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STUDY REVIEW

Efficacy and safety of prolonged-release melatonin for insomnia in children with autism spectrum disorder

Making Education Easy 2021

Independent commentary by Karen Waters

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Abbreviations used in this review:

ASD = autism spectrum disorder
DSM = Diagnostic and Statistical Manual of Mental Disorders
ICSD = International Classification of Sleep Disorders
SL = sleep latency
SMS = Smith-Magenis Syndrome
TST = total sleep time

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Publication overview

This review summarises the outcomes from a randomised, double-blind, placebo-controlled study,[1] and its open-label extension,[2] which investigated the efficacy and safety of prolonged-release melatonin (PRM) in children and adolescents with autism spectrum disorder (ASD) or Smith-Magenis Syndrome (SMS) who had an insufficient response to behavioural therapy.

In the 13-week, double-blind phase of the study, PRM was effective and safe compared with placebo for treatment of insomnia in children with ASD or SMS and resulted in improvements in total sleep time (TST), and sleep latency (SL), without causing earlier wake-up time. Data from the open-label extension study (after 39 weeks' follow-up) indicated that PRM was effective and well tolerated in the long term in this patient population. In addition, the improvements in the sleep outcomes in the children and adolescents resulted in improvements in the quality of life of the caregivers. The small odourless, flavourless PRM tablet was easily swallowed by the children and adolescents.[1,2]

Study background

Insomnia is a common problem in typically developing children and adolescents, with a prevalence of up to 40%.[3,4] It is even more prevalent in children and adolescents with neurodevelopmental or psychiatric comorbidities, including those with ASD, occurring in 50–80% of these patients.[4,5] Insomnia can exacerbate core and associated ASD features, contributing to negative effects on mood and emotional regulation, behaviour, and cognitive functioning, and can lead to stress in the whole family.[6,7]

For children continuing to experience sleep difficulties despite managing coexisting conditions and adopting behavioural strategies, sleep-promoting pharmacologic agents have been used in addition to behavioural interventions.[4] However, there is limited evidence supporting the use of medications to treat insomnia in children who have ASD, apart from studies involving melatonin, an indoleamine with sleep-promoting and chronobiotic (sleep phase-shifting) properties.[4,8]

The abnormal secretion and circadian rhythmicity of melatonin may be the explanation for the abnormal sleep–wake cycles reported in individuals with ASD.[9,10] As a consequence, melatonin is increasingly being used to treat insomnia in children, including those with ASD,[11,12] with a number of guidelines recommending melatonin for children/adolescents with ASD.[4,8,13]

Since melatonin has a very short half-life (40 minutes), a PRM formulation (Slenyto®) has been developed to more closely mimic the endogenous profile of melatonin.[14,15]

The small odourless, flavourless PRM tablet is easily swallowed by children and adolescents with ASD.[15]

This publication outlines the efficacy and safety of PRM in children and adolescents with ASD or neurogenetic disorders (e.g. Smith-Magenis Syndrome [SMS]) with insomnia, as reported in a 13-week randomised, double-blind, placebo-controlled study,[1] and during a long-term open-label extension phase of this study.[2] Data relating to the impact of the PRM tablet on child behaviour and caregiver's quality of life during the 13-week, randomised, double-blind, placebo-controlled phase have also been published and will be briefly discussed.[16]

Expert comment

A number of studies support there being a biochemical basis for a relative melatonin deficiency in children with ASD, which provides strong rationale for the study. In addition to sleep onset delay, reported sleep problems also include problems staying asleep, and parasomnias, which are a type of arousal disorder.[17] The problems with sleep maintenance and parasomnias underlies the need for a longer duration of action for exogenous melatonin, along with the rationale of a more physiologic profile.

Study design and methods

Design

This trial was conducted at 14 centres in the United States and 10 centres in Europe.[1]

The study comprised of five periods:[1,2,15]

- A pre-study period (4 weeks);
- A baseline single-blind, placebo period (2 weeks);
- A randomised, placebo-controlled treatment period (13 weeks);
- An open-label treatment period (91 weeks); and
- A single-blind, run-out period (2 weeks placebo).

Children and adolescents without a documented history of sleep behavioural intervention underwent a 4-week, parent-led, sleep behavioural intervention. Patients who still had impaired sleep (defined as ≤6 hours of continuous sleep and/or ≥0.5 hour SL from lights-off in 3 of 5 nights in the last 2 weeks, based on a parent-reported Sleep and Nap Diary[18]) following a 2-week, single-blind, placebo run-in period were randomised to 13 weeks' double-blind therapy with PRM (2 mg escalated to 5 mg) or placebo.[1] The double-blind phase of the trial occurred between December 2013 and May 2016.[1] The double-blind phase of the trial was followed by a 91-week, open-label phase comprising 13 weeks of PRM administered at the final dose (2/5 mg as in the double-blind phase dose), 78 weeks of PRM with optional dose escalation to 10 mg, and then a 2-week, single-blind placebo period.[1, 2, 15]

A Sleep and Nap Diary[18] was completed every morning at home by the parent/caregiver for 14 days prior to each study visit.

Patients

The trial involved 125 children with insomnia aged 2–17.5 years with physician-diagnosed ASD (according to the International Classification of Diseases–10th Revision or Diagnostic and Statistical Manual of Mental Disorders [DSM]-5 or DSM-IV criteria), or neurogenetic disorders; and sleep problems (minimum 3 months of impaired sleep, ≤6 hours of continuous sleep and/or ≥0.5 hour SL from lights-off in 3 of 5 nights) based on parent reports and patient medical history.[1] Children were excluded if they had other sleep disorders (e.g. moderate to severe sleep apnoea); use of prohibited medication or melatonin within 2 weeks prior to screening; allergy to melatonin or lactose; or unresponsiveness to previous circadin therapy; or participation in a clinical trial within the last 3 months prior to the study.

Study endpoints

The primary efficacy endpoint was the change from baseline in mean TST over the 14 days prior to the study visit.[1] Secondary endpoints included the change from baseline in mean SL, mean duration of wake after sleep onset, mean number of awakenings, mean longest sleep episode, and the change in Composite Sleep Disturbance Index (CSDI) score and subscores.[1]

Study results

Data from the 13-week, double-blind phase of the study[1] and after 39 weeks of follow-up in the open-label treatment phase[2] have been published and are reported below.

Patient characteristics

A total of 125 patients were randomised in the double-blind phase; 119 received treatment (58 were treated with PRM and 61 with placebo).[1] A total of 95 children/adolescents who completed the 13-week, double-blind phase of the trial enrolled in the 91-week, open-label phase.

Eighty patients completed 39 weeks of follow-up.[2]

Baseline characteristics are shown in **Table 1.**[1] There were no notable differences between the groups with regards to baseline disease characteristics or medication use.[1]

Table 1. **Baseline characteristics in the Full Analysis Set Population**[1]

	Overall (n=125)
Age, years	8.7 ± 4.15
Female, n (%)	33 (26.4)
Patients with ASD, n (%)	121 (96.8)
Patients with SMS, n (%)	4 (3.2)
Patients with sleep behaviour intervention, (%)	(83.2)
Patients with ADHD, n (%)	36 (28.8)
Patients with epilepsy, n (%)	16 (12.8)
Patients with ≤6 hours continuous sleep, (%)	(3.8)
Patients with SL ≤30 min, (%)	(40.2)
Patients ≤6 hours continuous sleep and SL ≤30 min, (%)	(56)

ADHD = attention-deficit/hyperactivity disorder; **ASD** = autism spectrum disorder; **SL** = sleep latency; **SMS** = Smith-Magenis syndrome.

Efficacy in the 13-week, placebo-controlled treatment period

Total sleep time: During the 13-week, double-blind period, PRM, compared with placebo, was associated with clinically meaningful improvements in TST (primary endpoint).[1] At baseline, mean TST was 457.2 minutes in the PRM and 459.9 minutes in the placebo group.[1] After 13 weeks of treatment, participants slept on average 57.5 minutes longer at night with PRM compared with 9.14 minutes with placebo (adjusted mean treatment difference between PRM and placebo was -32.43 minutes; p=0.034; **Figure 1**). The percentage of TST responders (patients with a mean TST improvement of 45 minutes or more after 13 weeks of double-blind treatment) was 37.9% with PRM compared with 16.4% with placebo (p=0.003).[1]

Sleep latency: At baseline, mean SL was 95.2 minutes in the PRM and 98.8 minutes in the placebo group. SL improved significantly with PRM compared with placebo (mean adjusted change from baseline -37.88 minutes vs -12.58 minutes; p=0.011) during the 13-week, double-blind period (**Figure 1**).[1] The percentage of SL responders (patients with ≥15 minutes reduction in SL after 13 weeks of double-blind treatment) was 63.8% with PRM compared with 32.8% with placebo (p=0.001).[1]

Responders: More children attained clinically meaningful responses in TST and/or SL with PRM compared with placebo (68.9% vs 39.3%, respectively; p=0.001).[1]

Wake-up time: The wake-up time was not significantly different in children treated with PRM compared with placebo.[1]

Longest sleep episode: The mean longest sleep episode increased by 72.18 minutes with PRM and by 30.02 minutes with placebo (p=0.052).[1]

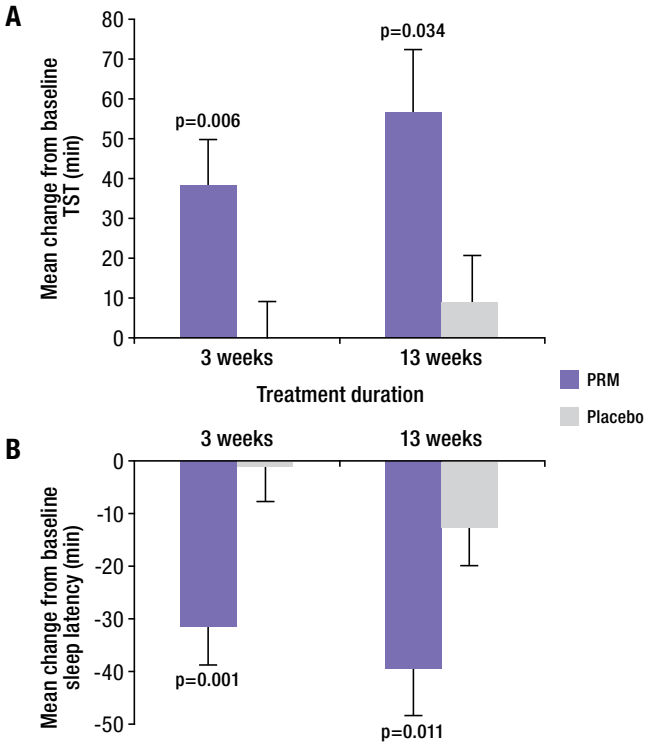

Figure 1. Caregivers' sleep and nap diary reported change from baseline during the 13-week, double-blind period in (**A**) mean total sleep time (minutes) (**B**) mean sleep latency (minutes)
Adapted from Gringras et al. Am Acad Child Adolesc Psychiatry. 2017;56:948-57. **TST** = total sleep time.

Impact on child's/adolescent's behaviour: PRM, compared with placebo, significantly improved externalising behaviours (hyperactivity, inattention, and conduct), but not internalising behaviours (peer relationship problems or emotional symptoms), as assessed by the Strength and Difficulties Questionnaire.[16] More recipients of PRM had a clinically relevant response (improvement in externalising behaviour score ≥1 unit) with PRM than with placebo (53.7% vs 27.7%; p=0.008).[16]

Impact on caregiver's quality of life: Caregivers benefitted from their children's treatment with PRM, compared with placebo, with a significant improvement in quality of life (assessed by the World Health Organization-5 well-being Index),[16] and a significant improvement in their satisfaction in the child's sleep pattern (as measured by the CSDI).[1]

Safety in the 13-week, placebo-controlled treatment period

Treatment-emergent adverse events (TEAE) were reported in a similar number of children treated with PRM or placebo (85.0% vs 76.9%) and were known symptoms in children with ASD (e.g. agitation, mood swings) or experienced generally in children (e.g. upper respiratory tract infection, cough, dyspnoea, and vomiting).[1] However, nervous system disorders were more common with PRM than placebo (41.7% vs 21.5%), with the difference driven mainly by somnolence (28.3% vs 10.8%) and headache (13.3% vs 6.2%).[1] TEAEs considered to be related to treatment occurred in 20% of patients in the PRM group and 16.9% of the placebo group. Severe adverse events were reported in 21.7% of patients treated with PRM and 20.0% of placebo recipients.

Efficacy and safety in the open-label extension period

Efficacy: The beneficial effects of PRM on sleep demonstrated in the 13-week, double-blind phase were maintained or augmented with long-term follow-up, with improvements in TST, SL, and the duration of uninterrupted sleep being maintained after 39 weeks of follow up (**Table 2**).[2]

Patients who received 52 weeks of continuous PRM (13 weeks in the double-blind phase and 39 weeks in the open-label phase) slept a mean 62.08 minutes longer ($p=0.007$), fell asleep 48.6 minutes faster ($p<0.001$), had 89.1 minutes longer uninterrupted sleep episodes ($p=0.001$), had 0.41 fewer nightly awakenings ($p=0.001$), and had a better sleep quality ($p<0.001$) than at baseline. Sleep variables after 39 weeks of open-label follow-up in all patients regardless of treatment during the randomised, double-blind period of the study are shown in **Table 2**.[2]

By the end of the 39-week follow-up, regardless of initial treatment during the 13-week, double-blind period of the trial, 55/72 (76%) of completers achieved an overall improvement of ≥1 hour in TST, SL, or both from baseline.[2]

Caregivers' outcomes: Caregivers-assessed Pittsburgh Sleep Quality Index ($p<0.001$) and WHO-5 well-being index ($p=0.001$) improved compared with baseline. Approximately 49% (38/77) of caregivers experienced a clinically relevant improvement of ≥10% over the baseline quality-of-life score at week 39 of the follow-up period.[2]

Table 2. **Sleep variables after 39 weeks of open-label, PRM in the combined population**[a2]

Variable	Mean change from baseline after 39 weeks of follow-up
Total sleep time (min)	44.35*
Sleep latency (min)	-41.36**
Number of awakenings	-0.39**
Longest sleep duration (min)	78.63**
Quality of sleep	0.72**
Sleep disturbance (CSDI)	-3.27**

[a]The combined population comprised all patients (n=72) regardless of what they had received during the double-blind period of the trial. It included those who had received a total of 52 weeks of PRM (including 13 weeks during the double-blind period of the trial and 39 weeks during open-label treatment) and patients who had received placebo during the 13-week, double-blind period of the trial and 39 weeks of continuous PRM during the open-label period of the study.
CSDI = Composite Sleep Disturbance Index. *p=0.002, **p<0.0001 vs baseline.

Safety: With long-term therapy, no unexpected TEAEs were reported. During the first 39 weeks of open-label follow-up, 77.9% of patients reported a TEAE. TEAEs were considered by the physician investigator to be definitely, probably, or possibly related to study medication in 17.9% of patients. Of these, the most commonly reported adverse events were fatigue (5.3% of patients), mood swings (3.2%), and irritability, aggression, hangover, and somnolence (2.1% each). There were no serious TEAEs reported.

Compliance: Adherence to the PRM was 100% on average throughout the long term (52 weeks of continuous treatment), with the investigators reporting that children were able to swallow the tablets.

Expert comment

The outcomes from this study are significant in terms of the changes in sleep. The reduction in time to sleep onset and the increase in total sleep duration are substantial. The impact on parents (caregivers) is a welcome outcome, and something clinicians are seeking when trying to improve children's sleep. While the reports are provided through sleep diaries and may be somewhat less if monitored objectively (for example actigraphy[19]), the additional impact on the children's behaviour and their families supports the benefits of this therapy.

Study interpretation

Children with ASD or SMS have a disproportionally high prevalence of insomnia compared with typically developing children.[4,5] This study demonstrated that a small PRM tablet has beneficial effects on sleep in children with ASD during the short term (13 weeks), and that these effects were maintained or augmented with continued long-term treatment. Efficacy was demonstrated in terms of significantly increased TST, reduced SL, longer uninterrupted sleep period, improved quality of sleep, and less sleep disturbance compared with baseline. The tablet was well tolerated with fatigue and mood swings being the most commonly reported adverse events. No changes to the safety profile of the prolonged-release tablets were reported with long-term use. Adherence to the prolonged-release tablets was 100%, and it was easily swallowed by the children. Improvements in the children's sleep parameters resulted in improvements in the caregivers' quality of life.[2,3]

Take home messages

- There is a high prevalence of insomnia in children and adolescents with ASD and/or SMS
- Children with ASD and/or SMS often have an abnormal pattern of melatonin secretion and circadian rhythmicity
- In a 13-week, randomised, double-blind study, PRM was effective and safe compared with placebo for treatment of insomnia in children with ASD or SMS
  - PRM resulted in improvements in TST and SL, without causing earlier wake-up time
- The open-label extension phase of this study (after 39 weeks' follow-up) demonstrated that PRM was effective and safe in the long term in this patient population
- Improvements in the sleep outcomes in the children and adolescents with ASD or SMS resulted in improvements in the quality of life of the caregivers
- The small odourless, flavourless PRM tablet was easily swallowed by the children and adolescents

Expert's concluding remarks

Poor sleep is an issue that is a recognised compounder in the care of children with neurodevelopmental disabilities such as autism. This study was well-conducted and provides high-level evidence supporting the use of long-acting melatonin in children with autism and SMS. The fact that melatonin is a natural hormone makes it acceptable to parents over the use of other pharmacologic agents. It will be important to have similar studies in children with other neurodevelopmental disorders to evaluate how widely this therapy has a role in paediatric sleep medicine.

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