Attention Deficit Hyperactivity Disorder Medications and Sleep

Mark A. Stein, PhD[a,*], Courtney Zulauf-McCurdy, PhD[b], Lourdes M. DelRosso, MD, PhD[c]

KEYWORDS

• Sleep disorders • ADHD • Insomnia • Stimulants

KEY POINTS

- Sleep problems are common and often increase when initiating pharmacotherapy.
- Delayed sleep onset/insomnia is associated with stimulants although daytime sleepiness is associated with nonstimulants.
- Younger children and adolescents are most vulnerable to adverse sleep effects, but sleep problems occur in all age groups.
- Wide variability in severity and duration of sleep effects, but most effects are mild and improve over time.
- Interventions include changing dose schedules, formulations, behavioral interventions, and adding a sleep-promoting agent.

INTRODUCTION

After Charles Bradley's serendipitous discovery of the therapeutic benefit of an amphetamine (AMP), Benzedrine, in children with behavioral problems, he also described the adverse and variable initial impact on sleep in a subset of children, noting "6 of the 30 children's nocturnal sleep was mildly disturbed, as evidenced by a delay in the time of falling asleep for the first night or two. One patient remained awake to a late hour for four nights".[1] Although Benzedrine is no longer used, there are now numerous AMP, methylphenidate (MPH), and nonstimulant medications approved for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

In the past few years, research on the intersection of ADHD medications and sleep problems has intensified.[2] Moreover, the prevalence of sleep problems in individuals with ADHD appears to be on the rise.[3] This may reflect more attention to or accuracy in measuring sleep, as well as the tendency to treat ADHD with longer-acting agents or dosing schedules for longer periods.

[a] Pediatrics, University of Washington, Seattle, WA, USA; [b] University of Washington, SMART Center, Building 29, 6200 NE 74th Street, Suite 100, Seattle, WA 98115, USA; [c] Seattle Children's Hospital Sleep Center, 1231 116th Avenue, NE Suite 385, Bellevue, WA 98004, USA
* Corresponding author. Seattle Children's Hospital, Box 5371, Seattle, WA 98105.
E-mail address: mstein42@uw.edu

Child Adolesc Psychiatric Clin N Am 31 (2022) 499–514
https://doi.org/10.1016/j.chc.2022.03.006
childpsych.theclinics.com

This article is focused on describing the literature on ADHD medications and sleep. We will first define common sleep problems, discuss the importance of screening for sleep disorders in ADHD, and review methodological issues related to measuring sleep. We then summarize what has been learned about ADHD medications and sleep effects across the lifespan, before discussing clinical management and several new directions.

PREVALENCE OF SLEEP PROBLEMS IN ADHD

Commonly, children with ADHD and comorbid behavioral problems have increased activity levels throughout the day and evening, are easily distracted from task performance, and have difficulty "shutting down" their brain, hence are more likely to have worse sleep hygiene and a higher prevalence of sleep disorders. Sleep problems in youth with ADHD are reported to be in the range of 25% to 55%.[4–7] Moderate-to-severe sleep problems occur at least once a week in 19.3% of the clinic-referred children with ADHD, 13.3% of the psychiatric controls, and 6.2% of the pediatric controls according to parents.[8] Overall when sleep is assessed using rating scales, sleep diaries, or questionnaires, children with ADHD display higher rates of bedtime resistance, sleep onset difficulties, night awakenings, morning awakenings, sleep-disordered breathing, and daytime sleepiness relative to youth without ADHD.[9]

In addition to these commonly recognized sleep problems, restless legs syndrome (RLS) can be found in up to 44% of children with ADHD[10,11] and restless sleep disorder in up to 10%.[12] In an ADHD population referred for sleep evaluations, 80% of parents of children with ADHD were concerned that their children's sleep was restless. In the majority of these children, an underlying sleep diagnosis (such as obstructive sleep apnea, periodic leg movement disorder, restless sleep disorder, or RLS) was found after polysomnography (PSG).[13]

It is very important to accurately evaluate sleep patterns and problems before medication initiation to rule out primary sleep disorders that mimic or exacerbate ADHD symptoms and to serve as a baseline. Sleep logs and diaries are often used to identify sleep patterns and can be used before and after treatment. The clinical interview is crucial to diagnose specific sleep disorders such as RLS, insomnia, and parasomnias.[14] Standardized questionnaires can be used to screen for sleep disorders, such as the *BEARS*, which screens for *B*edtime, *E*xcessive sleepiness, *A*wakenings during the night, *R*egularity of sleep, and *S*noring.[15] Other commonly used questionnaires include the Pediatric Sleep Questionnaire, which screens for sleep-disordered, breathing, sleepiness and behavior,[16] and the Children's Sleep Habits Questionnaire (CSHQ).[17] The CSHQ has eight subscales including circadian delay, parasomnias, breathing, bedtime resistance, daytime sleepiness, and nocturnal awakenings.

In terms of objective evaluations, PSG is considered the "gold standard" to diagnose sleep disorders such as obstructive sleep apnea. PSG has a great utility in research because it can reliably document brain activity patterns, body movements, arousals, and homeostatic indicators. The American Academy of Sleep Medicine has published guidelines on indications of PSG. PSG is indicated any time that sleep-disordered breathing is suspected, in cases of refractory insomnia, and when there is suspicion of periodic leg movement disorder or atypical parasomnias. Another test, the multiple sleep latency test (MSLT) is used to assess for daytime sleepiness[18] and consists of five daytime nap opportunities. Studies using MSLT have demonstrated that children with ADHD are sleepier during the day and have slower reaction times.[19]

Actigraphy is less invasive than PSG and a more ecologically valid method for recording motor activity by means of small, computerized, watch-like devices worn

on the wrist. Actigraphy provides an objective measure of body movements that provide a reliable estimate of several sleep parameters, including sleep duration and sleep onset latency (SOL). Actigraphy is particularly indicated when insufficient sleep or circadian disorders are suspected and allows monitoring for several days or even weeks in the home setting. Actigraphy can also provide information on night-to-night variability, a significant characteristic of ADHD youth who are taking stimulants.

Fig. 1 is an example of an actigraphy download from a teenager with ADHD. We can appreciate an inconsistent bedtime, with sleep occurring past midnight on some evenings. Such a pattern can lead to difficulty getting up the next morning and a delayed sleep phase disorder. The parents of children with ADHD could benefit from education on the importance of a bedtime routine including how to time medication to allow for a

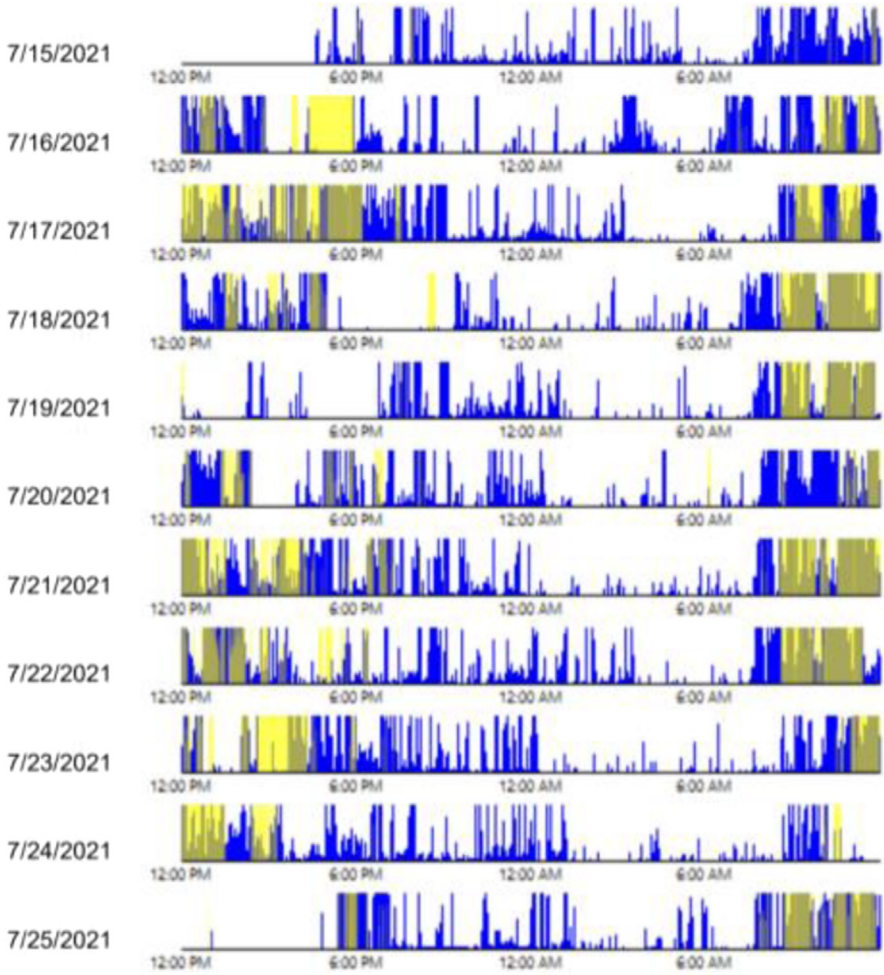

Fig. 1. Actigraphy findings on a teen with ADHD on stimulant medication. Findings show an inconsistent bedtime. Most night bedtime is past midnight consistent with a delayed sleep–wake circadian phase. There is also nocturnal awakening consistent with sleep maintenance insomnia.

bedtime of approximately 9 to 10 PM Adolescents need to sleep approximately 9 hours a night, and school-age children (7–12 year old) need approximately 10 hours of sleep at night. The morning awakening time, school schedule, and social demands (eg, sports, homework, peer interactions) need to be included in the planning for adequate sleep opportunities. Insufficient sleep has also been associated with worsening of ADHD; therefore, actigraphy and sleep diaries can be useful tools to assess sleep latency and calculate total sleep time.[20] Although commercial wearable devices are widely available, they should be used cautiously as most are not validated against the gold standard for sleep and sleep stage detection.[21]

The interrelationships between ADHD and sleep disorders, mutually exacerbating conditions, are further complicated by the use of medications to treat ADHD, which also impact sleep.[22] Research results often vary from study to study based on how and when sleep is measured,[23–25] with subjective and objective measures providing valuable, but different information (see references [9,26–28]). For instance, subjective evaluations based on self-, parent-, or observer-report can provide information about sleep initiation and maintenance, insomnia, sleep quantity and quality, and perceived time of awakening. Subjective reports, such as clinical interviews, sleep questionnaires, and diaries, can also capture summary observations over an extended time period in a naturalistic context and can reveal important aspects of clinically meaningful perceptions of sleep that may differ from objective assessments (such as those using PSG and actigraphy).

METHODOLOGICAL ISSUES IN CLINICAL TRIALS

Much of what is known about ADHD medications and their effects on sleep is based on reports of adverse events from short-term efficacy studies.[3,24,29] Most medication studies are relatively short term (ie, <7 weeks) and thus primarily measure acute effects. Due to a paucity of longitudinal data, less is known about intermediate and long-term effects on sleep.[30] There are also few comparative efficacy studies, as the majority of studies compare an active medication with a placebo (ie, basic efficacy). A recent meta-analysis of 35 studies of MPH formulations found that a wide range of study designs and sample features predicted the relative risk of insomnia, including the type of formulation, number of doses per day, age, sex, percentage of stimulant responders enrolled, year of study, number of sites, and type-of-rater.[3] Indeed, methodological differences between studies and samples present a significant challenge in evaluating the clinical implications of these studies.

One methodological factor that may influence results is ascertainment bias, which can occur when studies only include patients who complete long-term follow-up or if they exclude patients with negative prior medication history, resulting in samples enriched for positive responders. Studies that include stimulant naïve patients are useful for evaluating the impact of medication that is not confounded by prior medication history. On the other hand, these studies are less generalizable to older youth or those with complex medication histories. A second factor is the adequacy of the medication trial and how and when it is delivered. Titration, dose, and dosing strategies also impact findings. Fixed-dose or dose-response studies may provide more distinct information on the effects of medication, for example,[31] although flexible dosing may be more similar to usual care.

In one of the few longer-term studies of stimulant naive youth with ADHD, children on a waiting list were randomly assigned to immediate-release MPH or placebo for 16 weeks.[25] In contrast to findings from many short-term studies, MPH did not negatively affect sleep parameters measured at 8 weeks of treatment relative to placebo.

When sleep was measured a week after medication was discontinued (after 16 weeks of treatment), sleep efficiency was improved in the MPH group. This provocative finding requires replication but suggests that sleep problems are much more prevalent when first initiating treatment compared with after 8 weeks of treatment or after medication is discontinued.

STIMULANTS AND SLEEP PROBLEMS

Methylphenidate. Delayed sleep onset, typically defined as greater than 30 minutes, or insomnia are frequent adverse events associated with MPH,[22,32,33] the most common medication used to treat ADHD in children. In a recent meta-analysis of nine randomized stimulant trials that used objective measures of sleep in 246 children with ADHD,[34] stimulant treatment was associated with longer sleep latencies, worse sleep efficiency, and shorter sleep duration. The authors highlighted the importance of weighing the cognitive and behavioral benefits of stimulant treatment to the adverse impact on sleep. Similarly, Faraone and colleagues[3] found that children receiving MPH were at a 60% greater risk for sleep problems compared with children receiving placebo. The greatest relative risks were seen with longer-acting preparations, such as osmotic-release oral system, transdermal system, and MPH hydrochloride controlled-release.

There are also several studies that have used PSG in children with ADHD who were receiving MPH. For example,[35] compared 53 children taking stimulants, 34 children with ADHD who were not taking stimulants, and 53 controls and found no differences in sleep architecture. However, the rates of insomnia were not reported, children were not randomized to treatment, and children who may have discontinued medication may not have been identified, effecting the results that can be drawn from this study. MPH has been found to reduce total sleep time and reduce sleep efficiency but not alter sleep architecture in children diagnosed with ADHD.[36]

Amphetamine. Relative to MPH, there are far fewer studies of AMP effect on sleep. AMP is associated with longer and more variable pharmacokinetic profiles (eg,.[37] compared with MPH).[38] conducted a double-blind, forced dose, parallel-group study in which 290 children received either Lisdexamfetamine (LDX), an AMP prodrug, or a placebo for 4 weeks. More than half of the sample was stimulant naïve. Insomnia was the second most common, spontaneously reported adverse event after decreased appetite, and it occurred in approximately 15% of those prescribed LDX compared with only 2% of those taking the placebo. In another study comparing LDX and mixed AMP salts,[39] reports of insomnia were most common during the first week of treatment for both stimulants.

Examining sleep outcomes in more detail,[40] used parent ratings, actigraphy, and PSG to evaluate the sleep effects of LDX in 24 children with ADHD (6–12 years of age). Other than fewer nighttime awakenings in the LDX group, there were no significant differences between LDX and placebo. Although not statistically significant, latency to persistent sleep during PSG, was approximately 10 minutes longer for the LDX group compared with placebo controls. The small sample size, flexible dosing titration period, time to habituation to medication before assessment of sleep effects, and exclusion of subjects with a history of adverse or nonresponse to AMP may have led to a bias toward failing to find an effect on sleep.[41]

In one of the few comparative effectiveness studies of frequently used AMP and MPH stimulants, Stein and colleagues[31] used a placebo, controlled, crossover design to compare three dose levels of ER-mixed AMP salts with ER dexmethylphenidate and a placebo in 56 youth (30% stimulant naïve). Parent ratings of severe insomnia were

significantly higher for Mixed amphetamine salts extended release (ER-MAS) at the 10 mg dose level. However, at the higher dose levels, there was no drug-related difference in the percentage of youth with severe insomnia. Using actigraphy, higher doses were associated with later sleep start time and shorter actual sleep duration for both stimulants.[42]

Nonstimulants. Atomoxetine (ATX) was the first nonstimulant approved by the Food and Drug Administration (FDA) for ADHD. Somnolence, or the state of feeling drowsy, has been found to be an adverse event with ATX for children,[43] especially during the early stages of a trial period or if titration is done too rapidly.[44] Whereas, for adults, insomnia is a more common side effect of nonstimulants. In another comparative efficacy study, a study[45] found that ATX was associated with more frequent night awakenings, although MPH was associated with a greater incidence of insomnia and increased SOL in adults. Residual daytime somnolence seen in children can be minimized by dividing doses or taking ATX in the evening although daytime efficacy may be decreased.[44]

The alpha 2 agonists, clonidine and guanfacine, are other nonstimulants approved to treat ADHD as monotherapy or in combination with a stimulant. They have also been used off-label to treat insomnia. Few studies[46,47] conducted a chart review and found that low-dose clonidine had a beneficial effect on sleep disturbance in youth with ADHD at baseline.

The extended-release formulations of alpha-2 agonists have been found to be associated with somnolence, sedation, and fatigue in 20% to 40% of youth with ADHD when used as monotherapy.[48] Guanfacine has also been associated with increased wakefulness after sleep onset.[49] Although somnolence, sedation, and fatigue are significantly improved when coadministered with a stimulant, they still occur in 15% to 20% of children, especially at the beginning of a trial or during dose titration.[50,51]

SELECT POPULATIONS

Preschoolers. The preschool period is a time of marked changes in sleep routines and expectations as attending school for the first time encourages families to develop a more consistent sleep schedule. What is known about ADHD and sleep in school-age children cannot necessarily be applied to preschoolers (eg,[52] due to unique developmental and environmental factors during this time). *Difficulty initiating sleep* is the most common reported sleep problem in preschoolers with ADHD. Parents often struggle with their preschool children over bedtime, and in the past, this has been largely interpreted as bedtime resistance or behavioral insomnia. However, bedtime resistance in preschoolers with ADHD may be a behavioral manifestation of difficulty with circadian rhythm.[53–55] A recent medical records study of 497 children with ADHD under the age of 6 compared those being treated with stimulants to alpha agonists.[56] Although difficulty sleeping was more common in the stimulant treated group (21% vs 11%), daytime sleepiness was more common in those treated with alpha 2 agonists (38%) compared with only 3% for those treated with stimulants.

Stimulant medication trials in preschool children with ADHD have consistently found a relatively attenuated benefit to risk ratio compared with school-aged children.[57–59] In general, stimulant usage at a younger age is associated with more frequent side effects, including irritability, decreased appetite, and sleep problems. Moreover, findings of adverse effects, such as sleep disturbances, are complicated by families discontinuing clinical trials. For instance, in a recent study of 90 preschool-age children with ADHD,[60] 287 treatment-related side effects were reported in 65 children but only 10 (all of which discontinued) were reported as severe (eg, insomnia, aggression, decreased appetite). During the 1-year follow-up, 40% of the children treated

with stimulants dropped out for reasons other than adverse effects. However, this is not an unusual number of drop-outs in a long-term study.

A recent pilot study using both objective and subjective measures found increased motor activity during sleep and more night-to-night variability in sleep duration among preschoolers with ADHD.[61] Other sleep disorders that affect this age group, such as behavioral insomnia of childhood, combined with difficulty initiating sleep, and bedtime resistance can further complicate ADHD and its treatment.[22]

Adolescents. The adolescent period is marked by significant biological, physiologic, and social changes.[62,63] During adolescence, dopamine levels peak in various brain regions although serotonin decreases to adult levels by the age of 14. Norepinephrine levels reach the lowest at the onset of puberty, after which they tend to increase until the age of 40 to 60 years.[64] Similarly adrenergic receptors decline during the young adult years. There are also important sleep-related changes during the adolescence period as evidenced by electroencephalography. Slow-wave sleep (N3) decreases by more than 60% between the ages of 10 and 20 years.[65,66] This decline in N3 parallels a decline in sleep homeostatic pressure, which has important implications when evaluating adolescents for sleep delay. Furthermore, during adolescence, neuronal connections reorganize, unused synapses are eliminated, and maturation of cognitive functions occur, although asynchronously in different brain areas, therefore not all adolescents of the same age will have the same level of development in attention or executive function.[5] Although adolescents are faced with substantial increases in academic and social demands,[67] the ability to undertake new challenges is highly impacted by neurocognitive functioning and ADHD symptoms, which are also closely associated with sleep quality.[68]

Eighth-grade adolescents with ADHD who used stimulant medication reported more sleep–wake problems and longer SOL on school nights using a diary compared with peers without ADHD ($N = 140$).[2] As in children, initiation of a stimulant or dose changes was associated with delayed sleep onset. For example, a study[69] found that 4% of 171 adolescents (13–18 years of age) treated with once-daily Osmotic-release oral system (OROS) MPH-reported insomnia as an adverse effect. It is unclear how many youth were previously treated with MPH, but subjects with an adverse response were excluded from participation.

In addition to insomnia, inadequate sleep duration, and poor sleep efficiency, adolescents with ADHD are at high risk for a delayed sleep–wake phase, which involve a shift in the sleep–wake cycle such that the adolescent going to bed late and sleeping in late (see **Fig. 1**), sometimes to the point of day/night reversal. For example, as reported by [2] adolescents with ADHD were more likely than adolescents without ADHD to obtain insufficient sleep on school days (per diary) and weekends (per diary and actigraphy). Moreover, adolescents with ADHD were also more likely to report falling asleep in class and having stayed up all night at least twice in the previous 2 weeks (14% and 5% reported all-nighters for ADHD and comparison, respectively). Disruptions in circadian rhythm can have a devastating effect on school performance. Delayed sleep–wake phase disorder is of particular importance in that it has become a cultural norm to stay out late on the weekends, sleep late into the afternoon on Saturday and Sunday, and then try to shift back to a normal school schedule by Monday. Should a delayed sleep phase be present, treatment should center on rigorous maintenance of routine sleep and wake times, including no more than an hour difference on nonschool days.

Adults. Although sleep is far less studied in adults with ADHD compared with children, comorbidity of ADHD and sleep disorders is common in adults. In a sample of adults with ADHD, 44.4% of patients met the criteria for insomnia disorder according

to the Diagnostic and Statistical Manual of Mental Disorders, Fifth edition (DSM-5) and 63.9% had insomnia symptoms.[70] Higher ADHD severity, psychiatric comorbidity, and fewer months of stable ADHD treatment were independently related to a higher prevalence of insomnia although longer periods of stable treatment were associated with lower rates of insomnia. Regardless of the presence or absence of insomnia, adults with ADHD have been found to have delayed sleep time and wake up time with a late onset of dim light melatonin secretion.[71]

In contrast to studies of stimulants in children, in adults, there is a mixed picture. In several clinical trials, AMP formulations (the typical duration of action of 12–16 hours) have been shown to not affect sleep based on subjective sleep measures in adults with ADHD.[72,73] For example, a study[72] analyzed two large randomized, double-blind placebo-controlled trials of LDX and extended-release mixed AMP salts for shifts from good sleep at baseline to poor sleep and found no significant difference between drug and placebo. In another adult ADHD trial, one-third of stimulant-treated patients showed improvements in sleep efficiency.[74] Similarly, Sobanski and colleagues[75–77] reported improvement in sleep onset and sleep maintenance according to subjective and objective measures although total sleep time decreased.

As of yet, we do not have dose–response or fixed–dose studies of medication effects on sleep in representative samples of adults with ADHD. Nonetheless, these early reports suggest that the effects of stimulants on sleep in adults and children may differ significantly, and that children's sleep may be more sensitive to stimulant effects.[41]

MANAGEMENT OF CO-OCCURRING SLEEP AND ADHD

According to Sengal and colleagues[45] (2006), "Avoiding adverse effects on sleep may represent a considerable advantage for the clinician in developing effective ADHD treatment strategies". Dose adjustments to minimize total daily medication burden, plus environmental or sleep hygiene interventions are recommended as first-line treatment in the child with stimulant-induced or exacerbated insomnia that persists beyond a few days (**Fig. 2**). Often, adverse sleep effects from medications for ADHD decrease by adjusting the dose and/or timing, as well as other strategies aimed at optimizing sleep before initiation of and throughout treatment (see reference[78]).

Improving sleep hygiene and establishing a consistent bedtime schedule with structured routines, avoidance of electronics and caffeine, and keeping a sleep-promoting bedroom environment with respect to temperature, light, and noise can reduce SOL. Short-term behavioral interventions, such as the Sleeping Sound with ADHD program,[79] have demonstrated efficacy in reducing moderate to severe sleep problems in a sample where approximately 80% of children were receiving stimulants.[80] Nonetheless, 28%–35% in the treatment group still displayed sleep problems highlighting the need for multimodal interventions targeting sleep and ADHD symptoms.

Environmental and behavioral interventions remain the foundation for most successful sleep interventions. Focus on the maintenance of routine sleep onset and wake times even on nonschool days should also be included. Optimizing the sleep environment not just in the child's bedroom, but for the whole household/family, is critical. Other recommendations include having positive and consistent bedtime routines. In fact, using sticker charts, sleep fairies, and other reward methods can help to establish a positive bedtime environment and have been shown to be effective in the treatment of behavioral sleep problems in children.[81,82] Incidentally, the use of weighted blankets has also been reported to be beneficial in some children with ADHD.[83]

Melatonin. Melatonin, a commercially available supplement, is often used to treat insomnia.[84] More commonly, melatonin is used as a hypnotic, with doses of 1–6 mg.

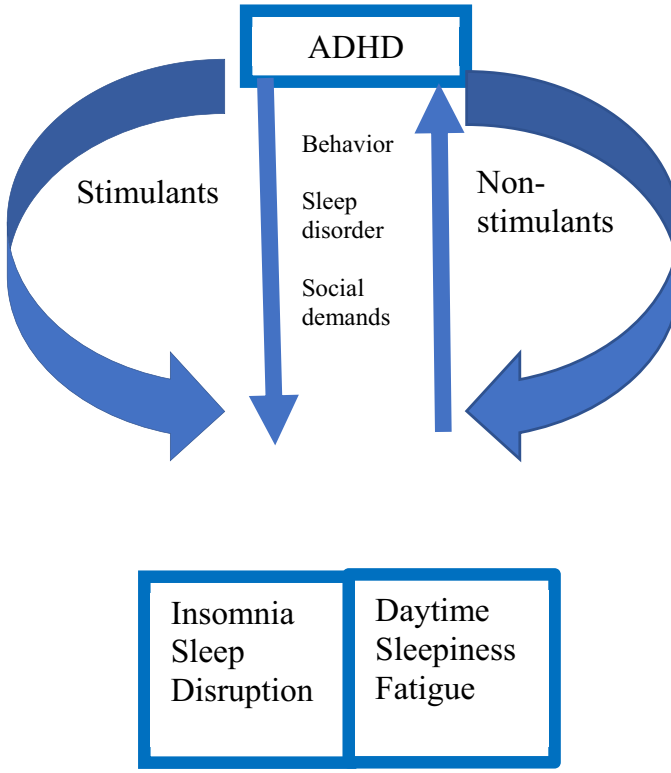

Fig. 2. Conceptual model for sleep problems in children with ADHD.

administered 30–60 minutes before desired sleep onset time. In cases of stimulant-induced or exacerbated insomnia that neither improves after several weeks nor is responsive to environmental and behavioral interventions, adding melatonin for the short term can be helpful. Melatonin is commonly used in children, for example, in the [80] trial of behavioral treatment conducted in Australia, 32.8% of children in the intervention group and 36.9% of children in the control group were receiving melatonin.[80] There are now several well-controlled melatonin studies. Van der Heijden and colleagues[85] (2007) found that 3 to 6 mg. of melatonin was superior to placebo in reducing SOL and that subsequently sleep hygiene improved. Similarly, a study[86] found that the mean sleep latency and total sleep disturbance scores were reduced in the melatonin group while the scores increased in the placebo group.

Weiss and colleagues[87] (2006) evaluated the impact of sleep hygiene procedures (eg, keeping a consistent sleep schedule, turning electronics off, discontinuing naps, and caffeinated beverage) and melatonin in a sample of children taking stimulant medication who also had a sleep latency of greater than 60 minutes. After sleep hygiene procedures, 15% of patients were sleep hygiene "responders," although the average SOL after sleep hygiene training was still quite long (73 minutes), as determined by actigraphy. The remaining patients who did not respond to sleep hygiene training were then randomized to receive either 5 mg of melatonin or placebo. Melatonin was well tolerated and statistically superior to placebo. The most effective treatment was a combination melatonin/sleep hygiene. Subjects were followed over time and eventually had complete normalization of sleep.

Box 1
Recommended strategies for sleep problems in children with ADHD and medication

1. Obtain thorough sleep history and rule out a primary sleep disorder
2. Treat primary sleep disorder if present (restless legs syndrome, obstructive sleep apnea)
3. Monitor sleep with sleep diaries or actigraphy at baseline and throughout medication trial
4. Encourage sleep hygiene
5. If sleep-onset latency or insomnia persists, consider reducing the dose of stimulants and observe
6. Consider adding melatonin, switching formulations, or combining with a nonstimulant

Typically, melatonin is well tolerated. Reported side effects include diarrhea, headache, enuresis, dizziness, nausea, and sleepiness. However, there are only a few long-term studies (up to 10 years) of melatonin at this time.[88] Given the evidence for melatonin and the benign side effect profile with widespread usage, melatonin may be recommended along with re-evaluation of ADHD medication dose and formulation and sleep hygiene strategies for ADHD medication-induced sleep problems (**Box 1**). However, despite the potential benefits, challenges exist to the effective use of melatonin, including wide variation in the potency and time course of melatonin formulation as the FDA does not regulate over-the-counter melatonin content,[89] allowing for the potential presence of contaminants.[90] Therefore, clinicians should be ready to speak to their patients about how to safely identify and use melatonin.

Other medications. Other medications for insomnia in children with ADHD have not been thoroughly studied. Limited evidence based on observational case series or retrospective chart reviews support the use of clonidine for sleep onset symptoms.[47,91] A single randomized controlled trial on Eszopiclone low dose (1 mg) versus high dose (3 mg) did not show improvement in sleep latency and demonstrated an 11% discontinuation rate due to side effects (eg, headache, dysgeusia, and dizziness).[92] Several potential areas of future research in children with ADHD and sleep disruption include orexin agonists (currently under development) and iron supplementation.

Several studies suggest a link between iron deficiency and ADHD.[93] Iron supplementation has been very successful in the treatment of RLS and restless sleep disorder in children.[94] The pathophysiology involves iron in the production of dopamine in areas of the brain involved in motor control (substantia nigra).

In summary, there is little evidence for sleep medications in children with ADHD. Although stimulants can decrease sleep latency, the opposite is usually true for nonstimulants (eg, ATX has been shown to increase somnolence). Although the effects of nonstimulants on fatigue and somnolence may be minimized with evening administration, although daytime efficacy for ADHD may be decreased, combined use of a stimulant and nonstimulant (eg, alpha2s, ATX) treatment may be helpful and optimal.

SUMMARY

Sleep disorders are common in individuals with ADHD both during and before pharmacologic intervention. If symptoms of a primary sleep disorder, such as obstructive sleep apnea, are present, it is important to further evaluate or refer to a sleep center. Insomnia and delays in latency to sleep onset greater than 30 minutes, either new onset or an exacerbation of prior sleep difficulties, are one of the most common adverse effects of stimulant medications and have been most studied in school-

age-children with ADHD. With the advent of more long-acting stimulant medications and the awareness that ADHD impacts afternoon and evening behavior, more children are being treated for longer periods and with higher total daily doses compared with treatment with immediate-release formulations. Effects on sleep latency are most pronounced during initiation of a new medication and after dose changes. Although higher and later doses are associated with a greater impact on sleep, only a minority of children with ADHD (<20%) display persistent or severe sleep effects. First-line treatments for sleep concerns are behavioral and environmental treatments focused on improving sleep hygiene. If problems persist, melatonin may be added under the guidance of a professional.

Variable dosing schedules can also contribute to circadian rhythm disturbances, such as administration on school days only or markedly different weekend and week-day schedules, which are common in adolescents. Adolescents are also at the highest risk for medication nonadherence, further contributing to night-to-night variability. Consequently, they are at heightened risk for delayed sleep–wake phase disorder and resultant daytime sleepiness when having to wake up earlier than their circadian schedule.

Children who take stimulants may experience fewer nighttime waking and may be more difficult to arouse in the morning. However, nonstimulants can affect sleep in different ways than stimulants, with somnolence seen as a common side effect. Clinical evaluation related to the start of medication and the timing of titration, in addition to counseling related to the timing of daily use, may lessen the negative effects of ADHD medication on sleep.

CLINICS CARE POINTS

1. Screen for sleep disorders that can mimic and coexist in children with ADHD before initiating pharmacotherapy and monitor throughout the medication trial.
2. Stimulant medications can adversely affect sleep latency, duration, and efficiency but also may decrease night awakenings although nonstimulants can increase daytime sleepiness.
3. Nonstimulants can contribute to daytime sleepiness despite being important for this population.
4. For the majority of ADHD youth, effects of ADHD medications on sleep tend to occur when initiating medication trial, during escalating dose titration, or with multiple doses used to extend the stimulant duration of action on ADHD symptoms
5. Chronic sleep deprivation can also occur, and night-to-night variability (eg, medication on school days) can adversely affect circadian rhythms, especially in adolescents.

ACKNOWLEDGMENTS

The authors are grateful to Dr. Margaret Weiss for her thoughtful review and suggestions.

REFERENCES

1. Bradley C. The behavior of young children receiving Benzedrine. Am J Psychiatry 1937;94:577–85.
2. Becker SP, Langberg JM, Eadeh HM, et al. Sleep and daytime sleepiness in adolescents with and without ADHD: differences across ratings, daily diary, and actigraphy. J Child Psychol Psychiatry 2019;60(9):1021–31.

3. Faraone SV, Po MD, Komolova M, et al. Sleep-associated adverse events during methylphenidate treatment of attention-deficit/hyperactivity disorder: a meta-analysis. J Clin Psychiatry 2019;80(3). https://doi.org/10.4088/JCP.18r12210.
4. Hodgkins P, Setyawan J, Mitra D, et al. Management of ADHD in children across Europe: patient demographics, physician characteristics and treatment patterns. Eur J Pediatr 2013;172(7):895–906.
5. Huttenlocher PR. Synaptic density in human frontal cortex - developmental changes and effects of aging. Brain Res 1979;163(2):195–205.
6. Owens JA. The ADHD and sleep conundrum: a review. J Dev Behav Pediatr 2005;26(4):312–22.
7. Sung V, Hiscock H, Sciberras E, et al. Sleep problems in children with attention-deficit/hyperactivity disorder: prevalence and the effect on the child and family. Arch Pediatr Adolesc Med 2008;162(4):336–42.
8. Stein MA. Unravelling sleep problems in treated and untreated children with ADHD. J Child Adolesc Psychopharmacol 1999;9(3):157–68.
9. Cortese S, Faraone SV, Konofal E, et al. Sleep in children with attention-deficit/hyperactivity disorder: meta-analysis of subjective and objective studies. J Am Acad Child Adolesc Psychiatry 2009;48(9):894–908. Available at. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19625983.
10. Picchietti MA, Picchietti DL. June). Restless legs syndrome and periodic limb movement disorder in children and adolescents. Semin Pediatr Neurol 2008; 15(No. 2):91–9. WB Saunders.
11. Pitzer M. The development of monoaminergic neurotransmitter systems in childhood and adolescence. Int J Dev Neurosci 2019;74:49–55.
12. Wajszilber D, Santiseban JA, Gruber R. Sleep disorders in patients with ADHD: impact and management challenges. Nat Sci Sleep 2018;10:453.
13. Kapoor V, Ferri R, Stein MA, et al. Restless sleep disorder in children with attention-deficit/hyperactivity disorder. J Clin Sleep Med 2021;17(4):639–43.
14. Taylor DJ, Wilkerson AK, Pruiksma KE, et al. Reliability of the structured clinical interview for DSM-5 sleep disorders module. J Clin Sleep Med 2018;14(3): 459–64.
15. Owens and Dalzell 2005.
16. Chervin et al., 2000.
17. Owens JA, Spirito A, McGuinn M. The Children's Sleep Habits Questionnaire (CSHQ): psychometric properties of a survey instrument for school-aged children. Sleep 2000;23(8):1043–51.
18. Biggs SN, Lushington K, van den Heuvel CJ, et al. Inconsistent sleep schedules and daytime behavioral difficulties in school-aged children. Sleep Med 2011; 12(8):780–6.
19. Lecendreux M, Konofal E, Bouvard M, et al. Sleep and alertness in children with ADHD. J Child Psychol Psychiatry 2000;41(6):803–12. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11039692.
20. Floros O, Axelsson J, Almeida R, et al. Vulnerability in Executive Functions to Sleep Deprivation Is Predicted by Subclinical Attention-Deficit/Hyperactivity Disorder Symptoms. Biol Psychiatry Cogn Neurosci Neuroimaging 2021;6(3):290–8.
21. Rentz LE, Ulman HK, Galster SM. Deconstructing commercial wearable technology: contributions toward accurate and free-living monitoring of sleep. Sensors (Basel) 2021;21(15). https://doi.org/10.3390/s21155071.
22. Stein MA, Weiss M, Hlavaty L. ADHD treatments, sleep, and sleep problems: complex associations. Neurotherapeutics 2012;9(3):509–17.

23. Chin WC, Huang YS, Chou YH, et al. Subjective and objective assessments of sleep problems in children with attention deficit/hyperactivity disorder and the effects of methylphenidate treatment. Biomed J 2018;41(6):356–63.
24. Cortese S, Panei P, Arcieri R, et al. Safety of methylphenidate and atomoxetine in children with attention-deficit/hyperactivity disorder (ADHD): data from the Italian National ADHD Registry. CNS drugs 2015;29(10):865–77.
25. Solleveld MM, Schrantee A, Baek HK, et al. Effects of 16 Weeks of methylphenidate treatment on actigraph-assessed sleep measures in medication-naive children with ADHD. Front Psychiatry 2020;11:82.
26. Hvolby A. Associations of sleep disturbance with ADHD: implications for treatment. Atten Defic Hyperact Disord 2015;7(1):1–18.
27. Rechtschaffen A. Polygraphic aspects of insomnia. In: Encephalography. 1967. Bologna: p. 109–25.
28. Stein MA, Blondis TA, Schnitzler ER, et al. Methylphenidate dosing: twice daily versus three times daily. Pediatrics 1996;98(4 Pt 1):748–56. Available at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8885956.
29. De Crescenzo F, Licchelli S, Ciabattini M, et al. The use of actigraphy in the monitoring of sleep and activity in ADHD: a meta-analysis. Sleep Med Rev 2016;26:9–20.
30. Becker SP, Langberg JM, Eadeh HM, et al. Sleep and daytime sleepiness in adolescents with and without ADHD: Differences across ratings, daily diary, and actigraphy. Journal of Child Psychology and Psychiatry 2019;60(9):1021–31.
31. Stein MA, Waldman ID, Charney E, et al. Dose effects and comparative effectiveness of extended release dexmethylphenidate and mixed amphetamine salts. J Child Adolesc Psychopharmacol 2011;21(6):581–8.
32. Storebø OJ, Ramstad E, Krogh HB, et al. Methylphenidate for children and adolescents with attention deficit hyperactivity disorder (ADHD). Cochrane Database Syst Rev 2015;11:CD009885.
33. Storebø OJ, Pedersen N, Ramstad E, et al. Methylphenidate for attention deficit hyperactivity disorder (ADHD) in children and adolescents–assessment of adverse events in non-randomised studies. Cochrane Database Syst Rev 2018;(5):CD012069.
34. Kidwell KM, Van Dyk TR, Lundahl A, et al. Stimulant medications and sleep for youth with ADHD: a meta-analysis. Pediatrics 2015;136(6):1144–53.
35. O'Brien et al. (2003).
36. Galland BC, Tripp EG, Taylor BJ. The sleep of children with attention deficit hyperactivity disorder on and off methylphenidate: a matched case-control study. J Sleep Res 2010;19(2):366–73.
37. McGough JJ, Biederman J, Greenhill LL, et al. Pharmacokinetics of SLI381 (ADDERALL XR), an extended-release formulation of Adderall. J Am Acad Child Adolesc Psychiatry 2003;42(6):684–91.
38. Biederman J, Krishnan S, Zhang Y, et al. Efficacy and tolerability of lisdexamfetamine dimesylate (NRP-104) in children with attention-deficit/hyperactivity disorder: a phase III, multicenter, randomized, double-blind, forced-dose, parallel-group study. Clin Ther 2007;29(3):450–63.
39. Biederman J, Boellner SW, Childress A, et al. Lisdexamfetamine dimesylate and mixed amphetamine salts extended-release in children with ADHD: a double-blind, placebo-controlled, crossover analog classroom study. Biol Psychiatry 2007;62(9):970–6.
40. Giblin and Strobel 2011.

41. Diaz-Roman et al., 2018.
42. Santisteban JA, Stein MA, Bergmame L, et al. Effect of extended-release dexmethylphenidate and mixed amphetamine salts on sleep: a double-blind, randomized, crossover study in youth with attention-deficit hyperactivity disorder. CNS drugs 2014;28(9):825–33.
43. Yildiz O, Cakin-Memik N, Agauglu B. Quality of life in children with (attention-deficit hyperactivity disorder): a cross-sectional study/Dikkat eksikligi hiperaktivite bozuklugu tanili cocuklarda yasam kalitesi: kesitsel bir calisma. Arch Neuropsychiatry 2010;47(4):314–9.
44. Block SL, Williams D, Donnelly CL, et al. Post hoc analysis: early changes in ADHD-RS items predict longer term response to atomoxetine in pediatric patients. Clin Pediatr 2010;49(8):768–76.
45. Sangal RB, Owens J, Allen AJ, et al. Effects of atomoxetine and methylphenidate on sleep in children with ADHD. Sleep 2006;29(12):1573–85. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17252888.
46. Wilens TE, Biederman J, Spencer TJ. Clonidine for sleep disturbances associated with attention-deficit hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 1994;33(3):424–6.
47. Prince JB, Wilens TE, Biederman J, et al. Clonidine for sleep disturbances associated with attention-deficit hyperactivity disorder: a systematic chart review of 62 cases. J Am Acad Child Adolesc Psychiatry 1996;35(5):599–605.
48. Daviss WB, Patel NC, Robb AS, et al. Clonidine for attention-deficit/hyperactivity disorder: II. ECG changes and adverse events analysis. Journal of the American Academy of Child & Adolescent Psychiatry 2008;47(2):189–98.
49. Rugino TA. Effect on primary sleep disorders when children with ADHD are administered guanfacine extended release. Journal of attention disorders 2018;22(1):14–24.
50. Kollins SH, Jain R, Brams M, et al. Clonidine extended-release tablets as add-on therapy to psychostimulants in children and adolescents with ADHD. Pediatrics 2011;127(6):e1406–13.
51. Faraone SV, Glatt SJ. Effects of extended-release guanfacine on ADHD symptoms and sedation-related adverse events in children with ADHD. J attention Disord 2010;13(5):532–8.
52. Charach A, Carson P, Fox S, et al. Interventions for preschool children at high risk for ADHD: a comparative effectiveness review. Pediatrics 2013;131(5):e1584–e1604.
53. Van der Heijden KB, Smits MG, Gunning WB. Sleep hygiene and actigraphically evaluated sleep characteristics in children with ADHD and chronic sleep onset insomnia. Journal of sleep research 2006;15(1):55–62.
54. Van der Heijden KB, Smits MG, Someren EJV, et al. Idiopathic chronic sleep onset insomnia in attention-deficit/hyperactivity disorder: A circadian rhythm sleep disorder. Chronobiology international 2005;22(3):559–70.
55. Van her Heijden, Smits, Van Someren, Ridderinkof, & Gunning, 2007
56. Harstad E, Shults J, Barbaresi W, et al. alpha2-Adrenergic agonists or stimulants for preschool-age children with attention-deficit/hyperactivity disorder. JAMA 2021;325(20):2067–75.
57. Ghuman JK, Aman MG, Lecavalier L, Riddle MA, Gelenberg A, Wright R, Fort C. Randomized, placebo-controlled, crossover study of methylphenidate for attention-deficit/hyperactivity disorder symptoms in preschoolers with developmental disorders. Journal of child and adolescent psychopharmacology 2009;19(4):329–39.

58. Greenhill et al., 2005.
59. Lee SS, Falk AE, Aguirre VP. Association of comorbid anxiety with social functioning in school-age children with and without attention-deficit/hyperactivity disorder (ADHD). Psychiatry research 2012;197(1-2):90–6.
60. Childress et al., 2021.
61. Melegari MG, Vittori E, Mallia L, Devoto A, Lucidi F, Ferri R, Bruni O. Actigraphic sleep pattern of preschoolers with ADHD. Journal of Attention Disorders 2020; 24(4):611–24.
62. Colrain IM, Baker FC. Changes in sleep as a function of adolescent development. Neuropsychology review 2011;21(1):5–21.
63. Darchia N, Cervena K. The journey through the world of adolescent sleep. Reviews in the Neurosciences 2014;25(4):585–604.
64. Abd-Allah NM, Hassan FH, Esmat AY, et al. Age dependence of the levels of plasma norepinephrine, aldosterone, renin activity and urinary vanillylmandelic acid in normal and essential hypertensives. Biol Res 2004;37(1):95–106.
65. Feinberg I, Campbell IG. Sleep EEG changes during adolescence: an index of a fundamental brain reorganization. Brain Cogn 2010;72(1):56–65.
66. Floros O, Axelsson J, Almeida R, et al. Vulnerability in executive functions to sleep deprivation is predicted by subclinical attention-deficit/hyperactivity disorder symptoms. Biol Psychiatry Cogn Neurosci Neuroimaging 2021;6(3):290–8.
67. Crockett LJ, Crouter AC. Pathways through adolescence: Individual development in relation to social contexts. Psychology Press 2014.
68. Carskadon MA. Sleep in adolescents: the perfect storm. Pediatric Clinics 2011;58(3):637–47.
69. McGough J, McCracken J, Swanson J, et al. Pharmacogenetics of methylphenidate response in preschoolers with ADHD. J Am Acad Child Adolesc Psychiatry 2006;45(11):1314–22.
70. Fadeuilhe C, Daigre C, Richarte V, et al. Insomnia disorder in adult attention-deficit/hyperactivity disorder patients: clinical, comorbidity, and treatment correlates. Front Psychiatry 2021;12:663889.
71. Snitselaar MA, Smits MG, van der Heijden KB, et al. Sleep and circadian rhythmicity in adult ADHD and the effect of stimulants. J Atten Disord 2017;21(1): 14–26.
72. Surman CB, Roth T. Impact of stimulant pharmacotherapy on sleep quality: post hoc analyses of 2 large, double-blind, randomized, placebo-controlled trials. The Journal of clinical psychiatry 2011;72(7):8683.
73. Brams, Matthew, et al. 2011.
74. Surman CB, Adamson JJ, Petty C, et al. Association between attention-deficit/hyperactivity disorder and sleep impairment in adulthood: evidence from a large controlled study. The Journal of clinical psychiatry 2009;70(11):1483.
75. Boonstra AM, Kooij JJ, Oosterlaan J, et al. Hyperactive night and day? Actigraphy studies in adult ADHD: a baseline comparison and the effect of methylphenidate. Sleep 2007;30:433–42.
76. Roth T, Zinsenheim J. Sleep in adults with ADHD and the effects of stimulants. Prim Psychiatry 2009;16:32–7.
77. Sobanski E, Schredl M, Kettler N, et al. Sleep in adults with attention deficit hyperactivity disorder (ADHD) before and during treatment with methylphenidate: a controlled polysomnographic study. Sleep 2008;31(3):375–81. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18363314.

78. Cortese S, Newcorn JH, Coghill D. A practical, evidence-informed approach to managing stimulant-refractory attention deficit hyperactivity disorder (ADHD). CNS Drugs 2021;35(10):1035–51.
79. Sciberras E, Efron D, Gerner B, et al. Study protocol: the sleeping sound with attention-deficit/hyperactivity disorder project. BMC Pediatr 2010;10:101.
80. Hiscock H, Mulraney M, Heussler H, et al. Impact of a behavioral intervention, delivered by pediatricians or psychologists, on sleep problems in children with ADHD: a cluster-randomized, translational trial. J Child Psychol Psychiatry 2019;60(11):1230–41.
81. Delemere E, Dounavi K. Parent-implemented bedtime fading and positive routines for children with autism spectrum disorders. J Autism Dev Disord 2018; 48(4):1002–19.
82. Díaz-Román A, Mitchell R, Cortese S. Sleep in adults with ADHD: systematic review and meta-analysis of subjective and objective studies. Neurosci Biobehavioral Rev 2018;89:61–71.
83. Larsson I, Aili K, Nygren JM, et al. Parents' experiences of weighted blankets' impact on children with attention-deficit/hyperactivity disorder (ADHD) and sleep problems—a qualitative study. Int J Environ Res Public Health 2021;18(24): 12959.
84. Masi G, Fantozzi P, Villafranca A, et al. Effects of melatonin in children with attention-deficit/hyperactivity disorder with sleep disorders after methylphenidate treatment. Neuropsychiatr Dis Treat 2019;15:663.
85. der HEIJDEN KBV, Smits MG, Van Someren EJ, et al. Effect of melatonin on sleep, behavior, and cognition in ADHD and chronic sleep-onset insomnia. J Am Acad Child Adolesc Psychiatry 2007;46(2):233–41.
86. Mohammadi MR, Mostafavi SA, Keshavarz SA, et al. Melatonin effects in methylphenidate treated children with attention deficit hyperactivity disorder: a randomized double blind clinical trial. Iranian J Psychiatry 2012;7(2):87.
87. Weiss MD, Wasdell MB, Bomben MM, et al. Sleep hygiene and melatonin treatment for children and adolescents with ADHD and initial insomnia. J Am Acad Child Adolesc Psychiatry 2006;45:512–9.
88. Andersen LPH, Gögenur I, Rosenberg J, et al. The safety of melatonin in humans. Clin Drug Invest 2016;36(3):169–75.
89. Owens JA, Moturi S. Pharmacologic treatment of pediatric insomnia. Child Adolesc Psychiatr Clin N Am 2009;18(4):1001–16.
90. Grigg-Damberger MM, Ianakieva D. Poor quality control of over-the-counter melatonin: what they say is often not what you get. J Clin Sleep Med 2017; 13(2):163–5.
91. Anand S, Tong H, Besag F, et al. Safety, tolerability and efficacy of drugs for treating behavioural insomnia in children with attention-deficit/hyperactivity disorder: a systematic review with methodological quality assessment. Pediatr Drugs 2017;19(3):235–50.
92. Sangal RB, Blumer JL, Lankford DA, et al. Eszopiclone for insomnia associated with attention-deficit/hyperactivity disorder. Pediatrics 2014;134(4):e1095–103.
93. East PL, Doom JR, Blanco E, et al. Iron deficiency in infancy and sluggish cognitive tempo and ADHD symptoms in childhood and adolescence. J Clin Child Adolesc Psychol 2021;1–12.
94. Joseph V, Nagalli S. Periodic limb movement disorder. StatPearls; 2021.