What is the role of melatonin in the management of sleep disorders in children?

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Part A: Evidence-based answer and summary

There is evidence to suggest that melatonin may be effective in the management of some sleep disorders in children, and that it is not harmful to the child. Although these results are based on higher-level evidence (randomized controlled trials), they are supported by a fewer number of studies with very small sample sizes. Moreover, the clinical significance of the reported effects is unclear. There is insufficient evidence to conclude on the efficacy and safety of melatonin in children with sleep disorders, and thus, additional large-scale randomized controlled trials are needed in this area.

This conclusion is based on a systematic review (1) recently conducted by the University of Alberta Evidence-based Practice Center (Edmonton, Alberta) on the use of melatonin for the management of sleep disorders. We were interested in the efficacy and safety of melatonin in sleep-disturbed populations of all ages, and thus, conducted subgroup analyses for children.

A number of electronic biomedical databases were searched, and the reference list of included studies was reviewed. Abstracts of the Associated Professional Sleep Society covering the period from 1999 to 2003 were handsearched. For the review of efficacy of melatonin, a study was included if it was a placebo-controlled, randomized trial and the population suffered from a sleep disturbance. The main outcomes of the efficacy review were sleep onset latency (the time between laying down to sleep and the onset of sleep) and sleep efficiency (the amount of time spent asleep as a percentage of the total time spent in bed). For the review of the safety of melatonin, a study was included in the review if it was a placebo-controlled trial and information on adverse events was reported.

The quality of studies relevant to the efficacy review was assessed using the Jadad scale (2). The scale assesses randomization, blinding, and reports of dropouts and withdrawals. The concealment of group allocation was assessed as 'adequate', 'inadequate' and 'unclear' using the Schulz et al (3) criteria. Allocation concealment was considered to be adequate if it was accomplished by using methods such as central randomization, numbered or coded containers, drugs prepared by a pharmacy, or serially numbered, opaque, sealed envelopes. The quality of studies relevant to the safety review was assessed using the Downs and Black (4) checklist. The checklist assesses reports, internal and external validity, and the statistical power of a study to detect a clinically important difference. The overall quality of evidence relevant to the efficacy and safety of melatonin was rated using a framework developed by the Centre for Evidence-Based Medicine in Oxford, United Kingdom. Two independent reviewers selected studies for inclusion in the review; disagreements were resolved through discussion and consensus. Data were analyzed using meta-analytic techniques to yield pooled estimates of the efficacy and safety of melatonin. We determined the efficacy of melatonin separately for populations with primary sleep disorders (sleep disorders not accompanied by another medical or psychiatric disorder that is likely to be its cause) and secondary sleep disorders (sleep disorders accompanied by another medical or psychiatric disorder that is likely to be its cause). A secondary sleep disorder was considered to exist in a population if the inclusion criteria were designed to target individuals with a comorbid condition that was thought to be the cause of the sleep disturbance.

Nine hundred thirty-five studies were evaluated for inclusion in the review. We identified two studies of children with primary sleep disorders (5,6) and four studies of children with secondary sleep disorders (7-10). All studies were described as double-blind, placebo-controlled, randomized trials. In general, the studies were of good quality; however, withdrawals and dropouts were often not described in reports of these studies. Likewise, the adequacy of the method of randomization or concealment of group allocation was often not clear. All of the studies had small sample sizes (median 21 participants, range nine to 62 participants). All of the studies provided some information on adverse events with melatonin use (5-10), four studies provided information on the effects of melatonin on sleep onset latency (6,7,9,10) and one study provided information

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on the effects of melatonin on sleep efficiency (9). The study that examined the effect of melatonin on sleep onset latency in children with primary sleep disorders (6) found that melatonin significantly reduced sleep onset latency in children with idiopathic chronic sleep-onset insomnia compared with placebo (mean difference [MD] –17.0 min, 95% CI –33.5 to –0.5, n=62). Neither of the two studies of children with primary sleep disorders reported on the effect of melatonin on sleep efficiency. Three studies examined the effect of melatonin on sleep onset latency in children with secondary sleep disorders (7,9,10). Overall, these studies found that melatonin significantly reduced sleep onset latency in children with secondary sleep disorders compared with placebo (MD –18.1 min, 95% CI –29.4 to –6.8, n=36). The comorbid conditions of children in these studies were developmental disabilities (7), Rett syndrome (9) and tuberous sclerosis (10). The study on children with sleep disorders and Rett syndrome reported a nonsignificant increase in sleep efficiency with melatonin compared with placebo (MD 3.4%, 95% CI –3.9 to 10.7, n=9). All of the studies provided some information on the safety of melatonin. Overall, there was no significant difference in the number of adverse events with melatonin and placebo for any of the outcomes examined in the review: headaches (risk difference [RD] –0.02, 95% CI –0.08 to 0.03, n=122); dizziness (RD 0.02, 95% CI –0.04 to 0.08, n=122); nausea (RD –0.02, 95% CI –0.08 to 0.03, n=122) and drowsiness (RD 0.00, 95% CI –0.06 to 0.06, n=60).

Part B: Clinical commentary

Sleep problems are common in children, and pharmacotherapy for children with sleep disorders is increasing (11). Over-the-counter and prescription medications for sleep disorders in children have not been systematically studied as they have been in adults. The available data are based on small sample sizes and provide no substantive, empirical proof of efficacy. There is emerging evidence that the use of medications for paediatric sleep problems is common practice in clinical settings in the United States (12), despite the fact that there are currently no medications approved by the Food and Drug Administration for the treatment of initiating or maintaining sleep in the paediatric population. In fact, in a community-based survey by Owens et al (12), over 50% of paediatricians recommended nonprescription medications for sleep problems in children, and 15% of respondents recommended either melatonin or herbal preparations. Melatonin is more appealing than hypnotics because of its sleep-promoting effect for sleep problems without alteration of sleep architecture. Behavioural treatments for bedtime struggles and night wakings have a well-documented empirical basis and are considered to be optimal treatment (11). The American Academy of Sleep Medicine also endorses nonpharmacological treatment as an essential component of any treatment package for paediatric sleep disorders. According to a recent consensus statement (11), pharmacological treatment for paediatric insomnia should be treated as an adjunct to behavioural treatment. The choice to use pharmacotherapy should be aimed at improving sleep parameters of the affected child, while minimizing associated side effects.

The studies outlined in Part A suggest that melatonin may help to reduce sleep onset latency in children with primary and secondary sleep disorders; however, the clinical significance of these findings is unclear. Before these findings can be generalized, an important caveat should be noted. The study by Smits et al (6), which included 62 patients, did not distinguish children with delayed sleep phase syndrome (a sleep timing disorder in which patients have difficulty falling asleep and waking up at desired bedtimes and wake times, respectively, such that it interferes with school or work) or altered circadian rhythm (an out-of-phase endogenous circadian pacemaker that is displaced to an earlier or later than normal phase, for example, jet lag), from those with insomnia (inability to obtain adequate sleep despite adequate opportunity or circumstances for sleep; insomnia can include difficulty falling asleep or maintaining sleep). Furthermore, insomnia in children is difficult to define because the child does not necessarily articulate the sleep difficulties; therefore, the behavioural sleep problems are often defined by the caregivers. Identification of insomnia in children should take into account the caregivers' perceptions and expectations, the child's development, biological variability and cultural factors. The distinction among various types of sleep disturbance in children is important because melatonin usage for circadian rhythm disorders has been shown to be helpful in adults, but its efficacy for other forms of sleep disorders in children is unclear. The children that improved substantially in the Smits et al (6) study may have had delayed sleep phase syndrome, which has been successfully treated with melatonin (13) resulting in improved daytime functioning.

Sleep disturbance is often multifactorial, and differences in age and comorbid conditions may explain the range in findings among studies with respect to the efficacy of melatonin. Most of the studies of participants with secondary sleep disorders had very small sample sizes. The clinical significance of the change in sleep parameters is unclear. Furthermore, there is a paucity of data related to the number of night-time wakings and total sleep time or sleep efficiency across the range of studies. There is also limited information about parental opinion, quality of life or changes in functioning. These endpoints are critical because the actual value of the change in sleep onset latency may not be as important as the perceived benefit for

the affected child and family. Outcomes such as improvement in daytime functioning may help to determine the clinically relevant improvements in sleep parameters.

Melatonin is an unregulated substance in Canada and the United States. It comes in a variety of formulations, either short-acting or sustained-release preparations. In addition, the trials on melatonin for the treatment of sleep disorders vary in formulation, timing, frequency and duration of melatonin administration. Given the variability in the content and quality of melatonin preparations, and the fact that it is an unregulated product, definitive dosage guidelines on melatonin usage cannot be provided. We recommend that clinicians refer to the Health Canada Web site (14) to ensure that the preparation of melatonin that is used has been evaluated. The dosage recommendations are not absolute because the preparations used can be variable; however, the studies that were reviewed in Part A used doses between 1 mg and 7.5 mg at bedtime. Based on the literature reviewed (5-10,15,16) and clinical experience, I recommend using known preparations of melatonin and starting with smaller doses and titrating for effect. The lack of efficacy could be related to various factors, including the dose, the preparation itself or the wrong indication. For example, melatonin has not been shown to help with sleep maintenance; there may be another medical reason for night-time waking for which melatonin is not effective.

There is no evidence to suggest that melatonin is harmful based on the findings of the systematic review described in Part A (1); however, it must be emphasized that most of the relevant studies evaluated short-term melatonin use. A theoretical but unconfirmed concern about melatonin's effect on the endocrine system remains because melatonin receptors are widely distributed in the ovaries and adrenal glands. The impact of melatonin administration during puberty may be substantial, especially with long-term use, and warrants further study.

In conclusion, the few studies on the use of melatonin in children suggest that melatonin can help to reduce sleep onset latency in children with sleep problems. The generalizability of these findings is limited because of the small sample size of these studies and the range of observed effects. Its widespread use in clinical settings suggests that large-scale randomized controlled trials are warranted to determine the safety and efficacy of melatonin for paediatric sleep disorders, including delayed sleep phase syndrome and paediatric insomnia.

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