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Pediatric Appropriate Prolonged-Release Melatonin Minitablet for Insomnia in Children and Adolescents with Autism Spectrum Disorder

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Abstract

Despite high rates of comorbid insomnia among children and adolescents with Autism Spectrum Disorder (ASD), and its negative impact on child development, health and quality of life, there is limited awareness among clinicians of screening for, and treatment of, insomnia in this population.

Prolonged-Release Melatonin (PedPRM, available commercially as Slenyto®) is the first authorized drug for the management of insomnia in children and adolescents with ASD or Smith Magenis Syndrome (SMS) but there is little evidence on how this new medicinal product performs in real life treatment.

This case series describes 6 children and adolescents (age 2 to 17 years) with ASD and insomnia and the decision-making process involved in PedPRM selection and treatment optimization. All patients were initially given behavioral and pharmacological products for their insomnia (e.g. iron supplementation, antihistamines, immediate-release melatonin) with no or partial success and subsequently prescribed PedPRM. Following PedPRM dose optimization, all patients attained acceptable sleep maintenance (longest sleep episode >6 h), initiation (sleep onset latency <30 min) and duration (>8 h at age 3 to 5 and >7 h at age 5 to 17 years). Significant positive effects on daytime behavior and parent satisfaction were noted in all cases.

Thus, real life evidence supports PedPRM clinical trial outcomes in which PedPRMis effective and safe strategy for managing insomnia in pediatric patients with ASD or SMS.

Keywords: Melatonin; Pediatric prolonged release sleep; Insomnia; Autism spectrum disorder

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Introduction

Autism Spectrum Disorder (ASD) is a complex, pervasive, multifactorial neurodevelopmental disorder (DSM-5) [1]. 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 highly prevalent in autism, impairing quality of life of children and their families [2]. Children with ASD sleep less than acceptable Total Sleep Time (TST) for their age according to the National Sleep Foundation (NSF) recommendations [3,4]. Other difficulties include Sleep Onset Latencies (SOL) of over 30 min, less than 6 h of uninterrupted sleep (Longest Sleep Episode LSE) and early morning awakenings [5]. Co-occurring sleep problems in children with ASD have been shown to predict more severe autistic core symptomatology, later development of Attention-Deficit/Hyperactivity Disorder (ADHD) symptoms in younger children and somatic complaints in older children, irritability, aggressive behavior, regression, stereotypic behavior and anxiety, poor cognition (memory, attention, overall IQ) as well as performance and delayed language acquisition [6-11]. Specifically LSE shows promise as being responsive to change, and appears to be correlated with changes in the child's behaviors and parent's quality of life [11,12]. Additional reports link chronic sleep disturbance in children with ASD with increased

risk of physical health problems, including changes in cardiovascular, immune, endocrine and nervous system function, as well as poorer overall health-related quality of life [13]. 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 [14]. Thus, identification and appropriate treatment of sleep problems in children with ASD may subsequently improve their development and the quality of life of both the child and family [5].

As a general tenet of pediatric practice, sleep hygiene measures and behavioral therapy are recommended first-line approaches to insomnia [15]. However, the response rate in children with ASD to these first line therapeutic approaches is just about 25% [16]. Until recently, there was no approved drug for insomnia in children and various medications that were used "off label" have limited evidence and no long term data to support their efficacy and safety in treating insomnia, particularly in children with ASD [15]. Melatonin is the neurohormone produced by the pineal gland during nocturnal periods to properly time circadian sleep-wake rhythms and enhance sleepiness [17]. Exogenous melatonin (mostly immediate release formulations (IR melatonin) available as food supplements in some countries, or as pharmaceutically compounded preparations, is effective mainly for sleep onset problems in children with ASD [18], but evidence-based data are needed to support clinical recommendations regarding their quality, effective doses, duration and safety of long-term treatment [19]. Pediatric appropriate formulation of Prolonged-Release Melatonin (PedPRM) available commercially as Slenyto® (Neurim Pharmaceuticals Ltd) is the first drug approved by the EU-EMA and other regulatory agencies for the treatment of insomnia in children and adolescents with ASD or Smith Magenis Syndrome (SMS). PedPRM (3 mm diameter odorless and taste-free film-coated mini tablet available as a prescription medicine at 1 mg and 5 mg dose strengths) can be easily swallowed by young children and circumvents the fast clearance of the hormone by releasing the hormone in the gut over an extended period of time [20,21]. Clinical trials of PedPRM in children and adolescents with ASD or SMS (age 2 to 17 years) demonstrated improvements in TST, LSE and SOL, and subsequently in child's externalizing behaviors, caregiver's quality of life and satisfaction of the child's sleep [22-24]. Somnolence and headaches were twice as common in PedPRM treated children compared to placebo. 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 [22]. During the 2 year follow-up period [25] the most frequent treatment-related adverse events associated with once daily PedPRM doses (2 mg to 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. There were no withdrawal effects following long-term use and no safety concerns on concomitant therapy with stimulants. For treatment optimization the starting dose is 2 mg once-daily, which is escalated to 5 mg and then 10 mg/day, independent of the child's age or weight, if the predefined treatment success criteria (LSE >6 h, SOL <30 min and TST acceptable for their age, 10 h to 13 h for age 3 to 5 years , 9 h to 11 h for 6 to 13 years and 8 h to 10 h for teenagers 14 to 17 years and no less than 8 h at age 3 to 5 and 7 h at age 5 to 17 years) are not met [5].

Randomized clinical trials are essential to demonstrate drug efficacy and safety in a defined target population as well as gaining regulatory marketing approval. Following the release of the new medicinal product as an approved medication, it is then essential to consider its benefits in clinical practice, taking into account the patient's perception and functioning, as well as the family situation. In this brief report, we present a case series of 6 children and adolescents with ASD treated with several drugs for insomnia, including PedPRM, demonstrating the decision-making process involved in the choice of drug, formulation and dose effects on child's sleep and behavior as well as family satisfaction (Table 1).

Case Series

Case 1

C1 is a 5.5-year-old female diagnosed with ASD (at age 20 months) secondary to Phelan McDermid syndrome (22q13 deletion), with moderate intellectual impairment, and comorbid ADHD. Her main clinical manifestations include deficits in reciprocal social interaction (although functional language is present), repetitive play, motor stereotypes, and severe hyperactivity. She has suffered since infancy from severe difficulty falling asleep (60 min to 90 min) and maintaining sleep (LSE~1.5 h), frequent awakenings during the night, and short sleep duration (TST~7 h) with early morning awakenings. Polysomnography recording (PSG) ruled out sleep disorders other than insomnia. C1 would be put to bed, following a good evening routine, between 19h30-20h30, fall asleep only with parental presence around 21h30 and experience five to six awakenings per night, 10 min to 60 min each (first awakening at around 23h00, for 1 h would end with her joining her parents in their bed). Her final awakening occurred at 6h00-6h30 and was almost always accompanied by crying. She did not sleep at all during the day, even during long car journeys. C1's impaired sleep affected her daytime behavior, with severe hyperactivity, inattention, temper tantrums, auto- and hetero-aggressive behavior (she bit herself on the back of her hand), and frequent crying. Parents described severe repercussions on the family's well-being including physical exhaustion, daytime sleepiness, and anger management issues for the father and mild depression for her mother. Former treatment for C1's sleep problems included sleep hygiene, behavioral therapy, iron supplementation and Vitamin D and finally Immediate-Release (IR) melatonin (1 mg) given at bedtime, and at two additional time points over the night (latest at 3h00), for 3 consecutive nights that had a paradoxical effect as C1 barely slept at all over the three nights (Table 1).

PedPRM treatment was then initiated at 2 mg, daily, at 19h00, for a bedtime between 19h30-20h00. After 2 weeks with PedPRM 2 mg, C1 fell asleep quicker (SOL 30 min to 45 min); nocturnal awakenings decreased to 3 on average, with a consecutive increase in LSE to about 2.5 h, and a morning awakening at 6h30. Due to a positive but sub-optimal response, the dose was increased to 5 mg daily resulting in further shortening of SOL to 15 min to 30 min, with one single, short duration, awakening during the night, and a morning awakening at 6h30-7h00. LSE increased to around 7 h and TST increased to 10.5 h (Table 1). Sleep was now considered within the norm for her age [3]. Moreover, parents described C1 to be calmer during sleep and waking up without crying. Finally, her daytime behavior also improved significantly at school (she was able to sit for 30 min during group activities) and at home (less impulsive with her siblings, less crying, fewer tantrums, decrease in hyperactivity and no auto- or hetero- aggressive behaviors). At 6 months follow up parents were very satisfied with treatment, with, testifying they are no longer tired

Table 1: Patient Characteristics and treatment outcome.

Case No/ sex Age	DSM-5 Diagnosis	Sleep medication history/concomitant therapy and treatment outcome	Initial melatonin formulation/dose	2nd melatonin formulation/ dose	3rd melatonin formulation/dose	Current therapy
Case 1 female Age 5.5 years	At age 2 years ASD/SMS with Phelan McDermid syndrome (22q13 deletion) comorbid ADHD and insomnia	Sleep hygiene and behavioral therapy, iron supplementation (over 5 months to reach ferritin >80 ng/ml), Vitamin D supplementation Treatment Outcome SOL 60 min-90 min TST 7 hours Behavior: hyperactivity, aggression Parents: Depression daytime sleepiness	IR melatonin (1 mg) at bedtime, and at additional two time points over the night (3 am the latest), for 3 consecutive nights Treatment Outcome paradoxical reaction	Slenyto initiated at 2 mg in the evening, for 2 weeks Treatment Outcome SL SOL 30-45 minutes TST>8 hours LSE 2.5 hours	Slenyto escalated to 5 mg in the evening 1 month Treatment Outcome SOL 15-30 minutes TST 10.5 hours LSE 7 hours Behavior: Improved Parents Satisfied	Slenyto 5 mg ongoing >6 months Treatment Outcome SOL 15-30 minutes TST 10.5 hours 7 hours Behavior: Improved Parents Satisfied
Case 2 male Age 2.2 years	At age 2 years ASD and insomnia	Iron supplementation plus 3 drops nightly of Alimemazine 4% (3 weeks) replaced with hydroxyzine syrup 2 mg/ml 6 ml nightly, also stopped after 2 months due to lack of efficacy. Treatment Outcome SOL 90 min-120 min TST 6.5 hours LSE< 2 hours Hyperactivity& tantrum Tired and stressed	IR Melatonin 2 mg Treatment Outcome SOL 10-45 min TST 7.5 hours LSE 2.5 hours Behaviour: improved	Slenyto initiated at 2 mg in the evening, for 2 weeks Treatment Outcome SOL 10 -35 min TST 9.75 hours LSE> 6 hours Behaviour: Calm, speech improved Parents Satisfied	Slenyto 2 mg for 6 months Treatment Outcome SOL 10-35 min TST 9.75 hours LSE> 6 hours Behavious: Calm, speech improved Parents Satisfied	Slenyto escalated to 5 mg due to period of more nocturnal awakenings ongoing>6 months Treatment Outcome SOL 10-35 min TST 9.45 hours LSE> 6 hours Behavious: Calm, speech improved Parents Satisfied
Case 3 male Age 8.25 years	At age 7 years High functioning ASD and insomnia	Treatment Outcome SOL >120 min TST 8.5 hours LSE<6 hours Tired irritability	IR-Melatonin 2 mg for 3 months Treatment Outcome SOL 15- 30 min TST LSE<< 6 hours Tired irritability	Circadin (adult prolonged release melatonin) 2 mg, 1 year Treatment Outcome SOL 15-30 min TST NOA/LSE Nocturnal wakes ↓ More stable mood	Slenyto 2 mg, 1 month Treatment Outcome SOL 15-20 min TST 10.75 hours LSE 10.75 hours Stable mood Parents Highly satisfied	Slenyto 2 mg ongoing NA
Case 4 male Age 17 years	At age 11 years ASD, without intellectual deficiency and insomnia since age 12 years and 2 months	Baseline, Treatment Outcome SOL 45 min TST 8.75 hours LSE/NOA 3Xweek nocturnal wakes Irritable attention ↓ anxiety Stress	Sleep hygiene, Sophrology for relaxation. Iron (to reach ferritin >80 ng/ml); Vitamin D+IR-Melatonin, 1 mg at bedtime which increased to 2 mg for 3 years Treatment Outcome SOL 25 min TST 8.00 hours LSE/NOA nocturnal wakes Irritable attention ↓ Stress	Slenyto initiated at 2mg in the evening, for 2 weeks Treatment Outcome SOL 20-30 min TST NOA Nocturnal wakes ↓ Once /2 weeks	Slenyto 2 mg for one month Treatment Outcome SOL 20-30 min TST 8.00 hours NOA <1 in 2 weeks LSE> 6 H Behaviour improved Parents Satisfied	Slenyto 2 mg ongoing >6 months Treatment Outcome Maintenance of the effects on sleep Behavior: Significant improvement

Case 5 male Age 11 years	ASD and comorbid ADHD. Insomnia since age 2 years	behavioral approaches, Alimemazine Tartrate liquid, 30 mg Treatment Outcome SOL 30 min-3.25 hours TST 4-7 hours LSE 1-4 hours Aggressive Stress, tired, mood ↓	Add-on IR melatonin 6 mg and safe space tent 4 years Treatment Outcome SOL 48 min TST 8.8 hours Improved Improved	After 4 years of IR melatonin 6mg and an increased dose of Alimemazine Tartrate (40mg) Treatment Outcome SOL 90 min TST 5.5 hours Anxious	Slenyto 5mg and a weaning schedule for the anti-histamine. 2 weeks Treatment Outcome SOL 15 min TST 8.5 hours LSE >6 hours Behavior improved Parents: Changed their life	Slenyto 5 mg ongoing >6 months Treatment Outcome Improvement maintained
Case 6 female Age 6 years	At age 2 years ASD/ SMS with de novo mutation SYNGAP1 and insomnia	Baseline Treatment Outcome SOL 90 min-120 min TST 7 hours Early awakening (4 am) Behavioral outburst agitation irritability Parents Depression irritability	Sleep hygiene+IR melatonin 1 mg during 8 weeks then Circadin (chewed) 2 mg for 8 weeks. Treatment Outcome SOL 15 min TST 8 hours Early awakening Behaviour No change	Hydroxyzine dichlorhydrate for 5 weeks (increased up to 20 mg) and stopped Treatment Outcome Ineffective + drowsiness	Slenyto 2 mg 10 days Treatment Outcome SOL 15 min TST 9.5 hours No early awakening Behaviour Reduced agitation and temper more attentive Parents Satisfied	Slenyto 2 mg ongoing Treatment Outcome Effects maintained

or exhausted and are less anxious.

Case 2

C2 is a 2.2 years-old male diagnosed with typical ASD (at age 2 years) and developmental delay. His main clinical manifestations include no interest in social interaction, repetitive play and motor stereotypes. C2 needs global therapeutic support, weekly speech therapy, parent-child therapies, and psychomotor therapy. He also experiences severe allergies (e.g., eczema, food allergies). The families are immigrants, under challenging living conditions and both parents are unemployed. C2's sleeping problems were present almost since birth and occurred every night. His night routine included a bottle of formula milk at 21h00, going to bed with his mother at 22h00 and falling asleep between 23h30-24h00 (SOL of 90 min to 120 min). C2 had very agitated sleep (LSE<2 h), with 3 to 4 long awakenings (lasting 5 min to 40 min each), during which he could drink between 250 ml to 400 ml milk. He finally woke up at 7h30 (TST~6.5 h), had no daytime naps in his bed, however, could fall asleep for short periods of no more than 20 min in his stroller. During the day C2 suffered from severe hyperactivity, significant crying, and frustration intolerance with several tantrums a day, in addition to social withdrawal and a constant sad facial expression. The severe sleep problems caused the parents to be very tired during the day, adding to the stress related to the recent ASD diagnosis and migration process.

C2's former insomnia treatment included iron supplementation, 3 drops nightly of alimemazine 4% for 3 weeks with limited treatment response and then 6 ml nightly of hydroxyzine syrup 2 mg/ml for 2 months, which was also stopped due to lack of efficacy. C2 was prescribed 2 mg Immediate-Release (IR) melatonin, given at 21h00. Sleep onset latency shortened significantly to 10 min to 45 min, TST improved to ~7.5 h but he continued to wake up 3 to 4 times during the night (5 min to 20 min each), LSE still was 2.5 h and his final awakening remained at 7h00. His parents reported positive effects on daytime behavior, such as being calmer, imitating and vocalizing more and crying less.

As treatment goals were not achieved, C2 was switched to 2 mg PedPRM, given 30 min-1 h before bedtime. After 2 weeks of treatment, parents reported improvements of all parameters: SOL further reduced to 10 min to 35 min, only up to two short awakening during the night (5 min duration), LSE improved to more than 6 h on some of the nights, final awakening in the morning was delayed by 1hour to 8h00, and TST improved to 9.75 h at night. Moreover, significant positive effects on daytime behavior were noted-C2 was calmer during the day, his speech progressed and he cried much less. His parents were very satisfied with his sleep. C2 remained on the 2 mg PedPRM treatment for 6 months, and then switched to 5 mg PedPRM, due to a period of more nocturnal awakenings, probably related to his allergies and not the treatment itself. On 5 mg the benefits described above were maintained and sleep is now considered normal for his age.

Case 3

C3 is a 8 years and 3 months old high functioning male diagnosed with ASD (at age 7 years) with comorbid dyspraxia and dysgraphia. His main clinical manifestations include deficits in reciprocal social interaction and restrictive interests. He attends a mainstream school with a support teacher. His sleep problems were present since birth but worsened at age 4 years. He would go to bed at 20h00, following a regular bedtime routine, and fall asleep around 22h30. During his attempts to fall asleep, he would be very anxious, leaving his room frequently, and needing parents to calm him down. During the night, parents suspected that he woke up frequently, although he didn't disturb them. On school days, he woke up at 7h30, so the TST was approximately 8.5 h and LSE most probably less than 6 h. During the day C3 was tired, suffering from irritability and attention difficulties at school. Additionally, he was reported to have emotional difficulties, unstable mood, and anxiety. His baseline objective sleep assessments by overnight polysomnography indicated slight upper airway resistance, TST of 9.2 h and a long nocturnal awakening for about one hour. An actigraphy recording over 2-weeks indicated delayed sleep onset (at 1h00) and agitated sleep, with wake bouts of 30 min to 90 min each at least three times a week.

C3 started treatment with 2 mg IR-melatonin, given at bedtime, for three months. Although with IR-melatonin SOL decreased to approximately 15 min to 30 min, the duration and frequency of the

nocturnal awakenings increased, LSE decreased and there were no significant effects on daytime behavior. He was then switched to 2 mg Circadin treatment, 1 hour before bedtime for a year. SOL remained stable (15 min to 30 min), and nocturnal awakenings decreased but still present irregularly. Additionally, he had more stable mood, and was less emotional. He then started 2 mg PedPRM and within 1 month the nocturnal awakenings disappeared, resulting in a significant improvement in LSE from less than 6 h a night to 10.75 h (equal to TST), SOL was 15 min to 20 min, and TST was 10.75 h, 2 h longer than at baseline. Sleep was now considered within the normal range for his age [3]. In addition, waking up for school became much easier and pleasant, during the day his mood was more stable and he cried less. His parents were highly satisfied having their evenings for themselves and the easier handling of C3's emotional difficulties during the day.

Case 4

C4 is a 17 year old male with normal intellectual abilities, diagnosed with ASD (at age 11 years). His main clinical manifestations include deficits in reciprocal social interaction, pragmatic language disturbances, and anxiety if rituals and routines are not respected. He attends a mainstream secondary school with a support teacher and has weekly speech therapy and group therapy to improve social skills.

At C4's first consultation regarding his sleep (at age 12 years and 2 months) he was having daily difficulties falling asleep, nocturnal awakenings, agitated sleep, early morning awakenings, associated with daytime fatigue but no excessive daytime sleepiness (Table 1). Bedtime during the week was at 20h45 he would fall asleep at 21h30 and wake up at 6h38 in the morning. TST was 8.75 h to 9 h during the week (and 8.5 h during weekends). C4 snores regularly during the night, does not have naps during the day, and suffers from mild irritability, and fluctuating anxiety and emotional sensitivity, more frequently following poor sleep. Polysomnography recording indicated periodic limb movement disorder during sleep (PLMS 18.9 per hour of sleep) in the context of iron deficiency and no sleep apnea but frequent arousals or micro-arousals from sleep (14.5 per hour of sleep) were observed. Initial treatment included iron (to reach serum ferritin levels of >80 ng/ml) and vitamin D supplementation, sleep hygiene, and sophrology for relaxation. Additionally, he began treatment with IR-melatonin, 1 mg increased to 2 mg at bedtime upon which SOL was reduced to ~25 min. During the week, bedtime was at 21h30, he fell asleep at 21h55, and final awakening was at 6h00 which provided a TST of 7.5 h to 8 h (and 9 h during weekends). He still experienced nocturnal awakenings 3 times per night, was emotionally disturbed, anxious, had mild attention difficulties and cried easily and was more irritable when tired. Due to his high anxiety levels he constantly needed reassurance and support from his mother, putting her under significant continuous stress. Following 3 years of IR melatonin treatment was switched to 2 mg PedPRM at 20h30, 1 h before bedtime, in attempt to improve night-time awakenings and daytime internalizing behavior. At a follow-up call two weeks after treatment initiation, parents reported that the SOL was 20 min to 30 min (same as under IR melatonin), but nocturnal awakenings decreased to once every two weeks. At a follow-up visit one month after treatment initiation, parents reported almost no nocturnal awakenings, and improvement in continuous sleep, achieving LSE>6 h most nights. Moreover, according to parents, C4 seemed less anxious during the day. At six month follow up he experienced stable benefits to sleep, with SOL of less than 30 min, LSE of more than 6 h most nights and sleep duration of 8 h, considered within the normal range for his age. Significant improvements in anxiety levels and attention difficulties during the day were also seen. Parents are satisfied with this improvement.

Case 5

C5 is an 11-year-old male diagnosed with ASD and moderate intellectual impairment. His main clinical manifestations include deficits in reciprocal social interaction and severe delay in expressive language skills, currently functioning at the level of a 2-year-old. He has long-standing PICA, is obsessed with food and his body mass index exceeds the 91st percentile. He has co-morbid ADHD that is unmedicated, as a prior trial of stimulants resulted in the emergence of tics and worsening in his self-harming behaviors. C5 attends a special educational provision for children with learning disabilities.

C5 had long-standing sleep difficulties from the 2nd year of life. At his first consultation regarding his sleep (at age 6 years) he had already been treated with 4 mg of IR melatonin but had intermittent difficulties falling asleep, daily problems with prolonged nocturnal awakenings and short TST. A typical bedtime routine would include IR melatonin at 18h30, bedtime at 19h30. On 2/3 of nights he would settle to sleep independently by 20h00 (Table 1) but on 1/3 of nights he would refuse to settle, kicking the bedroom door and screaming and fell asleep only at 23h00 with his parents at his bed. He would wake up every night between midnight and 3h00 and alert his parents by lying on the floor and kicking his door and would only resettle to sleep with a parent present (this could take up to 2 h) on 2/3 of nights and on the other nights he would not resettle and become increasingly agitated. If he was able to resettle to sleep, typical morning waking was 6h00 and he was described as alert and active. Total sleep time was highly variable from 4 h to 7 h and LSE from 1 h to 4 h with no excessive daytime sleepiness. C5 was noticeably more active, inattentive and aggressive after a restless night. His parents rated the sleep problem as severe. Mother noted that chronic sleep deprivation affected her mood and there was concern for father's safety as he is a lorry driver. Noise at night had caused complaints from neighbors, increasing the family's stress.

As behavioral approaches had limited effect, and the whole family was suffering, pharmacotherapy with an antihistamine was initiated. Without medication, following a bedtime of 20h00, mean SOL was 3.25 h and TST 6.8 h as assessed by actigraphy (Camntech). The antihistamine (alimemazine tartrate liquid 30 mg at bedtime) had no impact on SOL but successfully reduced night awakenings so that TST increased to 7.25 h. Add-on of IR melatonin 6 mg at bedtime resulted in noticeable improvement of SOL to 48 min and TST to 8.8 h and significant improvement in C5 daytime behavior and quality of life for the family. This was further supported by the use of a safe space sleep tent. After 4 years, at routine review, it was found that C5's sleep had deteriorated despite the combination of 6 mg of IR melatonin and an increased dose (40 mg) of alimemazine tartrate. He would take up to 90 min to fall asleep, wake up most nights around 03h00 and remain awake for the day (TST approximately 5.5 h) and was increasingly anxious during the day. PedPRM 5 mg taken an hour before bedtime was the prescribed as a direct substitute for his 6 mg IR melatonin, with a weaning schedule for the anti-histamine. Two weeks later, with PedPRM 5 mg as monotherapy at 19h30 he was falling asleep without any behavioral disturbance by 20h30 with SOL of 15 min after lights out. He would wake once in the night to take himself to the toilet but resettling himself to sleep within 5 min and was able to then sleep continuously until 5h00 giving him a TST

of approximately 8.5 h, within age-appropriate limits. The reduction in challenging behaviors at settling time and during night-time was reported as of significant benefit to the whole family. Similarly, improvements were noted in C5's daytime challenging behaviors, in his mother's words: 'this has changed our lives'. At six months follow up there is stable maintenance of treatment effect with lack of adverse events.

Case 6

C6 is a 6-year-oldnon-verbal female diagnosed (at age 2 years) with ASD/SMS with *de novo* mutation SYNGAP1and severe symptomatology including intellectual impairment and epilepsy. She presented with long-standing bedtime resistance, with SOL of 90 min to 120 min and early awakenings from sleep at 4h00 with behavioral outbursts and TST of 7 h. During the daytime she presented with agitation, psychomotor instability, irritability, emotional hyperactivity and tantrums. Parents were exhausted (dad-irritability, mom-depressive symptomatology and difficult relationship with the younger brother). Following consultation treatment included sleep hygiene in combination with IR-melatonin (1 mg during 8 weeks then 2 mg). IR-Melatonin reduced the SOL to approximately 15 min and extended TST to 8 h, but the early awakenings at 4h00 with behavioral outbursts (correct compliance) continued. She was then given Circadin (adult prolonged release melatonin 2 mg formulation) that was very difficult for her to swallow whole and she probably chewed the tablet. After 8 weeks with no additional benefit she was given add-on antihistamine for 5 weeks (hydroxyzine dichlorhydrate increased gradually up to 20 mg) that was ineffective and resulted in drowsiness and the drug combination was discontinued. PedPRM 2 mg was then initiated and, after 10 days treatment, the early awakening problem was resolved and it was not necessary to increase the treatment dose. With PedPRM SOL was approximately 15 min, TST was 9.5 h, sleep continuity improved and she no longer had early awakening. Child behavior improved with reduced agitation and temper. Treatment compliance is very good with no side effects after 7 months of treatment. Her family is very satisfied with this treatment and improvements of the relationship with her brother are noted. At the day care center the child's behavior is reportedly quieter and more attentive.

Discussion

Practice guidelines on treatment of insomnia and disrupted sleep behavior in children and adolescents with autism spectrum disorder [19] recommend counseling parents regarding sleep habits and offering behavioral strategies as first line, with pharmacologic approaches if these strategies have not been helpful. The case reports presented here are typical examples of children and adolescents with ASD and insomnia, as well as various other comorbidities that were seen by three expert clinics for treating children with neurodevelopmental disabilities. The children in this report had typical sleep disturbances for this population, namely sleep maintenance problems reflected by 6 h or less of uninterrupted sleep (LSE<6 h) and/or difficulties initiating sleep with sleep onset latency (SOL) >30 min. In line with published studies [4], most had less than recommended TST for their age before treatment initiation and there was no association between age and the sleep disturbances [3].

Initial treatment included behavioral interventions; iron supplementation (C1, C2, C4), vitamin D supplementation (C1, C4) and antihistamines (alimemazine (C2, C5) and hydroxyzine (C2, C6)) failed to provide adequate treatment response. Melatonin in IR formulation was then prescribed in all cases (1 mg escalated to 2 mg or 1×3 times per night) with partial or complete improvements in SOL in 5 of 6 cases and emergence of paradoxical insomnia in one (C1). As LSE was not resolved in any of the cases with IR melatonin, the adult PRM formulations was applied in 2 cases (C3 and C6) but because of compliance issues was probably chewed or crushed and had limited added value to IR melatonin. Following its approval as the first treatment for insomnia in children with ASD, PedPRM 2 mg was prescribed in 5 of 6 cases. In one case the starting dose was 5 mg and 2 of 5 escalated to 5 mg due to partial response.

Useful points for consideration for change in pharmacotherapy or dose optimization are therefore to attain treatment goals pertaining to (A) TST within the recommended range for the subject age (i.e. 10 h to 13 h for age 3 to 5 years, 9 h to 11 h for 6 to 13 years and 8 h to 10 h for teenagers 14 to 17 years and no less than 8 h at age 3 to 5 and 7 h at age 5 to 17 years) [3]; (B) SOL<30 min; (C) LSE>6 h [5]. In addition, important aspects of child behavior and parent satisfaction of child's sleep improved. In all cases PedPRM treatment provided the sought relief.

To our knowledge, this case series is the first description of PedPRM use in the clinic for insomnia in children and adolescents with ASD. It demonstrates the decision points and considerations for treatment modification in real life examples and provides supportive evidence to data from controlled clinical trials with this drug in this population [22-25].

Conclusion

Insomnia in a child with ASD tends to be persistent and is highly challenging to the child and the parents. Following initial sleep hygiene measures and behavioral interventions, many children with ASD and sleep disturbances will require additional pharmacotherapy to normalize their sleep patterns. Both IR and prolonged release melatonin formulations seem to adequately address Sleep Onset Problems (SOL), however, the pediatric appropriate prolonged release formulation (PedPRM) that can be swallowed whole without any difficulty, effectively resolves sleep maintenance (LSE) and duration (TST) problems as well as early morning awakenings to achieve sleep within the norms for their age. No safety issues were observed and subsequent improvements in child behavior (mainly due to longer uninterrupted sleep) and parent satisfaction and quality of life (mainly affected by the child behavior) were reported.

Clinical Significance

Sleep problems are common in children and adolescents with ASD. PedPRM represents a novel treatment option for insomnia in these subjects with a benign safety profile and excellent acceptance. These cases suggest that PedPRM may help achieve sleep onset latency of <30 min, uninterrupted sleep duration of at least 6 h and sleep duration considered within the norm for their age. PedPRM is an effective strategy for managing insomnia in clinical practice in pediatric patients with ASD.

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