



Safety issues regarding melatonin use in child and adolescent patients with sleep problems

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Several studies have reported that melatonin may be effective in treating sleep problems in children and adolescents. However, evidence regarding the safety of melatonin use in children and adolescents in their growth and developmental stages is warranted. Therefore, we aimed to summarize the literature on the safety of melatonin use in children and adolescents with insomnia and sleep disturbances. According to existing evidence, there are no serious adverse effects of long-term melatonin use in children and adolescents. The common adverse effects reported in long-term studies are fatigue, somnolence, and mood swings. In addition, there is no evidence that long-term use of melatonin inhibits the natural secretion of melatonin. It is necessary to monitor potential drug interactions with medications such as inhibitors and enhancers of cytochrome P450 1A2 (CYP1A2). Furthermore, low CYP1A2 expression in young children requires proper dose adjustment. Although sufficient experience of melatonin use in children and adolescents has yet to be attained, accumulating evidence suggests that the use of melatonin in children and adolescents with sleep problems might be effective and tolerable. Considering the abuse or overdose risk of hypnotics or benzodiazepines, melatonin supplements may be a good therapeutic alternative. Future studies on the long-term safety of melatonin for physiological and mental function in children and adolescents are required to establish certainty about melatonin use in children and adolescents.

Keywords: Adolescent; Child; Insomnia; Melatonin; Sleep

Introduction

Insomnia and sleep disturbances in children and adolescents are important mental health issues. The lifetime prevalence of insomnia in adolescents aged 13 to 16 years is 10.7% [1]. Insomnia in adolescents tends to be chronic [2]. In addition, sleep disturbances due to neurodevelopmental disorders and mood disorders are frequently experienced by children and adolescents. Patients with autism spectrum disorder (ASD) have sleep problems, such as

increased sleep onset latency, decreased sleep efficiency, decreased total sleep time, and lower amplitude [3-5]. Sleep abnormalities have also been reported in patients with attention deficit hyperactivity disorder (ADHD) [6,7]. The sleep-wake cycle is frequently delayed in patients with ADHD [8]. Sleep or circadian abnormalities have been observed in children and adolescents with mood disorders [9]. Therefore, sleep problems in children and adolescents should be addressed properly.

However, it is difficult to deal with sleep problems in

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children and adolescents because there are many concerns about the use of hypnotics or benzodiazepines differently from that in adults [10]. Early exposure to benzodiazepines during childhood and adolescence may lead to potential abuse or overdose [11]. In addition, there is a lack of research on whether long-term use is effective or safe in children and adolescents [10]. Given that sufficient sleep promotes the secretion of growth hormones [12], treatments for sleep problems might have a crucial influence on growth and development in children and adolescents [13]. In addition, stabilization of sleep-wake rhythms can be important for regulating various physical functions in children and adolescents [14,15]. For these reasons, it may not be desirable to delay treatment for insomnia or sleep disturbances despite therapeutic difficulties.

Several psychiatric treatments have been used to treat sleep disorders. Insomnia can be treated through psychosocial interventions, such as cognitive behavioral therapy or sleep hygiene, to help sleep [16,17]. However, some pediatric patients show poor compliance with cognitive behavioral therapy [18]; cognitive behavioral therapy also has limited use in patients with ASD [17]. Insomnia is also treated with antidepressants or antipsychotic medications, such as trazodone, doxepin, tricyclic antidepressants, quetiapine, benzodiazepine, or hypnotics [19]. However, these medications require adequate diagnosis and have potential side-effects [10,20]. Attempts have been made to control sleep problems with melatonin [10]. Melatonin and melatonergic agents have been reported to be helpful in shortening the sleep latency period and increasing sleep efficiency without serious side-effects in adults or older adults [21,22]. Exogenous melatonin supplements are widely used as an over-the-counter drug for sleep improvement in Canada and United States [23,24]. However, exogenous melatonin supplement is not officially approved for any indication by U.S. Food and Drug Administration. In the European Union, melatonin supplement was approved for medical use in 2007 [25]. Although melatonin supplement is not officially approved in all countries, several studies support that melatonin supplements may be useful in regulating sleep in children and adolescents. Therefore, we aimed to summarize the literature on the safety of melatonin use in children and adolescents with insomnia or sleep disturbances.

What are the adverse effects of melatonin use in children and adolescents?

Several studies have reported adverse effects of exogenous melatonin use in children and adolescents. A systematic review and meta-analysis on the efficacy and safety of melatonin for sleep problems in children with neurodevelopmental disorders was performed [26]. This study reported no serious medication-related adverse events. Another systematic review of randomized controlled trials in children and adolescents with ASD and ADHD also reported that melatonin 2–10 mg/day in the child and adolescent population was well tolerated and safe [27]. The most common adverse effects were fatigue (18.9%), vomiting (16.8%), mood swings (13.7%), and upper respiratory infections (10.5%) [27]. Another literature review summarized the adverse effects of exogenous melatonin reported in previous studies on children with ASD and ADHD [4]. Although this review stated adverse events, such as increased nocturnal enuresis, morning drowsiness, headache, dizziness, gastric complaints, and fatigue, most of the adverse effects were mild [4]. To date, serious adverse effects have not been reported.

Are there studies on safety of long-term melatonin use in children and adolescents?

Several studies have reported the long-term use of melatonin in children and adolescents (Table 1) [28-33]. One open study on long-term melatonin use was performed in eight children and young adults with non-24-hour sleep-wake syndrome [28]. The patients showed diurnal variations in serum and urinary melatonin levels, delayed peak of melatonin secretion, and body temperature variation before melatonin use. Melatonin treatment in the evening dramatically improved the sleep-wake pattern. The improvement was maintained during long-term melatonin use for 1 to 6 years in six patients. During long-term melatonin use, one patient returned to the previous sleep pattern after 6 to 8 months. Another patient with reflux esophagitis complained of increased sleep disturbances. No other adverse side effects were associated with long-term melatonin use.

Table 1. Adverse effects of melatonin use in long-term studies with children and adolescents

Study (year)	Design/duration	Sample	Age (yr) ^{a)}	Diagnosis	Dose	Administration time	Principal adverse effects
Palm et al. (1997) [28]	Case series (1–6 yr)	8	3–23	Blindness and intellectual disability with non-24-hr sleep-wake syndrome	Initial dose: 0.5–2 mg Maximal dose: 4 mg	30–60 min before bedtime	Reflux esophagitis complaints and increasing sleep disturbance
Carr et al. (2007) [29]	Placebo-controlled, double-blind cross-over trial Open-label study (3 mo–3.8 yr)	44	4.3	Neurodevelopmental disability and treatment-resistant circadian rhythm sleep disorders	Sustained melatonin: mean 1.4 mg	NA	No serious adverse effects
Hoebert et al. (2009) [30]	Randomized, double-blind, placebo-controlled trials Open-label follow-up study (mean 3.7 yr)	101	6–12	ADHD and chronic sleep onset insomnia	3 mg/day (<40 kg) 6 mg/day (≥40 kg)	NA	Dizziness (4.3%), bedwetting (3.2%), and sleep maintenance insomnia (3.2%)
Yuge et al. (2020) [31]	26-wk open-label study	99	6–15	Neurodevelopmental disorders with longer sleep onset latency (≥30 min for 3 or more mo)	Starting dose: 1 mg Final dose: 1, 2, 4 mg	30–60 min before bedtime	TEAEs: 14.1% All TEAEs: mild No TEAEs after 16 wk Withdrawal symptoms (–) Rebound phenomenon (–) Rebound
Maras et al. (2018) [32]	Total 52 wk 13-wk double-blind phase + 39-wk continuous phase	95	2–17.5	ASD and neurogenetic disorders (with/without ADHD) with insomnia	Prolonged-release melatonin 2, 5, 10 mg	30–60 min before bedtime	At least 1 TEAEs 17.9%, fatigue (5.3%), and mood swings (3.2%)
Malow et al. (2021) [33]	Total 104 wk 3-mo double-blind phase + 2-wk withdrawal phase + 90-wk continuous phase	80	2–17.5	ASD with insomnia	Starting dose: 2 mg After 3 wk: 2–5 mg After 12 wk: 5–10 mg	30–60 min before bedtime	Fatigue (6.3%), somnolence (6.3%), and mood swings (4.2%) No significant changes on children's growth and pubertal development such as weight, height, body mass index, or pubertal status

ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; NA, not assessed; TEAEs, treatment-emergent adverse events.

^{a)}Range or mean.

A follow-up study after a placebo-controlled trial of sustained-release melatonin also reported the long-term safety of melatonin use in 44 children with neurodevelopmental disabilities and treatment-resistant circadian rhythm sleep disorders [29]. This prospective study examined adverse events through structured telephone interviews with caregivers. Long-term melatonin use from 3 months to 3.8 years did not show any evident adverse reactions. In particular, adverse events in this study were rated using Likert 0–4 (0=never or not applicable, 4=very often). The mean ratings ranged from 0 to 0.27, representing rare occurrences of adverse events.

A similar follow-up study was performed to examine the

effectiveness and safety of long-term melatonin use in 101 children with ADHD and chronic sleep onset insomnia [30]. One-fifth of the children experienced adverse events. Approximately 50% of the children experiencing adverse events showed self-limiting course. The most frequent adverse event was dizziness (4.3%). In conclusion, this study reported that long-term melatonin use for a mean of 3.7 years had no safety concerns regarding serious adverse effects.

A multicenter, 26-week, open-label study in 99 children with neurodevelopmental issues (age 6–15 years) with problems in sleep onset latency (≥30 minutes) for 3 or more months reported the effectiveness of melatonin

in shortening sleep onset latency and safety [31]. Treatment-emergent adverse events (TEAEs) accounted in 14.1% of patients. In addition, all TEAEs were mild, and there were no TEAEs at 16 weeks after the initiation of medication. Neither medication withdrawal symptoms nor rebound phenomena were observed.

A 13-week double-blind randomized placebo-controlled study and a subsequent follow-up study for 1 year reported the long-term safety of prolonged-release melatonin (2, 5, and 10 mg) for insomnia in children and adolescents with ASD and neurogenetic disorders with or without ADHD comorbidity [32]. In this study, 1-year continuous treatment after a 3-month open-label use was performed. This study showed beneficial effects on sleep parameters, such as total sleep time, sleep latency, sleep fragmentation, and sleep quality, compared to placebo. Prolonged release of melatonin showed minimal adverse effects, such as fatigue (5.3%) and mood swings (3.2%).

A subsequent double-blind, placebo-controlled study for 2 years also demonstrated the long-term safety of prolonged-release melatonin (2, 5, and 10 mg) for insomnia in 80 children with ASD (2–17.5 years of age) [33]. This study evaluated the long-term effects of melatonin on sleep, growth, body mass index, and pubertal development for up to 104 weeks. This study also reported improvements in sleep disturbance, caregiver satisfaction, quality of sleep, and quality of life. Although these effects declined compared with the treatment period during the 2-week withdrawal placebo period, they were still improved compared with the baseline. During the 104-week continuous treatment, the most frequent adverse events were fatigue (6.3%), somnolence (6.3%), and mood swings (4.2%). There were no significant changes in the children's growth and pubertal development, such as weight, height, body mass index, or pubertal status. Based on the results of long-term clinical studies, melatonin supplements were generally safe, without serious adverse effects, developmental delay, or tolerance [28,32,33].

Does the use of melatonin inhibit the natural secretion of melatonin?

There is a concern that the use of melatonin may inhibit its endogenous secretion. However, there is still no evidence that melatonin use in children and adolescents can sup-

press or weaken melatonin secretion. In a study on adult shift workers, it was reported that the amplitude of endogenous melatonin secretion did not change after administration of melatonin (0.5 mg) for a week [34]. In addition, there was no change in endogenous melatonin secretion in a blind patient who received a high dose of melatonin 50 mg for 37 days [34]. Melatonin may alter the phase of endogenous melatonin, but does not inhibit or attenuate its secretion.

What drug interactions should be considered when using melatonin?

Melatonin has a short half-life of 30 to 40 minutes and is mainly metabolized to 6-hydroxymelatonin by cytochrome P450 1A2 (CYP1A2) and then excreted as 6-sulphatoxymelatonin [35]. Drug interactions with inhibitors or enhancers of CYP1A2 can lead to an increase or decrease in melatonin bioavailability [35]. When CYP1A2 inhibitors or enhancers are used in combination with melatonin, appropriate dose adjustments are required. In addition, the CYP1A2 enzyme is expressed at approximately 30% of the adult level in infants aged 3 to 12 months and at approximately 50% of the adult level in children aged 1 to 9 years [36,37]. When melatonin is used in younger children, bioavailability can be higher than expected.

Relative safety of melatonin use in children and adolescents

The safety of melatonin use in children and adolescents must differ according to individual characteristics. As such, melatonin deficiency associated with abnormal brain development in premature neonates or infants with a life-threatening event can be corrected with melatonin supplements [38–41]. Several studies have suggested that the free radical-reducing effect of melatonin may be protective in vulnerable infants who are likely to be melatonin deficient [42,43]. That is, the adverse effects of melatonin might be relatively small under special situations, such as melatonin deficiency or medical conditions requiring high levels of melatonin. In addition, the adverse effects of melatonin may differ depending on melatonin dosage and administration timing [22,44]. Fatigue, drowsiness, or mood swings with melatonin use may be related to a mis-

Table 2. Safety issues regarding melatonin use in children and adolescents

Safety issue	Current conclusion
What are the adverse effects of melatonin use in children and adolescents?	There were no serious adverse effects. Most TEAEs were mild. Frequent adverse effects were fatigue, somnolence, mood swings.
Are there studies on safety of long-term melatonin use in children and adolescents?	Several studies on the long-term use of melatonin in children and adolescents reported no serious TEAEs and no significant changes in children's growth and pubertal development.
Does the use of melatonin inhibit the natural secretion of melatonin?	There was no evidence for the inhibition of endogenous melatonin rhythm.
What drug interactions should be considered when using melatonin?	Melatonin is mainly metabolized through CYP1A2, and the expression of the CYP1A2 enzyme in children is low. When CYP1A2 inhibitors and enhancers are used together with melatonin, appropriate dose adjustment is required. In addition, when using melatonin in younger children, the bioavailability can be higher than would otherwise be expected.
Can the adverse effects of melatonin use appear differently depending on the individual child or adolescent?	The adverse effects of melatonin use might be somewhat different based on individual characteristics, such as medical condition, endogenous melatonin level, melatonin dosage, and administration timing.

alignment with the individual's melatonin rhythm [45,46]. If melatonin supplements are administered according to the individual's melatonin rhythm, the discomfort caused by melatonin might be alleviated. In future, studies on melatonin use according to individual characteristics may lead to precision treatment to reduce adverse effects.

Conclusions

This review summarized the evidence on the safety issue associated with melatonin use in children and adolescents (Table 2). To date, serious adverse effects of long-term melatonin use in children and adolescents have not yet been reported. Commonly reported side-effects include fatigue, somnolence, and mood swings. In addition, there is no evidence that long-term use of melatonin inhibits the natural secretion of melatonin. From the perspective of drug interactions, medications metabolized through CYP1A2 are required to be monitored for potential drug interactions. Accumulating evidence suggests that the use of melatonin in children and adolescents with sleep problems might be safe, although the experience of melatonin use in children and adolescents is not yet sufficient. In the future, it will be necessary to accumulate experience and research results on the long-term use of melatonin in children and adolescents according to individual characteristics.

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Conflicts of interest

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