

# Pharmacology of Sleep Disorders in Children and Adolescents

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## KEYWORDS

- Pediatric sleep disorders • Medications • Narcolepsy
- Restless legs syndrome • Obstructive sleep apnea • Insomnia

There is a high prevalence of sleep disorders in children and an apparent increasing need for pharmacologic management. However, because of the paucity of data available with regards to dosing, efficacy, tolerability, and safety profiles of medications as well as a lack of adequate well-designed clinical trials, medications are currently not approved in the pediatric population by the US Food and Drug Administration (FDA). No pharmacologic guidelines have been developed for the specific sleep disorders or the different pediatric age ranges. Additional research is needed for evidence-based pediatric sleep pharmacotherapy. This article reviews the various pediatric sleep disorders and the pharmacologic therapeutic options that are available.

## INSOMNIA

Pediatric insomnia is defined as repeated difficulty with sleep initiation, duration, consolidation, or quality that occurs despite age-appropriate time and opportunity for sleep and results in daytime functional impairment for the child and/or the family.<sup>1,2</sup> It is a common problem and one of the most frequently reported parental concerns in

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pediatric practices.<sup>3</sup> Prevalence rates range from 1% to 6% in the otherwise healthy pediatric population to as high as 50% to 75% in children and adolescents with psychiatric and neurodevelopmental disorders. Although most of the sleep disturbances are usually short-lived, emerging data indicate these can persist and become chronic.<sup>4-7</sup>

Several studies have shown the profound adverse consequences of pediatric insomnia, which affect not only the children and adolescents concerned but also their families. A few commonly reported daytime consequences in children include hyperactivity, poor memory, learning difficulties, impulsive behaviors, and an increase in accidental injuries. Parents of sleepless children are also more likely to have depressed mood, poor daytime performance, and increased stress levels. These symptoms have been shown to improve with the treatment of the pediatric insomnia.<sup>8-10</sup> Given the high prevalence and chronicity within select populations and negative consequences of pediatric insomnia, effective management of this condition is becoming increasingly necessary.

Two main therapeutic approaches are generally used: cognitive-behavioral therapy and pharmacologic therapy. Whereas the efficacy of cognitive-behavioral therapy or behavioral therapy alone is relatively well established, there is a paucity of evidence-based data for use of pharmacologic therapy within the pediatric population.<sup>2,11,12</sup> Despite this, it appears that the rate for the use of medications by physicians for the treatment of pediatric insomnia in an outpatient setting in the United States is increasing, which is concerning given the lack of information regarding specific guidelines for dosing regimens, efficacy, and safety profiles of these medications.<sup>13</sup> The medications currently used are not approved by the FDA for the different pediatric age ranges nor for the specific sleep disorder, leading to off-label use. Some of the commonly used medications include melatonin, antihistamines, and  $\alpha_2$  adrenergic agonists among others.

### **Melatonin**

Melatonin (*N*-acetyl-5-methoxytryptamine) is a hormone synthesized and secreted predominantly by the pineal gland. In a survey of 3424 community-based pediatricians, melatonin ranked as the third most frequently used medication after antihistamines and  $\alpha_2$  agonists.<sup>14</sup> It is synthesized from its precursor tryptophan, and the secretion from the pineal gland is regulated by the suprachiasmatic nucleus in the hypothalamus. Levels of endogenous melatonin are usually high at nighttime and decrease during the habitual wake-up time, suggesting that it may play a cardinal role in the control of the sleep-wake cycle in humans. Exogenous melatonin is hepatically metabolized, has a half-life of 30 to 50 minutes, and onset of action is typically within 30 to 60 minutes. Although dosing guidelines have not been established, exogenous melatonin doses of 0.3 mg typically produce physiologic nocturnal levels of 50 to 200 pcg/mL.<sup>15</sup>

Studies have reported a reduction in the latency to sleep onset as well as an increase in sleep maintenance and total sleep time, with doses ranging from 0.5 to 10 mg. Melatonin has both chronobiotic and weak hypnotic properties and its use has been suggested to be most effective in blind children, children with attention-deficit/hyperactivity disorder (ADHD), and autistic spectrum disorder or insomnia caused by circadian disorders such as circadian rhythm disorder-delayed sleep phase type.<sup>16-18</sup> Although melatonin is generally well tolerated, long-term effects of chronic use are unknown. Potential side effects may include disturbances of the central nervous system (CNS) and lowering of seizure threshold, along with rare reports of gynecomastia and autoimmune hepatitis. The National Sleep Foundation has urged avoidance of the use of melatonin in patients with immune disorders, or in patients taking immunosuppressants or corticosteroids.<sup>19-21</sup> The FDA does not regulate the

safety, purity, or efficacy of commercially available preparations of melatonin; one preparation may differ significantly from the other and results can thus vary.

### **Melatonin Agonists**

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Ramelteon is a melatonin agonist that acts by binding to the melatonin receptors MT<sub>1</sub> and MT<sub>2</sub> in the suprachiasmatic nucleus.<sup>22</sup> It is approved by the FDA for the treatment of insomnia in adults and is the only prescription sedative-hypnotic medication that is not a scheduled substance with the US Drug Enforcement Administration. Ramelteon has been shown to reduce latency to sleep onset, increase total sleep time, and result in reports of subjective benefit, although changes in sleep may increase slowly over weeks of nightly use.<sup>23</sup> It can be used for sleep initiation problems and is not associated with next-day hangover effect/residual sedation, rebound insomnia, or withdrawal. Side effects such as headache are rare.<sup>24</sup> Ramelteon has a half-life of up to 5 hours because of an active metabolite. The adult dose is 8 mg daily 30 minutes before bedtime, and patients should avoid a fatty meal before administration.<sup>25</sup> Ramelteon is primarily metabolized by cytochrome (CYP) 1A2 and should be used with caution when administered with other medications that inhibit this substrate (eg, fluvoxamine).<sup>25</sup> Ramelteon is currently not approved for use in children and adolescents.

### **Antihistamines**

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In pediatric practices, antihistamines are generally used in the treatment of allergies, and are often an active ingredient of many over-the-counter (OTC) cold and allergy preparations. However, despite the lack of randomized controlled trials showing the efficacy of antihistamines as hypnotic medications in children, antihistamines have increasingly become one of the more popular choices of pediatricians and parents and are currently the most commonly used medications to treat sleep disturbances in children.<sup>26</sup> Diphenhydramine is a lipophilic, first-generation antihistamine that causes sedation by easily crossing the blood-brain barrier and competitively blocking the histamine (H<sub>1</sub>) receptors. It is rapidly absorbed from the gastrointestinal system, undergoes extensive first-pass metabolism, and is hepatically metabolized. The peak sedative effect occurs 1 to 3 hours after administration and typically lasts 4 to 7 hours. Pediatric dosing ranges from 1 mg/kg up to 50 mg per day.<sup>15</sup>

Diphenhydramine reduces the latency to sleep onset but overall, an improvement in parental satisfaction or reduction in nighttime awakenings has not been shown when compared with placebo.<sup>27</sup> Side effects are anticholinergic in nature and include dry mouth, urinary retention, daytime drowsiness, hypotension, and tachycardia. Children have also been reported to experience paradoxical excitation, and tolerance to antihistamines, which can result in the administration of higher doses and greater risk of side effects.<sup>28</sup> Seizures, cardiac arrhythmias, rhabdomyolysis, and respiratory insufficiency are more serious but rare consequences reported predominantly in overdose situations.<sup>29</sup>

### **Chloral Hydrate**

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Chloral hydrate was commonly used as a sedative hypnotic in children but lost its popularity because of the significant side-effect profile, including respiratory compromise and the potential hangover effect that can occur because of the long half-lives of its active metabolite, trichloroethanol.<sup>15,30</sup> Chloral hydrate results in a reduction in latency to sleep onset, and hypnotic doses in children range from 25 to 50 mg/kg/dose (maximal dose 1 g) at bedtime. Maximal effect is typically seen within 30 to 60 minutes and lasts approximately 4 to 8 hours.<sup>15</sup>

Side effects can range from drowsiness, malaise, paradoxical excitement, nausea, vomiting, and gastric distress to depression of the CNS, arrhythmias, and respiratory compromise. Chloral hydrate should thus be used cautiously or avoided in children with sleep-disordered breathing, gastritis/esophagitis, severe cardiac disease, hepatic and renal dysfunction, and patients with porphyria or on stimulant medications.<sup>15</sup> Tolerance is also a concern, and used chronically (>2 weeks) chloral hydrate can become habit forming. Withdrawal symptoms, including seizures and delirium, may occur if discontinued abruptly after prolonged use.<sup>31,32</sup> The American Academy of Pediatrics recommends limiting the use of chloral hydrate to short-term sedation.<sup>33</sup>

### ***Benzodiazepines***

This class of sleep-promoting medications acts by binding to several  $\gamma$ -aminobutyric acid (GABA) type A receptor subtypes. Medications include temazepam, estazolam, triazolam, quazepam, flurazepam, and clonazepam.<sup>25,34</sup> They reduce the latency to sleep onset, the number of arousals or awakenings that occur between sleep-stage transitions, and increase total sleep time. Benzodiazepines have also been associated with an alteration in sleep structure including an increase in stage N2 sleep as well as rapid eye movement (REM) latency.<sup>25</sup> They have anxiolytic and anticonvulsant properties. Potential side effects include residual daytime sedation, memory impairment, behavioral disinhibition, and dependence with prolonged use.<sup>35</sup>

Benzodiazepines are not commonly used in the treatment of pediatric insomnia. Clonazepam is the possible exception in the treatment of disorders of partial arousal in children and adolescents when frequent and disruptive to the patient and family, predominantly because of its ability to increase the arousal threshold and suppress slow-wave sleep. The administered dose of clonazepam ranges from 0.25 mg to 0.5 mg at bedtime, although dosing guidelines have not been established. It has a prolonged half-life of 22 to 33 hours, onset of effect in 20 to 60 minutes, and levels typically peak within 1 to 4 hours of administration. Clonazepam is hepatically metabolized by CYP 3A4, and concomitant medications that inhibit or induce this substrate may affect the concentrations of clonazepam (**Tables 1 and 2**).<sup>15</sup>

### ***Selective benzodiazepine receptor agonists***

This class of medications includes zolpidem, zaleplon, and eszopiclone. Despite being known as benzodiazepine receptor agonists, these medications differ in their chemical structure from the benzodiazepines and bind more selectively to the benzodiazepine-1 receptor site.<sup>36</sup> They thus lack the anxiolytic, anticonvulsant, and muscle-relaxing properties of the traditional benzodiazepines associated with binding at the benzodiazepine-2 receptor.<sup>36</sup> They are not known to alter the sleep architecture and are less likely to result in rebound insomnia or hangover effects. Studies have shown a decrease in the latency to sleep onset and the number of awakenings during the night as well as an improvement in the sleep duration and quality.<sup>35</sup>

Zaleplon has a half-life of 1 to 2 hours, zolpidem, 2 to 3 hours, and eszopiclone, 5 to 7 hours. They typically reach peak values between 30 and 60 minutes and are hepatically metabolized.<sup>37,38</sup> Zolpidem and eszopiclone are major substrates for CYP 3A4 and have the potential for drug interactions. In adults zolpidem immediate release is considered for difficulty with sleep initiation and the controlled release can be used for difficulty with sleep onset and/or sleep maintenance. Zaleplon may be considered for sleep initiation problems and can also be used for the reinitiation of sleep during awakenings in the middle of the night because of its short half-life.<sup>39</sup> Eszopiclone can be considered for difficulty in initiating and maintaining sleep throughout the night.

| Table 1<br>Medications used for the treatment of insomnia |                               |              |                                                 |
|-----------------------------------------------------------|-------------------------------|--------------|-------------------------------------------------|
| Medication Class                                          | Medication                    | FDA Approved | Schedule                                        |
| Melatonin agonist                                         | Ramelteon (Rozerem)           | Yes          | Prescription<br>(noncontrolled)                 |
| Antihistamines                                            | Diphenhydramine<br>(Benadryl) | Yes          | OTC                                             |
|                                                           | Doxylamine (Unisom)           | Yes          | Often found in<br>combination<br>with analgesic |
| Nonbarbiturate hypnotic                                   | Chloral hydrate (Somnote)     | Yes          | C-IV                                            |
| Benzodiazepines                                           | Temazepam (Restoril)          | Yes          | C-IV                                            |
|                                                           | Triazolam (Halcion)           | Yes          |                                                 |
|                                                           | Flurazepam (Dalmane)          | Yes          |                                                 |
|                                                           | Estazolam (Prosom)            | Yes          |                                                 |
|                                                           | Quazepam (Doral)              | Yes          |                                                 |
|                                                           | Clonazepam (Klonopin)         | No           |                                                 |
|                                                           | Lorazepam (Ativan)            | No           |                                                 |
| Nonbenzodiazepines                                        | Zolpidem (Ambien)             | Yes          | C-IV                                            |
|                                                           | Zalepon (Sonata)              | Yes          |                                                 |
|                                                           | Eszopiclone (Lunesta)         | Yes          |                                                 |
| $\alpha_2$ agonists                                       | Clonidine (Catapres)          | No           | Prescription<br>(noncontrolled)                 |
| Antidepressants                                           | Amitriptyline (Elavil)        | No           | Prescription<br>(noncontrolled)                 |
|                                                           | Nortriptyline (Pamelor)       | No           |                                                 |
|                                                           | Doxepin (Sinequan)            | No           |                                                 |
|                                                           | Trazodone (Desyrel)           | No           |                                                 |
|                                                           | Mirtazapine (Remeron)         | No           |                                                 |
| Herbal supplements                                        | Melatonin                     | No           | Dietary supplements<br>Not FDA regulated        |
|                                                           | Kava-kava                     | No           |                                                 |
|                                                           | Valerian                      | No           |                                                 |
|                                                           | Lavender                      | No           |                                                 |
|                                                           | Chamomile                     | No           |                                                 |

Abbreviation: C-IV, controlled substance schedule IV.

Data from Refs. <sup>15,25,36,101</sup>

Eszopiclone is currently approved by the FDA for the treatment of chronic insomnia in adults because of evidence for long-term safety with no development of tolerance or dependence.<sup>40</sup> Typical adult dosages are zolpidem immediate release 5 to 10 mg, zolpidem extended release 12.5 mg, zaleplon 5 to 10 mg, and eszopiclone 1 to 3 mg. However, the use of these medications in children is considered off-label because they are currently not approved by the FDA. Dosing guidelines are not available for the pediatric population. Although these drugs are generally well tolerated, potential side effects can include excess sedation, dizziness, amnesia, parasomnias, complex sleep behaviors (eg, sleepwalking, sleep-related eating disorders, sleep-driving) and worsening of untreated sleep-disordered breathing. Eszopiclone has also been noted to have an unpleasant metallic taste.<sup>25</sup> Tolerance, dependence, and rebound effects are less common than benzodiazepines.<sup>41</sup>

### Centrally Acting $\alpha_2$ Agonists

Clonidine and guanfacine are both centrally acting  $\alpha_2$  receptor agonists indicated for the treatment of hypertension in the adult population. However, despite the lack of randomized clinical trials, these medications (particularly clonidine) are widely used

**Table 2**  
**Characteristics of FDA-approved medications for the treatment of insomnia**

| Medication                     | Adult Initial Dose           | Onset of Action | Sleep Latency | Total Sleep Time       | Delta Sleep |
|--------------------------------|------------------------------|-----------------|---------------|------------------------|-------------|
| <b>Melatonin agonists</b>      |                              |                 |               |                        |             |
| Ramelteon                      | 8 mg                         | 30 min          | Decreased     | Increased              | No effect   |
| <b>Antihistamines</b>          |                              |                 |               |                        |             |
| Diphenhydramine                | 0.5 mg/kg/dose (pediatric)   | 1–3 h           | Decreased     | Increased              | N/A         |
| Doxylamine                     | 25 mg                        | N/A             |               |                        |             |
| <b>Nonbarbiturate hypnotic</b> |                              |                 |               |                        |             |
| Chloral hydrate                | 25–50 mg/kg/dose (pediatric) | 10–20 min       | Decreased     | Increased              | No effect   |
| <b>Benzodiazepines</b>         |                              |                 |               |                        |             |
| Temazepam                      | 7.5–15 mg                    | 30–60 min       | Decreased     | Increased              | Decreased   |
| Triazolam                      | 0.125–0.25 mg                | 15–30 min       |               |                        |             |
| Estazolam                      | 1 mg                         | 60 min          |               |                        |             |
| Clonazepam                     | 0.25–0.5 mg (pediatric)      | 20–60 min       |               |                        |             |
| <b>Nonbenzodiazepines</b>      |                              |                 |               |                        |             |
| Zolpidem                       | 5–10 mg                      | 30 min          | Decreased     | Increased              | Increased   |
| Zaleplon                       | 5–10 mg                      | 20 min          |               | Increased or no effect |             |
| Eszopiclone                    | 1–2 mg                       | 30 min          |               | Increased              |             |

Abbreviation: N/A, not available.

Data from Refs. <sup>15,25,36,102</sup>

as soporifics in the pediatric population because of their sedating properties.<sup>26</sup> Clonidine use has also been reported for the management of sleep disturbances in children with ADHD.<sup>42</sup> It has a half-life of 8 to 12 hours in children, and plasma levels typically peak between 2 and 4 hours, with an onset of action within an hour.<sup>15</sup> As with other medications used in the treatment of pediatric insomnia, optimum soporific dosing guidelines have not been established, but clonidine is typically administered at a starting dose of 0.05 mg at bedtime and increased in increments of 0.05 mg every 3 to 4 days (usual maximum 0.3–0.4 mg/d) depending on efficacy.<sup>15,43</sup>

Effects on sleep include a reduced latency to sleep onset and REM sleep suppression. Clonidine has a narrow therapeutic index, and side effects include hypotension, bradycardia, dry mouth, irritability, and dysphoria. Tolerance can also develop over time, leading to an increase in dosage and the potential for adverse effects. A dramatic increase in clonidine overdoses has recently been reported.<sup>44</sup> Rebound hypertension and REM rebound can occur with abrupt discontinuation. Therefore, when discontinuing this medication, a gradual taper of over 1 week should be recommended to patients.

### **Antidepressants**

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Commonly used medications in this class include amitriptyline, trazodone, and doxepin. These antidepressants are sedating because of their anticholinergic or antihistaminergic activity and despite only a few randomized controlled and open-label trials in adults and no data in the pediatric population, they continue to be a popular choice amongst both adult and pediatric providers because of familiarity with the medications. However, the use of sedating antidepressants for the treatment of insomnia is not approved by the FDA. Tolerance can develop, resulting in the need for higher doses, and common side effects include hangover effect, dry mouth, dizziness, confusion, and constipation. Tricyclic antidepressants are also associated with cardiovascular toxicity (eg, tachycardia, orthostatic hypotension, and conduction abnormalities) and death can occur from overdosage.<sup>45,46</sup>

### **Herbal Supplements**

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There are few data with regards to efficacy and safety profile of herbal supplements in children. Adult studies have at best shown either a lack of beneficial effect<sup>47</sup> or safety concerns like severe hepatotoxicity with certain herbal supplements like kava-kava.<sup>48</sup>

## **RESTLESS LEGS SYNDROME**

Restless legs syndrome (RLS) is a neurologic sensorimotor disorder characterized by unpleasant paresthesias that occur primarily in the lower extremities and are accompanied by a strong and nearly irresistible urge to move. The paresthesias may include numbness, tingling, and aching and can also be experienced, albeit less commonly, in other parts of the body, including the arms and the trunk. These symptoms are brought on during periods of inactivity and display a circadian pattern such that the paresthesias are worse in the evening and night in those with normal circadian rhythm activity. A complete or partial improvement is usually seen with movement for as long as the movement continues.<sup>49</sup>

The 4 essential criteria for the diagnosis of RLS can be summarized in the mnemonic URGE, explained as U: urge to move the legs because of unpleasant sensations; R: worsening during periods of rest; G: gets better with movement; and E: worse in the evenings. To make a diagnosis of RLS in the pediatric population (aged 2–12 years), it is essential that in addition to meeting all 4 of these criteria, the

child should be able to describe the unpleasant sensations in their own words.<sup>49,50</sup> If the child is unable to do so, but does meet the 4 criteria, a diagnosis of RLS can be made if 2 of the following 3 criteria are also present: sleep disturbance appropriate for age, a biologic parent or sibling who has RLS, or a periodic limb movement in sleep index of greater than 5/h on polysomnography.

The adult diagnostic criteria can be used for adolescents (ie, older than 12 years).<sup>49,50</sup> Patients with RLS may experience 2 types of leg movements: voluntary and involuntary. The former are movements that are made to obtain relief from the unpleasant paresthesias, such as walking the floor or stretching. The involuntary leg movements are repetitive movements over which the patient has minimal control. These movements may occur during sleep (periodic limb movements in sleep) or while awake (periodic limb movements during wakefulness). Periodic limb movements in sleep are a common feature on polysomnography in about 80% of patients with RLS although they may also exist on their own.<sup>51</sup>

Although originally believed to be a disorder of adults, RLS has been increasingly described in the pediatric population, with an estimated prevalence rate of 1.9% in school-aged children and 2% in adolescents, with no gender differences reported. These prevalence rates are higher than that of diabetes or epilepsy.<sup>52</sup> Patients with RLS can have a prolonged latency to sleep and disrupted nocturnal sleep and other adverse consequences affecting mood, behavior, and quality of life.<sup>53</sup> There is increasing evidence suggesting a relationship of RLS with ADHD,<sup>54</sup> conduct disorder,<sup>55</sup> depression/anxiety, and parasomnias.<sup>56</sup>

The management of children and adolescents with RLS is challenging and there are currently no specific recommendations made by the American Academy of Sleep Medicine.<sup>57</sup> Children with mild or infrequent symptoms of RLS may be managed conservatively with nonpharmacologic therapy. The aim is to eliminate or reduce factors that may exacerbate the symptoms of RLS, including caffeine, alcohol, nicotine, selective serotonin reuptake inhibitors, dopamine antagonists, and antihistamines. Adherence to good sleep hygiene and avoidance of sleep deprivation is essential as a worsening of symptoms has been noted with drowsiness. Massaging the affected areas, application of hot/cold packs, and engaging in moderate exercise may also be beneficial.<sup>58</sup>

Commonly used classes of medications in the treatment of adult RLS include iron supplementation, dopaminergic agents, benzodiazepines, anticonvulsants, and opioids. Pharmacologic therapy for significant RLS in children is more challenging because of the limited data available with regards to efficacy and safety profile of these medications. Medications should be used in conjunction with nonpharmacologic therapy and started only after carefully considering the benefits of the medication compared with potential risks.

### ***Dopaminergic Medications***

Studies have suggested that hypofunction of the dopaminergic system may play a role in the pathophysiology of RLS. The improvement noted in clinical symptoms with dopaminergic medications further supports this finding.<sup>59,60</sup> Dopaminergic agents are currently considered to be first-line therapy in adult patients with RLS<sup>61,62</sup> and medications in this class that have been found to be effective include carbidopa/levodopa, and the nonergot dopamine agonists ropinirole and pramipexole. The last two are FDA-approved medications for the treatment of moderate to severe primary RLS in adults. The rare but serious consequences including the development of pleuropulmonary fibrosis<sup>63</sup> and cardiac valvulopathy<sup>64</sup> limit the use of ergot dopaminergic agents such as pergolide and bromocriptine.

Although there are currently no FDA-approved medications for the treatment of RLS in children, published reports have emerged suggesting the efficacy of dopaminergic agents in children with RLS.<sup>65–67</sup> However, there are no dosing guidelines currently available. Most providers usually start with the lowest dose and then adjust according to clinical symptoms. Potential side effects include nausea, vomiting, hallucinations, excessive daytime sleepiness, rebound, and augmentation. Augmentation is the development of RLS symptoms during the afternoon or early evening (ie, earlier in the day than noted prior to starting the medication) and is treated by either reducing the dose or switching to another dopaminergic medication. Administration of an earlier dose of the same dopaminergic agent should be avoided because this may lead to further exacerbation of augmentation symptoms. Although reported more commonly with levodopa/carbidopa, augmentation can also occur with the dopamine agonists.<sup>68</sup> Rebound phenomenon is the appearance of symptoms of RLS usually in the early morning compatible with the half-life of the medication.

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### **Iron**

Therapy with iron is based on increasing evidence that iron deficiency may play a role in the pathophysiology of RLS and periodic limb movements of sleep. Iron is a cofactor for tyrosine hydroxylase, the rate-limiting enzyme in dopamine synthesis, and has been found to be low in the substantia nigra, cerebrospinal fluid (CSF), and serum of adult patients with RLS.<sup>69,70</sup> Although the studies are not so robust in children, there is emerging evidence that low iron levels may also exist in children with RLS and period limb movements of sleep. Such children may benefit from iron therapy (3 mg/kg/d of elemental iron) to maintain serum ferritin levels greater than 50 ng/mL.<sup>71,72</sup> Absorption of iron is enhanced when combined with vitamin C and reduced with calcium, and the latter should be avoided at least 1 to 2 hours before or after iron administration. Patients on iron replacement should have regular follow-up appointments to assess for clinical improvement. The serum ferritin levels should also be monitored periodically to prevent iron overload. Medication doses may be adjusted according to clinical relevance and pertinent laboratory data.

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### **Miscellaneous**

Although the other medication classes have not yet been adequately studied, clonazepam, clonidine, and gabapentin<sup>73</sup> are often used by providers to treat RLS in children (**Table 3**).

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## **OBSTRUCTIVE SLEEP APNEA SYNDROME**

Obstructive sleep apnea is a sleep-related disorder characterized by intermittent episodes of complete or partial upper-airway obstruction, resulting in gas exchange abnormalities (hypoxia and hypercapnea) and fragmented sleep. It is a common disorder, with a high prevalence rate of 2% to 5% when compared with other childhood conditions such as sickle cell anemia and diabetes.<sup>74,75</sup> Pediatric obstructive sleep apnea can occur at any age, but because most cases are caused by adenotonsillar hypertrophy, the highest prevalence is observed to be between the ages of 2 and 6 years, coinciding with peak adenotonsillar hypertrophy relative to upper-airway size.<sup>76,77</sup>

The diagnosis of pediatric obstructive sleep apnea begins with a detailed history and physical examination followed by a diagnostic nocturnal polysomnogram, which continues to be the gold standard. The *International classification of sleep disorders second edition* (ICSD-2) diagnostic criteria for pediatric obstructive sleep apnea

| Table 3<br>Dopaminergic agents used in the treatment of RLS |                                                                                                                                                                                                 |                                                                     |                               |
|-------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------|-------------------------------|
|                                                             | Carbidopa/levodopa                                                                                                                                                                              | Ropinirole                                                          | Pramipexole                   |
| Brand name                                                  | Sinemet                                                                                                                                                                                         | Requip                                                              | Mirapex                       |
| Formulations                                                | Immediate release<br>Extended release<br>Generic available: IR and CR<br>Oral disintegrating                                                                                                    | Immediate release<br>Extended release<br>Generic available: IR only | IR<br>No generic available    |
| Initial dose (adult)                                        | 25/100 mg IR 30–60 min before bedtime                                                                                                                                                           | 0.25 mg IR 1–3 h before bedtime                                     | 0.125 mg 2–3 h before bedtime |
| Warnings                                                    | Augmentation (more common with levodopa)<br>Rebound (more common with levodopa)<br>Compulsive behaviors (eg, hypersexuality, binge eating)                                                      |                                                                     |                               |
| Adverse effects                                             | Gastrointestinal (nausea, vomiting, constipation)<br>Anorexia<br>Headaches/dizziness<br>Daytime sedation<br>Hypotension<br>Dry mouth<br>Peripheral edema<br>Nasal congestion<br>Abnormal dreams |                                                                     |                               |

Abbreviations: CR, controlled release; IR, immediate release.  
Data from Refs. <sup>15,103,104</sup>

require caregiver report of snoring, labored or obstructed breathing noted during sleep, and the observation of either diaphoresis, neck hyperextension during sleep, morning headaches, paradoxical inward rib-cage motion during inspiration, slow rate of growth, excessive daytime sleepiness/hyperactivity, or secondary enuresis. One or more scoreable respiratory events per hour on polysomnography in conjunction with the relevant history are required to make the diagnosis.<sup>1</sup> Commonly reported nocturnal symptoms include snoring, apneic episodes, enuresis, perspiration, restlessness, unusual sleeping positions, and parasomnias.<sup>78</sup> Daytime symptoms may include hyperactivity, learning deficits, inattention and less commonly hypersomnolence.<sup>79</sup>

Physical examination findings may be completely unremarkable or may include tonsillar hypertrophy, obesity, failure to thrive, craniofacial anomalies such as high-arched palate, retrognathia, and midface hypoplasia.<sup>80</sup> Several studies have shown profound adverse consequences of pediatric obstructive sleep apnea if left untreated, including neurobehavioral deficits such as inattention and hyperactivity<sup>81</sup> and cardiovascular complications such as cor pulmonale and hypertension.<sup>82,83</sup>

Pharmacologic therapy for obstructive sleep apnea is limited, and no medications are currently approved for use in the treatment of pediatric obstructive sleep apnea. Adenotonsillectomy remains the most frequently used treatment of pediatric obstructive sleep apnea, with resolution of the obstructive sleep apnea in 75% to 100% of otherwise healthy children.<sup>84</sup> Nasal continuous positive airway pressure is usually reserved for patients who have residual sleep apnea after surgery, are not surgical candidates, or based on patient and parental preference.<sup>85</sup> The concept of using pharmacologic agents for the treatment of pediatric obstructive sleep apnea is an attractive one when compared with the potential complications of surgery or the discomfort of wearing a nasal positive airway pressure interface device.

## Oxygen

Oxygen has limited use as the sole therapeutic intervention for children and adolescents with obstructive sleep apnea. It is usually reserved for patients who cannot tolerate nasal continuous positive airway pressure, have significant residual sleep apnea despite adenotonsillectomy and/or refuse tracheostomy. The major limitation of using oxygen as a sole therapeutic intervention is that although its use may result in higher oxygen saturations, it has no effect on apnea duration, frequency, or arousals from sleep.<sup>86</sup> It also has not been reported to improve daytime symptoms, including excessive daytime fatigue/sleepiness. Hypercapnea can occur with the use of supplemental oxygen, and children on supplemental oxygen need to be monitored carefully.<sup>86</sup>

## Nasal Steroids and Leukotriene Receptor Antagonists

Nasal steroids and leukotriene receptor antagonists have been investigated as potential pharmacologic interventions in the treatment of pediatric obstructive sleep apnea based on the rationale that nasal congestion and allergic rhinitis can narrow the size of the nasal airways, thus contributing to the severity of the apnea. Also, the presence of nasal and oropharyngeal mucosal inflammation noted in adult patients with obstructive sleep apnea raises the possibility that nasal steroids and leukotriene inhibitors could be used as an alternative to adenotonsillectomy in mild cases of pediatric sleep apnea.

Brouillette and colleagues<sup>87</sup> conducted a 6-week randomized, triple-blind, placebo-controlled, parallel-group trial of nasal fluticasone propionate versus placebo in 25 children aged 1 to 10 years. Although the study concluded that nasal fluticasone decreased the number of mixed and obstructive apneas and hypopneas, the post-treatment apnea hypopnea index remained high, and no improvement was noted symptomatically.<sup>87</sup>

Other studies have assessed the effect of 4 weeks and 6 weeks of intranasal budesonide, and these have shown an improvement, although with incomplete resolution of the apneas and hypopneas such that the posttreatment apnea hypopnea index still remained within the pathologic range.<sup>88,89</sup> Goldbart and colleagues<sup>90</sup> found that 16 weeks of therapy with daily montelukast resulted in significant reductions in adenoid size and respiratory-related sleep disturbances. These investigators concluded that therapy with a leukotriene receptor antagonist appeared to be associated with improved breathing during sleep but emphasized the need for further double-blind, placebo-controlled trials.

In summary, intranasal steroids cannot be advocated as the sole therapeutic intervention because of the incomplete resolution of apneas and hypopneas in the studies mentioned earlier as well as the lack of long-term trials assessing safety of these medications. Intranasal steroids and leukotriene modifiers may thus be considered as a bridge in mild to moderate cases of pediatric sleep apnea until surgery or nasal positive airway pressure is available.

## NARCOLEPSY

Narcolepsy is a chronic neurologic disorder characterized by instability of the sleep-wake cycle believed to be related to deficiency of the hypothalamic hypocretin system such that elements of sleep intrude into wakefulness and vice versa.<sup>91</sup> It is an uncommon disorder, with a prevalence of 0.02% to 0.18% and an equal male-to-female predominance. The prevalence increases to about 40 times in first-degree

relatives. Although the peak age of onset is usually in the second decade of life, there is frequently a 10- to 15-year delay in diagnosis from the time of onset of symptoms.<sup>1</sup>

Several studies have reported a reduction or absence of hypocretin in patients with narcolepsy and cataplexy. Because hypocretin is the hypothalamic neuropeptide that plays an important role in regulating wake-promoting mechanisms, its absence leads to abnormalities of the transition between wakefulness, REM sleep, and non-REM sleep. Most of the symptoms of narcolepsy, including sleep paralysis, hypnagogic hallucinations, and cataplexy, are caused by inappropriate intrusions of REM sleep into wakefulness. Ninety percent of patients who have narcolepsy with cataplexy have been found to have undetectable CSF levels of hypocretin. These levels are normal in patients who have narcolepsy but no cataplexy, suggesting a different pathophysiology for these patients.<sup>92,93</sup> Genetic, immunologic, and environmental factors have also been implicated.

The tetrad of narcolepsy symptoms includes excessive daytime sleepiness, cataplexy, sleep paralysis, and hypnagogic/hypnagogic hallucinations. Other features also commonly reported in patients with narcolepsy are disrupted sleep, repeated nighttime awakenings, terrifying dreams, and sleep initiation as well as maintenance problems. Children with narcolepsy may be inappropriately diagnosed as having ADHD because of behavioral problems, poor school performance, and inattentiveness. The hallmark feature found in 100% of patients is excessive daytime sleepiness, although the only feature that is specific to narcolepsy is cataplexy. This condition is the abrupt and reversible loss of muscle tone elicited by emotions like laughter and anger. The patient is usually fully conscious during these episodes, which typically last from a few seconds to minutes. Cataplexy may be misdiagnosed as epilepsy.<sup>1</sup>

In adults the diagnosis is usually made by clinical assessment and diagnostic testing, including nocturnal polysomnography and multiple sleep latency testing.<sup>94</sup> Rarely, cerebrospinal hypocretin level may be measured. The diagnosis in prepubertal children is more challenging, especially because there are few normative diagnostic testing data in this age population.<sup>95</sup> Narcolepsy when left untreated can lead to significant functional impairment.

The current mainstays of therapy are behavioral therapy and pharmacological therapy.<sup>96</sup> The former includes educating the patients, parents, and teachers about the nature of the disorder and extensively counseling them on the importance of maintaining adequate sleep hygiene and adhering to a structured sleep schedule. Patients should be given the opportunity to take short 20-minute naps at least twice a day and sleep deprivation should be avoided because it can worsen the narcolepsy symptoms.<sup>97</sup> Patients may also benefit from joining narcolepsy support groups.

The goal of pharmacologic therapy is to treat the excessive daytime sleepiness and cataplexy to the extent that patients can lead normal lives. There are no double-blind, placebo-controlled trials specifically for children with narcolepsy. Medication use is usually lifelong, and patients need to be carefully monitored for the development of side effects.

### ***Medications Used for the Treatment of Excessive Daytime Sleepiness***

Modafinil is a nonamphetamine wakefulness-promoting medication and is considered as first-line therapy for the treatment of excessive daytime sleepiness in narcoleptic adults. Although the mode of action is not completely clear it is believed to be related to dopaminergic signaling.<sup>98</sup> Modafinil has been studied in children with ADHD<sup>98–100</sup> and can be started at 100 mg daily preferably given before 2 PM to avoid nocturnal sleep disruption. The dose may be titrated up to 200 to 400 mg in divided doses. The advantage of this medication is its long half-life, which enables it to be

administered as a single morning dose, the good control of sleepiness, and relative lack of illicit use. Potential side effects include headache, nausea, and dry mouth. An alternative form of contraception should be recommended to women of child-bearing age who are using oral contraception, because modafinil can reduce the effectiveness of oral contraception.

Methylphenidate is a CNS stimulant, which acts by blocking the reuptake of norepinephrine and dopamine by the presynaptic neurons, thus increasing the concentration of these neurotransmitters in the extraneuronal space. It is a potent wakefulness-promoting medication but is considered second line because of its sympathomimetic side effects and potential for dependency. Patients taking this medication should have their weight, blood pressure, and pulse monitored carefully and should be informed about side effects, including psychosis, arrhythmias, anorexia, and sudden death. Starting doses for ADHD are 0.3 mg/kg/dose with titration weekly as clinically relevant.

Amphetamines are another class of CNS stimulants that improve daytime alertness but just like methylphenidate are considered second line in the treatment of narcolepsy due to the potential side effects. These side effects include hypertension, psychosis, sudden death, and addiction. Patients on this medication need to be monitored closely. Typical starting doses are 5 mg administered twice a day, with the last dose before 3 PM.

### ***Medications Used for the Treatment of Cataplexy***

Commonly used medications for the treatment of cataplexy include REM suppressing sleep medications such as tricyclic antidepressants, selective serotonin reuptake inhibitors, and noradrenergic reuptake inhibitors. These medications act by inhibiting reuptake of norepinephrine and serotonin by the presynaptic neurons, increasing the levels of these neurotransmitters in the neuronal space. These neurotransmitters in turn inhibit the brainstem circuits that generate REM sleep and hence reduce cataplexy or other REM-related phenomena. Care must be taken to avoid abrupt discontinuation of these medications as this may lead to rebound cataplexy.

$\gamma$ -Hydroxybutyrate (GHB) is a metabolite of GABA and acts by binding specifically to GABA<sub>B</sub> and GHB receptors. It is approved by the FDA for the treatment of narcolepsy with cataplexy in adults. It also improves the quality of nocturnal sleep and daytime alertness. GHB is a liquid and is given in 2 separate doses with the first at bedtime and the second 2.5–4 hours later because of its short half-life. There are no dosing guidelines for the various pediatric age ranges. Potential side effects include nausea, deep sedation leading to coma and death in overdoses, and a significant potential for abuse.

### **SUMMARY**

Pediatric sleep disorders are highly prevalent and there is evidence showing the development of adverse consequences when these disorders are not adequately treated. There is a need for more research to develop evidence-based pharmacologic guidelines for the specific sleep disorders, taking into account the different pediatric age ranges. Currently, there are no FDA-approved medications for the treatment of these disorders.

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