

# The Safety of Melatonin in Humans

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**Abstract** Exogenous melatonin has been investigated as treatment for a number of medical and surgical diseases, demonstrating encouraging results. The aim of this review was to present and evaluate the literature concerning the possible adverse effects and safety of exogenous melatonin in humans. Furthermore, we provide recommendations concerning the possible risks of melatonin use in specific patient groups. In general, animal and human studies documented that short-term use of melatonin is safe, even in extreme doses. Only mild adverse effects, such as dizziness, headache, nausea and sleepiness have been reported. No studies have indicated that exogenous melatonin should induce any serious adverse effects. Similarly, randomized clinical studies indicate that long-term melatonin treatment causes only mild adverse effects comparable to placebo. Long-term safety of melatonin in children and adolescents, however, requires further investigation. Due to a lack of human studies, pregnant and breast-feeding women should not take exogenous melatonin at this moment.

## Key Points

Short-term use of melatonin is safe, even in extreme doses.

Only mild adverse effects, such as dizziness, headache, nausea and sleepiness have been reported.

Long-term safety of melatonin in children and adolescents should be investigated further.

Pregnant and breast-feeding women should not take exogenous melatonin at this moment.

## 1 Introduction

The physiological functions of the pineal hormone melatonin are extremely diverse. The functions include direct and indirect modulations of anti-oxidative defense, blood pressure, body temperature, cortisol rhythm, reproduction and immune function [1]. Correspondingly, exogenous melatonin has been investigated as treatment for a number of medical and surgical diseases, demonstrating encouraging results [2–4]. In the USA, melatonin is available as an over-the-counter non-prescription drug. In most European countries, however, melatonin remains a prescription drug (Circadin®), and has only been approved as treatment for primary insomnia in people over 55 years of age. However, a recent Norwegian register study documented a 3- to 5-times increase in off-label use (magistral preparations) among children and adolescents in the time period 2004 to 2012 [5].

As a medical sleeping aid, a single dose of 1–10 mg is considered standard, although, optimal dosing and

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administration route have not been clarified for most indications [6]. Melatonin is generally considered safe [7], but the increasing clinical use with potentially increasing doses necessitates further investigations of the risks of both mild and serious adverse effects.

In experimental animal studies, exogenously administered melatonin has been given in doses up to 800 mg/kg without any acute toxic effects [8]. Interestingly, a lethal dose (LD)<sub>50</sub> could not be estimated due to the upper limit of solubility of the drug [8]. Also, very large doses up to 200 mg/kg/day were administered to rats during gestation (day 6–19), reporting no increased prenatal mortality of offspring, changes in fetal weight, or alterations in the rate of embryological malformations [9].

To our knowledge, to date, only two randomized studies have assessed the potential adverse effects of exogenous melatonin as primary outcomes [10, 11]. Hence, the recommendations concerning the safety of exogenous melatonin can only be established from translational findings from animal studies, and experimental and clinical studies in humans, assessing adverse effects as secondary outcomes.

The aim of this narrative review is to present and evaluate the literature concerning the potential adverse effects and safety of exogenous melatonin in humans. Furthermore, we provide recommendations concerning the possible risks of melatonin use in specific patient groups.

## 2 Studies in Infants, Children and Adolescents

A number of studies in preterm infants have investigated the anti-oxidative/anti-inflammatory and clinical effects of exogenous melatonin in different conditions, such as pain during tracheal intubation (10 mg/kg  $\times$  10 doses, randomized) [12], sepsis (10 mg  $\times$  2 doses, randomized) [13], asphyxia (10 mg  $\times$  8 doses, randomized) [14], respiratory distress (10 mg/kg  $\times$  10 doses, randomized) [15] (10 mg/kg  $\times$  10 doses, randomized) [16], surgical procedures

(10 mg/kg  $\times$  10, non-randomized) [17] and chronic lung injury (10 mg/kg  $\times$  10 doses, randomized) [18]. Despite repeated high doses of intravenous melatonin, no signs of adverse effects were observed [12–18]. Other randomized trials included children, aged 2–18 years, suffering from autism [19, 20], epilepsy [21] and mixed neurodevelopmental disorders [22, 23]. Oral melatonin in doses of 0.5–10 mg was administered daily from 10 days to 12 weeks to improve sleep quality [19–23]. The studies performed detailed registration of possible adverse effects, demonstrating a number of mild adverse effects, such as agitation, dizziness, headache, nausea, and sleepiness [19–23]. The distribution of these adverse events, however, did not differ in frequency between melatonin- and placebo-treated groups. Recently, a follow-up cohort study, which included 59 adolescents (mean age = 12 years) with chronic sleep onset insomnia, investigated the long-term effects of exogenous melatonin (mean administration length = 3.1 years; mean dose = 2.7 mg) [24]. The treatment group was compared to the general Dutch population of same age and sex. The groups were not significantly different with respect to sleep quality, pubertal development or mental health scores.

## 3 Experimental Studies in Adults

A recent randomized, double-blind, placebo-controlled study investigated the toxicity of oral melatonin as primary outcome [8]. Forty healthy subjects were allocated to either 10 mg of melatonin or placebo for 28 days. The subjects were examined in detail using polysomnographic testing, subjective sleep scales and extensive biochemical testing. Furthermore, subjects were instructed to report other possible subjective adverse effects. No differences between melatonin-treated individuals and those given placebo were reported for any of the outcomes. Other experimental studies have assessed the possible sedative effects and psychomotor impairment of exogenous melatonin [25–27].

**Table 1** Adverse effects of melatonin in selected patient groups. “Short-term”, “intermediate-term”, and “long-term” refer to days, weeks-to-months, and years of administration, respectively

| Patient groups                 | Short-term administration           | Intermediate-term administration   | Long-term administration        |
|--------------------------------|-------------------------------------|------------------------------------|---------------------------------|
| Infants in clinical studies    | No reported adverse effects [11–17] | No data                            | No data                         |
| Children in clinical studies   | Only minor adverse effects [17–21]  | Only minor adverse effects [17–21] | Only minor adverse effects [23] |
| Adults in experimental studies | Only minor adverse effects [24–26]  | Only minor adverse effects [9]     | No data                         |
| Adults in clinical studies     | Only minor adverse effects [29–31]  | Only minor adverse effects [29–31] | No data                         |
| Surgical patients              | Only minor adverse effects [6]      | No data                            | No data                         |
| Critically ill patients        | Only minor adverse effects [36–38]  | No data                            | No data                         |
| Pregnant women                 | No data                             | No data                            | No data                         |
| Breast-feeding women           | No data                             | No data                            | No data                         |

In an experimental randomized, double-blind, crossover study, 12 healthy male subjects were administered either placebo, or intravenous melatonin 10 or 100 mg, respectively [27]. Sedation, assessed as simple reaction times, and self-reported symptoms of adverse effects were recorded. No differences in either simple reaction times or self-reported symptoms of adverse effects were documented between the groups. Another experimental study in 23 volunteers investigated psychomotor impairment following the administration of 2 mg of oral melatonin [25]. Melatonin was compared to three other hypnotic drugs in a randomized double-blind, crossover design. While melatonin did not affect psychomotor function as opposed to other hypnotics, it increased subjective sleepiness [25]. Also, in a randomized study, which included 19 subjects who were administered 5 mg of oral melatonin or placebo [26], the subjects performed a computerized test battery, assessing attention, reaction times, concentration capacity, and sensory-motor coordination. The testing results were not affected by melatonin treatment, but subjective sleepiness was also increased by melatonin. Finally, previous experimental cohort studies have administered large oral doses of melatonin. An experimental study including five patients administered 1 g of melatonin for 25–30 days, assessed the plasma levels of growth hormone (GH), luteinizing hormone (LH)/follicle-stimulating hormone (FSH), adrenal/thyroid function, and skin color [28]. The study indicated that LH and GH levels were depressed by exogenous melatonin, although statistical comparisons were not performed. No adverse effects were reported. Similar high doses of melatonin were also administered as a treatment for Parkinsonism for 4 weeks without any signs of serious adverse effects apart from transient sedation [29].

#### 4 Clinical Studies in Adults

A randomized, double-blind, placebo-controlled study including 54 female patients undergoing breast cancer surgery were given 6 mg of oral melatonin or placebo to improve depressive symptoms and anxiety during a three-month investigational period [30]. The study provided a detailed investigation of potential adverse effects. Fifty-six percent of the individuals in the melatonin treatment group versus 50 % in the placebo treatment group experienced at least one adverse effect. The most common adverse effects in the melatonin treatment group were dizziness, headache, and paresthesia of the mouth, arm or legs. No statistical difference between the treatment groups was found. Similarly, another randomized study administered 3 mg of melatonin or placebo for a three-month period [31]. Melatonin improved dyspnea and

biochemical outcomes in chronic obstructive pulmonary disease (COPD) patients. Mild adverse events occurred in two patients in the melatonin group and in two patients in the placebo group, respectively. The reported adverse effects included a transient episode of numbness, mild headache, and worsening of dyspnea [31]. Finally, a randomized, double-blind, placebo-controlled study was conducted in elderly patients suffering from Alzheimer's disease who were administered 2 mg of melatonin or placebo for a 24-week period [32]. Outcomes were cognitive performance and sleep quality. Only mild adverse effects were observed, but none were considered related to melatonin treatment. No statistical differences in terms of adverse effects were documented between the treatment groups.

#### 5 Melatonin in Surgical Patients

A number of randomized trials have investigated the clinical effects of exogenous melatonin in surgical patients [3]. A recent systematic review, which included 10 randomized trials, concluded that no serious adverse effects of melatonin treatment were reported [7]. The included studies administered 2–10 mg of melatonin, 30–45 min prior to various types of surgery. Mild adverse effects, such as psychomotor impairment, sedation, disorientation, and amnesia were recorded. However, the findings were conflicting, with some studies indicating possible psychomotor impairment [33], sedation [33–36] and loss of orientation [36], due to melatonin. Interestingly, a recent randomized study investigating patients undergoing liver resection reported no signs of adverse effects or postoperative complications despite administrations of 3.5 g of oral melatonin [11].

#### 6 Critically Ill Patients

A randomized study assessed the sedative effects of exogenous melatonin in 82 patients in the intensive care unit (ICU) [37]. Patients were randomized to 6 mg of oral melatonin or placebo from the third day of admission until discharge (median ICU stay = 14/12 days). No serious adverse effects were observed in either group. Three patients discontinued treatments due to increased sleepiness (1 = treatment group; 1 = placebo group) and a skin rash (1 = placebo group), respectively. In another randomized study of 24 patients who were administered 10 mg of oral melatonin or placebo [38], outcomes included assessments of sleep quality and pharmacokinetic analysis. The only registered adverse effect was a mild headache in one patient in the melatonin group, treated

effectively by a single dose of acetaminophen. Similarly, no differences in sleepiness or use of sedatives were observed in a cohort study administering 3 mg of oral melatonin [39].

## 7 Discussion

This review documents that melatonin is safe for short-term use, even when given in extreme doses. Mild adverse effects, such as dizziness, headache, nausea and sleepiness have been reported in levels corresponding to placebo treatments. Final conclusions concerning long-term safety of melatonin are limited by a general lack of randomized, double blind, placebo-controlled studies, and methodical weaknesses in the reporting of possible adverse effects. However, the sparse data available suggest no serious adverse effects, even with long-term use (Table 1).

A substantial number of experimental and clinical studies have examined the physiological and clinical effects of exogenous melatonin. Adverse effects were reported in many of these studies; however, the quality of reporting varies extensively. Unfortunately, only two randomized studies have investigated possible adverse effects of melatonin as primary outcomes [9, 10]. Hence, other studies potentially did not possess the statistical power to detect possible differences between the treatment groups. Furthermore, some studies did not include a placebo treatment group, and lacked blinding. Finally, the studies did not a priori determine which adverse effects were relevant, making classifications and comparisons between studies even more difficult.

In clinical trials, melatonin is typically administered as a hypnotic, anxiolytic, analgesic or anti-inflammatory drug [3, 40]. Hence, the adverse effects and safety profile should be compared to drugs such as benzodiazepines, opioids, non-steroidal anti-inflammatory drugs (NSAIDs), and glucocorticoids. These drugs induce both short- and long-term adverse effects, and may also cause major complications and morbidity [41]. Benzodiazepines induce amnesia, confusion, dizziness, respiratory dysfunction and sedation [42]. The acute adverse effects of opioids include constipation, dizziness, itching, postoperative nausea and vomiting, respiratory dysfunction, and sedation [43]. Both benzodiazepines and opioids also induce tolerance, and may impose a risk of addiction. Recent studies also document that NSAIDs increase the risk of gastrointestinal bleeding, renal failure, cardiac and cerebral morbidity [44–47], and increase the risk of serious postoperative complications in general surgery [48]. Finally, corticosteroids cause a number of serious adverse effects, including osteoporosis, edema, hyperglycemia, glaucoma, and increased risk of infections [49]. In this context, the

previously described mild adverse effects of melatonin can be viewed as minimal. Furthermore, melatonin is neither physiologically nor psychologically addictive. However, the unestablished clinical efficacy of melatonin within most indications does not allow melatonin to replace any standard drug regimens at this moment, possibly with the exception of drug treatments in sleep disorders and as a preoperative anxiolytic [3, 50].

### 7.1 Children and Adolescents

A number of randomized studies have administered melatonin in children. The reported adverse effects have been mild and comparable to placebo treatments. It has been speculated that long-term melatonin may influence sexual maturation, although a recent cohort study refuted this [24]. In animals, exogenous melatonin affects seasonal reproduction capacity and sexual maturation [51]. Similarly, some studies in humans indicate an inhibitory effect of melatonin on hypothalamic-pituitary-gonadal function [52], although an exact relationship has not yet been established. Due to the possible impact on sexual maturation, however, large-scale randomized controlled trials are definitely needed before long-term safety of melatonin can be established in children and adolescents.

### 7.2 Pregnancy and Breast-Feeding Women

At this moment, no clinical trials have administered exogenous melatonin to pregnant women. In animals, high-dose melatonin did not induce developmental toxicity [9]. Actually, recent experimental studies indicate that the anti-oxidative effects of melatonin may even reduce the risk of serious pregnancy-related complications, such as preeclampsia [53]. At this moment, exogenous melatonin should, however, not be administered during pregnancy due to the lack of human studies supporting either clinical effects or risk of adverse effects. Correspondingly, melatonin, being a small amphiphilic molecule, is transferred to breast milk [54], and could potentially induce adverse effects, such as sedation and daytime sleepiness, in nursing infants. Especially as recent studies document significantly different pharmacokinetic properties with extended elimination half-lives in infants compared to an adult population [55].

Interestingly, experimental studies in vitro and in vivo indicate that melatonin is instrumental to optimal ovarian and placental function [56]. In humans, preliminary studies investigating in vitro fertilization treatments reported improved pregnancy rates after the administration of 3 mg of melatonin daily [57].

### 7.3 Elderly

More than 30 % of adults aged over 65 years use benzodiazepines for sleep and anxiety disorders, despite increased risks of adverse effects, morbidity and mortality [58, 59]. Natural endogenous melatonin levels are reduced during aging [60]. Correspondingly, supplementary melatonin has shown positive clinical results as an anxiolytic and hypnotic with limited adverse effects [2]. It should, however, be noted that reduced elimination rates may cause extended supraphysiological plasma levels (>10 h) in the elderly suffering from insomnia with oral doses  $\geq 4$  mg [61], also possibly increasing the risks of adverse effects, such as daytime sleepiness.

### 7.4 Drug Interactions

Pharmacokinetic studies in humans have documented that drugs metabolized by CYP (1A2) liver enzymes, such as fluvoxamine [62], caffeine [63] and oral contraceptives [64] increase plasma levels of melatonin following exogenous administration. Also, non-published industry data indicate that drugs, such as psoralen and cimetidine, may increase plasma melatonin levels. On the contrary, plasma levels are reduced by carbamazepine and rifampicin. Also, cigarette smoking has been shown to increase plasma melatonin levels [65]. The clinical impact of these plasma level changes in relation to the risk of adverse effects is, however, not established. Also, melatonin in combination with hypnotics induces additive adverse effects, such as impaired psychomotor performance and memory [66]. Finally, as melatonin can be purchased “over-the-counter” in several countries, good manufacturing practices (GMPs) are not monitored by regulatory authorities, increasing the risk of variable product quality, dosages and potential contamination.

## 8 Conclusions

A substantial number of both animal and human studies document that short-term use of melatonin is safe, even in extreme doses. No studies indicate that exogenous melatonin possesses any serious adverse effects. Also, randomized clinical studies indicate that long-term administration only induces mild adverse effects comparable to placebo treatment. Due to a lack of human studies, pregnant and breast-feeding women should not take exogenous melatonin. Also, long-term safety of melatonin in children and adolescents requires further investigation.

### Compliance with Ethical Standards

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