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Current Treatment of Selected Pediatric Sleep Disorders

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Abstract While pediatric sleep disorders are relatively common, treatments are often not straightforward. There is often a paucity of gold standard studies and data available to guide clinicians, treatments may yield arguably incomplete results, interventions may require chronic use, and/ or involve multiple modalities including behavioral interventions that require high parental and family commitment. This review points out diagnostic differences compared to adults and focuses on current therapy for selected common pediatric sleep disorders including sleep disordered breathing/ obstructive sleep apnea, narcolepsy, and restless legs syndrome. Other common pediatric sleep disorders, such as insomnia and parasomnias, are not covered.

Keywords Pediatric · Sleep disorder · Treatment · Narcolepsy · Restless legs syndrome · Sleep disordered breathing

Introduction

Many have heard the true if somewhat tired phrase in medicine, "children are not simply small adults." This is certainly true in the field of pediatric sleep disorders. While pediatric sleep disorders are relatively common, treatments are often not straightforward. There is often a paucity of gold standard studies and data available to guide clinicians, treatments may yield arguably incomplete results, interventions may require chronic use and/ or multiple modalities including behavioral interventions that require high parental and family commitment. That pediatric sleep disorders have somewhat different incidences and/or criteria for diagnosis compared to their adult analogues is an often overlooked point. In terms of treatment, it has been said that use of pharmacotherapeutic interventions to address pediatric sleep disorders is synonymous with the term "off label". With an emphasis on recent developments, this review will cover therapies for three common pediatric sleep disorders, including obstructive sleep apnea, narcolepsy, and restless legs syndrome. Since these topics are covered elsewhere in this issue, the focus will be on aspects unique to pediatrics.

Sleep Disordered Breathing

The term "sleep-disordered breathing" describes the clinical spectrum which includes snoring, upper airway resistance syndrome (UARS) and obstructive hypopnea syndrome. It can occur at any age, but like many sleep disorders, features in childhood may not mirror those seen in adulthood. The criteria for diagnosing OSA in children differ from the criteria used in adults, and clinical and research pediatric definitions may also vary. For example, according to the International Classification of Sleep Disorders-2, OSA is diagnosed in children with one or more scoreable respiratory events per hour (generally an Apnea Hypopnea Index, or AHI, ≥ 1), as compared to adults, in whom the cut-off for OSA is AHI≥5 [1]. Other definitions employed clinically and/or in research for pediatric OSA include AHI>1.5, Obstructive Apnea Index, or OAI, > 1, and others, depending on the study [2, 3]. This may lead to confusion and decreased generalizability of pediatric research results. Additionally, the definition itself of abnormal respiratory

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events is different in children compared to adults, including duration (at least 2 respiratory cycles) [1, 4] and hypopnea definition [4] with differences in both degree of desaturation and airflow reduction relative to the AASM Recommended adult hypopnea definition.

Just as there are definition differences between adults and pediatric sleep apnea, available treatments and response to treatments are variable in children. Defining the outcomes of importance in evaluating treatments in children with OSA is itself worth considering. Studies have identified and reported post-therapy AHI and/or oxygen saturation and other respiratory measures, sleep EEG analysis such as sleep stages, spindles, arousals, and spectral analysis, various neurocognitive and/or behavioral measures, parental and teacher report of improvement or satisfaction, academic performance, and more recently serologic markers [5–8] such as C- Reactive Protein, and other physiological tests [7, 9] as evidence of treatment effect. Interestingly, these outcomes do not necessarily show symmetry at baseline or in response to intervention ; for example, in children treated by adenotonsillectomy, hyperactivity, inattention, cognitive function, and other neurobehavioral morbidities all tended to be improved a year after treatment, but little correlation has been seen between some of these variables and polysomnographic measures before or after surgery, though esophageal pressure monitoring as a more sensitive measure of breathing abnormalities may offer some promise in this regard [10, 11].

That said, adenotonsillectomy is probably among the most common treatments used to treat SDB in children. Over 500,000 adenotonsillectomies are performed yearly in the U.S., with obstructive sleep apnea being a leading indication [12]. Recently released American Academy of Pediatrics guidelines for management of pediatric OSA recommend adenotonsillectomy as the first-line treatment of OSA in pediatric patients with adenotonsillar hypertrophy [13]. While adenotonsillectomy is typically considered first-line therapy for pediatric obstructive sleep apnea, it may not be completely successful, with residual OSA reported in 20 to 72 % children [14–17]. In a recent multicenter retrospective review of all sleep studies performed pre- and post-operatively, adenotonsillectomy resulted in a significant AHI reduction (from 18.2± 21.4 to 4.1±6.4, $p<0.001$), consistent with the notion that adenotonsillectomy is beneficial, though not necessarily completely curative [16]. Not enough is known about subject selection, how much and which individual features that may modify outcomes. Gold standard data in prospective trials has been limited. It has been argued that some improvements seen with adenotonsillectomy may be due to unrelated factors such as regression to the mean, growth, or other confounding variables [18]. Some studies have indicated that obesity is associated with poorer response to surgery, with residual OSA occurring in the majority of obese children [19, 20]. While typically an uneventful procedure, potential for complications of adenotonsillectomy, reported from 4-38 % in those with severe OSA [21], should be considered in the context of potential benefit.

Another understudied area is the overall longitudinal course of pediatric OSA into adulthood, whether treated or untreated, and duration of effectiveness of adenotonsillectomy. Growth velocity has been shown to predict recurrence of OSA one year after adenotonsillectomy in children aged 7-13 years, raising concern that the disease may recur as adolescence approaches in treated pre/ peri -pubertal children [22]. Another cohort study of neuropsychological and behavioral functioning at baseline and one year after adenotonsillectomy in 5 to 12 year olds with OSA and in healthy controls also showed no improvement or declines in some cognitive parameters at one year, despite improvements in PSG, sleepiness, and parental report of behavior [23].

Results from additional large enough studies prospectively and rigorously evaluating the impact of adenotonsillectomy are needed. Smaller or uncontrolled studies suggest that adenotonsillectomy may improve OSA-related deficits in attention, memory, performance, and/ or behavior [10, 11, 24, 25]. The Childhood Adenotonsillectomy Trial (CHAT) was recently undertaken to assess neuropsychological and health outcomes in children randomized to receive early AT (eAT) as compared to Watchful Waiting with Supportive Care (WWSC) [18]. The CHAT cohort included children aged 5 through 9 years of age, with greater than 450 participants at 6 sites, and about half of the group was categorized as overweight or obese. Recently presented unpublished preliminary data suggest that at least some measures of child behavior are significantly impacted by early adenotonsillectomy compared to watchful waiting, while other measures of neuropsychological function were not significantly impacted [26]. Certainly this data, when fully analyzed and published, will add to understanding of adenotonsillectomy as a therapy for OSA in children.

Orthodontic approaches, in particular rapid maxillary expansion (RME), are increasingly reported as playing a role in the treatment of OSAin preschool [27] and school-aged [28] children with narrow, arched palates, retrusive bites, or crossbite, with improvements maintained two years after intervention. Such approaches, alone and in combination with adenotonsillectomy, have been published for almost a decade although numbers are quite small [29, 30]. I However, despite near-normalization of sleep architecture and significantly improved AHI one year after intervention, some aspects of sleep microstructure were disturbed, suggesting incomplete response to therapy [31]. Furthermore, while subject selection is probably important for this therapy, not enough is known about impact of this therapy across AHI ranges. Finally, this treatment is dependent upon having access to an orthodontist familiar with this treatment approach for pediatric OSA. Beyond RME, there is some

data to suggest that in selected children with mandibular retropositioning, oral appliance/ mandibular repositioning devices may be helpful [32, 33]. Finally, in children with craniofacial anomalies and severe OSA, such as those with Pierre-Robin Sequence, surgical mandibular advancement may be employed to avoid the need for a tracheostomy.

Airway inflammation is present in children with OSA, as evidenced by analysis of excised tissues and exhaled breath condensates [34–36]. Whole tissue cell cultures of adenoids and tonsils from children with OSA demonstrate increased cellular proliferation and inflammatory cytokines [37]. In in vitro cultures, leukotriene antagonists such as montelukast reduced adenotonsillar cellular proliferation rates, suggesting that targeted pharmacologic disruption of the leukotriene pathways may provide nonsurgical alternatives for treatment of OSA in children [38]. Corticosteroids were also shown to reduce in vitro cellular proliferation and the production of pro-inflammatory cytokines in a tonsil/adenoid mixed-cell culture system [39]. Small studies evaluating the effects of anti-inflammatory therapies in children with OSA have been reported for longer than a decade. There is some evidence that nasal steroids may reduce AHI (though in an early study, not adenotonsillar size) [40] as well as symptoms, in children with mild sleep-disordered breathing [41]. The clinical effect has been reported to be maintained for several months after treatment. A more recent study of 62 children with polysomnographically diagnosed mild obstructive sleep apnea syndrome in a double-blind, randomized, placebo-controlled crossover trial of intranasal budesonide demonstrated that a 6-week treatment with intranasal budesonide reduced both AHI and adenoidal hypertrophy, an effect that persisted for at least 8 weeks after cessation of therapy [42]. In this study, normalization of sleep measures was obtained in 54 % of treated children. While it has been suggested that such data justifies the use of intranasal steroids in otherwise healthy children with mild to moderate OSA, which subgroup of patients will benefit most, the optimal dosage, and optimal duration of therapy are still unclear. Likewise, the use of a different medication to modify leukotriene-mediated inflammation, montelukast, has also been reported to improve tissues size and respiratory indices in milder pediatric OSA in an open-label 16 week trial [43]. In a recent double-blind, placebo controlled study of montelukast in 46 children with PSG-confirmed OSA, significant improvements were reported at 12 week follow up in polysomnography (obstructive apnea index), symptoms, and adenoid size (measured by lateral neck radiograph) [44]. Like nasal steroids, which subgroups of children will benefit most, optimal dose and treatment duration are unknown. Furthermore, reports of psychiatric adverse events such as nightmares, insomnia, and aggressive behavior have been reported in children using montelukast [45], and appropriate discussion regarding this possibility should be undertaken taken before starting therapy.

The influence of pediatric OSA on metabolic and cardiovascular function as well as systemic inflammation has gained attention in recent years, and a newer concepts of the inflammatory effects of OSA has led to exploration of new biomarkers for treatment effectiveness. In particular, the activation of inflammatory pathways by OSA has emerged as a possible important contributor to end organ injury associated with this disorder, perhaps especially in the presence of concomitant obesity [46–48]. The role of a systemic inflammatory process in OSA is supported by findings of increased C-reactive protein (CRP) and IL-6 levels and lower IL-10 levels in children with OSA, which has been reported to improve following adenotonsillectomy [49–51] and one month of nasal CPAP therapy. However, data is mixed regarding CRP improvement after adenotonsillectomy in obese children with OSA [6, 52].

Continuous positive airway pressure, or CPAP, is becoming a more commonly usedtherapy in pediatric OSA. Recent data indicates that even with suboptimal use, CPAP confers benefits in neurobehavioral outcomes in children with OSA [53]. However, while PAP is effective in lowering AHI and may be associated with improvements in domains of interest, it remains challenging due to adherence related concerns. Factors such as lack of approved pediatric masks and child-friendly equipment and support have also historically been a hurdle to successfully using CPAP, though in recent years more interfaces have become available. There is little published data regarding how newer CPAP technologies such as auto-titrating positive airway devices or pressure reduction “comfort” settings perform, change effectiveness, or alter adherence or acceptance in pediatric populations, though a recent study in 56 children comparing CPAP to Bilevel administration of pressure with added BiFlex (Phillips Respironics), a pressure relief technology, did not show differences in adherence or reported efficacy between the two pressure modalities [54]. Another small study noted that auto-titrating devices may be effective in the attended setting [55]. However, typical in-lab titrations, which are the standard in pediatrics [56], involve manual stepwise titrations.

Recent data has linked PAP adherence in children and adolescents to family and demographic factors, rather than severity of apnea or measures of psychosocial functioning, though previous retrospective data also linked OSA severity to adherence [57]. There is little published data assessing longterm adherence rates, especially into adolescence and early adulthood, even in children who initially seem to adhere to and benefit from therapy. There is some concern for, but little longitudinal data evaluating, risk of midface skeletal changes with longterm CPAP use in growing children.

Narcolepsy

While the criteria from diagnosing narcolepsy in children are not manifestly different that in adults, it should be noted that the Multiple Sleep Latency Test has not been validated in children less than 8 years of age, which may present some additional murkiness when trying to make the diagnosis [1, 58].

In addition, narcolepsy often starts in childhood or adolescence, and before the disease has reached fully classical symptomatology, it may be challenging to make the diagnosis. While excessive daytime sleepiness remains the hallmark of the disorder, cataplexy does not always manifest very early on, and a host of other positive and negative motor phenomena have been described in pediatrics, more so than in adult populations. Children with narcolepsy may display complex abnormal motor behaviors close to disease onset that do not meet the classical definition of cataplexy, including a complex array of 'negative' (hypotonia) and 'active' (ranging from perioral movements to dyskinetic–dystonic movements or stereotyped movement) motor disturbances [59]. In this way, it has been argued that pediatric narcolepsy with cataplexy often co-occurs with a complex movement disorder at disease onset, a phenomenon that may vanish later in the course of the disease [59]. Pediatric narcolepsy-cataplexy is also associated with excessive weight gain near symptom onset, and may be associated with other sleep disorders, including periodic limb movements and sleep apnea, which may obscure or delay the correct clinical diagnosis [60, 61].

Given growing evidence of its autoimmune underpinnings, including the recently reported association between H1N1 influenza or adjuvanted H1N1vaccine, and development of hypocretin-deficient narcolepsy-catalexy [62, 63], there has been increased interest in early diagnosis of narcolepsy-cataplexy, which would allow for the possibility of immunomodulators that may reduce the destruction of hypocretin-producing hypothalamic neurons and reduce the burden of this disease. However, most trials of steroid administration, plasmapheresis, or intravenous immunoglobulin therapy (IVIG) have so far been shown to be of little value, although a few reports described decreased cataplexy or sleepiness with the IVIG treatment [64–69].

At present, since there is no cure for narcolepsy-cataplexy, treatment goals include control of symptoms and optimization of lifestyle and psychosocial function. Successful treatment includes both behavioral and pharmacological treatments. Behavioral treatment includes developing healthy sleep habits and avoiding sleep deprivation. A brief, scheduled, 15-to-20 min nap taken generally one to twice a day should improve alertness and should be encouraged as a lifelong practice. Timing and length of scheduled naps practices vary between patients and practitioners. Likewise, working with schools and career counseling are important elements of guidance for children with narcolepsy-cataplexy. A child with narcolepsy may have difficulty maintaining attention in quiet situations without breaks, and schools should be contacted to help ensure reasonable accommodations are available for scheduled naps and arrangements made for breaks during test-taking. Finally, assessment regarding the child's quality of life, social relationships, and function at school or work should be made, with interventions when needed. Information about patient-oriented support groups such as the Narcolepsy Network may be provided.

Pharmacotherapies targeted to treating daytime sleepiness and cataplexy are the mainstays of narcolepsy treatment. Most studies have been performed in adults, and no double-blind, placebo-controlled trials of medication have been specifically conducted for children with narcolepsy.

Central nervous system stimulants have been the drugs most widely used in the treatment of sleepiness in narcolepsy, and amphetamines were first proposed in 1935 [43]. The use of methylphenidate was later encouraged because of a shorter half-life and lower incidence of side effects. Immediate release and extended release formulations allow for individual adjustments to be made based on the clinical situation. There are no specific dosing guidelines for narcolepsy, but generally pediatric ADHD guidelines may be helpful in guiding initiation and titration. Side effects with methylphenidate include insomnia, weight loss, decreased appetite, stomach ache, and dry mouth; and less commonly palpitations and elevations of blood pressure and heart rate. Motor tics can emerge. Tolerance can occur, requiring dose adjustments [70]. In the authors' experience, these side effects have made methylphenidate a less attractive treatment option in children with narcolepsy as newer therapeutic agents have become available.

Modafinil is considered a first-line therapy for excessive daytime sleepiness (EDS) associated with narcolepsy in adults [71]; however, in children, caution is again the rule, especially at younger ages, due to reports of serious adverse events at elevated modafinil doses [72, 73], and the manufacturer recommends against use of modafinil in younger children. During the pivotal trials skin reactions including one case of possible erythema multiforme/Stevens Johnson Syndrome were reported [73]. Modafinil is FDA- approved for use in children over age 16 years.

Despite this, most published adverse drug reactions have not been serious [74, 75], and the use of modafinil has been reported in the treatment of EDS in narcoleptic children [60, 76, 77]. Off-label use of the drug has also been reported in ADHD to be effective and well tolerated [78–81]. Most recently, it was shown to be as effective as methylphenidate in ADHD [82]. The mechanism of this wake-promoting drug is unknown, but it seems different from that of amphetamines and is hypothesized to work on hypothalamic wake-promoting circuits. The results of several multicenter trials

have demonstrated improvements in objective measures of sleepiness and improved wakefulness in narcoleptic adult patients, and additive effects have been demonstrated when used with gamma hydroxybutyrate (GHB) [83]. Dosing may start at 50 mg, depending on age and size,once or twice per day, and total daily dose should not exceed 200-400 mg, though sometimes less is needed. Importantly, modafinil can reduce the effectiveness of oral contraceptives, and advice regarding use of additional forms of contraception may be appropriate. Discontinuation of modafinil is not associated with rebound hypersomnolence; nor is there evidence of tolerance. In 2007, armodafinil, the R-enantiomer of modafinil characterized by a longer duration of action, was approved for the treatment of EDS in narcolepsy in adults. Case series and systematic studies reporting experience with armodafinil in children are not widely available in the literature.

Sodium oxybate (also known as Gamma Hydroxybutyrate, or GHB) is indicated in the treatment of narcolepsy with cataplexy and is FDA-approved for both the treatment of cataplexy and excessive daytime sleepiness (EDS) for those aged 16 years and above. GHB is an endogenous central nervous system metabolite with highest concentrations in the hypothalamus and basal ganglia. It is considered a neuromodulator/neurotransmitter affecting dopamine, serotonin, gamma-aminobutyric acid, and endogenous opioids; it also considered to be a GABA-B receptor agonist [84]. As a therapeutic agent in narcolepsy-cataplexy, its mechanisms of actions are incompletely understood, but clinically it has been shown to dramatically reduce cataplexy, as well as treat daytime sleepiness and improve sleep fragmentation/ disturbed sleep typical of narcolepsy-cataplexy [85–87]. As such, it may be used in children with the dual treatment goals of improved daytime alertness, and reducing cataplexy. The improvement in cataplexy is much more rapid than the effect on daytime sleepiness, which may take up to 6-8 weeks. In a pediatric narcolepsy series, 85 % of children (similar rates for pre, peri, and post pubertal children) were treated with sodium oxybate with a reportedly high positive effect on daytime sleepiness, disturbed nighttime sleep, and cataplexy [60]. Irritability and nausea were commonly reported side effects. That report found no impact of the use of sodium oxybate on the occurrence of subsequent puberty. The authors also reported that sodium oxybate alone, or in association with one other drug, modafinil, was sufficient treatment in half of prepubertal cases of narcolepsy-cataplexy [60]. Other published retrospective series reporting the use of GHB in pediatric narcolepsy-cataplexy have shown similar efficacy and tolerance [88, 89].

GHB has powerful central nervous system depressant effects and increases slow wave sleep. Its half life is 90-120 minutes, so the first dose is taken at bedtime and a second dose is most commonly taken 2.5-4 hours later, though timing is best individualized to patients. The recommended starting dose in adults is 4.5 grams/day divided into two equal doses of 2.25 grams, but may be lower in younger children. Dosing may be gradually increased over 8 weeks or longer (titrated for effect on cataplexy). Side effects include disorientation in the middle of the night, grogginess upon awakening, enuresis, and nausea (especially at initiation and at higher doses); more seriously, respiratory depression is also possible. Worsening of sleep disordered breathing has also been reported,and it is generally advised to evaluate and treat SDB in patients for whom GHB is being considered.

For the treatment of cataplexy, the only FDA approved medication is sodium oxybate which is discussed above. Prior to the availability of sodium oxybate, antidepressants were the mainstay treatment for cataplexy. Tricyclic antidepressants such as imipramine and clomipramine, which block presynaptic reuptake of catecholamines, were commonly used. However, anticholinerigc side effects were also common. Selective serotonin reuptake inhibitors largely replaced tricyclics in treatment of cataplexy. Newer antidepressants with selective noradrenergic/serotonergic uptake inhibition are considered better choices, with respect to both side effect profile and efficacy for cataplexy, sleep paralysis, and hypnagogic/hypnopompic hallucinations. The most commonly used drug in this class is venlafaxine at typical doses of 75-150 mg daily (as low as 37.5 mg in younger pediatric patients). Recent data in children with narcolepsy-cataplexy demonstrates reasonable retention rate (68 %) and good efficacy for cataplexy, with frequent side effects of irritability and weight gain reported both in pre- (18 %) and peri/post- (29 %) pubertal groups [60]. Atomoxetine, a highly specific noradrenergic reuptake blocker, has also been effective for treatment of cataplexy as well as EDS in adults and children, and may be useful in resistant cataplexy at doses of 18-100 mg in one or two divided doses [90, 91]. It may also provide some alerting effects, and as such may be considered to target multiple symptoms of narcolepsy [92]. Robust rebound cataplexy may occur at discontinuation of most antidepressants.

Restless Legs Syndrome (RLS)

Pediatric RLS may be difficult to diagnose because it is hard for caregivers to recognize, and children to verbalize, their symptoms. Pediatric-specific consensus criteria for childhood RLS exist for the diagnosis of definite cases; additional criteria exist for research and probable cases [93, 94]. These criteria are an extension of adult criteria and reflect a relative lack of published pediatric-specific information. Most studies of RLS focus on the adult population, although about 38 % of adults with RLS in one series reported a history of symptom onset before the age of 20 years of age [95], and recent prevalence estimates of pediatric RLS in the general population are about 1.9-2 % of children and adolescents in the U.S. and U.K., with 25-50 % reporting

moderate to severe symptoms [96]. Low ferritin levels, a positive family history in the majority [96], and/or ADHD [97, 98] or other mood disturbances have been identified as associations at diagnosis [99, 100]. Furthermore, despite the conventional differentiation between RLS and periodic limb movement (PLM) disorder, PLMs are common in pediatric RLS and the presence of PLMs is incorporated into the consensus criteria.

Guidelines developed by the Standards of Practice Committee of the American Academy of Sleep Medicine indicate that no specific recommendations can be made regarding treatment of children with RLS and PLMD [101]. Nonetheless, behavioral management, cessation of substances that may aggravate symptoms, iron supplementation, and in certain cases prescriptionmedications have been reported to be successful, although none of these interventions has been systematically, prospectively studied.

As with other pediatric sleep disorders such as parasomnias, sleep hygiene and obtaining adequate sleep is a cornerstone of therapy for children with RLS, as lack of sleep can aggravate RLS symptoms. Adequate daytime naps among toddlers are to be encouraged. In addition, local treatment may help alleviate symptoms, such as rubbing or massaging the legs, or warm baths. Recently, use of a pneumatic compression device on the legs was reported to relieve symptoms [102]. Relaxation techniques and cognitive restructuring have been advocated [100]. Regular physical exercise is advocated, whereas sedentary activity may worsen symptoms. However, most advocate avoiding exercise and excitement before bedtime [103]. Counseling regarding avoidance of caffeine and alcohol, especially amongst older school-aged children and teens, is important. Treatment of other coincident sleep disorders which may also lead to inadequate sleep are important; in particular, behavioral insomnias such as sleep onset associations and limit setting disorders, which may develop in response to increased parental intervention for RLS symptoms at bedtime, are not uncommon in children suffering from RLS.

Serum ferritin below 50 mcg/L has been associated with severity of RLS in adult studies [104–106] and has been proposed as a mechanism in pediatrics [100, 107]. There is some evidence of low iron stores in at least some children with RLS (ferritin below 50 mcg/L in 83-89 % and less than median for age and gender in 72-75 %) [108, 109] though no systematic studies have been completed. Some have argued that it is possible that low iron stores play a greater role in pediatrics than in adults, pointing out that serum ferritin below 50 mcg/L is more common in pediatrics than adults [110]. A proposed goal in children with ferritin less than 50 mcg/L is iron supplementation to 80-100mcg/L since saturation of peripheral iron stores occurs at about these levels [100]. Long-term iron is not recommended; in addition, a family history of hemachromatosis would be considered a contraindication to therapy. Iron therapy has been shown to be effective for treating RLS and PLMs in children [111–113]. Both IV and oral iron administration have been reported. Oral dosing is usually 3 mg/kg/day of elemental iron, taken on an empty stomach with vitamin C and avoiding concommitent calcium-containing foods or drinks, and a follow up ferritin 2-3 months after therapy is initiated is a reasonable approach.

Caffeine, nicotine, and medications such as over-the-counter antihistamines, as well as prescription medications such as selective serotonin reuptake inhibitors, metoclopramide, tricyclic antidepressants, and antidopaminergic medications may worsen symptoms of RLS/ PLMD [99]. For patients with comorbid ADHD, stimulant medications have not been reported to increase RLS/ PLMD symptoms, so long as stimulant effect as worn off by evening [114, 115].

No FDA-approved medications exist for treatment of pediatric RLS, and patchy, scant data exist to guide clinicians. Nonetheless, even after strict sleep hygiene and bedtime routines, behavioral management, iron supplementation, and other nonpharmacologic techniques, and elimination of possibly aggravating substances, some children will have significant impairment related to RLS symptoms. Medications that have been reported in small numbers to be effective for pediatric RLS include dopaminergic agents such as ropinirole and pramipexole [93, 116, 117]. Use of dopamine agonists may be associated with augmentation, which involves worsening of RLS symptoms, having symptoms occur earlier, or manifesting atypically, so this possibility should be carefully monitored and discussed at the outset of treatment. Augmentation may respond to a lowering dose, but may require discontinuation of the medication. Interestingly, low serum ferritin may be a risk factor for developing augmentation [118]. Impulse control problems have also been reported with these drugs in adults, although occurrence seems to be relatively uncommon at doses used to treat RLS. Even more than other prescription medications discussed below, for which there is some measure of clinical experience in the treatment of other pediatric conditions, there are few reports of longterm childhood dopaminergic therapy,and its effects are unknown. .

Other medications that have been used off-label to treat childhood RLS include gabapentin, which is FDA-approved as an anticonvulsant in children more than 3 years old, and which may improve sensory disturbance in RLS [119, 120]. Gabapentin's longer-acting analogue gabapentin enacarbil has recently been released on the market and has been studied in adults [121]. Clonidine, an antiadrenergic antihypertensive sometimes reported to be used for sleep onset difficulties in children, benzodiazepines, and opiates have all been reported or suggested for use in pediatric RLS, all with scant data [99]. Potential for cardiovascular effects of clonidine, and for daytime sedation associated with gabapentin and benzodiazepines should be taken

into consideration; as should the potential for dependence with some of these medications.

Conclusion

There is a great need for more information on the outcomes of management of sleep disorders in children. While differences in diagnosis exist for sleep disorders in pediatrics, and differences in clinical presentation have been highlighted in the literature, treatment guidelines specifically for sleep disorders in children are still somewhat lacking. Ideally, when interventions involve devices or drugs, interventions should be FDA-approved for specific sleep disorders and pediatric age group. Additional research and increased efforts to develop,test, and gain approval for such interventions is needed.Additionally, given the importance of behavioral aspects of management of some pediatric sleep disorders, integration of behavioral and pharmacological treatments may yield better patient outcomes. Such a goal may be best accomplished by ensuring that clinicians from a variety of fields, including psychology, medicine, orthodontics, and others, have a comprehensive understanding of clinical sleep disorders in children.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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