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Melatonin Treatment in Children with Developmental Disabilities

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Abstract

Melatonin is commonly recommended to treat sleep problems in children with developmental disabilities. However, relatively few studies document the efficacy and safety of melatonin in pediatric populations with developmental diagnoses. This chapter reviews recent studies of melatonin efficacy across a wide breadth of developmental disabilities. Overall, short treatment trials (1 week to 3 months) of melatonin were associated with a significant decrease in sleep onset latency time for each of the disorders reviewed, with one notable exception, tuberous sclerosis. In general, reported side effects were uncommon and mild in nature. Across disorders, additional research is needed to draw disability-specific conclusions. However, studies to date provide positive support for future trials that include larger groups of children with specific disabilities/syndromes.

Keywords

Melatonin; sleep; developmental disabilities; autism; Smith-Magenis Syndrome; Angelman Syndrome

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Introduction

Melatonin is the second most common medication recommended by clinicians for children with sleep disturbance (after antihistamines), with over a third recommending melatonin for children with developmental disabilities.¹ Despite its common use, relatively few clinical trials have documented the efficacy of melatonin in children with developmental disabilities. The following review presents clinical trials, chart reviews, and case study reports (for less common developmental disabilities) of melatonin treatment. The intent of this review is to provide a succinct summary to help inform clinical and research practices for children with developmental disabilities. The developmental disabilities assessed include children with unspecified developmental delays or cognitive impairments and specific disorders/syndromes (e.g., autism spectrum disorder, Smith-Magenis syndrome, Angelman's syndrome, Fragile X syndrome, Down syndrome, and Rett syndrome).

Pharmacologic Studies

Diverse Developmental Disabilities

Until recently, most studies of melatonin efficacy have assessed groups of children with diverse developmental disabilities. These studies have included children with autism, cerebral palsy, 18q deletion syndrome, Angelman syndrome, ART-X syndrome, Bardet-Biedl syndrome, Down syndrome, Prader-Willi syndrome, Sanfilippo syndrome, Saethre-Chotzen syndrome, 11q13 microdeletion, Leber amaurosis, CHARGE syndrome, and unspecified intellectual deficits (ID). With the broad disability/syndrome composition of these studies, it can be difficult to draw conclusions for individual children or disorders/syndromes.² However, even with this challenge the published studies are relatively consistent. Short trials of melatonin (10 days to 4 weeks), consistently report statistically significant decreases in sleep onset latency by about 20-30 minutes.^{3,4,5,6} Longer trials (3-72 months) also endorse shorter sleep latency over time.^{7,8}

Reports of total sleep duration are less consistent, with about half of the studies of children with ID (stemming from various disorders/syndromes) reporting increases in sleep duration with melatonin treatment and half reporting no difference when compared to placebo (see Table 1). Two studies, Braam et al (2008b)³ and De Leersnyder et al (2012)⁵, reported a decrease in night awakenings but three other studies of children with ID did not report a significant reduction in night awakenings with melatonin treatment.^{6,7,9} Unlike early reports of melatonin use¹⁰ and studies of specific disorders/syndromes, only one of the reviewed studies of children with ID reported melatonin-related side effects (i.e., daytime somnolence and naps).

Altered endogenous melatonin profiles have been documented in individuals with Down syndrome, Prader-Willi syndrome, and Sanfilippo syndrome.^{11,12,13,14} However, for these conditions, we found minimal information on the efficacy or safety of melatonin treatment in children. In studies of diverse developmental disabilities, individuals with these syndromes were included but syndrome specific findings were not reported. Trials focusing on groups of children with these syndromes are needed to evaluate not only melatonin

treatment efficacy but also possible differences in how melatonin may be metabolized within these syndromes.

Autism Spectrum Disorder and Associated Genetic Conditions

Several studies have assessed the efficacy of melatonin in treating sleep disturbance in children with autism spectrum disorder (ASD) and associated genetic conditions (Fragile X syndrome, tuberous sclerosis). Although the dose, duration, and elements of sleep affected by melatonin vary considerably across studies, the cumulative findings provide support for melatonin treatment. The review below is not an exhaustive list of ASD and melatonin studies. It focuses on the most recent studies and randomized placebo-controlled trials. The reader is directed to recent reviews of melatonin in ASD, which have highlighted some of the limitations of prior studies (which are also applicable to studies of melatonin in other developmental disabilities).^{15,16,17} These include (1) small sample size; (2) participants not limited to those with autism; (3) outcome measures of sleep are subjective (use of diaries rather than actigraphy, videosomnography, or polysomnography); (4) screening for medical comorbidities which can contribute to insomnia was not commonly done; (5) lack of parent- or child-directed sleep education; (6) assessment of effect on daytime behavior and family functioning was not performed; and (7) predictors of response (e.g., endogenous melatonin, age, IQ) were not assessed. These reviews concluded that while melatonin shows promise, large randomized trials are needed to establish its efficacy.

In a chart review study of 107 children with ASD, Andersen and colleagues (2008) reported 85% of children who were treated with melatonin (0.75 – 6 mg) reported improvements in sleep.¹⁸ Several smaller retrospective studies also report improvements in sleep (to varying degrees). For example, in Gupta and Hutchins' (2005) study of 9 children with autistic disorder, melatonin treatment (2.5 – 5 mg) was associated with shorter sleep onset latencies and longer sleep durations for about half of the children.¹⁹ In open-label trials, Paavonen et al. (2003), Gainnotti et al. (2006), and Malow et al. (2012) also reported decreases in sleep onset latency.^{20,21,22} Garstang and Wallis (2006) completed a randomized double-blind crossover trial with 11 children with ASD, revealing shorter sleep onset latency times, fewer night awakenings, and longer total sleep durations with melatonin treatment (5 mg). Similarly, Wirojanan and colleagues (2009) reported shorter sleep onset latencies, longer nighttime sleep durations, and earlier sleep onset times with melatonin treatment (3 mg) in a randomized double-blind crossover trial of 11 children with ASD and/or Fragile X syndrome.²³ In a slightly larger randomized double-blind control trial of 17 children with ASD, Wright and associates (2011) reported shorter sleep onset latency and longer total sleep times with melatonin treatment (up to 10 mg).²⁴ In the largest randomized placebo-controlled trial to date, Cortesi and colleagues (2012) study of 134 children (69 of whom received controlled-release melatonin, 3 mg) reported reduced sleep onset time and duration and increased sleep duration and efficiency.²⁵ These improvements were reported for children who received cognitive behavioral therapy and/or melatonin but not for children in the placebo group.

A study of girls with Rett syndrome echoed the ASD studies and reported decreased sleep onset time and total sleep duration with melatonin treatment (2.5 – 7.5 mg).²⁶ Conversely, in

a study of 5 children with tuberous sclerosis, a genetic condition associated with increased ASD risk, no significant sleep differences were noted with a 4 week randomized cross-over study of melatonin treatment.²⁷ Similarly, O'Callaghan et al (1999) did not report a decrease in sleep onset latency in their study of 7 individuals with tuberous sclerosis.²⁸ However, they did report an increase in nighttime sleep duration. These studies highlight that ASD etiology may affect melatonin efficacy and etiology (when known) should be considered when assessing melatonin as a treatment option.

The most consistent finding across studies of children with ASD and associated genetic conditions is decreases in sleep onset latency. Findings regarding other elements of sleep are less consistent. For example, some studies report increased night awakenings and others report decreased night awakenings.^{20,29} Although this inconsistency and others like it could stem from differences in dose, melatonin type (fast release or continuous release), administration time, duration of administration, and sleep measurement technique as well as individual differences in melatonin metabolism.

Melatonin's mechanism of influence in children with ASD is largely unknown. While prior studies of nocturnal blood melatonin³⁰, daytime blood melatonin³¹, and nocturnal melatonin metabolites³² have suggested a melatonin deficiency in ASD, a recent study of endogenous melatonin profiles in 11 children with ASD responding to supplemental melatonin highlighted that pre-treatment endogenous melatonin levels are neither low or delayed compared to normative values.³³ This indicates that the pathway of influence in ASD may not simply be low level melatonin replacement but rather other melatonin effects (e.g., hypnotic, phase-shifting, or antianxiolytic).

Overall, studies of melatonin in children with ASD are promising and report relatively few side effects (i.e., headaches, vomiting, upset stomach, dizziness, diarrhea, daytime sleepiness). Considering the relatively low rate(s) of side effects and the consistent findings regarding sleep onset latency, melatonin treatment for children with ASD who struggled with sleep onset is supported by the literature. Other types of sleep disturbances (e.g., early morning awakenings, several nighttime awakenings, circadian rhythm shifts) may be treated with melatonin but the research findings in these areas are less consistent.

Smith-Magenis Syndrome

Previous studies highlight circadian rhythm problems in some children with Smith-Magenis syndrome (SMS) reporting higher endogenous melatonin levels during the day than at night.^{34,35} Several case studies report effectively treating circadian sleep disturbances using melatonin and beta1-adrenergic antagonists.^{36,37,38,39} A research group from France carefully followed 9 children with SMS and reported a reversal of melatonin patterns with the treatment of beta1-adrenergic antagonists during the day and melatonin prior to bedtime.³⁴ In total these studies reflect the treatment of only 13 children. However, within a rare disorder such as SMS they present growing evidence that melatonin treatment (coupled with a beta1-adrenergic antagonist) may help children with SMS who present with inverted or altered circadian patterns. Further support is provided in a series examining open-label use of prolonged-release melatonin in 88 children with neurodevelopmental disorders, 47 of

whom had SMS, which documented improvements in parent-reported sleep latency, sleep duration, night awakenings, and sleep quality.³⁴

Angelman Syndrome

We identified two small studies of children with Angelman syndrome. The first was an open label trial in 13 children by Zhdanova and colleagues (1999) wherein sleep duration increased from baseline levels with melatonin treatment (.3 mg).⁴⁰ However, Zhdanova et al. also reported lower overall activity levels (as indexed by an actigraph) which in and of itself may have affected the actigraph estimates of sleep. A second study by Braam and associates (2008a) was a randomized double-blind placebo-controlled study of 8 individuals with Angelman syndrome.⁴¹ This study reported several improvements in sleep with melatonin (2.5 – 5 mg), when compared to baseline and placebo, including shorter sleep onset latencies, earlier sleep onset time, fewer night awakenings, and longer sleep durations. Melatonin treatment for children with Angelman syndrome requires more research before conclusions regarding its efficacy and safety may be drawn but the current studies provide a positive backdrop for further research.

Summary/Discussion

Studies of melatonin treatment for children with developmental disabilities provide mounting evidence of its efficacy and safety. The studies reviewed here and a recent meta-analysis by Braam and associates (2009) report beneficial effects with melatonin treatment with minimal side effects.⁴² With the exception of tuberous sclerosis, every study reviewed (Table 1) reported a significant decrease in sleep onset latency with melatonin treatment. Even with these promising reports it is important to note that melatonin is not approved by the Food and Drug Administration; in fact, no drug (or supplement) is approved for use in pediatric insomnia. However, the off-label use of melatonin is common, especially in children with developmental disabilities.¹ Based on this review, melatonin is most effective in treating sleep onset difficulties and may be beneficial for other elements of sleep depending on child specific factors. Additional studies, involving large randomized trials, are needed to establish its efficacy and the variables that may influence treatment response.

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Key Points

- Melatonin is commonly recommended for children with developmental disabilities.
- With a few notable exceptions, studies of melatonin efficacy in children with developmental disabilities document significantly shorter sleep onset latencies with melatonin treatment. This finding is best documented in children with autism spectrum disorders.
- Side effects of melatonin treatment were relatively uncommon and mild in nature.
- The use of melatonin to treat pediatric sleep disorders is not approved by the Food and Drug Administration but studies to date provide promising evidence that melatonin could be effective in treating difficulties associated with sleep onset.

Table 1

Summary of melatonin efficacy studies for children with developmental disabilities.

Participants				Melatonin Treatment				Sleep Parameter						
Reference	Diagnosis	N	Age (years)	mg	Duration ^a	Side Effects ^b	Design	SO Latency	SO Time	Sleep Duration	Awakenings	Nights with Awakenings	Sleep Offset	Sleep Efficiency
Anderson et al., 2008	ASD	107	2 – 18	.75 – 6	Varied	sleepiness, enuresis	CR	-	-	-	-	-	-	-
Braam et al., 2008	ID ^c	58	2 – 78	2.5 – 5	4 weeks	none	R, DB, PC	↓	↓	↑	↓	NS	NS	-
Braam et al., 2008	Angelman syndrome	8	4 – 20	2.5 – 5	4 weeks	none	R, DB, PC	↓	↓	↑	NS	↓	NS	-
Camfield et al., 1996	ID	6	3 – 13	.5 – 1	2 weeks	none	DB, PC	-	-	NS	NS	NS	-	-
Coppola et al., 2004	ID ^d	25	3 – 26	3 – 9	4 weeks	none	DB, PC	↓	-	NS	NS	-	-	-
Cortesi et al., 2012	ASD	134	4 – 10	3	12 weeks	none	R, PC	↓	↓	↑	-	-	-	↑
De Leersnyder et al., 2011	ID ^e	88	6 – 12	2 – 10	3 – 72 months	Daytime somnolence or naps	OL	↓	-	↑	↓	-	↑	↑
Dodge & Wilson, 2001	ID	20	1 – 12	5	2 weeks	none	DB, PC	↓	-	NS	NS	-	-	-
Gainnotti et al., 2006	ASD	25	2 – 9	3 – 6	6 months	none	OL	↓	↓	↑	↓	-	↑	-
Garstang & Wallis, 2006	ASD	7	4 – 16	5	4 weeks	none	R, DB, PC	↓	-	↑	↓	-	-	-
Gringras et al., 2012	ID	70	3 – 15	.5 – 12	12 weeks	melatonin = placebo	R, DB, PC	↓	-	↑	-	-	-	NS
Gupta & Hutchins, 2005	ASD	9	2 – 11	2.5 – 5	1 week – 1 year	none	CR	↓	-	↑	-	-	-	-
Hancock et al., 2005	tuberous sclerosis	8	1 – 31	5 – 10	2 weeks	none	R, DB, PC	NS	-	NS	NS	-	-	-
Malow et al., 2012	ASD	24	3 – 10	1 – 6	15 weeks	loose stools	OL	↓	-	NS	-	-	-	NS
McArthur & Budden, 1998	Rett syndrome	9	4 – 17	2.5 – 7.5	4 weeks	mood swings	DP, PC	↓	-	NS	NS	-	-	NS
O'Callaghan et al., 1999	tuberous sclerosis	7	2 – 28	5	2 weeks	none	R, DB, PC	NS	-	↑	NS	-	-	-
Paavonen et al., 2003	Asperger disorder	15	6 – 17	3	2 weeks	tiredness, headaches	OL	↓	-	NS	↑	-	-	NS
Wirojanan et al., 2009	ASD, FXS	12	2 – 15	3	2 weeks	none	R, DB, PC	↓	↓	↑	NS	-	-	-
Wasdell et al., 2008	ID	50	2 – 18	5	10–20 days, 3 months	none	R, DB, PC, OL	↓	-	↑	NS	-	-	NS
Wright et al., 2011	ASD	17	4– 16	2 – 10	3 months	melatonin = placebo	R, DB, PC	↓	-	↑	NS	-	-	-
Zhdanova et al., 1999	Angelman syndrome	13	2 – 10	.3	1 week	none	OL	-	-	↑	-	-	-	-

Note. R = randomized; DB = double-blind; PC = placebo controlled; OL = open label; SO = sleep onset; - not assessed in study; ↓ decreased (or was earlier) with melatonin treatment; ↑ increased (or was later) with melatonin treatment; NS = no statically significant change with melatonin treatment

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^d duration of melatonin treatment

^b reported side effects

^c autism, cerebral palsy, 18q deletion syndrome, Angelman syndrome, ART-X syndrome, Bardet-Biedl syndrome, Down syndrome, Prader-Willi syndrome, Sanfilippo syndrome

^d Angelman syndrome, Saethre-Chozen syndrome, 11q13 microdeletion, Leber amaurosis, CHARGE syndrome

^e Smith-Magenis syndrome, intellectual disability, encephalopathy, autism, Angelman syndrome, Rett syndrome, Boumeville syndrome, blindness.