Melatonin for children with autism spectrum disorder

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Abstract
Question I have several patients with autism spectrum disorder (ASD) who experience difficulties with sleep, affecting the quality of life of both the child and the family. Is melatonin an effective treatment for sleep problems in children with this condition?

Answer Autism spectrum disorder is prevalent among children in Canada and globally, with most affected children experiencing troubles with sleep. Behavioural therapy is the first-line treatment for sleep problems in children with ASD, and melatonin has been reported to be effective and safe in this population as an alternative or adjunctive treatment. A new pediatric, prolonged-release formulation of melatonin is not yet available in Canada, but initial studies in Europe have indicated that it is a potentially effective treatment for sleep problems in children with ASD.

La mélatonine pour les enfants atteints du trouble du spectre de l’autisme

Résumé
Question Certains de mes patients atteints du trouble du spectre de l’autisme (TSA) éprouvent des difficultés à dormir, ce qui nuit autant à la qualité de vie de ces enfants qu’à celle de leur famille. La mélatonine est-elle un traitement efficace pour les problèmes de sommeil chez les enfants atteints de ce trouble?

Réponse Au Canada et dans le monde, le trouble du spectre de l’autisme est prévalent chez les enfants, et la plupart d’entre eux éprouvent des difficultés à dormir. La thérapie comportementale est le traitement de première intention pour les problèmes de sommeil des enfants atteints du TSA, mais il a été signalé que la mélatonine était efficace et sécuritaire dans cette population comme traitement de rechange ou auxiliaire. Une nouvelle formule pédiatrique de mélatonine à libération prolongée n’est pas encore accessible au Canada, mais des études initiales en Europe ont indiqué qu’il s’agissait d’un traitement potentiellement efficace pour les problèmes de sommeil des enfants atteints du TSA.

Autism spectrum disorder (ASD), characterized by persistent deficits in social interactions with repetitive and restricted behaviour patterns, is estimated to affect up to 1.7% of children worldwide.1,2 According to a 2018 report by the Public Health Agency of Canada, which included almost 2 million participants (40% of Canada’s total population of those aged 5 to 17), approximately 1 in 66 Canadian children are diagnosed with ASD.4 Sleep problems with ASD
The prevalence of sleep abnormalities is as high as 60% to 86% in children with ASD, including complaints of early waking, poor sleep efficiency, somnambulism, and prolonged sleep-onset latency.5 Inadequate sleep can often cause excessive daytime sleepiness, leading to impaired daytime functioning and reduced cognitive abilities.6 Among 529 children aged 2 to 5 years from California, 53% of parents reported their children with ASD had at least 1 sleep problem “frequently” or “always” compared with 32% of parents with children without ASD (P < .0001).5 This translated to 21% of parents in the ASD group reporting that their child’s tricky sleep habits affected the child’s daily function and 23% reporting that it affected the family’s daily function (compared with 1.2% and 2.5%, respectively, in the non-ASD group),8 statistically significantly affecting the family’s quality of life.

Melatonin
The hormone melatonin is synthesized primarily by the pineal gland through regulation by the hypothalamic suprachiasmatic nucleus.9 As one of the primary modulators of the sleep-wake cycle, melatonin follows a circadian pattern of regulation, peaking in concentration at night with conversely low levels during the day.9 As a result, nighttime administration of melatonin has emerged as a common choice for treating insomnia in both children and adults.10,11 In its exogenous form, melatonin is considered a “natural health product” by Health Canada and is currently only recommended for use in adults.12 Use of melatonin is
Low melatonin levels in ASD
While the exact mechanisms of sleep disturbances in children with ASD remain unclear and are likely multifactorial, abnormalities in melatonin regulatory pathways might be a key contributor to the high prevalence of sleep disorders in this population. In a systematic review of 9 trials with more than 800 participants, 7 trials reported lower concentrations of melatonin or melatonin metabolites in children and adults with ASD compared with healthy controls. Notably, the largest of these studies (n = 505) reported that 65% of participants with ASD had low melatonin (<50% of mean control melatonin concentrations).

Melatonin treatment for ASD
The current first-line approach to sleep abnormalities in children with ASD is behavioural interventions such as sleep hygiene education and positive reinforcement of adaptive sleep behaviour, as recommended by the Sleep Committee of the Autism Treatment Network in Canada and the United States. However, sleep management in children with ASD is difficult, with only 25% responding to behavioural interventions. If behavioural therapy fails, pharmacotherapy is often pursued, with melatonin having the greatest body of evidence among potential medications.

In a meta-analysis of 5 small randomized controlled trials with a total of 96 children, treatment with immediate-release melatonin increased sleep duration by an average of 73 minutes and decreased sleep onset latency by an average of 66 minutes when compared with pre-melatonin treatment. Duration of melatonin treatment ranged from 14 days to more than 4 years, and minimal to no side effects were reported in these studies.

Among 160 children from Italy, melatonin (3 mg) in combination with cognitive-behavioural therapy was the most effective in reducing insomnia when compared with each intervention separately. Notably, 63% of the combination-treatment group achieved a clinically significant change after 12 weeks (>85% sleep efficiency, calculated as the ratio of total sleep time to total time in bed) compared with only 46% (P < .001) and 10% (P < .001) of those in the melatonin-only and cognitive-behavioural therapy-only groups, respectively. No adverse events were reported and none of the parents reported a loss of response to the melatonin during the 12-week period.

A subsequent meta-synthesis of 8 reviews compared various sleep interventions for children with ASD and reported that melatonin and behavioural interventions were the most effective treatment options. The 2018 guidelines by the British Association for Psychopharmacology recommend melatonin in combination with a behavioural intervention as the treatment of choice for sleep problems in this population.

In an open-label study of 24 children with ASD, melatonin was reported to improve autistic behavioural impairments in addition to the expected improvements in sleep. Fourteen weeks of melatonin treatment resulted in reduced withdrawal behaviour, as 66% of parents reported their child’s behaviour was withdrawn at the end of the study compared with 72% before treatment (according to the Child Behavior Checklist; P < .0001). Melatonin also improved both stereotypic and compulsive repetitive behaviour, with a reported incidence of 5.2% and 4.5%, respectively, after treatment compared with 6.6% and 7.1%, respectively, before treatment (measured with the Repetitive Behavior Scale; P = .008 and P < .0001, respectively). These findings suggest a potential role for melatonin in improving core and associated symptoms of ASD while concurrently improving sleep outcomes.

Prolonged-release melatonin
Given the short half-life (20 to 50 min) of immediate-release melatonin, one might consider a prolonged-release formulation. A new pediatric, prolonged-release melatonin minitablet (PedPRM), currently available only in Germany, Finland, Norway, Iceland, Switzerland, the United Kingdom, and Italy, is an easily swallowed tablet designed to mimic the endogenous releasing pattern of the hormone and sustain plasma melatonin levels for up to 8 to 10 hours.

Among 125 children with ASD (2 to 17.5 years of age), 69% of participants treated with PedPRM for 13 weeks (2 mg, increased to 5 mg after 3 weeks if the patient did not improve from baseline by at least 60 minutes in shortened sleep latency [SL] or increased TST) achieved clinically significant responses (increased TST by 45 min or decreased SL by 15 min or both) compared with 39% in the placebo group (P = .001, number needed to treat of 3.38). In an open-label follow-up study, 76% (95 of 125) of these children, regardless of their initial randomization group, continued with PedPRM treatment (2, 5, or 10 mg/day) for an additional 39 weeks. After the full 52-week period, 76% of participants had at least 60 minutes more sleep compared with baseline in TST, improved SL, or both. The most frequent treatment-related adverse events were fatigue (5.3%) and mood swings (3.2%); no serious treatment-related adverse events were reported. PedPRM appears to be an efficacious and safe option for children with ASD, although more clinical data are needed to assess long-term therapy.

Conclusion
Sleep abnormalities are common among children with ASD, affecting both the child’s and the family’s daily function. Melatonin has demonstrated efficacy both independently and in combination with behavioural therapy in improving sleep with minimal side effects. A new pediatric, prolonged-released formulation of melatonin has shown promise in initial clinical trials but has yet to be made available in Canada and requires more research on its long-term efficacy and safety in children with ASD.

Competing interests
None declared
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