Pediatric Sleep Pharmacology

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This article reviews the most common pharmacologic options in the treatment of sleep disorders in children. Despite the high prevalence of sleep disorders in children, there is a paucity of education and information available on the pharmacologic management of sleep disorders in children. The principles of sleep physiology and pathophysiology that help provide more rational pharmacologic management are discussed. Medications are typically not Food and Drug Administration (FDA) approved for the pediatric age range or for the specific sleep disorder. Medications have a role for insomnia, narcolepsy, parasomnias, and sleep-related movement disorders. The available choices of hypnotics are reviewed. Medications to increase alertness of narcoleptics and decrease cataplexy are discussed. The use of dopaminergic agents for Restless Legs Syndrome is reviewed. The potential use of medication in sleep apnea is also reviewed. Pharmacologic guidelines need to be developed specifically for sleep disorders in children. Ideally, these guidelines should be FDA approved for the specific sleep disorder and for the pediatric age range. The development of easy to swallow, chewable or liquid forms of these medications are needed. Training programs should play the lead role in enhancing pediatricians’ knowledge of the pharmacologic treatment of sleep disorders in children.

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This article reviews the most common pharmacologic options in the treatment of sleep disorders in children. With regard to pharmacologic treatments options, the learning process for all clinicians, whether they predominately treat adults or children, is very similar. First, we learn physiology, then pathophysiology, and for the rest of our careers we apply this knowledge to the pharmacologic management of our patients. When we learn of new pharmacologic treatment options, we try to place them within this framework of physiology and pathophysiology. Without knowledge of sleep physiology and pathophysiology, rational pharmacologic management is not possible. Despite their high prevalence in children, sleep disorders are not emphasized during the typical medical school or pediatric residency education. This paucity of education may account for the relatively little information available on the pharmacologic management of sleep disorders in children.

When medications are used to treat sleep disorders in children, they are typically neither Food and Drug Administration (FDA) approved for the pediatric age range or for the specific sleep disorder. Clonidine is an example of the latter. Clonidine is not an indicated medication for insomnia in adults. However, clonidine is one of the most commonly prescribed medications for insomnia in children despite the absence of any randomized control trials supporting its use. Pediatricians prescribe clonidine for children of all ages, infants through teens. How can this drug be such a popular choice among pediatricians? Is the pathophysiology of insomnia so different between adults and children that it is rational for an antihypertensive agent not be indicated for adult insomnia but somehow be routinely used in children? This article attempts to place the most common pharmacologic options within a framework of the pathophysiology of sleep disorders in children.

Stojanovski et al examined trends in physicians prescribing medications for children with sleep difficulties in outpatient settings in the United States. The study used data from the National Ambulatory Medical Care Survey collected from 1993 to 2004. The rate of medication prescriptions for children with sleep disorders appears to be increasing. The study found that approximately 18.6 million visits occurred for sleep-related difficulty in children. In this 12-year study period, 81% of patients with pediatric insomnia were prescribed sleep medication; 33% received antihistamines, and another 26% were prescribed alpha-2 agonists (presumably clonidine). The finding that 81% of children were prescribed medication is particularly remarkable considering that only 48% of the adult patients suffering from insomnia were prescribed medication.

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The paucity of information on the pharmacologic treatment of sleep disorders in children may not be surprising given the inherent problems of the clinical situation. Most pharmacologic guidelines were developed for sleep disorders in adults and must be empirically extrapolated to children. The physician is often forced to prescribe medications as an “off-label” indication. This may result in frustrating insurance reimbursement delays or denials for the family. These reimbursement problems may affect the availability of a specific medication and the family’s compliance with the medication or force the physician to prescribe a less desirable alternative. The medication may not be available commercially in an easily administered form. Younger children may not be able to swallow pills or ingest chewable tablets, requiring the local pharmacist to compound the medication into a suspension. In addition, because of the natural aversion among both parents and physicians to use medications for pediatric sleep disorders, medications are usually prescribed as a last resort or in the most refractory situations. At times, a decision to use medication in a child may be made not necessarily to assist the child as much as to help the parents or other family members sleep better. It is not unusual that parents may finally seek help for a child’s longstanding sleep problem when the parents feel they can no longer put up with interruptions to their own sleep. The clinician needs to be aware of this situation, which may cause guilty feelings to arise in the family members.

Further complicating the pharmacologic treatment of sleep disorders in children is the general lack of specialized training in sleep disorders available to all health care providers, not just pediatricians, who are working with these children. Failure to consider or properly apply nondrug treatments as part of the comprehensive management of the child may also lead to unsatisfactory results for the patient and the family. These factors result in children with sleep disorders that are not properly managed because of either underdosing or overdosing of medication or incorrect medication selection.

A key principle in sleep pharmacology is not to equate sedation with normal refreshing sleep. Perhaps the simplest and best known example of this principle is alcohol. Consuming large amounts of alcohol can be very sedating, but we do not wake up feeling particularly refreshed after a night of excessive drinking. There may be an overreliance on the effects of the medication by both the parents and health care provider without adequate understanding of the cause of the poor sleep or the appropriate application of behavioral techniques to help improve the child’s sleep.

A common scenario in clinical practice is a parent’s complaint of a child’s paradoxical reaction to a hypnotic medication. “He did not sleep at all” or “he became hyper” may be the parent’s complaint. From a physiological point of view, how can we explain that a child did not get sleepy when given a hypnotic agent? Is the child’s brain missing the usual gamma-aminobutyric acid (GABA) receptors? Of course not, but the child’s poor reaction to the medication is not typically questioned, and the medication is simply removed from the limited list of pharmacologic options available to the patient. A more physiological approach would be to understand why the medication failed to achieve the desired result. In the authors’ experience, the reason may not be because of the choice of medication per se. A more likely reason for the absence of efficacy and/or adverse reactions is the medication dose or the time of administration.

When prescribing a medication for a child, there is a natural inclination to give the lowest dose possible. However, children may have faster hepatic metabolism of the medication resulting in faster elimination. If the dose of the agent is too low, the medication may disinhibit a child but not make the child actually fall asleep. The parents would report unusual behavior. If a child typically fights their bedtime, because for example, of a fear of being alone in the dark and the medication dose given to the child only makes that child drowsy but without falling asleep, frightening hypnagogic hallucinations may occur. This might be particularly disturbing in children with an underlying psychiatric or neurologic condition for whom the outside world may already be confusing. With the resulting confusion or disorientation caused by too low a dose of a sedating medication, it is not surprising that parents may report paradoxical reactions to the putative hypnotic.

Not only is the specific medication and dosage key, but the timing of administration is also very important. It is important because of the circadian modulation of alertness. Humans will typically experience an enhanced alertness in the evening, which is often referred to as a “second wind.” During this circadian phase, it is harder to fall asleep. If the hypnotic medication is given during this circadian time window, it may not work. If the medication is given too early while the child is not ready to sleep but rather has heightened alertness, dissociative phenomenon such as frightening hypnagogic hallucinations may occur. In the situation of children with neurologic or psychiatric disorders, they may not understand that the medication was meant to help them sleep. Typically, hypnotics only shorten the usual falling asleep time (sleep latency) at most by only 20 or 30 minutes compared with placebo. Giving a medication 2 or 3 hours before the usual falling asleep time could elicit this common scenario. This same medication and dose given at a more appropriate circadian time could be effective.

This lack of proper management of the sleep problem may be particularly common among children with neurologic, psychiatric, behavioral, or emotional disorders. The use of psychotropic medication in children has been increasing. If the child cannot communicate what they feel is causing the sleep difficulty, incorrect assumptions may be made by the family and/or health care provider. In cases of insomnia, this can result in an escalating cycle of progressively more sedating agents with an increasing likelihood of adverse effects. Concomitant daytime sedation may occur, which may interfere with the child’s daytime therapeutic program and exacerbate the child’s disabilities. In some situations, the fear of putative addiction may limit the physician or the family from using pharmacotherapy adequately to improve the child’s sleep.

All discussions of pediatric sleep pharmacology need to take into account the cultural background of the family. The
parents need to be in agreement about their expectations of the child’s sleep, especially if the parents have different cultural backgrounds. The parents’ own prior sleep experiences both in childhood and as adults should be explored. Also, the influence of other family members, such as grandparents, in shaping the family’s views should be considered. If the child lives in 2 separate households, which typically occurs with divorce, is the sleep problem present in both homes or are their differences? Will any prescribed medication be given in both homes?

This article summarizes the authors’ opinion regarding the pharmacologic management of the most common sleep disorders in children. Given the paucity of evidence-based medicine in pediatric sleep pharmacotherapy, the reader should be particularly cautious when applying this information to individual patients. The need for greater research, in particular double-blind placebo-controlled trials, cannot be over emphasized.

**Insomnia**

Insomnia is characterized in adults by difficulty falling asleep and/or staying asleep associated with subjective daytime impairment. In children, this same definition may be applied but may need to be modified. Commonly, it is the parents’ subjective impairment that leads the family to seek medical attention. The young child may awaken for a variety of reasons but will often eventually fall back asleep. However, the parents’ sleep schedule is disrupted. The medical history is incomplete without a discussion of what the parents’ sleep was like before they were parents. If the parents’ had any prior sleep impairment, such as mild sleep apnea, they will have greater difficulty handling the typical sleep disruptions of parenthood. The amount and schedule of sleep each of the parents in the household preferred before they were parents should be reviewed before making any pharmacologic decisions.

The sleepless child can be a challenging situation for both the family and the primary health care provider. The primary health care provider may have limited training in pediatric sleep disorders. The insomnia’s manifestation and management will depend on the child’s age. In general, behavior techniques should be the mainstay of treatment. Medications may have a role as an adjunct in the insomnia management.

**Infants**

For infants, the pharmacologic options for insomnia are limited. Insomnia in an otherwise healthy infant is typically caused by behavioral problems such as behavioral insomnia of childhood sleep-onset association type or nocturnal feeding.\(^6\) The child can sleep well if the associations the child establishes with sleep onset are present throughout the sleep period. If the associations, such as the presence of the parents, are absent during the sleep period, the child may have difficulty returning to sleep after they have awoken. It is important to keep in mind that what wakes up the infant may not be what is keeping the infant awake.\(^7\)\(^8\)

Parents often seek medical attention for their sleepless infant because of concerns that the infant may have a physical cause for the problem. In general, if the child’s growth, development, and examination are normal, a physical cause for the poor sleep is less likely. Gastroesophageal reflux should be part of the differential diagnosis when evaluating these children. One simple way to distinguish if the sleep problems in the infant are physical versus behavioral is for the parent to see if there is a difference in the way the child sleeps if he/she sleeps alone or with a parent. This should be observed over several nights before reaching a conclusion. If the child sleeps much better when he/she is with the parent, the problem is more likely behavioral. If the infant sleeps as poorly with or without the parent, the problem may be physical. Gastroesophageal reflux and sleep-disordered breathing should be part of the differential diagnosis when evaluating these children. In some situations, a combination of both physical and behavioral factors may be playing a role.

The health care provider must specifically ask the parents if they have given the child any substance to improve the child’s poor sleep. The parents may not spontaneously mention that they have attempted to give the child a substance such as alcohol or over-the-counter acetaminophen or antihistamines. In addition, ambiguities and differences among the parents about how the child should sleep may complicate the clinical situation. For example, 1 parent may prefer to cosleep with the child but the other parent may not.

The medications that are most commonly used to help an infant sleep better are diphenhydramine and chloral hydrate. The dosage guidelines and common side effects are discussed later.

**Toddlers**

Among toddlers, parental complaints of poor sleep are not uncommon. The most common situations are behavioral insomnia of childhood limit setting type and nocturnal fears.\(^6\) The child may appear to be physiological ready to sleep but may either refuse to go to sleep or gets out of bed after he/she has been tucked into bed. Once the child falls asleep, the sleep should be of normal quality. Difficulty falling back to sleep may occur if the child’s sleep is disrupted. Medications are not typically given in these situations.\(^7\)\(^8\) If the problem has reached such a magnitude that the child’s poor sleep is causing a disruption of the household or the parents’ sleep, then medications may be requested by the family. Within the context of behavior-modification program, a brief adjunctive trial of medication might be attempted.

**Adolescents**

The most common form of insomnia in adolescents is sleep-onset insomnia typical of delayed sleep-phase syndrome. Delayed sleep-phase syndrome is a condition in which the child falls asleep later than expected, has normal sleep during the night, but has difficulty waking up at the expected time. Typically, the children are described as preferring to stay up late at night. The children usually have a later sleep and wake-up time on weekends and holidays. The treatment usually consists of behavioral changes when the child is motivated to change the behavior. These behavioral changes may
also include exposure to bright light at the desired wakeup time. The use of bright light to influence a circadian sleep disorder is called phototherapy.9,10

Children who are avoiding school may mimic this sleep disorder. To help the child fall asleep faster, different substances have been tried. Melatonin has been used with variable effect. Melatonin is further described later.

Prescription hypnotics do not have an FDA indication for adolescents younger than 18 years old. An “off-label” use as an adjunct to the behavioral modification of the circadian problem may be considered in certain clinical situations. Because these patients typically only have sleep-onset insomnia without significant nocturnal disruption, a short-acting hypnotic agent may be considered for a short period of time. Zaleplon, a nonbenzodiazepine hypnotic, may theoretically be used in adolescents with delayed sleep-phase syndrome because it has a fast onset of action and its hypnotic effects should wear off well before the desired wakeup time. Zaleplon has a short elimination half-life of approximately 1 hour. This short duration, unlike diphenhydramine, will minimize any next day sedation. Because the duration of medication treatment is expected to be of a relatively short time, zaleplon also had the additional benefit of minimal rebound insomnia. Rebound insomnia refers to an exacerbation of insomnia on abrupt cessation of a hypnotic. The degree of insomnia is more severe than the initial insomnia before starting hypnotics. Rebound insomnia is more typical of short-acting benzodiazepine hypnotics such as triazolam. Gradual tapering is helpful to avoid a significant rebound effect.

A potential medication to consider in the treatment of delayed sleep-phase syndrome in adolescents is ramelteon. Ramelteon is a selective melatonin receptor agonist that has been approved for sleep-onset insomnia in patients 18 years and older.11 It lacks the potential for abuse commonly associated with hypnotics. Systematic trials in younger patients are not available. A case study did report efficacy in an 18-year old and a 7-year old with autism and insomnia.12

Diphenhydramine
Diphenhydramine hydrochloride, 2-(diphenylmethoxy)-N, N-dimethylaminoethane hydrochloride, is a competitive H1-histamine receptor blocker that has multiple effects on the central and peripheral nervous systems. Diphenhydramine is rapidly absorbed from the gastrointestinal tract without any gastric irritation. Peak blood and tissue levels are achieved within 2 hours of ingestion. It is an active ingredient in many over-the-counter medications, including antihistamine, sedative, hypnotic, antitussive, and antiemetic preparations.13-19

Diphenhydramine is characterized by ethylamine moieties, which make them highly lipophilic and hence easily able to penetrate the blood-brain barrier and occupy H1-receptor sites in the brain, a large number of which are located on the frontal lobes and in the deep structures of the brain. Positron emission tomography studies conducted by Yanai et al20 showed that the first-generation agents occupy approximately 75% of the H1-receptor sites in the brain. Brain histamine is involved in a wide range of physiological functions such as regulation of the sleep-wake cycle, arousal, cognition, and memory mainly through interactions with histamine H1 receptors. Histaminergic neurons are located in the posterior hypothalamus and transmit histamine to almost all regions of the brain.21

Various studies have been performed to evaluate the usefulness of diphenhydramine in sleep disorders of both adults and children. When given shortly before bedtime, a significant decrease in sleep latency time and number of awakenings was observed. The duration of activity after an average dose of diphenhydramine is 4 to 6 hours.22 A plasma diphenhydramine level exceeding 30 ng/mL produces drowsiness.22,23 The recommended dosage for adults is 25 to 50 mg, whereas in children the lowest effective dose starts at 0.5 mg/kg (maximum, 25 mg).

Recently, a randomized controlled trial of infant response to diphenhydramine was published called the “TIRED study.”24 This study recruited 44 infants aged 6 to 15 months with frequent parent-reported nighttime awakenings. The primary outcome was a parental report of improvement in the number of night awakenings requiring parental assistance. The trial was stopped early because of the lack of effectiveness of diphenhydramine over placebo. Only 1 of 22 children receiving diphenhydramine showed improvement compared with 3 of 22 receiving placebo. The study concluded that during 1 week of therapy and at follow-up 2 and 4 weeks later, diphenhydramine was no more effective than placebo in reducing nighttime awakening or improving overall parental happiness with sleep for infants.24

The most common adverse reaction to diphenhydramine at therapeutic doses is impaired consciousness. The predominant features in an overdose are anticholinergic effects, which include fever, mydriasis, blurred vision, dry mouth, constipation, urinary retention, tachycardia, dystonia, and confusion. Other common symptoms of diphenhydramine poisoning include catatonic stupor, anxiety, and visual hallucinations.13 Rare presentations include respiratory insufficiency, rhabdomyolysis, cardiac rhythm disturbances, and seizures.13,25,26

Fatal intoxications with diphenhydramine in 5 infants were reported in a case series by Baker et al.17 The infants were 6, 8, 9, 12, and 12 weeks old. Postmortem blood diphenhydramine levels in the cases were 1.6, 1.5, 1.6, 1.1, and 1.1 mg/L, respectively. In 1 case, the child’s father admitted giving the infant diphenhydramine in an attempt to induce the infant to sleep; in another case, a daycare provider admitted putting diphenhydramine in the baby’s bottle.17

Chloral Hydrate
Chloral hydrate (CH) is a commonly used sedative hypnotic and is prescribed to both children and adults. The usual dosing ranges between 25 and 50 mg/kg/dose up to a maximum of 1 g per dose orally or rectually. Even at higher doses, 80 to 100 mg/kg has been given to children younger than 5 years with good effect and minimal toxicity.17 However, neonatal dosing may need adjustment, particularly when used in

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a multidose fashion.\textsuperscript{27} After it is absorbed from the gastrointestinal tract, CH is converted by alcohol dehydrogenase, to trichloroethanol (TCE), the active metabolite. TCE is slightly lipid soluble and therefore penetrates the blood-brain barrier. A central nervous system depressant, TCE causes drowsiness and sedation and then sleep within 1 hour. The plasma t\textsubscript{1/2} of TCE is 8 to 12 hours in older children and adults, but for neonates and infants it is 3 to 4 times longer.\textsuperscript{27} Therapeutic doses normally reduce blood pressure minimally and suppress respirations slightly, but protective airway reflexes are not affected.\textsuperscript{27} However, children with obstructive sleep apnea (OSA), wheezing, Leigh's disease, or other encephalitic white-matter or brainstem disorders may be at an increased risk for respiratory compromise. Respiratory suppression may also occur in overdose situations with deep stupor and coma. Furthermore, cardiovascular instability, in the form of decreased myocardial contractility, shortened refractory period, and changes in myocardial sensitivity to endogenous catecholamines, accounts for most of the mortality that occurs when CH is given in toxic levels. Similarly, CH may be contraindicated in children who are also on stimulants because of rare reports of malignant arrhythmias. Concomitant administration with diuretics such as furosemide may lead to marked vasomotor instability. Although coadministration with other classes of sedatives always acts synergistically on the central nervous system, taking CH with fluoxetine has also been reported to cause prolonged sedation but for unclear reasons. Tolerance to its sedating effects may occur. The chronic use of CH for insomnia should be discouraged given the potential for side effects and tolerance. A study comparing the use of CH to music therapy in children undergoing electroencephalographic testing found music therapy to be an effective alternative.\textsuperscript{28}

**Other Over-the-Counter Hypnotics**

Besides diphenhydramine, other H1 antihistamines are also often used for their sedative effects because they are lipid soluble and pass through the blood-brain barrier.\textsuperscript{29} Ethylenimines and phenothiazines have marked sedative effects, whereas ethylenediamines cause moderate sedation and alkylamines mild sedation.\textsuperscript{30} However, centrally acting H1 antagonists have also been shown to have convulsant effects, especially in young children, and overdosage has been associated with seizure and death.\textsuperscript{17} Furthermore, these agents may worsen OSA and also may suppress rapid eye movement (REM) sleep and produce a marked compensatory rebound after withdrawal of these agents, resulting in worsened sleep instability and fragmentation.\textsuperscript{31}

**Melatonin**

Its name is derived from its effect on melatonin pigmentation in frogs; melatonin (N-acetyl-5-methoxytryptamine) is the main hormone secreted by the pineal gland. Because the pineal gland lacks a blood-brain barrier, it is sensitive to the influence of peripherally active drugs.\textsuperscript{32} Melatonin is synthesized from its precursor tryptophan, which is hydroxylated to 5-hydroxytryptophan and then decarboxylated to serotonin. This is then N-acetylated and converted to melatonin by hydroxyindole-O-methyltransferase. Production by the pineal gland shows a high-amplitude circadian rhythm, resulting in low plasma levels during the day and high levels at night. This rhythmicity is comparable in humans and in experimental animals (either diurnal or nocturnal), with daily dark-phase levels 3 to 10 times higher than during the light phase.\textsuperscript{32} It is believed that the physiologic increase in blood melatonin concentration by 10- to 15-fold, which occurs 1 to 2 hours before bedtime, may be the final trigger for inducing sleep.\textsuperscript{33} The circadian rhythm of melatonin usually develops between the second and third month of life; nighttime melatonin is low or undetectable at to 2 to 3 months of age and then increases steadily. Neonates and infants depend on their mother's melatonin circadian rhythm through her milk.\textsuperscript{32} Melatonin may possess a phase-setting effect instead of, or in addition to, a direct hypnotic effect.\textsuperscript{32} Although its role in circadian rhythm-based sleep disorders like jet lag and delayed sleep-phase syndrome has been reported, the hypnotic effect of melatonin is less well shown. Improved subjective sleep has been noted. Conflicting reports on the efficacy of melatonin have been attributed to possible differences in melatonin dosages, the timing of administration, experimental approaches, and diversity of subjects. A recent meta-analysis published in the British Medical Journal concluded “...no evidence that melatonin is effective in treating secondary sleep disorders or sleep disorders accompanying sleep restriction, such as jet lag and shiftwork disorder.”\textsuperscript{34}

In adults, small physiologic doses of 0.1 to 0.3 mg of melatonin in the evening can generate serum concentrations that are within the normal nocturnal range (50-200 pg/mL). Melatonin is more effective when given 2 hours before bedtime than when given immediately before bedtime, and dose ranges between 0.3 mg and 10 mg are used for short-term insomnia. Although dosing guidelines have not yet been established, in adults doses starting between 0.3 and 1.0 mg may be used and increased to effect. Unfortunately, dosing in children is less clear, but in a case series of 15 neurologically impaired children with chronic sleep disturbances, including fragmented sleep and delayed sleep phase, 2 to 10 mg resulted in subjective improvement in their sleep.\textsuperscript{32} However, the National Sleep Foundation has warned against using melatonin in patients with immune disorders, lymphoproliferative disorders, and in those taking corticosteroids or other immunosuppressants, given its ability to enhance immune function.\textsuperscript{32} Finally, it must be kept in mind that melatonin is still considered a “diet supplement,” and the FDA does not regulate its safety, purity, or efficacy.\textsuperscript{33}

The use of melatonin for children may be most effective in insomnia caused by circadian factors. This would include children with delayed sleep-phase syndrome and blind children. Children with midline brain defects such as agenesis of corpus callosum sometimes seem to respond to melatonin treatment for insomnia. This may be caused presumably by associated defects in the pineal region.\textsuperscript{35,36} Smits et al\textsuperscript{36} con-
ducted a double-blind placebo-controlled trial of 5 mg of melatonin in children ages 6 to 12 years with sleep-onset insomnia. The melatonin-treated group reported falling asleep 63 minutes earlier and had an increased total sleep time of 41 minutes. Recently, Weiss et al. reported on the use of sleep hygiene and melatonin treatment for initial insomnia in children with attention-deficit/hyperactivity disorder (ADHD). This is analogous to the use of combination of hypnotics and cognitive behavioral therapy for adults with insomnia. In this study, 27 stimulant-treated children (6-14 years of age) with ADHD and sleep onset of insomnia (>60 minutes) received sleep hygiene intervention. Nonresponders were randomized to a 30-day double-blind, placebo-controlled, crossover trial of 5 mg pharmaceutical-grade melatonin. The results showed a significant reduction in initial insomnia of 16 minutes with melatonin relative to placebo. Of note, the improved sleep had no demonstrable effect on ADHD symptoms. A similar report by Van der Heijden et al. investigated the effect of melatonin treatment on sleep, behavior, cognition, and quality of life in children with ADHD and chronic sleep-onset insomnia. A total of 105 medication-free children, ages 6 to 12 years, with ADHD and sleep-onset insomnia participated in a randomized, double-blind, placebo-controlled trial using 3 or 6 mg melatonin or placebo for 4 weeks. Melatonin advanced circadian rhythms of sleep-wake and endogenous melatonin and enhanced total time asleep in children with ADHD and chronic sleep-onset insomnia. Similar to the Weiss study, they found that improved sleep with melatonin had no effect on problem behavior, cognitive performance, or quality of life.

**Clonidine**

Clonidine was originally marketed for the treatment of hypertension under the trade name Catapres (Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT), but its sedating properties have led to its use as a soporific. Clonidine is a central alpha2-adrenergic receptor agonist, with a half-life of 6 to 24 hours. Onset of action is within 1 hour, with peak effects at 2 to 4 hours. At least 50% is excreted unchanged in the urine. Although it is known to stimulate receptors on the presynaptic terminals of noradrenergic neurons with a resultant decrease in norepinephrine (NE) release, the actual mechanism of sedation is not clear. Side effects include hypotension, bradycardia, irritability, anticholinergic effects (eg, dry mouth), and REM suppression. With abrupt discontinuation, rebound hypertension and REM rebound can occur. Although not used as a hypnotic in adults, clonidine is widely used for sedation in pediatrics for patients with sleep disturbances associated with neurodevelopmental disorders or ADHD. There is no manufacturer-recommended hypnotic dose, but, in practice, the starting dose is usually 50 μg, increased in 50-μg increments.

**Benzodiazepines**

Benzodiazepine hypnotics have been used extensively in adults with insomnia. The mechanism of action is based on activation of the GABA receptor. Benzodiazepines may have muscle-relaxing properties and should be avoided in children with suspected obstructive sleep apnea syndrome. On a polysomnogram, benzodiazepines may alter the normal sleep stages referred to as sleep architecture. There can be drug-related artifacts such as atypical sleep spindles and suppression of slow-wave sleep. Benzodiazepine hypnotics are not commonly used for children with sleep disorders. An important exception is clonazepam. Clonazepam is rapidly and completely absorbed after oral administration. The bioavailability is about 90%. Maximum plasma concentrations are reached within 1 to 4 hours after oral administration. The half-life of clonazepam is typically 30 to 40 hours. Clonazepam can be used to prevent parasomnias associated with partial arousals such as sleep terrors or sleep walking. These parasomnias may decrease as the child gets older. When parasomnias are very frequent and disturbing to the patient and family, a low dose of clonazepam at 0.25 to 0.5 mg may be helpful. Clonazepam may increase the arousal threshold, allowing the child to sleep without interruption. Clonazepam is available in thin wafers that dissolve on the tongue obviating the need for the child to swallow a pill.

**Nonbenzodiazepine Hypnotics**

There are 3 nonbenzodiazepine hypnotics (perhaps a more accurate term is selective benzodiazepine receptor agonists) currently available in the United States: zolpidem (both immediate release and extended release), eszopiclone, and zaleplon. Their use in children is considered “off label,” and therefore no official dosing guidelines are available. None of these medications are available in liquid form, which makes them difficult to administer to small children. They arguably offer some advantages compared with older (nonselective) benzodiazepine hypnotics. These newer medications preserve the overall sleep architecture. At the recommended doses, they do not typically have the insomnia rebound effects experienced with benzodiazepine hypnotics when they are abruptly stopped.

The standard adult dose of immediate-release zolpidem and zaleplon is 10 mg. They both have a rapid onset of action and shorten sleep latency. Zolpidem has a half-life of 2.5 hours, and zaleplon has a half-life of 1 hour. This difference in duration is clinically important. Zolpidem may help improve both sleep onset and, to some degree, sleep maintenance insomnia symptoms. Zaleplon typically only improves the sleep-onset insomnia and is not expected to significantly increase the total sleep time. Zaleplon’s shorter half-life may allow it to be administered after sleep disruption in some situations to help the patient to return to sleep, but this practice has not been studied in children.

Zolpidem is widely prescribed for insomnia in adults both in the immediate-release and extended-release form. Although its use in children is off label, some limited data are available. Blummer and colleagues studied the pharmacokinetic profile of zolpidem in children. In this study of pharmacokinetics of zolpidem was assessed in an open-label protocol in children with insomnia. A total of 21 children, seven
per age group (2-6, >6 to 12, >12 to 18 years) were studied. Overall, the authors concluded zolpidem was well tolerated and a pediatric dose of 0.25 mg/kg was recommended for future efficacy studies with a maximum dose of 20 mg.

The standard adult dose of immediate release of zolpidem is 10 mg and the extended release dose is 12.5 mg. The standard adult dose may be prescribed to older children that can swallow the pill. It is not absolutely necessary to lower the dose since these medications have short half-lives and minimal side effects. Clearance of zolpidem in children is 3 times higher than in young adults, and is lower in elderly adults.42 A 5 mg size of immediate release zolpidem and 6.25 mg of extended release is available and intended for use in the elderly or patients with decreased hepatic clearance. As described above, in the authors' experience, giving a lower dosage to children may be either ineffective or result in frightening sleep epiphemomenon such as hypnagogic hallucinations. The medication is most effective when taken on an empty stomach.

Eszopiclone is a nonbenzodiazepine hypnotic that was more recently approved in the United States.46-48 This medication has a longer half life, 6 hours, than zolpidem and zaleplon. This may, theoretically, be helpful in children since they typically sleep longer than adults. To date there are no published studies in children.

Prescription hypnotics do not have an FDA indication for adolescents younger than 18 years old. An "off label" use as an adjunct to the behavioral modification of the circadian problem may be considered in certain clinical situations. Since these patients typically only have sleep-onset insomnia without significant nocturnal disruption a short acting hypnotic agent may be considered for a short period of time. Zaleplon, a nonbenzodiazipine hypnotic, may theoretically be used in adolescents with delayed sleep phase syndrome since it has fast onset of action and its hypnotic effects should wear off well before the desired wake up time. Zaleplon has a short elimination half-life of approximately 1 hour. This short duration, unlike diphenhydramine, will minimize any next-day sedation. Because the duration of medication treatment is expected to be relatively a short time, zaleplon also had the additional benefit of minimal rebound insomnia. Rebound insomnia refers to an exacerbation of insomnia on abrupt cessation of a hypnotic. The degree of insomnia is more severe than the initial insomnia before starting hypnotics. Rebound insomnia is more typical of short-acting benzodiazipine hypnotics such as triazolam. Gradual tapering may be helpful to avoid a significant rebound effect.

**Narcolepsy**

Narcolepsy is a chronic neurologic condition disorder in which the boundaries between the awake, sleeping, and dreaming brain are blurred.49 The awake narcoleptic will feel sleepy. The sleeping narcoleptic will have disturbed sleep because of arousals. A pathognomonic feature is the sudden loss of muscle tone elicited by emotions such as laughter called cataplexy. Narcolepsy often develops in childhood, particularly during the second decade. However, the diagnosis may not be established until years after the onset of symptoms.

Successful treatment for narcolepsy needs include both behavioral and pharmacological treatments. The situation is analogous to juvenile diabetes mellitus in which a combination of diet with medication can control the condition. With the discovery of a gene responsible for narcolepsy, novel potential therapeutic approaches may be discovered.50,51 The absence of hypocretin in the spinal fluid is diagnostic for narcolepsy.52

Drug therapy must take into account possible side effects, with the fact kept in mind that narcolepsy is a lifelong illness and patients will have to receive medication for years. Tolerance or addiction may be seen with some compounds. The treatment of narcolepsy thus balances the avoidance of side effects, including tolerance, with maintenance of an active life. Physicians need to monitor for the development of hypertension, abnormal liver function, depression, irritability, anorexia, insomnia, or psychosis associated with medications.49

There are no double-blind placebo-controlled trials of medication specifically for children with narcolepsy. The drugs most widely used to treat excessive daytime sleepiness are the central nervous system stimulants.53 Amphetamines were first proposed in 1935. The alerting effect of a single oral dose of amphetamine is at its maximum 2 to 4 hours after administration, and many patients require a single daily or twice-daily dose. However, a number of side effects including irritability, anxiety, nervousness, headache, psychosis, tachycardia, hypertension, nocturnal sleep disturbances, tolerance, and drug dependence may arise. The use of methylphenidate was later encouraged because of a shorter half-life and a lower incidence of similar side effects.

There are 2 drugs with different modes of action that have changed our first-line treatment for narcolepsy.54,55 The first one, modafinil, is considered more as a "somnolytic" than a nonspecific stimulant.56 Modafinil, which has been approved in the United States, has been reported to bring substantial improvement in adults.53 The mechanism of action of modafinil is not entirely clear, but it is not dopamine mediated in the same way amphetamines are thought to work.57 The neuronal targets for modafinil in the brain include nuclei of the hypothalamus and amygdala. The initial dose should be relatively low, 100 mg, to avoid headaches. The dosage can later be increased to 200 to 400 mg/d divided twice per day. The second dose should be given ideally before 2 PM because of the medication's long half-life. Modafinil does not have the typical side effects of amphetamine. The most common side effect is headache, and this negative effect may be eliminated if there is a progressive dose increase over time. Modafinil should be considered the initial pharmacologic agent used to treat the excessive daytime sleepiness of narcolepsy in children.53

Of note, there have been several studies on the use of modafinil in children with ADHD.58-61 A modified formulation modafinil under the trade name Sparlon had been developed but at this time has not received approval by the
FDA. A suspect case of Stevens Johnson reaction occurred during a clinical trial.

The second drug is gamma-hydroxybutyrate, GHB, which after much difficulty was approved in the United States by the FDA in July 2002. It is the first substance ever approved specifically for cataplexy in addition to excessive sleepiness. The drug generic name is sodium oxybate and is marketed under the brand name Xyrem (Jazz Pharmaceuticals, Palo CA). In the popular media, it has the infamous name of the “date rape drug.” Illegal use of this substance for recreational purposes has been of great concern. Important central nervous system adverse events associated with abuse of GHB include seizure, respiratory depression, and profound decreases in level of consciousness, with instances of coma and death. For events that occurred outside of clinical trials in people taking GHB for recreational purposes, the circumstances surrounding the events are often unclear (eg, dose of GHB taken and the nature and amount of alcohol or any concomitant drugs).

Sodium oxybate has powerful central nervous system–depressant effects. GHB can increase slow-wave sleep. This medication when given at bedtime may be of value to reduce cataplexy and enhance daytime alertness. Patients may prefer this medication over other medications used for cataplexy, particularly if insomnia is also present.

Sodium oxybate is rapidly but incompletely absorbed after oral administration; absorption is delayed and decreased by a high fat meal. It is eliminated mainly by metabolism with a half-life of 0.5 to 1 hour. Pharmacokinetics is nonlinear with blood levels increasing 3.7-fold as dose is doubled from 4.5 to 9 g (g). The pharmacokinetics is not altered with repeat dosing. Sodium oxybate is required to be taken at bedtime while in bed and again 2.5 to 4 hours later. The product’s package insert does not recommend using the medication in patients younger than 16 years of age. The recommended starting dose in adults is 4.5 g/d divided into 2 equal doses of 2.25 g. The starting dosage can then be increased to a maximum of 9 g/d in increments of 1.5 g/d (0.75 g per dose). Two weeks are recommended between dosage increases to evaluate clinical response and minimize adverse effects. Sodium oxybate is effective at doses of 6 to 9 g/d. The efficacy and safety of sodium oxybate at doses higher than 9 g/d have not been investigated, and doses greater than 9 g/d ordinarily should not be administered. Dosing guidelines for patients younger than 16 years old are not established. Sodium oxybate is sold as a liquid. This would allow this medication to be potentially given to younger children if clinically indicated.

Cataplexy seems to respond best to medications with noradrenergic reuptake-blocking properties. There are no systematic trials of anticonvulsants drugs on children. Postpubertal teenagers are usually treated as young adults. In this group, 2 medications have been more commonly used: clomipramine and fluoxetine. Both of these drugs have active noradrenergic reuptake-blocking metabolites (desmethylclomipramine and norfluoxetine). It is through these metabolites that the therapeutic effect may be mediated. Other compounds have been found to be effective in children with cataplexy, particularly imipramine and desipramine. Clomipramine and imipramine have anticholinergic side effects, which may be problematic. Treatment with fluoxetine or viloxazine may decrease these side effects.

OSA

Pharmacologic interventions for OSA are very limited. Oxygen and protriptyline have been used with limited success. Although most children with OSA will respond clinically and polysomnographically to tonsillectomy and adenoidectomy, nasal positive airway pressure therapy remains a viable option for those who are not completely cured after surgery or who have other associated medical conditions such as Down syndrome or obesity. In those with nocturnal desaturation related to OSA, supplemental oxygen may also be used, but generally only as a temporizing measure or in cases in which usual treatments (children in whom tonsillectomy/adenoidectomy is not curative and in those who cannot tolerate positive airway pressure therapy and who refuse tracheostomy) prove unsuccessful because its use does not address the pathophysiology associated with OSA, such as arousals from sleep and increased work of breathing. Furthermore, supplemental oxygen has not been shown to result in objective changes in symptoms such as excessive daytime sleepiness, at least in adults with OSA. However, hypercapnia may occur with supplemental oxygen and thus should be assessed before starting this type of therapy.

Pharmacologic agents, such as protriptyline (PROT), have been used in selected adults patients, but studies in children are lacking. A nonsedating tricyclic antidepressant, PROT was initially found to improve OSA by decreasing REM time. Because respiratory events tend to be worse during this stage of sleep and apneas tend to last the longest, oxygen saturation may improve with use of this medication and thus PROT may theoretically prove most useful in those with isolated to or significantly worse in REM sleep. However, severe anticholinergic side effects like dry mouth, constipation, urinary retention, and impotence occur in approximately 50% of patients taking this medication, with the last 2 side effects often limiting its use. Furthermore, the lack of controlled studies in children precludes its general use in this population.

Nasal steroids have been proposed as a treatment for OSA in children. Brouillette et al proposed a 6-week course of a nasal glucocorticoid spray, fluticasone, would decrease the severity of OSA in children with adenotonsilar hypertrophy. They conducted a randomized, triple-blind, placebo-controlled, parallel-group trial of nasal fluticasone versus placebo in children aged 1 to 10 years with OSA. Thirteen children received fluticasone, and 12 received placebo. The mixed/obstructive apnea/hypopnea index decreased from 10.7 ± 2.6 (standard error) to 5.8 ± 2.2 in the fluticasone group but increased from 10.9 ± 2.3 to 13.1 ± 3.6 in the placebo group. The frequencies of hemoglobin desaturation and respiratory movement/arousals also decreased more in the fluticasone group. Changes from baseline in tonsillar size,
improved daytime behavior. Dopamine precursors and ago-

RLS. Improving this condition has been associated with
treatment and in the children's symptoms. The role of nasal steroids in the treatment of children with OSA is not entirely clear.77 Steroids may play a temporizing role until surgery or continuous posi-

tive airway pressure is available.

More recently, the role of nasal steroids in conjunction with receptor antagonist montelukast was studied in children with residual OSA after adenotonsillectomy.78 Residual sleep disordered breathing (SDB) may be present in many children after surgery. In this study, children with residual SDB with apnea hypopnea index >1 were enrolled. Treatment with montelukast and intranasal budesonide aqueous solution was administered for a period of 12 weeks. Twenty-two chil-

dren received treatment and were compared with 14 chil-

dren with residual SDB who did not receive medication. The mean AHI after surgery was 3.9 ± 1.2/h, which improved to after treatment 0.3 ± 0.3/h. The arterial oxygen saturation nadir improved from 87.3% to 92.5%.

**Restless Legs Syndrome/Periodic Limb Movements of Sleep**

Restless Legs Syndrome (RLS) is an autosomal dominant chronic neurologic disorder.5 It is characterized by leg dis-

comfort that makes the patients want move their legs. The leg discomfort may be hard to describe and in children may be characterized as “growing pains.”79-81 The discomfort is re-

lieved with movement and is more common in the evening. Periodic limb movement of sleep (PLMS) may occur alone

without RLS. RLS/PLMS can result in significant daytime difficulty as a result of sleep disruption. RLS and PLMS are both associated with poor-quality sleep. This effect on sleep may lead to daytime behavior that mimics ADHD.82-84

The pathophysiology of RLS has been associated with iron metabolism.81-90 Iron is a cofactor for tyrosine hydroxylase in dopamine synthesis. Iron deficiency exacerbates RLS symp-
toms. Iron supplementation may be helpful in children with RLS.85 Improving this condition has been associated with improved daytime behavior. Dopamine precursors and ago-

nists have been effective in relieving both RLS and PLMS.91

**Carbidopa/Levodopa**

Levodopa (L-DOPA, LARODOPA, DOPAR, L-3,4-dihy-

droxyphenylalanine) the metabolic precursor of dopamine, is used for treating Parkinson's disease. It is also used to treat RLS/periodic limb movements (PLMs) in sleep in both adults and pediatric population.92,93 Levodopa in itself is largely inert. Its therapeutic as well as adverse effects result from the
decarboxylation of levodopa to dopamine. In the brain, levo-
dopa is converted to dopamine by decarboxylation. The do-

pamine produced is responsible for its therapeutic effects.13 In modern practice, levodopa is almost always administered in combination with a peripherally acting inhibitor of aromatic L-amino acid decarboxylase such as carbidopa. If levo-
dopa is administered alone, the drug is largely decarboxy-
lated by enzymes in the intestinal mucosa and other peripheral sites so that relatively little unchanged drug reaches the cerebral circulation. In addition, dopamine re-

leased into the circulation by peripheral conversion of levo-
dopa produces undesirable effects particularly nausea. The inhibition of peripheral decarboxylase markedly increases the fraction of administered levodopa that remains unme-
tabolized and available to cross the blood-brain barrier and reduces the incidence of gastrointestinal side effects like nau-

sea.13 The main complication of levodopa therapy for RLS/

PLM is the development of worsening symptoms during the afternoon or early evening, despite adequate control later at night. This phenomenon, which has been termed “restless legs augmentation,” may occur frequently sometimes within months after therapy has been instituted. Once augmentation has occurred, levodopa therapy should be discontinued, and a different agent should be used. Administering additional doses of levodopa earlier during the day usually results in further exacerbation of the augmentation phenomenon.83,94,95 In addition to motor fluctuations and nausea, other adverse effects may be observed with levodopa therapy such as induction of hallucinations, confusion, and ortho-

static hypotension. These other side effects are more typically seen in adult patients with Parkinson’s disease using higher dosages than used in the treatment of PLMS and RLS. In the clinical practice of treating children with PLMS and RLS, nausea is by far the most common side effect. Sensitivity to side effects makes it necessary to initiate therapy at very low doses (one half of a 25/100 levodopa/carbidopa tablet daily) and increase as tolerated every few days. The therapeutic dose for relief of PLMS and RLS symptoms will be lower than that used in Parkinson’s disease. The maximal dose is deter-

mined by side effects, but most adolescents require at least 75 mg carbidopa and up to 1.5 g l-dopa.90 Levodopa is valuable in the treatment of RLS/PLM disorder, but the mode of action of the drug is unknown. It seems likely that dopaminergic pathways are involved. Walters and Hening77 have suggested that the site of action is the postsynaptic dopamine receptor, whereas Guilleminault et al98 suggested spinal dopaminergic mechanism as the site of action. There may be differences in the mechanism of action of these medications between pa-

tients with RLS and those with only PLMS. Allen et al99 have developed a theory for the pathophysiology of idiopathic RLS.99-102 These patients have been found to improve with iron supplementation. Iron is a cofactor in the production of dopamine in the brain. Iron insufficiency in certain brain regions may occur in patients with RLS.90,101

**Selective Dopamine Agonists**

Selective dopamine agonists are potent treatments for PLMD and RLS. They tend to have less side effects than carbidopa/
levodopa. Pramipexole, ropinirole, and pergolide are the most commonly used medication in this category. Pramipexole and ropinirole were both FDA approved for the treatment of RLS. Selective dopaminergic agonists have similar side effects to carbidopa/levodopa but at a lower frequency. These agents are more potent and allow for lower dosages than with carbidopa/levodopa. Montplaisir et al. have found pramipexole to be effective in a double-blind placebo-controlled study in adults. The starting dose in adults in this study was 0.375 mg. In children, the lowest dose available is an empiric starting dose. Pramipexole is available in a 0.125-mg size tablet. This tablet is scored and can be halved if an even lower starting dosage is desired. It is important to make medication changes slowly because the symptoms of PLMS and RLS seem to fluctuate independently of the medication. In addition, if the dosage is too high, significant side effects may occur. We advise parents to only adjust the medication once a week at most when they first start the medication. Once an effective dose is found, it does not typically have to be adjusted except to allow for the child’s growth. In adults, the dosage of medication usually does not exceed 1.5 mg because it is often effective at a much lower dose.

Conclusions

There is a need for greater information on the pharmacologic management of sleep disorders in children. Pharmacologic guidelines need to be developed specifically for sleep disorders in children. Ideally, these guidelines should be modified for the specific sleep disorder and for the pediatric age range. The development of easy-to-swallow, chewable, or liquid forms of these medications is needed. The integration of behavioral and pharmacologic treatments may yield better patient outcomes. This would require pediatricians to have a comprehensive understanding of clinical sleep disorders in children. Training programs should play a lead role in enhancing pediatricians’ knowledge of the pharmacologic treatment of sleep disorders in children.

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