Neurotherapeutics (2012) 9:791–800
DOI 10.1007/s13311-012-0149-2

Current Treatment of Selected Pediatric Sleep Disorders

Shannon S. Sullivan

Published online: 3 October 2012

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.

Electronic supplementary material The online version of this article (doi:10.1007/s13311-012-0149-2) contains supplementary material, which is available to authorized users.

S. S. Sullivan (✉)
Department of Psychiatry, Division of Sleep Medicine,
Stanford University School of Medicine,
450 Broadway Street Mail Code 5704,
Redwood City, CA 94063, USA
e-mail: shannon.s.sullivan@stanford.edu

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

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.

References

1. American Academy of Sleep Medicine(2005) International classification of sleep disorders: diagnostic and coding manual (American Academy of Sleep Medicine, Westchester, IL), 2nd ed.
2. Witmans MB, Keens TG, Davidson Ward SL, Marcus CL. Obstructive hypopneas in children and adolescents: normal values. Am J Respir Crit Care Med. 2003 Dec 15;168(12):1540.
3. Katz ES, Marcus CL. Diagnosis of obstructive sleep apnea syndrome in infants and children. In: Sheldon SH, Ferber R, Kryger MH, eds. Principles and Practice of Pediatric Sleep Medicine. Philadelphia, PA: Elsevier Saunders; 2005:197–210
4. The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications. AASM, 2007.
5. Gozal D, Serpero LD, Kheirandish-Gozal L, Capdevila OS, Khalyfa A, Tauman R. Sleep measures and morning plasma TNF-alpha levels in children with sleep-disordered breathing. Sleep. 2010 Mar;33(3):319-25.
6. Gozal D, Capdevila OS, Kheirandish-Gozal L. Metabolic alterations and systemic inflammation in obstructive sleep apnea among nonobese and obese prepubertal children. Am J Respir Crit Care Med. 2008 May 15;177(10):1142-9.
7. Gozal D, Kheirandish-Gozal L, Serpero LD, Sans Capdevila O, Dayyat E. Obstructive sleep apnea and endothelial function in school-aged nonobese children: effect of adenotonsillectomy. Circulation. 2007 Nov 13;116(20):2307-14.
8. Kim J, Bhattacharjee R, Kheirandish-Gozal L, Spruyt K, Gozal D. Circulating microparticles in children with sleep disordered breathing. Chest. 2011 Aug;140(2):408-17.
9. Gozal D, Kheirandish-Gozal L, Bhattacharjee R, Spruyt K. Neurocognitive and endothelial dysfunction in children with obstructive sleep apnea. Pediatrics. 2010 Nov;126(5):e1161-7.
10. Chervin RD, Ruzicka DL, Giordani BJ, Weatherly RA, Dillon JE, Hodges EK, Marcus CL, Guire KE. Sleep-disordered breathing, behavior, and cognition in children before and after adenotonsillectomy. Pediatrics. 2006 Apr;117(4):e769-78.
11. Chervin RD, Ruzicka DL, Hoban TF, Fetterolf JL, Garetz SL, Guire KE, Dillon JE, Felt BT, Hodges EK, Giordani BJ Esophageal Pressures, Polysomnography, and Neurobehavioral Outcomes of Adenotonsillectomy in Children. Chest. 2012 Feb 2.
12. Cullen KA, Hall MJ, Golosinskiy A. Statistics National Center for Health Statistics. Hyattsville, MD: 2009. Ambulatory Surgery in the United States, 2006.
13. Marcus CL, Brooks LJ, Draper, KA, et al. Diagnosis and Management of Childhood Obstructive Sleep Apnea Syndrome Pediatrics; published online August 27, 2012.
14. Tauman R, Gulliver TE, Krishna J, et al. Persistence of obstructive sleep apnea syndrome in children after adenotonsillectomy. J Pediatr. 2006;149:803–8.
15. Apostolidou MT, Alexopoulos EI, Chaidas K, et al. Obesity and persisting sleep apnea after adenotonsillectomy in Greek children. Chest. 2008;134:1149–55.
16. Bhattacharjee R, Kheirandish-Gozal L, Spruyt K, Mitchell RB, Promchiarak J, Simakajornboon N, Kaditis AG, Splaingard D, Splaingard M, Brooks LJ, Marcus CL, Sin S, Arens R, Verhulst SL, Gozal D. Adenotonsillectomy outcomes in treatment of obstructive sleep apnea in children: a multicenter retrospective study.Am J Respir Crit Care Med. 2010 Sep 1;182(5):676-83.
17. Mitchell RB, Kelly J. Outcomes and quality of life following adenotonsillectomy for sleep-disordered breathing in children. ORL J Otorhinolaryngol Relat Spec. 2007;69(6):345-8.
18. Redline S, Amin R, Beebe D, Chervin RD, Garetz SL, Giordani B, Marcus CL, Moore RH, Rosen CL, Arens R, Gozal D, Katz ES, Mitchell RB, Muzumdar H, Taylor HG, Thomas N, Ellenberg S. The Childhood Adenotonsillectomy Trial (CHAT): rationale, design, and challenges of a randomized controlled trial evaluating a standard surgical procedure in a pediatric population. Sleep. 2011 Nov 1;34(11):1509-17.
19. Mitchell RB, Kelly J. Outcome of adenotonsillectomy for obstructive sleep apnea in obese and normal-weight children. Otolaryngol Head Neck Surg. 2007;137:43–8.
20. Tauman R, Gulliver TE, Krishna J, Montgomery-Downs HE, O'Brien LM, Ivanenko A, Gozal D. Persistence of obstructive sleep apnea syndrome in children after adenotonsillectomy. J Pediatr. 2006 Dec;149(6):803-8.
21. Hill CA, Litvak A, Canapari C, Cummings B, Collins C, Keamy DG, Ferris TG, Hartnick CJ. A pilot study to identify pre- and peri-operative risk factors for airway complications following adenotonsillectomy for treatment of severe pediatric OSA. Int J Pediatr Otorhinolaryngol. 2011 Nov;75(11):1385-90.
22. Amin R, Anthony L, Somers V, Fenchel M, McConnell K, Jefferies J, Willging P, Kalra M, Daniels S. Growth velocity predicts recurrence of sleep-disordered breathing 1 year after adenotonsillectomy. Am J Respir Crit Care Med. 2008 Mar 15;177(6):654-9.
23. Giordani B, Hodges EK, Guire KE, Ruzicka DL, Dillon JE, Weatherly RA, Garetz SL, Chervin RD. Changes in neuropsychological and behavioral functioning in children with and without obstructive sleep apnea following Tonsillectomy. J Int Neuropsychol Soc. 2012 Mar;18(2):212-22.
24. Friedman BC, Hendeles-Amitai A, Kozminsky E, Leiberman A, Friger M, Tarasiuk A, Tal A. Adenotonsillectomy improves neurocognitive function in children with obstructive sleep apnea syndrome. Sleep. 2003 Dec 15;26(8):999-1005.

25. Gozal D, Pope DW Jr. Snoring during early childhood and academic performance at ages thirteen to fourteen years. Pediatrics. 2001 Jun;107(6):1394-9.
26. Presented in oral format, ATS, Sunday May 20, 2012 San Francisco CA. Presenters Redline S, Marcus C, Rosen C, Chervin, R.
27. Marino A, Ranieri R, Chiarotti F, Villa MP, Malagola C. Rapid maxillary expansion in children with Obstructive Sleep Apnoea Syndrome (OSAS). Eur J Paediatr Dent. 2012 Mar;13(1):57-63.
28. Villa MP, Rizzoli A, Miano S, Malagola C. Efficacy of rapid maxillary expansion in children with obstructive sleep apnea syndrome: 36 months of follow-up. Sleep Breath. 2011 May;15 (2):179-84.
29. Pirelli P, Saponara M, Guilleminault C. Rapid maxillary expansion in children with obstructive sleep apnea syndrome. Sleep. 2004 Jun 15;27(4):761-6.
30. Guilleminault C, Monteyrol PJ, Huynh NT, Pirelli P, Quo S, Li K. Adeno-tonsillectomy and rapid maxillary distraction in prepubertal children, a pilot study. Sleep Breath. 2011 May;15 (2):173-7.
31. Miano S, Rizzoli A, Evangelisti M, Bruni O, Ferri R, Pagani J, Villa MP. NREM sleep instability changes following rapid maxillary expansion in children with obstructive apnea sleep syndrome. Sleep Med. 2009 Apr;10(4):471-8.
32. Villa MP, Bernkopf E, Pagani J, Broia V, Montesano M, Ronchetti R. Randomized controlled study of an oral jaw-positioning appliance for the treatment of obstructive sleep apnea in children with malocclusion. Am J Respir Crit Care Med 2002; 165:123–127.
33. Villa MP, Miano S, Rizzoli A. Mandibular advancement devices are an alternative and valid treatment for pediatric obstructive sleep apnea syndrome. Sleep Breath. 2011
34. Goldbart AD, Krishna J, Li RC, Serpero LD, Gozal D. Inflammatory mediators in exhaled breath condensate of children with obstructive sleep apnea syndrome.Chest. 2006 Jul;130(1):143-8.
35. Goldbart AD, Tal A. Inflammation and sleep disordered breathing in children: a state-of-the-art review. Pediatr Pulmonol. 2008 Dec;43(12):1151-60.
36. Malakasioti G, Alexopoulos E, Befani C, Tanou K, Varlami V, Ziogas D, Liakos P, Gourgoulianis K, Kaditis AG. Oxidative stress and inflammatory markers in the exhaled breath condensate of children with OSA. Sleep Breath. 2011 Aug 3.
37. Kim J, Bhattacharjee R, Dayyat E, Snow AB, Kheirandish-Gozal L, Goldman JL, Li RC, Serpero LD, Clair HB, Gozal D. Increased cellular proliferation and inflammatory cytokines in tonsils derived from children with obstructive sleep apnea. Pediatr Res. 2009 Oct;66(4):423-8.
38. Dayyat E, Serpero LD, Kheirandish-Gozal L, Goldman JL, Snow A, Bhattacharjee R, Gozal D. Leukotriene pathways and in vitro adenotonsillar cell proliferation in children with obstructive sleep apnea. Chest. 2009 May;135(5):1142-9.
39. Kheirandish-Gozal L, Serpero LD, Dayyat E, Kim J, Goldman JL, Snow A, Bhattacharjee R, Gozal D. Corticosteroids suppress in vitro tonsillar proliferation in children with obstructive sleep apnoea. Eur Respir J. 2009 May;33(5):1077-84.
40. Brouillette RT, Manoukian JJ, Ducharme FM, Oudjhane K, Earle LG, Ladan S, et al. Efficacy of fluticasone nasal spray for pediatric obstructive sleep apnea.J Pediatr 2001;138(6):838-44.
41. Alexopoulos EI, Kaditis AG, Kalampouka E, Kostadima E, Angelopoulos NV, Mikraki V, Skenteris N, Gourgoulianis K. Nasal corticosteroids for children with snoring. Pediatr Pulmonol. 2004 Aug;38(2):161-7.
42. Kheirandish-Gozal L, Gozal D. Intranasal budesonide treatment for children with mild obstructive sleep apnea syndrome. Pediatrics. 2008 Jul;122(1):e149-55.
43. Goldbart AD, Goldman JL, Veling MC, Gozal D. Leukotriene modifier therapy for mild sleep-disordered breathing in children. Am J Respir Crit Care Med. 2005 Aug 1;172(3):364-70.
44. Goldbart AD, Greenberg-Dotan S, Tal A. Montelukast for Children With Obstructive Sleep Apnea: A Double-blind, Placebo-Controlled Study. Pediatrics. 2012 Aug 6, epublished ahead of print.
45. Wallerstedt SM, Brunlöf G, Sundström A, Eriksson AL. Montelukast and psychiatric disorders in children. Pharmacoepidemiol Drug Saf. 2009 Sep;18(9):858-64.
46. Kim J, Hakim F, Kheirandish-Gozal L, Gozal D. Inflammatory pathways in children with insufficient or disordered sleep. Respir Physiol Neurobiol. 2011 Sep 30;178(3):465-74.
47. Kheirandish-Gozal L, Capdevila OS, Tauman R, Gozal D. Plasma C-reactive protein in nonobese children with obstructive sleep apnea before and after adenotonsillectomy. J Clin Sleep Med. 2006 Jul 15;2(3):301-4.
48. Tauman R, O'Brien LM, Gozal D. Hypoxemia and obesity modulate plasma C-reactive protein and interleukin-6 levels in sleep-disordered breathing. Sleep Breath. 2007 Jun;11(2):77-84
49. Kheirandish-Gozal L, Capdevila OS, Tauman R, Gozal D; Plasma C-reactive protein in nonobese children with obstructive sleep apnea before and after adenotonsillectomy, J Clin Sleep Med 2006 23 301-304.
50. Kelishadi R, Nilforoushan N, Okhovat A, Amra B, Poursafa P, Rogha M. Effects of adenoidectomy on markers of endothelial function and inflammation in normal-weight and overweight prepubescent children with sleep apnea. J Res Med Sci. 2011 Mar;16 Suppl 1:S387-94.
51. Gozal D, Serpero LD, Sans Capdevila O, Kheirandish-Gozal L. Systemic inflammation in non-obese children with obstructive sleep apnea. Sleep Med. 2008 Mar;9(3):254-9.
52. Chu L, Yao H, Wang B. Impact of Adenotonsillectomy on High-Sensitivity C-Reactive Protein Levels in Obese Children with Obstructive Sleep Apnea. Otolaryngol Head Neck Surg. 2012 Apr 20.
53. Marcus CL, Radcliffe J, Konstantinopoulou S, Beck SE, Cornaglia MA, Traylor J, DiFeo N, Karamessinis LR, Gallagher PR, Meltzer LJ. Effects of positive airway pressure therapy on neurobehavioral outcomes in children with obstructive sleep apnea. Am J Respir Crit Care Med. 2012 May 1;185(9):998-1003.
54. Marcus CL, Beck SE, Traylor J, Cornaglia MA, Meltzer LJ, DiFeo N, Karamessinis LR, Samuel J, Falvo J, DiMaria M, Gallagher PR, Beris H, Menello MK. Randomized, double-blind clinical trial of two different modes of positive airway pressure therapy on adherence and efficacy in children. J Clin Sleep Med. 2012 Feb 15;8(1):37-42.
55. Palombini L, Pelayo R, Guilleminault C. Efficacy of automated continuous positive airway pressure in children with sleep-related breathing disorders in an attended setting. Pediatrics. 2004 May;113(5):e412-7.
56. R. Nisha Aurora, MD; Rochelle S. Zak, MD; Anoop Karippot, MD; Carin I. Lamm, MD; Timothy I. Morgenthaler, MD; Sanford H. Auerbach, MD; Sabin R. Bista, MD; Kenneth R. Casey, MD; Susmita Chowdhuri, MD; David A. Kristo, MD; Kannan Ramar, MD Practice Parameters for the Respiratory Indications for Polysomnography in Children SLEEP. 2011 March 1; 34(3); 379-88
57. Difeo N, Meltzer LJ, Beck SE, Karamessinis LR, Cornaglia MA, Traylor J, Samuel J, Gallagher PR, Radcliffe J, Beris H, Menello MK, Marcus CL. Predictors of positive airway pressure therapy adherence in children: a prospective study.J Clin Sleep Med. 2012 Jun 15;8(3):279-86.
58. Sullivan SS, Kushida CA. Multiple sleep latency test and maintenance of wakefulness test. Chest. 2008 Oct;134(4):854-61.
59. Plazzi G, Pizza F, Palaia V, Franceschini C, Poli F, Moghadam KK, Cortelli P, Nobili L, Bruni O, Dauvilliers Y, Lin L, Edwards MJ, Mignot E, Bhatia KP. Complex movement disorders at disease onset in childhood narcolepsy with cataplexy. Brain. 2011 Dec;134(Pt 12):3480-92.

60. Aran A, Einen M, Lin L, Plazzi G, Nishino S, Mignot E. Clinical and therapeutic aspects of childhood narcolepsy-cataplexy: a retrospective study of 51 children. Sleep. 2010 Nov;33(11):1457-64.
61. Sullivan SS. Narcolepsy in adolescents. Adolesc Med State Art Rev. 2010 Dec;21(3):542-55.
62. Nohynek H, Jokinen J, Partinen M, Vaarala O, Kirjavainen T, Sundman J, Himanen SL, Hublin C, Julkunen I, Olsén P, Saarenpää-Heikkilä O, Kilpi T. AS03 adjuvanted AH1N1 vaccine associated with an abrupt increase in the incidence of childhood narcolepsy in Finland. PLoS One. 2012;7(3):e33536.
63. Dauvilliers Y, Montplaisir J, Cochen V, Desautels A, Einen M, Lin L, Kawashima M, Bayard S, Monaca C, Tiberge M, Filipini D, Tripathy A, Nguyen BH, Kotagal S, Mignot E. Post-H1N1 narcolepsy-cataplexy. Sleep. 2010 Nov;33(11):1428-30.
64. Dauvilliers Y, Carlander B, Rivier F, Touchon J, Tafti M. Successful management of cataplexy with intravenous immunoglobulins at narcolepsy onset. Ann Neurol. 2004; 56: 905-908.
65. Dauvilliers Y . Follow-up of four narcolepsy patients treated with intravenous immunoglobulins. Ann Neurol. 2006; 60: 153.
66. Fronczek R, Verschuuren J, Lammers G J. Response to intravenous immunoglobulins and placebo in a patient with narcolepsy with cataplexy. J Neurol. 2007; 254: 1607-1608
67. Plazzi G, Poli F, Franceschini C, et al. Intravenous high-dose immunoglobulin treatment in recent onset childhood narcolepsy with cataplexy. J Neurol. 2008; 255: 1549-1554.
68. Dauvilliers Y, Abril B, Mas E, Michel F, Tafti M. Normalization of hypocretin-1 in narcolepsy after intravenous immunoglobulin treatment. Neurology. 2009; 73: 1333-1334.
69. Knudsen S, Biering-Sørensen B, Kornum BR, Petersen ER, Ibsen JD, Gammeltoft S, Mignot E, Jennum PJ. Early IVIg treatment has no effect on post-H1N1 narcolepsy phenotype or hypocretin deficiency. Neurology. 2012 Jul 3;79(1):102-3.
70. Peterson P C, Husain A M. Pediatric narcolepsy. Brain Dev. 2008; 30: 609-623.
71. Wise M S, Arand D L, Auger R R, Brooks S N, Watson N F. Treatment of narcolepsy and other hypersomnias of central origin. Sleep. 2007; 30: 1712-1727.
72. Spiller H A, Borys D, Griffith J R, et al. Toxicity from modafinil ingestion . Clin Toxicol (Phila). 2009; 47: 153-156.
73. Rugino T. A review of modafi nil fi lm-coated tablets for attention-defi cit/ hyperactivity disorder in children and adolescents. Neuropsychiatr Dis Treat. 2007; 3: 293-301.
74. Aagaard L, Hansen EH. The occurrence of adverse drug reactions reported for attention deficit hyperactivity disorder (ADHD) medications in the pediatric population: a qualitative review of empirical studies. Neuropsychiatr Dis Treat. 2011;7:729-44.
75. Lecendreux M, Bruni O, Franco P, Gringras P, Konofal E, Nevsimalova S, Paiva T, Partinen M, Peeters E, Peraita-Adrados R, Plazzi G, Poli F. Clinical experience suggests that modafinil is an effective and safe treatment for paediatric narcolepsy. J Sleep Res. 2012 Aug;21(4):481-483.
76. Ivanenko A, Tauman R, Gozal D. Modafi nil in the treatment of excessive daytime sleepiness in children. Sleep Med. 2003; 4: 579-582.
77. Yeh SB, Schenck CH. Efficacy of modafinil in 10 Taiwanese patients with narcolepsy: findings using the Multiple Sleep Latency Test and Epworth Sleepiness Scale. Kaohsiung J Med Sci. 2010 Aug;26(8):422-7.
78. Kahbazi M, Ghoreishi A, Rahiminejad F, Mohammadi M R, Kamalipour A, Akhondzadeh S. A randomized, double-blind and placebo-controlled trial of modafi nil in children and adolescents with attention defi cit and hyperactivity disorder. Psychiatry Res. 2009; 168: 234-237.
79. Biederman J, Pliszka S R. Modafi nil improves symptoms of attentiondeficit/hyperactivity disorder across subtypes in children and adolescents. J Pediatr. 2008; 152: 394-399.
80. Amiri S, Mohammadi M R, Mohammadi M, Nouroozinejad G H, Kahbazi M, Akhondzadeh S. Modafinil as a treatment for attentiondeficit/hyperactivity disorder in children and adolescents: A double blind, randomized clinical trial. Prog Neuropsychopharmacol Biol Psychiatry. 2008; 32: 145-149.
81. Wigal S B, Biederman J, Swanson J M, Yang R, Greenhill L L. Efficacy and safety of modafi nil fi lm-coated tablets in children and adolescents with or without prior stimulant treatment for attention-defi cit/hyperactivity disorder: Pooled analysis of 3 randomized, double-blind, placebo-controlled studies. Prim Care Companion J Clin Psychiatry. 2006; 8: 352-360.
82. Goez HR, Scott O, Nevo N, Bennett-Back O, Zelnik N. Using the Test of Variables of Attention to Determine the Effectiveness of Modafinil in Children With Attention-Deficit Hyperactivity Disorder (ADHD): A Prospective Methylphenidate-Controlled Trial. J Child Neurol. 2012 Mar 23.
83. Black J, Houghton W C. Sodium oxybate improves excessive daytime sleepiness in narcolepsy. Sleep. 2006; 29: 939-946.
84. Huang Y S, Guilleminault C. Narcolepsy: Action of two gammaaminobutyric acid type B agonists, baclofen and sodium oxybate. Pediatr Neurol. 2009; 41: 9-16.
85. Lammers G J, Arends J, Declerck A C, Ferrari M D, Schouwink G, Troost J. Gamma-hydroxybutyrate and narcolepsy: A double-blind placebocontrolled study. Sleep. 1993; 16: 216-220.
86. Lammers G J, Bassetti C, Billiard M, et al. Sodium oxybate is an effective and safe treatment for narcolepsy. Sleep Med. 2010; 11: 105-106: author reply 6–8.
87. The U. S. Xyrem Multicenter Study Group. Sodium oxybate demonstrates long-term efficacy for the treatment of cataplexy in patients with narcolepsy. Sleep Med. 2004; 5: 119-123.
88. Lecendreux M, Poli F, Oudiette D, Benazzouz F, Donjacour CE, Franceschini C, Finotti E, Pizza F, Bruni O, Plazzi G. Tolerance and efficacy of sodium oxybate in childhood narcolepsy with cataplexy: a retrospective study. Sleep. 2012 May 1;35(5):709-11.
89. Mansukhani MP, Kotagal S. Sodium oxybate in the treatment of childhood narcolepsy-cataplexy: A retrospective study. Sleep Med. 2012 Mar 23.
90. Billiard M. Narcolepsy: current treatment options and future approaches. Neuropsychiatr Dis Treat. 2008 Jun;4(3):557-66.
91. Mignot E, Nishino S. Emerging therapies in narcolepsy-cataplexy. Sleep. 2005 Jun;28(6):754-63.
92. Sullivan S and Pelayo R, Narcolepsy in Children, in Therapy in Sleep Medicine; Teri J. Barkoukis, MD, Jean K. Matheson, MD, Richard Ferber, MD and Karl Doghramji, MD, eds; Saunders, 2012.
93. Picchietti MA, Picchietti DL. Advances in pediatric restless legs syndrome: Iron, genetics, diagnosis and treatment. Sleep Med. 2010 Aug;11(7):643-51.
94. Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisi J; Restless Legs Syndrome Diagnosis and Epidemiology workshop at the National Institutes of Health; International Restless Legs Syndrome Study Group. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. Sleep Med. 2003 Mar;4(2):101-19.
95. Montplaisir J, Boucher S, Poirier G, Lavigne, Lapierre O, Lesperance P. Clinical, polysomnographic, and genetic characteristics of restless legs syndrome: a study of 133 patients diagnosed with new standard criteria. Mov Disord. 1997;12:61–5.
96. Picchietti D, Allen RP, Walters AS, Davidson JE, Myers A, Ferini-Strambi L. Restless legs syndrome: prevalence and impact in children and adolescents–the Peds REST study. Pediatrics. 2007 Aug;120(2):253-66.
97. Cortese S, Konofal E, Lecendreux M, Arnulf I, Mouren MC, Darra F, Dalla Bernardina B. Restless legs syndrome and

attention-deficit/hyperactivity disorder: a review of the literature. Sleep. 2005 Aug 1;28(8):1007-13.
98. Picchietti DL, Underwood DJ, Farris WA, Walters AS, Shah MM, Dahl RE, Trubnick LJ, Bertocci MA, Wagner M, Hening WA. Further studies on periodic limb movement disorder and restless legs syndrome in children with attention-deficit hyperactivity disorder. Mov Disord. 1999 Nov;14(6):1000-7.
99. Frenette E. Restless legs syndrome in children: a review and update on pharmacological options. Curr Pharm Des. 2011;17 (15):1436-42.
100. Durmer JS, Quraishi GH. Restless legs syndrome, periodic leg movements, and periodic limb movement disorder in children. Pediatr Clin North Am. 2011 Jun;58(3):591-620.
101. Chesson AL Jr, Anderson WM, Littner M, Davila D, Hartse K, Johnson S, Wise M, Rafecas J. Practice parameters for the nonpharmacologic treatment of chronic insomnia. An American Academy of Sleep Medicine report. Standards of Practice Committee of the American Academy of Sleep Medicine. Sleep. 1999 Dec 15;22(8):1128-33.
102. C.J. Lettieri, A.H. Eliasson. Pneumatic compression devices are an effective therapy for restless legs syndrome: a prospective, randomized, double-blinded, sham-controlled trial Chest, 135 (1) (2009), pp. 74–80.
103. Simakajornboon N, Kheirandish-Gozal L, Gozal D. Diagnosis and management of restless legs syndrome in children. Sleep Med Rev. 2009 Apr;13(2):149-56.
104. Sun ER, Chen CA, Ho G, Earley CJ, Allen RP.Iron and the restless legs syndrome. Sleep. 1998 Jun 15;21(4):371-7.
105. Trenkwalder C, Hening WA, Montagna P, Oertel WH, Allen RP, Walters AS, Costa J, Stiasny-Kolster K, Sampaio C. Treatment of restless legs syndrome: an evidence-based review and implications for clinical practice. Mov Disord. 2008 Dec 15;23 (16):2267-302.
106. Trenkwalder C, Högl B, Benes H, Kohnen R. Augmentation in restless legs syndrome is associated with low ferritin. Sleep Med. 2008 Jul;9(5):572-4. Epub 2007 Oct 24.
107. D. Picchietti Is iron deficiency an underlying cause of pediatric restless legs syndrome and of attention-deficit/hyperactivity disorder? Sleep Med, 8 (7-8) (2007), pp. 693–694
108. Kotagal S, Silber MH. Childhood-onset restless legs syndrome. Ann Neurol. 2004;56:803–7.
109. Picchietti D, Steven HE. Early manifestations of restless legs syndrome in childhood and adolescence. Sleep Med. 2008;9:770–81.
110. Earley CJ. Clinical practice. Restless legs syndrome. N Engl J Med. 2003 May 22;348(21):2103-9.
111. Kryger MH, Otake K, Foerster J. Low body stores of iron and restless legs syndrome: a correctable cause of insomnia in adolescents and teenagers. Sleep Med. 2002 Mar;3(2):127-32.
112. Davis BJ, Rajput A, Rajput ML, Aul EA, Eichhorn GR. A randomized, double-blind placebo-controlled trial of iron in restless legs syndrome. Eur Neurol. 2000;43(2):70-5.
113. Mohri I, Kato-Nishimura K, Kagitani-Shimono K, Kimura-Ohba S, Ozono K, Tachibana N, Taniike M. Evaluation of oral iron treatment in pediatric restless legs syndrome (RLS). Sleep Med. 2012 Apr;13(4):429-32.
114. Picchietti DL, England SJ, Walters AS, Willis K, Verrico T. Periodic limb movement disorder and restless legs syndrome in children with attention-deficit hyperactivity disorder. J Child Neurol. 1998 Dec;13(12):588-94.
115. L.M. O'Brien, A. Ivanenko, V.M. Crabtree, C.R. Holbrook, J.L. Bruner, C.J. Klaus et al. The effect of stimulants on sleep characteristics in children with attention deficit/hyperactivity disorder Sleep Med, 4 (4) (2003), pp. 309–316.
116. Walters AS, Mandelbaum DE, Lewin DS, Kugler S, England SJ, Miller M. Dopaminergic therapy in children with restless legs/periodic limb movements in sleep and ADHD. Dopaminergic Therapy Study Group. Pediatr Neurol. 2000 Mar;22(3):182-6.
117. Muhle H, Neumann A, Lohmann-Hedrich K, Lohnau T, Lu Y, Winkler S, Waltz S, Fischenbeck A, Kramer PL, Klein C, Stephani U. Childhood-onset restless legs syndrome: clinical and genetic features of 22 families. Mov Disord. 2008 Jun 15;23(8):1113-21
118. Frauscher B, Gschliesser V, Brandauer E, El-Demerdash E, Kaneider M, Rücker L, Poewe W, Högl B. The severity range of restless legs syndrome (RLS) and augmentation in a prospective patient cohort: association with ferritin levels. Sleep Med. 2009 Jun;10(6):611-5.
119. Happe S, Sauter C, Klösch G, Saletu B, Zeitlhofer J. Gabapentin versus ropinirole in the treatment of idiopathic restless legs syndrome. Neuropsychobiology. 2003;48(2):82-6.
120. Garcia-Borreguero D, Larrosa O, de la Llave Y, Verger K, Masramon X, Hernandez G. Treatment of restless legs syndrome with gabapentin: a double-blind, cross-over study. Neurology. 2002 Nov 26;59(10):1573-9.
121. Lal R, Ellenbogen A, Chen D, Zomorodi K, Atluri H, Luo W, Tovera J, Hurt J, Bonzo D, Lassauzet ML, Vu A, Cundy KC. A randomized, double-blind, placebo-controlled, dose-response study to assess the pharmacokinetics, efficacy, and safety of gabapentin enacarbil in subjects with restless legs syndrome. Clin Neuropharmacol. 2012 Jul;35(4):165-73.