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Pediatric Sleep Pharmacology: A Primer

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"What will you give my child to help him sleep?" is a common question parents ask and some health care providers abhor hearing. Entire families may suffer when one member does not sleep well. Poor sleep may complicate the management of other comorbid conditions. Health care providers may have received only limited education on sleep disorders and are frequently forced to choose between treatment options that are poorly studied in children. Fortunately, when addressed correctly, many children with chronic sleep disorders may improve their sleep and daytime behavior in a relatively short time. This review provides a framework to help understand the causes of poor sleep in children and the potential pharmacologic options.
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Introduction

This primer will initiate the reader to the world of pediatric sleep medicine. This is a world often ignored, but for the pediatric specialist, it is one that cannot be avoided. How well we sleep and what we do when we are asleep affect many neurodevelopmental aspects of our lives, including our level of alertness, our family dynamics, our ability to concentrate, our mood, and our seizure threshold to name just a few.

In medical school, we are taught to ask about many domains as we take a history, and our subspecialty training hones these questions down even further. Discussion of sleep quality, quantity, and problems is often absent and the sleep questions on a review of systems, with their potential lethality to your 15-minute visit answers, are skimmed over. Sleep medicine is not typically emphasized in medical school and residency training. Pediatric sleep medicine, aside from sleep training advice we might have picked up in our ambulatory pediatrics rotations, is particularly minimized. For some, it is the third rail of a history, not to be touched without significant consequences of tangential conversations. The results of this may lead to management plans and interventions with which many of us are not comfortable.

This primer is intended to take some of the mystery out of the management (pharmacologic and otherwise) of pediatric sleep problems. Regrettably, little evidenced-based medicine exists to guide us. Federal Drug Administration (FDA)–approved medications for sleep problems in children do not exist currently either. Practice parameters and guidelines that can be helpful are unavailable. Mainly, we rely on expert opinion, which is much of what you are about to read. We encourage the reader to be thoughtful applying the concepts put forth in this primer. We look forward to double-blind placebo-controlled clinical trials to guide us into future years of pediatric sleep problem management.

There are several approaches to the third rail of sleep history taking. Perhaps the most important concept is that there are 4 dimensions to any sleep question asked: amount, quality, timing, and state of mind. The sleep history can be further guided by the BEARS acronym (Bedtime resistance or sleep-onset delay; Excessive daytime sleepiness; Awakenings at night; Regularity, patterns, and duration of sleep; and Snoring and other symptoms).[1] To emphasize the importance of snoring, some prefer S-BEAR (letters all standing for the same things). It turns out that asking about snoring specifically is a high-yield question and that snoring alone has significant neurodevelopmental consequences relevant to the pediatric neurologist.[2-4] How you ask the question about snoring may also be important. Some parents find the term snoring almost pejorative in reference to their child. Asking, "Can you hear your child breathing while he is awake?" followed by, "Can you hear your child breathing while asleep?" may increase yield.

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Pediatric Sleep-Disordered Breathing

Historically, oxygen (as a temporizing measure for nocturnal desaturations), protriptyline, (intended to decrease rapid eye movement [REM] sleep where sleep-disordered breathing symptoms are typically at a maximum), and tracheostomy[5,6] were advocated for the treatment of obstructive sleep apnea (OSA); however, this is no longer the case.[7] Adenotonsillectomy remains the gold standard treatment of pediatric OSA, although there is some value in watchful waiting.[8] Continuous positive airway pressure is the mainstay for residual disease along with weight loss in obese children, and orthodontia in the form of maxillary or palatal expansion and mandibular advancement.[9,10]

Nasal steroids have been demonstrated to be useful in reducing the apnea hypopnea index (AHI) in children via a randomized, blinded, and placebo-controlled study by Brouillette et al. They demonstrated a reduction in the mixed and obstructive AHI from 10.7 ± 2.6 to 5.8 ± 2.2 in the fluticasone group. Oddly, although the AHI decreased by nearly 50%, the average index was still in the pathologic range and there was no improvement in the children's symptoms.[11] Other authors have subsequently demonstrated a positive effect of intranasal steroids in a randomized, blinded manner.[12] Overall, 62 children were given 32 μg per nostril of budesonide at bedtime for 6 weeks. Adenoid size decreased, polysomnographic features of sleep quality and respiratory disturbance improved, and in 54% of children, sleep measures normalized. Accordingly, the role of nasal steroids in anything other than perhaps mild disease or mild residual disease postoperatively remains unclear, but potentially promising, in particular if there is a history of allergies.[13]

Leukotriene modification as a treatment of OSA was initially studied as an open-label intervention by Goldbart et al.[14] Overall, 24 children were administered montelukast daily for 16 weeks, resulting in reduced adenoid size.

Leukotriene modification was later studied in a randomized and blinded manner in children with nonsevere (AHI < 10) OSA.[15] Overall, 23 children received 4 or 5 mg of montelukast vs placebo. In 62.5% of treated children, there was a 50% decrease in AHI. Additionally, symptoms improved and adenoids were reduced in size. There were no behavioral side effects noted in the treatment arm (perhaps because of the small sample size) as have been previously described with montelukast.[16,17]

Nasal steroids in combination with leukotriene modification in children with residual OSA after adenotonsillectomy were studied by Kheirandish et al.[18] Intranasal budesonide plus montelukast vs no medication for 12 weeks reduced mean AHI postoperatively from 3.9 ± 1.2/h to 0.3 ± 0.3/h, and arterial oxygen saturation nadir increased as well. Unanswered questions remain, but the combination of leukotriene modifiers and nasal steroids for mild sleep-disordered breathing likely has some merit. If these medications are indeed effective, this supports a systemic inflammatory mechanism in OSA, and if these medications work, future allergy medications may be likewise useful.

Restless Legs Syndrome

Restless Legs Syndrome (RLS) is an urge to move the legs, usually accompanied by or thought to be caused by uncomfortable and unpleasant sensations in the legs. These symptoms begin or worsen during periods of rest or inactivity, are partially or totally relieved by movement, and occur exclusively or predominately in the evening or at night.[19] This discomfort can disrupt sleep and have daytime consequences. RLS symptoms can be mistaken for "growing pains" in children and are distinguished by the relief of symptoms with movement or sometimes someone rubbing the child's legs.[20] There are some nuances to this diagnosis in the pediatric population as the children really need to describe the symptoms in their own words, which may be different from the words in the adult diagnostic criteria.[21] Perhaps the most useful historical question to ask is, "Do your legs bother you at night?" If the answer is yes, a reasonable follow-up is "Does it get better when you move your legs?" Often, the parent will then chime in that the child wants her or his legs massaged at night. As RLS tends to be a familial disorder, when asked, the birth mothers may report that they had RLS symptoms during pregnancy. Pregnancy exacerbates the symptoms. A history of RLS in a first-degree relative may influence a decision to initiate a therapeutic medication trial for RLS.

RLS is thought to be possibly a disorder of iron metabolism. Patients may be particularly sensitive to low iron levels and may be symptomatic with iron levels in the lower range of normal. Serum ferritin has been found to be lower in adults and children with RLS than in control subjects. Oral iron repletion has been recommended by some authors for a serum ferritin <50 μg/L.[22-24] Iron is a cofactor for tyrosine hydroxylase in dopamine synthesis, and the pathophysiology of RLS has long been associated with iron metabolism.[25,26] Vitamin C can help aid iron absorption. Dairy products should be avoided around the time of iron administration. Iron repletion takes time, and if the patient is particularly miserable at night, alternative agents may be necessary for more immediate relief of symptoms.

Metabolic precursors of dopamine and dopamine agonists are known to be effective agents in the treatment of RLS.[27] Pediatric specific data sets are lacking, but these agents are used to treat RLS in the pediatric population.[28] Dopamine agonists are routinely used in children in other clinical situations such as dopamine-responsive dystonia.

Levodopa in combination with carbidopa, a peripherally acting inhibitor of aromatic L-amino acid decarboxylase, can relieve RLS symptoms in children.[28] The main consequence of levodopa and carbidopa therapy is augmentation where there is a worsening of RLS symptoms during the afternoon or early evening with normal anticipated resolution of symptoms at night. Augmentation requires discontinuation of the inciting agent and initiation of an alternative therapy. Other side effects of levodopa and carbidopa include nausea, hallucinations, confusion, and orthostatic hypotension. Selective dopamine agonists have largely supplanted use of levodopa and carbidopa in the treatment of pediatric RLS.[29]