FEATURE ARTICLE

Myths and Evidence Regarding Melatonin Supplementation for Occasional Sleeplessness in the Pediatric Population

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ABSTRACT

Occasional sleeplessness in children is common, with as many as 25% of all healthy children experiencing a problem sleeping at some point over the course of their childhood. Occasional sleeplessness is poorly understood, has a significant impact on quality of life in children and their families, and is often challenging to manage. There is substantial evidence supporting the safe and effective use of the widely available dietary supplement melatonin for children with chronic conditions. This article summarizes the views expressed in a recent Consensus Panel meeting convened to evaluate the use of melatonin in children, as well as the published scientific literature related to the effectiveness and safety of melatonin, with a focus on occasional sleeplessness in healthy children. We provide an evidence-based framework for the implementation of a standard process to effectively manage occasional sleeplessness in children and adolescents. Unsubstantiated concerns in the past may have limited melatonin's use in children with conditions for which the supplement may support a better sleep pattern and, by doing so, may help to improve quality of life. Melatonin dietary supplements using high quality standards may be provided to children together with cognitive-behavioral therapy after proper sleep evaluation and after improved sleep hygiene, family education, and sleep diary activities have failed to resolve sleep difficulties. **[*Pediatr Ann*. 2021;50(9):e391-e395.]**

Good sleep is essential for physical strength, mental health, and well-being and is important for energy conservation, restoring normal physiological processes, promoting physical growth, and healthy mental development.[1] Although there is no definition of what constitutes optimal, healthy sleep, higher sleep continuity has been recognized as a measure to enhanced sleep quality. Shorter sleep latencies, fewer awakenings, and reduced wake after sleep onset (SO) would all be expected for optimal and enhanced sleep quality.[1]

Prioritizing sleep health in children has been gaining momentum globally and there is growing interest in promoting longer sleep and better sleep quality in children. Sleep irregularities in children may be associated with comorbidities. Therefore, sleep health has been adopted as a measure of higher overall quality of life.[2] This review focuses on efficacy and safety of melatonin for occasional sleeplessness in healthy children, referring to irregularities in sleep quality without underlying pathology. Occasional sleeplessness is a common complaint among children and their caregivers,[3] carrying a potential individual and family impact.[4]

The timing and quality of sleep are determined by circadian rhythms and homeostatic processes. Circadian rhythms are controlled by the internal biological or circadian clock that synchronizes with environmental cues and is coordinated by the suprachiasmatic nucleus (SCN), a small region in the hypothalamus, located above the optic chiasm.[5] The endogenous hormone melatonin (N-acetyl-5-methoxytryptamine) is released by the pineal gland during darkness, under control of an endogenous oscillator in the SCN, maintaining a rhythm close to 24 hours. Melatonin concentration is commonly considered a phase marker of the circadian clock[6] and plays a key role in regulating the sleep-wake cycle and promotes SO.[7,8]

Melatonin is widely available as a dietary supplement in the United States and was documented to have a 7-fold increase in use from 2007 to 2012 in children age 4 to 17 years (from 0.1% to 0.7%), becoming the second most commonly used non-vitamin/non-mineral dietary supplement in children.[9] This trend continued to grow in recent years.

Several misconceptions related to the safety of melatonin use in children have surfaced, including concerns related to delayed onset of puberty and potential reduction of endogenous melatonin secretion if exogenous melatonin is consumed. To review the efficacy and safety of melatonin, a Consensus Panel of academics and clinicians convened in December 2019 to review up to date evidence on the benefits and risks of melatonin supplementation for occasional sleeplessness in children with the objective of providing

guidance to health care providers and to develop a standardized approach for managing sleep concerns in healthy children.

LITERATURE REVIEW: EFFICACY AND SAFETY OF MELATONIN FOR SLEEP CONCERNS IN CHILDREN

In anticipation of the Consensus Panel meeting, a literature search was conducted using MEDLINE (PubMed) in November 2019, and updated for this article in May 2020, using the terms "melatonin," "sleep," and "children" or "adolescents." The search criteria were inclusive of primary research studies, systematic reviews, and meta-analyses related to melatonin use for sleep concerns. For evaluating melatonin efficacy, the focus of the review was on studies in healthy children. To assess safety, we reviewed all available studies, including those patients with neurodevelopmental comorbidities and sleep disorders.

EFFICACY OF MELATONIN FOR SLEEPLESSNESS IN THE PEDIATRIC POPULATION

Several reports evaluated melatonin for sleep irregularities in children. In a crossover randomized controlled clinical trial (RCT), students (age 14 to 19 years) who were experiencing sleep onset (SO) difficulties during 5 weeks of school received daily melatonin (1 mg), administered between 4:30 pm and 6 pm. The students fell asleep earlier ($P < .005$) and slept longer ($P < 0.05$) each night and reported less daytime sleepiness ($P < .05$), and increased evening sleepiness with melatonin ($P < .005$), compared to placebo.[10]

In a retrospective analysis of 32 children (mean age 9.6 ± 4.5 years) with chronic sleep initiation and sleep maintenance concerns, melatonin was administered at an average dose of 2 mg 1 hour before bedtime for an average of 2.1 months. Results were partial improvement or complete resolution of sleep latency time and improvement in the number of awakenings reported by parents in 91% of the children (29 of 32).[11]

Melatonin administration in healthy children (age 6 to 12 years) with chronic sleep onset insomnia (CSOI) resulted in improvement, as measured using actigraphy.[12,13] In one RCT with 40 children receiving melatonin (5 mg) or placebo for 4 weeks after a 1-week baseline, children in the melatonin group fell asleep earlier (sleep diary, 63 [95% confidence interval or CI, 32-94] minutes; actigraphy, 75 [95% CI, 36-114] minutes; and with increased total sleep time (41 [95% CI, 19-62] minutes) as compared to the placebo group.[12]

In another study for CSOI, 62 healthy children (age 6 to 12 years) received melatonin (5 mg) or placebo at 7 pm for 4 weeks after establishing a 1-week baseline. Although total sleep time was similar in both groups, melatonin significantly improved SO by 57 minutes ($P = .003$), sleep offset by 9 minutes ($P = .024$), melatonin onset (as measured by salivary samples) by 82 minutes ($P < .001$), and decreased sleep latency by 17 minutes ($P = .048$).[13] A combined analysis of the two RCTs[14] reconfirmed the findings (melatonin onset, $P < .001$; SO, $P = .004$; sleep latency, $P = .019$).

In a recent RCT with predominantly healthy children (age 7 to 12 years) with CSOI using sleep diaries and actigraphy,[15] melatonin was compared to daily blue-green light therapy or placebo pills for 3 to 4 weeks. Endogenous dim light melatonin onset (DLMO) and sleep onset latency (SOL) improved with both melatonin and light therapy ($P \leq .01$ for both). SO, total sleep time, and sleep ef-

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ficiency (i.e., total time asleep per time in bed) ($P < .001$ for all as measured by actigraphy) were improved with melatonin. Assumed sleep time (defined as the time between SO and wake-up time) was also increased for children receiving melatonin treatment (Cohen's $d = 0.63$). An improvement in sleep was associated with improvement in children's health and behavior.[15]

The Melatonin Dose Finding study established a dose-response relationship for melatonin in advancing DLMO, SO, and SOL in children with CSOI (age 6 to 12 years). Seventy-two children received either melatonin (0.05 mg/kg, 0.1 mg/kg, 0.15 mg/kg) or placebo for 1 week. Melatonin significantly advanced DLMO in the 0.1 and 0.15 mg/kg group ($P < .001$) compared to placebo. SO advanced in all three melatonin groups compared to placebo ($P < .001$ for all melatonin groups); the SO shift difference between melatonin treatment and placebo treatment was 42 to 56 minutes. SOL was reduced in all three melatonin groups compared to placebo ($P = .007$, $P = .001$, and $P < .001$, respectively); SOL shift difference between melatonin treatment and placebo treatment was 31 to 42 minutes. Effect size was similar between groups suggesting efficacy of melatonin at 0.15 mg/kg when given at least 1 to 2 hours before DLMO and before desired bedtime for children with CSOI.[16]

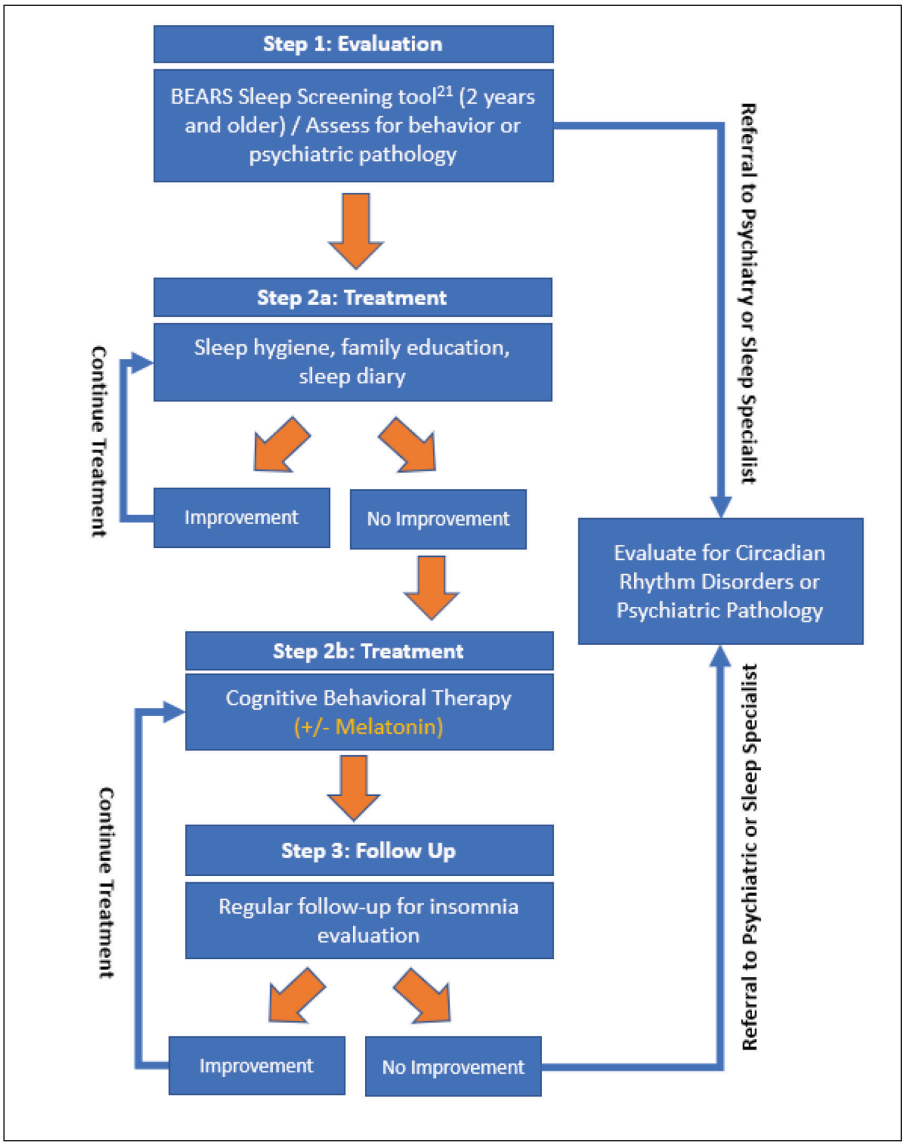

Figure 1. Framework for managing occasional sleeplessness in the pediatric population.

SAFETY OF MELATONIN IN CHILDREN

Melatonin has been used in children for many years, with a favorable safety profile. A recent systematic review of 18 RCTs (with 1,021 children) evaluating the use of melatonin for sleep concerns in various pediatric populations, reported infrequent adverse events.[17] Studies ranged in duration from 1 to 13 weeks (median 4 weeks) and administered in doses of 1 to 12 mg/day (median 4.8 mg/day). Withdrawal due to adverse events was uncommon, and serious adverse events were rare and not considered related to treatment. Adverse events reported in children receiving melatonin included fatigue/somnolence and bed-wetting or increased urination in the evening. Dizziness and hyperactivity were described in some studies, but adverse events were inconsistent across trials.[17]

In a long-term follow-up to a dose-range finding study, melatonin was administered for approximately 3 years ($n = 51$) with an average dose of 2.69 mg. Satisfaction was high and only a few adverse events were reported. Social development of study participants did not deviate from the control group (children without sleep problems in the general population) and puberty onset was normal.[18]

In a study from the Netherlands,[19] melatonin therapy initiated in prepubertal children with CSOI was still used by 27% of the participants after a

mean of 10.8 years. Melatonin administration was deemed safe with few adverse events.

Several reported misconceptions include delayed puberty onset and reduction in endogenous melatonin secretion output when exogenous melatonin is administered. When recently reviewed, there was no foundation to suggest pubertal timing changes in children receiving melatonin.[20] Another recent 2-year evaluation of 80 children with autism spectrum disorder given 2 mg, 5 mg, or 10 mg prolonged release melatonin, provided no evidence for pubertal or growth delay and no withdrawal or safety issues were reported.[21] Sleep terrors have been anecdotally reported at the onset of melatonin use and, although not substantiated in controlled clinical studies, families should be aware of this possibility.[7]

Although numerous products are available on the market, use of melatonin from manufacturers with well documented, high-quality manufacturing standards, is essential. One study evaluating 31 melatonin-containing products and supplements demonstrated significant variability of melatonin content (-83% to +478% of the labeled content) and 26% of the tested products contained serotonin, a biosynthetic precursor of melatonin and neurotransmitter whose levels correlate with many neurological disorders.[22]

In summary, with short-term and long-term data now available on the safe profile of melatonin in recommended dosages in children, the risk-benefit ratio is favorable for children that have an indication to use melatonin.

GUIDELINES FOR SUPPLEMENTAL MELATONIN USE IN HEALTHY CHILDREN

There are no universal guidelines on melatonin use in the healthy pediatric population, including optimal dose, timing of administration, or length of therapy. Furthermore, with considerable variation in response in patients, melatonin dose can be determined by clinical responsiveness[23] rather than age or weight[24] and based on regular follow-up with health care providers. Based on the data available from the present review, the Consensus Panel suggested melatonin administration to healthy children at 1 to 5 mg, 30 minutes to 1 hour before bedtime, when indicated.

AN EVIDENCE-BASED FRAMEWORK FOR OCCASIONAL SLEEPLESSNESS IN HEALTHY CHILDREN

Health care providers should consider using melatonin (with or without cognitive-behavioral therapy [CBT]) for treatment of occasional sleeplessness in healthy children as part of a standard clinical protocol, after conducting a systematic sleep evaluation using sleep diaries, ruling out psychiatric pathologies and comorbidities, and failure of family education and sleep hygiene procedures. Appropriate follow up by the provider is essential. Sleep hygiene should include lifestyle modifications such as regular exercise, limiting daytime naps, elimination of heavy or rich foods before sleep time, reduction of stimulation such as screen time, pleasant sleep environment, and bedtime routine. Tools that providers can use may include the 5-domain BEARS Sleep Screen that aim at triggering questions for children and adolescents age 2 to 18 years and their caregivers.[25]

The Consensus Panel recommends an actionable approach for managing occasional sleeplessness in healthy children **(Figure 1)**. After the evaluation of sleep, circadian rhythm disorders and/or psychiatric pathology and comorbidities, a combination of sleep hygiene, family education, and sleep diary activities should be implemented. Next, melatonin, with or without CBT, should be considered. If failed, the family should see a sleep specialist or seek a psychiatric consultation when appropriate.

CONCLUSIONS

Melatonin is widely available as a dietary supplement and recent short- and long-term safety evaluations suggest its favorable safety profile, with only mild and self-limiting adverse events. Unsubstantiated concerns in the past may have limited its use among children with conditions for which melatonin may offer a better sleep pattern, and improved quality of life. High-quality melatonin dietary supplements may be offered to children, with or without CBT, after proper evaluation by primary care providers, and if improved sleep hygiene, family education, and sleep diary activities have failed to resolve sleep difficulties.

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