Review Article

Sleep in Children with Neurodevelopmental Difficulties

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Abstract:

Sleep disorders in children with neurodevelopmental disorders are complex and reflect underlying genetic/biological and behavioural components. The sleep disorders are the same as in the typically developing child, although may have some modifications to the presentation or the frequency depending on the phenotype. Consideration of the known phenotypes and the environmental issues are important in defining management strategies. Despite this complexity, defined behavioural strategies with good sleep hygiene can have a significant effect on the sleep problem and on parental management of the behaviours.

3 key points

- Sleep problems are common, burdensome and high on the list of key issues for parents of children with a disability.
- Sleep disorders in children with neuro-disability are generally the same as their typically developing peers but are more common.
- A clear understanding of the individual phenotype is important in developing individualised treatment strategies.

5 key words

Sleep, Children, Behavioural management, Developmental Disorders,

3 MCQs

1. **Key features of good sleep hygiene are:** *(mark all that are appropriate)*

- a. Clear routine and expectations at bedtime
- b. Cool shower 30 minutes before bed
- c. Low light
- d. Calm activities
- e. Screen time until 20 minutes before bed

2. **Sleep onset association disorder is:**

- a. More common in autism
- b. Common in toddlers
- c. Frequently associated with night waking and coming to parent's room
- d. Best treated with melatonin
- e. Likely to resolve spontaneously

3. **Melatonin is:**

- a. Useful for treatment of short sleepers with ADHD
- b. Primarily useful for sleep initiation
- c. An antioxidant
- d. Useful for sleep phase shift
- e. Safe for long term use

Answers:

1. a, c, d Sleep hygiene varies in the exact elements, but darkness or low light, calm activities, and clear routines are always part of it. A warm bath may be recommended to facilitate vasodilation and cooling of body temperature once out of bath thus mimicking the body's systems as sleep onset occurs. Screen time is generally recommended to be reduced at least an hour before bedtime which may be very challenging for some but at least reducing the background lighting may help.

2. b, c Toddlers are commonly trying to assert independence but are often transitioning from parental presence or bottles to self-settle to sleep. Children with autism may be harder to shift to self-settling and may have more fears of being alone. If parental presence is required at sleep-onset then the child is likely to need this to re settle during the night. Melatonin will only help to assist the child in getting off to sleep but behavioural strategies are still required and are often more successful. It will generally require some active behavioural management.
3. b, c, d Evidence in children with neurodevelopmental disorders is strongest for reducing sleep latency and for shifting sleep phase earlier. It is also an antioxidant and it this mechanism that many advocates suspect it may assist in other roles but is largely unknown at this point to what extent.

Introduction

Sleep is essential for growth and development. Sleep disorders in children impose a huge psychosocial and financial burden for families and society. The overall cost of sleep disorders is great: in the US an estimated 1.23 million working days are lost secondary to sleep insufficiency¹.

Sleep disorders affect between 18-23% of typically developing (TD) children and up to 80% of children with neurodevelopmental problems. Some neurodevelopmental disorders are known for sleep problems including attention-deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), Smith-Magenis syndrome (SMS)^{2,3}, Prader-Willi syndrome (PWS), Angelman's syndrome (AS) and many neurological disorders. Factors which predispose children with neurodevelopmental problems to sleep disorders include genetic control of melatonin timing (SMS)⁴, melatonin metabolism (ASD, AS), medication (ADHD) and behavioural factors. Craniofacial and neurological factors are also important, e.g. Down syndrome where a small mid-face as well as low tone may predispose to obstructive disease. Associated medical conditions such as eczema, epilepsy, gastro-oesophageal reflux, and chronic pain can also impair sleep.

The impact of poor sleep in children with neurodevelopmental issues is less well understood than that in TD peers. The impact may be on the body's functions that are driven by circadian scheduling including the melatonin cycle, arousal, immune system functioning and growth hormone secretion.

In general, the sleep disorders described in children with special needs do not differ from those seen in the TD population (Table 1).

[Table 1 here]

Disorders of initiating and maintaining sleep

These are generally behavioural in nature and may be related to the child's challenges in self-settling, the parent's challenges in limit-setting in a child who may have suffered, and communication challenges. Sleep association disorder is where a child needs a particular set of circumstances to fall asleep and will need these to be the same when they arouse normally during the night. Delayed sleep onset is common in children with hyperactivity, ASD and AS. Frequent waking occurs in children with AS, epilepsies and those night feeding. Some delays may be related to delayed sleep phase (i.e. where a child has shifted their whole sleep schedule later into the night) and the typical adolescent

delays can occur in these children too. Sleep initiation problems can be managed in most disorders by good sleep hygiene and behavioural strategies⁵⁻⁹.

Disorders of hypersomnolence

Hypersomnolence disorders occur as in the TD with some exceptions, including PWS where severe hypersomnolence can often present during childhood, sometimes meeting criteria for narcolepsy. The aetiology is not understood but needs investigation as these children are also prone to central and obstructive sleep apnoea (OSA) as well as obesity hypoventilation syndrome. The other notable exception is with SMS where melatonin secretion occurs maximally around 9-10am, making these children excessively sleepy and prone to sleep attacks. Narcolepsy should be in the differential of any child presenting with hypersomnolence and collapsing episodes (cataplexy). The criteria for narcolepsy diagnosis are adult-based and repeated assessment may be required with expectant interim management. Narcolepsy is often present young but not diagnosed until later. It is commonly associated with HLA type DQB1*06:02 and can present after an infection or injury and is commonly managed with stimulants as first line therapy.

Sleep related breathing disorders (SRBD)

OSA is particularly common in children with abnormal tone and /or abnormal craniofacial structure. Hypotonic children are prone to airway collapse in rapid eye movement REM sleep, as opposed to children with high tone who are more prone to obstruction in non-REM sleep when tone is high. For children with cerebral palsy this can be very problematic as they will arouse with obstruction and increase tone even more at this time. The management of tone is especially important for these children and the use of continuous positive airway pressure (CPAP) can be challenging. CPAP can be used in most situations with good results but requires significant family commitment and a child who can tolerate treatment.

Poor central control of breathing problems is often associated with developmental delay (immature patterns) or brain malformations such as Arnold-Chiari malformation. Respiratory failure is common in disorders especially those with significant obesity where it may be related to an obesity hypoventilation scenario or where scoliosis or weakness are common (e.g. in muscular dystrophies or Rett syndrome). Respiratory support in sleep can provide an improved quality of life for these children but does not usually lengthen their life. Discussions about limitations of respiratory support should start early in children at risk.

Circadian sleep disorders

These are commonly secondary phenomena in childhood related to delayed sleep times (i.e. child goes to bed later) resulting in delayed wake time which may mean sleep time is cut short because the child needs to be ready for school. In contrast, some children have an advanced sleep cycle and wake early in the morning. This is often secondary to medication and may improve with alterations in timing of medications that induce drowsiness such as anti-epileptics and risperidone.

Managing common sleep problems

The treatment of sleep disorders in children with developmental difficulties is based on extrapolation from treatment in TD children (Table 2). We assess the amount of sleep required by daytime symptoms which in this population can be difficult. A good history will generally direct diagnosis and management strategies. Detailed bedtime routines and behaviour should be clearly noted as well as any other contributors to sleep. Note should be made of noise, light and other environmental issues that may affect sleep as well as the child's own temperament.

Behavioural strategies should be informed by individual history and family capacity but just initiating good sleep hygiene can ameliorate up to 50% of problems for families. Simple behavioural strategies delivered by paediatricians in a recent real world randomised controlled trial significantly decreased sleep initiation problems in ADHD by up to 20% (personal communication). Sleep hygiene generally consists of key principles: low light; low noise; calming activities for an hour before bed with no screen time; clear routines; warm bath or shower (based on the vasodilation and then cooling of body temperature prior to sleep)¹⁰.

The evidence is increasing for behavioural strategies such as positive routines, limit setting, ensuring consistent, parent-independent settling to sleep associations, call outs, camping out techniques, graduated extinction, cognitive behavioural therapy, physical activity, and bedtime fading in those with developmental problems^{7,9}.

[Insert Table 2]

A recent study trialling building knowledge and applying suitable strategies to parents of children with ADHD and comorbid ASD found improvements in sleep parameters as well as in behavioural symptoms when administered by sleep researchers^{7,9}. The results of an educational intervention taught to and delivered by paediatricians are awaited.

Developing consistent, parent-independent sleep associations is fundamental to self-settling. The child needs to have the same approach to settling to sleep at the beginning of the night as for overnight when they naturally arouse from sleep. Addressing the beginning of the night will often effect change for later arousals.

Using the circadian rhythm

Key regulatory processes affect the timing of our sleep and can be manipulated to improve a child's sleep. Processes include:

1. Circadian timing: usually a little over a 24-hour cycle but entrained to 24 hours with routines. This includes melatonin production which occurs with dim light in the evening. Use of dim light in the evening and bright light in the morning can help to entrain a child's circadian cycle.
2. Sleep pressure: the longer time since our last Stage 3 sleep, the greater our drive to go to sleep. Ensuring an older child does not nap during the day may help them fall asleep quicker at night.
3. The ultradian system: usually around 90 minutes and explains the second wind children may get. When a child takes longer than 30 minutes to get to sleep, the use of bedtime fading is likely to help.

A child's vigilance and attention to threat are also associated with longer sleep latency and reduced sleep maintenance. Anxiety disorder alone was not associated with these parameters in a recent paper in a peri-pubertal population¹⁹. This is consistent with clinical practice: children who are fearful often have more difficulty initiating sleep and can stay awake for long periods at night¹¹. The assessment of trauma and fear in children with disabilities is challenging but may be necessary as children who have experienced domestic violence or abusive situations can find settling to sleep challenging.

Sleep problems and their treatment in specific disorders

ADHD: Many of the identified problems are around short sleep and delayed sleep onset and may be related to stimulant medication side effects (Table 3). Sleep problems are also associated with poor sleep hygiene and parenting styles¹². There has been recent interest in the chronotype of adults with ADHD and its relationship to sleep disorders and neuropsychological effects¹³. However, the only study conducted in children found that children with an evening chronotype had greater bedtime resistance¹³. Behavioural interventions outlined above should be the first line of any treatment plan.

ASD: Children with ASD have many reasons for sleep disturbance. Co-morbid conditions may predispose to sleep disturbance including anxiety, fear, ADHD, sensory attributes¹⁴, cognitive challenges, repetitive review of activities or anticipation of activity. Children may also have biological and genetic reasons for rapid or slow metabolism of melatonin and dysregulation of the circadian clock^{15,16}. Treatment should be individualised. A recent paper evaluating sensory profiles and sleep disturbance found that hypersensitivity to touch explained 24% of the variance in sleep disturbance in the ASD group as opposed to other domains such as visual and auditory. A multifaceted approach may be required including environmental modification, good sleep hygiene and behavioural strategies. Melatonin is effective in reducing sleep onset latency, but not all children will respond. We know there is high heritability for polymorphisms in the melatonin synthesis pathway (NAS and ASMT) which may influence the sleep cycles in these children¹⁶. There is good evidence that weighted blankets do not improve sleep onset or total sleep time in children with ASD¹⁷.

Angelman syndrome: Sleep disorders are reported in up to 80% of children with AS. The types of problem can include difficulty with night settling/sleep initiation and extended night waking. Sleep EEGs demonstrate less and shorter spindle formation and greater coherence across spectra¹⁸. Sleep disturbance can be associated with poorer health¹⁹ and management of sleep is the second parental priority for therapeutic interventions after control of epilepsy (*Adams D. in preparation 2018*). Sleep hygiene and behavioural interventions which acknowledge the AS phenotype of reward via facial response - i.e. treating waking with ignoring unless distressed - is effective¹⁹. However, for many, medications such as promethazine or trimeprazine may be required. Melatonin is rarely effective for night waking. Targeted therapies for the underlying sleep disturbance are required.

Cerebral palsy: Children with severe cerebral palsy, with and without epilepsy, have a high incidence of sleep problems (up to 60%). These can relate to obstruction with hypertonia, issues with muscle or bone pain, reflux, and frequent waking with exaggerated startle responses. If it is tone-related, the obstruction may be worse in NREM as opposed to REM in TD children and may be difficult to treat with over 50% failing to tolerate non-invasive ventilation²⁰. Other causes such as reflux, pain and tone management should be considered first.

Epilepsy: Epilepsy has a key impact on sleep. Even children with self-limiting centrottemporal spikes have a longer REM latency and longer sleep latency²¹. Macro- and micro-sleep architecture also suggest possible alterations in cyclic alternating patterns. Distinct patterns are seen in nocturnal frontal lobe²² epilepsies with increases sleep latencies and 98% of seizures occurring in NREM sleep.

Giving anti-epileptic medications in the evening when seizures are more common may help and the medicating may be sedating.

Fragile X syndrome: Sleep disturbance is common in children who have fragile X syndrome (34%) and in Fragile X carriers²³, mostly sleep initiation and frequent night waking. Likely contributors are the behavioural profile including ASD features and age; carriers with FXTAS are more than 3 times as likely as controls to develop sleep apnoea²⁴. Animal models suggest genetic influencers²⁵. Other moderators could include EEG abnormalities, seizures and neurocognitive features of the child. Again, behavioural treatments are most effective²⁶. In a small randomised controlled trial, melatonin reduced sleep onset latency by 28 minutes, sleep onset time by 42 minutes and increased sleep duration by 21 minutes²⁷.

Prader Willi syndrome: Children with PWS tend to have all the age-dependent sleep disorders²⁸, but in infancy can have problems with central control of breathing, and may also have low tone and obstruction. As the children age, variants of OSA and central disorders may arise, variably exacerbated by growth hormone therapy. Protocols exist for close monitoring of sleep-related breathing in this population²⁹. All children should have a sleep study prior to instigation of growth hormone therapy²⁷. There is also a high risk in the obese patient of severe obesity hypoventilation syndrome. Another subgroup seems to be at high risk of hypersomnolence to the extent of meeting criteria for narcolepsy.

Rett syndrome: Children with RS have a high prevalence of sleep problems (80–94%) and a wide variety of sleep-related abnormalities including irregular breathing, bruxism, sleep disturbances, night laughter, night screaming and nocturnal seizures³⁰. As they get older, untreated scoliosis, pain and progressive respiratory failure can also affect sleep.

Smith-Magenis Syndrome: SMS (17pdel) is known for an inverted melatonin rhythm: in general peak melatonin levels occur during the morning resulting in sleep attacks and increasing irritability during the day. Some children have disturbed nocturnal sleep and may have other challenges such as sleep association requiring parental presence. In a small trial (n=10), acebutalol at 8am and melatonin at 8 pm were able to reconstitute the melatonin cycle in most children². Recent studies suggest common pathways in a variety of syndromes that influence sleep disorders (e.g. MBD5 haplo-insufficiency dysregulates circadian gene expression in 2q23.1 and fragile X syndrome³¹).

Pharmacological management of sleep problems

[Table 3 here]

A number of medications may be used to treat sleep disorders in children including melatonin, guanfacine, clonidine, trimeprazine/ antihistamines, and melatonin agonists such as agomelatine and ramelteon (Table 3)³². However, evidence in children with neurodevelopmental disorders is scant, except for melatonin. A recent systematic review identified 13 RCTs and a meta-analysis: melatonin improved total sleep time by a mean of 48 minutes, sleep onset latency by 28 minutes but demonstrated no change in sleep wakings³³. No adverse events were recorded. Melatonin pathways in children with neurodevelopmental issues are poorly researched; melatonin measurement is expensive and rarely available. Melatonin is available as both short and sustained release formulations. There are important interactions with other medications, especially beta-blockers and warfarin^{34,35}. Iron therapy is recommended for children (with low or borderline iron stores) with restless leg syndrome or increased periodic limb movements, often more common in some neurodevelopmental disorders³⁶. Newer therapies such as ramelteon may be effective for disorders such as night terrors³⁷. The evidence for other pharmacotherapeutic interventions, including clonidine which is often used, is minimal to weak at best.

Adenotonsillectomy remains the mainstay treatment for most childhood OSA, successfully reducing obstruction in around 80%. However, children with neurodevelopmental disorders should be reviewed post-surgery to ensure resolution because they are more likely to have persistent OSA (57% non-resolution)³⁸.

In conclusion, sleep disorders are common in children with neurodevelopmental disorders and can have devastating consequences for child and family. Ensuring good sleep hygiene and using behavioural strategies are the *mainstay* of treatment, with medication second line and in conjunction with behavioural efforts. Individualised strategies tailored to the child's specific behavioural phenotype and family capacity are likely to be most successful.

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Table 1: Diagnostic framework

Disorders of sleep in children
Sleep related breathing disorder <ul style="list-style-type: none"> • Obstructive sleep apnoea (OSA) • Central control of breathing disorders (including congenital central hypoventilation disorder) • Respiratory failure
Disorders of initiating and maintaining sleep <ul style="list-style-type: none"> • Limit setting disorder • Sleep association disorder • Childhood insomnia
Disorders of hypersomnolence <ul style="list-style-type: none"> • Narcolepsy 1 • Narcolepsy 2 • Idiopathic hypersomnolence • Others such as Klein-Levin
Circadian disorders

<ul style="list-style-type: none"> • Delayed sleep phase • Advanced sleep phase
Parasomnias <ul style="list-style-type: none"> • Nightmares • Night terrors • Somniloquy/ Somnambulism

Table 2: Behavioural strategies

Behaviour modification strategy	What is it?	What does it help?
Positive routines	Positive calm associations before bed in wind-down period and reward for effort depending on age	Improved sleep onset latency Improved total sleep time
Limit setting	Being able to be firm and set limits	Sleep onset latency and often empowers parents to manage other behaviours
Consistent, parent-independent sleep associations	Strategies for sleep onset associations to be able to be the same all night and initiated by child (not parent)	Sleep onset latency and waking during night requiring parental presence
Camping out	Sleeping in the same room but then graded withdrawal	Sleep onset latency and waking during night requiring parental presence
Checking out	Leaving the room for short periods but coming back	Sleep onset latency and waking during night requiring parental presence
Call outs/bed time pass outs	Card/pass out to have 1-2 get ups but each time hands card over	Recurrent getting up and sleep onset latency, sleep maintenance
Graduated extinction	Delaying response to crying or behaviour	Not in very young children Decreases requirement for parental presence
Cognitive behavioural therapy	For older children and particularly useful for older more cognitively aware and anxious child	Decreases night waking Improves sleep onset latency
Bedtime fading	Works on principle of morning and evening chronotypes Delay sleep by 30 mins if it takes more than 30 minutes to fall asleep and advance if takes less than 15 minutes to fall asleep	Improved sleep onset latency Improved total sleep time

Table 3: Medication effects on sleep

Medication	Effect on sleep	Use in sleep disorders
<i>Anti-convulsants</i>	Mixed effects independent of anticonvulsant effect - weight gain may affect sleep disorder behaviour	If drowsiness is a side effect, then occasionally increased dosing at night
<i>Antidepressants</i> <i>Selective serotonin release inhibitors</i> <i>Tricyclic anti-depressants</i>	Reduce REM amount, increase REM latency, and sleep fragmentation Abrupt withdrawal can result in REM rebound	
<i>Antihistamines</i>	Reduce sleep latency and can promote sleep. In ~ 10% of children may have a paradoxical effect, and can intensify restless legs syndrome	May induce drowsiness
<i>Benzodiazepines</i>	Reduce SWS, can worsen SRBD, increase daytime sleepiness and has neurocognitive effects. Rarely used in children	May be used to manage severe night terrors for a short course or to manage tone in children with cerebral palsy
<i>Corticosteroids</i>	Increased sleep and REM latency, increased fragmentation, decreased total sleep time.	
<i>Beta blockers</i>	Specific S enantiomers ³⁴ (specific beta-blocking) of propranolol and atenolol reduces melatonin production by up to 86% ³⁴	
<i>Montelukast</i>	Profoundly unusual dreams and night behaviours including agitation	
<i>Behavioural medications: e.g.</i> <i>Stimulants</i> <i>Atypical antipsychotics</i>	May increase sleep latency but depends on timing May improve sleep fragmentation in conjunction with improved behaviours	Melatonin may assist

REM = Rapid eye movements

SWS = Slow wave sleep or deep sleep (Stage 3)

SRBD = Sleep related breathing disorders

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