Drugs which affect Sleep

24

Nicholas-Tiberio Economou, Konstantinos Papoutsis, Luigi Ferini-Strambi, and Georgia Trakada

Abbreviations

ADHD	Attention deficit hyperactivity disorder
AHI	Apnea–hypopnea index
CNSS	Central nervous system stimulant
CRSWD	Circadian rhythm sleep–wake disorder
FDA	Food and Drug Administration
NREM	Non-rapid eye movement
OSA	Obstructive sleep apnea
PLMD	Periodic limb movement disorder
REM	Rapid eye movement
RLS	Restless legs syndrome
SM	Smith–Magenis syndrome
SSRI	Selective serotonin reuptake inhibitors
SWD	Sleep–wake disorder

Introduction

Sleep medicine in pediatrics has been widely involved for the assessment of sleep disturbances such as insomnia or somnolence, or other more severe sleep–wake disorders (SWD) like narcolepsy [1]. However, it should be noticed that the Food and Drug Administration (FDA) does not provide a guide on how physicians should treat (with the most fruitful potential medical transcription) those SWDs, which are peculiar to children [2–4]. Nevertheless, wide research has been done in order to have safe and potential drugs/and or therapies for young people under 18 years old, who experience an SWD [5].

While the prevalence of SWDs in the non-adult population is 10–28% [6–8], engendering cognitive, emotional, and behavioral issues [9], the comorbidities of SWDs with other disorders/diseases provide a wider understanding of how pharmacotherapy affects sleep. For instance, prazosin, which is approved by the FDA as a treatment for hypertension, has shown promising results for ameliorating PTSD symptomatology and nightmares, although no particular FDA approval for prazosin exists for sleep disturbance in children and adolescents [10]. Another example is the use of melatonin, which is a safe treatment for insomnia in children with autism, with very few mild side effects, mostly daytime somnolence [11].

Moreover, theophylline, which is employed for asthma in children, seems to have a protective effect toward apnea and arterial oxygen saturation, while it does not have any effect on sleep quality [12, 13]. In more complicated respiratory diseases, such as cystic fibrosis, children have reported sleep disturbances [14]. When it is about lung transplantation, the immunosuppressive drugs taken in order to prevent rejection by the immune system, lead to insomnia [15]. Further regarding transplantation, lung or heart transplants were correlated with sleep apnea [16, 17] and poor quality of sleep [18], while hand transplants may create sleep issues, due to the use of immunosuppressive drugs [19].

Until now there has been limited literature review at the heart of sleep research to garner the drug effect on child or adolescent sleep in a more extensive view. Thus, the purpose of this study is to discuss this topic in a combined way, not only for SWDs, but also how drugs used in common pediatrics may affect sleep.

N.-T. Economou (✉)
Division of Pulmonology, Department of Clinical Therapeutics, National and Kapodistrian University of Athens School of Medicine, Alexandra Hospital, Athens, Greece

"Enypnion" Sleep/Wake-Epilepsy Center, Bioclinic Hospital, Athens, Greece

K. Papoutsis
"Enypnion" Sleep/Wake-Epilepsy Center, Bioclinic Hospital, Athens, Greece

L. Ferini-Strambi
Sleep Disorders Center, Department of Neurology, Vita-Salute San Raffaele University, Milan, Italy

G. Trakada
Division of Pulmonology, Department of Clinical Therapeutics, National and Kapodistrian University of Athens School of Medicine, Alexandra Hospital, Athens, Greece

D. Gozal, L. Kheirandish-Gozal (eds.), *Pediatric Sleep Medicine*, https://doi.org/10.1007/978-3-030-65574-7_24

Analysis

It is crucial to understand how many hours children should sleep during the newborn to adolescent stages, orienting the normal range of sleep duration. In a more detailed manner, newborns tend to sleep 12–18 hours per day, while infants and toddlers sleep 14–15 and 12–14 hours, respectively. Sleep hours tend to decrease in preschoolers (11–13), school age (10–11), and adolescents (8–9.25) [1]. However, the age stages can be interrupted by sleep disturbances, reducing or increasing the sleep duration.

Sleep–Wake Disorders and Their Pharmacotherapy: An Ambiguous Perspective

The lack of approved view of the FDA toward pharmacotherapy in sleep disorders in children is correlated with the lack of efficient and limited clinical trials. Nevertheless, there is a drug in the pediatric population (aged 7–17), which has been approved by the FDA such as sodium oxybate for narcolepsy. However, for other drugs, the FDA has saturated this praxis with dysfunction [20]. For this reason, stressing the drugs for sleep–wake disorders is cardinal to be established by research results (see Table 24.1).

Insomnia

Insomnia is characterized by a sense of sleeplessness with symptoms of lethargy or non-restfulness. Nine different types of drugs were found for the treatment of insomnia for individuals who are under 18 years old. Starting with sleep-promoting hormone melatonin, which has mostly been employed for treatment for children's insomnia. More specifically, based on meta-analysis, melatonin decreased the sleep onset latency [21]; there are side effects such as somnolence and nightmares in children [22]. The range of melatonin doses varies from 0.05 to 5 mg/kg, and it is recommended that melatonin should be consumed 1–2 hours before bedtime.

Moreover, other types of drug can ameliorate insomnia symptoms based on research evidence. Antihistaminergic drugs such as diphenhydramine (0.5–20 mg/kg) and hydroxyzine (1 mg) aim to reduce H1 histamine levels. Insomnia tends to be associated with high levels of histamines, because histamines promote arousal in the sleep–wake cycle during wakefulness. These drugs should be used 30 minutes before bedtime. Adverse effects such as sedation were observed [2].

Furthermore, though alpha-adrenergic receptor agonists (clonidine and guanfacine) enhance sleep, their mechanism on sleep is still unknown. But clonidine evokes REM suppression, and REM rebounds when clonidine is discontinuous. Recommended doses for clonidine ranged from 0.025 to 0.1 mg and for the dosing range of guanfacine waves 0.05–4 mg. These drugs are taken twice per day, namely at morning and evening [2, 4, 23].

Also, benzodiazepines hypnotics are prescribed more in adults than in children. The soporific effects of clonazepam have been used for insomnia treatment in children. It reduces arousals, and it is prescribed at doses between 0.25 and 0.5 mg, at bedtime [4]. Similarly, non-benzodiazepine receptor agonists may alleviate insomnia symptoms. Specifically, zolpidem (0.125–0.50 mg/kg at bedtime) is beneficial on treating sleep onset insomnia, and rarely for sleep-maintenance insomnia [24].

Regarding the antidepressants (trazodone, 5-HT2 receptor antagonist, 50 mg at bedtime), and tricyclic antidepressants like imipramine (0.05 mg/kg at bedtime) and amitriptyline (0.05 mg/kg at bedtime), though of vast use in the adult population for insomnia treatment, children are much less recommended, due mostly to the anticholinergic side effects [2, 25]. Therefore, a serotonin and melatonin precursor, namely $_{L}$-5-hydroxytryptophan (1–2 mg, at bedtime), is considered a safer therapeutic choice for insomnia, as well as the hypnotic agent, chloral hydrate (25–50 mg/kg or 1 g maximum; 15–30 minutes before bedtime) [2].

The most recent drug in research for insomnia in children is suvorexant, which is a hypocretin/orexin receptor antagonist [26]. Regarding non-adults, a single study from Japan was identified, which advocated that suvorexant (20 mg, 30 minutes before bedtime) reduced insomnia symptoms and improved overall sleep quality in adolescents suffering from insomnia. A total of 56.7% of the participants continued this drug, whereas the therapy was mostly abandoned due to unpleasant dreams (e.g., nightmares, which are reported anyway as known side effects). Nightmares are quite common in children/adolescents (their prevalence in adolescents in Japan is 35.2%), thus the prescription of this drug should be made carefully [26].

Parasomnia

Parasomnia (involuntary body movements involved during sleep) is mainly classified in two categories (according to the sleep stage they occur), namely NREM (non-rapid eye movement)-related parasomnias and REM-related parasomnias. These disorders are commonly treated by benzodiazepines (clonazepam, 0.125–2 mg, at bedtime), antidepressants (trazodone 25–50 mg, at bedtime), serotoninergic antide-

Table 24.1 Drugs for sleep–wake disorders in pediatric population

Sleep–wake disorders	Drug classes	Drugs and their doses	Timing of medication
Insomnia	Melatonin	0.05–5 mg/kg	1–2 hours before bedtime
	Antihistaminergics	Diphenhydramine (0.5–20 mg/kg) and hydroxyzine (1 mg)	30 minutes before bedtime
	Alpha-adrenergic receptor agonists	Clonidine (0.025–0.1 mg) and guanfacine (0.05–4 mg)	Twice daily dosing (morning and evening)
	Benzodiazepines hypnotics	Clonazepam (0.25–0.5 mg)	Bedtime
	Nonbenzodiazepine receptor agonists	Zolpidem (5 mg or 0.25 mg/kg)	Bedtime
	Antidepressants	Trazodone (50 mg), imipramine (0.05 mg/kg) and amitriptyline (5–50 mg)	Bedtime
	$_{L}$-5-Hydroxytryptophan	1–2 mg	Bedtime
	Chloral hydrate	25–50 mg/kg or 1 g maximum	15 to 30 minutes before bedtime
	Hypocretin/orexin receptor antagonists	Suvorexant (20 mg)	30 minutes before bedtime
Parasomnia	Benzodiazepines	Clonazepam (0.125–2 mg)	Bedtime
	Antidepressants	Trazodone (25–50 mg), paroxetine (20 mg) and imipramine (0.25–0.5 mg)	Bedtime
	$_{L}$-5-Hydroxytryptophan	2 mg/kg	Bedtime
	Melatonin	3–12 mg	30 minutes before bedtime or at bedtime
	Alpha-agonist hypotensive agents	Prazosin (1–15 mg)	Bedtime
	Antipsychotics (for nightmare disorder)	Risperidone (no data for children)	–
	Calcium entry blockers (for explode head syndrome)	Flunarizine (no data for children)	–
	Anticholinergics (for sleep enuresis)	Oxybutynin (0.1–0.3 mg/kg) and propiverine (0.8–1 mg/kg)	Bedtime
	Antidiuretics (for sleep enuresis)	Desmopressin (0.1–0.4 mg)	1 to 2 hours before water intake
Hypersomnolence	Central nervous system stimulants	Dextroamphetamine (5–30 mg) and methylphenidate (10–40 mg)	Twice daily dosing (morning and evening)
	Wake promoting agents	Modafinil (50–400 mg) and armodafinil (50–400 mg)	Twice daily dosing (morning and evening)
Cataplexy	Antidepressants	Imipramine (10–100 mg), clomipramine (10–150 mg), fluoxetine (10–30 mg), protriptyline (2.5–5 mg) and venlafaxine (37.5–75 mg)	Once a day
	Immunoglobulin therapy	Immunoglobulin G (400 mg-1 g/kg)	For 2 (1 g/kg) or 5 (400 mg) days per week
	Sodium oxybate	2–8 g	Twice daily dosing (bedtime and 2.5 to 3 hours later)
Circadian rhythm sleep–wake disorders	Melatonin	1–3 mg	Morning
	β1-adrenergic antagonists	Acebutolol (10 mg/kg or 200 mg)	Morning
	Vitamin B12	1.5 mg	Once a day
Sleep apnea	Antibiotics	Azithromycin (12 mg/kg)	Days of the month: 1–5, 11–15 and 21–25
	Leukotriene receptor antagonists	Montelukast (4–5 mg)	Once a day
	Corticosteroids	Fluticasone (50 μg)	Once a day
Sleep-related movement disorders	Iron supplementation	Ferrous sulfate (3–6 mg/kg)	Twice daily dosing
	Benzodiazepines	Clonazepam (0.25–0.50 mg) and temazepam (7.5–22.5 mg)	1 to 2 hours before bedtime
	Anticonvulsant	Gabapentin (100–900 mg)	30 minutes to 1 hour before bedtime
	Alpha-2 adrenergic agonists	Clonidine (0.05–0.4 mg)	30 minutes before bedtime
	Dopamine agonists	$_{L}$-dopa (250–600 mg), pramipexole (0.125–0.250) and ropinirole (0.125–0.250 mg)	For $_{L}$-dopa 4 doses (breakfast, lunch, afternoon, and evening) and in the evening or 2 or 3 hours prior to the start of RLS symptoms for pramipexole and ropinirole

pressants (paroxetine, 20 mg, at bedtime) and tricyclic antidepressants (imipramine, 0.25–0.5 mg, at bedtime), although solid evidence from randomized controlled trials, etc. is missing in pediatric sleep medicine [27–30]. Besides these classical treatments, there are anecdotally referred other remedies in pediatric sleep medicine; an open pharmacological therapy trial was conducted by Bruni et al. [31], where $_{L}$-5-hydroxytryptophan (2 mg/kg at bedtime) showed beneficial effects for the reduction of sleep terrors (a cardinal NREM parasomnia); the latter finding was attributed to the fact that $_{L}$-5 hydroxytryptophan tends to ameliorate the abnormal serotoninergic system dysfunction, connected with parasomnia disorders.

Furthermore, melatonin (3–12 mg at bedtime or 30 minutes before bedtime) was used for the treatment of NREM parasomnias (sleepwalking and sleep terrors) in a case study [32]. In particular, a 12-year-old male with Asperger's syndrome consumed 5 mg melatonin, 30 minutes before bedtime. During the treatment process, sleepwalking and sleep terrors vanished, and there was no recurrence of them for over 6 months. Melatonin has also been used in REM parasomnias (in REM sleep behavior disorder—RBD, which is a cardinal REM parasomnia characterized by dream-enactment motor behavior); melatonin in RBD seems to repair the normal REM-related muscle atonia, which is abolished in RBD, although this effect is modest and certainly needs more investigation [33].

Other drugs used in parasomnias with no sufficient data in pediatric sleep medicine, include clonidine, a α2 adrenergic agonist (which has been used for sleep paralysis, another known REM parasomnia), atypical antipsychotic drugs (e.g., risperidone, used for nightmare disorder, a REM parasomnia) and calcium entry blockers (flunarizine; tested for exploding head syndrome in adult population, which is a rare parasomnia) [30]. In a recent study with follow-up findings, prazosin (a sympatholytic drug, 1–15 mg at bedtime) reduced the severity of nightmares in children with PTSD-associated nightmares [34].

In sleep enuresis (another frequent parasomnia in pediatric sleep medicine), drugs such as anticholinergics, antidiuretic peptides, and antidepressants are mostly used [34]. For example, desmopressin (an antidiuretic drug, 0.1–0.4 mg 1–2 hours before water intake) can reduce bedwetting in 70% of the pediatric population, improving the quality of life of children [35]. Beneficial results were found with some other drugs: Imipramine, which is a tricyclic antidepressant, tends to reinforce the bladder by holding larger amounts of urine before a urinary urge; moreover, anticholinergics agents (oxybutynin, 0.1–0.3 mg/kg at bedtime; propiverine, 0.8–1 mg/kg at bedtime) improve the function of bladder capacity via increasing threshold volume, and by decreasing involuntary detrusor contractions [36].

Central Disorders of Hypersomnolence

This sleep disorder entity includes four main disorders: narcolepsy type 1, narcolepsy type 2, idiopathic hypersomnia, and Kleine–Levin syndrome. The most common finding in these disorders is hypersomnolence (a condition of abnormal prolonged sleep), while in narcolepsy there may be also cataplexy, which is the sudden partial or total loss of muscle tone triggered by strong emotions and driven by a deficit of orexin [37].

For the drug treatment of hypersomnolence, central nervous system stimulants (CNSS) and wake promoting agents are first line therapy. In practice, dextroamphetamine (a CNSS drug, 5–30 mg, with a twice daily dose regimen) has a more efficient effect on the increasing of alertness (four times) than methylphenidate (10–40 mg, with a twice daily dose regimen), while methylphenidate tends to alleviate somnolence in children [38]. CNSS drugs release dopamine and norepinephrine via presynaptic terminals or inhibited reuptakes. Also, wake promoting agents like Modafinil (50–400 mg with a twice daily dose regimen) and armodafinil (50–400 mg, again with a twice daily dose regimen) enhance the cortical arousal and increase histamine levels, as a result of which somnolence gets reduced [38]. Modafinil improves somnolence as shown by both subjective and objective measurements [39].

Moreover, antidepressants, immunoglobulin therapy and sodium oxybate have shown promising results for cataplexy [38]. The anticholinergic effects of tricyclic antidepressants (imipramine, 10–100 mg; clomipramine, 10–150 mg) modestly decreased cataplexy attacks [40]. Other types of antidepressants such as selective serotonin reuptake inhibitors (fluoxetine, 10–30 mg) and serotonin-norepinephrine reuptake inhibitors (venlafaxine, 37.5–75 mg) are also used for cataplexy in narcolepsy [41]. Finally, sodium oxybate (2–8 g), which is a gamma-aminobutyric acid (GABA) receptor agonist, which is the only FDA drug approved for pediatric narcolepsy with cataplexy, improves both daytime sleepiness and cataplexy [42]. Moreover, sodium oxybate may influence other REM phenomena in the context of narcolepsy (i.e., sleep paralysis); nevertheless, its mechanism of action remains equivocal. Sodium oxybate is administrated by twice-daily dosing with the first dose administered at bedtime and the second dose 2.5–3 hours later [42].

Finally, in a small sample of narcolepsy type 1 patients (four patients, two children), Dauvilliers et al. [43] used immunoglobulin G therapy (400 mg-1 g/kg), with a beneficial effect on both daytime sleepiness and cataplexy after a 7-month follow-up. On the other hand, the immunoglobulin G therapy gave beneficial evidence only on severe type narcoleptic children. The immunoglobulin G therapy is taken for 2 or 5 days per week, with doses of 1 g/kg and 400 mg, respectively [43].

Circadian Rhythm Sleep–Wake Disorders

Circadian rhythm sleep–wake disorders (CRSWD) are characterized by abnormalities in sleep architecture, affecting the timing of sleep and waking across the day. Melatonin (1–3 mg, taken in the morning) is the most used therapy for CRSWD. Melatonin has sleep-inducing and chronobiotic effects, with a beneficial effect on sleep onset latency reduction [44]. In a randomized double-blind placebo-controlled trial in pediatric population (3–12 years), Gringras et al. [45] found that though melatonin therapy reduced sleep onset latency, there was a non-statistically significant result on sleep efficacy; the authors stressed the importance of melatonin as a chronobiotic mechanism (phase-shift of the sleep–wake rhythm).

Nevertheless, in pediatric sleep medicine several issues regarding melatonin , that is, the required dosages, the type of melatonin to be used (e.g., immediate release versus extended release), its prolonged effect etc., remain to be clarified [44]. Melatonin is implicated in CRSWD also indirectly; β1-adrenergic antagonists (i.e., acebutolol, 10 mg/kg or 200 mg, taken in the morning) decreases melatonin production during the day via the noradrenaline stimulating pathway. Thus, acebutolol in children (aged 3–17) with Smith–Magenis syndrome (SMs), which is a developmental syndrome that includes sleep disturbances, that is, CRSWD due to high diurnal levels of melatonin, improved their sleep/wake profile by reducing naps, fatigue, sleepiness, and consequent attention issues during the day [46]. Ramelteon and Tasimelteon have been considered as possible treatments in SMs, but no large well-controlled pharmaceutical trials have been reported to date [47]. Finally, Vitamin B12 (1.5 mg) has been administered in a 15-year-old blind girl suffering from a free-running sleep–wake rhythm, with beneficial effects [48].

Sleep-Related Breathing Disorders

Sleep Apnea

Obstructive sleep apnea (OSA) is one of the most common sleep-related breathing disorders in children. The main therapeutic approach in pediatric OSA is based on surgery, because adenotonsillar hypertrophy is a common cause of OSA. However, a surgical approach may add risks during the operation and postsurgery period and proper criteria for this kind of surgery for OSA are still lacking today [2].

Drug therapy in OSA and especially in pediatric OSA has been scarcely investigated. Montelukast, which is a leukotriene receptor antagonist and a common drug for asthma treatment, and corticosteroids have been mostly used. In a randomized control trial with 6 weeks' corticosteroid treatment (fluticasone, 50 μg), OSA severity was reduced modestly; thus, apnea–hypopnea index (AHI) after steroid treatment was decreased from 11/h to 5/h [49]. Similarly, AHI reduction (AHI was decreased by >50%) in a sample of 23 children was achieved using montelukast (4 or 5 mg) in a treatment period of 12 weeks [50]. In a systematic literature review and meta-analysis, Liming et al. [51] have observed that montelukast and corticosteroids provide beneficial outcomes only for children with mild OSA and for short-term management only.

Another drug category that has been tested for OSA in pediatric sleep medicine is antibiotics. Don and colleagues [52] showed that azithromycin (a common macrolide), when given at 12 mg/kg and for the first 5 days of the month (the dose was repeated on days 11–15 and 21–25), ameliorated OSA when compared with placebo, by reducing adenoid and tonsil sizes; actually, azithromycin led to the relief of OSA symptoms, but surgery remained still the treatment of choice [52]. Azithromycin is also useful for the reduction of elevated levels of C-reactive protein [53], which not only is a potential biomarker of OSA, but also increases after adenotonsillectomy [54].

Sleep-Related Movement Disorders

The most common sleep-related movement disorders in the pediatric population are restless legs syndrome (RLS) and Periodic Limb Movement Disorder (PLMD). RLS, which is a common neurologic sleep disorder (2–4% in children), is described as an urge to move the legs, usually accompanied by uncomfortable or unpleasant sensations. The symptoms begin or worsen during rest or inactivity, are relieved by movement, and occur exclusively or predominantly in the evening or night [55]. There is a recent update on the pediatric diagnostic criteria [56, 57], while diagnosis of RLS is done on a clinical basis. PLMD is characterized by clinical sleep disturbance and by repetitive limb jerking during sleep (known as periodic limb movements of sleep) that is not better explained by another condition, medication use, or substance use [55]. Diagnosis of PLMD is done by specific polysomnographic criteria. PLMD is closely related to RLS existence, especially in the pediatric population, while both diseases are related to iron deficiency and have a genetic predisposition [57].

There is no FDA guidance for PLMD and RLS in children. Regardless of that, iron supplements mostly and dopamine agonists have been used as treatments of choice [58]. Iron supplementation in pediatric population (ferrous sulfate 3–6 mg/kg, dividing in two doses) with RLS and PLMD, showed a significant and long-term improvement after 2 years [59]. Moreover, iron supplement does not seem to have severe adverse effects on children with PLMD [60]. However, Reynold [58] has stressed that 27% of children with concomitant autism spectrum disorder and RLS developed gastrointestinal symptoms following iron treatment and the range of this side effect was 5–60% in treatment processing.

Benzodiazepines like clonazepam have been used in children with RLS, even though this was in younger children,

aged from 8 months to 2 years old. The recommended dose ranges from 0.25 to 0.5 mg, daily, and should be taken 1–2 hours before bedtime [61]. Also, research has bolstered the efficacy of clonazepam on the amelioration of anxiety issues, which may be comorbidities to RLS or PLMD; besides clonazepam, temazepam (7.5–22.5 mg depending on the age of the patient) has been used as well [62, 63].

Alpha-2-delta calcium channel ligands, such as pregabalin and gabapentin, which are mostly used in the treatment of RLS in adults, should be used with caution when about pediatric RLS/PLM, although they have already shown a good safety profile when used for pediatric epilepsy [64]. Gabapentin improves states of RLS or PLMD in children 6 years old and above. Gabapentin dosage increases along the age increase; more specifically, children between 6 and 12 years should get 100 mg/day, and if the symptoms are not alleviated, the regimen should be increased up to a maximum of 600 mg/day. For children between 12 and 18 years old, dosage ranges between 100 and 900 mg/day. Gabapentin should be taken 30 minutes to 1 hour before bedtime [61].

Alpha-2 adrenergic agonists (e.g., clonidine) are also an alternative for the treatment of RLS; however, their short-lasting action makes these drugs not suitable for sleep maintenance disturbances due to RLS. Side effects like nightmares or vivid dreams have been reported in 5% of children taken clonidine. Suggested dose is 0.05–0.4 mg, 30 minutes before bedtime [65].

Finally, the most widely used drugs for adult RLS/PLM, dopamine agonists and $_{L}$-Dopa, are certainly less indicated for pediatric RLS/PLM due to considerable side effects (i.e., sleepiness, hallucinations, nausea, obsessive and/or compulsive symptomatology). Dopamine agonists (pramipexole and ropinirole) have provided essential efficacy against moderate-to-severe RLS or PLMD. However, in adults, these drugs are associated with potential side effects of augmentation. Pramipexole and ropinirole should be consumed in the evening or 2 or 3 hours prior to RLS symptomatology onset and their doses range from 0.125 to 0.250 daily, according to RLS or PLMD severity [61]. $_{L}$-dopa (250–600 mg, in 4 doses (breakfast, lunch, afternoon, and evening)) has been used successfully in a double-blind study for the reduction of RLS and PLMD symptomatology [66].

What Pediatric Somnologists Should Take into Consideration When Drugs Used in Common Pediatric Practice Impact Sleep

Several medical therapies have adverse effects on sleep [67, 68]. Thus, we provide some examples of drugs that affect in pediatric population. Common pediatric drugs are mentioned in the World Health Organization (WHO) 2017 List (Table 24.2) [69].

Table 24.2 Medical specialties and the impact of drugs on sleep

Medical specialties	Drug categories or vaccines	Sleep side effects
Internal medicine	Corticosteroid drugs	Somnolence, insomnia, longer sleep, daytime naps and less awakening
	Beta-blocker drugs	Insomnia, nightmares, and restless sleep
	Immunosuppressive drugs	Insomnia, snoring, somnolence, restless legs syndrome and periodic limb movement disorder
	Phosphodiesterase-5 inhibitor	Insomnia
	Methylxanthine drugs	Improved sleep apnea
	First-generation antihistamines	Drowsiness
	Anesthetics	Midazolam: bed-wetting, night terrors and prolonged sleep Meperidine and hydroxyzine: prolonged sleep Ketamine: reduced REM sleep
Neurology and psychiatry	Antiepileptic drugs	Increased sleep tendency, somnolence, and insomnia
	Stimulants for attention deficit/hyperactivity disorder	Decreased sleep time, quality and efficiency, increased sleep tendency
	Antidepressants	Selective serotonin reuptake inhibitors: increased levels of arousals, REM density and stage 1 sleep. Tricyclics: increased stage 2 sleep, sleep architecture disruptions, decreased slow wave sleep, REM sleep suppression and sleep fragmentation
	Antipsychotic	Risperidone: somnolence and insomnia Haloperidol: improved total sleep time
	Non-benzodiazepine hypnotic	Zolpidem: increased the number of awakenings, sleep slow wave and rapid eye movement
Vaccines	Human papilloma virus vaccine	Insomnia and other unspecific sleep disturbances
	ASO-3 adjuvanted swine flu vaccine	Narcolepsy
	Diphtheria-tetanus-pertussis vaccine, H influenza type b vaccine, pneumococcal conjugate vaccine, inactivated poliovirus vaccine, and hepatitis B vaccine	Increased sleep durations

Internal Medicine

Dexamethasone, a common drug for allergies, immunological diseases, or tumors, affects sleep by modifying the level of alertness. Garbutt et al. [70] reported that 40% of children receiving dexamethasone for croup, complained about sleep disturbances. Rosen et al. [71] reported that children receiving dexamethasone for leukemia slept longer than usual during the first 5 days of therapy, with more daytime naps and less awakenings. Furthermore, in a recent review regarding steroids in pediatric population, 4.3% of children receiving corticosteroids reported sleep disturbances [72]. Other immunosuppressive drugs, like tacrolimus, cellcept, and prednisone have also sleep side effects such as insomnia, snoring, somnolence, RLS, and PLMD [73–75].

Beta-blockers have been widely used in children for the management of arrhythmias, hypertension, and benign tumors. Bernabeu-Wittel et al. [76] reported that among children receiving beta-blockers and more specifically propranolol, insomnia, and nightmares were the most common side effects. In a recent systematic review 3.7% of 1175 children with infant hemangioma treated with propranolol suffered from nightmares, with consequences on memory and learning [77]. De Graaf et al. [78] also reported that restless sleep appeared in 29% of children with hemangioma undergoing beta-blocker therapy. Moreover, 24% of pediatric population reported insomnia after treatment with phosphodiesterase-5 inhibitor, sildenafil, for pulmonary hypertension. However, in this study, it was not clear if insomnia was a clear side effect of sildenafil or consequence of the combination therapy of sildenafil with bosentan or ambrisentan (endothelin receptor antagonists) [79].

Methylxanthine or theophylline for asthma therapy, decreased apnea and oxyhemoglobin desaturation during sleep probably because of its bronchodilator effect, reduction of airways inflammation and normalization of pulmonary arterial pressure [12, 13, 80]. On the contrary, antihistamines, for the treatment of allergic rhinitis, wheezing, and other pulmonary diseases or infections, were not associated with improvement of apnea in infants when compared with placebo. Moreover, drowsiness was observed in children with allergic rhinitis treated with first-generation antihistamines due to their prominent CNS action [81].

Surgery and Anesthesia

Drugs used in anesthesia may change sleep structure in the postoperative period. Ritwik et al. investigated the side effects of the combination of meperidine and hydroxyzine versus midazolam in dental care. They observed that, in the first 8 to 24 hours, all children in the combined drug group had experienced prolonged sleep compared with the children in the midazolam group (66.7%) [82]. Furthermore, regarding midazolam, McGraw and Kendrick noticed that in the first postoperative week, children who got midazolam experienced bed-wetting and night terrors [83].

In randomized crossover studies in a pediatric intensive care unit, in children under zolpidem (a non-benzodiazepine hypnotic) or haloperidol (a typical first-generation antipsychotic agent) (due to severe burns), Zolpidem tended to increase the number of awakenings, whereas haloperidol did not have any significant effect on awakenings. There was a significant improvement with haloperidol in terms of total sleep time, which increased by 23% compared with the control group. Zolpidem on the other hand, increased slow wave sleep and REM sleep. In the same study population, administration of ketamine was related with low percentages of REM sleep, while there was no impact on slow wave sleep, frequency of awakenings, total sleep time and on percentages of stages 1 and 2 [84]. Similarly, in another postoperative study, sevoflurane, and halothane (another two common anesthetics) did not affect sleep at all [85].

Neurology and Psychiatry

Children with epilepsy under treatment have complaints about sleep disturbances. In 1992, Palm et al. [86] assessed sleepiness in pre-adolescents under antiepileptic drugs (valproate and carbamazepine) while and after drug withdrawal. It was shown that children who were receiving treatment experienced more sleep tendency and sleepiness than when off treatment. In another study, parents of epileptic children under antiepileptic drugs reported several sleep disorders such as sleep apnea, parasomnia, and daytime somnolence; the latter symptom, though very common in this study (75.8% of the children suffered from daytime sleepiness), seemed to be attributed to sleep apnea and to parasomnia rather than to antiepileptic drugs [87]. To be mentioned that potential side effects of antiepileptic drugs on sleep (i.e., insomnia, restless legs syndrome, parasomnia) have been mostly studied in adults, while data on children are quite scarce [88].

It is important to mention the effect of stimulants drugs on children with attention deficit hyperactivity disorder (ADHD), which are among the drugs of choice for this disorder; it has been shown by employing objective measurements, that stimulants decrease the sleep quality in these children [89]. Stimulants tend to increase alertness by reducing total sleep time, sleep efficiency in children with ADHD [90]. On the other hand, there has been data in favor of possible amelioration of sleep issues (e.g., insomnia or bedtime resistance) of children with ADHD following ther-

apy with stimulants [91]. Given the debatable data regarding the effect of stimulants on sleep of children with ADHD, Kidwell and her colleagues [92] conducted a meta-analysis; thus, it was shown that stimulants increased sleep latency and consequently decreased total sleep time and sleep efficiency, suggesting a negative effect on sleep in children with ADHD.

Antidepressants when used for depression seem to disturb both sleep quality and quantity in children and adolescents with major depression. Fluoxetine, which is a quite common SSRI drug, increases the number of arousals, stage 1 sleep, and REM density [93]. Tricyclic antidepressants such as imipramine cause sleep architecture disruptions and sleep fragmentation, decreased slow wave sleep, REM sleep suppression, and increased stage 2 sleep [94].

Antipsychotic drugs such as risperidone, commonly used in case of autism, may have adverse events such as somnolence. Kent et al. reported that daytime somnolence in autistic children following antipsychotic therapy with risperidone, was dose-related; the prevalence of somnolence was lower (3%) in children with low-dose risperidone, while it was quite high (55%) when about high dose [95]. In another study on children with developmental disorders under risperidone, somnolence was mostly prevalent (72.5%), but insomnia occurred as well (15.4%) [96].

Vaccines

Vaccination for human papilloma virus (HPV) was associated with insomnia in 3 out of 18 girls after the first dose; insomnia was alleviated after the second and third dose [97]. However, another study revealed a prevalence of 47.2% of any sleep complaint among girls vaccinated for HPV [98]. Increased risk of narcolepsy (4.7 to 14 times) was observed following vaccination with a monovalent 2009 H1N1 influenza vaccine, which was used in several European countries during the H1N1 influenza pandemic [99]. In China, a threefold increased risk of narcolepsy was observed during postepidemic H1N1 vaccination in 5.6% of the population [100]. It seems that Pandemrix may trigger the gene HLA DQB0602, which generates disturbance of the orexin system, and the vaccinated children were positive for this gene [99].

Finally, Franck and colleagues [101] used prophylactic acetaminophen in infants after several vaccinations (diphtheria-tetanus-pertussis vaccine, H influenza type b vaccine, pneumococcal conjugate vaccine, inactivated poliovirus vaccine, and hepatitis B vaccine) and observed shorter sleep duration in this population when comparing with non-receiving acetaminophen infants.

Discussion

The aim of this chapter was to investigate the effect of drugs on pediatric sleep medicine. Disturbed, “not normal”, sleep in children is associated with developmental and cognitive deficits and reduced learning or social skills and is a matter of special attention. However, this assessment is complicated as guidelines and official approvals regarding pharmacotherapy lack, mainly because of the absence of randomized, controlled trials. In addition, sleep disorders’ symptoms in children vary from adults’ and/or between different ages and special training in pediatric sleep medicine is still overall insufficient. Finally, several pediatric drugs in “daytime”, clinic practice affect sleep.

For the treatment of insomnia in children, several drugs such as melatonin, antihistaminic drugs, a-agonists, benzodiazepines and nonbenzodiazepine receptor agonists, antidepressants, $_{L}$-5-hydroxytryptophan, hypocretin/orexin receptor antagonists, and chloral hydrate have been proposed, in addition to behavioral therapies and sleep hygiene [2, 28]. However, the limited amount of available data in the literature and the lack of specific guidelines lead to caution in the selection of drug therapy and suggest that non-pharmacological treatments should be engaged first [2–4].

For parasomnias, again non-pharmacological assessments (i.e., avoiding parasomnia triggering factors, or adopting safety measures) are mostly suggested; if conservative measures are not adequate and drugs should be given, slow wave sleep suppressants such as benzodiazepines or tricyclic antidepressants, given for a short period and followed by slow tapering, are the most appropriate [2].

Regarding excessive daytime sleepiness (EDS) and hypersomnolence of central origin, there is only one drug with FDA approval; sodium oxybate is the only drug, which has received indication for the treatment of both EDS and cataplexy in the context of narcolepsy type 1 (narcolepsy with cataplexy) [50]. Besides that, several other drugs – not FDA approved – are used for the treatment of either hypersomnolence or cataplexy; thus, stimulants and wake-promoting agents have been used for the treatment of EDS, in hypersomnolence of central origin (i.e., amphetamines and modafinil), whereas norepinephrine reuptake inhibitors, histamine H3 receptor antagonists, could be an alternative therapy, while tricyclic antidepressants, SSRIs, and SNRIs have also been used for cataplexy treatment [42]. Finally, sleep hygiene rules, frequent and prescheduled naps against EDS, and education about the triggers and the nature of the episodes of cataplexy are extremely useful in the therapeutic approach.

Concerning pediatric RLS/PLM, again no FDA indications exist. For mild cases non-pharmacologic measures (sleep hygiene, physical exercise, and trigger control) are mostly indicated, while drugs are proposed only for chronic,

moderate to severe cases [61]. For children with iron deficiency and RLS or PLMD, oral iron supplementation is suggested [59, 60]. Limited data exist about benzodiazepines as an alternative therapy, whereas dopaminergic agents or alpha-2-delta calcium channel ligands should be used with caution in pediatric populations [61].

Surgery is the therapy of choice for OSAS in children, whereas nasal continuous positive airway pressure can be an alternative therapy for children not eligible for surgery or in case of residual disease. Nocturnal supplemental oxygen therapy can be suggested only as a temporary until definitive therapy [102]. For mild OSA when surgery (adenotonsillectomy) in not indicated or mild postoperative residual OSA, intranasal corticosteroids, leukotriene modifiers, and their combination could be a treatment of choice [51]. The minimum duration of therapy for sustained benefit is not known. Antibiotics may not fully provide persistent relief of apneas or prevent surgical therapy [52].

Also, several common pediatric medical therapies can affect independently sleep quality or quantity. Children receiving corticosteroids or other immunosuppressive drugs complain about sleep disturbances, such as insomnia, snoring, somnolence, RLS, and PLMD. Beta-blockers and especially propranolol and phosphodiesterase-5 inhibitor, sildenafil, can cause insomnia and nightmares. Methylxanthine or theophylline reduce apneas and oxyhemoglobin desaturation during sleep. On the contrary, treatment with first-generation antihistamines is associated with drowsiness in children. As far as the drugs used in common neurological/neurodevelopmental/psychiatric disorders (i.e., epilepsy, autism, ADHD, depression) is concerned, the overall impression is that the indicated drugs for these diseases may alter sleep/wake cycle by disturbing sleep's quantity and quality and by producing and/or increasing daytime sleepiness**.** Finally**,** vaccination is sometimes implicated in sleep disorders in children, with increased risk of narcolepsy reported during postepidemic H1N1 vaccination.

In summary, though pediatric sleep medicine is an important part of sleep medicine and of pediatrics as well, robust evidence and guidelines regarding its pharmacologic treatment are still lacking. Furthermore, several drugs used in common pediatric practice may affect sleep (its quality and quantity) and wakefulness as well. Therefore, more attention (i.e., more studies, more evidence and/or guidelines) should be paid in order to improve sleep and consequently overall well-being of the children.

References

1. Kotagal S. Sleep-wake disorders of childhood. Continuum (Minneapolis, Minn.). 2017;23(4):1132–50.
2. Economou NT, Ferini-Strambi L, Steiropoulos P. Sleep-related drug therapy in special conditions: children. Sleep Med Clin. 2018;13(2):251–62.
3. Pelayo R, Dubik M. Pediatric sleep pharmacology. Semin Pediatr Neurol. 2008;15(2):79–90.
4. Pelayo R, Huseni S. Pharmacotherapy of insomnia in children. Curr Sleep Med Rep. 2016;2(1):38–43.
5. Felt BT, Chervin RD. Medications for sleep disturbances in children. Neurol Clin Pract. 2014;4(1):82–7.
6. Mindell JA, Owens JA, Carskadon MA. Developmental features of sleep. Child Adolesc Psychiatr Clin N Am. 1999;8(4):695–725.
7. Ipsiroglu OS, Fatemi A, Werner I, Tiefenthaler M, Urschitz MS, Schwarz B. Prevalence of sleep disorders in school children between 11 and 15 years of age. Wien Klin Wochenschr. 2001;113(7):235–44.
8. Byars KC, Yolton K, Rausch J, Lanphear B, Beebe DW. Prevalence, patterns, and persistence of sleep problems in the first 3 years of life. Pediatrics. 2012;129(2):276–84.
9. Kotagal S, Chopra A. Pediatric sleep-wake disorders. Neurol Clin. 2012;30(4):1193–212.
10. Akinsanya A, Marwaha R, Tampi RR. Prazosin in children and adolescents with posttraumatic stress disorder who have nightmares: a systematic review. J Clin Psychopharmacol. 2017;37(1):84–8.
11. Gringras P, Nir T, Breddy J, Frydman-Marom A, Findling RL. Efficacy and safety of pediatric prolonged-release melatonin for insomnia in children with autism Spectrum disorder. J Am Acad Child Adolesc Psychiatry. 2017;56(11):948–57.
12. Avital A, Steljes DG, Pasterkamp H, Kryger M, Sanchez I, Chernick V. Sleep quality in children with asthma treated with theophylline or cromolyn sodium. J Pediatr. 1991;119(6):979–84.
13. Margay SM, Farhat S, Kaur S, Teli HA. To study the efficacy and safety of doxophylline and theophylline in bronchial asthma. J Clin Diagn Res. 2015;9(4):5–8.
14. Meltzer LJ, Beck SE. Sleep patterns in children with cystic fibrosis. Child Health Care. 2012;41(3):260–8.
15. Rohde KA, Schlei ZW, Katers KM, Weber AK, Brokhof MM, Hawes DS, et al. Insomnia and relationship with immunosuppressant therapy after lung transplantation. Prog Transplant. 2017;27(2):167–74.
16. Mansfield DR, Solin P, Roebuck T, Bergin P, Kaye DM, Naughton MT. The effect of successful heart transplant treatment of heart failure on central sleep apnea. Chest. 2003;124(5):1675–81.
17. Naraine VS, Bradley TD, Singer LG. Prevalence of sleep disordered breathing in lung transplant recipients. J Clin Sleep Med. 2009;5(5):441–7.
18. Reilly-Spong M, Park T, Gross CR. Poor sleep in organ transplant recipients: self-reports and actigraphy. Clin Transpl. 2013;27(6):1–20.
19. Badet L, Petruzzo P, Lefrançois N, Morelon E, Martin X, Dubernard JM. Side-effects and potential complications. In: Lanzetta M, Dubernard JM, editors. Hand transplantation. New York: Springer; 2007. p. 223–6.
20. Sullivan SS. Current treatment of selected pediatric sleep disorders. Neurotherapeutics. 2012;9(4):791–800.
21. Ferracioli-Oda E, Qawasmi A, Bloch MH. Meta-analysis: melatonin for the treatment of primary sleep disorders. PLoS One. 2013;8(5):e63773.
22. Parker A, Beresford B, Dawson V, Elphick H, Fairhurst C, Hewitt C, et al. Oral melatonin for non-respiratory sleep disturbance in children with neurodisabilities: systematic review and meta-analyses. Dev Med Child Neurol. 2019;61(8):880.
23. Ingrassia A, Turk J. The use of clonidine for severe and intractable sleep problems in children with neurodevelopmental disorders–a case series. Eur Child Adolesc Psychiatry. 2005;14(1):34–40.
24. Blumer JL, Reed MD, Steinberg F, O'Riordan MA, Rosen CL, Springer MA, et al. Potential pharmacokinetic basis for zolpidem

dosing in children with sleep difficulties. Clin Pharmacol Ther. 2008;83(4):551–8.
25. Owens JA, Rosen CL, Mindell JA, Kirchner HL. Use of pharmacotherapy for insomnia in child psychiatry practice: a national survey. Sleep Med. 2010;11(7):692–700.
26. Kawabe K, Horiuchi F, Ochi M, Nishimoto K, Ueno S, Oka Y. Suvorexant for the treatment of insomnia in adolescents. J Child Adolesc Psychopharmacol. 2017;27(9):792–5.
27. Attarian H, Zhu L. Treatment options for disorders of arousal: a case series. Int J Neurosci. 2013;123(9):623–5.
28. Howell MJ. Parasomnias: an updated review. Neurotherapeutics. 2012;9(4):753–5.
29. Attarian H. Treatment options for parasomnias. Neurol Clin. 2010;28(4):1089–106.
30. Proserpio P, Nobili L. Parasomnias in children. In: Nevšímalová S, Bruni O, editors. Sleep disorders in children. Basel: Springer; 2016. p. 305–35.
31. Bruni O, Ferri R, Miano S, Verrillo E. L -5-Hydroxytryptophan treatment of sleep terrors in children. Eur J Pediatr. 2004;163(7):402–7.
32. Jan JE, Freeman RD, Wasdell MB, Bomben MM. A child with severe night terrors and sleepwalking responds to melatonin therapy. Dev Med Child Neurol. 2004;46(11):789.
33. Lloyd R, Tippmann-Peikert M, Slocumb N, Kotagal S. Characteristics of REM sleep behavior disorder in childhood. J Clin Sleep Med. 2012;8(2):127–31.
34. Keeshin BR, Ding Q, Presson AP, Berkowitz SJ, Strawn JR. Use of prazosin for pediatric PTSD-associated nightmares and sleep disturbances: a retrospective chart review. Neurol Ther. 2017;6(2):247–57.
35. Fagundes SN, Lebl AS, Azevedo-Soster L, Sousa E, Silva GJ, Silvares EF, Koch VH. Monosymptomatic nocturnal enuresis in pediatric patients: multidisciplinary assessment and effects of therapeutic intervention. Pediatr Nephrol. 2017;32(5):843–51.
36. Siddiqui JA, Qureshi SF, Allaithy A, Mahfouz TA. Nocturnal enuresis: a synopsis of behavioral and pharmacological management. Sleep Hypn. 2019;21(1):16–22.
37. Sateia MJ. International classification of sleep disorders-third edition: highlights and modifications. Chest. 2014;146(5):1387–94.
38. Nishino S, Kotorii N. Modes of action of drugs related to narcolepsy: pharmacology of wake-promoting compounds and anticataplectics. In: Goswami M, Thorpy MJ, Pandi-Perumal SR, editors. Narcolepsy: a clinical guide. New York: Springer; 2016. p. 307–29.
39. Ivanenko A, Tauman R, Gozal D. Modafinil in the treatment of excessive daytime sleepiness in children. Sleep Med. 2003;4(6):589–2.
40. Ristanovic RK, Liang H, Hornfeldt CS, Lai C. Exacerbation of cataplexy following gradual withdrawal of antidepressants: manifestation of probable protracted rebound cataplexy. Sleep Med. 2009;10(4):416–21.
41. Cak HT, Haliloğlu G, Düzgün G, Yüce A, Topçu M. Successful treatment of cataplexy in patients with early-infantile Niemann-pick disease type C: use of tricyclic antidepressants. Eur J Paediatr Neurol. 2014;18(6):811–5.
42. Kotagal S. Treatment of narcolepsy and other organic hypersomnias in children. Paediatr Respir Rev. 2018;25:19–24.
43. Dauvilliers Y, Carlander B, Rivier F, Touchon J, Tafti M. Successful management of cataplexy with intravenous immunoglobulins at narcolepsy onset. Ann Neurol. 2004;56(6):905–8.
44. Richdale AL, Baker EK. Circadian rhythm sleep disorders. In: Accardo JA, editor. Sleep in children with neurodevelopmental disabilities: an evidence-based guide. Basel: Springer; 2018. p. 111–22.
45. Gringras P, Gamble C, Jones AP, Wiggs L, Williamson PR, Sutcliffe A, et al. Melatonin for sleep problems in children with neurodevelopmental disorders: randomised double masked placebo-controlled trial. BMJ. 2012;345:e6664.
46. De Leersnyder H, de Blois MC, Vekemans M, Sidi D, Villain E, Kindermans C, et al. β1-adrenergic antagonists improve sleep and behavioural disturbances in a circadian disorder, Smith-Magenis syndrome. J Med Genet. 2001;38(9):586–90.
47. Shayota BJ, Elsea SH. Behavior and sleep disturbance in Smith-Magenis syndrome. Curr Opin Psychiatry. 2019;32(2):73–8.
48. Okawa M, Mishima K, Nanami T, Shimizu T, Iijima S, Hishikawa Y, et al. Vitamin B12 treatment for sleep-wake rhythm disorders. Sleep. 1990;13(1):15–23.
49. 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.
50. Goldbart AD, Greenberg-Dotan S, Tal A. Montelukast for children with obstructive sleep apnea: a double-blind, placebo-controlled study. Pediatrics. 2012;130(3):e575–80.
51. Liming BJ, Ryan M, Mack D, Ahmad I, Camacho M. Montelukast and nasal corticosteroids to treat pediatric obstructive sleep apnea: a systematic review and meta-analysis. Otolaryngol Head Neck Surg. 2019;160(4):594–602.
52. Don DM, Goldstein NA, Crockett DM, Ward SD. Antimicrobial therapy for children with adenotonsillar hypertrophy and obstructive sleep apnea: a prospective randomized trial comparing azithromycin vs placebo. Otolaryngol Head Neck Surg. 2005;133(4):562–8.
53. Ratjen F, Saiman L, Mayer-Hamblett N, Lands LC, Kloster M, Thompson V, et al. Effect of azithromycin on systemic markers of inflammation in patients with cystic fibrosis uninfected with Pseudomonas aeruginosa. Chest. 2012;142(5):1259–66.
54. Bhattacharjee R, Kheirandish-Gozal L, Kaditis AG, Verhulst SL, Gozal D. C-reactive protein as a potential biomarker of residual obstructive sleep apnea following adenotonsillectomy in children. Sleep. 2016;39(2):283–91.
55. American Academy of Sleep Medicine. International classification of sleep disorders. 3rd ed. Darien: American Academy of Sleep Medicine; 2014.
56. Picchietti DL, Bruni O, de Weerd A, Durmer JS, Kotagal S, Owens JA, et al. Pediatric restless legs syndrome diagnostic criteria: an update by the international restless legs syndrome study group. Sleep Med. 2013;14(12):1253–9.
57. Allen RP, Picchietti DL, Garcia-Borreguero D, Ondo WG, Walters AS, Winkelman JW, et al. Restless legs syndrome/Willis-Ekbom disease diagnostic criteria: updated International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria–history, rationale, description, and significance. Sleep Med. 2014;15(8):860–73.
58. Reynolds A. Sleep-related movement disorders: an evidence-based guide. In: Accardo JA, editor. Sleep in children with neurodevelopmental disabilities. Basel: Springer; 2018. p. 123–35.
59. Dye TJ, Jain SV, Simakajornboon N. Outcomes of long-term iron supplementation in pediatric restless legs syndrome/periodic limb movement disorder (RLS/PLMD). Sleep Med. 2017;32:213–9.
60. Simakajornboon N, Gozal D, Vlasic V, Mark C, Sharon D, McGinley BM. Periodic limb movements in sleep and iron status in children. Sleep. 2002;26(6):735–8.
61. Pereira JC, Pradella-Hallinan M, Alves RC. Childhood restless legs syndrome. Med Ex. 2014;1(3):116–22.
62. Picchietti DL, Rajendran RR, Wilson MP, Picchietti MA. Pediatric restless legs syndrome and periodic limb movement disorder: parent-child pairs. Sleep Med. 2009;10(8):925–31.
63. Picchietti DL, Stevens HE. Early manifestations of restless legs syndrome in childhood and adolescence. Sleep Med. 2008;9(7):770–81.

64. Troester MM, Pelayo R. Pediatric sleep pharmacology: a primer. Semin Pediatr Neurol. 2015;22(2):135–47.
65. Picchietti MA, Picchietti DL. Advances in pediatric restless legs syndrome: iron, genetics, diagnosis and treatment. Sleep Med. 2010;11(7):643–51.
66. England SJ, Picchietti DL, Couvadelli BV, Fisher BC, Siddiqui F, Wagner ML, et al. L-Dopa improves restless legs syndrome and periodic limb movements in sleep but not attention-deficit-hyperactivity disorder in a double-blind trial in children. Sleep Med. 2011;12(5):471–7.
67. Lenz TL. Drugs that negatively affect sleep. Am J Lifestyle Med. 2014;8(6):383–5.
68. Lewandowski AS, Ward TM, Palermo TM. Sleep problems in children and adolescents with common medical conditions. Pediatr Clin N Am. 2011;58(3):699–713.
69. World Health Organization. WHO Model List of Essential Medicines for Children. [Online].Geneva: World Health Organization; 2017 Mar [cited 2017 Mar] Available from: https://www.who.int/medicines/publications/essentialmedicines/6th_EMLc2017.pdf.
70. Garbutt JM, Conlon B, Sterkel R, Baty J, Schechtman KB, Mandrell K, et al. The comparative effectiveness of prednisolone and dexamethasone for children with croup: a community-based randomized trial. Clin Pediatr (Phila). 2013;52(11):1014–21.
71. Rosen G, Harris AK, Liu M, Dreyfus J, Krueger J, Messinger YH. The effects of dexamethasone on sleep in young children with acute lymphoblastic leukemia. Sleep Med. 2015;16(4):503–9.
72. Aljebab F, Choonara I, Conroy S. Systematic review of the toxicity of short-course oral corticosteroids in children. Arch Dis Child. 2016;101(4):365–70.
73. Armitage JM, Fricker FJ, Del Nido P, Cipriani L, Starzl TE. The clinical trial of FK 506 as primary and rescue immunosuppression in pediatric cardiac transplantation. Transplant Proc. 1991;23(6):3058–60.
74. Andersen MN, Dore-Stites D, Gleit R, Lopez MJ, Fredericks EM. A pilot study of the association between sleep disturbance in children with liver transplants and parent and family health-related quality of life. J Pediatr Psychol. 2014;39(7):735–42.
75. Fredericks EM, Dore-Stites D, Calderon SY, Well A, Eder SJ, Magee JC, et al. The relationship between sleep problems and health related quality of life among pediatric liver transplant recipients. Liver Transpl. 2013;18(6):707–15.
76. Bernabeu-Wittel J, Narvaez-Moreno B, de la Torre-Garcıa JM, Fernandez-Pineda I, Domınguez-Cruz JJ, Coserrıa-Sanchez F, et al. Oral Nadolol for children with infantile hemangiomas and sleep disturbances with Oral propranolol. Pediatr Dermatol. 2015;32(6):853–7.
77. Marqueling AL, Oza V, Frieden IJ, Puttgen KB. Propranolol and infantile hemangiomas four years later: a systematic review. Pediatr Dermatol. 2013;30(2):182–91.
78. de Graaf M, Breur JM, Raphael MF, Vos M, Breugem CC, Pasmans SG. Adverse effects of propranolol when used in the treatment of hemangiomas: a case series of 28 infants. J Am Acad Dermatol. 2011;65(2):320–7.
79. Siehr SL, McCathy EK, Ogawa MT, Feinstein JA. Reported sildenafil side effects in pediatric pulmonary hypertension patients. Front Pediatr. 2015;3(12):1–4.
80. Onatibia-Astibia A, Martínez-Pinilla E, Franco R. The potential of methylxanthine-based therapies in pediatric respiratory tract diseases. Respir Med. 2016;112:1–9.
81. Del Cuvillo A, Sastre J, Montoro J, Jáuregui I, Ferrer M, Dávila I, et al. Use of antihistamines in pediatrics. J Investig Allergol Clin Immunol. 2007;17:28–40.
82. Ritwik P, Cao LT, Curran R, Musselman RJ. Post-sedation events in children sedated for dental care. Anesth Prog. 2013;30(2):54–9.
83. McGraw T, Kendrick A. Oral midazolam premedication and postoperative behaviour in children. Paediatr Anaesth. 1998;8(2):117–21.
84. Kudchadkar SR, Aljohani OA, Punjabi NM. Sleep of critically ill children in the pediatric intensive care unit: a systematic review. Sleep Med Rev. 2014;18(2):103–10.
85. Kain ZN, Caldwell-Andrews AA, Weinberg ME, Mayes LC, Wang SM, Gaal D, et al. Sevoflurane versus halothane: postoperative maladaptive behavioral changes: a randomized, controlled trial. Anesthesiology. 2005;102(4):720–6.
86. Palm L, Anderson H, Elmqvist D, Blennow G. Daytime sleep tendency before and after discontinuation of antiepileptic drugs in preadolescent children with epilepsy. Epilepsia. 1992;33(4):687–91.
87. Maganti R, Hausman N, Koehn M, Sandok E, Glurich I, Mukesh BN. Excessive daytime sleepiness and sleep complaints among children with epilepsy. Epilepsy Behav. 2006;8(1):272–7.
88. Al-Biltagi MA. Childhood epilepsy and sleep. World J Clin Pediatr. 2014;3(3):45–53.
89. Ironside S, Davidson F, Corkum P. Circadian motor activity affected by stimulant medication in children with attention-deficit/hyperactivity disorder. J Sleep Res. 2010;19(4):546–51.
90. Corkum P, Panton R, Ironside S, Macpherson M, Williams T. Acute impact of immediate release methylphenidate administered three times a day on sleep in children with attention-deficit/hyperactivity disorder. J Pediatr Psychol. 2008;33(4):368–79.
91. Findling RL, Childress AC, Cutler AJ, Gasior M, Hamdani M, Ferreira-Cornwell MC, et al. Efficacy and safety of lisdexamfetamine dimesylate in adolescents with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2011;50(4):395–405.
92. Kidwell KM, Van Dyk TR, Lundahl A, Nelson TD. Stimulant medications and sleep for youth with ADHD: a meta-analysis. Pediatrics. 2015;136(6):1144–53.
93. Armitage R, Emslie G, Rintelmann J. The effect of fluoxetine on sleep EEG in childhood depression: a preliminary report. Neuropsychopharmacology. 1997;17(4):241–5.
94. Shain BN, Naylor M, Shipley JE, Alessi N. Imipramine effects on sleep in depressed adolescents: a preliminary report. Biol Psychiatry. 1990;28(5):459–62.
95. Kent JM, Kushner S, Ning X, Karcher K, Ness S, Aman M, et al. Risperidone dosing in children and adolescents with autistic disorder: a double-blind, placebo-controlled study. J Autism Dev Disord. 2013;43(8):1773.
96. Shea S, Turgay A, Carroll A, Schulz M, Orlik H, Smith I, et al. Risperidone in the treatment of disruptive behavioral symptoms in children with autistic and other pervasive developmental disorders. Pediatrics. 2004;114(5):e634–41.
97. Palmieri B, Poddighe D, Vadala M, Laurino C, Carnovale C, Clementi E. Severe somatoform and dysautonomic syndromes after HPV vaccination: case series and review of literature. Immunol Res. 2017;65(1):106–16.
98. Ozawa K, Hineno A, Kinoshita T, Ishihara S, Ikeda SI. Suspected adverse effects after human papillomavirus vaccination: a temporal relationship between vaccine administration and the appearance of symptoms in Japan. Drug Saf. 2017;40(12):1219–29.
99. Thebault S, Vincent A, Gringras P. Narcolepsy and H1N1 vaccination: a link? Curr Opin Pulm Med. 2013;19(6):587–93.
100. Han F, Lin L, Warby SC, Faraco J, Li J, Dong SX, et al. Narcolepsy onset is seasonal and increased following the 2009 H1N1 pandemic in China. Ann Neurol. 2011;70(3):410–7.
101. Franck L, Gay CL, Lynch M, Lee KA. Infant sleep after immunization: randomized controlled trial of prophylactic acetaminophen. Pediatrics. 2011;128(6):1100–8.
102. Diblasi RM. Nasal continuous positive airway pressure (CPAP) for the respiratory care of the newborn infant. Respir Care. 2009;54(9):1209–35.