Complementary, Holistic, and Integrative Medicine: Melatonin

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Definition and Description

Melatonin is synthesized primarily in the pineal gland, although it also can be produced in the retina and gastrointestinal tract. Melatonin helps regulate circadian rhythms, specifically sleep-wake cycles. These cycles are under the control of the suprachiasmatic nucleus, through which patterns of light and darkness are transferred from the retina to the pineal gland. Melatonin is formed from the essential amino acid tryptophan via serotonin, based on specific patterns. Simply stated, in the presence of light, melatonin production is inhibited; in the darkness, it is synthesized.

Melatonin also can be taken as an exogenous supplement, which is synthesized to be chemically identical to its endogenous counterpart, and is classified as a natural health product by Health Canada or dietary supplement by the United States Food and Drug Administration. Due to its involvement in the sleep cycle, exogenous melatonin has been investigated extensively for sleep disorders.

Evidence of Efficacy for Sleep Disorders

Difficulties initiating and maintaining sleep affect 15% to 25% of the pediatric population. Thirty minutes is believed to be the normal time to initiate sleep or sleep onset latency (SOL), which is defined as the amount of time between the person laying down to sleep and the onset of stage 1 sleep. (1)(2)(3)(4) A difference of 15 minutes in SOL typically is considered clinically important. (4)

The literature evaluating melatonin for the treatment of sleep disorders was reviewed systematically in 2004 by the Agency for Healthcare Research and Quality (AHRQ). (5) Efficacy reports of melatonin for primary and secondary sleep disorders, including examination of pediatric subgroups, appeared in subsequent publications following the AHRQ report. Findings indicate that melatonin may be safe and effective for managing some primary (Table 1) and secondary (Table 2) sleep disorders.

Primary Sleep Disorders

In the review by Buscemi and associates, (6) three double-blind randomized, controlled trials (RCTs) assessed the effectiveness of melatonin in primary sleep disorders. (12)(13)(14) One study was only published in abstract format and did not have extractable data. (12) The two remaining studies included children ages 6 to 12 years who had idiopathic chronic sleep-onset insomnia (defined by authors as "sleep onset later than 8:30 PM") who were randomized to either placebo or 5 mg of fast-release melatonin before bedtime over a 4-week period. The earlier study examined melatonin administration at 6 PM (n=40) (14) and the later trial at 7 PM (n=70). (13) Melatonin significantly improved SOL over placebo by 16.7 minutes (95% confidence interval [CI] −29.4, −4.0). Effects on other sleep variables were not reported. One study also measured health status using the RAND General Health Rating Index and found a significant

Abbreviations

ADHD: attention-deficit/hyperactivity disorder
AHRQ: Agency for Healthcare Research and Quality
ASD: autism spectrum disorder
CI: confidence interval
LH: luteinizing hormone
NHPD: Natural Health Products Directorate
RCT: randomized, controlled trial
SOL: sleep onset latency

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NOTE: The agents discussed in this series are designated as dietary supplements rather than drugs. Although dietary supplements are regulated by the United States Food and Drug Administration (FDA), their manufacturers may make claims with little evidence and need not prove safety prior to marketing. The burden is on the FDA to monitor safety after the product is on the market. Readers are referred to the 1994 Dietary Supplement Health and Education Act (www.cfsan.fda.gov/~dms/dietsupp.html).

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Table 1. **Study of Melatonin in Primary Sleep Disorders**

Author and Year	Study Design	Population	Intervention/Control	Dose/Frequency/Duration	Outcome
Buscemi 2005 (6)	SR	N: 2 RCTs; 110 participants Age: 0 to 18 years Condition: idiopathic chronic sleep-onset insomnia	I: Fast-release melatonin C: Identical placebo	5 mg/once per day before bedtime/4 weeks of treatment	Reduction in SOL: 16.7 min (95% CI −29.4, −4.0)

CI=confidence interval, RCT=randomized, controlled trial, SOL=sleep-onset latency, SR=systematic review

improvement in overall health status associated with melatonin use (P=0.013). (13)

Secondary Sleep Disorders

Secondary sleep disorders are sleep problems that are comorbid with medical, neurologic, or substance misuse disorders. (7) Meta-analysis of three crossover designed studies containing a total of 66 participants indicated a significant improvement in SOL with a reduction of −18.1 minutes (95% CI −29.4, −6.8) for melatonin over placebo for children who had developmental disabilities, (15) Rett syndrome, (16) and tuberous sclerosis. (17) These findings are supported by another systematic review including the same three studies. (1) Further large-scale studies would be beneficial and help increase confidence in these results in diverse pediatric populations.

Since publication of the systematic reviews by Buscemi and associates and Phillips and colleagues, at least five additional clinical studies of melatonin for secondary sleep disorders have been identified.

Thirty-two children, ages 3.6 to 26 years, who had developmental delay participated in a crossover RCT. (18) The children, of whom approximately 50% had epilepsy, received 3 to 9 mg of melatonin (3-mg increase per week as needed for efficacy) concurrent with their routine antiepileptic drugs for 4 weeks. Although the children did not experience significant mean differences in reduction in SOL with melatonin over placebo (P=0.28), the authors concluded efficacy based on inappropriate statistical tests to analyze the data. They tested for significance of mean difference in SOL between placebo and melatonin groups using a test for categorical rather than continuous data; SOL is a continuous variable and any categorization would be arbitrary and was not stated.

Promising results have been recorded in children who have autism spectrum disorder (ASD). In a cohort study performed by Andersen and associates, (11) 107 children who had ASD and were taking melatonin, ages 2 to 18 years, received 0.75 to 1 mg if younger than 6 years of age with 1-mg increments every 2 weeks until 3 mg or 1.5 mg if older than 6 years increased to 3 mg after 2 weeks if no response. All children who had no response to lower doses received 6 mg after 4 weeks. Follow-up lasted for a mean of 1.8 years (standard deviation, 1.4). Although there was no follow-up of specific sleep parameters, after treatment initiation, 25% of parents reported no sleep concerns, 60% reported improved sleep, 13% reported no effect on sleep parameters, 1% reported worse sleep, and 1% had an undetermined response. Overall, melatonin showed beneficial outcomes when given to remedy sleep disturbances in children who had ASD.

Attention-Deficit/Hyperactivity Disorder (ADHD)

Sleep problems in children who have ADHD are common and troubling. In one study, sleep problems were reported in 29% of affected children receiving long-term stimulant medication, 19% of children not receiving stimulant medication, and 6% of children who did not have ADHD. (19) Between 54% and 64% of children receiving methylphenidate have been reported to experience insomnia. (9)(20)(21)(22)

In an open-label, uncontrolled study of melatonin to treat sleep disorders in children who had ADHD, 3 mg of melatonin before bedtime significantly reduced SOL by 135 minutes at 1 week (n=27) and 16 minutes at 3 months (n=13) (P<0.01). (2) A crossover RCT examined the effect of 5 mg/day of melatonin in 23 children (6 to 14 years) who had ADHD and were receiving concomitant stimulant medication. (4) Melatonin use was associated with a reduction in SOL of 16 minutes (P<0.01) and an average 15-minute increase in total sleep time (P<0.01).

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Table 2. **Studies of Melatonin in Secondary Sleep Disorders**

Author and Year	Study Design	Population	Intervention/Control	Dose/Frequency/ Duration	Concurrent Medications	Significant Outcomes
Buscemi 2006 (7)	SR	N: 3 DB CO RCTs (66 participants) Age: 0 to 18 years Condition: developmental disabilities, Rett syndrome, tuberous sclerosis	I: melatonin C: identical placebo	2.5 to 7.5 mg/once per day/2 to 4 weeks	Not stated	Reduction in SOL: 18.1 min (95% CI −29.4, −6.8);
Camfield 1996 (8)	Series of N of 1 RCTs	Developmental disability	I: melatonin C: identical placebo	0.5 to 1.0 mg/once per day at 6 PM/2-week paired periods	N/A	
Jan 1996 (9)	Series of N of 1 RCTs	Neurologic impairment	I: melatonin C: identical placebo	2 to 5 mg at bedtime	Not stated	Quantitative reductions in specific outcomes not stated
van der Heijden 2007 (10)	DB RCT	N: 105 Age: 6 to 12 years Condition: ADHD	I: fast-release melatonin C: identical placebo	3 mg for <40 kg; 6 mg for >40 kg/once per day at 7 PM/4 weeks	None	Reduction in SOL: 24.3 min (95% CI −36.7, −11.9); Increased total sleep time: 33.4 min (95% CI 11.8, 55.0)
Tjon Pian Gi 2003 (2)	Open label study	N: 27 Age: Not stated Condition: ADHD	I: melatonin C: none	3 mg/single dose/3 months	Methylphenidate	Reduction in SOL 1 wk: 15 to 240 min; 3 mo: 15 to 64 min
Weiss 2006 (4)	CO DB RCT	N: 23 Age: 6.5 to 14.7 years Condition: ADHD	I: melatonin C: placebo All patients underwent a sleep hygiene intervention 10 days prior to the trial period	5 mg/once per day 20 minutes before bedtime	67% methylphenidate; 30% dextroamphetamine	Not significant reduction in SOL: 15.7 (95% CI 32.1, 0.72)
Anderson 2008 (11)	Cohort	N: 107 Age: 2 to 18 years Condition: ASD	I: melatonin C: none	0.75 to 6 mg/once per day 30 to 60 minutes before bedtime/ participants followed for mean of 1.8 years (SD 1.4)	10% no medication; 56% antidepressants; 64% antipsychotics; 45% sedative-hypnotics; 34% antiepileptics; 43% stimulants	No data provided; after treatment initiation, 25% of parents reported no sleep concerns, 60% reported improved sleep, 13% reported no effect on sleep parameters, 1% reported worse sleep, and 1% had an undetermined response

ADHD=attention-deficit/hyperactivity disorder, ASD=autism spectrum disorder, CI=confidence interval, CO=crossover, DB=double-blind, N/A=not available, RCT=randomized, controlled trial, SD=standard deviation, SR=systematic review, SOL=sleep-onset latency

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In a double-blind RCT, 107 stimulant-free children who had ADHD, ages 6 to 12 years, were randomized to receive either 3 mg/day of melatonin for those whose body weights were less than 40 kg and 6 mg/day for those whose body weights were 40 kg or more or identical-appearing placebo daily for 4 weeks. (10) A 24.3-minute (95% CI −36.7, −11.9, $P<0.001$) reduction in SOL was reported for melatonin compared with placebo, accompanied by an increased total sleep time of 33.4 minutes (95% CI 11.8, 55.0, $P=0.01$).

Safety

In Canada and the United States, melatonin is "generally recognized as safe." In addition, the systematic review by Buscemi and associates (5) found that short-term supplementation with exogenous melatonin is relatively safe, over a period of days or weeks, and is safe at relatively high doses and in various formulations without the appearance of adverse effects. The safety of long-term use (more than 4 weeks of administration) has not been examined sufficiently in children and remains unclear. (5)

The effect of melatonin on reproductive endocrinology is uncertain, with conflicting evidence of its effect on luteinizing hormone (LH). Although earlier trials concluded that melatonin had a minor, if any, effect on LH secretion, (23)(24) at least one more recently published trial suggested a significant reduction in LH attributable to melatonin administration, (25) and another suggested a reduction, albeit not statistically significant. (26) These emerging data suggest cautious use in prepubertal children and the need to consult a physician before taking melatonin.

Adverse Events

Few serious adverse events associated with melatonin administration have been reported. The incidence of adverse events (headaches, dizziness, nausea, and drowsiness) (n=122) was not significantly different between melatonin and placebo groups, as reviewed by Buscemi and associates. (5) Restless sleep was reported by one child in the open-label study by Tjon Pian Gi. (2) One child of 27 studied by Weiss and associates (4) reported a severe migraine, although the authors did not report which study medication the child was receiving. Among children who had ASD taking up to 6 mg of melatonin, 3 of 107 reported morning sleepiness, "fogginess," or increased enuresis. (11)

A British questionnaire examining prescribing practices of pediatricians obtained data on adverse events representing 1,918 children receiving doses of 0.5 mg to 24 mg of melatonin. (27) Eighteen percent of pediatricians reported adverse events, including new onset of seizure activity (n=2), increased seizure frequency (n=3), hyperactivity (n=5), agitation/behavioral changes (n=6), worsening sleep patterns (n=6), nightmares (n=2), and constipation (n=2). Because these effects were observed in an uncontrolled setting, it is unclear whether the reported adverse events were causally associated with melatonin use. The authors did not report whether adverse event occurrence was dose-related.

Few incidents of rash, gynecomastia, and autoimmune hepatitis have been reported in individuals following melatonin use. (28) Again, it should be noted that in all such cases, direct causation between adverse event and melatonin has not been identified. (29)

A cohort of six children (9 months to 18 years of age) who had multiple neurologic deficits received 5 mg of melatonin orally or by gastronomy tube before bedtime (the duration of administration was not reported). (21) Although melatonin improved sleep parameters in all children, four of six had increased seizure activity that returned to normal after discontinuation of the study medication. Another cohort of six children, ages 2 to 15 years, who received 3 mg of oral melatonin 30 minutes before bedtime concurrent with their antiepileptic drugs, reported no adverse events over a 3-month period of administration. (30) Further, clinical improvement in seizure activity occurred in five of six patients. Potential confounders may contribute to the conflicting results of these studies. Adverse event monitoring in a controlled setting would be beneficial.

Precautions/Contraindications

Although melatonin has demonstrated relative safety in children, its use is not recommended in the pediatric population without consultation with a health-care professional. The Natural Health Products Directorate (NHPD) of Health Canada recommends, due to interaction or potential interaction with medications, that people who have the following conditions avoid melatonin use: hormonal disorders, diabetes, liver or kidney disease, cerebral palsy, seizure disorders, migraine, depression, and hypertension. The NHPD also contraindicates the use of melatonin with blood pressure, sedative/hypnotic, and immunosuppressive medication.

Pharmacokinetics

Melatonin most often is administered orally and is metabolized rapidly by the liver, with pronounced first-pass effects. (31)(32) Bioavailability following the first pass

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through the liver has been reported to be between 10% and 56%. (31) The natural half-life of melatonin in the body is 30 to 60 minutes, although some oral supplements have been shown to release over a 4- to 12-hour period. (33) Other forms of administration, such as sublingual or intravenous, allow direct entry into the circulatory system and enhanced bioavailability.

Summary

Research suggests that melatonin appears to be efficacious in ameliorating SOL in both primary and secondary sleep disorders in children. Overall, melatonin appears to be safe in children who do not have contraindicated conditions or medications at doses between 0.5 and 7.5 mg before bedtime, with a low occurrence of mild adverse effects. Depending on the desired effect, parents and doctors should decide on the type of formulation to be used: long-term release (recommended for sustaining sleep) or short-term release (recommended for initiating sleep). Potential risk versus benefit of melatonin should be assessed on an individual basis, taking into account the child's health and concurrent medications.

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