as sleep disorders and jet lag and discuss this substance as a potentially effective support for the treatment of obesity, migraine, and gastrointestinal disorders. We will also consider the safety of the administration of this hormone.

## METHODS

The authors searched the scientific literature utilizing search engines such as Science Direct, Cochrane, PubMed, Google Scholar and UpToDate. The literature review focused on the association of melatonin with issues such as sleep, migraines, Gastroesophageal reflux disease (GERD), irritable bowel syndrome (IBS), and jet lag.

## SLEEP

Gholami et al. conducted a meta-analysis based on The Pittsburgh Sleep Quality Index and included 2642 articles, though 23 remained after exclusions. The study indicated that melatonin supplementation significantly improved sleep quality, additionally showing positive use in primary sleep disorders. (20) Another meta-analysis looked at the effect of melatonin on sleep quality. The study showed that while the substance reduces the time to fall asleep and improves sleep efficiency, but it showed no positive effect on patients with secondary sleep disorders. (21) Timothy et al. conducted a Randomized trial of people with sleep disorders. They demonstrated that low-dose exogenous melatonin (0.5 mg) significantly reduced the time to fall asleep and improved patient's subjective wellbeing.(22) In this meta-analysis, researchers analyzed the effect of higher doses of melatonin and also showed bedtime improvements in terms of falling asleep faster and sleep quality in individuals, who took supplementation. (23) Moreover, the researchers, led by Jeanne F Duffy, decided to summarize the magnitude of indoleamine on sleep in one study. They presented that low (0.3 mg) and higher (5mg) doses improved sleep performance. However, it is worth noting that the positive effects were only evident in the older population, whereas younger participants showed no remarkable advantage. (24) What is more, researchers from the Royal Infirmary Edinburgh, Ninewells Hospital, and the University of Surrey analyzed the action of this hormone in people with visual impairment, during which they discovered that it is also able to regulate circadian rhythms in this population. (25) The randomized controlled trial conducted at Hospital de Base São José do Rio Preto and Hospital do Câncer de Barretos evaluated a total of 203 patients in the intensive care unit. The researchers showed that melatonin positively affected the quality of sleep-in individuals in that department, which increased the care possibilities of patients in critical conditions. (26)

## JET LAG AND SHIFT WORK

Current times allow long-distance travel by passenger aircraft. Long-distance flights lead to jet lag, which can manifest in several non-specific symptoms, including gastrointestinal distress, fatigue, headache, irritability, or loss of concentration. (27,28)
Moreover, a comparable situation exists for shift workers to a certain degree.(29)

Maintaining a regular circadian rhythm has an intrinsically positive influence on the productivity and well-being of our functioning throughout the day. This guarantees the maintenance of homeostasis in our body. (30) Interestingly, these destinations also have a different impact on the human body. For example, manic episodes were more frequent in people traveling from west to east, while the reverse direction of travel increases the risk of depression. (31) In these instances, melatonin again becomes an instrument to help us. When supplemented, it positively affects sleep cycles and speeds up the synchronization of diurnal rhythms disrupted by travel or shift work. Consequently, an individual experiences a reduction in symptoms and recovers from them faster. (8) Furthermore, supplementation with melatonin preparations is likewise widespread in the application of athletes, who are prone to jet lag due to attending international tournaments spread across the globe. In this study, researchers analyzed the hormone intake in graduated decreasing doses, starting with a high concentration of 7-8 mg, with positive effects observed. (32) On the other hand, in another study by Alfred J. Lewy et al., the researchers looked at free-running athletes who took low doses of supplements of around 0.5 mg. They, too, declared a faster adaptation to the new time zone. Perhaps the fact that the individuals were blind has a bearing on the fact that a lower dose of melatonin was sufficient. (33)

According to the above-mentioned investigations, one may conclude that melatonin contributes to faster recovery and implementation after jet lag. However, additional research is needed to analyze and determine the most optimal dose of melatonin for supplementation.

## GASTROINTESTINAL DISORDERS

Melatonin is also known to have favorable effects on different levels. These include the gastrointestinal tract. Beginning in its initial region, the oral cavity, the hormone stimulates the immune system, thus reducing inflammatory conditions such as periodontal disease and herpes. In addition, it can also be used in patients with known oral cancer and in the case of xerostomia. (34) Subsequently, numerous papers focusing on gastric complaints showed that melatonin

relieved symptoms. In a study that researchers in Iran conducted, 78 participants were recruited from a selection of 163 individuals with GERD symptoms to investigate the influence of sublingual 3 mg indolamine supplementation on perceived oesophageal complaints. Following 5 months, participants taking the hormone claimed significant improvement and a reduction in pain. (35) Furthermore, an eight-week study conducted at Mansoura University showed that daily supplementation with 3 mg of melatonin resulted in a comparable outcome to the use of omeprazole. (36) Furthermore, the study by Konturek et al. highlighted the protective effect of the oesophageal mucosa by reducing the reflux effect. They also highlighted the use of Helicobacter pylori (H. pylori) in infections, gastric ulcers, and inflammatory bowel disease. (37–39)

Finally, patients with intestinal complaints may also find relief when taking sleep hormone supplementation. (40) In a meta-analysis by Si Nae Oh et al. where 30 trials were analyzed, a reduction in the intensity of persistent pain among IBS patients was observed. (41) Another study conducted at the Tehran University of Medical Sciences found that melatonin reduced abdominal pain and additionally promoted defecation in patients diagnosed with IBS. (42) A randomized, double-blind, placebo-controlled trial was conducted in 2023, which included 136 patients with IBS. Over a period of eight weeks, 3 mg of melatonin was administered on an empty stomach and 3 mg before bed, giving a daily dose of 6 mg. The results showed that sleep hormone supplementation resulted in a significant reduction in gastrointestinal complaints, including bloating and abdominal pain, as well as satisfaction with bowel habits in IBS patients. (43)

## MIGRAINE

Migraine is a chronic multifactorial disorder that is one of the most common neurological problems encountered in clinical practice. Its prevalence is between 12 and 20% of the population. (44) It manifests as paroxysmal, recurrent attacks of headache, which may be accompanied by nausea, vomiting, drowsiness, and hypersensitivity to light and sound. (44) Migraine patients report lower quality of life and indicate a disease-related social and economic burden. (45,46) Treatment is mainly based on preventive measures. (47–49) Beta-blockers without sympathomimetic activity, namely ethanol, metoprolol, and propranolol, are used as first-line formulations. (50) In the second line, however, flunarizine, amitriptyline, and sodium valproate are used. (48) It has been proven that the hypothalamus may be important in the pathophysiology of this disorder. (51,52) In addition, studies show that three out of four patients

suffering from migraines also report problems with insomnia. (53,54) Therefore, melatonin as a hypothalamic neuropeptide has gained interest as possibly effective in the treatment of migraine. (55)

A 2022 meta-analysis conducted by Puliappadamb et al. demonstrated that taking melatonin prophylactically at a dose of 2 to 3 mg reduces the severity and average duration of a migraine attack and the amount of pain medication used compared to placebo. (56) Similar results were provided by a meta-analysis by Tseng et al., which showed a positive effect of taking 3 mg of melatonin before sleeping on the number and severity of attacks, with no side effects. (47) As well as a study by Liampas et al. showed efficacy similar to amitriptyline, sodium valproate or propranolol and better than pizotifen. (57) A randomized clinical trial conducted by Mehramiri et al. in 2024, which included 60 migraine patients, showed that taking melatonin at a dose of 3 mg, 1 hour before bedtime, for a period of 2 months, help to reduce the frequency and duration of attacks and reduced the amount of analgesic medication taken, compared to placebo. In this study, effects were seen for 4 months after the end of therapy. (58) Similarly promising results were provided by earlier clinical trials conducted by Ali et al. (59), Goncalves et al. (46) and Ebrahimi et al. (60) In the later mentioned study, melatonin as an adjunct to treatment with nortriptyline and propranolol, lasting 8 weeks, resulted in reductions in migraine attacks compared to placebo, comparable to valproate's effectiveness. (60) In addition, in a study by Goncalves et al., the hormone had a beneficial effect on migraine symptoms, demonstrating efficacy similar to amitriptyline, but importantly, while being better tolerated than it. (46)

Several aspects underlie its effectiveness in treating migraine. It has been proven that the relationship between pain and sleep is bi-directional, that is, both migraine attacks can impair the quality of sleep, and sleep disturbances can negatively affect the severity of headache attacks. (61) Therefore, it is speculated that treating a patient's existing sleep disorders and insomnia may indirectly affect the alleviation of migraine symptoms. (53,62) Another aspect is that melatonin also interacts with opioid, gamma-aminobutyric acid Gamma-aminobutyric acid (GABA), adrenergic, serotonergic, and cholinergic receptors, as well as melatonergic (MT) receptors, resulting in an antinociceptive role. (63,64) This hormone also has anti-inflammatory properties (65) and has a decreasing effect on the production of vasoactive substances such as calcitonin gene-related peptide (CGRP) and nitric oxide (NO), (66) It is significant, considering that there is evidence that inflammation and neurogenic vasodilation are important in the pathophysiology of migraine attacks. (65,67) In summary, the positive effects of melatonin on migraine attacks may be multidirectional.

## OBESITY

Obesity and overweight are common conditions, affecting more than two out of three adults in the US (68) and in England, in 2017, these statistics reached 64%. (69) These numbers are expected to increase in both countries in the future, resulting in huge healthcare expenditures in this area. (70,71) Moreover, by 2050, the percentage of obese people will exceed 50%. (72) There are many factors underlying this disease, such as excessive calorie intake, low physical activity, sedentary lifestyle, and genetic factors. (73) The disease can also lead to the co-morbidity of many other serious conditions, including diabetes, ischaemic heart disease, and osteoarthritis.(74)

There is evidence that melatonin supplementation may help treat obesity. A 2021 meta-analysis involving 16 studies and 1,065 patients found that patients taking doses of the hormone < 8 mg had reduced body weight compared to those taking placebo. No beneficial effect on BMI or waist circumference was proven. (75) Mostafavi et al., in another meta-analysis from 2017, did not confirm the weight-reducing impact of melatonin but hypothesized, based on the study's results, that it may be a buffering factor for weight fluctuations. (76) Another study conducted in 2019 also did not prove the effect of indolamine on anthropometric measurements but found that it may be effective in improving lipid parameters and should be considered as a preventive measure against cardiovascular disease. (77)

The mechanisms of indolamine's effect on weight loss are not fully understood. Research indicates that this process may be influenced by various factors, such as modulation of adipose tissue activity, impact on musculoskeletal metabolism, cardiovascular and lipid profile, glucose homeostasis and insulin sensitivity, biochemical modulation of hepatic parameters, and mitochondrial modulation. (78)

## SAFETY

Generally, studies indicate that exogenous melatonin supplementation is safe. (79,80) It has been confirmed that even high doses should not result in serious side effects in the short term. Mild adverse effects such as dizziness, headache, nausea, and drowsiness may occur. (79) Besag et al. conducted a study in 2019 that analyzed 37 randomized clinical trials in which patients took doses ranging from 0.15 to 12 mg of the substance. Several mild-to-moderate side effects were reported in the participants, such as daytime sleepiness (1.66%), headache (0.74%), other sleep-related adverse events (0.74%), dizziness (0.74%) and hypothermia (0.62%). More

serious adverse events such as agitation, fatigue, mood swings, nightmares, skin irritation, and palpitations were reported very rarely. (81) In a 12-month long-term study by Russcher et al., the hormone showed no serious side effects. (82) However, research suggests that exogenous melatonin intake is not recommended for pregnant and breastfeeding women. (79,81)

## CONCLUSION

Melatonin's role is crucial in regulating circadian rhythms, sleep-wake cycles, and all sorts of neurohormonal processes. Hence, it could potentially be a valuable instrument that can be administered as an additive to the treatment of conditions unrelated to sleep.

The literature review above discusses the value of melatonin supplementation in various medical conditions. The scientific studies confirmed its benefits in improving sleep quality, especially in people suffering from primary sleep disorders, jet lag, and shift work. Furthermore, in addition to its impact on sleep, it demonstrates positive effects in treating gastrointestinal conditions such as GERD and IBS, and chronic migraines and obesity offering significant clinical potential. However, more detailed clinical studies are needed to establish optimal doses and treatment protocols. Melatonin is generally well tolerated in terms of safety, with mild side effects such as dizziness and daytime sleepiness reported infrequently.

In summary, melatonin appears to have pleiotropic effects, offering potential therapeutic benefits beyond its initial association with sleep regulation. Additional research is required to uncover its full benefits and establish more precise clinical guidelines for its use in various conditions.

## ABBREVIATIONS

**GERD** Gastroesophageal reflux disease
**IBS** Irritable bowel syndrome
**US** United States
**GABA** Gamma-aminobutyric acid
**MT** Melatonergic
**CGRP** Calcitonin gene-related peptide
**NO** Nitric oxide

## DISCLOSURE

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