Treating Sleep Disturbances in Children with Developmental Disorders

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Abstract

The treatment of sleep disturbances in children with developmental disorders requires a stepwise approach to understanding the nature of the sleep disturbance, the unique characteristics of underlying neurodevelopmental disorder (NDD), and familial and environmental factors that contribute to the child's disordered sleep. The aim of this chapter is to provide the reader with an understanding of the types of sleep disturbances associated with some of the most common neurodevelopmental disorders, as well as best practices for evaluation and treatment. The chapter presents autism spectrum disorders (ASDs) in depth and briefly examines sleep disorders that occur in children with other NDDs (many of which often overlap with ASD). This chapter highlights the ways that common mental health and medical comorbidities associated with ASDs and NDDs contribute to disordered sleep. The text provides an overview of evidence-based practices for evaluating and treating sleep disturbances in this population of children and reviews the pharmacological approaches that can be considered when nonpharmacological interventions fail. Finally, the authors provide clinical pearls gleaned from decades of combined experience in working with children with concomitant neurodevelopmental and sleep disorders.

Keywords

Sleep disorder · Epilepsy · Autism · Insomnia · Attention-deficit/hyperactivity disorder · Melatonin

Introduction

Difficulties with sleep onset and maintenance are experienced by 33% of toddlers and preschoolers and up to 80% of children with autism spectrum disorder (ASD) (Gail Williams et al., 2004) These challenges negatively affect the child as well as family members. Children with poor-quality sleep may display increased aggressive behaviors, anxiety, and developmental regression. The nature of these sleep difficulties varies across developmental stages. Typically, younger children may have sleep anxiety, bedtime resistance, difficulties with falling asleep in their own beds, nighttime awakenings, and early morning awakenings. Adolescents may exhibit poor sleep

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hygiene, anxiety related to sleep difficulties, circadian rhythm difficulties (generally delayed sleep phase), and daytime sleepiness (Goldman et al., 2012).

The vulnerability of patients with ASD to sleep difficulties is not surprising. Children with ASD often have difficulties with emotional regulation and anxiety, contributing to difficulties with initiating sleep and returning to sleep after nocturnal awakenings. These children may rely on certain stimuli (e.g., rocking) to fall asleep and return to sleep. Bedtime refusal behaviors may also be pronounced. Due to comorbid conditions such as anxiety and obsessive compulsive disorder (OCD), children with autism may take selective serotonin reuptake inhibitors (SSRI), which are known to affect the rapid eye movement (REM) stage of sleep. In some cases, treatment with SSRIs induces aggressive and violent motor dream enactment (Kotagal & Broomall, 2012). These alterations in the quality and quantity of sleep often lead to insufficient sleep and daytime sleepiness.

One challenge in the diagnosis and management of sleep issues in this population is the differentiation of night wakings associated with ASD from those associated with behavioral insomnia of childhood. Because of the complexity of these issues, the sleep specialist is a valuable member of the medical home team, with additional specialty training beyond that offered in residency and the capacity to translate recent advances in the field of sleep medicine into practice and clinical results. In this chapter, four sleep specialists review sleep disturbances that are common among children with ASD, with a focus on night wakings.

Sleep Disturbances in Children with ASD

In children with ASD, it may be difficult to differentiate night wakings from the behavioral insomnia of childhood. As defined by the International Classification of Sleep Disorders, third edition (ICSD -3), which is the official textbook of the American Academy of Sleep Medicine (AASM), insomnia in young children is "often the result of inappropriate sleep associations or inadequate limit setting" (p. 24). Specifically, if a child is dependent on a specific stimulus, such as being held or nursing, to initiate sleep, then sleep onset may be significantly delayed in the absence of said stimulus. In the case of limit-setting issues, stalling at bedtime or "bedtime refusal" occurs when a parent or caregiver has few or no limits that are inconsistently or unpredictably applied. Poorly set limits can lead to prolonged nocturnal awakenings.

The sleep problems observed in children with ASD are diverse in presentation and severity. Some studies note that particular subpopulations of children with ASD may be more prone to sleep problems than others. Giannotti et al. found that children with regressive ASD show significantly longer sleep latency, more difficulties with sleep maintenance, and more sleep disorders than children with nonregressive ASD (Giannotti et al., 2011). Others have found links between ASD symptom severity and sleep problems (Cortesi et al., 2010; Mayes & Calhoun, 2009; Polimeni et al., 2005). In a similar vein, ASD symptom severity and sleep problems may have a bidirectional relationship (Adams et al., 2014). Others suggest that sleep difficulties in children with ASD occur independently of ASD symptom severity (Gunes et al., 2019). Other studies speculate that ASD symptom severity may have a *negative* relationship with sleep problems, as children with Asperger disorder (i.e., less severe symptoms of ASD) had more severe sleep disturbance than children with ASD (Polimeni et al., 2005). To serve the patient best, the clinician should evaluate each child independently of such assumptions and explore ASD symptom severity in addition to other mental health factors.

Which features of ASD contribute most powerfully to difficulties with sleep? Sleep onset difficulties may especially be increased by hypersensitivity, particularly at bedtime, when lights are dim and sensitivity to touch and sound is heightened (Mazurek & Petroski, 2015; Tzischinsky et al., 2018). As children are in a supine position for sleep, their skin comes into increased contact with bedtime materials, such as

blankets and bedtime clothing, exacerbating issues with sleep onset in a child with hypersensitivity to touch (Tzischinsky et al., 2018).

Children with ASD are also at higher risk of developing comorbid mental health disorders than typically developing counterparts (Simonoff et al., 2008; Smalley et al., 2007). Researchers have reported particularly high rates of anxiety and depression in those with ASD (Joshi et al., 2010). These mental health issues are commonly associated with sleep problems (American Psychiatric Association, 2013; Giannotti et al., 2011). It can be difficult to parse out which facet of a child's psychosocial profile is affecting sleep the most: concomitant mental health symptoms, parenting issues/behavioral mismanagement of the child's sleep patterns and routines, or challenges related to ASD itself. An awareness of common mental health symptoms that present in children with ASD may help the clinician to navigate treatment. It is therefore important to consider as many psychosocial factors as possible when assessing sleep problems in a child with ASD. The following sections detail some of the more common mental health symptoms related to ASD as well as issues common to ASD that may affect sleep.

Sleep Disturbances in Children with Internalizing Disorders

Studies consistently show that children with ASD are at increased risk for internalizing disorders, which include mood disorders, anxiety disorders, and trauma and stress-related disorders (Simonoff et al., 2008). Internalizing disorders are associated with sleep problems in children with ASD (Reynolds et al., 2017; Thomas et al., 2015) The following sections examine specific internalizing disorders and how they impact sleep in children with ASD.

Anxiety

Several studies also show that children with ASD tend to have higher levels of anxiety than typically developing children, and anxiety is related to poor sleep in children with ASD (Hollway et al., 2013; Mazurek & Petroski, 2015). Individuals with anxiety disorders often experience prolonged sleep onset latency (American Psychiatric Association, 2013). For children with ASD, nighttime can be a particularly anxiety-provoking part of daily living. At night, children have little to distract them from their thoughts as they lay in bed, which may lead to rumination on anxious thoughts and subsequent difficulty with sleep onset or maintenance. Fear of the dark, an upcoming test, or an impending new routine/experience the following day are all examples of things that might cause anxiety for a child. These fears and worries may be exacerbated in a child with ASD who tends to perseverate on their thoughts, particularly if the child's source of anxiety and rigid/repetitive interests converge (e.g., an adolescent with ASD who has an intense interest in his train collection and is anxious about a younger cousin coming to visit the following day who will want to play with his trains). The combination of anxiety and ASD in children seems to have a particularly strong influence on sleep.

Mood Disorders

Studies consistently link mood disorders and sleep problems in children with ASD (Malow et al., 2006; Richdale et al., 2014) For example, children with ASD who exhibit good sleep patterns display fewer mood issues than do those with poor sleep (Malow et al., 2006; Richdale et al., 2014). Adolescents with ASD have significantly depressed mood and increased pre-sleep arousal, compared to typically developing adolescents (Richdale et al., 2014). In major depressive disorder, insomnia or hypersomnia is listed as one of the nine primary symptoms (American Psychiatric Association, 2013). From a psychopathology perspective, sleep and mood disorders may have a reciprocal relationship (Dahl, 1995). Some suggest that, in children, sleep problems are more closely associated with depression than with anxiety (Gregory et al., 2006). Others suggest that the association between sleep problems and depression strengthens as children reach adolescence (Gregory & O'Connor, 2002).

Children with ASD who have mood disorders may have difficulty with sleep onset due to rumi-

nation about various stressors in their lives. It has been the observation of this writer that children with ASD often tend to present with comorbid anxiety at an earlier age, and as they develop into adolescence, the longstanding nature of their anxiety and lack of relief from chronic worry dampens their mood, leading often to depression. Moreover, this writer has observed that as children with ASD develop into adolescence, they become more cognizant of their social skills deficits and (oftentimes) resulting lack of peer relationships, further contributing to mood difficulties (MGM).

Sleep Disturbances in Children with Externalizing Disorders

Externalizing disorders involve difficulties with self-control and behavioral regulation, such as attention-deficit/hyperactivity disorder (ADHD) and/or delinquent and aggressive behaviors (Mayes & Calhoun, 2009; Smalley et al., 2007). The impact of externalizing problems on sleep can be profound, particularly during times of day that are close to sleep onset.

Attention-Deficit Hyperactivity Disorder

ADHD, which is defined by the *Diagnostic and Statistical Manual of Mental Disorders* (DSM–5) as "a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development" (American Psychiatric Association, 2013, p. 59), is observed in 75% of children with ASD (Devnani & Hegde, 2015; Mayes & Calhoun, 2009; Smalley et al., 2007). Although sleep problems are not directly listed as a symptom of ADHD, difficulties with regulation can make bedtime routines and sleep onset difficult. Children who struggle with poor working memory may often find it difficult to adhere to the steps involved in a bedtime routine such as taking a bath, changing clothes, and brushing teeth. Moreover, children with ADHD may become easily distracted during bedtime routines, resulting in delayed sleep and decreased total sleep time. Hyperactivity may also play a part at bedtime as children with ADHD may struggle to regulate their bodies and lay still to bring on asleep (Sung et al., 2008). Executive function difficulties appear to persist across the trajectory of development for individuals with ASD (Demetriou et al., 2018).

Insufficient sleep in children with ASD may be the primary reason behind inattention and difficulty with regulation (Cremone-Caira et al., 2019; Gunes et al., 2019). One possible mechanism by which ADHD impacts sleep in children with ASD may involve co-occurring internalizing problems (Jensen et al., 1997) As previously noted, children with ASD are at increased risk for internalizing disorders such as anxiety and depression (Simonoff et al., 2008).

Although the relationship between multiple mental health disorders, sleep, and ASD in children is complex, it does appear that there is a cumulative effect of psychiatric symptoms on sleep problems in children with ASD (Chen et al., 2015).

Night Wakings in ASD and Developmental Disabilities (DD)

Roughly 65% of parents of children with ASD report sleep problems, including insomnia, difficulty falling asleep, bedtime resistance, prolonged night wakings, and short sleep duration. Children with ASD often have prolonged night wakings (1–3 hours), with a return to sleep in the early morning hours. These night wakings are strongly associated with problematic daytime behaviors, presenting a challenge when the child has to wake up for daily activities at a scheduled time.

As early as 1999, Diomedi et al. reported an increased number of arousals in children with ASD, compared to their typically developing controls. The most common tools used to evaluate night wakings include polysomnography, sleep diaries, and parental questionnaires. The evaluation of a child with autism and NDD should, at the minimum, include parental inquiries about the nature and duration of any night wakings. Parents typically report a prolonged night waking of multiple hours, during which time it is very difficult to have the child reinitiate

sleep. The Childhood Sleep Habits Questionnaire (CSHQ) is one of the most widely used pediatric sleep questionnaires (Owens et al., 2000). It has two questions about night wakings: "Does your child wake up once during the night?" and "Does your child wake up multiple times throughout the night?" The questionnaire does not ask about the duration of each night waking. A study by Honomichl et al. evaluated 100 children with pervasive developmental disorder using the CSHQ and sleep diaries (Honomichl et al., 2002). The results revealed more night wakings in younger children, compared with older children. However, Malow et al. (2009) showed that the Family Inventory of Sleep Habits was significantly correlated with the CSHQ for night wakings for typically developing children but not in children with ASD.

Data from parental reports may not always match that obtained through diagnostic evaluation. In 2008, Sitnick et al. found that actigraphy had poor sensitivity for the detection of night wakings compared to concurrent polysomnography with video in looking at preschoolers with ASD, preschoolers with developmental delay but not ASD, and neuro-typical controls (Sitnick et al., 2008). The effects of these night wakings can be significant including negative effects on behavior, severity of autism, inattention, irritability, and effects on the family (Mazurek & Sohl, 2016). In 2014, Taylor et al. (2012) demonstrated a significant negative effect of night wakings on communication. This work fits with the findings of Kheirouri et al. that night wakings are correlated with ASD severity (Kheirouri et al., 2016). Mazurek & Sohl, (2016) showed that night wakings are significantly associated with physical aggression.

Another challenge in the identification of night wakings is that they may occur as part of other sleep disturbance. Parents may not think to differentiate them from difficulties with sleep initiation or early morning wakings. The high rate of chronic sleep disturbance in children with ASD may compel parents to stop differentiating the nature of the sleep disturbances, because they feel that these sleep issues are "normal" for their child. Parents with this mindset are even less likely to raise these issues during a routine healthcare visit, unless specifically questioned.

Disruptive and Aggressive Behaviors

Hyperactivity and aggression are particularly strong predictors of sleep difficulties in children with ASD (Mayes & Calhoun, 2009; Thomas et al., 2015) Children with ASD who have a tendency toward aggression may likely exhibit that aggression at bedtime, causing difficulties during the bedtime routine. While bedtime can often be a point of contention between typically developing children and their caregivers, children with ASD who become aggressive at bedtime have increased risk of sleep issues. Malhi et al. found that parent-reported daytime behavior difficulties were associated with more sleep problems in children with ASD and that children with ASD exhibited more bedtime resistance compared with typically developing children (Malhi et al., 2019). Children with ASD are also reported to have more variability in hours slept and less total sleep time, compared to typically developing children (Malhi et al., 2019).

Comorbid Conditions

The assessment of sleep disturbance in children with ASD or other DD includes identifying comorbid conditions that may make the child more prone to sleep disturbance. Common co-occurring medical conditions that impact sleep include gastrointestinal disorders (nighttime pain or discomfort from constipation and/or gastroesophageal reflux disease (GERD)), sleep apnea, epilepsy, asthma, and concomitant neuropsychiatric disorders such as anxiety and depression (Stores, 2014). In addition, medications used to treat co-occurring disorders, such as attention deficit disorders (ADD), seizure disorders, and psychiatric disorders, often have side effects that disrupt sleep (Coleman et al., 2019; Williams Buckley et al., 2019).

Respiratory Conditions

In the pediatric population, estimates for obstructive sleep apnea (OSA) range from 1% to 4%, but these may even be underestimated due to trends in pediatric obesity and the limited availability of pediatric sleep medicine providers and access to accredited pediatric sleep diagnostic centers (Bixler et al., 2009; Lumeng & Chervin, 2007). Typical symptoms include snoring, frequent nocturnal awakenings, restless sleep, witnessed apneas, and a preference for sleeping in a prone position with the mouth open and/or the neck hyperextended. Typical daytime sequelae include hyperactivity, difficulty with attention and focus, irritability, and excessive daytime sleepiness. Children may also complain of headaches. Diagnosis requires an overnight polysomnography study. In the case of adenotonsillar hypertrophy, evaluation by an otolaryngologist is recommended. When OSA persists despite surgical intervention or when surgery is not possible, as in the case of obese patients, continuous positive airway pressure (CPAP) is recommended. Although adherence to CPAP can often be challenging in this patient population, a specialized PAP desensitization program can increase the likelihood of PAP tolerance and compliance. This is typically achieved in a multidisciplinary setting with psychologists, child life specialists, and sleep medicine physicians who can closely monitor progress with therapy.

Other respiratory conditions linked to sleep disruption include allergic rhinitis and asthma. Children with allergic rhinitis may snore even in the absence of OSA. The antihistamine medications used to treat allergic rhinitis have known sedative side effects that may lead to daytime somnolence. Children with asthma may have nocturnal symptoms including cough, wheezing, and shortness of breath, which can lead to difficulties with sleep maintenance.

Vision Impairment

Children that have vision impairment, particularly those who are blind, often experience non–24-hour sleep–wake rhythm disorder, a type of circadian rhythm disturbance. Because daily retinal light exposure is necessary to synchronize circadian rhythms with the external 24-hour solar environment, vision disturbances often impair light entrainment of the body's internal pacemaker, the suprachiasmatic nucleus in the anterior hypothalamus. Affected individuals experience cyclical or periodic episodes of poor sleep and daytime dysfunction, which may severely interfere with social life and school. Strategies for management include behavioral modification and the use of melatonin or tasimelteon, a melatonin receptor 1 and 2 agonist (Quera Salva et al., 2017).

Epilepsy

Thirty percent of children with ASD have epilepsy (Trickett et al., 2018). Seizures and interictal discharges, the pathological brain activity observed between seizures, are often activated during sleep; some types of epilepsies occur only at night. Frequent nocturnal seizures and/or interictal discharges will interrupt sleep and lead to daytime sleepiness. In 33% of children with medically intractable epilepsy, OSA exacerbates seizure burden (St. Louis, 2011). The effective management of OSA provides therapeutic benefit comparable to that of adding another antiepileptic medication for seizure treatment. One study found a 50% reduction in the frequency of seizures in 50–60% of patients whose OSA was managed effectively (Maris et al., 2016). Recognizing and treating co-existent sleep disorders in children with epilepsy may improve seizure burden and quality of life. Primary sleep disorders may even mimic epilepsy; for example, parasomnias manifest similarly to nocturnal seizures. By using video electroencephalography (EEG) in combination with polysomnography to localize seizures and to identify the sleep stages affected most severely, clinicians may be able to differentiate parasomnias from seizures. The prevalence of periodic limb movement disorder is noted to be as high as 47% in children with autism, compared to 8% in neuro-typical con-

trols. Periodic limb movement disorder was also associated with decreased serum ferritin levels (Youssef et al., 2013). These nocturnal movements not only cause sleep fragmentation but also make it increasingly difficult for parents to identify seizure-like activity that is separate from sleep-related limb movement.

Sleep deprivation is a known trigger for seizures. Some children with nocturnal seizures may experience sleep anxiety if seizures occur at night, which can lead to an overall decreased quality of life for the parent as well as the child. The parent plagued with worry that their child may have a seizure at night is likely to have difficulty sleeping. Such parents may allow a co-sleeping arrangement, which can significantly decrease the quality and quantity of the parent's sleep and negatively impact a marriage (Larson, 2012).

Down Syndrome

Children with Down syndrome commonly report sleep disturbance, insomnia, excessive daytime sleepiness, parasomnias, and OSA. OSA occurs in more than 50% of children with Down syndrome. In a study by Maris et al. (2016), 66.4% of children with Down syndrome had OSA. This high prevalence was found across age groups. Even in those with a negative history of symptoms suggestive of OSA, the prevalence was 53.8%. Therefore, it is important to screen all children with Down syndrome with polysomnography, irrespective of age or parental reports of symptoms of sleep-disordered breathing. In 2011, the American Academy of Pediatrics began recommending polysomnography studies for all children with Down syndrome by 4 years of age, regardless of symptom history. The high prevalence of OSA in children with Down syndrome is likely due to anatomic factors (macroglossia, adenotonsillar hypertrophy, midface hypoplasia) and comorbid conditions, including obesity, hypothyroidism, hypotonia, and gastroesophageal reflux disease (GERD). Untreated OSA can lead to significant morbidity in patients with Down syndrome. Children with Down syndrome are at increased risk for cardiovascular complications (up to 56% have congenital heart disease), which, in turn, increases risk for pulmonary hypertension, especially in the setting of untreated OSA (Simpson et al., 2018). Children with Down syndrome also exhibit a wide spectrum of neurodevelopmental issues at baseline, including deficits in memory, language, visual perception, and executive function. These cognitive outcomes are often worse in children with comorbid OSA (Simpson et al., 2018).

Craniofacial Abnormalities

Children with certain craniofacial abnormalities are at increased risk for OSA. Airway obstruction may occur at different levels depending on the specific craniofacial abnormality. Children with craniosynostosis syndromes (e.g., Apert syndrome, Crouzon disease, Pfeiffer syndrome, Saethre–Chotzen syndrome) often have abnormalities of the skull base and accompanying maxillary hypoplasia, which can lead to nasopharyngeal obstruction. In children with syndromes that involve micrognathia (e.g., Treacher–Collins syndrome, Pierre Robin syndrome, Goldenhar syndrome), obstruction typically occurs at the hypopharyngeal level (Chan et al., 2004). The surgical management of OSA is typically more complex in this population. The patient should ideally be evaluated by a craniofacial team that includes pediatric specialists from plastic surgery, oral surgery, and otolaryngology.

Gastroesophageal Reflux Disease

The relationship between GERD and sleep disturbance is likely bidirectional. GERD is associated with many sleep disturbances, including decreased sleep duration, difficulty with falling asleep, arousals during sleep, poor sleep quality, and early morning wakings. Sleep deprivation has been found to induce esophageal hyperalgesia to acid perfusion. GERD patients with sleep disturbances report more severe symptoms and poorer quality of life than those without sleep disturbance (Fujiwara et al., 2012)

Neuromuscular Disorders

Children with neuromuscular disorders involving hypotonia are at increased risk for sleep-related breathing disorders such as OSA, hypoventilation, and central sleep apnea (due to diaphragmatic weakness). It is important to note that sleep-disordered breathing may be observed when muscle weakness is still mild and diurnal respiratory dysfunction is not yet apparent. The child may demonstrate other symptoms (excessive daytime sleepiness, insomnia, poor sleep quality, morning headaches, mood disturbance, attention deficit, and learning difficulties). Nocturnal symptoms such as air hunger, intermittent snoring or pauses in breathing, orthopnea, cyanosis, restlessness, and insomnia should prompt further diagnostic studies, including polysomnography. Children with neuromuscular disorders are at higher risk for developing complications of nocturnal hypoxemia, including pulmonary hypertension, cor pulmonale, and neurocognitive dysfunction (Alves et al., 2009). While OSA may be caused by fixed (e.g., adenotonsillar hypertrophy) or dynamic upper airway abnormalities (e.g., pharyngeal wall collapse, laryngomalacia), dynamic abnormalities are more common in children with hypotonia (Goldberg et al., 2005) Children with dynamic abnormalities are less likely to respond to surgical interventions and may require other treatment modalities, such as PAP or assisted ventilation.

Rett Syndrome

Approximately 87% of children with Rett syndrome have sleep problems, including daytime napping, nighttime laughter, teeth grinding, night screaming, and nocturnal seizures (Young et al., 2007). Irregular breathing patterns are observed during the day and at night, when hypoventilation and central and obstructive apnea manifest (Sarber et al., 2019). Polysomnography is a useful tool for evaluation. Typical treatments include adenotonsillectomy and PAP.

Angelman Syndrome

Sleep disturbances are observed in 48–70% of children with Angelman syndrome. Common symptoms include shorter sleep duration, longer sleep onset latency, more frequent nocturnal awakenings with difficulty falling back asleep, early morning waking, limb movements during sleep, sleep-disordered breathing, and daytime somnolence. Approximately 80% of children with Angelman syndrome have seizures, and, as previously discussed, poor sleep can impact seizure burden. Other common health conditions that impact sleep in this population include scoliosis and obesity, as children with Angelman syndrome may have impaired satiety and exhibit behaviors such as taking and storing food. Obesity increases the risk for OSA and the severity of GERD symptoms (Trickett et al., 2018).

Smith–Magenis Syndrome

It is estimated that 100% of children with Smith–Magenis syndrome (SMS) experience sleep disturbances, including decreased total sleep time, night waking, earlier final morning wake times, and inverted circadian rhythm. Seizures affect up to 18% of children with SMS. Other common comorbid health conditions that affect sleep in this population include scoliosis, chronic otitis media, and obesity. Many children with SMS have sleep-disordered breathing, likely related to obesity, but also likely due to midface hypoplasia, which affects over 90% of individuals with SMS. Symptoms indicative of GERD are also associated with sleep-disordered breathing in this population (Trickett et al., 2018).

Tuberous Sclerosis Complex

Approximately 74% of children with tuberous sclerosis complex (TSC) experience sleep disturbances, including decreased total sleep time, difficulties with sleep onset, and nocturnal awak-

enings. Seizures affect up to 70% of children with TSC, and a higher prevalence of night waking has been found in children with TSC who experienced seizures in the last 6 months or who had ≥3 seizures per night (Trickett et al., 2018).

Williams–Beuren Syndrome

Approximately 65% of children with Williams–Beuren syndrome (WBS) exhibit sleep disturbances, including sleep-disordered breathing, bedtime resistance, anxiety, frequent nocturnal awakenings, and daytime sleepiness. These children have lower nocturnal melatonin levels, which can lead to circadian rhythm dysfunction. Daytime sequelae include behavioral issues and memory problems (Santoro et al., 2016).

Prader–Willi Syndrome

Children with Prader–Willi syndrome (PWS) are at risk for OSA and sleep-related alveolar hypoventilation. The clinical features that contribute to these conditions include hypotonia, obesity, scoliosis, restrictive lung disease (and resulting alveolar hypoventilation), narrowed upper airway, facial dysmorphism, abnormalities of central respiratory control, and reduced ventilatory responses to hypoxia and hypercapnia. Central apnea is also frequently reported. Polysomnography should be considered for patients with symptoms suggestive of sleep-disordered breathing. The recommended treatment options include weight loss, adenotonsillectomy, and nocturnal ventilation (Nixon & Brouillette, 2002). Children with PWS often have hypersomnia, as indicated on multiple sleep latency tests (MSLT), and abnormalities in REM sleep (including sleep-onset REM periods, reduced latency to REM sleep, and reduced intervals between REM periods). These effects may be related to hypothalamic dysfunction. The hypothalamus is known to regulate NREM–REM cycling, which has been found to be abnormal in children with PWS (Camfferman et al., 2008).

Neoplasms of the Central Nervous System

Children with neoplasms of the central nervous system (CNS), especially the hypothalamus, thalamus, and brainstem, often have frequent, severe sleep problems. Approximately 80% of children with CNS neoplasms in these brain areas report excessive daytime sleepiness, and 46% have sleep-disordered breathing (Rosen & Brand, 2011). In these children, it is important to consider other comorbid health conditions and treatments, including seizures, adenotonsillar hypertrophy, side effects of medication, obesity, pain, anxiety, and drug use. Treatment may include sleep hygiene, behavioral counseling, PAP therapy, ventilation, sedative hypnotics, antidepressants, and/or stimulants (Rosen & Brand, 2011).

Delayed Sleep Phase

There are also normal variants in sleep behavior as children mature from infancy to adulthood. A common circadian disorder in teens and young adults is adolescent delayed sleep-phase syndrome. Crowley et al. established a "perfect storm" model that describes the multi-factorial nature of adolescent sleep behavior and includes both the circadian changes in adolescent maturation as well as psychosocial and societal pressures (Crowley et al., 2018). These effects are not well known in children with DD, who may be even more influenced by their frequent use of technology for both entertainment and communication.

Sleep disturbance is common among children with ASD or other DD. The nature of the sleep disturbance varies. The presence of a comorbid condition should dictate an individualized approach to assessment and treatment. A comprehensive, multidisciplinary approach to evaluation by pediatric subspecialists is often useful for the patient and their family members, as well as for the care team.

Molecular Basis of Sleep Disturbances in Children with ASD

ASD may cause abnormalities in the hypothalamic–pituitary–adrenal axis, which mediates the production of hormones and neurotransmitters, resulting in dysregulation of the child's circadian rhythm (Devnani & Hegde, 2015). A regular sleep–wake cycle requires a finely tuned balance in levels of serotonin, GABA, and melatonin; impaired levels of any of these hormones or neurotransmitters will directly impact sleep.

Melatonin is needed to maintain and synchronize the circadian rhythm. An enzyme called N-acetyl serotonin O-methyltransferase, which mediates the final step of melatonin synthesis, has impaired activity in children with ASD. Blood and urine samples from this population have low levels of melatonin; low levels of melatonin are associated with difficulty falling asleep and irregular sleep–wake patterns. Treatment with exogenous melatonin has been shown to improve sleep patterns in children with ASD.

GABA is secreted from the preoptic area in the hypothalamus, which regulates the sleep–wake cycle. The migration and maturation of interneurons that release GABA may be affected in autism. A region of genetic susceptibility has been identified on chromosome 15q, which contains GABA-related genes and is commonly implicated in ASD (Goldman et al., 2012).

Polysomnography studies have identified changes in sleep architecture that are common in children with ASD. These include decreased time in bed, decreased total sleep time, decreased quantity of REM sleep, increased latency to sleep onset, increased REM latency, and increased waking after sleep onset. These factors reduce sleep efficiency. Less total sleep time, lower proportion of REM sleep, and increased REM latency have been shown to correlate with increased severity on the childhood autism rating scale (Devnani & Hegde, 2015).

In children with ASD or other DD, sleep disturbance can lead to cognitive impairment, including difficulties with learning, memory, and academic achievement. Sleep disturbance is also associated with behavioral concerns such as increased aggression, irritability, hyperactivity, and social difficulties. The health concerns associated with sleep disturbance in these patients include poor appetite and impaired growth, perhaps caused by decreased secretion of growth hormone, which occurs during non-REM (NREM) stage 3 sleep (Kotagal & Broomall, 2012). When children with ASD or DD have poor sleep, their caregivers are also affected. The effects on caregivers include increased maternal stress, parental sleep disruption, and increased stress levels (Kotagal & Broomall, 2012).

Interventions for the Treatment of Sleep Disturbance

A recent Practice Guideline developed by the American Academy of Neurology (AAN) reviewed the literature for evidence-based treatments for insomnia and disrupted sleep in children and adolescents with ASD. The reviewers differentiated among bedtime resistance, sleep onset latency, sleep continuity (sleep efficiency and night wakings), total sleep time, and daytime behavior (Williams Buckley et al., 2020).

Behavioral management, including parent education and training on sleep hygiene and modification of a child/adolescent's behaviors are the most effective ways to treat sleep disorders in this population. Previous studies have also demonstrated that improving mood with traditional treatment methods such as behavioral activation can decrease sleep onset latency in children with ASD (Brand et al., 2015).

It is incumbent on the treating clinician to explore the presence of concomitant disorders and/or treatment medications for those disorders that may interfere with sleep. With the exception of melatonin, few pharmacologic interventions have been the subjects of high-quality Class I or Class II studies (Malow et al., 2012; Robinson-Shelton & Malow, 2016; Williams Buckley et al., 2019). Before considering pharmacologic treatment for sleep disorders, the following practices should be considered:

1. Assess for and treat medical comorbidities that can interfere with sleep (e.g., H2-blockers or proton pump inhibitors for GERD, CPAP for OSA, drugs for epilepsy).
2. Assess for and manage potential medication-induced insomnia or nighttime activation (certain antidepressants such as SSRIs can cause activation or restless legs; stimulants for ADHD cause prolonged latency).
3. Initiate sleep education program (e.g., sleep toolkit, cognitive behavioral therapy, parent training).

Behavioral Interventions

The simultaneous treatment of multiple comorbid symptoms may improve sleep in children with ASD (McCrae et al., 2020). A recent study by McCrae et al. found that cognitive behavioral therapy for childhood insomnia (CBT-CI) can improve sleep onset latency and decrease irritability, hyperactivity, and lethargy in children with ASD. As CBT-CI can involve relaxation skills and other techniques to improve not only sleep onset but also mood and anxiety, a shotgun approach that addresses both sleep and mental health symptoms may be most beneficial in improving the overall functioning of a child with ASD.

Aerobic exercise has been shown to improve sleep onset latency, efficiency, duration, and inhibitory control in children with ASD (Tse et al., 2019). Though the nature of the relationships between these variables is unknown, one might speculate that improved inhibitory control may facilitate bedtime routines and decrease bedtime resistance. Some sleep issues may require specialist intervention in the form of surgery or use of a CPAP device. To select the optimal approach to treatment, the clinician must understand the contributions of myriad medical, psychiatric, environmental, and social factors. In choosing the best treatment approach, be it educational, behavioral, or pharmacologic, it is critical to identify the type of sleep disturbance being addressed (Stores, 2016).

Many agree that adopting a biopsychosocial framework is best when conceptualizing and assessing mental health disorders, sleep, and ASD (Schreck & Richdale, 2020). Utilizing a biopsychosocial approach will encourage a broad-to-narrow approach, helping the clinician to uncover not only the mental health symptoms that might contribute to sleep problems but also to determine how caregivers and family members may unknowingly sustain sleep problems in their child.

Pharmacological Interventions

In general, evidence for the efficacy of pharmacologic treatment of sleep disorders specifically in children with ASD/DD is slim, often consisting of small randomized controlled trials that were short in duration, open-label trials lacking a control group, or retrospective studies and case series. Nearly all of the treatments to be discussed are off-label uses of approved medications or over-the-counter agents (Brown, 2019; Bruni et al., 2019; Cuomo et al., 2017; Robinson-Shelton & Malow, 2016).

Melatonin and Related Medications

Melatonin (N-actyl-5-methoxytryptamine) is a naturally occurring neurohormone derived from serotonin that is produced in the pineal gland. It is released in response to low light/darkness and plays a critical role in regulating circadian rhythm (Esposito et al., 2020; Kennaway, 2000). It is also noted to be an antioxidant, anti-inflammatory compound that plays a role in early neural development. Previous studies have shown that dysfunctional melatonin synthesis and release may play a role in sleep disorders in children and adolescents with ASD/DD (Kotagal & Broomall, 2012). However, other studies have reported normal levels of melatonin in children with concurrent developmental disabilities and sleep disruption. Several high-quality studies have demonstrated the effectiveness of short-acting and prolonged-release melatonin in treating multiple aspects of sleep disorders, over the short as

well as long term (Coppola et al., 2004; Gringras et al., 2012, 2017). Doses of 0.5–12 mg given 3–60 minutes prior to bedtime have been reported to be effective. Decreases in sleep dysfunction are observed even in children with normal endogenous melatonin production (Goldman et al., 2014; Leu, 2019). While there were initial reports that long-term melatonin use may lead to tolerance, studies out to at least 4 years demonstrate continued effectiveness. Nonetheless, some children and adolescents may no longer experience benefit from melatonin after a period of effectiveness, and increased dosing does not overcome the issue, suggesting that tolerance is not at play in these instances (Andersen et al., 2008; Carr et al., 2007).

Melatonin has been shown to be effective when used alone or in combination with cognitive behavioral therapy (CBT) (Cortesi et al., 2012) Studies have also demonstrated melatonin's effectiveness in treating sleep-onset latency, sleep continuity, and total sleep time, both alone and in combination with CBT (Cortese et al., 2020; Cortesi et al., 2012; Cuomo et al., 2017; Malow et al., 2012; Parker et al., 2019; Williams Buckley et al., 2020; Wirojanan et al., 2009).

Melatonin's effectiveness in improving sleep appears to cross a wide range of DDs, though the effects on various subtypes of sleep dysfunction differ. For instance, while latency, total sleep time, and number of night wakings improved with melatonin in children with Angelman syndrome, ASD, and intellectual disability, the effectiveness of melatonin in Fragile X and tuberous sclerosis is based on improvements in latency and sleep time, but not on decreased night wakings. Moreover, studies evaluating the effectiveness of melatonin in treating sleep dysfunction in Rett syndrome have yielded inconsistent results, with some evidence suggesting positive effects on latency and sleep time (but not wakings) only in subjects with more severe sleep dysfunction at baseline (Leu, 2019; McArthur & Budden, 2008; Wirojanan et al., 2009).

In summary, melatonin is the most studied pharmacologic intervention for children with ASD/DD, with a significant weight of evidence favoring its use across multiple DDs for treating specific aspects of sleep disorders. The AAN practice guideline for Treatment for Insomnia and Disrupted Sleep Behaviors in Children and Adolescents with Autism Spectrum Disorder rates the evidence for melatonin as "probably effective" alone or in combination with CBT for treating most types of sleep disturbances in children with ASD (Williams Buckley et al., 2020).

Melatonin is commercially available in many forms, including liquid, tablet, rapid-dissolve tablets, chewables, and gummies, as well as concentrated liquid. There are several extended or prolonged-release formulations available at different strengths, though most (if not all) appear to require swallowing the dose whole, making them difficult to use in children who cannot swallow tablets. Most experts strongly recommend choosing pharmaceutical-grade melatonin to ensure consistent and reliable formulation, absorption, and purity (Cerezo et al., 2016; Erland & Saxena, 2017)

Randomized controlled trials have shown that the side effects of melatonin are mild. The most commonly reported adverse events are headaches, dizziness, nausea, diarrhea, enuresis, rash, daytime fatigue, and clouded thinking. Though not common, sleep terrors and vivid dreams have also been reported (Leu, 2019). Because melatonin is metabolized by CYP1A2 cytochrome enzymes, dosing adjustments may be necessary for use in conjunction with medications that inhibit this enzyme (e.g., fluvoxamine, mexiletine, cimetidine). Conversely, melatonin can inhibit CYP1A2 and CYP3A enzymes; adjustments may need to be made for concurrently administered medications metabolized by those enzymes (Horn & Hansten, 2007; Leu, 2019).

Ramelteon, a melatonin-1 (MT_1) receptor agonist, was approved for the treatment of prolonged sleep latency in adults. It has six-fold greater affinity for the MT_1 receptor than melatonin (Hatta et al., 2015; Kato et al., 2005). A limited number of case reports have reported its effectiveness in children with ASD (Asano et al., 2014; Hollway & Aman, 2011; Kawabe et al., 2014).

Alpha-2 (α2) Agonists

Clonidine, which is a noradrenergic *α2* agonist indicated for treating hypertension and ADD, is probably the second most widely used medication for treating sleep disorders in children with ASD/NDD. Several studies, mostly open label in nature, have demonstrated moderate effectiveness for reducing latency and night waking (Hollway & Aman, 2011; Ingrassia & Turk, 2005; Ming et al., 2008). Clonidine dosing typically starts at 0.05 mg and can go as high as 0.2–0.3 mg in adolescents with adult habitus. Formulations include oral tablet, weekly transdermal patch, and extended-release oral tablet. Tolerance is occasionally seen. The most frequent adverse events reported by respondents of a national survey of medications used to treat psychiatric and seizure disorders in children and adults who used clonidine included daytime fatigue/drowsiness, aggression/agitation/irritability, behavior problems, anxiety and dizziness, gastrointestinal symptoms, and paradoxical sleep problems (Coleman et al., 2019; Macleod & Keen, 2014).

Guanfacine is another *α2* agonist. Like clonidine, it was approved for treating hypertension and ADD. However, it is less sedating than clonidine and therefore less useful for promoting sleep in children with ASD/DD. In the parent/patient survey of psychiatric medications used in ASD referred to above, the rated benefit was small and far less than that of clonidine for reducing latency and improving sleep maintenance (Coleman et al., 2019). Indeed, other studies in children with ADD and ADD with ASD reported that extended-release guanfacine was found to have no effect or even to decrease total sleep time (Bruni et al., 2019; Politte et al., 2018; Rugino, 2018).

In summary, clonidine may have a moderate effect size in treating sleep disorders by improving sleep-onset latency, sleep continuity, and total sleep time, while decreasing the number of night wakings (Cuomo et al., 2017). The positive effects of these agents should be weighed against the known adverse effects, such as decreased REM-phase sleep. Nonetheless, they may be beneficial in children who do not respond to other behavioral therapies and/or melatonin.

Antipsychotic Medications

Risperidone is one of the two agents approved for the treatment of irritability in children and adolescents with ASD. In one study designed to examine the long-term effects of risperidone in children and adolescents with ASD, investigators noted improvement in sleep-onset latency, but not in sleep duration (Aman et al., 2005; Brown, 2019). However, other studies found a positive effect of risperidone on sleep duration (Cortese et al., 2020; Cuomo et al., 2017). Given the substantial metabolic and endocrinologic adverse events (e.g., weight gain, gynecomastia, dyslipidemia), as well as negative effects on REM sleep and the counterproductive potential to induce restless legs syndrome (and concomitant sleep disturbance), caution should be used in prescribing this medication solely for the purpose of treating sleep dysfunction in children with ASD/DD.

In one small study of adolescents with ASD, quetiapine was reported to be beneficial in improving sleep. The authors noted improvement on the CSHQ when quetiapine was tested in open-label fashion on children with concurrent aggressive behavior and elevated sleep scores (Golubchik et al., 2011). In a national survey ranking parent/patient-reported risk-benefit analyses of psychiatric medications in individuals with ASD, quetiapine was reported to have some benefit in treating sleep, though the risk:benefit ratio was reported as close to even (Coleman et al., 2019).

Antidepressants

Trazodone is an antidepressant (AD) that acts as a serotonin-2a ($5HT_{2a}$) and histamine-1 (H_1) receptor antagonist, and also modulates adrenoreceptor function. It has substantial sedating side effects, even at doses lower than used for their AD activity, a fact that has been capitalized on for use in childhood and adult sleep disorders. Although child psychiatrists frequently use trazodone in treating children and adolescents with

ASD/DD and other neuropsychiatric disorders, there is a paucity of literature supporting its use in children with ASD/DD (Brown, 2019; Hollway & Aman, 2011; Owens et al., 2010).

Similar to trazodone, mirtazapine is a sedating AD that is an H_1 and 5-HT_2 blocker. However, mirtazapine is a tetracyclic AD that also blocks 5-HT_3 and alpha-2 receptors, leading to increased release of norepinephrine and serotonin. It has the effect of reducing latency and increasing sleep duration without affecting REM. A small open-label study in children with ASD/DD showed improved sleep in a subset of children (Brown, 2019; Hollway & Aman, 2011; Owens et al., 2010; Posey et al., 2001). The side effects of both medicines include daytime drowsiness, dizziness, dry mouth, and constipation. Trazodone can also cause vision changes, and, rarely, hypotension, priapism, and cardiac arrhythmias (Brown, 2019; Hollway & Aman, 2011).

GABA Receptor Agonists

Clonazepam, a long-acting GABA receptor agonist, shares some properties with sleep agents approved for the treatment of insomnia in adults (Browne, 1976). Indicated for treating some seizure subtypes as well as panic disorder (in adults), it has been reported to be of some utility in treating children with ASD/DD. It can be particularly useful in children with concurrent seizure disorders and has been of benefit in helping with sleep and seizures in children with Angelman syndrome (Cuomo et al., 2017; Robinson-Shelton & Malow, 2016).

Anti-epileptic Medications

There is some evidence that gabapentin, dosed at 5 mg/kg up to 15 mg/kg at bedtime, may provide benefit for sleep latency and maintenance across several NDDs in children, including ASD, cerebral palsy, and ADHD. The reported side effects include paradoxical worsening of agitated awakening or prolonged sleep-onset latency due to activation in a subset of individuals. Gabapentin may be an especially good choice if co-occurring restless legs syndrome or seizure disorder is suspected in a child with ASD/DD (Accardo & Malow, 2014; Brown, 2019; Reynolds, 2019; Robinson & Malow, 2013).

Other anti-epileptics that have been associated with improvements in sleep latency and sleep efficiency including tiagabine, pregabalin, clobazam, and carbamazepine. (Accardo & Malow, 2014; Brown, 2019; Jain & Glauser, 2014; Reynolds, 2019; Robinson & Malow, 2013) However, it would be difficult to advise the use of these agents outside of a presentation of sleep dysfunction in the setting of epilepsy. Indeed, in the child with ASD/DD and co-occurring epilepsy, the clinician should be mindful of anti-epileptic drugs that may promote sleep rather than having no effect or even interfering (as can be seen with phenobarbital and phenytoin) (Nita & Weiss, 2019).

Cannabis

Barchel showed that cannabidiol may decrease bedtime resistance (Barchel et al., 2018). Administering cannabidiol to children with ASD helped with the child's motivation and ability to communicate with family and caregivers, ultimately decreasing disruptive behavior at night and bedtime resistance (Barchel et al., 2019).

In a review of cannabis in the treatment of ASD, the findings concerning the effects on sleep were inconsistent and mostly based on open-label or retrospective studies. In one study, parents reported improvement in 71% of children in whom sleep problems were present at the outset of the study. However, peer-reviewed studies found no significant improvement compared with "conventional" treatment methods (Barchel et al., 2019). Another study in children from Chile with ASD reported improved sleep after treatment with cannabis (Kuester et al., 2017). In contrast, a retrospective study that reported improvement in anxiety-related symptoms in children with ASD also reported significant side effects of hypervigilance, leading to exacerbated sleep concerns in 14% of children (Aran et al., 2019). The authors of the review confirmed the inconsistency of the effects of cannabis in treating sleep disorders in children with ASD, recognizing a need for more rigorous controlled studies to determine

whether these treatments are of any benefit (Agarwal et al., 2019).

Antihistamines

Once a frequent go-to choice for inducing sleep in children with ASD/DD, studies have demonstrated that diphenhydramine is no better than placebo at improving sleep, despite its sedative effects. With the exception of an older study from 1976, which studied typically developing children and demonstrated improvements in latency and night wakings, there is no support for the use of this agent (Hollway & Aman, 2011; Russo et al., 1976). Hydroxyzine, indicated for anxiety, pruritis, and pre- and post-operative sedation, has also been reported to be a safer alternative for inducing sleep, but its use has not been well studied (Brown, 2019; Bruni et al., 2019).

While pharmacologic treatment may play a role in treating some aspects of sleep disorders in children with ASD/DD, its role should be secondary to parent education, training, and behavioral interventions. With the possible exception of melatonin, pharmacologic treatment should be used as an adjunct when parent training and behavioral interventions do not work, or in the rare instances where there is a need for more rapid temporizing measures to be employed while nonpharmacologic treatments can be optimized. The literature on melatonin is quite substantive, but also stands in stark contrast to the relative paucity of evidence for other pharmacologic options. As previously mentioned, the agents discussed in this section should be used with caution and in a parsimonious manner, based on the presence of other co-occurring conditions that might also benefit from treatment with a given agent.

Clinical Pearls

It is the opinion of this author (MGM) that the effective management of sleep disturbances requires careful attention to comorbid mental health disorders. The optimal approach will require close coordination among members of the medical home team, including a sleep specialist and mental healthcare provider. Healthcare providers with special training in sleep are essential because the average amount of sleep education received by pediatric residents is only 4 hours (Mindell et al., 2013). Despite the limited attention to sleep medicine in the conventional residency curriculum, sleep health plays a critical role in overall health and ongoing physician education and family education are vital.

In this writer's experience, misguided efforts to treat sleep without a proper evaluation and treatment of comorbid mental health symptoms can lead to exacerbation of the sleep problems *and* the mental health issues (MGM). A closely coordinated approach is even more warranted when a patient presents with severe psychiatric symptoms such as suicidal ideation or psychosis (symptoms that were not in the scope of this chapter). Thus, although a patient and family members may have initially presented at our multidisciplinary sleep clinic seeking treatment for sleep issues, we often educate the patient and family about the risks of prematurely addressing sleep problems without proper treatment of comorbid mental health symptoms. At our clinic, the treatment of sleep issues often begins with a referral for mental health care.

When investigating sleep disturbance in a child with DD, it is important to review the entire sleep history to fully characterize the sleep disturbance. Routine surveillance may allow night wakings to be overlooked, so the clinical evaluation should include attention to overall sleep habits, bedtime routine, behavioral sleep associations, and possible medical pathology contributing to sleep disturbance. The approach must encourage good sleep hygiene with consistent sleep and wake times, limited screen time prior to bedtime, limiting daytime naps, and daily physical activity. In 2014, Knight et al. demonstrated the significant effect of a behavioral treatment plan in the treatment of night wakings (Knight & Johnson, 2014). Similar results using bedtime fading and positive routines were reported by Delmere et al. (Delemere & Dounavi, 2018).

The overall sleep needs of the individual child must be considered carefully. A child with ASD/DD may have a different total sleep duration than

their neuro-typical peers. If a child is consistently sleeping and waking at the same time with little to no night wakings and is able to participate in therapies and activities of daily living without somnolence or significant behavioral disturbance, then the total sleep time may be sufficient. Often, we find that parents have an expectation for children with ASD/DD to sleep the same amount as their neurotypical peers, which leads to inappropriate expectations for the child. There are significant demands upon the caregiver of a child with DD, and so they may put children to bed at 7–8 pm while trying to accomplish other work or household tasks – when the child's more physiologic sleep need may be sleeping from 11 pm to 7 am. The issue of misaligned parental expectations is often most notable for adolescent patients, who have a tendency for delayed sleep phase. Reviewing the individual sleep needs of the family and the child can realign the expectations for sleep and decrease parental anxiety.

If sleep hygiene strategies are not successful, sleep aids should be tried. As described above, endogenous melatonin is less effective in children with ASD than their neurotypical peers, and supplemental melatonin can be effective in the treatment of sleep-onset delay and night wakings. Some previous studies have indicated the effectiveness of nontraditional therapies. A 2017 study by Narasingharao et al. showed that a structured yoga intervention was effective in decreasing night wakings (Narasingharao et al., 2017). Despite the existence of few double-blind, placebo-controlled studies, there is significant popular demand for these therapies. Physicians may want to explore the utility of local resources, such as yoga for children and age-appropriate mindfulness training.

Night wakings in children with ASD/DD can have profound effects on patients and caregivers. Future work should focus on the incidence and prevalence of night wakings as well as treatment strategies. Even simple changes to the pediatric residence curriculum may offer significant opportunity to better understand night wakings in this population. This population of patients may have limited expressive language or atypical methods for communicating pain and discomfort.

These children may also have more difficulty than their neuro-typical peers in tolerating the multiple leads and diagnostic equipment required for in-lab polysomnography in addition to common fears associated with hospital- or medical facility-based diagnostics. Children with DD may not tolerate traditional polysomnography. If they are evaluated in a sleep lab used primarily to evaluate adult patients or undergo home testing, they may not be accurately diagnosed because of differences in the scoring systems used for adults vs. children. The 2017 AASM Pediatric Task Force published a position paper stating that home sleep apnea testing is not recommended for the pediatric population and cited references that the recommendation was in part due to a lack of available tests with sufficient sensitivity and specificity.

Another limitation in a typical visit with a child with DD is the number of concerns parents have that need to be addressed during a single visit. There is not always enough time for parents to address all concerns in 30–60 minutes, especially when the child is anxious or exhibiting behavioral issues, or the parent is chronically sleep deprived and managing multiple medical concerns. This highlights the importance of good referral information and preparing the family for the visit and perhaps collecting information with questionnaires ahead of time.

In terms of pharmacological interventions, the adverse event profile for antipsychotic medications should preclude their use solely for the purpose of treating sleep in children with ASD/DD. Assuming a parsimonious approach to medication choice, the practitioner should choose this class of medication to treat sleep if there is a need to target other symptoms susceptible to improvement with the same agent. We have had success with using low-dose quetiapine at night in children and/or adolescents who present with cyclic mood changes, especially when other interventions have been unsuccessful. We have also used it as a bridge while behavioral interventions are employed in cases where sleep disruption of the child has had significant negative effects on the entire family system (JTM).

We use trazodone (starting dose 25 mg, titrating up if needed to 150 mg) in the adolescent when family education and interventional techniques have failed due to uncontrollable environmental or psychosocial barriers and when melatonin, clonidine, and other options have failed. In our experience, there is a tendency to build tolerance with trazodone. Thus, its use as a long-term agent is questionable. As a result, we often ask families to reserve its use for evenings where latency has exceeded a pre-specified duration. Once a normal sleep pattern is established, we attempt to titrate the dose down to discontinuation or the lowest effective dose (JTM).

Conclusion

The relationship among sleep, psychopathology, and ASD in children is complex. One must consider the interplay between ASD and reported mental health symptoms and its effect on sleep (Bartlett et al., 1985; Johnson, 1996; Köse et al., 2017). The clinician is strongly encouraged to screen for mental health symptoms that are common to children with ASD, which may not be at the forefront of the reporting patient or family's concerns.

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