Melatonin Treatment in Children with Developmental Disabilities

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KEYWORDS

• Melatonin • Sleep • Developmental disabilities • Autism • Smith–Magenis syndrome • Angelman syndrome

KEY POINTS

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

INTRODUCTION

Melatonin is the second most common medication recommended by clinicians for children with sleep disturbance (after antihistamines), with more than one-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. This 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 (eg, autism spectrum disorder, Smith-Magenis syndrome, Angleman'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

Funding Sources: NIH/NIMH (R00 MH092431, PI: A.J. Schwichtenberg); NIH/NICHD (RO1 HD59253, Vanderbilt General Clinical Research Center), NIH/NCRR (M01 RR00095, PI: B.A. Malow).
Conflict of Interest: None to report.

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Sleep Med Clin 10 (2015) 181–187
http://dx.doi.org/10.1016/j.jsmc.2015.02.008

syndrome, Prader–Willi syndrome, Sanfilippo syndrome, Saethre–Chotzen syndrome, 11q13 microdeletion, Leber amourosis, 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–4 weeks), consistently report significant decreases in sleep onset latency by about 20 to 30 minutes.[3–6] Longer trials (3–72 months) also endorse shorter sleep latency over time.[7,8]

Reports of total sleep duration are less consistent, with about one-half of the studies of children with ID (stemming from various disorders/syndromes) reporting increases in sleep duration with melatonin treatment and one-half reporting no difference when compared with placebo (**Table 1**). Two studies—by Braam and colleagues[3] and De Leersnyder and colleagues[9]—reported a decrease in night awakenings, but 3 other studies of children with ID did not report a significant reduction in night awakenings with melatonin treatment.[6,7,10] Unlike early reports of melatonin use[11] and studies of specific disorders/syndromes, only one of the reviewed studies of children with ID reported melatonin-related side effects (daytime somnolence and naps).

Altered endogenous melatonin profiles have been documented in individuals with Down syndrome, Prader–Willi syndrome, and Sanfilippo syndrome.[12–15] 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 presented herein 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).[16–18] 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 that 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 (eg, endogenous melatonin, age, IQ) were not assessed. These reviews concluded that, although 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[19] reported that 85% of children who were treated with melatonin (0.75–6 mg) reported improvements in sleep. Several smaller retrospective studies also report improvements in sleep (to varying degrees). For example, in Gupta and Hutchins' study[20] 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. In open-label trials, Paavonen and colleagues,[21] Giannotti and colleagues,[22] and Malow and colleagues[23] also reported decreases in sleep onset latency. Garstang and Wallis[24] 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[25] 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. In a slightly larger randomized, double-blind, controlled trial of 17 children with ASD, Wright and associates[26] reported shorter sleep onset latency and longer total sleep times with melatonin treatment ($\leq$10 mg). In the largest randomized placebo-controlled trial to date, Cortesi and colleagues[27] studied134 children (69 of whom received controlled-release melatonin, 3 mg) and reported reduced sleep onset time and duration and increased sleep duration and efficiency. These improvements