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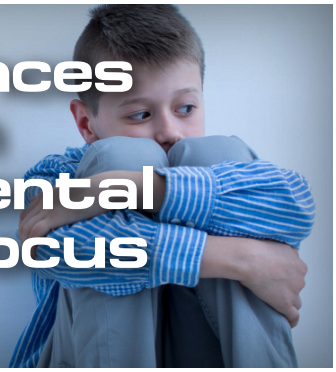
EDUCATIONAL SERIES

Sleep disturbances in children with neurodevelopmental disorders – a focus on melatonin



Making Education Easy 2018

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Abbreviations used in this review:
ACh = acetylcholine
ADHD = attention-deficit hyperactivity disorder
ASD = autism spectrum disorder
GABA = gamma-aminobutyric acid
NDD = neurodevelopmental disorders
NNT = number needed to treat
RCT = randomised controlled trial
REM = rapid eye movement

This publication is intended as an educational resource for healthcare professionals involved in the management of children with sleep disturbances associated with neurodevelopmental disorders (NDDs). This review focuses largely on the treatment of insomnia in this paediatric group and defines the place of melatonin in its management. In 2012, The Royal Australia New Zealand College of Psychiatrists (RANZCP) provided a submission to PHARMAC for the funding of melatonin for secondary insomnia in children and adolescents with neurodevelopmental comorbidities.[1] In 2015, the Pharmacists and Therapeutics Special Interest Group of the Paediatric Society of New Zealand asked PHARMAC to reconsider the priority of funding melatonin 2 mg prolonged-release tablets. As of July 2017, prolonged-release melatonin is fully funded via Special Authority for patients ≤18 years of age who have persistent and distressing insomnia secondary to NDDs (this is an off-label indication). This review is supported by an educational grant from Aspen.

Introduction

Neurodevelopmental disorders (NDDs) result from an impairment of the growth and development of the central nervous system as a result of genetic, metabolic, toxic or traumatic factors (including traumatic brain injury).[2] NDDs affect over 2% of the general population and are associated with varying degrees of physical, cognitive and emotional impairment.[3] Individuals with NDD exhibit a high prevalence of chronic sleep disturbance, which tends to develop early in infancy and may extend into adolescence and adulthood.[4-6] Sleep difficulties frequently aggravate the symptoms of NDD, further adding to the difficulties experienced by affected children and their families.

Specific NDDs associated with sleep disorders include autism spectrum disorder (ASD), attention-deficit hyperactivity disorder (ADHD), cerebral palsy, Rett syndrome, Williams syndrome, Angelman syndrome, Prader-Willi syndrome, Smith-Magenis syndrome, Down syndrome, and tuberous sclerosis.[3,7] For some NDDs, sleep disturbances are so common that they form part of the diagnostic criteria for the disorder itself.[7]

Prevalence estimates for sleep disturbances in children with NDDs range from 80-94%, compared with approximately 25-32% in typically developing children.[4,5,8] The most common sleep complaints in children with NDDs are insomnia (difficulty settling at night [51%] and/or nocturnal awakenings [67%]) and hypersomnia (excessive daytime sleepiness).[3,4,6] Other sleep problems in children with NDDs include bedtime resistance, fragmented sleep, sleep-disordered breathing, parasomnias (such as sleep walking, night terrors, excessive nightmares and bedwetting), seizures, nocturnal laughing, bruxism, morning rising difficulties, early morning waking, and daytime sleepiness.[4,7,9-12] Sleep disturbances are particularly prevalent in children with ASD and ADHD.[7] In children with ASD, insomnia is 10-fold more common than in typically developing children.[9]

The burden of sleep disturbances

Sleep disturbances in NDDs can have an huge impact on the whole family's health and well-being, with sleep deprivation and stress disrupting siblings, and marital relationships.[13,14] For the child or adolescent with NDD, chronic insomnia is associated with poorer developmental outcomes, emotional lability, impaired attention/concentration and hyperactive behaviour, impaired cognition, headaches, excess weight, and behavioural disturbances.[3,9,14]

A recent systematic review involving 33 studies examining sleep and fatigue outcomes in parents of children with NDDs, found that parents consistently reported significantly poorer subjective sleep quality compared with parents of typically developing children.[15]

The aetiology of sleep disturbances in NDD

Sleep disturbances in NDDs are caused by the interplay of multiple factors, including behavioural problems (e.g. poor sleep hygiene and environmental factors), medical and neurological disorders (e.g. epileptic seizures and gastro-oesophageal reflux), medication use, psychiatric disorders (e.g. anxiety) and sleep disorders (e.g. restless legs syndrome and obstructive sleep apnoea).[4] Epileptic seizures may significantly disrupt sleep architecture and alter REM sleep, with the severity of epilepsy correlating with the severity of sleep disturbance.[4]

While genetic and/or epigenetic abnormalities in sleep/wake regulation predispose patients with NDDs to insomnia, poor sleep hygiene and lack of limit-setting contribute to maintaining sleep disruption.[3] Furthermore, communication and emotional difficulties may prevent children from following a parent's instructions about falling asleep and often there is refusal to go to bed.[4,12]

In a number of NDDs, including ASD, Angelman syndrome, cerebral palsy, Down syndrome and Smith-Magenis syndrome, sleep disturbances (primarily insomnia) have been attributed to circadian sleep-wake cycle abnormalities as a result of abnormally low levels of melatonin or a delay in dim-light melatonin onset (DLMO).[7,16]

Identifying insomnia in NDD

Identifying and assessing sleep issues is essential to facilitating effective treatment, however, a considerable proportion of healthcare professionals fail to directly ask their paediatric patients and their parents about their sleep habits.[14] Furthermore, many parents have poor knowledge about sleep development and sleep issues and may present with concerns about their child regarding impulsivity, aggression, inattention, hyperactivity or other behavioural issues that may be secondary to a sleep disorder, but unidentified as such.[8] Complicating the diagnosis of insomnia in childhood are variations in normal sleep patterns during development, cultural beliefs and differences in sleep practice, and reliance on the parent to report symptoms.[7]

Given the high prevalence of insomnia in ASD, it is recommended that all children with this disorder be screened for this sleep disturbance.[14] The recommended first step in assessing sleep issues in this patient group is to ask patients and their parents to complete a sleep diary. If a sleep diary hasn't been completed prior to the clinical evaluation, a screening tool such as the BEARS Sleep Screening Tool may be useful to obtain and assess sleep-related information.[14] This validated screening tool has five domains that address common sleep irregularities. If difficulties are reported in ≥2 domains, further assessment is advised.

The second step in evaluating insomnia is to identify any potential medical contributors (comorbid conditions) that can affect sleep, including upper airway anatomic problems and obstructive sleep apnoea, neurologic conditions and other sleep disorders.[8] The US Sleep Committee of the Autism Treatment Network has developed a useful set of questions (available here) to help identify underlying medical conditions. Psychiatric conditions such as depression and anxiety, and medication use, should also be considered, as these may contribute to insomnia.[8] If significant comorbidities are detected these should be investigated further and the patient referred to a relevant specialist where appropriate.

Managing insomnia in NDDs

Understanding the multifactorial aetiology of sleep disturbances in children and adolescents with NDDs is essential for appropriate treatment.[4] Firstly, medical contributors and other primary sleep disorders must be excluded (and if identified, referred to a relevant specialist). First-line treatment for insomnia comprises parent-based education regarding sleep hygiene, and behavioural interventions.[3] Primarily, the behavioural management of insomnia in children and adolescents with NDDs consists of optimising the sleep environment and ensuring appropriate sleep hygiene, however, in a sizeable proportion of patients such therapy may need to be complemented with pharmacological treatment.[6,9] For example, some patients may need supplemental melatonin to treat insomnia or circadian rhythm disorders, while others may require specialist treatment of anxiety or hyperactivity.[4]

As with all interventions, healthcare providers must assure timely follow-up (after 2 weeks to 1 month) to monitor progress and resolution of symptoms.[8] Referral to a paediatrician is recommended if insomnia is not improving with initial interventions.[8]

The algorithm depicted in **Figure 1** shows a useful practice pathway, developed by the US Sleep Committee of the Autism Treatment Network, for managing patients with insomnia secondary to ASD (this can also be applied to paediatric patients with others NDDs).

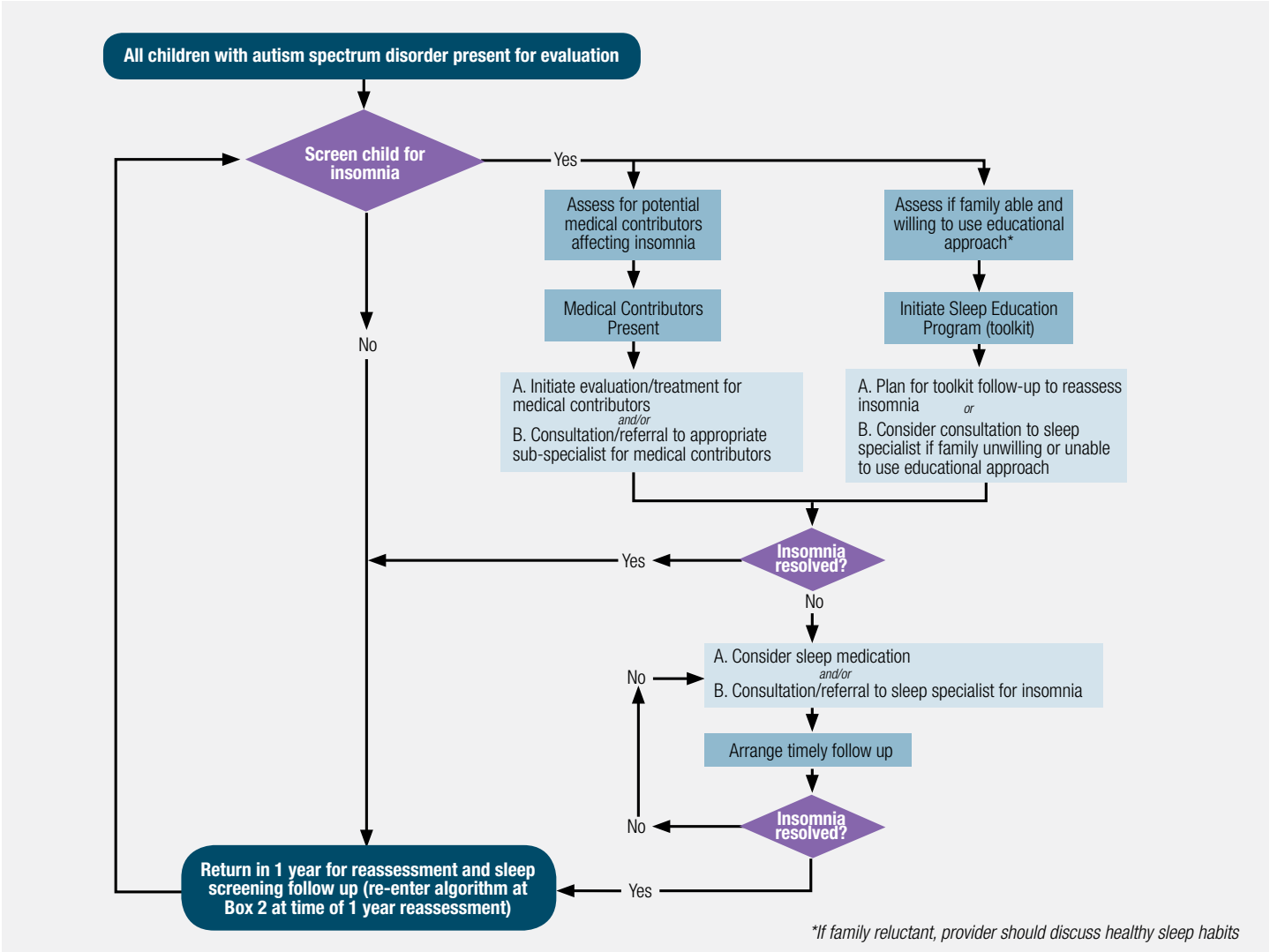


Figure 1. US Sleep Committee of the Autism Treatment Network algorithm for managing patients with insomnia secondary to ASD.[8]

Non-pharmacological management

Once any obstructive sleep problems have been addressed and if necessary treated, the following interventions are recommended. Parents should also be directed to the Paediatric Society of New Zealand's parent information website kidshealth.org.nz, which provides excellent advice on managing sleep issues.

Sleep hygiene

Parents should be educated about sleep hygiene and the detrimental effects of caffeinated drinks, screen time in the evenings and bright lights and noise on sleep.[14] Parents should ensure that the child has a dark, quiet, relatively cool, non-stimulating environment to sleep in.[3] A calming and consistently followed bedtime routine must be maintained, with the child woken at the same time each morning, avoiding sleeping later to make up for lost sleep.[3,7]

Behavioural interventions

Studies have documented improvement in both sleep and daytime behaviour upon the initiation of behavioural therapies.[4] Almost all behavioural techniques promote self-soothing skills that allow the child to fall asleep and return to sleep independently.[3] Some of these interventions will need to be adapted depending on the child's disabilities (e.g. extinction may not be suitable for a child with physical disabilities or self-injurious behaviour).[17]

Pharmacological interventions

For children continuing to experience sleep difficulties despite behavioural therapy, sleep-promoting pharmacological agents may be added while continuing behavioural interventions.[3] On the whole, robust evidence for pharmacotherapy in sleep disturbances in children with NDDs is lacking, and so use is off-label.[7] Choice of therapy is typically determined on a case-by-case basis taking into consideration the type of sleep disturbance and its cause, the child's developmental age, comorbidities, the half-life of the agent, and potential drug-drug interactions with concomitant medications or non-prescription agents.[7]

Pharmacological interventions target some of the various wake- and sleep-promoting neurotransmitters or neurotransmitter-like compounds that are released in the brain during the sleep cycle.[14] The sleep-promoting compounds include melatonin, acetylcholine (ACh; during REM sleep), gamma-aminobutyric acid (GABA), adenosine, galanin and glycine, while the wake-promoting neurotransmitters include ACh, glutamate, dopamine, norepinephrine, serotonin, histamine and orexin/hypocretin.[14]

Melatonin

Melatonin (*N*-acetyl-5-methoxytryptamine), a naturally occurring hormone produced by the pineal gland, is a chronobiotic crucial for the regulation of the circadian rhythm or sleep-wake cycle and also has hypnotic properties.[3,16] The production and secretion of melatonin in typically-developing older children and adults begins in the evening and peaks between 2 and 4 am (**Figure 2**).[3]

Melatonin production is suppressed by short wavelength light (blue end of spectrum) such as produced by self-illuminating devices.[18] Restricting use of devices prior to planned sleep is a part of environmental and behavioural management of sleep. Blue light filtering lenses have proven benefit in reducing the effects of device blue light exposure.[19,20] Modern portable devices have a 'night mode' setting that reduces screen blue light output after a set time to try to minimise the effects on sleep.

When nocturnal melatonin production/secretion is inappropriately timed or impaired in relation to the environment, timed melatonin replacement therapy will often be beneficial. Melatonin for supplementation is available in immediate-release and prolonged-release forms and these have very different pharmacokinetic profiles, with prolonged-release melatonin mimicking the endogenous profile of melatonin (**Figure 3**).

Melatonin supplementation in insomnia associated with NDDs

Children with NDDs often exhibit a disruption to the normal pattern of nocturnal melatonin secretion or a reduction and/or delay in its secretion at night.[3] **Figure 4** demonstrates the typical pattern of abnormal melatonin secretion in children with ASD.[21]

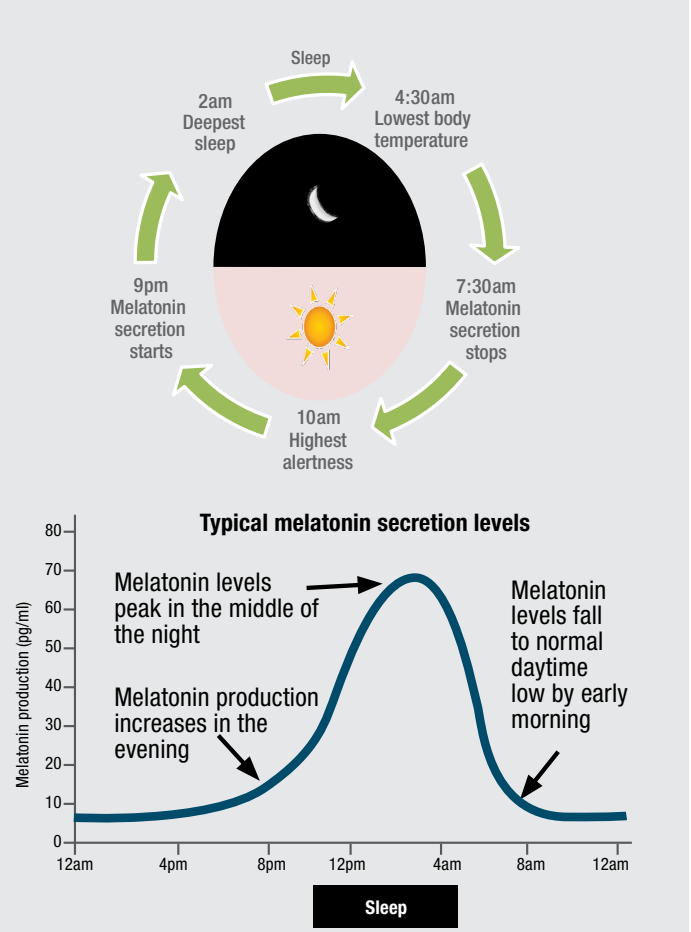
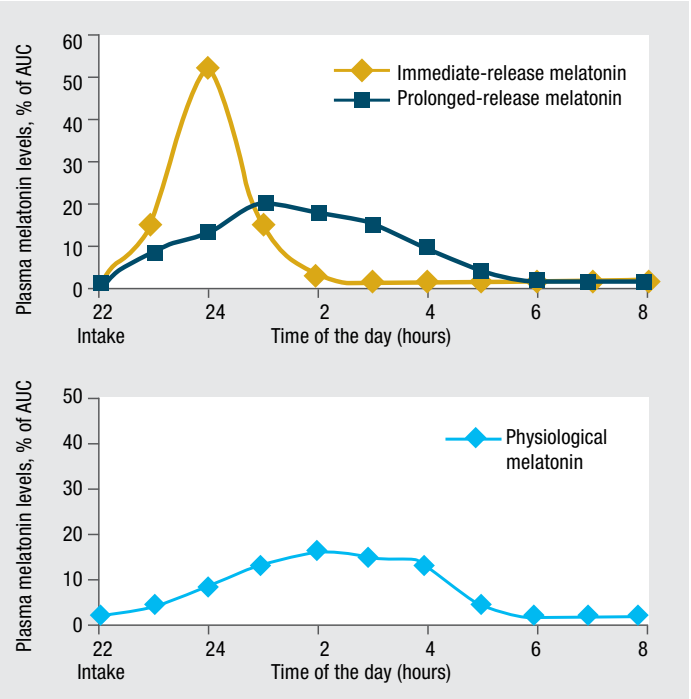
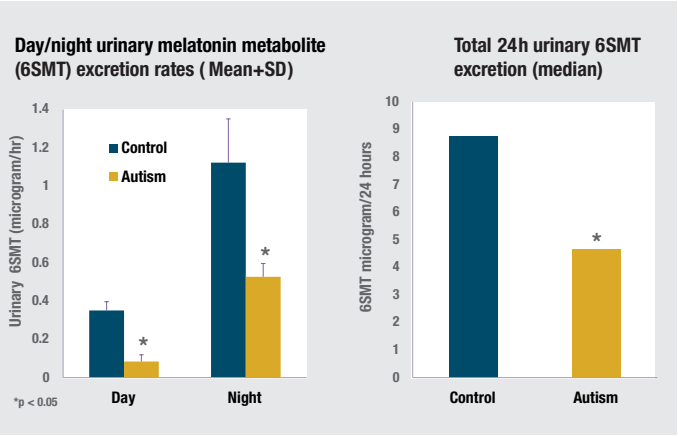


Figure 2. Typical melatonin secretion levels throughout a 24-hour cycle



AUC = area under the curve

Figure 3. Pharmacokinetic profiles of immediate-release, prolonged-release and physiological melatonin.

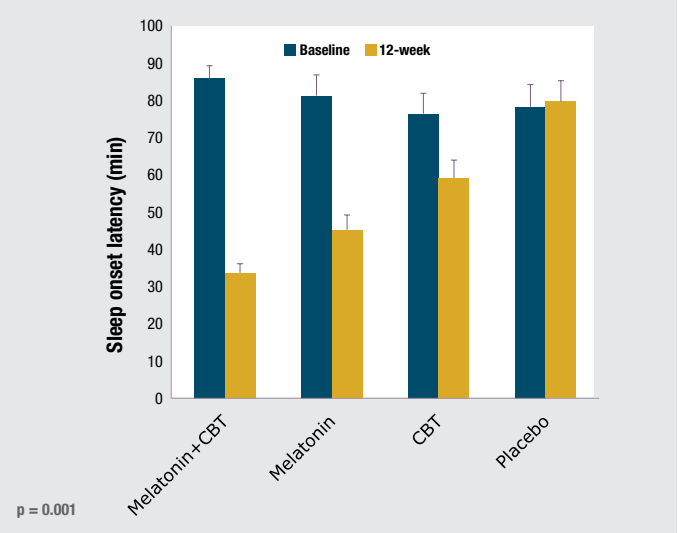


6SMT = 6-sulfatoxymelatonin; SD = standard deviation

Figure 4. Abnormal melatonin secretion in children with ASD.[21] Adapted from Tordjman 2012

Melatonin supplementation has proven efficacy and safety in children with sleep onset problems and/or difficulty waking in the morning.[22] Parents of children treated with melatonin for insomnia report significant benefits not only to the child, but to the entire family, as a result of improvements in the child's sleep and behaviour.[23] Furthermore, the perceived 'naturalness' of melatonin is valued, and it is often favoured by parents over other medications prescribed for sleep.[23]

A number of studies have investigated the use of prolonged-release melatonin in NDD populations. An Italian study in 160 children aged 4-10 years with insomnia secondary to ASD found improvements with moderate-to-large effect sizes from baseline to week 12 across all sleep outcome measures in prolonged-release melatonin recipients, behavioural therapy recipients and recipients of these therapies combined.[24] In the study melatonin therapy alone was more effective than behavioural therapy alone in improving bedtime resistance, sleep onset latency (**Figure 5**), night-wakings and sleep duration.



CBT = cognitive behavioural therapy

Figure 5. Controlled-release melatonin for insomnia in children with ASD.[24] Adapted from Cortesi 2012

Statistically significant short- and long-term clinically relevant effects and safety in total sleep time and sleep initiation with prolonged-release melatonin were also seen in a phase III clinical trial involving 125 children with ASD who had failed to improve on basic sleep hygiene and behavioural therapy.[25] Also looking at the long-term efficacy and safety of prolonged-release melatonin, Maras and colleagues revealed that after 52 weeks of continuous treatment, subjects slept a mean of 62.08 minutes longer ($p = 0.007$), fell asleep 48.6 minutes faster ($p < 0.001$), had 89.1 minutes longer uninterrupted sleep episodes ($p = 0.001$), 0.41 fewer nightly awakenings (>50% decrease; $p = 0.001$), and better sleep quality ($p < 0.001$) compared with baseline.[26] The Composite Sleep Disturbance Index child sleep disturbance and caregivers' satisfaction of their child's sleep patterns, the Pittsburgh Sleep Quality Index (PSQI global), and the WHO-5 wellbeing-index ($p = 0.001$) improved significantly compared with baseline values. The most frequent treatment-related adverse events were fatigue (5.3%) and mood swings (3.2% of patients).

Another study investigating the long-term efficacy and safety of prolonged-release melatonin at a dose of 4-6 mg daily in 88 children (mean age 10.2 years) with NDDs found that within 3 months, sleep latency decreased by 44.0% ($p < 0.001$), sleep duration increased by 10.1% ($p < 0.001$), the number of awakenings decreased by 75% ($p < 0.001$), and sleep quality improved by 75% compared with baseline ($p < 0.001$).[27] The study did not report any serious adverse events or treatment-related comorbidities associated with the use of prolonged-release melatonin. The safety of very long-term melatonin use (average melatonin treatment duration 7.1 years) was demonstrated in a Dutch study involving adolescents and young adults receiving melatonin for chronic sleep onset insomnia.[28]

The efficacy and safety of prolonged-release melatonin for insomnia in children with ASD was further confirmed in a randomised, double-blind, placebo controlled trial involving 125 children and adolescents aged 2-17.5 years, whose sleep had failed to improve on behavioural therapy alone.[29] Patients received either prolonged-release melatonin at a dose of 2 mg escalated to 5 mg, or placebo. Evaluation at 13 weeks revealed an adjusted mean change from baseline in total sleep time of 51.16 minutes for melatonin recipients and 18.73 minutes for placebo recipients ($p = 0.034$), and a mean reduction in sleep latency of 39.6 minutes versus 12.5 minutes ($p = 0.011$), respectively. Clinically meaningful sleep responses were seen in 68.9% of melatonin recipients versus 39.3% of placebo recipients (NNT 3.38). No unexpected safety issues were identified.[29]

Unlike traditional hypnotics (e.g. chloral hydrate and benzodiazepines), treatment with melatonin does not alter sleep architecture.[30] The rates of adverse events with prolonged-release melatonin are reported to be similar to those with placebo, and include somnolence, asthenia (weakness), fatigue, headache, back pain and respiratory infections.[22,29,30]

Prescribing melatonin

Prolonged-release melatonin 2 mg is approved by Medsafe for use as monotherapy in adults aged ≥55 years with primary insomnia. It is the only registered form of melatonin in NZ. Use in children is considered 'off label'. Registered products (even if used off label) should be prescribed in preference to unlicensed products.

Prolonged-release melatonin 2 mg, is fully funded via Special Authority for patients ≤18 years of age who have persistent and distressing insomnia secondary to NDD. Authority applications (initiation and renewal) must be from a relevant specialist or any other medical practitioner on the recommendation of such a specialist. The NZ Formulary for Children recommends that treatment with melatonin be initiated and supervised by a specialist, but a general practitioner may manage continued treatment under a shared-care agreement; treatment should be reviewed every 6 months.[31]

Dosing: For children aged 1 month to 18 years, The NZ Formulary recommends an initial dose of 2-3 mg daily, 1-2 hours before bedtime, with the dose increased if necessary after 1-2 weeks to 4-6 mg daily before bedtime (maximum dose of 10 mg daily).[31]

Crushing or halving of tablets is not recommended, but if necessary, prolonged-release melatonin tablets may be crushed and mixed with cold food or drink; crushing makes this an immediate release preparation and therefore it should be taken immediately before bed.[31] Crushed tablets may also be administered via a gastrostomy or nasogastric tube.[30]

Other treatments

It is thought that the sleep-wake cycle is in part regulated by the dopamine-opiate system, which requires iron as a cofactor for proper function.[7] Limited evidence suggests that iron supplementation may be useful in children suspected of having low iron stores, but any potential benefit of such supplementation must be weighted against any adverse gastrointestinal effects.

EXPERT'S CONCLUDING REMARKS:

Melatonin therapy for improving sleep induction and duration is a moderately effective and very safe treatment modality for use in NDDs after implementation of environmental and behavioural measures. Melatonin is preferred to other sedative hypnotics available for use in childhood, owing to good efficacy and a better safety and side-effect profile than the other agents, which do however have a place in selected cases. Improving sleep in children and young people with NDDs can not only improve their daytime behaviour and learning, but has significant benefits on family function and well being.

Useful resources:

US Sleep Committee of the Autism Treatment Network questionnaire: https://pdfs.semanticscholar.org/779a/7e669b8b3c6e2d092ffd0d67f725cf2eddfb.pdf

Prolonged-release melatonin Special Authority form: https://www.pharmac.govt.nz/tools-resources/forms/special-authority-application-forms/

Kidshealth.org.nz

TAKE-HOME MESSAGES

- In NZ, prolonged-release melatonin is fully funded via Special Authority for patient's ≤18 years of age who have persistent and distressing insomnia secondary to NDDs (this is an off-label indication).
- Individuals with NDD exhibit a high prevalence of chronic sleep disturbance
- Sleep disturbances in NDDs can have an huge impact on the whole family's health and well-being
- Sleep disturbances in NDDs are caused by the interplay of multiple factors, including behavioural problems, medical and neurological disorders, medication use, psychiatric disorders and sleep disorders
- First-line treatment for insomnia comprises parent-based education regarding sleep hygiene, and behavioural interventions
- For children continuing to experience sleep difficulties despite behavioural therapy, sleep-promoting pharmacological agents may be added while continuing behavioural interventions
- Children with NDDs, often exhibit a disruption to the normal pattern of nocturnal melatonin secretion or a reduction and/or delay in its secretion at night
- Melatonin supplementation has proven efficacy and safety in children with sleep onset problems and/or difficulty waking in the morning.

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