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

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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.2 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.4,5 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, Williams syndrome, Angelman syndrome, Prader-Willi syndrome, Smith-Magenis syndrome, Down syndrome, and tuberous sclerosis.2,5 For some NDDs, sleep disturbances are so common that they form part of the diagnostic criteria for the disorder itself.7 Prevalece estimates for sleep disturbances in children with NDDs range from 80-94%, compared with approximately 25-32% in typically developing children.15,16 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).3,4,8 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.10-12 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 a 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.13-14

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.5 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

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
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. 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. 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.

Given the high prevalence of insomnia in ASD, it is recommended that all children with this disorder be screened for this sleep disturbance. 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. 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. 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. 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. 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. 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. 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.

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

Figure 1. US Sleep Committee of the Autism Treatment Network algorithm for managing patients with insomnia secondary to ASD.
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 kidhealth.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. The 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.17

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.2 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 chronobiologic crucial for the regulation of the circadian rhythm or sleep-wake cycle and also has hypnotic properties.1,16 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).5

Melatonin production is suppressed by short wavelength light (blue end of spectrum) such as produced by self-illuminating devices.19,20 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. Figure 4 demonstrates the typical pattern of abnormal melatonin secretion in children with ASD.21

Melatonin levels peak in the middle of the night

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

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

AUC = area under the curve
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.

Melatonin supplementation has proven efficacy and safety in children with neurodevelopmental disorders – a focus on melatonin by Cortesi 2012

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

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

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.

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 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.29 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.28,29,30

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.
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

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