



Melatonin use for sleep disturbance in children with cerebral palsy: a narrative review

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Background and Objective: Current evidence on melatonin use for sleep disturbances in children with cerebral palsy is, limited; however, in clinical practice, melatonin is used to treat different types of sleep disturbances in children with cerebral palsy. Studies suggest that between 20% and 80% of patients with cerebral palsy and other neurological disorders report sleep disturbances. Our objective in conducting this literature review was to identify evidence supporting the use of melatonin to treat sleep problems in children with cerebral palsy.

Methods: We conducted a literature search using online database PubMed, specifically for studies related to the use of melatonin in cerebral palsy and neurodevelopmental disabilities in children and adolescents from 1996 to 2020. Our search was limited to English language publications. In addition to PubMed, we also consulted standard textbooks. We included original research as well as systematic reviews and meta-analysis type of articles. The key search terms included cerebral palsy, sleep disorders, melatonin, and neurodevelopmental disorders.

Key Content and Findings: Studies suggest that sleep latency may be decreased in patients who have cerebral palsy. Significant limitations of the studies exist that include: cerebral palsy was not the sole disorder in the randomized controlled studies, the lack of oversight in the dietary supplement market, as well as an unestablished pediatric dose of melatonin. Overall, minimal adverse effects were reported with use of melatonin, although this could be explained by the small sample sizes. The studies propose that patients with severe brain injury, or who are prone to seizures, may experience adverse events from melatonin use.

Conclusions: Due to the variance in the product, minimal number of studies, adverse effect potential, and lack of data on doses in children, melatonin should be used with caution in children with cerebral palsy. Additional research is needed on the use of melatonin in the treatment of sleep disorders, specifically in children who have cerebral palsy.

Keywords: Cerebral palsy; melatonin; insomnia

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Introduction

Cerebral palsy (CP) is reported to occur in 1.5 to 2.5 children per 1,000 live births in developed countries (1,2). Cerebral palsy (CP) is a neurological disorder that leads

to varying degrees of motor dysfunction (1,2). In addition to the motor dysfunction these individuals may also have seizures, vision disorders, sleep disturbance, and intellectual disability (1,2). CP is defined as a group of disorders of

Table 1 Sleep disturbances in cerebral palsy

Disorders of sleep initiation
Disorders of sleep maintenance
Sleep-wake transition disorders
Parasomnias
Obstructive sleep apnea
Central sleep apnea

movement and posture associated with a variable degree of activity limitations (2). There are many ways that a child can develop CP, with each cause centering on an injury inflicted upon the child's developing brain in a congenital or acquired manner (2). Different types of sleep disturbances have been described in individuals with cerebral palsy (*Table 1*) (3-9).

A thorough clinical evaluation should be performed to identify and characterize any underlying specific cause for sleep disturbance in these patients. Sleep disturbance in patients with cerebral palsy can be attributed to multiple causes (*Table 2*) (3-9).

Sleep disorders in this population have numerous hypotheses, including diminished melatonin secretion, higher diurnal and lower nocturnal melatonin content, vision impairment, and severe motor impairment (3-10). Vision impairment is believed to be the most likely cause of sleep difficulty due to a disturbance of melatonin secretion (9).

We present the following article in accordance with the Narrative Review Checklist (available at <https://pm.amegroups.com/article/view/10.21037/pm-20-92/rc>).

Objective

Although the evidence on the use of melatonin for the treatment of sleep disorders in children with cerebral palsy is limited, it is commonly used in clinical practice. Our main objective was to review relevant literature on the use of melatonin in children with cerebral palsy.

Methods

We conducted a literature search using online database PubMed, specifically for studies related to the use of melatonin in cerebral palsy and neurodevelopmental disabilities in children and adolescents from 1996 to 2020.

Table 2 Reasons for sleep disturbances in patients with cerebral palsy

Muscle spasms
Decreased ability to change position
Seizures
Side effects of some anti-epileptic drugs
Cortical visual impairment
Gastroesophageal reflux
Excessive salivation
Pain from unrecognized trauma such as dislocated hip
Pain from unrecognized infections such as urinary infection
Circadian rhythm disturbance

Our search was limited to English language publications. In addition to PubMed, we also consulted standard textbooks. We included original research as well as systematic reviews and meta-analysis type of articles. The key search terms included cerebral palsy, sleep disorders, melatonin, and neurodevelopmental disorders.

Discussion

Key findings

Numerous studies have described the use of melatonin in a wide range of sleep problems in children and adolescents, including in children with neurodevelopmental disorders (11-34). Melatonin has had increasing use for sleep disorders such as jet lag, and children with attention deficit hyperactivity disorder (ADHD). In addition to these indications, melatonin has been used for sleep in children and adolescents with neurodevelopmental disabilities such as cerebral palsy and traumatic brain injuries (15-40). Melatonin (N-acetyl-5-methoxytryptamine) is a chronobiologic agent that is essential for the appropriate regulation of sleep-wake cycle in humans (41-44). Generally, melatonin secretion begins in the evening and peaks between 2 AM and 4 AM (9,41). Exposure to natural light is the most important inhibitor of melatonin secretion. Exogenous melatonin is appealing because of its rapid onset of action (30-60 minutes) and its short elimination half-life (30-50 minutes for immediate release formulations) (20).

According to Wasdell *et al.* (2008), approximately 13-85% of patients with cerebral palsy and other neurological injuries have a sleep disorder (34). Difficulties sleeping can lead to numerous other difficulties and strain on the child's

family. Sleep detriments are typically something that can be avoided; however, there is limited research performed on interventions for sleep disorders in children with cerebral palsy (3,6,8,35,37).

Systematic reviews, clinical reviews and meta-analysis have been published regarding the use of melatonin for impaired sleep in children with neurodevelopmental or developmental disabilities (12-22). However, the terms neurodevelopmental disabilities or developmental disabilities were used in studies to describe a variety of disabilities including cerebral palsy. Disabilities could include intellectual disability, learning disabilities, communication disorders, autism spectrum disorders, neural tube defects, cerebral palsy, and ADHD. Of the studies on the use of melatonin in children with neurodevelopmental or developmental disabilities, seven studies reported the number of patients with cerebral palsy included in their studies (14,29-31,33-35), and reviewed studies on interventions for insomnia in children with cerebral palsy or a post-traumatic brain injury (23). There are no studies or guidelines published exclusively on the use of melatonin to treat sleep disorders in children with cerebral palsy (37). Two studies had 50% or more of their subjects with a diagnosis of cerebral palsy listed in the baseline characteristics (34,35).

Wasdell *et al.* (2008), performed a randomized, placebo-controlled, double-blind, crossover trial to measure total sleep time in fifty children aged 2-18 with neurodevelopmental disabilities (34). In addition, the secondary outcomes included, sleep latency, sleep efficiency, and number of nighttime awakenings. Twenty-six of the participants had cerebral palsy. Participants were required to have delayed sleep phase syndrome (>30 minutes delay) or impaired sleep maintenance (>2 prolonged awakenings during the night and daytime symptoms are present). Results were observed through a caregiver-completed somnollog (sleep log), as well as nightly actigraph wrist watch readings. Subjects received 10 days of 5 mg controlled release (CR) melatonin or placebo (20-30 min before bed), followed by 3-5 days of washout, then 10 days of the other treatment. Following this, the caregivers of the subjects were made aware of the treatment and were given the option to participate in a 3-month open label study; the melatonin could be increased in 5 mg increments, with a maximum dose of 15 mg.

A 31-minute difference in total sleep time between melatonin and placebo groups was found, based on somnollog (P value <0.01). Sleep latency was also found to

improve in the melatonin group, with a time difference of 32.7 minutes, P value <0.01. Actigraph reading showed improvements in total sleep time (23.7 minutes) and latency (24.3 minutes). The caregivers were surveyed via Parents' Global Assessment Scale (PGAS) and Family Stress Scale, and reported statistically significant improvements in severity and family stress. Parents reported 0.31 score decrease in impairment and a 0.1 score decrease in family stress (P<0.01 and <0.05, respectively). Adverse events reported included seizures, flulike symptoms, agitation, and headache. Adverse events were determined to coincide with the patient's baseline medical history and were therefore not attributed to melatonin. The study achieved an effect size of 0.4 for total sleep time (P<0.01) and 0.9 for sleep latency (P<0.01).

There have not been dosage studies of melatonin use in children; however, a review recommends 2-10 mg once daily (23,34,41). While benefit is shown in the small sample, the specific benefit in patients with cerebral palsy was not evaluated. Adverse effects were reported as minimal, although seizures were observed in eleven patients. Due to its crossover design, the 3-5-day washout period may not have been a proper length of time. Additional limitations include the subjective nature of the caregiver-completed somnollog, Global Assessment Scale, and the Family Stress Scale. Additionally, while the effect size does show a large magnitude of effect, this test was done against placebo and not a standard treatment.

Dodge *et al.* (2001), performed a randomized, double-blind, placebo controlled trial to observe total sleep time, sleep latency, and number of night time awakenings in 20 children age 1-12 years of age, with moderate to severe developmental disability; 15 subjects had cerebral palsy (35). Subjects received 5 mg melatonin or placebo at bedtime for 2 weeks. Results were obtained through a caregiver-conducted sleep log. The study required 30 patients to achieve a power of 74%. A significant difference in sleep latency was shown between the two groups, P<0.05 (0.7 vs. 1.2 hours). There was a difference in total sleep time from baseline in the melatonin group; however, this was not significant between the treatment and placebo groups. Adverse effects were mild, with two parents reporting moodiness or hyperactivity. Sixteen of the twenty participants were reported to have improved sleep by their parents.

Limitations included that being a supplement, the melatonin formulations may vary. This study had a small sample size and the method used for data collection was

subject to the subjectivity of the caregivers. Additionally, melatonin was compared to placebo and not a standard treatment. Data on total sleep time sleep latency, and number of nighttime awakenings was not reported.

Sheldon (1998) performed an observational study in six children with severe neurological deficits and sleep disturbances given 5 mg of melatonin orally at bedtime (36). Five of the six patients did show improvements in total sleep time, and sleep latency. In four of the six patients new or increased seizure activity was observed, which returned to baseline after discontinuing the melatonin.

Besag *et al.* (2019) systematically reviewed adverse events associated with melatonin (0.15 to 12 mg daily) for the treatment of primary or secondary sleep disorders (38). The most commonly reported adverse events were daytime sleepiness, headache, dizziness and hypothermia; all occurring at a rate of less than 1% with the exception of daytime sleepiness (1.66%). However, the data collected suggests that melatonin is safe. Melatonin should be used with caution in patients with epilepsy and neurological deficits due to the observed seizure activity. It is unknown whether this event may be due to patient history or due to potential antiepileptic effects of melatonin. Boafó, *et al.* (2019) reported on the effect of melatonin on pubertal development (39). They noted that long-term, high-dose use of melatonin might contribute to delayed onset of puberty. Melatonin plays a role on the physiological progression of puberty. Melatonin receptors are present in the adrenal glands and ovaries and melatonin may suppress the gonadotropin-releasing hormone from the hypothalamus.

Jan *et al.* (2004) recommended that in children with multiple disabilities the dose of melatonin might start at 1–2 mg and gradually increase to optimal response (40). As the severity of the disabilities increase, so may the melatonin dose, with a maximum reported dose of 15 mg. Tolerance to melatonin does not seem to develop.

Limitations

Research is limited on the use of melatonin in the treatment of sleep disorders in children with cerebral palsy. Most studies include many other disorders in which melatonin is used. Most studies report small sample size. Another limiting factor is the variability of different formulations of melatonin being used. Melatonin products are not regulated as drugs and it is difficult to ascertain the quality of each product. No large-scale studies are available to provide

guidance on the use of melatonin specifically in children with cerebral palsy.

Future research

Larger prospective studies on the use of melatonin to treat sleep disorders in children with cerebral palsy will be useful in guiding clinical decisions on such use.

Summary

While melatonin is commonly used to decrease sleep onset latency and improve sleep maintenance, there is little evidence or specific clinical guidelines on its effectiveness and recommended dose in the treatment of sleep disorders in patients with cerebral palsy. Each of the studies used a melatonin dose of 5 mg at bedtime. Quality of melatonin products in the US remains a concern. Erland *et al.* (2017) found more than 70% of the 31 melatonin supplements were tested outside the acceptable range of 90–110% of the label claim (42). Furthermore, serotonin was identified in eight of the supplements at levels of 1 to 75 µg. The United States Food and Drug Administration (FDA) states that the responsibility to ensure, safety, and content of the products is on the manufacturers of dietary supplements (43). The FDA does not currently approve dietary supplements for safety; it only review reports of serious adverse events. While the FDA does not currently regulate dietary supplements, such as melatonin, United States Pharmacopeia (USP) verified products provides information on the safest products to use (18). The USP aims to standardize dietary supplements and improve their quality (44) USP-verified is defined as meeting USP-NF standards for quality, purity, potency, performance, consistency, and good manufacturing practice (44).

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References

- Centers for Disease Control and Prevention. Cerebral Palsy (CP) [Internet] Available online: <https://www.cdc.gov/ncbddd/cp/facts.html> accessed 9/2/2020
- Johnson T, Chin EM, Hoon AH. Cerebral palsy. In: Batshaw ML, Roizen NJ, Pellegrino L, eds. Children with disabilities. 8th edition, Baltimore: Paul H. Brookes Publishing, 2019:423-56.
- Gringras P. Sleep disorders in cerebral palsy. *Dev Med Child Neurol*. 2017;59:349-50.
- Blake SF, Logan S, Humphreys G, et al. Sleep positioning systems for children with cerebral palsy. *Cochrane Database Syst Rev* 2015;11:CD009257
- Angriman M, Caravale B, Novelli L, et al. Sleep in children with neurodevelopmental disabilities. *Neuropediatrics* 2015;46:199-210.
- Peterson S, Harvey A, Reddihough D, et al. Children with cerebral palsy: why are they awake at night? A pilot study. *J Spec Pediatr Nurs* 2015;20:98-104.
- Bruini O, Alonso-Alconada D, Besag F, et al. Current role of melatonin in pediatric neurology: clinical recommendations. *Eur J Paediatr Neurol* 2015;19:122-33.
- Blackmer AB, Feinstein JA. Management of sleep disorders in children with neurodevelopmental disorders: a review. *Pharmacotherapy* 2016;36:84-98.
- Santos JS, Giacheti CM, Dornelas LS, et al. Day/night melatonin content in cerebral palsy. *Neurosci Lett* 2018;686:23-7.
- Barlow KM, Esser MJ, Veidt M, et al. Melatonin as a treatment after traumatic brain injury: a systematic review and meta-analysis of the pre-clinical and clinical literature. *J Neurotrauma* 2019;36:523-37.
- Hendaus MA, Jomha FA, Alhammadi AH. Melatonin in the management of perinatal hypoxic-ischemic encephalopathy: light at the end of the tunnel? *Neuropsychiatr Dis Treat* 2016;12:2473-9.
- Simard-Tremblay E, Constantin E, Gruber R, et al. Sleep in children with cerebral palsy: a review. *J Child Neurol* 2011;26:1303-10.
- Abdelgadir IS, Gordon MA, Akobeng AK. Melatonin for the management of sleep problems in children with neurodevelopmental disorders: a systematic review and meta-analysis. *Arch Dis Child* 2018;103:1155-62.
- Braam W, Smits MG, Didden R, et al. Exogenous melatonin for sleep problems in individuals with intellectual disability: a meta-analysis. *Dev Med Child Neurol* 2009;51:340-9.
- Schwichtenberg AJ, Malow BA. Melatonin treatment in children with developmental disabilities. *Sleep Med Clin* 2015;10:181-7.
- Sajith SG, Clarke D. Melatonin and sleep disorders associated with intellectual disability: a clinical review. *J Intellect Disabil Res* 2007;51:2-13.
- Willey C, Phillips B. Is melatonin likely to help children with neurodevelopmental disability and chronic severe sleep problems? *Arch Dis Child* 2002;87:260.
- McDonagh MS, Holmes R, Hsu F. Pharmacologic treatments for sleep disorders in children: a systematic review. *J Child Neurol* 2019;34:237-47.
- McDaid C, Parker A, Scantlebury A, et al. Outcome domains and outcome measures used in studies assessing the effectiveness of interventions to manage non-respiratory sleep disturbances in children with neurodisabilities: a systematic review. *BMJ Open* 2019;9:e027205.
- Hollway JA, Aman MG. Pharmacological treatment of sleep disturbance in developmental disabilities: a review of the literature. *Res Dev Disabil* 2011;32:939-62.
- Gill I, McBrien J. Effectiveness of melatonin in treating sleep problems in children with intellectual disability. *Arch Dis Child* 2017;102:870-3.
- Phillips L, Appleton RE. Systematic review of melatonin treatment in children with neurodevelopmental

- disabilities and sleep impairment. *Dev Med Child Neurol* 2004;46:771-5.
- 23 Galland BC, Elder DE, Taylor BJ. Interventions with a sleep outcome for children with cerebral palsy or a post-traumatic brain injury: a systematic review. *Sleep Med Rev* 2012;16:561-73.
 - 24 Appleton RE, Jones AP, Gamble C, et al. The use of melatonin in children with neurodevelopmental disorders and impaired sleep: a randomised, double-blind, placebo-controlled, parallel study (MENDS). *Health Technol Assess* 2012;16:i-239.
 - 25 Niederhofer H, Staffen W, Mair A, et al. Brief report: melatonin facilitates sleep in individuals with mental retardation and insomnia. *J Autism Dev Disord* 2003;33:469-72.
 - 26 De Leersnyder H, Zisapel N, Laudon M. Prolonged-release melatonin for children with neurodevelopmental disorders. *Pediatr Neurol* 2011;45:23-6.
 - 27 Pillar G, Shahar E, Peled N, et al. Melatonin improves sleep-wake patterns in psychomotor retarded children. *Pediatr Neurol* 2000;23:225-8.
 - 28 Gringras P, Gamble C, Jones AP, et al. Melatonin for sleep problems in children with neurodevelopmental disorders: randomised double masked placebo controlled trial. *BMJ* 2012;345:e6664.
 - 29 Camfield P, Gordon K, Dooley J, et al. Melatonin appears ineffective in children with intellectual deficits and fragmented sleep: six "N of 1" trials. *J Child Neurol* 1996;11:341-3.
 - 30 Ross C, Davies P, Whitehouse W. Melatonin treatment for sleep disorders in children with neurodevelopmental disorders: an observational study. *Dev Med Child Neurol* 2002;44:339-44.
 - 31 Coppola G, Iervolino G, Mastro Simone M, et al. Melatonin in wake-sleep disorders in children, adolescents and young adults with mental retardation with or without epilepsy: a double-blind, cross-over, placebo-controlled trial. *Brain Dev* 2004;26:373-6.
 - 32 Braam W, Didden R, Smits M, et al. Melatonin treatment in individuals with intellectual disability and chronic insomnia: a randomized placebo-controlled study. *J Intellect Disabil Res* 2008;52:256-64.
 - 33 Ayyash HF, Preece P, Morton R, et al. Melatonin for sleep disturbance in children with neurodevelopmental disorders: prospective observational naturalistic study. *Expert Rev Neurother* 2015;15:711-7.
 - 34 Wasdell MB, Jan JE, Bomben MM, et al. A randomized, placebo-controlled trial of controlled release melatonin treatment of delayed sleep phase syndrome and impaired sleep maintenance in children with neurodevelopmental disabilities. *J Pineal Res* 2008;44:57-64.
 - 35 Dodge NN, Wilson GA. Melatonin for treatment of sleep disorders in children with developmental disabilities. *J Child Neurol* 2001;16:581-4.
 - 36 Sheldon SH. Pro-convulsant effects of oral melatonin in neurologically disabled children. *Lancet* 1998;351:1254.
 - 37 Bruini O, Angriman M, Calisti F, et al. Practitioner review: treatment of chronic insomnia in children and adolescents with neurodevelopmental disabilities. *J Child Psychol Psychiatr* 2018;59:489-508.
 - 38 Besag FMC, Vasey MJ, Lao KSJ, et al. Adverse events associated with melatonin for the treatment of primary or secondary sleep disorders: a systematic review. *CNS Drugs*. 2019;33:1167-86.
 - 39 Boafu A, Greenham S, Alenezi S, et al. Could long-term administration of melatonin to prepubertal children affect timing of puberty? *Nat Sci Sleep* 2019;11:1-10.
 - 40 Jan JE, Freeman RD. Melatonin therapy for circadian rhythm sleep disorders in children with multiple disabilities: what have we learned in the last decade? *Dev Med Child Neurol* 2004;46:776-82.
 - 41 Melatonin. Available online: https://online.lexi.com/lco/action/doc/retrieve/docid/fc_rnp2/3750262?cesid=1WSaFysjnbD&searchUrl=%2F%2Faction%2Fsearch%3Fq%3Dmelatonin%26t%3Dname%26va%3Dmelatonin accessed 9/2/2020
 - 42 Erland LA, Saxena PK. Melatonin natural health products and supplements: presence of serotonin and significant variability of melatonin content. *J Clin Sleep Med* 2017;13:275-81.
 - 43 U.S. Food and Drug Administration [Internet]. Questions and Answers on Dietary Supplements. Silver Spring, Maryland. Available online: http://www.fda.gov/Food/DietarySupplements/QADietarySupplements/default.htm#FDA_oversight accessed 9/2/2020
 - 44 The United States Pharmacopeial Convention. USP Verified Dietary Supplements-For Healthcare Professionals [Internet]. 2015. Available online: <http://www.usp.org/usp-verification-services/usp-verified-dietary-supplements/healthcare-professionals> accessed 9/2/2020

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