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SLEEP AND SLEEP APNEA AT THE EXTREMES (D GOZAL, SECTION EDITOR)

Updates on Pediatric Sleep Disorders

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Abstract

Purpose of Review Pediatric sleep medicine is a developing field with recent advances in pathophysiology, diagnosis, and/or management of circadian rhythm disorders, obstructive sleep apnea, narcolepsy, and parasomnias. This article aims to provide a review and highlight recent updates in these specific sleep disorders.

Recent Findings Our understanding of circadian rhythms and melatonin profiling is becoming clearer, which opens up new diagnostic possibilities and treatment refinement. In obstructive sleep apnea, symptoms do not clearly correlate with the apnea-hypopnea index, and other sleep measures need to be studied in order to understand how treatments may provide benefit to patients. There has been the first clinical treatment trial in pediatric narcolepsy and promising drugs are on the horizon. While parasomnia treatment has not advanced much, our understanding of its pathophysiology and associated diagnostic features is growing.

Summary Advancements across a number of areas of pediatric sleep medicine offers exciting avenues for more accurate and timely diagnoses and evidence-based management to improve patient care.

Keywords Delayed sleep phase syndrome · Obstructive sleep apnea · Narcolepsy · Parasomnias

Introduction

Sleep needs are greatest in infancy and childhood, and sleep is critical for many processes including learning and memory consolidation [1], immune regulation [2, 3], and metabolic regulation [3]. Roughly 30% of young children are estimated to have significant difficulties with bedtime problems or night wakings [4, 5]. Insufficient sleep is also a widespread problem, with about 25% of adolescents obtaining the recommended 9 h minimum per night and 56–71% of toddler and school-aged children sleeping for their recommended amounts [6, 7]. While certainly insufficient sleep is a critical health issue, this review focuses on 4 specific sleep disorders that are commonly seen in pediatric sleep clinics: circadian rhythm disorders, obstructive sleep apnea, narcolepsy, and NREM parasomnias. These sleep disorders can cause nocturnal sleep disruption with disrupted or insufficient sleep, daytime functioning difficulties, and secondary health risks [3, 8, 9]. Here, we aim to help readers identify, diagnose, and treat these pediatric sleep disorders; be informed about relevant research updates; and recognize continued gaps in the field.

This article is part of the Topical Collection on *Sleep and Sleep Apnea at the Extremes*

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Circadian Rhythm Disorders

Circadian rhythm sleep-wake disorders are defined by a misalignment between the body's internal near-24-h biological rhythm and the required timing of school, work, or social activities [10]. There are different forms of the disorder, including delayed sleep-wake phase disorder (DSPS), advanced sleep-wake phase disorder, and shift work disorder to name a few. In clinical pediatric practice, DSPS is most frequently encountered and will serve as our focus.

Delayed Sleep Phase Syndrome

Delayed sleep-wake phase disorder is when the phase of the major sleep episode is delayed in relation to the desired or required sleep time and wake-up time [10]. This causes delays

in bedtimes and subsequent wake times and can impair the ability to fulfill social expectations (namely wake for school).

Epidemiology

Epidemiology can be hard to estimate due to underreporting and different definitions used. Accounting for both delayed and advanced sleep-wake phase syndrome, prevalence estimates range from 1.5 to 8.9% in adults in a recent survey [11]. A study assessing Swedish adolescents and young adults found a 4.6% prevalence of evening chronotype and 4% prevalence of delayed sleep phase disorder [12].

Pathophysiology and Risk Factors

Current theories of sleep involve the sleep homeostatic drive (process S) and the circadian pacemaker (process C) [13]. There is growing evidence that these two processes are intertwined with respect to timing of sleep in normal individuals [13]. Light stimuli are used as one method of entraining the circadian pacemaker located in the suprachiasmatic nucleus (SCN) of the hypothalamus, but other inputs like activity level and timing of meals are likely also important [13]. In general, sleep occurs when the sleep homeostatic drive is high and the circadian alerting system is low with time-courses influenced by physiological and behavioral variables.

Circadian rhythms change with age. Multiple studies have shown that later sleep onset and delayed dim-light melatonin onset (DLMO) (a marker of circadian phase) occur with puberty [14–16]. Post-pubertal children accumulate sleep pressure at a slower rate than pre-pubertal children [17•, 18]. Despite these changes, sleep homeostatic drive remains stable through adolescence when measured with build-up and dissipation of slow-wave activity during sleep [17•, 19]. Optimal sleep duration for health among children aged 13–18 years is 8–10 h per night based on the American Academy of Sleep Medicine Guidelines [20]. Yet based on population data, adolescents self-report getting over 7 h of sleep about 60% of the time at 13 years of age and only 32% of the time at 18 years of age, and these durations have been decreasing over time [21]. Part of this reduction in sleep duration can be attributed to delayed sleep phase disorder and early school timings. Current school times do not allow adolescents to "sleep in," thus curtailing sleep duration. Technology and societal pressures to stay awake also contribute. A recent study in adults under laboratory conditions found exposure to a light-emitting tablet caused increased sleep latency, suppression of melatonin release, and delays in circadian phase [22•]. Exposure to LED lights while comparing the effects of blue-light blocking glasses to clear glasses leads to a statistically significant increase in sleepiness and decreased objective vigilance testing but did not alter sleep characteristics or melatonin onset time [17•, 23]. This at least suggests that avoiding light at night may mitigate alerting effects, even if the effect on melatonin rise is not fully clear.

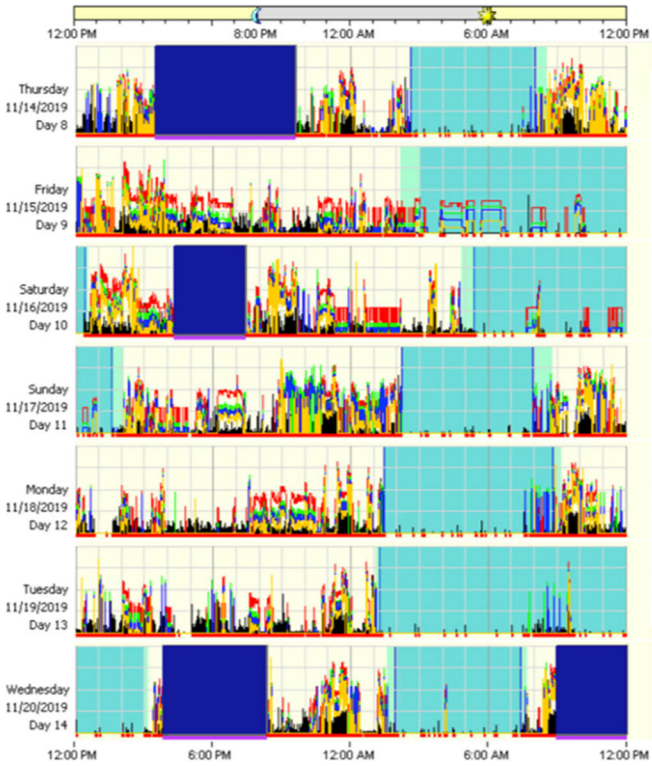
Presentation and Diagnosis

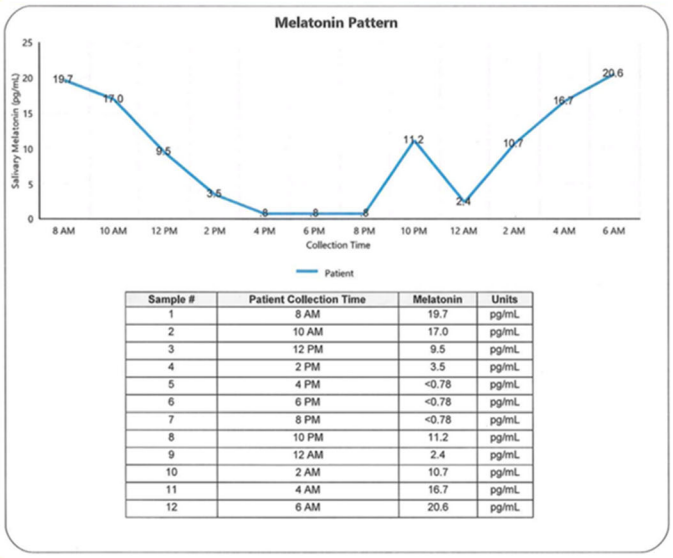
Patients with delayed sleep phase typically report difficulties in initiating sleep and/or with waking in the morning. This is often mistaken for insomnia, and clinical criteria for insomnia are met in over 50% of individuals on one survey of adolescents [24]. In our experience, patients will only complain about these symptoms when they result in school tardiness or interferes with alertness during school/social activities. Typically, patients will report sleep inertia upon awakening and daytime fatigue and/or sleepiness that is worse in the morning and dissipates by the afternoon. A key feature of the disorder is improvement of symptoms when the desired sleep schedule is followed such as during summers or school vacations.

Diagnosis relies on taking a careful sleep history, including distinguishing the weekday and weekend schedule. Days without responsibilities often reveal the true biologic preference. Questionnaires may be useful but are less used in the clinical environment. Sleep logs and actigraphy (see Fig. 1) are helpful in that they offer a way of objectifying data [25]. Melatonin profiling (see Fig. 1) from multiple salivary samples is used in research settings and starting to gain popularity in clinical settings. The goal is to identify the dim-light melatonin onset (DLMO), which typically occurs 1–3 h prior to the biologic bedtime [26]. Measuring this in individuals with suspected circadian rhythm disorders or irregular sleep patterns offers a more reliable way to identify the onset of biologic night [27]. Currently, DLMO testing has not been FDA approved for clinical use. Polysomnography studies are not required for diagnosis.

Treatment

Addressing delayed sleep phase disorder is often multifactorial. Patients should optimize behavioral changes to improve sleep hygiene, including avoiding electronics in the 1–2 h prior to bedtime, keeping sleep onset and wake times similar on all days, and avoiding caffeine or exercise close to bedtime [25]. Bright light stimuli are also important for treatment and for phase advancement; a 10,000 lx light box upon waking (ideally after the core body temperature minimum, which occurs about 2 h before the typical preferred wake time) is recommended. The patient is asked to gradually wake earlier each morning by about 15–30 min and thus advancing use of the light box till they get to the desired wake and sleep onset time. In our experience, it is better for patients to phase advance in this fashion during a vacation period when they can get unconstrained sleep and advance their wake time in a gradual fashion (i.e., wake 30 min earlier each morning).





Sample #	Patient Collection Time	Melatonin	Units
1	8 AM	19.7	pg/mL
2	10 AM	17.0	pg/mL
3	12 PM	9.5	pg/mL
4	2 PM	3.5	pg/mL
5	4 PM	<0.78	pg/mL
6	6 PM	<0.78	pg/mL
7	8 PM	<0.78	pg/mL
8	10 PM	11.2	pg/mL
9	12 AM	2.4	pg/mL
10	2 AM	10.7	pg/mL
11	4 AM	16.7	pg/mL
12	6 AM	20.6	pg/mL

Fig. 1 In the actigraphy result figure, the sleep zone is represented by the light blue shading (dark blue is time that the unit was removed from the wrist). **a** demonstrates a delayed sleep/wake phase. The typical bedtime is constant around 2–3 a.m. Wake times appear only on most days around 8:00 a.m. due to social commitments to school. On weekends and occasional weekdays, there is a dramatically later wake time of approximately 1–2 p.m. **b** is a 12-sample melatonin profiling plot. DLMO is assigned at 3–4 pg/ml during the phase of consistent rise. The sample demonstrated DLMO after midnight, indicating preferred bedtime of likely 2–3 a.m. and remains elevated until 2 p.m.

Melatonin at chronobiotic doses of 0.02 to 0.3 mg nightly have been shown to advance the circadian phase in adults [28]. This should be given in relation to the DLMO, as 5 h prior to the DLMO produces the maximal phase advancement [27]. Since DLMO is often unknown, clinically, we will typically recommend administering 2–3 h prior to the desired bedtime. Practitioners should be aware that a 2017 study of 31 over-the-counter melatonin supplements found that these products have widely differing amounts of melatonin compared to what is listed on the label and have other additives including serotonin (noted in 26% of samples) [29]. Also, melatonin is not FDA approved for children but is generally considered safe for short-term use. Like light therapy, the timing of melatonin use can be advanced as needed until the desired bedtime is reached. Once the desired sleep/wake times are achieved, maintaining the sleep schedule everyday with light therapy is recommended.

Later school start times in high schools have been promoted to accommodate the common occurrence of delayed sleep phase in adolescents, and it has been shown to increase mean sleep duration, bringing adolescents closer to recommended sleep amounts [30]. A recent Cochrane review of delayed school start times showed an increase in sleep duration and trend towards improved alertness and school performance but recommended caution in interpretation due to the absence of randomized controlled trials and risk of bias in current data [31••].

Sleep-Disordered Breathing

The term sleep-disordered breathing covers a range of potential disorders, including primary snoring, upper airway resistance syndrome, obstructive hypoventilation, obstructive sleep apnea, and even centrally mediated respiratory disorder [3]. For the purposes of this review, we will focus on obstructive sleep apnea.

Obstructive Sleep Apnea

In pediatric patients, there must be symptoms of snoring, obstructed breathing (potentially accompanied by paradoxical or labored breathing), and associated symptoms of sleepiness, hyperactivity, behavioral problems, or learning problems with polysomnography demonstrating at least one or more obstructive events per hour of sleep [10]. Obstructive events are characterized by either hypopneas (partial obstruction with restricted airflow) or apneas (complete obstruction).

Epidemiology

Obstructive sleep apnea occurs in 1–5% of the pediatric population [3, 32]. Primary snoring occurs in 10% or greater of pediatric patients [3]. There are a number of anatomic and physiologic risks that increase the incidence of obstructive sleep apnea, which will be covered below.

Pathophysiology and Risk Factors

OSA is primarily a disorder of limited airflow through the upper airway. This can be due to underlying reasons that relate to the risk and rate of airway collapse during sleep episodes. Any factor that limits the effective airspace or relaxes the musculature of the airway will tend to increase the appearance of obstructive sleep apnea.

In healthy children, enlarged tonsillar and adenoidal tissue is the most common cause of OSA [3]. In otherwise healthy children with suspected sleep-disordered breathing, 15.5% had a posterior crossbite, and significant retrognathia (overjet > 7 mm) was reported in 4.8% of patients which had indicated need for maxillary expansion and mandibular advancement respectively [33]. Inflammatory disorders (such as asthma and allergies) can also contribute to the emergence of obstructive sleep apnea [3] likely because they cause tonsillar and adenoidal tissue to enlarge by inflammatory mechanisms. A study of individuals born with Pierre-Robin sequence, which limits upper airway space, found an AHI greater than 1 event/h in over 80% of its sample [34]. Other genetic syndromes associated with hypotonia, like Prader Willi syndrome and Trisomy 21, have prevalence estimates of 80% and 31–63% respectively [35, 36]. Children with epilepsy also appear to be at increased risk, with OSA prevalence in treatment-resistant epilepsy reaching 30% [37, 38]. Approximately 19–61% of obese children and adolescents also have a diagnosis of OSA based on a recent review [39]. The presence of obesity may also indicate treatment challenges: 35% of obese children vs. 5% of non-obese children aged 7–13 years old with sleep-disordered breathing had residual OSA (as defined by AHI > 3/h) after tonsillectomy and adenoidectomy and the prevalence increases to 79% vs. 27% respectively at 1-year follow-up [40].

Presentation and Diagnosis

Many physicians know to look for the classic signs of snoring, gasping arousals, observed apneas, or increased work of breathing at night in screening for OSA. Odd sleeping positions and snoring can be found in up to 74% of children with OSA [41]. These measures are helpful, but did not distinguish OSA patients from those with primary snoring [41]. Data from the TuCASA study suggested that even occasional snoring had only a 50% sensitivity with regard to obstructive sleep apnea [42]. Excessive daytime sleepiness is often reported in adults with sleep-disordered breathing (SDB) but is only seen in 23–28% of children with SDB [41, 43]. Attention deficit hyperactivity disorder symptoms are related to sleep-disordered breathing with a medium effect size, and sleep-disordered breathing is found in up to 50% of children with ADHD [44]. Nocturnal enuresis has also been found to occur more often in children with symptoms of sleep-disordered breathing [45]. Thus, we recommend practitioners screening for OSA to obtain broad history from patients and parents that includes presence and severity of snoring and gasping at night, witnessed apneas, sleep position, feelings about sleep quality, daytime sleepiness, and daytime executive functioning and behavioral concerns.

There are a number of pediatric sleep questionnaires that assess for symptoms of sleep-disordered breathing but should be used with an understanding of the questionnaire's goals and limitations of clinical symptoms [46]. Physical exam is important to assess for obesity, hypotonia, or tonsillar hypertrophy, which may accompany sleep-disordered breathing but should not be used as the sole contributor to a decision.

The gold standard of diagnosis remains the overnight in-lab polysomnography study. This helps quantify the number of obstructive events by American Academy of Sleep Medicine scoring criteria. An AHI of at least 1/h or pattern of obstructive hypoventilation is required for diagnosis [10]. In general, most sleep centers use the cutoffs of AHI < 1/h to be considered a normal study, 1–5/h as mild OSA, 5–10 as moderate OSA, and > 10 as severe OSA [3].

Cognitive Consequences of OSA

There is no consensus about the cognitive effects of OSA in children. A recent systematic review by da Silva Gusmao Cardoso et al. found conflicting evidence across studies on associations between OSA and memory, attention, or executive function, but children with OSA did have lower, but still average, scores on other measures of cognitive and intellectual function [47•]. Severe OSA in children 7–11 years has been shown to be associated with significant reductions in regional gray matter volume including superior frontal and prefrontal and superior and lateral parietal cortices [48]. Perhaps surprising, these regional brain changes did not correlate with the severity of respiratory disturbance during sleep and there was no association with cognitive ability.

This lack of association OSA severity and cognitive function was more recently highlighted in secondary analysis of the Childhood Adenotosillectomy Trial (CHAT) study. CHAT was a randomized controlled trial of early adenotonsillectomy in children with OSA. The CHAT study did not find an association between OSA and cognitive outcomes over 6 months; however, children assigned to adenotonsillectomy showed greater improvements in

behavior, daytime sleepiness, and sleep symptoms and larger improvements on the Connor's Rating Scale (measure of restlessness, impulsivity, and emotional lability) compared to the watchful waiting group [49]. However, in secondary analysis, researchers found that the majority of improvements in daytime behaviors found in treated participants were not mediated or predicted by AHI [50]. Plausibly, the cognitive measures used to determine OSA effects are insensitive to associations with AHI and/or additional measures of sleep such as sleep spindles need to be studied. For example, children 5–7 years of age with mild OSA showed a 18.7% decline in memory consolidation (memory retention across a period of time) compared to controls and their deficits were mediated by deficits in a sleep spindle measure (NREM stage 2 sigma power) [1].

Treatment

The first-line treatment is adenotonsillectomy in uncomplicated OSA according to clinical guidelines issued by the American Academy of Pediatrics [51] The CHAT trial in 5–9-year-old children [49] showed that 79% of participants randomized to early adenotonsillectomy had resolution of OSA, but 46% of participants in the watchful waiting group also had normal AHI over the 7-month study period [49]. Thus, for OSA patients > 5 years who were not black, not obese, and had a baseline AHI less than 4.7 (factors associated with normalization of PSG), watchful waiting could be considered an appropriate management strategy [49]. Close follow-up is recommended in this group to ensure no worsening of OSA.

OSA can recur, and data has shown an increase in AHI years out from adenotonsillectomy even in the absence of obesity [52]. Other procedures are being investigated, and a recent randomized controlled trial of tonsillotomy versus tonsillectomy showed non-inferiority, although it should be noted some individuals in the tonsillotomy group needed a repeat surgery and was limited by a 1-year follow-up period [53]. In patients with residual OSA after adenotonsillectomy, who are not candidates for surgery, or do not respond to surgery, continuous positive airway pressure (CPAP) is recommended [51]. CPAP has shown to significantly reduce AHI but is limited by concerns over midface development with long-term use and adherence to therapy [54, 55]. There are a number of medical therapies that show promise in select individuals, including nasal steroids and leukotriene inhibitors [56]. Rapid maxillary expansion and oral appliances may also play a role in children with the appropriate dental or oropharyngeal structure, although dental appliances are less studied in pediatric patients [57, 58]. In addition, many of these studies focus on PSG improvement, which may not necessarily correlate as well with improvement of symptoms of sleep-disordered breathing.

Treatment advances are rapidly moving forward. Drug-induced sleep endoscopy (DISE) or cine MRI studies are now being employed in select centers to identify the actual level of obstruction and help plan surgical interventions [59, 60•]. DISE has been used to identify surgical targets when there is no significant tonsillar hypertrophy and has even identified the tonsils at the site of obstruction in 45% of a sample in one such study [59]. Aside from the tonsils, a systematic review found that both DISE and cine MRI identify the level of the tongue as the next most common obstructive site amenable to surgical procedures [61]. DISE has even been used prior to any surgical intervention and was found to change treatment targets in up to a third of cases, including with non-surgical approaches [62•]. Although many studies focus on healthy children, this also offers hope for underlying genetic conditions that may be more associated with multilevel obstructions.

In Trisomy 21, a novel therapy called hypoglossal nerve stimulators have shown reductions in AHI to the mild range [63]. Hypoglossal nerve stimulators are implantable devices that stimulate the tongue to draw it forward during sleep to maintain airway patency. Risks are similar to other surgeries as there is a risk of wound site infection and pain, but out of a 20 participant group studied, two also required surgical exploration for mechanical difficulties with the device [63]. Although AHI was not normalized, this gives a promising therapy to investigate, especially in populations that have significant OSA but are not surgical candidates or have difficulty tolerating CPAP.

Narcolepsy

Narcolepsy is considered a disorder of hypersomnolence (increased sleepiness) and has been subdivided into type 1 and type 2. Narcolepsy type 1 is defined by daily periods of irrepressible need to sleep or daytime lapses into sleep for more than 3 months, in addition to cataplexy and a diagnostic polysomnogram with multiple sleep latency testing or deficient hypocretin on CSF testing [10]. Narcolepsy type 2 can be diagnosed in the same manner, but cataplexy is absent and hypocretin levels are usually normal or mildly low [10].

Epidemiology

Narcolepsy is relatively rare, with estimates of prevalence varying from 5 to 50 per 100,000 people [64, 65]; however, there is wide variability in populations with regard to risk factors and methods of assessing the frequency of diagnoses. Diagnostic delays are common and nearly double in the pediatric population, and narcolepsy is frequently mislabeled as another condition such as epilepsy, mood disorder, or attention deficit disorder before a final diagnosis is reached [66, 67].

Pathophysiology and Risk Factors

Narcolepsy type 1 is defined by a loss of hypocretin (otherwise known as orexin) neurons, which are located in the lateral hypothalamus [68]. Narcolepsy type 1 is likely of autoimmune origin as nearly 90–95% of NT1 patients are positive for the HLA DQB1*06:02 haplotype [69], and symptom onset has been reported after outbreaks of streptococcal infections [70] and H1N1 flu outbreaks [71]. The exact process of autoimmune destruction is still unknown. Recent studies have identified CD4+ T-cells and cytotoxic CD8+ T-cells in adults and children with narcolepsy that target fragments of the hypocretin peptides [72–74]. These T-cells also cross-react with influenza antigens, suggesting that molecular mimicry may underlie the attack on the hypocretin-producing neurons [75].

Hypocretin itself regulates sleep/wake stability and REM sleep [68]. Loss of these neurons leads to difficulty sustaining wakefulness as well as nocturnal sleep fragmentation, which occurs more frequently with lower hypocretin levels [76]. Due to REM sleep dysregulation (a sleep stage characterized by dream imagery and muscle atonia), patients experience sleep paralysis, hypnagogic hallucinations, hypnopompic hallucinations (typically visual imagery upon awakening from sleep), and cataplexy. The etiology of narcolepsy type 2 is not known. Narcolepsy type 2 may exist as an entity on a spectrum between narcolepsy type 1 and idiopathic hypersomnia.

Presentation

The cardinal feature of narcolepsy is severe daytime sleepiness, which should prompt further investigation when a patient does not endorse insufficient sleep or other sleep disorder symptoms. Cataplexy manifests as episodes of abrupt and transient decreases in skeletal muscle tone, most frequently elicited by strong emotions such as laughter, anger, and surprise [77]. The severity and extent of cataplexy attacks can vary from a state of complete cataplexy, which involves all voluntary muscles, to partial cataplexy with limited involvement of certain muscle groups or no more than a fleeting sensation of weakness. In children and rarely in adults, atypical cataplexy can occur without emotional triggers, usually in the first 6 months after symptom onset. This form of cataplexy is characterized by persistent, generalized hypotonia, usually with an unsteady gait and "cataplectic facies" (slack jaw, tongue protrusion, and ptosis) [78]. Positive motor movements similar to dyskinesias (i.e., tongue thrusting, chewing movements with the mouth) can also co-occur with atypical cataplexy in pediatric narcolepsy patients [78]. Misdiagnosis of cataplexy as epilepsy, tremor, or tics is common in the initial evaluation process [78].

The frequency of other core narcolepsy symptoms—sleep paralysis, hypnagogic hallucination, and hypnopompic hallucinations—can be more variable in pediatric narcolepsy patients and may occur only sporadically. Patients describe sleep paralysis as feeling awake but paralyzed, unable to move the limbs, to speak, or even to breathe deeply upon waking from sleep. Vivid and often unpleasant auditory, visual, or tactile hallucinations can occur at sleep onset (hypnagogic) or upon awakening (hypnopompic), during daytime naps or at night [79]. Other common symptoms and signs reported by patients with narcolepsy include vivid, highly realistic dreams [80]; REM behavior disorder (characterized as pantomime behaviors [81]); periodic limb movements of sleep; and frequent nocturnal wakings [82].

Diagnosis

Narcolepsy typically presents in adolescence, but diagnosis is typically made 3–10 years from symptom onset [67]. The presence of cataplexy at onset typically leads to a quicker diagnosis as it is a more recognizable symptom. There are a few validated questionnaires to assess the severity of excessive daytime sleepiness, including the Epworth Sleepiness Scale for Children and Adolescents, Pediatric Daytime Sleepiness Scale, and the Cleveland Adolescent Sleepiness Questionnaire [43, 83, 84]. A careful and detailed neurologic examination will help to rule out any secondary causes of narcolepsy.

With increasing types of testing available, the next steps may depend on the clinical scenario. The International Classification of Sleep Disorders (ICSD) version 3 [10] recommends PSG followed by multiple sleep latency test (MSLT) to establish the diagnosis of narcolepsy. The specified diagnostic criteria include a mean sleep latency of ≤ 8 min on MSLT and the presence of ≥ 2 sleep-onset REM periods (SOREMP defined as within 15 min of sleep onset) on the PSG and MSLT studies [10]. A recent study validated these adult criteria in pediatric narcolepsy type 1, but found the same diagnostic accuracy when considering just 2 SOREMPs across PSG and MSLT or a mean sleep latency of less than 8.2 min on the MSLT [85••]. The reliability of the PSG MSLT diagnostic criteria is poor at 18–47% in adult patients with narcolepsy type 2 [86•, 87], but it is unknown if this is a problem in the pediatric population. Ordering providers should be aware that antidepressants, stimulants, atypical anti-psychotic agents, clonidine, and guanfacine can suppress REM sleep and thus cause false negative testing [88]. Practice guideline recommends weaning these drugs 2 weeks prior to PSG-MSLT testing [89]. Alternatively, the ICSD 3 allows diagnosis of narcolepsy type 1 by CSF hypocretin testing and analysis is now available in the USA through Mayo labs (available at https://www.mayocliniclabs.com/test-catalog/Clinical+and+Interpretive/604230). In our practice, we generally

Table 1 Pharmacologic treatments for pediatric narcolepsy

Drug	Symptom targeted	Mechanism of action	Dosing	Major side effects	Special notes
Traditional stimulants (methylphenidate and dextroamphetamine salts)	EDS	Dopamine and norepinephrine transporter blockade	Refer to specific formulation dosing. Max dosing 60 mg/day	Headaches, appetite loss, hypertension, tachycardia, agitation, worsened behavior	Have addiction potential Potentially associated with risk of psychosis [93] FDA approved.
Modafinil	EDS	Dopamine transporter blockade	50–400 mg/day	Headaches, appetite loss, hypertension, tachycardia, agitation/irritability, worsened behavior, decreased oral contraceptive efficacy	Case reports of Stevens-Johnson syndrome reported Pediatric narcolepsy experience suggests good safety profile [94]
Armodafinil	EDS	Dopamine transporter blockade	50–150 mg/day	Headaches, appetite loss, hypertension, tachycardia, agitation/irritability, worsened behavior, decreased oral contraceptive efficacy	Risk of Stevens-Johnson syndrome reported
SSRIs	Cataplexy	Selective serotonin reuptake inhibitor	Refer to specific formulation dosing	Weight gain, GI disturbance, sleep disruption, dry mouth, dizziness	Black box warning for increased suicidality for adolescents Modest improvement in mean wakefulness testing [88]
SNRIs	Cataplexy	Serotonin and norepinephrine reuptake inhibitor	Refer to specific formulation dosing	GI disturbance, sleep disturbance, dizziness	Black box warning for increased suicidality for adolescents Modest improvement in mean wakefulness testing [88]
Atomoxetine	Cataplexy	Norepinephrine reuptake inhibitor	Children less than 70 kg: 0.5 mg/kg/day to a maximum of 1.4 mg/kg/day. 70 kg and over 40–100 mg/day	Headaches, sleep disturbance, hypertension, irritability, dizziness	
Tricyclic antidepressants	Cataplexy	Likely inhibition of norepinephrine and serotonin reuptake	Refer to specific formulation dosing	Dizziness, sedation, anticholinergic effects, cardiac dysrhythmias	Clomipramine used most often clinically
Sodium oxybate	EDS and cataplexy	Unknown	20–30 kg: 2–6 g/night 30–45 kg: 3–7.5 g/night >45 kg: 4.5–9 g/night [95••]	Enuresis, nausea, vomiting, headache, appetite loss, dizziness	2 patients had serious adverse effects (severe psychosis and suicidal ideation) out of 104 participants taking the study drug [95••] Safety data still consistent with adult data FDA approved

Table 1 (continued)

Drug	Symptom targeted	Mechanism of action	Dosing	Major side effects	Special notes
Pitolisant	EDS and cataplexy	Histamine inverse agonist	8.9–35.6 mg daily	Headache, nausea	Recently FDA approved for adults with narcolepsy [96] Pediatric narcolepsy clinical trial in progress
Solriamfetol	EDS	Selective dopamine and norepinephrine reuptake inhibitor	75–150 mg daily	Headache, nausea, decreased appetite, dry mouth, anxiety	Recently FDA approved for adults with narcolepsy No pediatric data. [97]

This table shows commonly used medications and new medications for symptom management in narcolepsy. Of note, only traditional stimulants and sodium oxybate are FDA approved for use in children with narcolepsy. Dosing is not well-established, and in general, clinicians should start at lower doses and titrate to effectiveness

utilize CSF hypocretin testing when a patient is positive for the HLA DQB1*06:02 haplotype and cannot be weaned off potential REM suppressing medications, reports atypical cataplexy, or PSG/MSLT testing was inconclusive in a patient with cataplexy symptoms.

Co-morbidities

There are a number of conditions that have an increased rate of occurrence in individuals with narcolepsy, although the link is not well understood. Mood disorders (depression, anxiety, obsessive compulsive disorder) have been reported in up to 25% of pediatric narcolepsy patients, and attention deficit hyperactivity disorder–like symptoms occur in 20–35% of narcolepsy patients [90]. Overweight status and obesity are common, affecting 25–74% of narcolepsy patients, and weight gain can be rapid in younger children at the onset of narcolepsy [91]. Precocious puberty occurs in 17% of pediatric narcolepsy patients and develops independent of obesity [91]. Other co-morbid conditions including thyroid disease, hypertension, hyperlipidemia, obstructive sleep apnea, and autonomic dysfunction have been reported among narcolepsy patients [92].

Treatment

Treatment focuses on managing the most bothersome symptoms of patients, which are typically excessive daytime sleepiness and cataplexy. Sleep hygiene ensuring an age-appropriate amount of nocturnal sleep and 1–2 daytime naps lasting 10–30 min is important for overall disease management. Students with narcolepsy benefit greatly from school accommodations permitting naps in quiet environment, movement breaks in lectures, and "stop the clock" breaks during long testing periods to mitigate daytime sleepiness and optimize academic performance. Daytime sleepiness can sometimes be managed behaviorally with naps alone, but most individuals will also require medication therapy. Refer to Table 1 for a summary of commonly used and potentially upcoming medicines in pediatric narcolepsy. Most notably, the first pediatric narcolepsy randomized controlled study was conducted with sodium oxybate for children aged 7–17 years and showed significant improvements in cataplexy frequency and daytime sleepiness [95••]. However, there were rare but serious adverse effects reported including depression, central sleep apnea, and suicidal ideation.

NREM Parasomnias

As defined by the *International Classification of Sleep Disorders, Third Edition*, parasomnias are undesirable physical events or experiences that occur during entry into sleep, within sleep, or during arousal from sleep [10]. NREM

Table 2 Overview of parasomnias and treatment

Parasomnia	Sleep stage	Description	Diagnosis	Treatment
Confusional arousal	N3	Incomplete awakening with inappropriate or absent responsiveness to intervention; limited dream imagery	Clinical history	Reassurance and education Avoid waking or intervening Scheduled awakening could be considered but our clinical experience suggests this just delays emergence of events until later in the night [98, 99].
Sleepwalking	N3	Apparent mental confusion or confused behavior in bed with an absence of autonomic arousal or terror when ambulating	Clinical history If seizure (such as nocturnal wandering) is suspected, EEG may be helpful	Ensure safety of home environment (gate off stairs, window locks, etc.) Reassurance and educations Avoid waking or intervening In severe cases, clonazepam may be considered
Sleep terrors	N3	Abrupt terror, alarm, or screaming associated with autonomic arousal and signs of fear	Clinical history	Reassurance and education Avoid waking or intervening other than to ensure safety
REM sleep behavior disorder	REM	Vocalization and/or complex motor behaviors during REM sleep, with evidence of REM without atonia	Clinical history Polysomnography necessary to demonstrate REM without atonia	Evaluate for narcolepsy if presenting in childhood Melatonin or clonazepam effective in adult patients. [100] Case reports of improvement with sodium oxybate [101]
Sleep paralysis	REM	Inability to move the trunk and limbs upon awakening or at sleep onset lasting seconds to minute, usually causing significant distress	Clinical history; often associated with sleep deprivation	Correct underlying sleep disorder Reassurance and education
Nightmare disorder	REM	Repeated occurrences of well-remembered dreams typically scary or involving threat to the person with rapid orientation upon awakening and distress due to the dreams	Clinical history; best studied as it relates to post-traumatic stress disorder	Imagery rehearsal therapy Prazosin/clonidine used in adults but unstudied in children Clinical trial in veterans with PTSD showed no benefit of prazosin [102]

This table provides an overview of parasomnias. N3 sleep represents NREM sleep, stage 3, commonly known as slow-wave sleep. NREM parasomnias may arise from other stages of NREM, but are most common in N3

parasomnias range from sleepwalking, which is relatively benign, to episodes of night terrors that can include disruptive screaming and escape-like behaviors. Further descriptions are given in Table 2, along with a review of some REM parasomnias.

Epidemiology

Prevalence of NREM parasomnias is difficult due to many different types of sleep behavior. For more traditional parasomnias, such as sleepwalking, night terrors, and confusional arousals, lifetime prevalence ranges from 5 to 18% [103, 104]. Most of these events occur during childhood.

Pathophysiology and Risk Factors

NREM-related parasomnias typically arise from slow-wave sleep [105] and thus typically occur in the first 1/3 of the night when slow-wave sleep is most concentrated. Parasomnias are thought of as a problem with sleep-state dissociation, such that wake and different stages of sleep "blend" together [10]. Factors that increase cortical arousals or sleep inertia appear to lead to an increase in the emergence of NREM-parasomnia behavior [105, 106]. Cyclical alternating pattern (CAP) is a marker of intrinsic oscillation of subcortical and cortical arousal in sleep, and etiologies that increase this pattern (neuropsychiatric diseases, sleep-disordered breathing, and external environmental factors) also increase the frequency of parasomnia behaviors [105, 106].

Presentation, Diagnosis, and Treatment

The mainstay is a careful history to delineate length of events, characteristics, and timing of events, which may be all that is needed to make a clinical diagnosis. PSG or EEG monitoring may be helpful to distinguish sleep states and rule out concern for seizure activity. Markers on polysomnography are also being researched, as they may eventually aid in diagnosis. Slow-wave sleep fragmentation index is defined as the amount of slow-wave sleep interruptions in 1 h, and values above 6.8/h were associated with a specificity of 82% and sensitivity of 79% for disorders of arousal [107•]. Likewise, an EEG pattern of slow/mixed arousal frequencies in slow-wave sleep were also found to be predictive of disorders of arousal [107•]. Please refer to Table 2 for further details on characteristics of parasomnias and potential treatments.

Conclusion

This review provided an update on research in selected areas of pediatric sleep medicine. The understanding of circadian rhythm disorders is rapidly advancing, and this offers exciting potential avenues for further treatment. The gap is how to feasibly obtain accurate circadian measures such as melatonin profiling to obtain personalized treatments. There is a greater understanding that the apnea/hypopnea index for obstructive sleep apnea does not tell the whole story with regard to symptoms, and further work will need to be done to identify reliable biomarkers of symptoms and response to treatment. Treatment options for pediatric narcolepsy are improving, but diagnosis of this condition still greatly lags from symptom onset. Our understanding of parasomnias and their pathophysiology has been evolving but mysteries remain regarding utility of testing and optimal treatment strategies for children. Pediatric sleep medicine is an advancing field but continued research is needed to address these gaps.

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Compliance with Ethical Standards

Conflict of Interest Dr. Maski reports grants from Jazz Pharmaceuticals and consulting honorarium from Harmony Biosciences, Uptodate, and Medscape outside the submitted work. Jazz Pharmaceuticals and Harmony Biosciences make drugs for narcolepsy and the article covers updates in narcolepsy treatments.

Dr. August has nothing to disclose.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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