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Prolonged-Release Melatonin for Pediatric Insomnia in Autism and/or ADHD: A Four-Case Series

*Valeria Mammarella[1], Maria Breda[1], Raffaele Ferri[2] and Oliviero Bruni[3]**

[1]Department of Psychology, Sapienza University of Rome, Italy

[2]Sleep Research Centre, Oasi Research Institute-IRCCS, Troina, Italy

[3]Department of Human Neuroscience, Sapienza University of Rome, Italy

Abstract

Background: Insomnia is highly prevalent in children with autism spectrum disorder (ASD) and/or attention-deficit/hyperactivity disorder (ADHD), and often persists despite optimized sleep hygiene, behavioral interventions, and, in some cases, immediate-release melatonin. This study describes real-world use of pediatric prolonged-release melatonin (PedPRM) in four such complex cases when first-line strategies are insufficient.

Case Presentation: Consecutive clinic cases underwent baseline clinical assessment, parent sleep diaries, the Sleep Disturbance Scale for Children (SDSC), and actigraphy when available; targeted sleep hygiene and behavioral strategies were implemented before and during PedPRM. (1) An 8-year-old boy with ADHD on extended-release methylphenidate had persistent sleep-onset insomnia and fragmented sleep; PedPRM 2 mg nightly reduced sleep latency and nocturnal awakenings, consequently improving emotional regulation and daily attention, with stable benefit at 3–6 months. (2) A 4-year-old girl with ASD had long nighttime awakenings despite 4 mg immediate-release melatonin; switching to PedPRM 2→5 mg reduced latency, greatly shortened the prolonged awakening, and improved daytime irritability. (3) An 8-year-old boy with severe ASD and epilepsy had nightly 3–5 h awakenings unresponsive to behavioral measures or immediate-release melatonin; PedPRM 3 mg markedly reduced the awakenings; discontinuation led to relapse and re-initiation restored benefit. (4) A 14-year-old girl with ASD and ADHD presented sleep-onset insomnia and nocturnal awakenings unresponsive to sleep hygiene and behavioral techniques; 3 mg PedPRM reduced sleep latency and nocturnal awakenings.

Conclusions: These cases support randomized studies showing PedPRM is effective and safe in ASD and/or ADHD, consistent with European guidelines for insomnia related to these conditions when sleep hygiene fails. PedPRM is an option if behavioral strategies do not address sleep-onset or maintenance issues.

Keywords: Autism spectrum disorder; ADHD; Pediatric insomnia; Melatonin; Prolonged-release

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Correspondence:
Oliviero Bruni, Department of Human Neuroscience, Sapienza University, Via Cornelio Nepote 21 00136 Rome (Italy), Tel: +39-3356078964; E-mail: oliviero.bruni@uniroma1.it

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Introduction

Sleep disturbances, particularly insomnia related to difficulties in initiating and maintaining sleep, are highly prevalent among children with neurodevelopmental disorders, especially autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD). Sleep disturbances are associated with exacerbation of core symptoms, emotional dysregulation, impaired daytime functioning, and reduced quality of life for both patients and families [1,2]. Furthermore, in ADHD, sleep disturbances are often exacerbated by stimulant medication. First-line interventions typically include structured sleep hygiene and behavioral strategies, sometimes complemented by immediate-release melatonin [3]. However, these approaches are often insufficient, especially in cases where sleep-maintenance problems predominate [4].

Pediatric prolonged-release melatonin (PedPRM) has emerged as an evidence-based therapeutic option for children whose insomnia does not adequately respond to non-pharmacological measures. PedPRM can be used for both sleep onset and maintenance regardless of prior use of immediate-release formulations [5-8].

In addition to randomized data, clinical case series and real-world observations suggest that

PedPRM may be beneficial in children with ADHD-related insomnia, improving not only objective sleep parameters but also behavioral outcomes and caregiver satisfaction [9].

Taken together, current evidence supports the consideration of PedPRM as a valid treatment for pediatric patients with ASD and/or ADHD whose insomnia is refractory to behavioral strategies, especially in cases of delayed, fragmented, or disrupted sleep.

The following case reports illustrate how PedPRM can be useful in children with neurodevelopmental disabilities and how practical tools can be used for diagnosis and follow up of insomnia severity. Clinical records include anamnestic data and parent sleep reports, as well as scores on the Sleep Disturbance Scale for Children (SDSC) and actigraphic data for two cases. The SDSC is a validated 26-item parent questionnaire; its Disorders of Initiating and Maintaining Sleep (DIMS) subscale helps quantify insomnia severity and track change in routine care [10].

Case Presentations

Case 1 — 8-year-old male Caucasian child with ADHD presenting sleep-onset insomnia and fragmented sleep.

Background. This patient was an 8-years-old male child, diagnosed with combined-type (hyperactive-inattentive) ADHD and treated with extended-release methylphenidate 18 mg per day from the age of 7. From the start of drug treatment, parents reported a sleep-onset latency (SOL) of >60 min, two or more nocturnal awakenings, morning irritability, fatigue, reduced concentration, and greater impulsivity. Parents also reported heavy evening screen exposure. The Sleep Disturbances Scale for Children (SDSC) revealed the presence of clinical disorders of initiating and maintaining sleep (DIMS score = 27, cut-off 17). Actigraphy showed marked sleep fragmentation. A behavioral plan was established, including a fixed schedule, a screen curfew, and a structured calming routine, but it was insufficient due to the child's resistance. Therefore, PedPRM 2 mg 30–60 min before bedtime was prescribed.

Outcome. After 1 month of treatment, a clear reduction in SOL (< 30 minutes) and fewer awakenings were reported, along with improved emotional regulation and daily attention; benefits persisted at 3 and 6 months without dose escalation.

Case 2 — 4-year-old female Caucasian child with ASD presenting prolonged middle-of-the-night awakening.

Background. This 4-year-old patient received a diagnosis of ASD confirmed by standardized assessments at the age of 3. She presented significant sensory hyperreactivity and sleep disruption. Sleep complaint included SOL >45 min, near-nightly prolonged awakening (~2–3 h) around 02:00–04:00 am, and a daytime nap ~2 h. She usually fell asleep in her mother's arms and has difficulty falling back asleep without parental intervention. SDSC revealed a clinical score on the DIMS scale (score = 29, cut-off 17). Actigraphy showed fragmented sleep with reduced total sleep time and high motor activity. At the time of consultation, the child was taking immediate-release (IR) melatonin 4 mg, with only modest benefit on SOL; in the week before, she fell asleep at around 3:00 despite taking IR melatonin. Firstly, a behavioral plan was established, including a structured bedtime sequence with visual supports, reduction of interactions during awakenings, use of a transitional object and white noise, and elimination of screens. At the same time, she started taking PedPRM 2 mg, which was then raised to 5 mg after two weeks to enhance the initial efficacy.

Outcome. After 3 weeks, SOL was shorter (< 20 minutes) and the prolonged awakenings were reduced; daytime irritability and core symptoms of autism improved.

Case 3 — 8-year-old male Caucasian child with severe ASD and epilepsy presenting prolonged awakenings.

Background. At 2 years and 2 months, this child was diagnosed with ASD through standardized assessments. At the age of 6 years, he started presenting severe epileptic seizures for which drug therapy was prescribed (valproate 400 mg twice daily and clobazam 2.5 mg twice daily). He presented severe behavioral dysregulation with self/hetero-aggression, for which various antipsychotics had been prescribed and then stopped due to side effects or inefficacy; periciazine was added with some improvement on daytime behavior. Sleep complaint included difficulty at bedtime with nightly prolonged awakening (duration 3–5 h) at approximately 02:00–03:00, and minimal daytime napping. At the time of consultation, he was taking IR melatonin, with improved SOL but not maintenance. A behavioral plan was implemented, with a structured routine, environmental adjustments, limited parent intervention during awakenings, no screens use, and a low-intensity night light. PedPRM 2 mg, and later 3 mg, was added.

Outcome. Parents reported marked shortening of awakenings and longer continuous sleep (6–8 h vs ~4 h). Discontinuation of PedPRM led to relapse and re-initiation restored benefit. Tolerability was good alongside periciazine 10 mg. Behavioral dysregulation also improved and self/hetero aggressive behavior were better controlled.

Case 4 — 14-year-old female Caucasian patient with ASD and ADHD presenting sleep-onset insomnia and nocturnal awakenings.

Background. This girl received an ADHD diagnosis at 9 years of age, with a later diagnosis of ASD at 14 years, both confirmed through standardized tools and clinical observation. She underwent various psychological therapies between 9 and 14 years of age for emotional dysregulation and anxiety. At the age of 14, she started pharmacological treatment for psychotic-risk symptoms with aripiprazole (5 mg), which was replaced with quetiapine (50 mg) after seven months due to side effects. Reported sleep issues included sleep-onset delay with co-sleeping. Sleep hygiene guidance was provided, and behavioral techniques were suggested to reduce co-sleeping. After the reduction of co-sleeping she presented with a longer SOL and an increase in nighttime awakenings. Therefore, she started PedPRM 2 and then 3 mg, 30 minutes before bedtime.

Outcome. Parents reported benefits on SOL (< 30 minutes) and a reduction in frequency and duration of night awakenings after the start of PedPRM. The sleep improvement led to a better mood, decreased anxiety and improved sustained attention.

A summary of the four cases is provided in Table 1. To better highlight the shared characteristics across our four cases, we summarized the common clinical aspects, interventions, and outcomes in a separate table (Table 2). This synthesis emphasizes the recurring features of insomnia presentation, prior insufficient response to behavioral or immediate-release melatonin strategies, consistent benefits from PedPRM on sleep initiation and/or maintenance, absence of adverse effects, and improvements in daytime functioning.

Table 1: Clinical characteristics, interventions, and outcomes of four pediatric cases with ASD and/or ADHD treated with PedPRM.

Case	Diagnosis/Comorbidities	Baseline sleep	Intervention	Outcome sleep	Outcome behavior
1 (M, 8yrs)	ADHD; on methylphenidate ER 18 mg	SOL >60 min; ≥2 nightly awakenings; fragmented sleep	PedPRM 2 mg 30–60 min pre-bed	SOL around 30 min; fewer awakenings; stable at 3–6 months	Improved emotional regulation and daily attention
2 (F, 4 yrs)	ASD; sensory hyperreactivity; daytime nap ~2 h	SOL >45 min; nightly 2–3 h awakening (02:00–04:00)	Switch from IR melatonin 4 mg to PedPRM 2→5 mg	SOL < 20 min; prolonged awakening largely resolved;	Improvement in daytime irritability and autism core symptoms
3 (M, 8yrs)	Severe ASD; epilepsy (valproate, clobazam); behavioral dysregulation	Night awakening of 3–5 h duration at ~02:00–03:00 am; minimal naps	Add PedPRM 2→3 mg with behavioral plan	Shortening of awakenings; longer continuous sleep (6–8 h); relapse off-drug, benefit on re-start	Better control of behavioral dysregulation and self/hetero aggressive behaviors.
4 (F, 14yrs)	ASD; ADHD; severe anxiety and emotional disregulation	SOL > 60 min; co-sleeping; sleep time 3:00-8:00. After elimination of co-sleeping, increase of night awakenings	Add PedPRM 2→3mg	SOL < 30 min; reduction in frequency and duration of night awakenings	Decreased anxiety improved mood and sustained attention.

Legenda: ASD: Autism Spectrum Disorder; ADHD: Attention-Deficit/Hyperactivity Disorder; SOL: Sleep-Onset Latency; IR: Immediate-Release; PedPRM: Pediatric Prolonged-Release Melatonin

Table 2: Common Clinical and Therapeutic Aspects Across the Four Cases.

Domain	Shared Features	Notes/Variations
Age range	Pediatric (4–14 years)	Two children 8 yrs, one 4 yrs, one 14 yrs
Diagnoses	All had ASD and/or ADHD	One case with comorbid epilepsy, one with anxiety/psychotic risk
Main sleep complaints	Sleep-onset insomnia and/or prolonged nocturnal awakenings	SOL >45–60 min in three cases; midnight awakenings predominant in two
Previous interventions	Behavioral strategies and/or immediate-release melatonin	Consistently insufficient
PedPRM intervention	All switched/initiated PedPRM	Dose adjusted in two cases
Clinical response	Improved SOL and/or reduced night awakenings across all cases	Case 3 relapse after discontinuation, reversed by re-start
Adverse effects	None reported	Good tolerability even with polytherapy
Daytime effects	Better mood, attention, emotional regulation	Reported in all cases

Legenda: ASD: Autism Spectrum Disorder; ADHD: Attention-Deficit/Hyperactivity Disorder; SOL: Sleep-Onset Latency; PedPRM: Pediatric Prolonged-Release Melatonin

Discussion and Conclusions

This case series highlights pragmatic scenarios in pediatric sleep clinics where prolonged-release melatonin can be beneficial: stimulant-associated or circadian-delayed sleep initiation problems in ADHD, ASD with persistent midnight awakenings, and complex ASD with comorbid epilepsy where sleep-maintenance failure predominates. Across the four cases, PedPRM consistently improved sleep initiation and/or maintenance, with beneficial ripple effects on daytime functioning and behavioral regulation. The patterns and responses observed in our cases parallel controlled data in ASD and support the mechanistic rationale for a prolonged-release profile to extend nocturnal melatonin exposure and improve sleep maintenance [5-7]. In a pivotal randomized controlled trial involving children and adolescents with ASD, with or without ADHD or other comorbid neurodevelopmental disorders, PedPRM significantly increased total sleep time and reduced sleep latency compared with placebo over 13 weeks [5]. Long-term follow-up studies have further demonstrated sustained efficacy and favorable safety over two years, with no detrimental effects on growth or pubertal development [6,7].

In Case 1, the child developed delayed SOL and frequent awakenings after initiation of extended-release methylphenidate, consistent with stimulant-related insomnia patterns. In fact, in children with ADHD, MPH treatment has been associated with longer sleep latency, reduced sleep efficiency, and shorter sleep duration [11], even though data are mixed [12-14]. A placebo-controlled trial conducted by Mohammadi et al. [15] on the effect of melatonin in children with ADHD and MPH treatment reported reduced SOL and improvements in overall sleep with 3-6 mg/day of melatonin. Masi et al. [16] reported improvements in sleep problems in 60.8% of patients, most of whom were taking a prolonged-release formulation of melatonin, with no changes in efficacy according to gender and comorbidities, and without side effects during follow-up. In our Case 1, adjunctive PedPRM 2 mg was associated with reduced sleep latency and improved sleep continuity, mirroring findings from randomized studies on melatonin use in untreated and stimulant-treated children [15,17]. In routine practice, melatonin is often used adjunctively with stimulant optimization and behavioral measures in case of worsening or onset of sleep disturbances after the start of MPH administration.

Cases 2–4 illustrate the frequent occurrence of prolonged nighttime awakenings in ASD, often resistant to behavioral strategies and immediate-release melatonin. In line with Gringras et al. [5] and Maras et al. [7], PedPRM was superior to IR melatonin in sustaining sleep, reducing prolonged awakenings, and increasing continuous sleep duration. By reducing nocturnal awakenings, PedPRM may also alleviate parental sleep disruption and caregiver stress, an outcome of major clinical relevance. For instance, Case 3 demonstrated relapse upon discontinuation of PedPRM, with restoration of benefits after re-initiation, echoing the long-term efficacy and safety observed in controlled extensions [6]. The tolerability of PedPRM alongside antiepileptics and antipsychotics in our series aligned with randomized evidence [5] and supports its use in children with complex comorbidities where other hypnotics may be less suitable. Case 2, a younger child with ASD, also highlighted that dose

escalation (from 2 mg to 5 mg) may be required for optimal effect, a finding consistent with dose-titration clinical studies. These cases underscore the importance of real-world dose titration of PedPRM, which is less visible in RCTs but essential in clinical practice. In both ASD and ADHD, when frequent night waking with or without sleep-onset delay predominates, clinicians should consider recommending prolonged-release melatonin, even following unsatisfactory use of IR melatonin [3]. Our cases also highlight that pharmacological benefit was maximized when combined with structured behavioral and sleep hygiene strategies.

The SDSC (DIMS subscale) and actigraphy supported diagnosis and monitoring in our series (DIMS score = 27 in Case 1; 29 in Case 2). These tools can standardize follow-up and quantify real-world effects alongside sleep diaries [10]. Routine incorporation of actigraphy or other objective tools could enhance clinical follow-up and support individualized treatment adjustments.

Clinical implications

When structured sleep hygiene and behavioral strategies are insufficient, pediatric prolonged-release melatonin is a reasonable, evidence-informed next step for ASD and/or ADHD-associated insomnia. PedPRM can be used in children that were not previously medicated for sleep disorders and in children who were treated with IR melatonin. IR melatonin can be switched with PedPRM using, as initiation dose the lowest recommended dose according to the Summary of Product Characteristics (i.e. the recommended starting dose is 2 mg in children with ASD and 1-2 mg in children with ADHD. The dose may be adjusted on an individual basis to 5 mg per day regardless of age of the child. If clinically needed, the maximum daily dose may be increased to 10 mg) [18]. Clear goal-setting (e.g. reducing SOL; prevent prolonged middle-of-the-night awakenings), parent coaching, and regular follow-up are essential to sustain benefit.

Limitations and future directions

This uncontrolled case series relies on parent-reported outcomes with limited objective metrics across time points; nonetheless, the inclusion of actigraphy in two children strengthens objectivity, and the consistency with prior literature supports external validity. Placebo effects and concurrent behavioral interventions cannot be disentangled. Doses reflect real-world practice (2–5 mg), within approved ranges but individualized. Since the pediatric population with ASD and/or ADHD and chronic insomnia can be very heterogeneous in terms of concomitant problems, pharmacological history, and pattern of insomnia, future controlled trials should evaluate predictors of response to PedPRM, as well as explore long-term developmental outcomes.

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