of sleep disorders in children and adolescents

C Cummings; Canadian Paediatric Society
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Abstract
Problems of sleep initiation and maintenance occur in 15% to 25% of children and adolescents. Studies of the benefits of melatonin for sleep disorders have been published for healthy populations, for children and adolescents with attention-deficit hyperactivity disorder, for children and youth with autism, and for several other special populations. These studies demonstrate benefit with minimal side effects. However, all studies have involved small numbers of subjects and address only short-term use of melatonin. There are no good data concerning the safety and efficacy of long-term melatonin use. Further studies are needed to confirm the usefulness and safety of melatonin for sleep disorders in children and adolescents.

Key Words: Attention-deficit hyperactivity disorder; Autism; Developmental disabilities; Melatonin; Sleep disorders

Difficulties in initiating and maintaining sleep affect 15% to 25% of children and adolescents [1]. Insomnia refers to loss of daytime function resulting from unsatisfactory sleep. The symptoms of insomnia include fatigue, inattention, irritability, lack of energy, and anxiety. Chronic insomnia can lead to depression, learning difficulties and poor school performance [2]. As well, chronic insomnia has the potential to affect the functioning of families and not just the child whose sleeping pattern is the object of concern.

Secretion of melatonin by the pineal gland in response to darkness is an important mechanism in maintaining the circadian rhythm of the sleep-wake cycle. Exposure to electronic media and screen light prior to sleep onset may be a factor in the significant frequency of sleep disorders [3]. Additional contributing factors include caffeine (eg, from ‘energy’ drinks), alcohol and cigarette smoking [2].

Of the sleep disorders defined in the International Classification of Sleep Disorders-2, the two encountered most frequently in the paediatric age group are the ‘delayed sleep phase type’ and ‘behavioural insomnia of childhood’.

The delayed sleep phase type of sleep problem is defined by initiation of sleep significantly later than the desired bedtime. Sleep latency – the amount of time between lying down to sleep and onset of sleep – is increased to longer than the normal 30 mins. The shortened sleep time is often then associated with difficulty awakening in the morning [2].

Children with behavioural insomnia exhibit either the sleep-onset association type (in which special conditions are required of caregivers before the child goes, or returns, to sleep at night) or the limit-setting type (in which the child stalls or refuses to go to bed or to return to bed and the caregiver demonstrates unsuccessful limit-setting behaviours) [4].

Managing sleep disorders
The evaluation of sleep problems should include consideration of medical issues that can lead to insomnia. These include sleep apnea, anxiety, depression and inappropriate use of media at bedtime.

Sleep hygiene
The first step in the management of all sleep disorders is establishing good sleep hygiene. A consistent routine includes a stable bedtime and morning wake time, an age-appropriate number of hours in bed, a dark and quiet sleep space, avoiding hunger (and eating) prior to bedtime, relaxation techniques before bed, and avoiding caffeine, alcohol and nicotine [4]. Relaxation may best be achieved by a strict avoidance of television, computers and video games, and by encouraging reading prior to bedtime.

The limit-setting type of behavioural insomnia frequently will respond to this type of intervention. The process of
changing behaviour in both child and caregiver can take a significant amount of time [4]. The sleep-onset association type of insomnia often responds to sleep hygiene and other behavioural interventions. However, some cases will be refractory to this approach and may benefit from pharmacological treatment.

**Melatonin availability in Canada**

Melatonin is considered by Health Canada to be a ‘natural health product’. Under both the Natural Health Products Regulations and the Food and Drugs Act, standards to assure the reliability of preparations sold in Canada have been in effect since 2004. The most recent update to these standards was published in August 2010 [5]. Melatonin is available in both short-acting and sustained-release forms. At time of writing, some 114 melatonin products were licensed in Canada [6], but there is not necessarily bioequivalence among products claiming to contain the same number of milligrams of melatonin (Personal correspondence with Calvin Cheung, Regulatory project officer, Health Canada, May 10, 2011). Health Canada considers melatonin to be recommended for use for sleep problems in adults only. Therefore, melatonin use is considered to be ‘off-label’ for the treatment of sleep problems in children and teens [7].

**Melatonin for sleep problems in healthy populations**

Of the several medications studied in the treatment of insomnia in children, only melatonin is considered safe and effective for short-term use [8]. No evidence is available to support the use of melatonin in children younger than two years of age. While there is no evidence to support the practice, short-acting forms of melatonin are used primarily for problems of sleep initiation, while long-acting forms are used for problems of sleep maintenance.

**Types of sleep disorder**

1. **Delayed sleep phase type**: Since this is a circadian rhythm sleep disorder, the potential for melatonin to advance the onset of sleep is high. Typical doses of melatonin are 2.5 mg to 3 mg in children, and 5 mg to 10 mg in adolescents [9]. Melatonin is administered from 30 min to 60 min prior to the desired bedtime. However, studies in the use of melatonin for delayed sleep phase type disorder are typically open-label or carried out in adults.

2. **Sleep-onset association type**: The use of melatonin to improve sleep in this disorder has been studied in randomized, double-blind, placebo-controlled trials [10,11]. In one study, school-age children received a 5 mg dose of melatonin or an identical placebo at 19:00 for four weeks. Melatonin improved sleep onset and sleep duration. Sleep latency improved from 60 mins or more to approximately 30 mins. Measures of health status and sleep improved significantly more in the melatonin than in the placebo group. A few patients reported feeling cold, dizzy, or having a decreased appetite at the onset of treatment, but all these possible adverse effects resolved within three days of the start of treatment. Improvements in sleep parameters with melatonin were similar to an earlier study by the same authors [11].

**Melatonin for sleep problems in special populations**

**Attention-deficit hyperactivity disorder (ADHD):** Children with ADHD suffer from dysregulation that commonly includes sleep problems. As well, medications used to treat ADHD may increase sleep difficulties.

One study [12] evaluated the efficacy of sleep hygiene and melatonin in a group of 27 children from six to 14 years of age with ADHD. Participants receiving stimulants had insomnia defined by a sleep latency of at least 60 mins. All children were given a sleep hygiene intervention. Five children responded with an improvement to <60 mins of delay in onset of sleep. The ‘nonresponders’ then participated in a 30-day, double-blind crossover trial of 5 mg melatonin. During the study phase of melatonin treatment, there was a decrease in the mean time to onset of sleep from 91 mins to 31 mins.

A similar study [13] investigated the effect of melatonin treatment in 105 children six to 12 years of age with ADHD and sleep-onset insomnia. However, participants were not stimulant-treated at the time of the study. They received 3 mg or 6 mg of melatonin (according to body weight) or placebo for four weeks. There was a mean advancement of sleep onset of 44 mins in the treated group and a further delay of sleep onset of 12 mins in the placebo group. Total time asleep also increased in the treatment group. Adverse effects of headache, dizziness and abdominal pain occurred in the melatonin group. None of these events required treatment or led to withdrawal from the study. The improvement in sleep did not carry over in this study to measures of behaviour, cognitive performance or quality of life.

**Autism spectrum disorder (ASD):** Up to 67% of autistic children have been reported to have sleep difficulties. One double-blind, crossover, random control trial involving 11 children from five to 15 years of age with ASD and a sleep onset of at least one hour later than desired examined the efficacy of 5 mg of melatonin. Each treatment period was four weeks with a one-week ‘washout’ between treatment periods.
Mean sleep latency improved during melatonin treatment from 2.6 h at baseline to 1.06 h on treatment. Night awakenings improved from a mean baseline of 0.35 to 0.08. Total sleep improved from a baseline mean of 8.05 h to a treatment result of 9.84 h. All children completing the trial were continued on melatonin after the study ended at the request of their parents [14].

An open-label study of melatonin for insomnia in 107 children with ASD [16] examined clinical response based on parent reports. Trial participants were two to 18 years of age, and their sleep problems were defined as sleep-onset insomnia, sleep-maintenance insomnia, or both. They received melatonin 30 min to 60 min before bedtime. Doses in children younger than six years of age began at 0.75 mg to 1 mg, and parents were instructed to increase the dose every two weeks if they observed no response. Children six years of age and older began with a 1.5 mg dose, and parents were instructed to increase the dose to 3 mg if there was no clinical response in that time; a further increase to 6 mg was allowed if there was no response within the next four weeks.

Parents no longer reported sleep concerns for 25% of treated children. Another 60% were reported as having improved sleep, but their parents still expressed concerns regarding sleep at subsequent visits. In 6% of cases, melatonin improved sleep initially but problems returned after three to 12 months despite dose escalations. Continued sleep problems as a major concern of parents remained in 14% of cases. Only 1% had worse sleep reported with melatonin treatment.

There is also evidence that melatonin may be helpful in treating sleep problems in children with intractable epilepsy [18], neurodevelopmental disabilities [17-19], and with Angelman syndrome [20].

Conclusions
Melatonin treatment for certain sleep problems in children and adolescents can be useful. Studies in special populations provide the best evidence for the usefulness of melatonin in these sleep disorders. Adverse effects appear to be mild and self-limited. Pharmacological therapy for sleep problems should be considered only after a trial of sleep hygiene intervention.

There are significant limitations in the studies done to date supporting melatonin use. The small number of randomized, placebo-controlled trials and the small number of subjects in these trials limit the power of evidence in favour of melatonin treatment. As well, the lack of long-term studies limits our knowledge both of relapse risk and of long-term efficacy and safety. More research in the future would help to focus these issues.

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