

# 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,<sup>1</sup> is estimated to affect up to 1.7% of children worldwide.<sup>2,3</sup> 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.<sup>4</sup>

### Sleep problems with ASD

The prevalence of sleep abnormalities is as high as 60% to 86% in children with ASD,<sup>5</sup> including complaints of early waking, poor sleep efficiency, somnambulism, and prolonged sleep-onset latency.<sup>6</sup> Inadequate sleep can often cause excessive daytime sleepiness, leading to impaired daytime functioning and reduced cognitive abilities.<sup>7</sup>

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 ( $P < .0001$ ).<sup>8</sup>

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),<sup>8</sup> 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.<sup>9</sup> 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.<sup>9</sup> As a result, nighttime administration of melatonin has emerged as a common choice for treating insomnia in both children and adults.<sup>10,11</sup>

In its exogenous form, melatonin is considered a "natural health product" by Health Canada and is currently only recommended for use in adults.<sup>12</sup> Use of melatonin is

considered “off label” for the treatment of sleep problems in children and adolescents.<sup>13</sup>

### 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 sleeping disorders in this population.<sup>5,14</sup> 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.<sup>15</sup> Notably, the largest of these studies (n=505) reported that 65% of participants with ASD had low melatonin (<50% of mean control melatonin concentrations).<sup>16</sup>

### 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.<sup>17</sup> However, sleep management in children with ASD is difficult, with only 25% responding to behavioural interventions.<sup>18</sup> If behavioural therapy fails, pharmacotherapy is often pursued, with melatonin having the greatest body of evidence among potential medications.<sup>17</sup>

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.<sup>15</sup> Duration of melatonin treatment ranged from 14 days to more than 4 years, and minimal to no side effects were reported in these studies.<sup>15</sup>

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.<sup>19</sup> 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 [TST] 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.<sup>19</sup> No adverse events were reported and none of the parents reported a loss of response to the melatonin during the 12-week period.<sup>19</sup>

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.<sup>6</sup> 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.<sup>20</sup>

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.<sup>21</sup> 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;  $P<.0001$ ).<sup>21</sup> 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).<sup>21</sup> These findings suggest a potential role for melatonin in improving core and associated symptoms of ASD while concurrently improving sleep outcomes.<sup>21</sup>

### Prolonged-release melatonin

Given the short half-life (20 to 50 min) of immediate-release melatonin, one might consider a prolonged-release formulation.<sup>22-24</sup> A new pediatric, prolonged-release melatonin minitab (PedPRM), currently available only in Germany, Finland, Norway, Iceland, Switzerland, the United Kingdom, and Italy, is an easily swallowed tablet<sup>22</sup> designed to mimic the endogenous releasing pattern of the hormone and sustain plasma melatonin levels for up to 8 to 10 hours.<sup>25</sup>

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).<sup>22</sup> 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.<sup>23</sup> 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.<sup>23</sup> The most frequent treatment-related adverse events were fatigue (5.3%) and mood swings (3.2%); no serious treatment-related adverse events were reported.<sup>23</sup> PedPRM appears to be an efficacious and safe option for children with ASD, although more clinical data are needed to assess long-term therapy.<sup>22,23</sup>

### 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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## References

- American Psychiatric Association, American Psychiatric Association DSM-5 Task Force. *Diagnostic and statistical manual of mental disorders*. 5th ed. Washington, DC: American Psychiatric Association; 2013.
- Baxter AJ, Brugha TS, Erskine HE, Scheurer RW, Vos T, Scott JG. The epidemiology and global burden of autism spectrum disorders. *Psychol Med* 2015;45(3):601-13. Epub 2014 Aug 11.
- Baio J, Wiggins L, Christensen DL, Maenner MJ, Daniels J, Warren Z, et al. Prevalence of autism spectrum disorder among children aged 8 years—autism and developmental disabilities monitoring network, 11 sites, United States, 2014. *MMWR Morb Mortal Wkly Rep* 2018;67(6):1-23. Erratum in: *MMWR Morb Mortal Wkly Rep* 2018;67(19):564, *MMWR Morb Mortal Wkly Rep* 2018;67(45):1280.
- Ofner M, Coles A, Decou ML, Do MT, Bienek A, Snider J, et al. *Autism spectrum disorder among children and youth in Canada 2018. A report of the National Autism Spectrum Disorder Surveillance System*. Ottawa, ON: Public Health Agency of Canada; 2018.
- Souders MC, Zavodny S, Eriksen W, Sinko R, Connell J, Kerns C, et al. Sleep in children with autism spectrum disorder. *Curr Psychiatry Rep* 2017;19(6):34.
- Cuomo BM, Vaz S, Lee EAL, Thompson C, Rogerson JM, Falkmer T. Effectiveness of sleep-based interventions for children with autism spectrum disorder: a meta-synthesis. *Pharmacotherapy* 2017;37(5):555-78.
- Richdale AL, Schreck KA. Sleep problems in autism spectrum disorders: prevalence, nature, and possible biopsychosocial aetiologies. *Sleep Med Rev* 2009;13(6):403-11. Epub 2009 Apr 24.
- Krakowiak P, Goodlin-Jones B, Hertz-Picciotto I, Croen L, Hansen R. Sleep problems in children with autism spectrum disorders, developmental delays, and typical development: a population-based study. *J Sleep Res* 2008;17(2):197-206. Erratum in: *J Sleep Res* 2012;21(2):231.
- Owens JA, Moturi S. Pharmacologic treatment of pediatric insomnia. *Child Adolesc Psychiatr Clin N Am* 2009;18(4):1001-16.
- Pandi-Perumal SR, Srinivasan V, Spence DW, Cardinali DP. Role of the melatonin system in the control of sleep: therapeutic implications. *CNS Drugs* 2007;21(12):995-1018.
- Johnson KP, Malow BA. Assessment and pharmacologic treatment of sleep disturbance in autism. *Child Adolesc Psychiatr Clin N Am* 2008;17(4):773-85, viii.
- Cummings C, Canadian Paediatric Society, Community Paediatrics Committee. Melatonin for the management of sleep disorders in children and adolescents. *Paediatr Child Health* 2012;17(6):331-3.
- Health Canada. *Drugs and health products. Monograph: melatonin - sublingual*. Ottawa, ON: Health Canada; 2018. Available from: <http://webprod.hc-sc.gc.ca/nhp/nd/bdpsn/monoReq.do?id=137&lang=eng>. Accessed 2019 Aug 15.
- Tordjman S, Najjar I, Bellissant E, Anderson GM, Barbuoth M, Cohen D, et al. Advances in the research of melatonin in autism spectrum disorders: literature review and new perspectives. *Int J Mol Sci* 2013;14(10):20508-42.
- Rossignol DA, Frye RE. Melatonin in autism spectrum disorders: a systematic review and meta-analysis. *Dev Med Child Neurol* 2011;53(9):783-92. Epub 2011 Apr 19.
- Melke J, Botros HG, Chaste P, Betancur C, Nygren G, Anckarsäter H, et al. Abnormal melatonin synthesis in autism spectrum disorders. *Mol Psychiatry* 2008;13(1):90-8. Epub 2007 May 15.
- Malow BA, Byars K, Johnson K, Weiss S, Bernal P, Goldman SE, et al. A practice pathway for the identification, evaluation, and management of insomnia in children and adolescents with autism spectrum disorders. *Pediatrics* 2012;130(Suppl 2):S106-24.
- Gringras P, Gamble C, Jones AP, Wiggs L, Williamson PR, Sutcliffe A, et al. Melatonin for sleep problems in children with neurodevelopmental disorders: randomised double masked placebo controlled trial. *BMJ* 2012;345:e6664. Erratum in: *BMJ* 2012;345:e8409.
- Cortesi F, Giannotti F, Sebastiani T, Panunzi S, Valente D. Controlled-release melatonin, singly and combined with cognitive behavioural therapy, for persistent insomnia in children with autism spectrum disorders: a randomized placebo-controlled trial. *J Sleep Res* 2012;21(6):700-9. Epub 2012 May 22.
- Howes OD, Rogdaki M, Findon JL, Wichers RH, Charman T, King BH, et al. Autism spectrum disorder: consensus guidelines on assessment, treatment and research from the British Association for Psychopharmacology. *J Psychopharmacol* 2018;32(1):3-29. Epub 2017 Dec 14.
- Malow B, Adkins KW, McGrew SG, Wang LL, Goldman SE, Fawkes D, et al. Melatonin for sleep in children with autism: a controlled trial examining dose, tolerability, and outcomes. *J Autism Dev Disord* 2012;42(8):1729-37.
- Gringras P, Nir T, Breddy J, Frydman-Marom A, Findling RL. Efficacy and safety of pediatric prolonged-release melatonin for insomnia in children with autism spectrum disorder. *J Am Acad Child Adolesc Psychiatry* 2017;56(11):948-957.e4. Epub 2017 Sep 19.
- Maras A, Schroder CM, Malow BA, Findling RL, Breddy J, Nir T, et al. Long-term efficacy and safety of pediatric prolonged-release melatonin for insomnia in children with autism spectrum disorder. *J Child Adolesc Psychopharmacol* 2018;28(10):699-710.
- De Leersnyder H, Zisapel N, Laudon M. Prolonged-release melatonin for children with neurodevelopmental disorders. *Pediatr Neurol* 2011;45(1):23-6.
- Schroder CM, Malow BA, Maras A, Melmed RD, Findling RL, Breddy J, et al. Pediatric prolonged-release melatonin for sleep in children with autism spectrum disorder: impact on child behavior and caregiver's quality of life. *J Autism Dev Disord* 2019;49(8):3218-30.



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