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Pediatric Appropriate Prolonged-Release Melatonin Minitablet for Insomnia in Children and Adolescents with Attention-Deficit/Hyperactivity Disorder: Case Reports

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Abstract

Despite high rates of sleep impairments among children and adolescents with attention-deficit/hyperactivity disorder (ADHD), and its negative impact on child development, behavior, health and quality of life, there is limited awareness among clinicians of screening for and treatment of insomnia in this population.

Pediatric Prolonged-Release Melatonin (PedPRM, Slenyto®) is the first authorized drug for the management of insomnia in children and adolescents (aged 2-18) with autism spectrum disorder (ASD) and neurogenetic disorders (NGD) and it is now approved for children and adolescents (aged 6-17) with ADHD, but there is little evidence on how it may act on ADHD related symptoms and insomnia in real life treatment.

This case series reports 12 children and adolescents (aged 6-13 years) with ADHD and insomnia, and describes the decision-making process involved in PedPRM selection and treatment optimization. Some patients initiated cognitive behavioral therapy and/or immediate release (IR) melatonin as a first line treatment for their insomnia, with no or partial success. The administration of PedPRM, followed by dose optimization resulted in 9 patients attaining acceptable sleep duration (>7 h), sleep maintenance (longest sleep episode >6 h) and sleep initiation (sleep onset latency <30 min). The other 3 patients attained acceptable sleep in two out of the 3 variables. Significant positive effects on daytime behavior and parent satisfaction were noted in all reported cases.

Thus, real life evidence supports PedPRM as an effective and safe strategy for managing insomnia in pediatric patients with ADHD.

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Introduction

ADHD is a Neurodevelopmental Disorder characterized by ongoing pattern of one or more complaint of inattention, hyperactivity and impulsivity [1]. The ADHD/HD worldwide-pooled prevalence is around 5%, although this estimate is associated with significant variability [2-4]. Based on US national representative data (2017-2022), the estimated ADHD incidence among children and adolescents aged 4-17 years is 10.28% [4].

Up to seventy percent of children with ADHD experience sleep disturbances [5,6] as opposed to only twenty to thirty percent in children from the general population [6-8]. Children with ADHD experienced 30 to 60 minutes shorter sleep duration and reported significantly more awakenings at night compared to controls [9-12]. Moreover, stimulant medications used as first line ADHD treatment have the potential to further increase sleep latency [39-41].

Co-occurring sleep problems in children with ADHD predicted more severe core symptoms and exaggerated daytime sleepiness [13-16]. Treating sleep onset and maintenance insomnia early-on

might improve the sleep-related difficulties in core ADHD symptoms and the quality of life of children and their parents [17].

Recent findings suggest that children with ADHD may struggle to maintain their circadian sleep-wake rhythm due to a phase-delayed melatonin secretion [18-21]. Several global guidelines recommend the use of melatonin for sleep problems in children with neurodevelopmental conditions including ADHD where sleep hygiene measures have been insufficient [22-26]. Over recent years several immediate-release melatonin formulations (IRM) have been authorized in the EU/EEA for the treatment of sleep disorders in children and adolescents with ADHD (https://www.medicines.org.uk/emc/product/10419/smpc#gref). Those formulations deliver rapid, transient, high levels of melatonin that subside rapidly and thus predominantly improve sleep onset latency (SOL), but do also cause earlier morning awakenings due to the phase-shifting chronobiotic effects of IR melatonin [18,27]. A pediatric appropriate prolonged-release minitablet formulation of melatonin (PedPRM) that circumvents the fast clearance of the hormone by releasing it in the gut over an extended period of time [28-31] was approved for insomnia in children aged 2-18 years with ASD and NGD and is now approved for children with ADHD (https://www.ema.europa.eu/en/medicines/human/EPAR/slenyto). Among children with ASD, the prevalence of clinically significant ADHD symptoms – defined as causing a high degree of impairment in cognitive, social, and adaptive functioning - ranges from 29% to more than 40% [32]. Clinical trials of PedPRM in children and adolescents with ASD demonstrated improvements in sleep duration (TST) and maintenance (longest sleep episode, LSE) as well as SOL, and subsequently in child's behaviors and caregiver's quality of life [33-35]. PedPRM does not have phase-shifting chronobiotic properties due to its bioavailability (circadian time zero) and thus, does not cause earlier morning awakenings. In previous studies, PedPRM was globally safe; the most frequent treatment related adverse events were asthenia (6.3%), somnolence (6.3%), and mood swings (4.2%) [36]. The recommended starting dose for children with ASD is 2 mg once daily for 2 to 4 weeks, increased to 5 mg and then 10 mg/day, regardless of age or weight, if the pre-defined treatment success criteria (LSE >6 h, SOL <30 min and TST acceptable for their age) are not met [37].

PedPRM indication was recently extended to children and adolescents with ADHD aged 6-17 and starting dose is 1 mg escalated to 10 once daily [38]. To evaluate the benefit of PedPRM in clinical practice, we present here a case series of 12 children and adolescents with ADHD demonstrating the decision-making process involved in the choice of PedPRM and dose effects on child's sleep and behavior as well as family satisfaction (detailed in Table 1).

Case Presentation (C1-C12) (Table 1)

C1 - 12-year-old male with ADHD, comorbid anxiety and insomnia and treated with methylphenidate (MPH) for ADHD.

C1 had difficulty falling asleep (SOL 60 min), frequent awakenings, and short sleep duration (TST 6.5-9 h), early morning awakenings with fatigue, associated with increased ADHD symptoms.

Treatment with PedPRM (2 mg, escalated to 5 mg after 2 months) led to significant improvement in the insomnia (SOL <30 min, LSE ~ 9 h, and morning awakening at 7 a.m. with less fatigue). Parents reported satisfaction with the quality of their child's sleep, and associated decrease in irritability, anxiety and emotional dysregulation.

C2 - 7-year-old male diagnosed with ADHD, and comorbid dysgraphia, insomnia and oppositional defiant disorder (ODD). He was treated with MPH for ADHD.

C2's sleep problems included difficulty falling and staying asleep with increased difficulty concentrating, restlessness, frequent outbursts of anger, and indirect endangerment.

Following treatment with PedPRM 2 mg, SOL decreased from 60-90 min to <30 min, number of awakenings (NOA) from ~3 (30-60 min each) to 1 per night (15-20 min each), LSE increased from 5 to 7 h, with consequent improvement in ADHD symptoms and temper tantrums. Parents became less exhausted following their child's improved sleep quality and behaviour.

C3 - 8-year-old female diagnosed with ADHD at the age of 7 years, with comorbid mild anxiety and learning disorder (dyslexia). She exhibited a persistent pattern of inattention that impacted her daily functioning at home and school, frequently making careless errors, being easily distracted, and having difficulty coping with academic demands.

Her sub-threshold insomnia worsened after initiation of MPH treatment (SOL 60-90 min, NOA 2-3/night 20-60 min each, TST 7-8 h, LSE ~4 h) with daytime tiredness.

Sleep hygiene optimization and adjustments to MPH yielded minimal improvements. Following 2 weeks of treatment with PedPRM, the child's sleep patterns significantly improved, (SOL 20-30 min, TST 8-9 h, LSE 6-7 h, NOA 0-1 per night for 5 min).

Marked improvement was noted in the child's daytime behaviour, less fatigue and anxiety, with better attention and school performance. Parents reported relief and satisfaction, noting they felt more rested and capable of managing daily tasks.

C4 - 6-year-old male diagnosed with ADHD and mild anxiety at the age of 5 years, and insomnia at the age of 6 years, with difficulties falling and staying asleep and short sleep duration (LSE 60-120 min, TST 7-8 h per night, LSE 3 h and NOA 2-3 times per night, 10-60 min each). C4 exhibited increased irritability, reduced attention span, and high hyperactivity during the day. A structured sleep hygiene program resulted in minimal improvements. No pharmacological intervention for ADHD or insomnia was provided.

Treatment with PedPRM 2 mg resulted in significant improvements in the child's sleep patterns (SOL 20-30 min, 1-2 awakenings for ~5 min each, LSE 5-6 h, TST 8-9 h). Parents reported a substantial improvement in children's ADHD symptoms (less irritable, more focused during school hours, and reduced hyperactivity) and their wellbeing.

C5 - 13-year-old male diagnosed with ADHD, dyspraxia and insomnia at the age of 10 years (SOL >3h, TST 4-5h, NOA 3-4 per night). Treatment with IRM did not improve the insomnia symptoms. Following PedPRM 5 mg daily, sleep patterns markedly improved (SOL 45 min, TST 9-10 h). IRM 1.5 mg spray resulted in further improvement in sleep initiation (SOL 20 min).

However, the treatment was stopped because the family could not afford the costs.

C6 - 8-year-old male diagnosed with insomnia at age 3 years, with ADHD and difficulties in social cognition at age 6 years, and comorbid ODD at age 7 years (SOL 60-80 min, TST 8 h, LSE 4-5 h,

Table 1:

Case No./ Gender, Age	DSM-5 Diagnosis	Medication History/ Baseline Insomnia	SLENYTO Dose/ Treatment Outcome	Treatment Goals Reached [1]
Case 1 Male 12 years	At age 12 years ADHD, anxiety and insomnia	No treatment for sleep disorders. MPH from age 12. <u>Insomnia Parameters</u> SOL 60 min TST 6.5-9 h LSE 6.5-9 h NOA 0	SLENYTO 5 mg <u>Treatment Outcome</u> SOL <30 min TST 7-9 h LSE 9 h NOA 0	YES for all variables
		Increased irritability, anxiety and emotional dysregulation. Parents are tired and worried.	Decreased irritability, anxiety and emotional dysregulation. Parents are satisfied with the quality of their child's sleep.	
Case 2 Male 7 years	At age 6 years ADHD, dysgraphia and ODD. Insomnia since age of 4 years	No treatment for sleep disorders. MPH from age 7.	SLENYTO 2 mg	YES for all variables
		<u>Insomnia Parameters</u> SOL 60-90 min TST 7-10 h LSE 5 h NOA 3	<u>Treatment Outcome</u> SOL <30 min TST 8-10 h LSE 7 h NOA 1	
		Increased difficulty concentrating and restlessness.	Improvement in ADHD symptoms, reduction in temper tantrums.	
		Parents are exhausted.	Parents are less exhausted.	
Case 3 Female 8 years	At age 7 years ADHD, mild anxiety and dyslexia Sub-threshold insomnia, exacerbated after starting MPH	No treatment for sleep disorders. MPH from age of 7.	SLENYTO 2 mg	YES for all variables
		<u>Insomnia Parameters</u> SOL 60-90 min TST 7-8 h LSE 4 h NOA 2-3	<u>Treatment Outcome</u> SOL 20-30 min TST 8-9 h LSE 6-7 h NOA 0-1	
		Daytime tiredness due to sleep deprivation.	Less fatigue and anxiety, better attention and performance at school.	
			Parents felt more rested and capable of managing daily tasks.	
Case 4 Male 6 years	At age 5 years ADHD, mild anxiety and insomnia	No treatment for sleep disorders. No MPH or other drugs for ADHD	SLENYTO 2 mg	YES for all variables
		<u>Insomnia Parameters</u> SOL 60-120 min TST 7-8 h LSE 3 h NOA 2-3	<u>Treatment Outcome</u> SOL 20-30 min TST 8-9 h LSE 5-6 h NOA 1-2	
		Increased irritability and hyperactivity, reduced attention span.	Less irritability and hyperactivity, more focus during school hours.	
		Parents are fatigued and frustrated.	Parents are more rested and better able to manage daily tasks.	
Case 5 Male 13 years	At age 10 years ADHD, dyspraxia and insomnia	Treatment with IR melatonin since the age of 10. No MPH or other drugs for ADHD.	SLENYTO 5 mg with melatonin rapid effect spray 1.5 mg	YES for all variables
		<u>Insomnia Parameters</u> SOL >180 min TST 4-5 h NOA 3-4	<u>Treatment Outcome</u> SOL 20-45 min TST 9-10 h NOA 0	
		Child's behaviour is a disaster in class, with major impulsivity issues.	The child was stabilised with SLENYTO, but they had to stop because the family can't afford to pay it.	
		Parents claim their life is a disaster as the teenager does not sleep.		
Case 6 **Male** **8 years**	At age 6 years ADHD. ODD diagnosed at age 7. Insomnia diagnosed at the age of 3.	Behavioural therapy in the early years. IR melatonin 1 mg at 5-7 years.	SLENYTO 2 mg	YES for all variables
		<u>Insomnia Parameters</u> SOL 20-80 min TST 8-9 h LSE 4-5 h NOA 2-4	<u>Treatment Outcome</u> SOL 20 min TST 10 h LSE 9 h NOA 0-1	
		Common oppositional-defiant behaviour. Many temper tantrums during the day, very agitated, can't sit still even during meals, refuses to sleep.	Improvement of emotional regulation, less impulsive and oppositional-defiant behaviours.	
		Parents are exhausted.	Parents are now fully satisfied with their child's sleep and feel more rested and energetic.	

Case 7 Male 6 years	ADHD diagnosed at the age of 6 years, possibly associated learning difficulties. Insomnia diagnosed at the age of 3 years.	No pharmacological treatment for sleep disorders.	SLENYTO 5 mg, after 1 month with SLENYTO 2 mg	YES for all variables
		<u>Insomnia Parameters</u> SOL 60 min TST 7-8 h LSE 5 h NOA 2-3	<u>Treatment Outcome</u> SOL 5-10 min TST 10 h LSE 9 h NOA 0-1	
		Child is very dispersed at school. From early afternoon on, he is very cranky, seems tired, cries very often, gets into temper tantrums; these get worse in the evening.	Motor hyperactivity is decreased, as is impulsivity and concentration difficulties. The child is much less tired and cranky in the afternoon and early evening, with less bedtime resistance.	
		Parents are very tired and anxious.	Parents are satisfied with the improvement in sleep maintenance and child's behaviour.	
Case 8 Male 7 years	ADHD diagnosed at the age of 4 years, with comorbid psychomotor instability. Insomnia was diagnosed at the age of 28 months.	No pharmacological treatment for sleep disorders.	SLENYTO 6 mg, increased gradually after some time (3-4 months) with SLENYTO 3 mg	YES for all variables
		<u>Insomnia Parameters</u> SOL 15 min TST 1-2 h LSE 2 h NOA 1	<u>Treatment Outcome</u> SOL 15 min TST 10 h LSE 10 h NOA 0	
		Unstable behaviour, endangerment, and development delay.	An amelioration of instability, concentration, and step-by-step learning was notable.	
		Parents are very unsatisfied with child's sleeping disorder.	Parents reported improved well-being and satisfaction with their child's sleeping pattern.	
Case 9 Female 7 years	ADHD was first diagnosed at the age of 4 years, with comorbid ODD. Insomnia was diagnosed before the age of 12 months.	No pharmacological treatment for sleep disorders.	SLENYTO 3 mg, after one year with SLENYTO 2 mg	YES for SL and LSE TST improved by >100%
		<u>Insomnia Parameters</u> SOL 1 h TST 2-3 h LSE 3 h	<u>Treatment Outcome</u> SOL 15 min TST 6 h LSE 6 h	
		NOA 1 – long, without going back to sleep	NOA 2-3 – short (5 min each)	
		Normal ADHD-related behaviour.	Normal ADHD-related behaviour.	
		Parents are unsatisfied with child's sleeping pattern.	Parents' improved well-being and satisfaction with their child's sleeping pattern.	
Case 10 **Male** **9 years**	ADHD diagnosed at the age of 7 years, with associated learning and writing difficulties, verbal and gestural tics. Insomnia diagnosed at the age of 4 years.	No pharmacological treatment for sleep disorders.	SLENYTO 5 mg, after 1 year with SLENYTO 1 mg, increased gradually	YES for all variables
		<u>Insomnia Parameters</u> SOL 4 h TST 4 h LSE 3 h NOA 2-3	<u>Treatment Outcome</u> SOL 30 min TST 10 h LSE 9 h NOA 2-3	
		Child shows academic difficulties.	Child shows better concentration at school.	
		Parents are unsatisfied with child's sleeping pattern.	Parents' improved well-being and satisfaction with their child's sleeping pattern.	
Case 11 Male 12 years	ADHD diagnosed at the age of 6 years, with comorbid dyslexia. Insomnia diagnosed at the age of 7 years.	No pharmacological treatment for sleep disorders.	SLENYTO 3 mg, after 1 month with SLENYTO 2 mg	YES for SOL and TST LSE improved by 33%
		<u>Insomnia Parameters</u> SOL 45 min TST 8.5 h LSE 3 h NOA 4-6	<u>Treatment Outcome</u> SOL 20 min TST 9 h LSE 4 h NOA 2	
		Child behaviour is characterized by irritability and hyperactivity.	Less irritability and hyperactivity. Parents are satisfied by improvement in child's sleep pattern	
		Parents are unsatisfied with child's sleeping pattern.	Parents' improved well-being and satisfaction.	
Case 12 Male 6 years	ADHD diagnosed at the age of 4.5 years, with comorbid tics and anxiety Insomnia diagnosed at the age of 3 years.	Treatment with melatonin-IR, 1.9 mg.	SLENYTO 3 mg, after 2 weeks with SLENYTO 2 mg	YES for SOL and TST LSE improved by 100%
		<u>Insomnia Parameters</u> SOL 55 min TST 9 h LSE 2 h NOA 5-7	<u>Treatment Outcome</u> SOL 15 min TST 9.5-10 h LSE 4-5 h NOA 2	
		Child exhibits anxiety and tics which increase at bedtime.	Child shows less tics and bedtime anxiety. Parents feel better about their child improvement in sleeping pattern.	
		Parents are unsatisfied with child's sleeping pattern.	Parents report improved well-being and satisfaction.	

NOA 2-4 per night with difficulty waking-up in the morning). The child was agitated, cried frequently, constantly refused to perform tasks and had many temper tantrums. Sleep hygiene training, and behavioral therapy did not achieve significant improvement.

IRM 1 mg treatment at age 5- 7 resulted in improved sleep onset and duration (SOL 20 min, TST 9 h). However, sleep maintenance (LSE and NOA) did not improve. Any other/additional sleep disorders were excluded by overnight polysomnography. MPH treatment, which started at age 7, improved motor hyperactivity, impulsiveness and ODD behavior, but not sleeping pattern.

PedPRM 2 mg, initiated at age 8 years led to a notable amelioration of insomnia (SOL 20 min, TST 10 h, LSE 9 h, NOA 0-1), improvement of emotional regulation, impulsiveness and ODD. Parents reported full satisfaction with their child's night sleep and daytime behaviour.

C7 - 6-year-old male diagnosed with insomnia at age 3 years and with ADHD and comorbid learning difficulties at age 6 years.

Due to insomnia (bedtime resistance, SOL 60 min, NOA 2-3/night 15-20 min each, TST 7-8 h, LSE 5 h), the child exhibited daytime tiredness, was easily distracted at school, and unable to focus; and from early afternoon, he was cranky, crying, and getting into temper tantrums.

PedPRM treatment (2 mg, escalated to 5 mg after a month), led to significant improvements in the child's sleep patterns (SOL 5-10 min, TST 10 h, LSE 9 h, NOA 0-1 per night). The teacher observed improvements in motor hyperactivity, impulsiveness and concentration difficulties at school (Conner's rating scale). The child was much less tired and cranky in the afternoon, and bedtime resistance was notably reduced. Parents reported high satisfaction from the child's sleep maintenance and behaviour during the day. They feel that no ADHD treatment is needed for their child anymore.

C8 - 7-year-old male diagnosed with sleep maintenance insomnia (TST 1-2 h, LSE 2 h, SOL 15 min, NOA 1) at age 28 months, and ADHD with comorbid developmental delay, psychomotor instability and academic difficulties at age 4 years.

At age 5 years, the child started treatment with PedPRM (2 mg, escalated to 5 mg four months later) which led to a notable correction in all sleeping parameters (SOL 15 min, TST 10 h, LSE 10 h, NOA 0). Parents reported improved well-being and satisfaction with their child's sleeping pattern. Consequently, an amelioration of instability, concentration, and step by step learning was notable.

C9 - 7-year-old female diagnosed with insomnia at age 3 years, and with ADHD and comorbid ODD at age 4 years.

PedPRM (2 mg escalated one year later to 3 mg) led to significant improvement in the child's sleep patterns although the acceptable TST (> 8 h) was not reached. TST and LSE improved from 2-3 to 6 h and NOA increased from 1 that terminated night sleep to 2-3 per night, 5 min each.

C10 - 9-year-old male diagnosed with insomnia at age 4 years, and with ADHD at age 7 years, with comorbid learning and writing difficulties, verbal and gestural tics.

PedPRM (1 mg dose, escalated to 5 mg one year later) led to a significant improvement in the child's sleep patterns (TST was prolonged from 4 to 10 h, reaching the acceptable sleep duration according to the National Sleep Foundation (NSF) (TST >8h) and LSE improved from 3 to 9 h. PedPRM improved the time to fall asleep and the possibility to fall asleep again after midsleep night awakenings.

C11 - 12-year-old male diagnosed with ADHD with comorbid dyslexia at age 6 years, and with insomnia at age 7 years. Treatment with PedPRM (2 mg escalated to 3 mg a month later) led to a notable improvement in all sleep parameters (SOL 20 min, TST 9 h, LSE 4 h, NOA reduced from 4-6 to 2 per night). The child's behavior was initially characterized by a high level of hyperactivity and lack of attention with a score of 35 on the ADHD rating scale (ADHD-RS) which was reduced to 25 following improvements of the sleep patterns at the dose of 2 mg and 22 at the dose of 3 mg.

C12 - 6-year-old male diagnosed with insomnia at age 3 years, and with ADHD with comorbid tics and anxiety at age 4.5 years. The child was first treated with IRM (1.9 mg daily), without major improvement (SOL 55 min, NOA 5-7/night, 3-8 min each, and LSE 2 h). During the daytime, the child showed anxiety and tics, worsening at bedtime.

PedPRM (1 mg escalated to 3 mg two weeks later) led to significant improvement in the child's sleep patterns (SOL 15 min, LSE 4-5 h, NOA 2 per night, < 2 minutes each). Tics and bedtime anxiety decreased. Parents reported improved well-being and satisfaction of child's sleep pattern.

Discussion

This case report series typically highlights the challenge of treating children and adolescents with ADHD and insomnia. All children in this report displayed typical sleep disturbances observed in ADHD, namely difficulties initiating sleep with sleep onset latency (SOL) >30 min and/or sleep maintenance problems reflected by 6 hours or less of uninterrupted sleep (LSE <6 h). In line with the literature [14], most had less than recommended TST for their age before treatment initiation [3]. Moreover, stimulant medications used as first line ADHD treatment have the potential to further increase sleep latency [39-42].

Initial treatment for insomnia included 3 cases of recommended prior sleep hygiene and behavioral interventions and/or IRM with partial or no improvements: Cases 5 and 12 – no improvement, case 6 improved in SOL and TST but not in sleep maintenance. The other 9 cases did not take any drug for their sleep impairments before PedPRM was initiated.

Nine cases attained treatment goals with PedPRM treatment: TST within the recommended range for the subject age [43]; SOL <30 min; LSE >6 h [37], and 3 cases met treatment goals in only 2 out of 3 parameters. In parallel, all children improved their daytime performance patterns, and all parents reported improved daily functioning, feeling less exhausted, more rested and satisfied with their child's sleep and behaviour.

To our knowledge, this case series is the first report of PedPRM use in the clinic for insomnia in children and adolescents with ADHD and provides supportive evidence to data from controlled clinical trials with this drug in this condition.

Conclusion

Based on our report, insomnia in children with ADHD tends to be persistent and is highly challenging to the child and parents. Following initial sleep hygiene measures and cognitive behavioral interventions, many children with ADHD and insomnia require

additional treatment to improve their sleep difficulties. Both IRM and PRM formulations seem to adequately address SOL. However, PedPRM that can be swallowed whole with minor reported difficulties allows additionally for significant improvement in sleep maintenance (LSE) and duration (TST) to achieve sleep recommendations within the normal range for the age and improve daytime behaviour. No safety issues were observed, leading to a highly favorable risk-benefit ratio when prescribing PedPRM in children with ADHD and sleep difficulties resisting first line interventions.

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