Medications for sleep disturbances in children

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Summary

At least 25% of infants, children, and adolescents have a sleep problem at some point during this developmental period. The management of pediatric sleep-related disorders often begins with behavioral strategies. While medications can be a useful adjunct, they are used off-label for sleep problems in this age group. When used, medications should be chosen carefully and targeted to specific outcomes as part of a comprehensive approach to management. This article reviews medications used for common pediatric sleep problems with a focus on pediatric insomnia and the importance of a multifactorial approach to evaluation and management.

At least 25% of children have a sleep-related problem between infancy and adolescence, and functional consequences due to poor sleep duration or quality are common.¹ Problems in learning, memory, attention, activity, mental health conditions, and quality of life occur as a consequence of poor sleep.^{2,3} Sleep problems—and insomnia and bedtime struggles in particular—are among the top 5 concerns for parents at primary care visits.⁴

Common contributors to sleeplessness in children, other than pain, transient infections, or other primary medical conditions, include medical sleep disorders (e.g., sleep-disordered breathing [SDB], restless legs syndrome [RLS], and periodic limb movement disorder [PLMD]); circadian rhythm disorders (e.g., delayed sleep phase syndrome [DSPS]); and problems in child-parent behaviors (e.g., behavioral insomnia of childhood [BIC], sleep-onset association [SOA] or limit-setting [LS] type).⁴ Factors such as the child's developmental stage, comorbid health or mental health problems, family or cultural expectations or stress, and the necessary reliance on caretaker reporting increase the complexity of evaluation.^{1,4} The most successful approach to pediatric sleep problems begins by considering all etiologic and maintenance factors.

Management of pediatric sleep problems

Case A 3-year-old girl presents for frequent night waking. She has leg pain in the evening, heroic snoring, and restless sleep. The mother tries to enforce a 10 PM bedtime upon arrival

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home from work; however, her daughter protests until finally falling asleep about midnight while held by the mother (living room, television on). The mother transfers the girl to her own bed; however, 2 hours later she hears the first of several night awakenings.

DISCUSSION

A stepwise approach can solve such night waking and bedtime problems. In this case, the first priority is evaluation with a polysomnogram (PSG) for SDB, as suggested by the snoring and restless sleep. If present, SDB might preclude safe use of some hypnotics. Leg pain and bedtime resistance suggest an evaluation for RLS is indicated. In addition, further evaluation and management for behavioral factors is indicated. Both types of behavioral insomnia (BIC-SOA, BIC-LS) are suggested by the history.

Behavioral treatments

Education is the first step to address behavioral components of pediatric sleep problems.^{4,5} Important topics include developmentally appropriate expectations for sleep duration and pattern and the components of good sleep hygiene (e.g., regular bedtime routines, sleep-wake schedules, and shaping sleep-onset circumstances to align with those encountered during sleep). Evidence-based interventions are available for behavioral sleep problems and the choice depends on sleep problem type, child developmental stage, and family circumstances.^{4,5} For instance, extinction (standard or gradual) and bedtime fading are effective interventions to change bedtime habits for BIC-SOA.⁴ The bedtime pass technique improves the predictability of parent responses and incents cooperation for BIC-LS.⁴ Cognitive behavioral therapy (CBT) is useful for psychophysiologic insomnia and anxiousness. CBT for sleep involves a program of strategies that can include stimulus control (adopt regular schedules, consolidate sleep to nighttime, and improve bed-sleep association); sleep restriction (temporarily limit hours in bed to increase sleep efficiency); reduced arousal (quieting pre-bedtime activities and relaxation-imagery); and reduced negative cognitions.⁴ Chronotherapy is an efficient intervention for DSPS.⁴ Often such strategies are successful without the need for medications; however, short-term use can be helpful for some. For complex or persistent cases, a pediatric sleep specialist may be needed.

Medication treatments

Despite effective behavioral interventions, medications remain in common use for pediatric sleep problems. In a survey of nearly 700 community pediatricians, more than 75% had recommended a nonprescription or prescription medication for insomnia.⁶ In 2005, a consensus statement on medications for pediatric insomnia provided important guidance because all are used off-label.⁵ This and other reviews highlight the need for more evidence-based studies in this area.⁷⁻⁹ Therefore, in this review we discuss medications used for insomnia and other common pediatric sleep problems in the text and table e-1. The table provides detailed information (mechanism of action, dose, side effects, relative cost) regarding medications for pediatric insomnia in particular. The cited reviews are recommended to the reader for more detailed information.^{5,7-9}

Insomnia

Insomnia includes sleep initiation and maintenance problems. In children and teens, BIC-SOA, BIC-LS, and DSPS are common causes. Insomnia may also accompany other medical, developmental, neurologic, and mental health disorders. Medication choice and administration

Supplemental Data

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Behavioral treatments for excessive sleepiness include planned naps and regular sleep-wake schedules, but medications are often needed when a treatable underlying disorder is not the cause.

time depends on insomnia type (initiation, maintenance, both); usual sleep-wake pattern; co-occurring medical problem(s); and the balance of benefit vs side effects. Hypnotic medications play a role for recalcitrant sleep-wake cycle disturbances related to autism, Smith-Magenis syndrome, and other conditions. These include over-the-counter and prescription medications, although none are currently US Food and Drug Administration (FDA) approved for this purpose in young children.^{5,7-9}

Antihistamines Diphenhydramine and hydroxyzine, histamine receptor blockers, act in the CNS to affect sleep onset and arousal. Studies in children have demonstrated variable results. One study reported reduced sleep onset latency (SOL) and night awaking and another reported no improvement. Tolerance can occur.^{5,7-10}

Melatonin Endogenous melatonin is a hormone, synthesized from tryptophan, that has circadian rhythmicity: higher levels before and during sleep and lower levels during the daytime. Exogenous melatonin enhances the mild hypnotic effects or is used for phase-advancing effects (for jet lag, blindness, and some developmental disabilities).^{5,7-9} Time of administration and dose vary depending on the desired result. For initial insomnia, 1–3 mg is administered 30–60 minutes before bedtime. Melatonin reduces SOL, and sustained-release formulations may help sleep maintenance. To advance the sleep-wake pattern, smaller doses (0.3–0.5 mg) are used ~5–6 hours before sleep onset. Melatonin is over-the-counter and not regulated by the FDA. Risk therefore exists for impurities and variable concentrations.^{5,7-9} Ramelteon, a synthetic selective melatonin agonist, is used in adults but is not approved for children.⁷⁻⁹

Alpha agonists Clonidine and guanfacine are antihypertensive agents with sedative effects that reduce SOL. To avoid hypertensive rebound upon discontinuation, doses should be gradually weaned.^{5,7-9}

Benzodiazepines and related agents Benzodiazepines activate γ -aminobutyric acid (GABA) type A (GABA_A) receptor to reduce SOL and night awakenings and increase total sleep time. Zolpidem, zaleplon, and eszopiclone are related agents that bind selectively to these receptors. Off-label use is increasing, particularly in adolescents.^{5,7-9,11}

Other Chloral hydrate is still occasionally used for pediatric insomnia. However, safety, side effects, and tolerance concerns should substantially limit its use.^{5,7-9} Trazodone, an atypical antidepressant, is prescribed for adults, but no studies support its use in children.^{5,8,9} Doxepin is available for adult use and has mixed effects, including histamine receptor blockade.

Sleep-disordered breathing

Obstructive sleep apnea (OSA) is characterized by episodes of complete or partial upper airway obstruction with co-occurring sleep fragmentation and gas exchange abnormalities. Adenotonsillectomy (first-line treatment for children) usually resolves or improves OSA. Continuous positive airway pressure (CPAP) is available for nonsurgical candidates or children requiring intervention after adenotonsillectomy. Nasal steroids can be considered if CPAP is not tolerated, congestion or allergic rhinitis are suspected contributors, or for mild OSA. Medications in this group that have demonstrated improvements by PSG findings in randomized controlled trials include budesonide and fluticasone propionate.^{7,9,12}

Restless legs syndrome and periodic limb movement disorder

RLS affects 2%–4% of children and is characterized by an urge to move the legs that is often accompanied by uncomfortable sensations, is worse during inactivity and the evening, is relieved by movement, and is not better accounted for by another medical problem. Some children are able to describe the sensation; however, many present with other sleep complaints or daytime behavioral concerns.¹³ The presence of periodic limb movements of sleep (PLMS) supports an RLS diagnosis in children who cannot describe discomfort. Pediatric PLMD is characterized by PLMS >5/hour and sleep disturbance or daytime symptoms not better accounted for by RLS or another sleep disorder.¹³

RLS management begins with good sleep hygiene. Medication may also benefit RLS or PLMD. Deficits in CNS dopaminergic pathways have been implicated in both conditions, and iron is a cofactor for steps in the dopamine synthesis pathway. Altered brain iron and regulatory protein profiles have also been demonstrated in autopsy and MRI studies.^{7,9,13,14} Pharmacologic management usually begins with treatment of iron deficiency, if identified based on serum ferritin <50 ng/mL and other parameters of low iron status. If iron supplementation fails, ferritin levels are not low, or symptomatic relief is required while iron stores are treated, other pharmacologic options are available. These include gabapentin, clonazepam, clonidine, and dopamine agonists such as pramipexole, although once again none are FDA approved for these purposes in children.^{7,9,13}

Narcolepsy-excessive daytime sleepiness

Narcolepsy affects <0.2% of the population and most often develops in adolescence. In addition to excessive daytime sleepiness, symptoms can include sleep attacks, hypnagogic hallucinations, sleep paralysis, and cataplexy (loss of muscle tone with laughter or emotional excitement). Narcolepsy is classified as occurring either with or without cataplexy.^{7,9,15} Excessive daytime sleepiness can also be idiopathic or related to another underlying primary sleep disorder. Behavioral treatments for excessive sleepiness include planned naps and regular sleep-wake schedules, but medications are often needed when a treatable underlying disorder, such as SDB, is not the cause. The first-line treatment is the nonstimulant modafinil. Second-line treatment includes stimulant medications such as methylphenidate and dextroamphetamine.^{7,9,15} In adults, treatment for cataplexy also may include tricyclic antidepressants and serotonin or norepinephrine reuptake inhibitors for their REM-suppressing properties, and γ -hydroxybutyrate.^{9,15}

CONCLUSION

Medications are commonly used by parents and practitioners for child sleep problems. However, the state of the current literature suggests that use should be limited and within the context of a comprehensive approach that addresses the primary underlying sleep disorders.

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