

Management of sleep disorders among children and adolescents with neurodevelopmental disorders: A practical guide for clinicians

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Specialty type: Pediatrics

Provenance and peer review:

Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

P-Reviewer: Xiao CF, China

Received: March 23, 2021

Peer-review started: March 23, 2021

First decision: July 27, 2021

Revised: August 9, 2021

Accepted: March 25, 2022

Article in press: March 25, 2022

Published online: May 9, 2022



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Abstract

There is a complex relationship between sleep disorders and childhood neurodevelopmental, emotional, behavioral and intellectual disorders (NDEBID). NDEBID include several conditions such as attention deficit/hyperactivity disorder, autism spectrum disorder, cerebral palsy, epilepsy and learning (intellectual) disorders. Up to 75% of children and young people (CYP) with NDEBID are known to experience different types of insomnia, compared to 3% to 36% in normally developing population. Sleep disorders affect 15% to 19% of adolescents with no disability, in comparison with 26% to 36% among CYP with moderate learning disability (LD) and 44% among those with severe LD. Chronic sleep deprivation is associated with significant risks of behavioural problems, impaired cognitive development and learning abilities, poor memory, mood disorders and school problems. It also increases the risk of other health outcomes, such as obesity and metabolic consequences, significantly impacting on the wellbeing of other family members. This narrative review of the extant literature provides a brief overview of sleep physiology, aetiology, classification and prevalence of sleep disorders among CYP with NDEBIDs. It outlines various strategies for the management, including parenting training/psychoeducation, use of cognitive-behavioral strategies and pharmacotherapy. Practical management including assessment, investigations, care plan formulation and follow-up are outlined in a flow chart.

Key Words: Sleep; Emotional; Behavioural difficulties; Neurodevelopmental disorders; Pharmacotherapy; Non-pharmacologic interventions; Cognitive therapy; Melatonin; Adolescents; Psychoeducation

Core Tip: Up to 75% of children and young people with neurodevelopmental, emotional, behavioural and intellectual disorders (NDEBID) are known to experience different types of insomnia, associated with significant behavioral, emotional, cognitive and academic impairments, as well as negative impact on the wellbeing of other family members. This paper provides a brief overview of sleep physiology, aetiology, classification and prevalence of sleep disorders among children and adolescents with NDEBIDs. It outlines different strategies for the management of sleep disorders, including parenting training/psychoeducation, the use of cognitive-behavioural strategies and pharmacotherapy. Practical management including clinical assessment, investigations, care plan formulation and follow-up are outlined.

Citation: Ogundele MO, Yemula C. Management of sleep disorders among children and adolescents with neurodevelopmental disorders: A practical guide for clinicians. *World J Clin Pediatr* 2022; 11(3): 239-252

URL: <https://www.wjgnet.com/2219-2808/full/v11/i3/239.htm>

DOI: <https://dx.doi.org/10.5409/wjcp.v11.i3.239>

INTRODUCTION

Sleep problems are common in children from preschool age to adolescence, especially among those who have recognizable neurodevelopmental (and related neurodisability), emotional, behavioural and intellectual disorders (NDEBID). The prevalence of sleep problems among typically developing children and adolescents ranges from 3% to 36%, while affecting up to three-quarters of children with NDEBIDs, depending on the diagnostic criteria used[1,2].

There is a complex relationship between sleep disorders and childhood NDEBID. Sleep deprivation is known to cause clinically elevated externalizing and internalizing behaviour disorders, including inattention, mood variability, disruptive and rule-breaking behaviours, and school problems[3]. It can also affect children's cognitive development and learning abilities, by exacerbating memory and concentration problems, and mood disorders[4,5]. There is clear evidence that various sleep disturbances among children and adolescents increase the risk of mental health disorders such as depression, suicidal and self-harm behaviours, as well as other psychiatric and health outcomes including obesity and metabolic disorders[6]. It can negatively impact the cardiovascular, immune and metabolic systems, including growth disorders[7].

Sleep disorders in children also significantly affect the wellbeing of other family members. Among a cohort of 156 care-givers of children aged 1.5 to 10 years with insomnia, 47% of primary caregivers had clinically significant parenting stress associated with bedtime resistance, daytime sleepiness, parent history of sleep problems, parent history of psychiatric conditions, and child externalizing behaviour[8].

Management of sleep problems is important for long-term mental health and optimization of functioning, prevention of deficits in daily functioning and for halting the progression of psychiatric pathology of affected children and young people (CYP) into adulthood[4,9]. However, healthcare professionals have insufficient training on sleep disorders[10].

This narrative literature review presents important themes identified from search of electronic databases including PubMed, PubMed Medical Central, OVID, EMBASE, PsycINFO and Cochrane databases up to October 2020, using combinations of keywords including 'melatonin', 'ASD', 'developmental disorder', 'ADHD', 'sleep disorder' and 'children'.

It provides a brief overview of the research evidence on the diagnosis and management of sleep disorders among CYP with NDEBID conditions such as attention deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), cerebral palsy (CP), epilepsy and learning (intellectual) disorders.

SLEEP PHYSIOLOGY

Definitions and classifications of sleep disorders

Various definitions of sleep disorders have been used in sleep studies in terms of age, frequency, severity, and duration of symptoms and sample populations[6]. Some studies define insomnia vaguely as parental report of difficulty falling and/or staying asleep[3]. Furthermore, there is considerable variability in children's sleep duration.

Both the 5th edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-5)[11] and the 3rd edition of the International Classification of Sleep disorders (ICSD-3)[12] are the key reference standards for the diagnosis of sleep disorders. Paediatric insomnia has been defined as “repeated difficulty with sleep initiation, duration, consolidation, or quality that occurs despite age-appropriate time and opportunity for sleep and results in daytime functional impairment for the child and/or family”[6]. The ICSD-3 classification includes 6 categories (Table 1).

Why is sleep important?

Sleep is essential to refresh and rejuvenate the body and mind. An average person spends a third of their life sleeping (122 d every year). It is a good practice to emphasise the benefits of sleep to provide a positive message to children, parents, and carers. Table 2 illustrates positive effects of adequate sleep and negative consequences of insomnia.

How much sleep is ideal for children and adolescents?

There is a wide variation about sleep requirement dependent on the child’s age. It is important for health professionals to discuss and provide parents/carers and children written information about sleep duration as in Table 3.

Aetiology and pathogenesis of sleep disorders

The aetiology of sleep disturbances in CYP with NDEBID is heterogeneous and often disease specific. The diagnosis and management of sleep disorders in this population are complex, and little high-quality data exist to guide a consistent approach to therapy[13]. Three main causes of insomnia are biologic, behavioural (including environmental) and psycho-medical[14]. Table 1 shows common causes and examples of sleep disorders.

Chronic sleep deprivation, insomnia, and delayed sleep phase disorder are the commonest sleep disorders in childhood[9]. Other common sleep problems in children with NDEBIDs include difficulty falling asleep, difficulty maintaining sleep, and early morning awakenings[15].

SLEEP DISORDERS AND NDEBID

What are NDEBID?

Childhood NDEBID such as ADHD, tic disorder/Tourettes syndrome, developmental delay, development coordination disorder are commonly managed by Community Child Health Paediatricians, working within integrated teams involving the education, social care and voluntary sectors[16]. Neurodisability describes a group of congenital or acquired long-term conditions that are attributed to disturbance of the brain and or neuromuscular system and create functional limitations in sensory, motor, speech, language, cognition or behaviour. The estimated prevalence of NDEBID reported in developed countries varies widely, ranging up to 15%, depending on the diverse methodologies and definitions used[17,18].

Prevalence of sleep disorders in NDEBID

Sleep disorders in ASD: ASD is a heterogeneous group of neurodevelopmental disorders (NDD) caused by a combination of genetic variation with complex interactions with environmental factors.

Some studies have found that sleep disturbance is the second most common physical co-morbidity in children with ASD, with prevalence estimated to be between 33% and 81%[15,19,20]. Sleep disturbances in CYP with ASD are significantly associated with severity of autism symptoms and deterioration in daytime challenging behaviour including physical aggression, irritability, inattention, and hyperactivity [20-22].

The causes of poor sleep in CYP with ASD are multifactorial and include disturbances in neurotransmitters that promote sleep, including serotonin and melatonin, abnormal sensitization to environmental stimuli, behavioural insomnia and delayed sleep phase syndromes (DSPs), rapid eye movement sleep behaviour disorders, decreased time in bed, increased proportion of stage 1 sleep, as well as coexisting psychiatric symptoms, such as anxiety, depression, and epilepsy[23-25]. The core behavioural deficits associated with ASD could impair the establishment of sound bedtime behaviours and routines. The parents may also struggle with arranging the sleep environment to promote sleep and conveying sleep expectations effectively, while trying to deal with multiple other priorities and stressors[15].

Recent meta-analysis of 38 published studies on various non-pharmacological strategies for management of sleep disorders among CYP with ASD has shown conclusively that no single intervention is reliably effective in managing all the wide range of sleep problems seen in this group of individuals[26]. A recent clinical guideline from the American Academy of Neurology (AAN) concluded that behavioural strategies should be offered as first-line treatment approach for sleep disturbance in CYP with autism, either alone or in combination with pharmacologic treatment with melatonin [with or without cognitive behavioural therapy (CBT)][27].

Table 1 Showing majority of sleep disorders can be grouped into 6 main categories

Category	Description	Conditions and causes, some examples
Insomnias	Inability to fall asleep or stay asleep	Environmental: Poor sleep hygiene, bedroom noise, bright light. Behavioural insomnia of childhood (sleep onset/limit setting/combined). Psychiatric, trauma and substance misuse: Anxiety, depression, OCD, PTSD, abuse or neglect, bullying, drug and substance misuse. Medical: Pain (headaches, joint pains), lung problems (asthma, cystic fibrosis), skin (eczema, allergies), neuromuscular, obesity, medication side effects
Sleep related breathing disorders	Breathing difficulties during sleep	Obstructive sleep apnoea. Central sleep apnoea
Central disorders of hypersomnolence	Excessively sleepy	Narcolepsy
Circadian rhythm sleep-wake disorders	Sleep times are out of alignment	Delayed sleep phase syndrome. Jet lag
Parasomnias	Unwanted events or experiences that occur at the time of falling asleep, sleeping or waking up	During NREM sleep Confusional arousals. Sleep terrors. Sleep-walking
		During REM sleep Nightmares
		Others Enuresis
Sleep related movement disorders	Unusual body movements during sleep	Bruxism. Restless legs syndrome. Periodic limb movement disorder. Rhythmic movement disorder (head banging, body rocking)

OCD: Obsessive-compulsive disorder; PTSD: Post traumatic stress disorder; NREM: Non-rapid eye movement; REM: Rapid-eye-movement.

Table 2 Showing positive effects and negative consequences

Positive effects of adequate and good quality sleep	Negative consequences of lack of adequate and good quality sleep
Promotes growth. Strengthens immunity. Helps cell growth and body repair. Consolidates memory (https://www.sleepscotland.org/support/gateway-to-good-sleep/why-is-sleep-important/). Promotes learning and cognitive development[69]. Maintains physical health and emotional wellbeing	Increased association with excess weight gain and obesity [69]. Impairs immune function. Affects physical coordination. Affects ability to learn new information and problem solve. Affects mood and emotional regulation and increases risk of mental health problems <i>e.g.</i> , mood or anxiety disorder, suicidal ideation

Table 3 Showing National Sleep Foundation's sleep duration recommendations (<https://www.sleepfoundation.org/press-release/national-sleep-foundation-recommends-new-sleep-times>)

Age of the child	Recommended	May be appropriate	Not recommended
Pre-schoolers (3-5 yr)	10-13 h	8-14 h	Less than 8 h or more than 14 h
School-aged children (6-13 yr)	9-11 h	7-12 h	Less than 7 h or more than 12 h
Teenagers (14-17 yr)	8-10 h	7-11 h	Less than 7 h or more than 11 h

Sleep disorders in ADHD: ADHD affects approximately 5% of CYP worldwide[28]. The brain regions, such as dorsolateral and ventrolateral prefrontal and dorsal anterior cingulate cortices, implicated in ADHD pathophysiology, are known to be sensitive to sleep deprivation. Genetics studies have also pointed to the involvement of the catecholaminergic system in both ADHD and sleep regulation[29].

Common sleep problems affecting up to 70% of paediatric ADHD patients include behaviourally based insomnia (limit-setting disorder), bedtime resistance, latency of sleep onset, dim light melatonin onset delay, decreased duration of sleep, increased number of overnight awakenings, daytime somnolence, sleep-disordered breathing, and restless legs syndrome (RLS)/periodic limb movement disorder (PLMD)[30,31]. They may also have sleep disturbances due to co-morbid psychiatric disorders or ADHD medications such as delayed sleep onset and shortened sleep duration[32,33]. In a study of 195 children with ADHD aged 5 to 13 years, sleep problem was observed to be variable over a 12-mo period in 60% of the children and transient in most cases but it was more persistent in a sub-group (10%) of the children[34].

Table 4 Below illustrates some useful resources

Users	Resources	Free access	Website links
Parents and carers	CEREBRA-Sleep Advice service	Free access	https://cerebra.org.uk/get-advice-support/sleep-advice-service/
	Sleep for better day ahead-leaflet	Free access	https://www.qvh.nhs.uk/wp-content/uploads/2020/08/Sleep-for-a-better-day-ahead-0127.pdf
	Sleep hygiene in children and young people: Information for families-leaflet	Free access	https://media.gosh.nhs.uk/documents/Sleep_hygiene_F1851_FINAL_Jun20.pdf
	Encouraging good sleep habits in children with learning disabilities-leaflet	Free access	https://www.oxfordhealth.nhs.uk/wp-content/uploads/2014/05/Good-sleep-habits-for-children-with-Learning-Difficulties.pdf
	Sleep problems and sleep disorders in school aged children	Free access	https://www.sleephealthfoundation.org.au/sleep-problemsand-sleep-disorders-in-school-aged-children.html
	Further useful facts sheets and resources-website	Free access	https://www.sleephealthfoundation.org.au/fact-sheets.html
	Other websites	Free access	https://www.nhs.uk/live-well/sleep-and-tiredness/healthy-sleep-tips-for-children/ ; https://www.sleepscotland.org/
Adolescents	How to sleep well and stay healthy-A guide for teenagers. This is an interactive guide with animations, sounds and external links to useful educational video clips	Free access	https://books.apple.com/gb/book/how-to-sleep-well-and-stay-healthy-a-guide-for-teenagers/id1397176909
	Sleep tips for teenagers	Free access	https://www.nhs.uk/live-well/sleep-and-tiredness/sleep-tips-for-teenagers/
Children	Sleep poster: Interactive pdf for children and parents/carers	Free access	https://www.cambscommunityservices.nhs.uk/docs/default-source/Luton---NDD-Webpages/Sleep/sleep-poster76ddec06f4f66239b188ff0000d24525.pdf?sfvrsn=2
	I see the animals sleeping: A bedtime story-an app	Free on Google play, App store and Kindle store	http://school.sleepeducation.com/childrensapps.aspx
	The animal sleep: A bedtime book for biomes-an app	Free on Google play, App store and Kindle store	http://school.sleepeducation.com/childrensapps.aspx ; https://www.youtube.com/watch?v=zLQ3bkn8Gu8

ADHD is most commonly treated using psychostimulants, with potential side-effects including sleep disorders. Use of psychostimulants may however improve some aspects of sleep in ADHD children[2].

Moderate to severe sleep problems have been associated with increasing ADHD severity and poorer child quality of life (QoL), daily functioning and caregiver mental health, increased likelihood of missed/being late for school, and the caregivers being late for work[30]. Disorders of sleeping pattern is associated with inattention, problematic behaviour, progressive psychopathology, and attenuated emotional regulation, all of which can mimic the symptoms of ADHD. It is therefore necessary for the clinician to assess for sleep problems before confirming a diagnosis of ADHD[33].

The management of sleep disorders in ADHD children include recommendation of good sleep hygiene and other behavioural interventions as the first-line treatment option[33]. There is ample evidence for the effectiveness of behavioural interventions from several studies. Sixty-seven percent of parents of children with ADHD reported complete resolution, with improved child QoL, daily functioning and parental anxiety, five months after randomization into two groups of either brief (1 session, $n = 13$) or extended (2-3 sessions, $n = 14$) behavioural sleep programme[30]. Similar findings as well as improvement of ADHD symptoms have been reported[35].

Other strategies include modifying the dose regimens, formulation, or use of alternative to stimulants such non-stimulant atomoxetine and alpha agonists guanfacine or clonidine, and melatonin[32]. Combined strategy of behaviour modification techniques with use of stimulant medication have been reported to yield sustained improvement in ADHD symptoms, sleep duration, and QoL in a randomized controlled trial (RCT) of 244 children with ADHD[36].

There is lack of robust and reliable evidence for prescribing drugs for behavioural insomnia in children with ADHD. A systematic review of 12 studies, mostly of low quality, was recently reported for the pharmacological treatment of insomnia in CYP with ADHD[37]. The strongest evidence from published literature supports the use of melatonin in reducing sleep-onset delay, but the evidence for

other medications is weaker, with reported significant advancement of sleep onset by 26.9 ± 47.8 min and advancement of dim light melatonin onset by 44.4 ± 67.9 min, when compared to placebo[33,38]. From a recent systematic review of 12 studies including RCTs and observational studies, clonidine, melatonin and L-Theanine demonstrated positive responses in sleep-onset latency and total sleep duration while zolpidem, eszopiclone and guanfacine failed to show significant efficacy when compared with placebo. Zolpidem was associated with neuropsychiatric adverse effects[37].

Sleep disorder in epilepsy and other chronic disabilities: Insomnia, especially maintenance insomnia, is widely prevalent in epilepsy and other chronic conditions. Some expert opinions and a few small studies have presented inconclusive findings suggesting that melatonin either lowers or increases seizure thresholds[39].

MANAGEMENT OF SLEEP DISORDER IN CYP WITH NDEBID

Published clinical guidelines

The American Academy of Pediatrics published a consensus document on pharmacologic management of insomnia in 2006, which focused mainly on future research recommendations[40]. The Sleep Committee of the Autism Treatment Network later developed an expert consensus practice pathway in 2012, which documented best practices for screening, identification, and treatment for sleep problems in people with autism[41].

Other recommendations and clinical guidance have been published more recently for the management of chronic insomnia in children associated with NDD in children including Autism, CP, and genetic syndromes like Rett syndrome, Angelman syndrome, Williams syndrome, and Smith-Magenis syndrome, mostly based on consensus opinions[13]. A consensus statement has been produced by multidisciplinary professional associations in Spain[7]. A clinical practice guideline has recently been published by the AAN for management of insomnia and disrupted sleep behaviour in CYP with autism [27]. An evidence-based sleep management clinical guidance and flow chart designed by the authors is included as [Supplementary Material](#).

Clinical assessment and triage

The diagnosis of sleep disorders in CYP is essentially clinical, based on the information provided by the parents/caregivers and the child and from detailed clinical examination[7]. In view of the high prevalence of sleep problems among CYP, it has been suggested that clinicians need to ensure that questions about sleep are incorporated into their routine health assessment of children, and try to distinguish sleep disturbances from normal age-related changes[42,43].

A clear and comprehensive history that includes all the relevant family, social, academic and lifestyle information is essential to provide an accurate differential diagnosis. History should include the sleep/wake schedule, sleeping environment and bedtime routines, abnormal movements or behaviour during sleep, daytime effects of sleep deprivation, and sleep onset latency (SOL) (which need to be differentiated from delayed circadian rhythm)[1,42]. Clinical assessment should also evaluate the primary and secondary contributing factors and maladaptive behaviours related to sleep[42]. Common parameters to be documented include: (1) Sleep-onset latency; (2) Number and duration of night wakings; and (3) Sleep efficiency (total time of sleep divided by the total time in bed). Box 2 outlines common items to be included in a detailed clinical assessment in [Supplementary Material](#).

Previously rarely reported sleep disorders among children with NDEBID such as narcolepsy and nocturnal epilepsy should be explored, as they have been identified to be commoner than previously thought[44]. Use of validated sleep problems questionnaires including BEARS screening tool and Children's Sleep Habit Questionnaire is recommended to supplement the clinical assessments.

Detailed clinical assessment should lead to formulation of a sleep disorder diagnosis or consideration of potential differential diagnosis (see [Table 1](#)) and exclude other physical explanations for insomnia including obesity, tonsillar hypertrophy, facial dysmorphism, nasal septal deviation, craniofacial abnormalities, hypotonia, chronic rhinitis or other physical illness or discomfort (for example, reflux, ear or toothache, bedwetting, constipation or eczema).

This assessment should lead to the formulation of a sleep plan with the parents or carers. A sleep plan should include specific behavioural interventions which address the identified sleep problems and help restore a regular sleep pattern. This plan needs to be reviewed regularly until a regular sleep pattern is established.

Investigations

Clinical assessment should be supplemented by sleep diary over a 2-wk period. Diagnostic tools such as validated questionnaires, sleep diary and actigraphy are essential to properly detect sleep disorders at early stages[9].

Actigraphy monitors body motion, sleep and wake patterns in individuals. It can measure the total sleep time (TST), sleep efficiency, wake after sleep onset, and SOL, help to determine sleep patterns and document response to treatment in the patient's normal sleep environment[7].

Major indications for polysomnography include strong clinical suspicion of sleep-related breathing disorder, atypical parasomnia, PLMD, clinically unconfirmed RLS or nocturnal seizures when the clinical history and conventional encephalography are inconclusive.

Differential diagnosis

Detailed assessment should lead to formulation of a sleep disorder diagnosis or consideration of potential differential diagnosis including as follows.

RLS and PLMD: Common causes of childhood onset RLS include familial predisposition and systemic iron deficiency. Treatment options include iron supplementation and Gabapentin (researched mainly in adults). PLMD is a sleep disorder that is associated with periodic and repetitive movements of legs and less often arms during sleep. These include bending of toes, foot or ankle, kicking or jerking of legs. There is conflicting evidence on using iron therapy for RLS and PLMD in children[45]. Dopamine agonists and anticonvulsants have not been trialled in children.

Parasomnias: Arousal parasomnias such as confusional arousals are often triggered by sleep apnoea, RLS, or acid reflux. They often respond to specific treatment of these disorders. Parasomnias should be managed with reassurance and safety measures, using benzodiazepines sparingly for severe, potentially dangerous cases. Low dose clonazepam at bedtime may help resolve sleep walking and confusional arousals[46].

Obstructive sleep apnoea: Obstructive sleep apnoea (OSA) affects about 2 percent of children and any suspicion should trigger a referral to the ENT surgeons. Adeno-tonsillar hypertrophy, cranio-facial anomalies, and obesity are common predisposing factors. Mild symptoms of OSA often responds to management with a combination of nasal corticosteroids and a leukotriene antagonist. Moderate to severe OSA would require surgery (adeno-tonsillectomy), positive airway pressure breathing devices or weight reduction as required[47].

DSPS: DSPS is common and can be treated with chronotherapy, light therapy and potentially melatonin as long as the patient is motivated.

COMPREHENSIVE MANAGEMENT STRATEGIES

Most authors and professional guidelines have consistently emphasized the role of effective sleep hygiene strategies, parent and care-giver education and training and behavioral interventions as first line in the management of childhood sleep disorders, with pharmacotherapeutic treatment only considered if sleep hygiene strategies alone have failed[13,48]. The flow chart shows a recommended sleep management guidance based on the published evidence in [Supplementary Material](#).

NON-PHARMACOLOGICAL/BEHAVIOURAL INTERVENTIONS

Non-pharmacological treatment options include sleep hygiene, behavioural interventions, parent education/training programmes, alternative therapies (such as massage therapy, aromatherapy, nutrients and multivitamin or iron supplementation) and CBT for older children and adolescents[9,26,42]. There is sufficient evidence to support the recommendation of these cognitive-behavioral strategies as the most effective approach in the management of paediatric insomnia[7,49].

The most common behavioural interventions are different types of extinction ranging from complete (total removal of reinforcement to reduce a behaviour) to various forms of graduated extinction, bedtime fading/positive routines (including positive bedtime routines, delaying the child's bedtime to match when he/she is currently falling asleep, and stimulus control techniques) and scheduled awakenings (deliberately waking and then soothing a child back to sleep 15-30 min before their typical spontaneous nocturnal awakening) (definitions and practical tips are listed in Box 4 in [Supplementary Material](#)).

Previous literature reviews have shown strong empirical evidence for the effectiveness of behavioural interventions based on learning principles when implemented in the short- or medium-term, but long-term evidence for their efficacy is limited. It is not yet possible to postulate any long-term conclusions about the effects of these treatments over time. A recent review confirmed a significant overall effect with small to medium effect size on different sleep outcomes among typically developing children of all ages, but limited evidence is available for CYP with NDEBIDs. For example, there were no clinically significant improvements for any of the studied sleep outcome measures for two trials involving children with autism or Down syndrome[6]. A meta-analysis of 16 controlled trials found small to large

Table 5 Showing drugs used to treat insomnia[17]

Pharmaceutical	Class	Mechanism of action	Half life (h)	Site of metabolism	Peak concentration	Interactions	Effect on sleep
Diphenhydramine	Antihistamine	H1 agonist. Crosses blood-brain barrier	4-6	Hepatic	Fast absorption. Fast onset of action. Peak at 2-4 h	CNS depressants	Reduces latency. May decrease quality
Hydroxyzine	Antihistamine	H1 agonist. Crosses blood-brain barrier	6-24	Hepatic	Fast absorption. Fast onset of action. Peak at 2-4 h	CNS depressants	Reduces latency. May decrease quality
Melatonin	Neuro-hormone	Hypnotic	90% excreted in 4	Hepatic	30-60 min	Unknown	Reduces latency. Maximum circadian effect
Clonazepam	Benzodiazepine	Central GABA receptors	30-40	CYP 450 3A oxidation	60-240 min	Fluoxetine	Suppresses slow-wave sleep. Reduces arousal
Flurazepam	Benzodiazepine	Central GABA receptors	2-100	CYP 450 3A oxidation	30 min to 13 h	Fluoxetine	Suppresses slow-wave sleep. Reduces arousal
Zolpidem	Z-drug	Benzodiazepine-like	2.5-3	CYP 450 3A oxidation	90 min		Reduces latency. Weak effect on sleep architecture
Clonidine	Alpha agonist	Inhibits noradrenaline release	6-24	50%-80% in urine	Fast absorption 100% bioavailability. Onset of action: 1 h. Peak effect: 2-4 h		Reduce REM. Reduces slow-wave sleep

REM: Rapid-eye-movement; CYP: Children and young people.

effect sizes for a number of sleep outcomes including SOL, number of night wakings, duration of night wakings, and sleep efficacy among typically developing children. Two studies conducted with special needs populations also showed no evidence of significant improvements[6].

A recent trial of sleep clinics offered by specialists' advice to parents over the phone and in one to one sessions, based on Behavioural non-medication social prescribing, led to CYP gaining an extra 2.4 h sleep per night, significant improvement in their mental state, time taken to get to sleep falling by more than half, and improved QoL and wellbeing of the parents and carers (NHS England, 2019). The RCT of melatonin in children with NDD and impaired sleep (MENDS) study showed that about 40% of the initial cohort of CYP with NDD did not need to proceed to randomization for melatonin treatment as they responded to one-month parent-led behavioural sleep hygiene strategies[50].

Parent-training and psychoeducation

Psychoeducation is considered a fundamental part of managing sleep problems/disorders in children and adolescents and can contribute towards better understanding of their condition, self-management strategies, partnership working, and improved compliance, resulting in positive outcomes. [Table 4](#) below illustrates some useful resources for parents and adolescents.

Good sleep hygiene

Sleep hygiene involves proven practical strategies that parents and adolescents can implement to attain more optimal sleeping patterns. These include modifiable daytime, bedtime, and night-time practices such as diet, exercises and sleeping environment[42]. There is insufficient data to support sleep hygiene strategies as an evidence-based, stand-alone treatment[9]. Parents can also use reward charts, objects of reference such as applying parents pyjamas or perfume on teddy bear, pink or white noise (or music), night or daytime indicators such as Glo-clock or side lamps[10]. Box 1 shows tips for effective sleep hygiene in [Supplementary Material](#).

Neurofeedback to improve sleep onset insomnia

Some authors have suggested that that Sensory-Motor Rhythm and Slow-Cortical Potential neurofeedback may have positive effect on the normalization of sleep onset insomnia, especially in children with ADHD[51].

Pharmacological treatments

Many hypnotics are widely prescribed for the management of paediatric insomnia, mostly as off-label prescriptions, with limited research evidence to determine the efficacy and safety of their use in the

medium and long term basis (Table 5)[37].

Antihistamines (alimemazine, promethazine, diphenhydramine, hydroxyzine): Antihistamine agents, including hydroxyzine or diphenhydramine, represent the most widely prescribed sedatives in the paediatric population, despite the lack of research evidence to back up their use. There is a risk of paradoxical reaction with some antihistamines. A single, small RCT of diphenhydramine reported small effect size efficacy in sleep outcomes (8-10 min improvement in sleep latency and duration) after a 1 wk trial[52].

Clonidine: Clonidine is a central alpha2-adrenergic receptor agonist, with a half-life of 6-24 h. The mechanism of its sedative effect is unclear but it has been a favorite agent employed in the treatment of sleep disorders among children with NDD despite little evidence in literature regarding its efficacy[10]. Clonidine, melatonin and L-theanine showed some improvements in SOL and TST for children with ADHD, while zolpidem, eszopiclone and guanfacine did not reveal any improvement when compared with placebo[37].

Limited evidence supports the use of alpha-agonists such as clonidine to improve SOL, especially in ADHD subjects. In a United States National survey, alpha agonists were the most commonly prescribed insomnia medication for children with ADHD (81%)[29].

Z-drugs: Only few studies have been carried out in CYP regarding use of zolpidem, zaleplon, and eszopiclone, with contrasting results[42]. In a recent study, children taking eszopiclone or zolpidem experienced more frequent undesirable effects compared with melatonin or placebo[52].

Benzodiazepines like clonazepam and flurazepam: Benzodiazepines are not recommended for routine management of sleep disorders in children but may have a place for treatment of transient insomnia, especially if associated with daytime anxiety[42]. Clonazepam may be used for severe parasomnia/night terrors with specialist advice from a tertiary sleep centre[10].

Tricyclic antidepressants: Tricyclic antidepressants are frequently used in adults with insomnia but not recommended in children because of their poor safety profile. Trazodone and mirtazapine have potential use in the paediatric population but their wider application require further studies[42]. Trazodone may be considered in children with Angelman syndrome with specialist advice from a tertiary sleep centre[10].

Selective serotonin reuptake inhibitors: Use of selective serotonin reuptake inhibitors such as sertraline may be considered for disabling bedtime anxiety. Benzodiazepines and tricyclic antidepressants are not recommended in children[10].

ALTERNATIVE THERAPIES

Many parents self-manage with a wide range of herbal and other counter formulations for relieving sleep disturbances, including use of Valerian, Lavender, Chamomile and Kava. In the absence of research-based evidence, their use remains largely based on empirical tradition[7].

BRIGHT LIGHT THERAPY

Sleep-onset insomnia associated with late melatonin onset is one of the common causes of chronic sleep disorders in childhood. Studies have shown that melatonin or bright light therapy (BLT) is effective in treating these sleep problems, both decreasing sleep latency and advancing dim-light melatonin onset (effects on sleep onset was stronger for melatonin[53].

Fargason *et al*[54] reported the efficacy of 2-wk trial of 30-min morning 10000-lux BLT commencing 3 h after mid-sleep period among a group of adult ADHD patients. BLT significantly advanced the phase of dim light melatonin onset by 31 min mean time SEM, and mid-sleep time by 57 min, associated with significantly decreased ADHD rating scale total scores ($P = 0.027$ and 0.044) and hyperactive-impulsivity sub-scores ($P = 0.014$ and 0.013) respectively. There was however no evidence of significant effects in TST, sleep efficiency, wake after sleep onset, or proportion of wakefulness during sleep.

MELATONIN

What is melatonin

Melatonin is an endogenous neurohormone produced by the pineal gland, with its secretion being regulated by the hypothalamic suprachiasmatic nucleus, which controls the circadian physiological

rhythms in response to the ambient 24 h light-dark cycle, for example, controlling sleep/wake blood pressure, body temperature and metabolism[39]. The circadian cycle of high levels of melatonin secretion at night and low levels during the day begins in infants at the age of 3 mo. Melatonin helps in maintaining and synchronizing the circadian rhythm through its daily pattern of secretion[39]. Its rate of secretion generally declines after the first 12 mo as the pineal gland remains static in size while the pituitary gland continues to grow with age[55]. Melatonin has a chronobiotic effect, and acts by its circadian phase-shifting effect, but a less established hypnotic and sleep-promoting effect. Melatonin is also reported to have some immunomodulating properties and is not recommended in children with immune and lymphoproliferative disorders, and in those taking immunosuppressants[56].

Circadin (slow-release melatonin) is currently only licensed for patients with primary insomnia aged 55 and over, and its widespread use for the treatment of sleep disorders especially in the paediatric population is practically “off-label”[57]. The European Medicines Agency has recently granted paediatric-use authorisations for a brand of melatonin (Slenyto), which is available in age-appropriate forms as small tablets[58]. Box 2 shows list of licensed melatonin products in [Supplementary Material](#).

Side effects of melatonin treatment are known to be relatively uncommon and mild in nature[59]. While melatonin is generally considered to be safe in the short term, its long-term safety is yet to be extensively researched. There is limited evidence to suggest that exogenous melatonin suppresses the hypothalamic-pituitary-gonadal axis, due to the observation that endogenous levels of melatonin were elevated in 7 male patients with gonadotropin-releasing hormone deficiency. Sudden termination of melatonin treatment might potentially lead to sleep phase shift in the absence of effective behavioural sleep hygiene implementation. CYP with NDEBID managed with melatonin would require regular follow-up by clinicians to re-evaluate insomnia and determine if continuation of melatonin is still necessary[39].

Use of melatonin for paediatric insomnia and NDEBID

A number of studies and review articles have demonstrated the effectiveness of melatonin treatment in children with NDEBID. Studies have documented significantly shorter sleep onset latencies with melatonin treatment, especially in children with autism. Ayyash *et al*[60] reported a cohort of children with NDEBID (including intellectual disability; autism and ADHD) and sleep disturbances, with 69% of them responding to either low or moderate doses of melatonin (2.5-6 mg), with significantly increased total hours of sleep per night, decreased sleep onset delay and decreased number of awakenings (all: $P = 0.001$), identified with the use of sleep diaries. Only 9% of them benefited from any dose above 6 mg.

A recent systematic review and meta-analysis of thirteen randomized controlled trials showed that melatonin significantly improved TST compared with placebo [mean difference (MD) = 48.26 min]. In 11 studies ($n = 581$), SOL improved significantly with melatonin use (MD = -28.97). However, the overall quality of the evidence is limited due to study heterogeneity and inconsistency[61].

Limitations of melatonin effectiveness

There is limited availability of high quality published evidence on the management of sleep disorders among children with NDEBIDs[62]. Despite the widespread use of melatonin for the management of sleep disturbances in children with NDEBIDs, there is limited evidence on effective dosage and lack of documentation on type-specific efficacy on different categories of sleep problems. There is no evidence that extended-release melatonin confers advantage over immediate release. There is convincing evidence that melatonin decreases SOL and increases TST but does not decrease night awakenings. From a systematic review of 19 RCTs, melatonin was shown to significantly improve sleep latency (median 28 min; range: 11-51 min), sleep duration (median 33 min; range: 14-68 min), and wake time after sleep onset (range: 12-43 min), but did not significantly reduce the number of sleep interruptions per night (range: 0-2.7)[52].

Decreased CYP1A2 activity, either genetically determined or from use of certain concomitant medication, can slow down melatonin metabolism, with loss of day-night time variation and loss of effectiveness[63]. Limited studies have shown reduced activities of cytochrome P450 enzyme, CYP1A2 in the liver, with slow metabolization of exogenous melatonin is almost exclusively responsible for the loss of response to treatment. In patients with loss of response to melatonin, a period of melatonin clearance for up to 3 wk and a considerable dose reduction has been advised[64].

The initial MENDS trial was based on a cohort of children who failed to fall asleep within 1 h of lights out or who slept for less than 6 h of continuously[65]. The efficacy of melatonin is likely going to be less significant for children who are able to sleep more than 6 h at night. The overall effectiveness of melatonin compared to placebo was also modest, increasing TST by 22.43 min and reduced SOL by (-37.49 min) using sleep diary or (-45.34 min) by actigraphy. Using a definition of one hour as the minimum clinically worthwhile difference after the intervention, the upper limit of the confidence interval for increased TST did not reach the level of clinical significance. The children fell asleep slightly faster but they gained little additional sleep duration on melatonin. Overall behaviour rating and family functioning outcomes showed no significant improvement[50]. It is also worth considering some potential and reported side effects associated with melatonin use. There are some areas of uncertainties including long-term effects on puberty development and immune system[66].

Melatonin 1 mg/mL oral solution (Colonis Pharma Ltd) contains propylene glycol excipients which may be potentially problematic when used in children[3]. These are generally safe for children above the age of 5 to 6 years, unless they are requiring very high doses[58].

COMBINED TREATMENT MODALITIES

Only limited studies have assessed the efficacy combining behavioural and pharmacological therapies. The combination of controlled-release melatonin over 12 wk and four sessions of cognitive-behavioural therapy among a group of ASD children aged 4-10 years, revealed a better efficacy compared to other treatment modalities, fewer participant dropouts and higher rate of clinically significant response to treatment[67].

A similar small Canadian study among 27 ADHD children reported the effect size of the combined sleep hygiene and melatonin intervention was 1.7 after 90 d of treatment, compared to 0.6 on average for either sleep hygiene or melatonin alone. However, the decreased sleep latency and improved sleep had no demonstrable effect on ADHD symptoms[68].

CONCLUSION

Sleep difficulties and sleep disorders are more prevalent in children and adolescents with NDEBID. They can result in a significant impact on the child's cognitive development, behaviour, physical and mental health. This can also affect peer and family relationships.

It is important for clinicians to evaluate for sleep disorders when assessing children and adolescents with cognitive, behavioural, and emotional problems. Assessment can include screening tools such as BEARS questionnaire, Child Sleep Habit Questionnaire, a 2-wk sleep diary and relevant physical examination in order to identify sleep schedule and duration and any underlying potential sleep disorders. Parents/carers should be provided with sleep/psychoeducation. Sleep hygiene measures and also specific behavioural interventions where appropriate should be offered as first line management for sleep disorders such as behavioural insomnia and certain parasomnias. Management of DSPS involves a combination of strategies including, chronotherapy, light therapy and melatonin. In children and adolescents with NDD and insomnia, use of melatonin should be carefully considered only following an unsuccessful trial of sleep hygiene and behavioural measures and emphasis should remain on continuing the appropriate sleep hygiene measures. Referrals should be made to appropriate specialist/sleep centre for further evaluation and management of sleep disorders, including OSA, PLMD and narcolepsy.

FOOTNOTES

Author contributions: Ogundele MO conceived the idea, performed the literature review and prepared part of the manuscript; Yemula C reviewed the literature and prepared rest of the manuscript.

Conflict-of-interest statement: The authors declare no conflict of interest for this article.

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S-Editor: Wang JJ

L-Editor: A

P-Editor: Wang JJ

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