Research Review™
EDUCATIONAL SERIES

Sleep disturbances in children with Autism Spectrum Disorder (ASD) and/or Smith-Magenis syndrome (SMS)

Making Education Easy 2020

Independent expert commentary provided by Dr Arthur Teng

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Abbreviations used in this issue:

ADHD = attention-deficit hyperactivity disorder
ASD = autism spectrum disorder
DSM = Diagnostic and Statistical Manual of Mental Disorders
ICSD = International Classification of Sleep Disorders
NDD = neurodevelopmental disorders
REM = rapid eye movement
SMS = Smith-Magenis syndrome

This publication is intended as an educational resource for healthcare professionals involved in the management of insomnia in children and adolescents aged 2-18 years with Autism Spectrum Disorder (ASD) and/or Smith-Magenis syndrome (SMS), where sleep hygiene measures have been insufficient. This review focuses on the treatment of insomnia in this paediatric group and defines the place of melatonin in its management.

Introduction

Sleep is essential at all stages of life, but especially during childhood and adolescence when neuronal development is occurring.[1-3] The Australian Government Department of Health recommends an uninterrupted 9–11 hours of sleep per night for children and young people aged 5–13 years and 8–10 hours per night for adolescents aged 14–17 years.[4] Sleep affects cognitive abilities such as memory formation, attention, learning and abstract reasoning, as well as perception and motor skills.[5, 6] Ensuring that children and adolescents have the correct quality and quantity of sleep is important for their growth, learning and development; inadequate sleep can result in physical and mental health problems.[5, 7, 8] Children with specific neurodevelopmental disorders (e.g. autism spectrum disorder; ASD)[9-11] or neurogenetic disorders (e.g. Smith-Magenis syndrome; SMS) are at increased risk of sleep disorders.[12]

Defining insomnia

Insomnia is one of the most commonly reported sleep difficulties in children and adolescents.[13] Insomnia can be defined as poor sleep quality or quantity, a sleep disturbance that causes clinically significant distress or impairment in daytime functioning, and sleep difficulty occurring at least three nights per week and having been present for at least three months, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5).[14, 15] Individuals with insomnia are affected the next day; they feel tired, unrefreshed and often find it difficult to function during the day causing distress and impairment in social, occupational, educational, behavioural and other important areas of daytime functioning.[15] Another definition and classification of insomnia are provided in the International Classification of Sleep Disorders (ICSD) manual produced by the American Academy of Sleep Medicine.[16] The criteria for diagnosis of chronic insomnia according to the ICSD manual include (1) a report of sleep initiation or maintenance problems, (2) adequate opportunity and circumstances to sleep, and (3) daytime consequences. As with the DSM-5, the frequency criterion is at least three nights per week and the duration criterion is at least three months.[16]

Insomnia in children and adolescents is often the result of the interplay of multiple factors, including genetic abnormalities, neurobiological disorders, behavioural problems and cultural influences.[17, 18] Neurobiological factors may include aberrations in neurotransmitter systems that promote sleep and establish a regular sleep-wake cycle (e.g. melatonin) or medical disorders that disrupt sleep continuity (e.g. epilepsy, gastrointestinal disorders or sleep apnoea).[19] Insomnia may be exacerbated by psychiatric comorbidities, such as anxiety/depression, ADHD and obsessive/repetitive behaviour.[19] Children and adolescents with genetic and/or epigenetic abnormalities in sleep/wake regulation may be predisposed to insomnia.[20-22] In addition, social and cultural factors play a role by setting expectations for normal sleep-related behaviours, as well as developing attitudes and beliefs about sleep.[23]

Defining ASD/SMS

ASD is characterised by impairments in two core domains: (1) social communication and social interactions across contexts; and (2) restricted, repetitive patterns of behaviour, interests or activities.[14] ASD is the singular diagnosis for a continuum of disorders that includes Asperger's syndrome, autism or autistic disorder, and pervasive developmental disorder not otherwise specified.[14] In addition to these core symptoms, ASD is often associated with a range of co-morbid conditions including attention-deficit/hyperactivity disorder (ADHD), seizures, psychiatric illness, gastrointestinal disorders and sleep disorders.[24-27] ASD was estimated to affect approximately 0.7% of the Australian population (in 2015) representing approximately 164,000 individuals, with approximately 83% of these individuals aged under 25 years.[28]

SMS is linked to a microdeletion of chromosome 17, with its main clinical features including intellectual disability, disturbances of the sleep-wake rhythm and maladaptive daytime behaviour.[12, 29]

Insomnia and ASD

Insomnia is more prevalent in children and adolescents with ASD (approximately 40–80%) than in typically developing children (approximately 10–40%), with the variation in prevalence related to study methodology, different definition of insomnia and study inclusion criteria.[11, 19, 30-32]

Insomnia can exacerbate core and associated ASD features, contributing to negative effects on mood and emotional regulation, behaviour and cognitive functioning.[32, 33] Individuals affected by ASD already have numerous difficulties engaging in social interaction, and lack of sleep can make this even worse by causing daytime impairments such as increased hyperactivity and irritability, greater anxiety and higher sensory sensitivity.[11, 19, 34] Insufficient sleep in children/adolescents with ASD may also impact the wider family, reducing caregiver's quantity and quality of sleep, and increasing caregiver stress.[35, 36]

Medications used to treat seizures and psychiatric conditions may also disrupt sleep,[19] as may behavioural causes such as the ingestion of stimulants (such as caffeine and alcohol), irregular bedtimes or excessive screen time.[37] The core behavioural deficits associated with ASD may also hinder healthy bedtime behaviours and routines being established.[19] Children with ASD may have difficulty following a caregiver's instructions about falling asleep and may refuse to go to bed.[18]

Sleep architecture and ASD

Children and adolescents with ASD commonly exhibit differences in sleep architecture compared with typically developing peers, with difficulties initiating and maintaining sleep, frequent and prolonged night awakenings, irregular sleep–wake patterns, and/or having nonrestorative sleep which causes distress or impairment in important areas of functioning.[10, 11] Polysomnography studies involving children with ASD indicate that the percentage of rapid eye movement (REM) sleep was lower than in children with typical development, which may be related to an abnormality in neural maturation and organisation.[18]

Melatonin, insomnia and ASD

Abnormalities in endogenous melatonin secretion (**Figure 1**) and abnormal circadian rhythmicity have been reported in children and adolescents with ASD,[22, 38-40] and have been associated with changes in sleep architecture and daytime sleepiness.[41]

Variations in genes involved in the regulation of endogenous melatonin modify sleep patterns and have been implicated in some cases of ASD.[22] However, the relationship between insomnia, melatonin processing and genes that regulate endogenous melatonin levels in ASD is complex, and continues to be investigated.

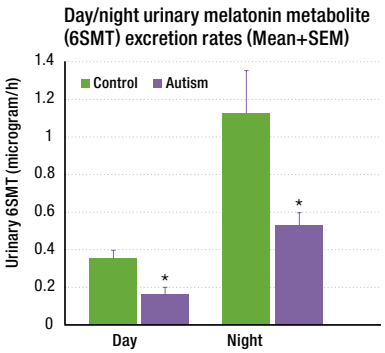

Figure 1. Melatonin secretion in children with autism (n=43) and in controls (n=26), measured according to 6-sulphatoxymelatonin (6SMT) excretion rates in the urine.[38]

*p<0.05 vs control. **SEM**=standard error of the mean.

Adapted from Tordjman S, et al. Psychoneuroendocrinology. 2012;37:1990-7.

Expert comment

Recent research data from the Tordjman group have identified abnormal melatonin secretion in ASD, giving parents some neurochemical basis for the high incidence of chronic insomnia in that group of children.[38] As in typically developing children, poor sleep in ASD may lead to excessive daytime sleepiness, cognitive impairment, and impaired daytime functioning.[36, 42-44] Sleep problems in children with ASD also dramatically alter the sleep of their parents and are associated with family stress,[35, 36, 44, 45] possibly amplifying ASD symptoms and interfering with treatment. Conversely, it is reported that successful management of sleep may improve daytime global functioning in children with ASD.

Our own research has shown that teaching of sleep disorders and sleep-related management is sadly lacking at both under-graduate and post-graduate levels.[46, 47]

Management of insomnia

This section outlines the various steps for managing patients with insomnia secondary to ASD/SMS. An algorithm that summarises these steps has been developed by the US Sleep Committee of the Autism Treatment Network (ATN) for managing patients with insomnia secondary to ASD and is shown in **Figure 2**.

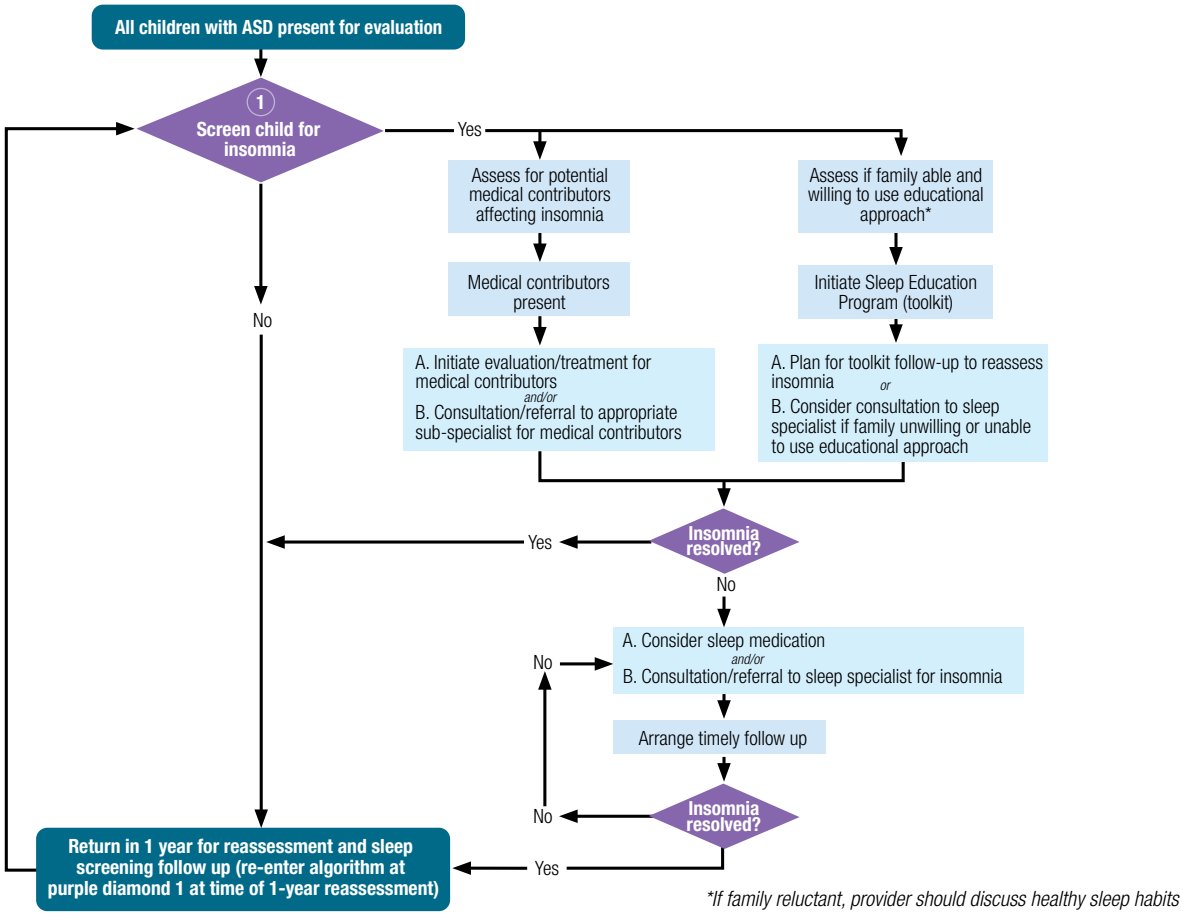

Figure 2. US Sleep Committee of the Autism Treatment Network algorithm for managing patients with insomnia secondary to ASD.[48]

Screening for and identifying insomnia

Screening for and identifying sleep difficulties are essential to enabling effective management; however, many healthcare professionals fail to directly ask paediatric patients and their caregivers about their sleep habits.[13] Furthermore, many parents of children with ASD have poor knowledge about sleep development and sleep issues and may present with concerns regarding their child's impulsivity, aggression, inattention, hyperactivity or other behavioural issues that may be secondary to a sleep disorder.[48]

Given the high prevalence of insomnia in ASD, healthcare providers should screen all children with ASD for this disorder.[48]

A recommended first step in assessing insomnia is to ask patients and their parents a series of short questions,[48] such as those from the Children's Sleep Habits Questionnaire (CSHQ).[49] When completed prior to a clinical evaluation, sleep diaries may also help to provide evidence of insomnia and are available in many forms, for example https://thesleepconnection.com.au/wp-content/uploads/2015/10/Sleep_Diary.pdf). If a sleep diary hasn't been completed, a screening tool such as the BEARS Sleep Screening Tool may be useful to obtain and assess sleep-related information.[13] This validated screening tool has five domains that address common sleep irregularities. If difficulties are reported in two or more of the domains, further assessment is advised.

Patients with ASD should also be screened for factors (e.g. comorbid conditions, medications) that could be contributing to sleep disturbances.[11, 48] Comorbid conditions that can affect sleep include gastrointestinal problems, sleep apnoea, depression, anxiety, psychosis and bipolar disorder.[11, 48] The Sleep Committee of the Autism Treatment Network (ATN) has developed a useful questionnaire to help identify underlying medical conditions.[48] If significant comorbidities are detected, these should be investigated further and the patient referred to a relevant specialist where appropriate. A careful review of all medications should also be performed, since many medications may contribute to insomnia.[48]

Non-pharmacologic interventions

For first-line treatment of insomnia, both the American Academy of Neurology (AAN) guidelines and the ATN recommend the counselling/education of parents regarding behavioural strategies for improved sleep hygiene in children and adolescents with ASD.[11, 48] The AAN also suggest that pharmacologic or nutraceutical approaches may be also added to this approach for children and adolescents with ASD, depending on the individual circumstances.[11]

Sleep hygiene

Improving sleep hygiene involves implementing changes that can improve the quality of night-time sleep and promote daytime alertness.[13] Parents should be educated on sleep hygiene measures and the detrimental effects of caffeinated drinks, screen time in the evenings, and bright lights and noise on sleep.[13] Parents should ensure that the child has a dark, quiet, relatively cool, non-stimulating environment to sleep in.[13] A calming and consistently followed bedtime routine should be maintained, as well as the management of physiologic factors such as night-time hunger.[13, 50]

Behavioural interventions

A limited number of studies have investigated the use of behavioural sleep interventions for children with ASD; however, robust evidence for parental education and behavioural strategies to improve sleep in children and adolescents with ASD is lacking.[11, 51-53] Nevertheless, some studies have documented improvements in both sleep and daytime behaviour upon the initiation of behavioural therapies such as the *Sleeping Sound* programme.[54, 55] The *Sleeping Sound* intervention was tailored to the family and included behavioural strategies targeted to the child's specific sleep problems.

Approaches suggested by the recent AAN guidelines include parents imposing a set bedtime and wake-up time and ignoring protest behaviour that occurs after the bedtime and before the wake-up time (unmodified extinction), or for specified periods that are fixed or get progressively longer (graduated extinction).[11] Other suggested behaviours include parents developing and strictly adhering to regular pre-bed calming rituals (positive routines), or parents putting their child to bed close to the time the child begins to fall asleep (bedtime fading).[11] Family-based cognitive behavioural therapy (CBT) may also improve several aspects of sleep.[11]

Pharmacologic interventions

For children continuing to experience sleep difficulties despite managing coexisting conditions and adopting behavioural strategies, the AAN recommend that sleep-promoting pharmacologic agents should be added in addition to behavioural interventions.[11]

However, there is limited evidence supporting the use of medications to treat insomnia in children who have ASD, apart from studies involving melatonin.[11, 48] Prolonged-release melatonin is the only Therapeutic Goods Administration (TGA)-approved treatment option for insomnia in children/adolescents with ASD/SMS.[56] Nevertheless, various other pharmacologic interventions have been used off-label including over-the-counter treatments (e.g. antihistamines) and off-label hypnotic drugs, which are used for their sedative side effects despite a lack of proven safety, efficacy or dosing regimens for use in children.[50] A survey of Australian paediatricians found that the most commonly prescribed medications for poor sleep initiation in children were melatonin (89.1% of the paediatricians), clonidine (48%) and antihistamines (29%).[57] A small open-label trial investigated the efficacy of the alpha-2 adrenergic agonist, clonidine, in children with ASD, and although this agent reduced the time to sleep and night-time awakenings,[58] it can result in rebound hypertension if withdrawn abruptly.[59] Clonidine is not a TGA-approved agent for the treatment of insomnia in this group of children.

Expert comment

Non-pharmacologic management of chronic childhood insomnia is time-consuming, and sadly medications are often prescribed, yet usually without evidence or regulatory approval. Research has long confirmed that parents often do not bring up sleep problems with their general practitioners.[60] Conversely, medical practitioners often feel untrained and unskilled in addressing sleep problems in children. Most medical courses have less than two hours in the entire medical curriculum devoted to sleep problems!

Focus on melatonin

Endogenous melatonin

Melatonin (*N*-acetyl-5-methoxytryptamine) is an indoleamine secreted from the pineal gland, with L-tryptophan as an indirect precursor.[61] The secretion of melatonin is regulated by the suprachiasmatic nucleus (SCN) in the hypothalamus, the site of the biological clock.[37]

Endogenous melatonin is synthesised in a diurnal pattern in typically developing older children and adults beginning in the evening soon after dark and peaking between 2 and 4 am, before receding to a trough during the daytime (**Figure 3**).[62] The synthesis and secretion of melatonin is enhanced by darkness and inhibited by light. Melatonin synthesis from the pineal gland is influenced by the retinal perception of light and the endogenous rhythmicity of neurons within the SCN.[37] In particular, the maximum suppressing effect of light exposure occurs at the shortest wavelengths (424 nm), although the melatonin concentration recovers rather rapidly, within 15 minutes of ceasing the exposure.[63]

Melatonin activates two membrane-specific receptors: the high-affinity ML1 and low-affinity ML2 receptors.[37] The ML1 receptor has two sub-types: Mel1a (or MT1) and Mel1b (or MT2).[37] The activity of melatonin at the MT1 and MT2 receptors is believed to contribute to its sleep-promoting properties via their distinct actions on the circadian clock.[56] The MT1 receptors are thought to inhibit neuronal firing, and the MT2 receptors have been implicated in the phase-shifting response.[56]

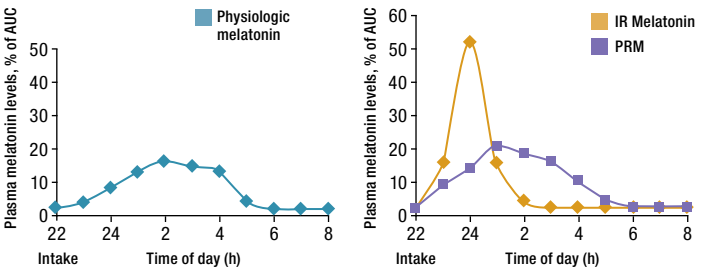

Figure 3. Mean plasma levels of endogenous and ingested melatonin.[62]

Adapted from Zisapel N. Br J Pharmacol. 2018;175:3190-9.

AUC=area under the curve; **IR**=immediate-release; **PRM**=prolonged-release melatonin.

Melatonin and ASD

Melatonin is increasingly used to treat insomnia in children, including those with ASD.[63-64] A number of guidelines are available that recommend melatonin for children/adolescents with ASD.[11, 48, 65, 66] In the US, where there is no prescription requirement, melatonin use in children has increased from 0.1% in 2007 to 0.7% in 2012.[67] However, the over-the-counter formulations of melatonin available in countries such as the US may include differing concentrations of melatonin, and may be contaminated with other products (e.g. serotonin).[11, 68, 69]

In Australia, melatonin is only available through a doctor's prescription, ensuring a more controlled use of the drug in the management of the insomnia. A prolonged-release formulation is available for primary insomnia in patients aged ≥55 years;[70] however, if this 2 mg tablet is crushed to facilitate swallowing, the tablets lose the controlled-release properties, as the active ingredient is immediately released. Moreover, children have reported difficulty swallowing adult preparations, or they may dislike the taste associated with them.[71]

Rapid-release formulations of melatonin can be obtained from a compounding pharmacy and have been used to treat insomnia in children, including those with ASD.[57, 72] However, compounded formulations are not regulated in the manner that registered, approved medications are, and different pharmacies may dispense different dosages and formulations (tablets, capsules, drops).[57]

Given the need for a melatonin formulation appropriate for use in the paediatric population, a small, prolonged-release melatonin mini-tablet (Slenyto®) has been developed.[56] This formulation is the focus of this review.[56]

Prolonged-release melatonin in children/adolescents with ASD/SMS

Method of administration

The prolonged-release formulation of melatonin (Slenyto®) is a small (3 mm in diameter) odourless, flavourless tablet that can be easily swallowed whole by children.[56] The tablets can also be hidden in food such as yoghurt, orange juice or ice-cream to facilitate swallowing and improve compliance.[56] If the tablets are broken, crushed or chewed, they will lose their prolonged-release properties.[56] The tablets are available as a 1 mg or 5 mg strength, enabling appropriate dose titration according to response.[56]

Dosage

The approved product information for Slenyto® recommends a starting daily dose of 2 mg, taken 30 to 60 minutes before bedtime.[56] If an inadequate response occurs with this dosage, the daily dose should be increased to 5 mg, with a maximal dose of 10 mg per day.[56] Similarly, the AAN guidelines for insomnia in children/adolescents with ASD recommend that clinicians offering melatonin for sleep dysregulation should start by initiating a low dose (1–3 mg/day), 30–60 minutes before bedtime, and titrated to effect, but not exceeding 10 mg/day.[11]

Pharmacokinetics

In contrast to immediate-release melatonin which has a rapid onset, with an associated spike, and then a rapid decline and a very short half-life,[62] the pharmacokinetic profile of prolonged-release melatonin more closely mimics the normal physiological profile of melatonin (**Figure 3**).[62]

A pharmacokinetic study in 16 children with ASD children aged 7-15 years who experienced insomnia demonstrated that administration of prolonged-release melatonin 2 mg (2 x 1 mg prolonged-release tablets) after a standardised breakfast resulted in melatonin concentrations peaking within 2 hours after administration and remaining elevated for 6 hours.[56]

Clinical trial of prolonged-release melatonin in children and adolescents with ASD/SMS

The efficacy and safety of prolonged-release melatonin (Slenyto®) were investigated in a multicentre (Europe and USA) trial.[73] Patients without a documented history of sleep behavioural intervention underwent a 4-week, parent-led, sleep behavioural intervention. Patients who still had sleep problems were recruited into the study which comprised a 2-week, single-blind, placebo run-in period, followed by a randomised, 13-week, double-blind treatment period of prolonged-release melatonin (2 mg escalated to 5 mg if required) or placebo. The trial involved 125 children with insomnia aged 2–17.5 years with ASD (96.8%) or SMS (3.2%).[73]

A total of 95 children/adolescents who completed the 13-week, double-blind phase of the trial enrolled in a 91-week, open-label phase.[56, 74] Patients received open-label, prolonged-release melatonin (2/5 mg as in the double-blind phase dose), with an optional dose adjustment to 5 or 10 mg/day after the first 13 weeks of the follow-up period.

Impact on sleep: During the 13-week, double-blind phase, prolonged-release melatonin, compared with placebo, was associated with clinically meaningful improvements in total sleep time (adjusted mean change from baseline 51.16 minutes vs 18.73 minutes; p=0.034), and sleep latency (mean adjusted change from baseline -37.88 minutes vs -12.58 minutes; p=0.011) (**Figure 4**), without causing earlier wake-up time.[73] More children attained clinically meaningful responses in total sleep time (increase of 45 minutes or more from baseline) and/or sleep latency (a decrease of 15 minutes or more from baseline) with prolonged-release melatonin compared with placebo (68.9% vs 39.3%, respectively; p=0.001).[73]

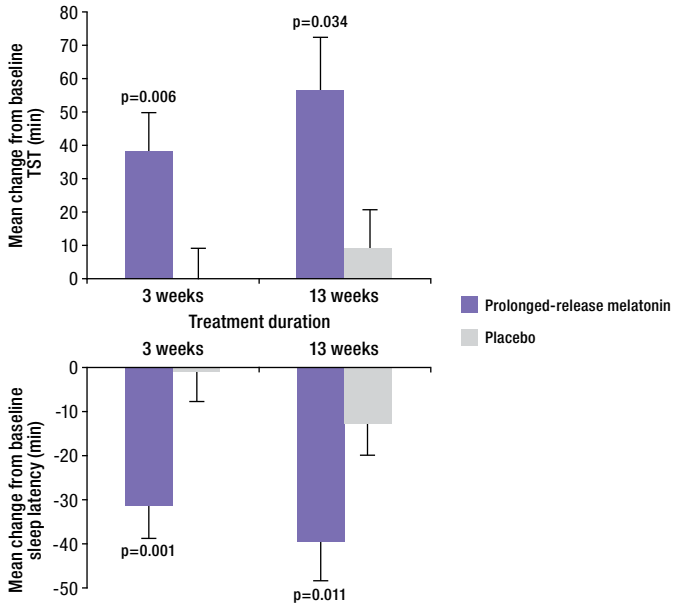

Figure 4. Caregivers' sleep and nap diary reported change from baseline during the 13-week, double-blind period in (**A**) mean total sleep time (minutes) (**B**) mean sleep latency (minutes).
Adapted from Gringras et al. Am Acad Child Adolesc Psychiatry. 2017;56:948-57. **TST**=total sleep time.

Impact on child's/adolescent's behaviour: During the 13-week, double-blind phase, prolonged-release melatonin, compared with placebo, significantly improved externalising behaviours (hyperactivity, inattention and conduct), but not internalising behaviours (peer relationship problems and emotional symptoms), as assessed by the Strength and Difficulties Questionnaire.[75] More recipients of prolonged-release melatonin had a clinically relevant response (improvement in externalising behaviour score ≥1 unit) with prolonged-release melatonin than with placebo (53.7% vs 27.7%; p=0.008).[75]

Impact on caregiver's quality of life: Caregivers benefitted from their children's treatment with prolonged-release melatonin, compared with placebo, with a significant improvement in quality of life (assessed by the World Health Organization-5 well-being Index),[75] and in their satisfaction in the child's sleep pattern (as measured by the Composite Sleep Disturbance Index).[73]

Adverse events: Treatment-emergent adverse events were reported in a similar number of children treated with prolonged-release melatonin or placebo (85.0% vs 76.9%) and were known symptoms in children with ASD (e.g. agitation, mood swings) or experienced generally in children (e.g. upper respiratory tract infection, cough, dyspnea and vomiting).[73] However, nervous system disorders were more common with prolonged-release melatonin than placebo (41.7% vs 21.5%), with the difference driven mainly by somnolence (28.3% vs 10.8%), and headache (13.3% vs 6.2%).[73]

Long-term treatment: The beneficial effects of prolonged-release melatonin on sleep demonstrated in the 13-week, double-blind phase were maintained or augmented with long-term follow-up, with improvements in total sleep time, sleep latency and the duration of uninterrupted sleep being maintained after 39 weeks of follow up.[74] With long-term therapy, no unexpected safety issues were reported, with fatigue (18.9% of patients completing the follow-up), vomiting (17.9%), somnolence (16.8%), cough (13.7%), mood swings (13.7%), and upper respiratory tract infection (10.5%) being most commonly reported.

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

Expert comment

There is increasing evidence that exogenous melatonin can shorten latency to sleep and prolong sleep time in children.[76] Medication should always be only an adjunct to behavioural measures to optimise sleep, once potential medical and environmental factors have been addressed. In the past, there has been great difficulty in getting children, especially those with developmental needs, to swallow medications whole so that a prolonged or controlled-release effect can be utilised. Liquid and immediate-release melatonin has been shown to decrease sleep latency, but not decrease arousals.[76] Exogenous melatonin has also been shown to be mainly free of serious side effects.[77]

Take-home messages:

- There is a high prevalence of insomnia in children and adolescents with ASD and/or SMS
- Insomnia in children/adolescents with ASD and/or SMS is caused by the interplay of multiple factors, including genetic mutations, neurobiological disorders, behavioural problems and cultural influences
- Insomnia can exacerbate core and associated ASD features, contributing to negative effects on mood and emotional regulation, behaviour and cognitive functioning
- Insomnia in children/adolescents with ASD and/or SMS can have an impact on the caregiver's quality of life
- Children with ASD and/or SMS often exhibit a disruption to the normal pattern of nocturnal melatonin secretion or a reduction and/or delay in its secretion at night
- First-line treatment for insomnia comprises parent-based education regarding sleep hygiene, and behavioural interventions
- For children/adolescents continuing to experience sleep difficulties despite behavioural therapy, sleep-promoting pharmacological agents may be added while continuing behavioural interventions
- Treatment with prolonged-release melatonin (Slenyto®) was effective and safe in children with ASD and/or SMS with insomnia who did not improve with sleep hygiene measures in a 13-week, randomised trial, with improvements in sleep parameters being maintained over the long-term in the open-label extension phase
- The small odourless, flavourless, prolonged-release melatonin tablet (Slenyto®) was easily swallowed by the children and adolescents

Expert's concluding remarks:

The development of a tiny tablet of long-acting melatonin that could potentially be swallowed whole by young children, many with developmental challenges, is a major advance in the field of paediatric sleep disorders. However, it is imperative that pharmaceutical companies should also invest in research and education of health professionals in paediatric sleep medicine so that non-pharmacological issues can also be optimally addressed prior to committing to medication.

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This article was commissioned by Aspen Australia. Aspen Australia includes Aspen Pharmacare Australia Pty Ltd (ABN 51 096 236 985) and Aspen Pharma Pty Ltd (ABN 88 004 118 594). All sales and marketing requests to: Aspen Pharmacare Pty Ltd, 34-36 Chandos Street, St Leonards NSW 2065. Tel: +61 2 8436 8300. Email: aspen@aspenpharmacare.com.au Web: https://www.aspenpharma.com.au

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