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SPECIAL REPORT

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# Pediatric prolonged-release melatonin for insomnia in children and adolescents with autism spectrum disorders

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**ABSTRACT**

**Introduction**: Insomnia is common among children and adolescents with Autism spectrum disorder (ASD). The first drug licensed for insomnia in this population, a pediatric-appropriate prolonged-release melatonin (PedPRM) formulation is described.

**Areas covered**: Literature search on PedPRM efficacy and safety profile in clinical trials, and a proposed decision-making algorithm to optimize outcome in the treatment of insomnia in children and adolescents with ASD.

**Expert opinion**: PedPRM treatment effectively improves sleep onset, duration and consolidation, and daytime externalizing behaviors in children and adolescents with ASD and subsequently caregivers' quality of life and satisfaction with their children's sleep. The coated, odorless and taste-free mini-tablets are well-accepted in this population who often have sensory hypersensitivity and problems swallowing standard tablet preparations. The most frequent long-term treatment-related adverse events were fatigue (6.3%), somnolence (6.3%), and mood swings (4.2%) with no evidence of delay in height, BMI, or pubertal development, or withdrawal effects. The starting dose is 2 mg once daily independent of age or weight, escalated to 5–10 mg/day if predefined treatment success criteria are unmet. Slow melatonin metabolizers (~10% of children), may require lower doses. Given its long-term efficacy, safety and acceptance, PedPRM may ameliorate long-term consequences of insomnia in this population.

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**KEYWORDS**
Prolonged-release melatonin; insomnia; child; adolescent; autism spectrum disorder

## 1. Introduction

### 1.1. Sleep in children and adolescents with autism spectrum disorder (ASD)

ASD is a complex, pervasive, and multifactorial neurodevelopmental disorder (DSM-5) [1] affecting about 1 in 54 live births [2]. Its core features are persistent deficits in social interaction and communication and restricted, repetitive patterns of behavior or interests. Co-occurring mental health or psychiatric conditions such as attention-deficit/hyperactivity disorder (ADHD) and sleep disorders, particularly insomnia, are common, impairing quality of life [3–7]. In pediatric patients with ASD, or certain neurogenetic disorders (e.g., Smith Magenis Syndrome (SMS); chromosome 17p11.2 deletion syndrome associated with physical and intellectual difficulties and autistic traits)), the prevalence of insomnia is as high as 50%–75% [1,8–11]. Of children with ASD and insomnia 41% have difficulties initiating sleep and 54% have difficulties maintaining sleep and/or early awakening culminating in insufficient sleep duration (total sleep time; TST) [12,13]. Sleep problems in early childhood may precede the diagnosis of ASD [14–16].

Sleep plays a fundamental role in the neurological, psychological and physical development and health of children and adolescents [17,18] TST deficits in early childhood are associated with externalizing problems such as hyperactivity-impulsivity, poor cognitive and mental performance, and have detrimental effects on the child's social development in both typically developing (TD) children [19–21] and those with ASD [22–27]. The risk of having ADHD as a comorbidity is significantly higher when a child with ASD has sleep problems [3–5,15,28]. Importantly, lower TST is associated with poorer total and psychosocial pediatric quality of life (PedsQoL) in children with ASD [29]. If left untreated, especially in children under 6 years of age, insomnia also has the potential to exacerbate the core symptoms of ASD [16].

Sleep continuity (LSE; the longest continuous sleep episode) is also important [30,31]. Less than 6 hours of uninterrupted sleep has been associated with negative behavioral

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**Article highlights**

- Insomnia is common among children and adolescents with Autism spectrum disorder (ASD)
- A pediatric-appropriate prolonged-release melatonin (PedPRM) formulation is the first insomnia pharmacotherapy licensed to meet the need of this population.
- PedPRM improves sleep onset, duration and consolidation, and daytime externalizing behaviors in children and adolescents with ASD and subsequently caregivers' quality of life and satisfaction with their children's sleep.
- The coated, odorless and taste-free mini-tablets are well-accepted in this population who often have sensory hypersensitivity and problems swallowing standard tablet preparations.
- The most frequent long-term treatment-related adverse events were fatigue (6.3%), somnolence (6.3%), and mood swings (4.2%) with no evidence of delay in height, BMI, or pubertal development, or withdrawal effects.
- A treatment decision-making algorithm is presented: The starting dose is 2 mg once daily independent of age or weight, escalated to 5- 10 mg/day if predefined treatment success criteria are unmet. Slow melatonin metabolizers (˜10% of children), may require lower doses.

This box summarizes key points contained in the article.

outcomes in children with ASD; children with high irritability and high stereotypic behaviors had shorter continuous sleep periods, compared to children with lower irritability, or less stereotypies [32].

The severity of sleep problems is of particular concern in light of the increased burden and stress experienced in parenting a child with ASD and the potentially adverse effects of sleep problems and insufficient sleep on the child's daytime behavior and functioning [33–37]. Sleep disruption in the child affects overall family sleep, health and well-being and may negatively impact parental employment, education and health [38–43], and is associated with maternal depression and family disorganization [44–46]. Both parents and children perceive insomnia to be one of the most challenging health effects of autism and generally regard improved sleep as one of the most important benefits sought when considering treatment options for autism [47,48].

### 1.2. Overview of the pediatric insomnia pharmacotherapy market

As a general tenet of pediatric practice, sleep hygiene measures and/or behavioral therapy are first-line approaches to insomnia, and entail techniques intended to improve sleep habits [49]. Behavioral sleep interventions for autism have, on average, moderate effectiveness [50] and may be followed by collateral improvement in children's daytime functioning and wellbeing [51].

Until recently, there was no approved drug for the treatment of insomnia in children. Various medications were used 'off-label' despite limited efficacy and long-term safety data supporting their use in treating insomnia in children and particularly children with ASD [6,49,52,53]. Melatonin is a neuro-hormone produced by the pineal gland during nocturnal periods (production is suppressed by ambient light, predominantly blue light) to properly time circadian sleep-wake rhythms and enhance sleepiness [54]. Reasons for the increased frequency of sleep disturbances in children and youth with ASD include, *inter alia*, differences in melatonin metabolism and abnormal melatonin secretion [23,55–58]. Exogenous melatonin (available as a food supplement in some countries, or pharmaceutically compounded preparations in most countries) is most commonly used for sleep problems in ASD [59], related to the pathophysiology of insomnia in this population. A meta-analysis of five double-blind randomized cross-over studies of melatonin preparations vs placebo in children with ASD showed improvement in sleep duration (44 min compared with placebo) and sleep-onset latency (39 min compared with placebo) [23]. A randomized double-blind study of immediate release (IR) melatonin or matched placebo capsules in 112 children with neurodevelopmental disorders (43% with ASD) who failed behavioral intervention indicated that melatonin (3 months) increased total sleep time by 22.4 minutes and reduced sleep onset latency measured by sleep diaries (−37.5 minutes) but was associated with earlier waking times than placebo (29.9 minutes) [60]. The effects of behavioral intervention and controlled release melatonin are reportedly additive [61] A prolonged-release melatonin (Circadin®), prescription drug designed to mimic the endogenous pattern of melatonin production, is licensed for insomnia characterized by poor quality of sleep in patients aged ≥55 years [62]. However, evidence-based data to support clinical recommendations regarding quality, effective doses, acceptability, duration, and safety of long-term treatment in these children have until recently been lacking [63]. In line with consensus recommendations that clinicians should offer melatonin if behavioral strategies have not been helpful [63], the development and regulatory approval of the pediatric-appropriate prolonged-release melatonin mini-tablets (PedPRM)for this indication (currently approved by EMA (27 EU states), SwissMedic (Switzerland), TGA (Australia), MOH (Israel), MHRA (UK)) represents in-label use that provides the proof of quality, efficacy, dosing, and safety including long-term safety and acceptance needed for regulatory drug approval.

### 1.3. Introduction to the compound: melatonin

Melatonin, the signal of darkness in the organism, plays a major role in the circadian regulation of sleep, thermoregulation and blood pressure [54,64]. Exogenous melatonin, administered at appropriate circadian times (mainly during the diurnal phase) simulates nocturnal circadian physiology (i.e., reduced body temperature and blood pressure during the night, reduced arousal, increased heat loss, fatigue, sleepiness) and acts as a chronobiotic (e.g., in jet lag, delayed sleep phase syndrome or non-24-hours sleep wake cycle in the totally blind), to phase shift or synchronize the free running circadian sleep/wake rhythm to the 24 h day/night cycle [65,66]. In insomnia patients, melatonin may facilitate sleep onset and improve the restorative value of sleep [62].

Melatonin undergoes first-pass hepatic metabolism. It is hydroxylated by cytochrome CYP1A2 with wide variance in

CYP1A2 activity between individuals [67] and over 80% is excreted in the urine as 6-sulfatoxymelatonin. Melatonin is rapidly absorbed following oral administration with peak plasma levels occurring after about 40–60 minutes that persist for up to 1.5 hours (depending on dose) before declining [68,69]. Due to the short half-life (40–50 minutes) [68] maintaining effective bodily concentrations of melatonin throughout the night requires either high doses (with concomitant risk of circadian phase shifts and receptor desensitization) or a prolonged-release formulation. Prolonged-release melatonin received an ATC code N05CH01-'melatonin receptors agonists'- within the subgroup N05C that designates Hypnotics and Sedatives and is distinct from traditional hypnotics, which target $GABA_A$ receptors.

## 2. PedPRM for the treatment of insomnia in children and adolescents with ASD

### 2.1. Composition, pharmacokinetics and metabolism

Immediate-release melatonin formulations result in supra-physiologic serum melatonin concentrations that decline rapidly afterward; this profile may enhance sleep onset but not duration. PedPRM (Slenyto® Neurim Pharmaceuticals Ltd.) is a matrix mini-tablet comprising an insoluble polymer and water soluble lactose which gradually dissolves and forms micro-tunnels to prolong and control the release of melatonin. The release in the gut over an extended period of time after oral intake circumvents the fast clearance of the hormone [62,70] to achieve a therapeutically effective concentration of melatonin in the systemic circulation through the night, for better control of sleep maintenance and duration. Matrix tablets must be swallowed whole and lose their prolonged release properties when crushed [71]. Children with ASD are a notoriously challenging population to medicate [72] due to sensory hypersensitivity [72] resulting in restrictive eating and drinking patterns and they often struggle to swallow tablets. This led to the development of a miniature 3 mm diameter mini-tablet (Ped-PRM) containing 1 mg (purple) or 5 mg (orange) melatonin, which can be easily swallowed by young children [73]. The tablets are film-coated to ensure they are odorless and taste-free, and can be put into food such as yogurt, orange juice or ice-cream to facilitate swallowing and improve compliance [74]. PedPRM is available as a prescription medicine indicated for the treatment of insomnia in children and adolescents with ASD or SMS where sleep hygiene measures have been insufficient. It is taken once daily 0.5–1 hour before bedtime with or after food [74].

Following administration of PedPRM mini-tablet, melatonin concentrations in plasma reach sleep- inducing levels (30–60 pg/ml) [75] within 30 minutes, peak within 3 hours and supra-physiological levels persist for an additional 3.5–5 hours thus covering the nocturnal period (Figure 1). Under fasting conditions melatonin levels in plasma peak earlier (within 2 hours), Cmax is ~50% lower (1.73 ng/ml), and supraphysiological levels persist for longer periods with a minor effect on AUC-∞ (−14%) as compared to fed-state. The particular pharmacokinetic profile of PedPRM may be of major importance for the ability to improve sleep onset, consolidation and duration in children and adolescents with ASD [76–79].

### 2.2. Effects on the child's sleep

The short- and long-term efficacy of PedPRM for insomnia in children with ASD were investigated in a randomized, 13-week, placebo controlled trial followed by a long-term (up to 2 years) open-label treatment phase and 2 weeks withdrawal on placebo [76–79].

The children in the study had the typical sleep disturbances for this population with difficulties in sleep continuity (LSE≤6 hours) and/or initiation (sleep onset latency (SOL) ≥ 30 minutes).

In line with published studies [26], the vast majority of participants fell below the recommended TST for their age before treatment initiation with no association between age and the sleep disturbances [80]. The main effects of PedPRM treatment compared to placebo in children and adolescents with ASD were significant improvements in sleep duration (TST) and continuity (LSE) and onset latency (SOL) without

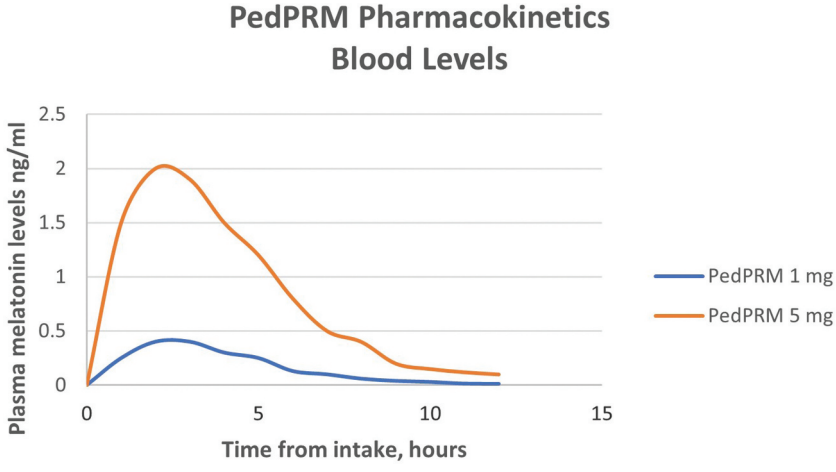


Figure 1. Mean concentration-time profiles of melatonin in plasma following administration of 1 and 5 mg doses of PedPRM mini-tablets (after EMA [70]).

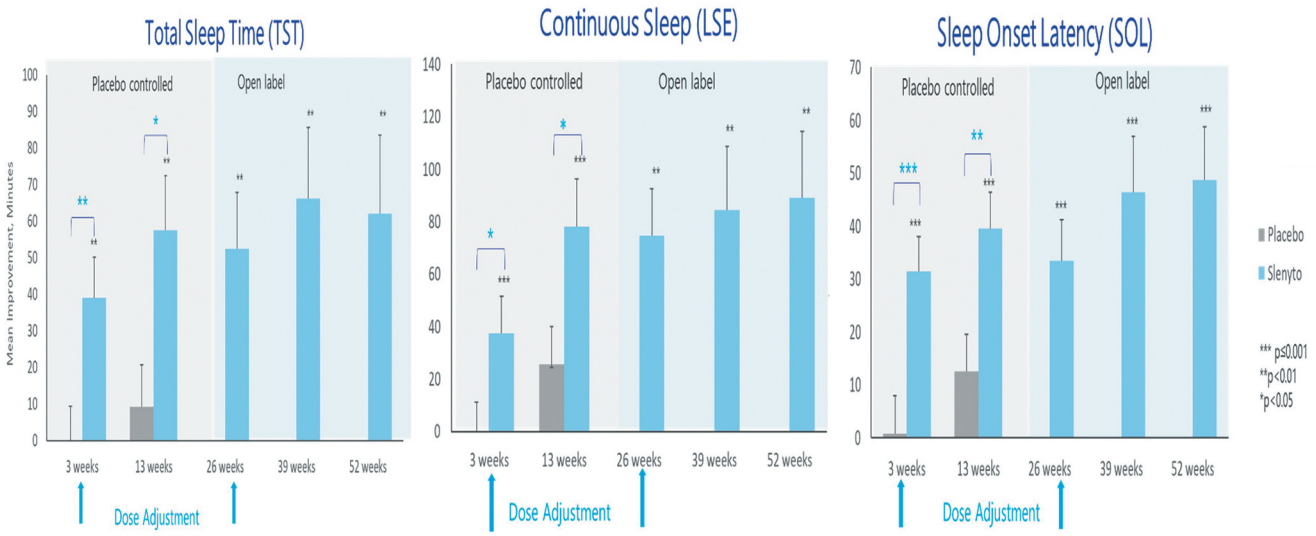


Figure 2. Improvement from baseline in mean total sleep time (TST), continuous sleep (LSE) and sleep onset latency (SOL) after 3 and 13 weeks with PedPRM vs placebo and 52 weeks open label follow-up in children and adolescents with ASD.

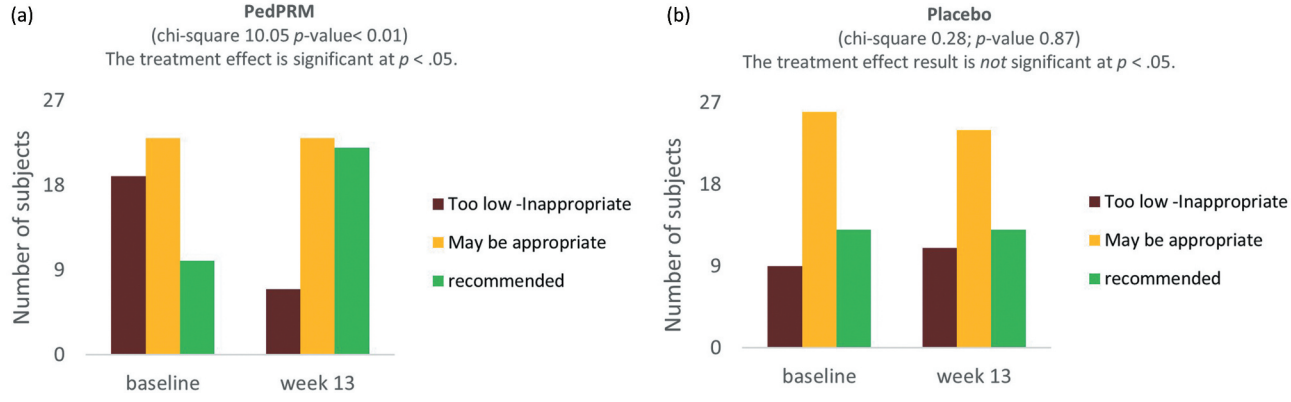


Figure 3. Number of children who attained total sleep time (TST) within the recommended, acceptable and inappropriate sleep duration for their age at baseline and after 13 weeks treatment with PedPRM (upper panel) or placebo (lower panel).

causing early awakenings. The effect developed rapidly and was maintained in the long-term follow-up [76–79] (Figure 2)[80].

### 2.2.1. Sleep duration (TST)

Following 3 months treatment, participants slept on average 57 minutes longer at night with PedPRM compared to 9 minutes with placebo [76] (Figure 2). At optimal dose of PedPRM (at 52 weeks) participants slept on average 62 minutes longer at night, compared to baseline [78]. Comorbid ADHD (28.8%) did not affect response, regardless of stimulant use [76,79].

There were no differences at baseline in TST by age distribution between the PedPRM and placebo groups (Figure 3). Following 3 months treatment with PedPRM, the number of children with TST within the recommended sleep duration for their age more than doubled (from 19.2 to 42.3% of participants) and the number of those with inappropriate low TST values for their age decreased significantly (from 36.5 to 13.4% of participants). There were no such changes (and even a slight deterioration) with placebo treatment (Figure 3). PedPRM treatment effect on TST was similar across the age groups and maintained throughout the long-term observation period [76,78]. No children were reported to have excess sleep above recommendations for his/her age following treatment.

### 2.2.2. Sleep onset latency (SOL) and early awakening–

SOL, another major difficulty in ASD [12,13,60,76] also improved significantly with PedPRM 2/5 mg compared to placebo treatment (39.6 vs 12.5 minutes, respectively; Figure 2)[76]. The effect developed rapidly and was maintained at long-term follow-up. At optimal dose of PedPRM (at 52 weeks) participants fell asleep on average 49 minutes faster compared to baseline [78]. The effect-size of PedPRM on SOL was similar to or greater than that reported with immediate-release melatonin preparations in children and adolescents with neurodevelopmental disorders [23,60]. Of note,

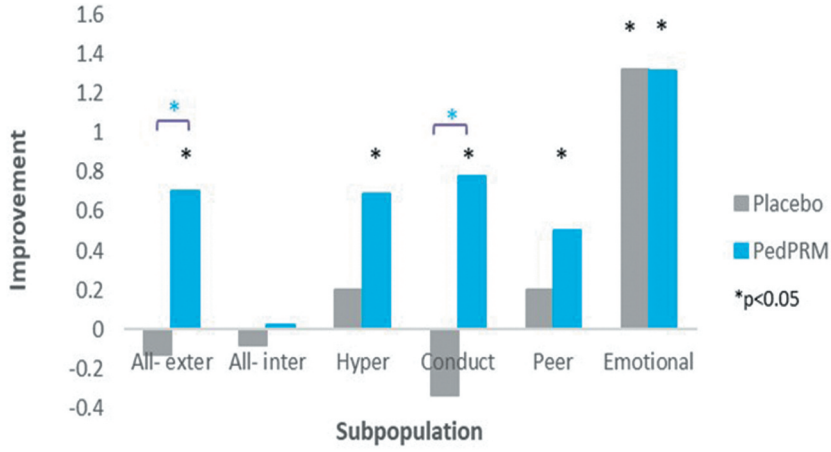


Figure 4. Effects of 13 weeks PedPRM and placebo treatment on externalizing (All-exter) and internalizing (All-inter) behaviors (SDQ) and on respective behavior scores in subpopulations of subjects with abnormal Hyperactivity/inattention (Hyper), conduct, peer relationship (Peer) and emotional behavior scores at baseline. The blue and black asterisks denote * $p < 0.05$ compared to placebo and baseline, respectively.

the undesired earlier awakening that may occur with immediate release melatonin [60] did not occur with PedPRM treatment [76,78].

#### 2.2.3. Continuous sleep (longest sleep episode ; LSE)

LSE also improved significantly with PedPRM compared to placebo (Figure 2). The effect developed rapidly and was maintained at long-term follow-up. At optimal dose of PedPRM (52 weeks) participants' LSE was on average 89 minutes longer than before treatment [76,78] equivalent to the addition of one or two complete sleep cycles in young children [81,82].

### 2.3. Child daytime behavior

Externalizing (i.e., aggressive, hyperactive, noncompliant, and under-controlled) behaviors, specifically hyperactivity and aggression, are reportedly exacerbated in children with ASD with difficulties in initiating and maintaining sleep [24,25,31,34,83]. PedPRM treatment (13 weeks) resulted in a significant improvement in externalizing behavior (as measured by the Strengths and Difficulties questionnaire; SDQ) compared to placebo (Figure 4) with 53.7% of PedPRM-treated participants displaying a significant and clinically-relevant improvement in externalizing behavior versus 27.6% of placebo-treated participants [79,84]. Improvements of the total cohort in internalizing behaviors, SDQ total score and subscales with PedPRM were not significant compared to placebo. However, in the subpopulation with abnormal-hyperactivity score (77% of the study cohort) PedPRM treatment resulted in significant improvements in the total SDQ score and hyperactivity score compared to placebo [79]. In subpopulations with abnormal baseline scores in the specific behavioral attributes (hyperactivity/inattention, conduct, peer relationship, emotional or total difficulties) PedPRM resulted in significant improvements in the respective behavioral score. In contrast, placebo treatment did not have significant effects on hyperactivity/inattention, conduct or peer relationship in the respective subpopulations [79] (Figure 4).

The change in total SDQ score correlated with the change in TST and specifically with LSE but not SOL [79]. This could explain why immediate-release melatonin treatment, which mostly affects SOL, does not cause significant changes in behavior compared to placebo [60] emphasizing the importance of treating sleep duration and maintenance problems in the young children [32,79,83].

### 2.4. Parental well-being

Compared to placebo, the beneficial effects of PedPRM treatment on the child's sleep were associated with significant improvements in parents' well-being (World Health Organization (WHO)-5 [85]) and satisfaction with their child's sleep patterns (Composite Sleep Disturbance Index (CSDI) that persisted throughout the 2 year follow-up [77]. There was a highly significant correlation between the improvement in caregiver's quality of life (WHO-5) from baseline and the improvement (decrease) in child's total SDQ score [79]. These findings suggest that the improvement in parents' well-being is mediated by a noticeable improvement in children's daytime behavior and further support the clinical benefits of improved sleep duration and continuity.

### 2.5. Safety, tolerability, growth, and pubertal development

Somnolence and headaches were twice as common in PedPRM treated children compared to placebo [76]. Fatigue, agitation, cough, and dyspnea were less common but more frequently reported in the PedPRM-treated group, whereas mood swings and nightmares were more commonly reported in placebo-treated children [76]. In the long-term (2 years) follow-up period the most frequent treatment-related adverse events associated with once daily PedPRM doses (2–10 mg p.o.) intake were fatigue (6.3%), somnolence (6.3%), and mood swings (4.2%) with no evidence of effect on height, BMI or pubertal development [77]. There were no withdrawal effects following long-term use and no safety concerns on concomitant therapy with stimulants [77].

### 2.6. Dose compliance and acceptance by patients and caregivers

The pharmacokinetic and pharmacodynamic profiles of PedPRM were similar across the age groups and doses and were not predicted by age, weight, or puberty [70]. The PedPRM Summary of Product Characteristics (SmPC) recommends an initial dose of 2 mg, which may be increased to 5 mg in case of an inadequate response to a maximal dose of 10 mg/day [74]. Escalating the daily dose from 2 mg to 5 mg or from 5 mg to 10 mg significantly improved response to treatment in the group of patients that were not adequately responding to the lower doses. Among those escalated to the 10 mg dose 43.3% slept on average 119 minutes longer at night and fell asleep on average 49 minutes faster compared to baseline, similar to those who responded adequately to the 2-mg or 5-mg PedpRM doses. The response to melatonin is seen quite rapidly (within 1 week) [49,60,76] allowing rapid evaluation of treatment success and dose optimization if such is needed.

In contrast to the usual difficulties with tablet and liquid formulations experienced by children with ASD, acceptability and compliance with PedPRM were excellent, without the need to crush or dissolve the mini-tablets (thus preserving the prolonged-release properties). Treatment compliance calculated by returned mini-tablets after 104 weeks of double-blind treatment was almost 100% throughout the study [76,77].

## 3. Expert opinion

PedPRM is the first pharmacotherapy developed and approved by health regulatory agencies. and is indicated for the treatment of insomnia in children and adolescents aged 2–18 with ASD and/or SMS, where sleep hygiene measures have been insufficient [74]. Efficacy was demonstrated over placebo in several sleep aspects [76–78]: (1) increased total sleep time, (2) reduced sleep latency, (3) improved sleep continuity (LSE), (4) there was no undesired advance of the sleep-wake cycle phase, (5) long-term efficacy and safety demonstrated [78]. The beneficial effects of PedPRM on sleep continuity and lack of undesired sleep-wake cycle phase advance (which occurs with the immediate release formulations), are ascribed to the prolonged-release formulation. PedPRM also had favorable effects on daytime externalizing behavior, in particular hyperactivity and inattention in the children, and on parental well-being [79].

Patients' compliance and acceptance of PedPRM was very good supporting the use of the age appropriate mini-tablets in this population, allowing a full benefit of the correct dose and prolonged- release properties. No major safety issues were observed even after 24 months [76–78].

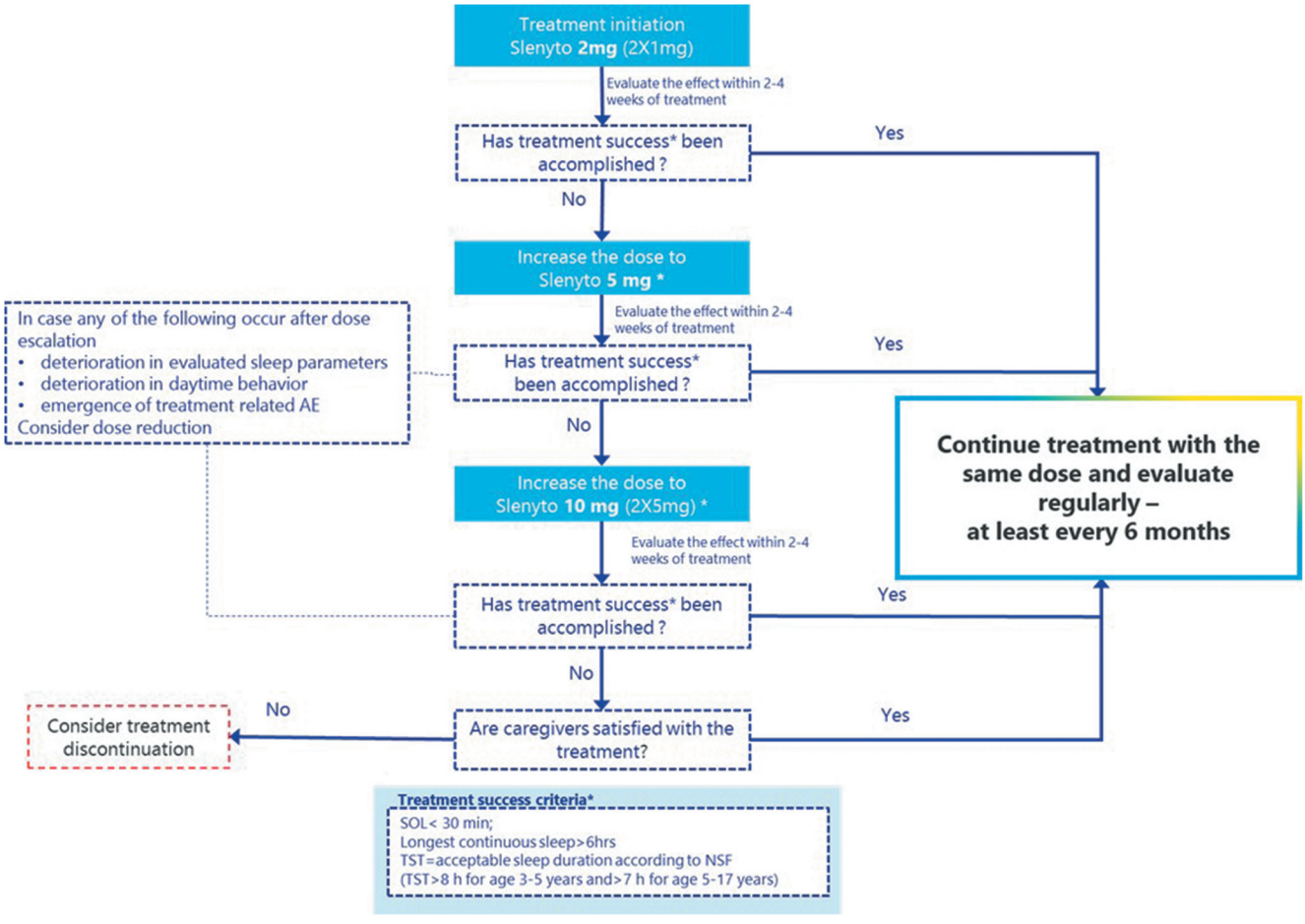


Figure 5. PedPRM Insomnia treatment algorithm.

Because the pharmacokinetic and pharmacodynamic profiles of PedPRM are not predicted by age, body weight or puberty, the preferred dosing strategy for PedPRM is a personalized titration to optimal dose. Once a decision has been taken to use pharmacological therapy, a simple algorithm for PedPRM dose optimization is presented in Figure 5.

The recommended starting dose for children who fail sleep hygiene/ behavioral intervention is 2 mg per day, with optional increase to 5 mg/day and then 10 mg/day. Dose escalation can take place every 2–3 weeks and is driven by the need to attain treatment success in one or more of the following (depending on the individual symptoms and severity): (A) TST within the recommended range [80] for the subject age (i.e. 10–13 h for age 3–5 years, 9–11 hours for 6–13 years and 8–10 hours for teenagers 14–17 years); (B) SOL <30 minutes; (C) LSE>6 hours. It should be noted that the recommended age-dependent TST range can vary due to genetically driven factors, e.g., inherited sleep homeostatic need leading to decreased sleep need. In addition, child behavior, parent satisfaction of child's sleep and safety should be considered in the decision to escalate or to continue the dose. If treatment success criteria are not achieved, despite a maximal dose of 10 mg, parents' or subject's (if applicable) satisfaction should be considered before stopping treatment.

For children who are using other medication to treat insomnia, e.g., antihistamines, alpha adrenergic agonists (clonidine), anti-psychotics etc., it is advised to taper them off according to their respective labeling before starting PedPRM. In case, such drugs are used for an indication other than sleep disturbance they can be maintained without major drug interaction problems. Immediate release melatonin may be stopped just prior to starting PedPRM.

If treatment effects are reduced, daytime behavior deteriorate or adverse events related to the drug (e.g. daytime somnolence) appear after dose escalation, the prescriber should first consider a down-titration to a lower dose before deciding on a complete discontinuation of treatment. Gradual loss of effect of melatonin after initial positive effect may occur in subjects with slow CYP1A2 metabolism, resulting in excessively high melatonin levels [86]. In such cases, efficacy could be reinstated by tapering down the dose [86].

As PedPRM is a newly approved drug, its effectiveness in the 'real world' remains to be demonstrated. Intervention studies can be placed on a continuum, with a progression from efficacy trials (i.e., the performance of an intervention under ideal and controlled circumstances), to effectiveness trials (i.e. the drug performance under 'real-world' conditions). However, the distinction between the two types of trial is a continuum rather than a dichotomy ([87,88]. The clinical trials of PedPRM progressed from an efficacy trial (double blind placebo controlled 3 months phase), into an effectiveness phase (21 months open label phase) where clinicians had an opportunity to increase the dose further, reduce or maintain the dose and parents could leave at any time. Although this was done under well controlled conditions, it is important to note that parents were not shy of dropping out if they felt the treatment did not help, as pointed out in Gringras et al 2017 [76]: "Dropout rates were significantly higher in the placebo than in the PedPRM group (21 participants, 32.3% compared to 9 participants, 15.0% Chi-Square p = .040), and there were not many dropouts during the long term effectiveness period [77].

In summary, considering the recommendations that clinicians should offer melatonin if behavioral strategies have not been helpful [63] the long-term effectiveness, quality, benign safety profile, and favorable compliance place PedPRM as the appropriate first-line in-label pharmacological treatment for insomnia in children with ASD; in addition to improving sleep, child behavior and parental and caregiver well-being, PedPRM given early on may also prevent long-term consequences of insomnia in the developing child.

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## Declaration of interest

C Schroder has served in an advisory or consultancy role for Neurim pharmaceuticals related to the work under consideration for publication and reports personal fees and non-financial support from Biocodex for expert group and lectures, travel to meetings and personal fees from Takeda for lecture outside the submitted work. T Banaschewski has served in an advisory or consultancy role for ADHS digital, Infectopharm, Lundbeck, Medice, Oberberg GmbH, Neurim Pharmaceuticals, Roche, and Takeda. They received conference support or speaker's fee by Medice and Takeda. Received royalities from Hogrefe, Kohlhammer, CIP Medien, Oxford University Press; the present work is unrelated to these relationships. J Fuentes has received research support from Policlinica Gipuzkoa Foundation (PGF), Servier, and AIMS-2 Trials (Project ID 777,394). They have received partial support for professional meetings attendance from PGF, ESCAP & AACAP. MB Posserud meanwhile reports Scientific Advisory Board meeting reimbursement from Takeda paid to their institution, outside the submitted work. Finally, O Bruni has served in an advisory or consultancy role for Neurim pharmaceuticals related to this work. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

## Reviewer Disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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