Research Article ISSN 2689-1050

Chemical & Pharmaceutical Research

Pediatric Insomnia Disorder: Treatment Options beyond Melatonin

Mandeep Kaur M.D[1*] and Sabhyata Agrawal M.D[2]

[1]*Department of Psychiatry and Behavioral Medicine, Cone Health Behavioral Health Hospital, 700 Walter Reed Drive, Greensboro, NC 27403, U.S.A.*

[2]*Department of Pediatric Respiratory, Allergy, Immunology and Sleep Medicine; Yale School of Medicine, 333 Cedar Street, New Haven, CT 06510, U.S.A.*

***Correspondence:**
Mandeep Kaur, M.D. General, Child and Adolescent Psychiatrist, Department of Behavioral Medicine, Cone Health Behavioral Health Hospital,700 Walter Reed Drive, Greensboro, North Carolina 27403, Tel: 336-890-2700.

Received: 01 Feb 2022; **Accepted:** 07 Feb 2022; **Published:** 16 Feb 2022

Citation: Kaur M, Agrawal S. Pediatric Insomnia Disorder: Treatment Options beyond Melatonin. Chem Pharm Res. 2022; 4(1): 1-11.

ABSTRACT

Objective: *Pediatric insomnia disorders significantly affect the lives of the patients and their caregivers. Currently available behavioral management techniques and therapy are not effective for everyone. There is extensive literature on the efficacy and safety data on melatonin however, it too can be ineffective for some patients. The aim of this narrative review is to provide an analysis of various pharmacological and nonpharmacological options, other than melatonin, that can be considered as treatment options for pediatric insomnia.*

Methods: *The databases PubMed, Medline, Scopus were searched using the key terms "pediatric insomnia", "insomnia in children", "insomnia in adolescents", "therapies in pediatric insomnia", "behavioral management of pediatric insomnia, "pharmacological agents in pediatric insomnia", "complementary treatment of pediatric insomnia", and "herbal therapies in pediatric insomnia" which yielded 128 articles. Additionally, database clinicaltrials.gov was searched for trials with key words "insomnia in children", "insomnia in adolescents" and "pediatric insomnia" which yielded 42 studies. The articles and studies were reviewed as pertinent to the topic.*

Results: *Based on the search, evidence for effectiveness for several novel therapeutics such as melatonin agonists, orexin receptor antagonists, nutritional supplements, herbal medicines, complementary and alternative treatment options came in to light. However, a remarkable deficit of large-scale studies depicting the efficacy and safety of all these in pediatric populations was noted.*

Conclusions: *With pediatric insomnia disorders being a challenging clinical situation for clinicians not just limited to one specialty, a joint effort is needed to explore these treatment options with help of large-scale clinical studies.*

Keywords

Pediatric insomnia, Behavioral treatment, Pharmacotherapy, Nutritional supplements, Complementary medicine, Herbal medicines.

Introduction

Caregivers often report sleep-related problems to healthcare providers. Typical caregiver complaints include trouble falling asleep, night waking, snoring, excessive diurnal tiredness, and poor daytime functioning [1]. Pediatric sleep disturbances are not uncommon and can result in daytime sleepiness, mood dysregulation, impulsivity, hyperactivity, cognitive deficits, social deficits and decreased quality of life [2]. Ongoing pediatric sleep-related issues also impact the caregiver's routines and functioning; making them an important consideration for timely management. Persistent sleep problems in childhood have been linked to development of anxiety in adulthood [3].

Insomnia Disorder in children can be defined as difficulty initiating sleep (considered in children as difficulty to fall asleep without a caregiver's intervention); maintaining sleep (frequent awakenings during the night and difficulty returning to sleep without a caregiver's intervention); or waking up earlier than the usual schedule with inability to return to sleep [4]. Another way

of defining pediatric insomnia is repeated difficulty with sleep initiation, duration, consolidation, or quality that occurs despite age-appropriate time and opportunity for sleep and results in daytime functional impairment for the child and/or family [5].

The prevalence rates vary as pediatric insomnia is a less understood condition [5]. The prevalence rates as per ICSD-3 are: insomnia 20-30%, sleep-disordered breathing 2-3%, hypersomnia 0.01-0.20%, circadian rhythm disorders 7%, parasomnias 25%, sleep-related movement disorders 1-2% [6]. According to one review, the prevalence of pediatric insomnia varies across age groups [7]. Frequent night awakenings are reported among 40% of infants, disruptive nighttime awakenings are seen in 25% to 50% of preschoolers, bedtime resistance in school-age children ranges from 15% to 27%, and insomnia in adolescents is reported to be ~11% [7]. Higher prevalence is noted in children with other neurodevelopmental or psychiatric comorbidities [5]. A population-based study examined the prevalence of insomnia symptoms in 700 children between ages 5-12 and noted that the insomnia symptoms peaked in girls age 11–12 at 30.6% that was more attributable to puberty-onset related hormonal changes rather than anxiety and depression [8].

Clinical Assessment

Thorough clinical history and physical examination are crucial for the diagnosis. Current evidence suggests that onset of pediatric sleep problems could complicate co-morbid medical conditions such as obesity and asthma, and psychological problems such as depression, anxiety, and substance abuse [9]. A few of the commonly used screening questionnaires and diagnostic tests for evaluation of pediatric insomnia have been summarized in Table 1. BEARS, which stands for bedtime resistance/sleep onset delay; excessive daytime sleepiness; awakenings at night; regularity, patterns, and duration of sleep; and snoring and other symptoms, maybe useful during initial screening of sleep difficulties [10]. Graphic diaries appear to be more helpful in understanding sleep-wake cycles in pediatric patients rather than descriptive data [9]. Self-report questionnaires, such as the School Sleep Habits Survey and Children's Sleep Habits Questionnaire are beneficial to screen for specific sleep disorders in adolescents and school-aged children, respectively [9].

The diagnosis of insomnia can be made clinically and typically does not require sleep studies unless specific disorders need to be excluded [9]. Sleep-related breathing disorders such as obstructive sleep apnea can be diagnosed with help of polysomnography. Sleep movement disorders like restless leg syndrome should include iron levels as part of the work-up. Multiple sleep latency test is useful to quantify daytime sleepiness and explore the presence of sleep disorders such as narcolepsy. Actigraphy helps obtain objective sleep-wake measures like nocturnal awakenings and helps with diagnosis of delayed/ advanced sleep phase syndrome.

One of the most common causes of insomnia in preschool age group is behavioral in origin. The term Behavioral Insomnia of Childhood (BIC) was introduced in the International Classification of Sleep Disorders–Second Edition, American Academy of Sleep Medicine (2005) [11]. The hallmark is difficulty falling or staying asleep in children below the age of five. BIC has been divided in to three sub-types: sleep-onset association type, limit-setting type and combination of both [10]. In sleep-onset association type condition, the infant/toddler learns to sleep under a specific condition (object, circumstance), usually requiring intervention/ presence of caregiver. Limit-setting type is typical in preschool and school age children, characterized by the caregivers' difficulty in setting limits/rules for bedtime or having them followed.

In adolescence, insomnia may be related to inadequate sleep hygiene and delayed sleep phase, or have a psychophysiological origin [10]. Inadequate sleep hygiene includes sleeping after 11 pm and wake-time after 8 am; irregular sleep schedule; use of stimulating substances/drugs, excess caffeine consumption in the late afternoon/at night; and use of electronic devices before going to bed. Delayed sleep phase insomnia is a circadian rhythm disorder that occurs in adolescents due to hormonal changes, with a shift in the nocturnal sleep time as a function of the endogenous pacemaker that causes late awakening. Psychophysiological insomnia is characterized by a combination of previously experienced associations and hypervigilance. Preoccupation with sleep, getting to sleep, and the adverse effects of not sleeping on the following day are common complaints.

Sleep problems relate strongly to the intensity of symptoms associated with psychiatric disorders such as attention-deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), anxiety disorders, and major depressive disorder (MDD) [12]. Evaluation to rule out and manage any associated psychiatric conditions remains imperative as treating the underlying/co-

Table 1: Evaluation of pediatric insomnia.

Screening Questionnaires	**Clinical Utility**
BEARS - Bedtime resistance, Excessive daytime sleepiness, Awakenings at night, Regularity, patterns, duration of sleep, Snoring and other symptoms	Initial screening
Sleep diaries	Sleep-wake cycle assessment
Children's Sleep Habits Questionnaire (CSHQ)	Behaviorally based and medically-based sleep problems in school-aged children.
School Sleep Habits Survey	Behaviorally based and medically-based sleep problems in adolescents
Sleep Disturbance Scale for Children (SDSC)	Specific sleep disorder (obstructive sleep apnea)
Commonly Used Diagnostic Tests	**Clinical Utility**
Polysomnography	Sleep-related breathing disorders (obstructive sleep apnea)
Multiple Sleep Latency Test	Excessive daytime sleepiness (narcolepsy, idiopathic hypersomnia)
Actigraphy	Rest and activity cycles (Circadian rhythm disorders)

morbid condition impacts the outcomes significantly.

Non-Pharmacological Management

Behavioral interventions such as sleep hygiene education (consistent sleep schedule, avoidance of use of electronic devices before bedtime, bedtime routines, consistent and regular wake-up time), sleep restriction, relaxation techniques and cognitive restructuring are considered the mainstays of treatment for pediatric insomnia [5-10]. Good sleep practices such as avoiding caffeinated beverages, age-appropriate sleep/wake schedules, limit-setting regarding practices of late-night television/screen viewing and behavioral strategies (extinction programs or bedtime fading) should be the first lines of treatment [5,10].

As per AASM taskforce, specific behavioral therapies have shown evidence in being effective for bedtime problems and night waking in children below 5 years of age [13]. These include unmodified extinction, extinction with parental presence, preventive parent education, graduated extinction, bedtime fading/positive routines and scheduled awakenings. Cognitive behavioral therapy for insomnia (CBTI) in group setting as well as internet guided form has evidence depicting its effectiveness for treatment of insomnia in adolescents with medium to large effect sizes [14,15].

Pharmacological Management

Robust evidence-based literature related to efficacy, safety, and tolerability of medications used in treating pediatric insomnia is deficient. It is notable that currently, there are no medications approved by the US Food and Drug Administration (FDA) for pediatric insomnia [5,7]. Current recommendations suggest that pharmacotherapy should only be considered when behavioral techniques are ineffective and in combination with behavioral interventions [7].

Melatonin has the most empirical evidence for use and best pharmacokinetic/pharmacodynamics profile for treatment of sleep disorders in normally developing and developmentally disabled children and adolescents [16]. Off-Label medications such as alpha agonists (Clonidine, Guanfacine), anti-depressants with sedative properties (Trazodone, Mirtazapine, Amitriptyline, and Doxepin), anti-psychotics with sedative properties (Quetiapine, Risperidone, and Olanzapine) are also commonly prescribed for treatment of pediatric insomnia [17].

A survey to examine patterns of non-prescription and prescription medication use for insomnia by child and adolescent psychiatrists in the U.S. concluded that 88% of them recommended over the counter (OTC) medications [18]. As per a similar survey among pediatricians, >75% of practitioners recommended non-prescription medications for insomnia treatment. And among the prescription medications antihistaminic agents (Diphenhydramine, Hydroxyzine, Cyproheptadine) were the most commonly prescribed [19]. Alpha agonists were the most commonly prescribed insomnia medication by both child psychiatrists and pediatricians for co-morbid ADHD [18,19]. Trazodone was the most commonly prescribed insomnia medication for mood (78%) and anxiety disorders (72%) [18]. Atypical antipsychotics, anticonvulsants, and short-acting hypnotics were more likely to be prescribed with co-morbid mood disorders [18].

Benzodiazepines with short half-life may be useful for short-term or transient insomnia in pediatric populations, especially with coexisting conditions like anxiety [20]. Their use in the pediatric population remains quite limited owing to their concerning side effect profile of daytime sleepiness, dizziness, headaches, anterograde amnesia, and rebound insomnia in addition to the risk of addiction and potential for withdrawal symptoms on discontinuation [7,20]. A literature review regarding the use of benzodiazepines for pediatric insomnia with co-morbid neurodevelopmental disabilities concluded that benzodiazepines are not recommended in this subset and should only be used for transient insomnia, if associated with daytime anxiety [21].

Novel Medications

Despite existing evidence suggesting the efficacy of non-pharmacological treatments for pediatric insomnia, many children and adolescents do not respond to them and need pharmacological agents to help their symptoms. Many medications that are commonly used as hypnotics in children are used for their sedative adverse effects rather than for primary effects on sleep/wake mechanisms or hyper arousal [5]. Below, we discuss a few novel therapeutics that need further large-scale clinical trials/studies for establishing efficacy and safety in treating pediatric insomnia (summarized in table 2).

Methods and Materials

This study comprises of a narrative review of the existing literature. The databases PubMed, Medline and Scopus were searched for original articles, guidelines, previous reviews published between January 1, 2000 and January 31, 2021 in English language. Key terms “pediatric insomnia”, “insomnia in children”, “insomnia in adolescents”, “therapies for pediatric insomnia”, “behavioral management of pediatric insomnia, “pharmacological agents for pediatric insomnia”, “complementary treatment for pediatric insomnia”, and “herbal therapies for pediatric insomnia” were used. Furthermore, a manual search of bibliographical cross-referencing was conducted and the articles that were relevant to our topic were utilized. 128 papers were identified relevant to the topic. Additionally, the online database clinicaltrials.gov was searched for trials with key words “insomnia in children”, “insomnia in adolescents” and “pediatric insomnia” which yielded 42 studies. The results obtained were manually screened and it was noted that majority of the trials were focusing on CBTI and melatonin.

Melatonin Agonists

Melatonin is a hormone produced by the pineal gland that mediates circadian rhythms and the sleep cycle. Melatonin is a well-tolerated and safe medication in the dose range of 2-10 mg/day in the pediatric population [22]. The FDA does not regulate melatonin, and commercially available formulations often vary in strength, purity, and efficacy. One study looked at 31 OTC melatonin supplements to quantify the melatonin content [23]. The supplements were

Table 2: Summary of novel therapeutics for pediatric insomnia.

Pathophysiological Class	Medication/Agent/Modalities	Pharmacological Action	Evidence in Pediatric population (number of participants)
Melatonin Agonists	Ramelteon	Highly-selective melatonin receptor type 1 and type 2 agonist	1 RCT (11 combined minors and adults with developmental disabilities) 1 case report (2)
	Agomelatine	Melatonin agonist and selective serotonin antagonist	2 RCTs (54 and 10 respectively)
	Pediatric Prolonged-release Melatonin	Prolonged-release melatonin agonist	1 RCT (125 minors with ASD and neurodevelopmental disorder)
Non-Benzodiazepine Receptor Agonists	Zolpidem	GABA-A receptor agonism	1 RCT (136 minors) showed improvement in CGI scores in adolescents, however, did not show improvement on polysomnography
	Zaleplon	GABA-A receptor agonism	No RCTs, 2 case reports of adverse reactions following overdose
	Eszopiclone	GABA-A receptor agonism	1 RCT in ADHD-related insomnia (486) failed to show improvement on polysomnography
Orexin Antagonists	Suvorexant	Orexin A and B receptor antagonism	1 RCT (30)
Anticonvulsant	Gabapentin	Exact mechanism unknown	Observational studies/reviews showing favorable response in idiopathic insomnia, insomnia related to RLS and chronic pain. One ongoing RCT looking at role of gabapentin as adjunct to morphine for chronic mixed/neuropathic pain.
Nutritional Supplements	Ferrous Sulphate	Treatment of underlying iron deficiency in RLS	1 RCT (20) for RLS 1 Retrospective chart review (97)
	Long Chain Fatty Acids	Role in sleep regulation	1 RCT (810)
	Tryptophan/5-Hydroxytryptophan	Exact mechanism unknown	1 RCT (30 infants) 1 RCT (45) for sleep terrors 1 RCT (165) for parasomnias
	Vitamin D	Role in sleep regulation, also plays role in RLS	No RCTs, 2 studies (209 and 800 respectively)
	L-Theanine	Exact mechanism unknown	1 RCT (98 boys)
Complementary and Alternative Medicine	Valerian	Constituents and reciprocal interactions with GABA and Adeonsine systems	1 RCT (5 children with Intellectual Disability) 1 RCT in combination with Lemon Balm (918) for dyssomnia and restlessness
	Lemon Balm	Exact mechanism unknown	1 RCT (52) for sleep bruxism 1 RCT in combination with Valerian (918) for dyssmonia and restlessness
	St. John's Wort	Inhibition of the reuptake of serotonin, norepinephrine, dopamine, GABA, and L-glutamate	2 studies (101 and 33 respectively) focusing on effect on depressive symptoms
	Passionflower	Exact mechanism unknown	1 study (115) looked at combination of Valerian, St. John's Wort and Passionflower for agitated depression
	German Chamomile	Preclinical studies suggest sedative effects are secondary to modulation of GABA receptors	No studies in pediatric population, though is a commonly used herbal agent in children
	Aromatherapy (Lavender)	Exact mechanism unknown	1 study (13 infants) 1 RCT (12) with ASD
	Massage therapy	Unclear	1 RCT (51)

electrochemically analyzed and the findings concluded that melatonin content was found to range in significant variations of the labelled content. Due to these variations, the use of pharmaceutical-grade melatonin (available on the Internet) should be considered [7,20]. Based on this melatonin agonists like Ramelteon, Agomelatine, Prolonged-Release Melatonin that are FDA-regulated need to be explored further for use in pediatric populations.

Ramelteon

Ramelteon is a highly selective melatonin receptor type 1 and type 2 agonist that is FDA approved for insomnia treatment in adults. One RCT looked at the efficacy and safety of ramelteon in 11 severely disabled children and adults aged between 3-25 years [24]. The patients received 3-8 mg of Ramelteon at bedtime, which was found to be effective in eight out of eleven patients with mild daytime sleepiness reported in three patients. One case report showed potential effectiveness and tolerability of ramelteon at doses 4-8 mg in two youths age 7 and 18 with ASD [25]. A comprehensive literature review of pharmacological treatment of sleep disturbance in children and adults with developmental disabilities found that ramelteon holds promise but requires further investigation in this population [16]. Literature search indicates that all the studies and case reports seem to have targeted developmentally disabled pediatric populations, therefore, future large-scale RCTs are needed to establish efficacy in normally developing pediatric age groups. A phase I interventional RCT was designed to look at the pharmacokinetic profile, safety, and tolerability of ramelteon in adolescents with insomnia, children with ADHD associated with insomnia and gender- and race-matched healthy adults, however, the results of this RCT have not been published [26].

Agomelatine

Agomelatine is a melatonin agonist and a selective serotonin antagonist. One RCT comprising of 54 children and adolescents

ages 6-15 looked at the role of agomelatine in treatment of ADHD in children and adolescents who failed to respond to or did not tolerate stimulants [27]. Six weeks of treatment demonstrated a favorable safety and efficacy profile in children and adolescents with ADHD. Another smaller RCT of 10 adolescents looked at the role of Agomelatine for treatment of ADHD in stimulant-refractory patient subset [28]. The study concluded that Agomelatine might be a useful second-line medication for individuals with ADHD, particularly if they suffer from additional sleep disorders. Due to several reports of hepatotoxicity in adult studies, monitoring of hepatic function is recommended. Recent availability of intranasal agomelatine is helpful in managing this adverse effect [29].

Pediatric Prolonged-Release Melatonin (PedPRM)

As melatonin has a very-short half-life (40 minutes), a prolonged-release melatonin formulation designed to mimic the endogenous profile by releasing melatonin throughout the night, may help to improve both sleep initiation and maintenance [30]. In a double-blind RCT, a total of 125 participants; ages 2-17.5 years; 96.8% with ASD, 3.2% with Smith-Magenis syndrome; whose sleep failed to improve on behavioral intervention alone received PedPRM (2-5 mg) or placebo for 13 weeks [31]. PedPRM was noted to be efficacious and safe for treatment of insomnia with ASD with/without ADHD and neuro-genetic disorder. Another study using the same dataset concluded that there were no observed detrimental effects of PedPRM on children's growth/pubertal development after 2 years of use and no withdrawal symptoms were noted after discontinuation [32].

Non-Benzodiazepine Receptor Agonists

These include zolpidem, zaleplon and zopiclone; mechanism of action is through increased γ-aminobutyric acid (GABA) transmission at the GABA-type a receptor [20]. Eszopiclone is an active enantiomer of zopiclone.

Zolpidem

Zolpidem has been linked to complex sleep-related behaviors such as sleep eating, sleepwalking, and sleep driving in adult studies, which raise concerns about its use in the pediatric population [20]. Consequently, a satisfactory number of large-scale studies are lacking. One 8-week placebo-controlled RCT evaluated the hypnotic efficacy of zolpidem at 0.25 mg/kg/day (maximum dose 10 mg/day) in 136 children age 6 to 17 experiencing insomnia associated with ADHD [33]. Zolpidem failed to reduce the latency to persistent sleep on polysomnography after 4 weeks. However, differences favoring zolpidem were observed for the older age group in Clinical Global Impression (CGI) scores at weeks 4 and 8. No next-day residual effects and rebound phenomena after discontinuation were observed. 7.4% patients discontinued zolpidem treatment because of adverse events including dizziness, headaches and hallucinations. Hallucinations were noted in 4 participants from the younger age group.

One RCT evaluated the relationship between zolpidem administration and sleep parameters in children age 3-18 with severe (total burn surface ≥20%) burn injuries [34]. Children age 2-4 years received 2.5 mg, children 5-10 years received 5 mg, and children >10 years received 10 mg of zolpidem. Ten children received two doses of zolpidem at 22:00 and 02:00 hours. Serial blood samples were obtained. Higher zolpidem serum concentrations were associated with restoration of stage 2 sleep to normal levels indicating a modest improvement in sleep efficacy parameters on polysomnography. However, large aberrations in slow-wave and REM sleep characteristic of severely burned patients were not ameliorated.

Zaleplon

Zaleplon has an ultra-short half-life of 1-2 hours therefore; it appears to be most useful in improving sleep initiation [20]. There are no RCTs on zaleplon use for pediatric insomnia. One case report indicated that zaleplon overdose was associated with sleepwalking and complex behavior [35]. Another case report of Zaleplon overdose in an adolescent noted concomitant somnolence, blurred speech, slowdown, ataxia, tachycardia and hypokalaemia [36].

Eszopiclone

One 12-week, placebo-controlled RCT evaluated efficacy and safety of low and high dose eszopiclone (1 or 2 mg in children aged 6-11 years, 2 or 3 mg in children ages 12-17 years), in 486 patients with ADHD-related insomnia for 12 weeks [37]. Eszopiclone failed to reduce latency to persistent sleep on polysomnography at 12 weeks. Most frequent treatment-emergent adverse events were headache, dysgeusia, and dizziness. Eszopiclone was further studied for one -year open-label treatment in 55 patients who completed the study, and 249 patients with no previous eszopiclone exposure. The results demonstrated that eszopiclone was well-tolerated over one year of treatment.

Orexin Antagonists

Orexin A and B are neuropeptides produced by hypothalamic neurons that promote wakefulness. FDA-approved dual orexin receptor antagonists suvorexant and lemborexant for adult insomnia inhibit these resulting in improvement of both sleep onset and maintenance [38].

Suvorexant

One RCT evaluated the efficacy and safety of suvorexant in adolescents of mean age 15.7 ± 2.4 years [39]. Thirty patients were administered suvorexant at dose range 10-20 mg. CGI score significantly decreased in 17 patients who completed the study. Among the 13 patients who discontinued treatment, only 2 reported adverse effects namely abnormal dreams as the reason for discontinuation. The study concluded that suvorexant could be considered as a treatment option for insomnia in adolescents.

Anticonvulsants

Anticonvulsants are used for mood stabilization in the pediatric populations and anticonvulsants with sedative effects are prescribed for insomnia.

Gabapentin

Gabapentin is FDA-approved for treatment of partial onset seizures in children 3 years and above. Gabapentin has shown

potential in treating adult insomnia [40]. One study looked at prescribers' experience with using gabapentin to treat insomnia in 23 children over 3.2 years [40]. The mean patient age was 7.2 years and 87% of them had co-existing neurodevelopmental or neuropsychiatric disorder. Doses ranged from 5mg/kg to 15 mg/kg. At follow-up, improved sleep was noted in 78% of the children. In another review, authors looked at the most common medications and supplements prescribed for the treatment of sleep problems in children with neurodevelopmental disabilities [41]. They concluded gabapentin may be beneficial for sleep problems in this population but vigorous RCTs are needed.

Currently no FDA-approved medications exist for treatment of pediatric restless legs syndrome (RLS); gabapentin has been used as off-label for management [42]. One RCT assessed the effects of gabapentin on sensory/motor symptoms of RLS in adults [43]. Sleep studies showed significantly reduced periodic leg movements during sleep and improved sleep architecture: increased total sleep time, sleep efficiency, and decreased stage 1 sleep. One 4-week open RCT compared gabapentin with dopaminergic agent ropinirole in treatment of idiopathic-RLS in adults [44]. Polysomnographic data showed reduction of periodic leg movements during sleep in both groups and symptoms were still improved in most participants at 6-10 month follow-up. Both were effective and well tolerated.

Chronic neuropathic pain conditions are associated with sleep disturbances and poor quality of sleep. Gabapentin has shown efficacy in the treatment of chronic neuropathic or mixed pain in adults [45]. A placebo-controlled, phase-two RCT in children with severe chronic neuropathic or mixed pain is looking at the role of efficacy of a gabapentin liquid formulation as adjunctive therapy to morphine [45]. There have been other small-scale studies looking at the role of gabapentin in management of non-cancer pain in pediatric population; however, there appears to be a gap between how it is used in clinical practice and how this class has been examined in clinical trials [46]. It is recommended that patient-informed trials analyzing clinically-meaningful outcomes be designed.

Nutritional Supplements

Ferrous Sulfate

Pediatric RLS occurs in about 1.9% of individuals between ages 8 and 18. There is evidence-suggesting role of iron deficiency in pediatric RLS and there is data indicating the benefit of iron therapy in reducing the symptoms [47]. Evidence also suggests that low iron stores are common in children with ASD suspected secondary to picky-eating habits [48]. A placebo-controlled RCT looked at the role of oral ferrous sulfate to treat insomnia in 20 children with ASD including low-normal ferritin levels over time-span of 3 months [48]. No improvement in sleep onset latency and wake-time after sleep onset as measured by actigraphy was noted, which was attributed to low sample size. However, improvement in the overall severity score on Sleep CGI Scale was noted. A retrospective chart review of 97 children between ages 5 and 18 diagnosed with RLS at a sleep clinic was conducted to determine if iron supplementation effectively treats RLS [49]. 65% of the children received iron monotherapy or combined with other treatments and approximately 80% of this showed improvement/ resolution of symptoms.

Long Chain Fatty Acids

Deficiencies of long-chain omega-3 fatty acids such as docosahexaenoic acid (DHA) have been linked with sleep disturbances [50]. Evidence suggests that the balance of DHA and arachidonic acid in the pineal gland regulates melatonin production elucidating the role of DHA in sleep regulation [51]. One study looked at the role of consumption of a combination of omega-3 and omega-6 fatty acids as well as magnesium and zinc over 12-weeks on symptoms of ADHD in 810 children from ages 5 to 12 [52]. In addition to improvement in hyperactivity and impulsivity symptoms, it was noted that sleeping disorders decreased significantly during the 12-week consumption of PUFA in combination with magnesium and zinc. Girls were noted to have more benefit than boys and older children having sleep-onset problems showed outcomes that are more positive. One large-scale RCT explored associations between pediatric sleep and biochemical measures of blood fatty acid status in 395 children (age 7-9); and assessed the effect of DHA supplementation (dose 600 mg) on 362 children's sleep for 16 weeks [50]. Actigraphy results showed that sleep duration improved by additional 58 minutes with fewer and shorter night waking and sleep efficiency was improved. The study concluded that higher blood DHA levels were associated with better sleep.

Tryptophan/5-hydroxytryptophan (5-HTP)

Tryptophan/5-HTP is an essential amino acid implicated in many metabolic pathways where it is converted into different bioactive molecules such as serotonin, melatonin, kynurenine, and niacin. Tryptophan at doses of 1 g/day or more has been linked to increased total sleep time and decreased sleep latency and arousal after sleep-onset in adults with insomnia [53]. One RCT looked at the impact of 5-HTP and sleep-facilitating nutrients adenosine-5-phosphate, uridine-5-phosphate on the quality of sleep in 30 infants (age 8-16 months) with at least three nocturnal-waking episodes [54]. The study concluded that the administration of nutrient enriched cereals at night led to an improvement in sleep. Tryptophan supplementation has also proved to be effective in reducing NREM parasomnias in pediatric populations [53]. One RCT in 45 children with sleep terrors (ages 3-10) found that those taking 5-HTP (2 mg/kg/day at bedtime) had not only acute symptom improvement, but also the improvements were maintained at 6-month follow-up [55]. Another RCT looked at the outcome of using 5-HTP to manage parasomnias in children (ages 3-18) and to examine sleep architecture and subjective psychological/sleep symptoms with parasomnias [56]. 84% of the 165 participants who were prescribed 5-HTP (dose range 500-4500 mg, mean dose 2400 mg) experienced improvements in parasomnia symptoms. Polysomnography revealed that children with parasomnias had an altered sleep architecture based on age-related normative values and were subjectively more fatigued and endorsed more depressive symptoms.

Vitamin D

Vitamin D is a pro-hormone obtained by endogenous production in the skin through the action of B-band ultraviolet solar radiation on a precursor molecule. A smaller amount comes from dietary intake and supplementation. Studies have shown that vitamin D plays a role in sleep regulation by modulation of receptors in sleep-regulating areas of the CNS such as the anterior and posterior hypothalamus and also by regulating the enzyme tryptophan-hydroxylase 2 which impacts the production of 5-HTP, precursor of serotonin and melatonin [53]. Furthermore, vitamin D has also been linked to the pathophysiology of RLS through two mechanisms: dopaminergic dysfunction and iron dysregulation [57]. One retrospective-study looked at the association between vitamin D in cord blood or venous blood in 209 children and their sleep-wake patterns from birth to two years of age [58]. The cord blood vitamin D level was not associated with children's sleep at age two years. Children with vitamin D deficiency at two years had shorter night sleep and total sleep duration on actigraphy. A school-based cross-sectional study was conducted among 800 Chinese participants ages 8 to 14 to evaluate association of vitamin D and sleep duration [59]. The results revealed that participants with vitamin D deficiency had a significantly higher odds ratio for shorter duration of sleep compared with participants with normal vitamin D levels after adjusting for confounders.

L-theanine (Gamma Glutamylethylamide)

L-theanine is a non-protein amino acid found in green tea leaves. It is produced in a purified form using a patented enzymatic process from a mixture of glutamine with ethylamine derivative [60]. One RCT involving 98 boys, age 8-12, diagnosed with ADHD was conducted to investigate the efficacy and safety of L-theanine as an aid for sleep in ADHD [61]. Participants received 400 mg of L-theanine or placebo for six weeks and were evaluated using wrist actigraphy at baseline, and at the end of the six-weeks. Actigraphy findings indicated that boys who consumed L-theanine obtained significantly higher sleep percentage and sleep efficiency scores, compared to those in the placebo group. Sleep latency and other sleep parameters were unchanged. The study concluded that 400 mg dose of L-theanine is safe and effective in improving some aspects of sleep quality in boys diagnosed with ADHD. Further studies inclusive of females and other conditions are needed.

Complementary and Alternative Medicine (CAM)

Complementary and alternative medicine describes a set of practices and treatments used in addition to or as alternatives to Western medical practices [62]. It is not uncommon for patients to use CAM for the treatment of headaches, insomnia, depression, anxiety, and fatigue [63]. 2012 National Health Interview Survey (NHIS) dataset was assessed for prevalence of sleep difficulties and CAM use in children [62]. Out of 8,738 children ages 6-17, 6.4% of children reported regular sleeping difficulty in the last year and 29% reported use of at least one CAM therapy. Non-vitamin, non-mineral supplements like herbal agents were the most commonly used (14.6%), followed by manipulation therapies (9.2%). Parental education and parental CAM use were most strongly associated with CAM use in children.

Herbal Therapies

Herbal and dietary supplements are not subjected to the FDA-approval process. Dietary Supplement Health and Education Act passed in 1994 led to the classification of herbal products as dietary supplements wherein manufacturers can make claims about health and nutrient content and how they affect bodily structure and function but cannot claim to cure, prevent, or treat specific diseases [63]. The studies evaluating herbal supplement use in treating insomnia and other disorders are limited [53,63].

Valerian (*Valeriana spp.*)

Valerian is the most studied herbal remedy for insomnia. The therapeutic effects of valerian may arise both from the individual effects of its constituents and from their reciprocal interactions with GABA and adenosine systems [53]. As a sedative, valerian is used at an average daily dose of 912 mg (ranging from 300 to 3645 mg/day in different studies) [53]. Potential adverse effects include gastrointestinal upset, contact allergies, headache, restless sleep, and mydriasis. One RCT looked at role of valerian in the treatment of sleep problems in children with intellectual deficit [64]. Five children with varying intellectual deficits and different sleep problems underwent 8 weeks of monitoring via sleep diaries. Valerian treatment led to significant reductions in sleep latencies and nocturnal time awake; lengthened total sleep time and improved sleep quality. The treatment was most effective in children with deficits that involved hyperactivity and was noted to be safe in this population. Another RCT looked at the combination of valerian with lemon balm for management of dyssomnia and restlessness in 918 children [65]. Reduction in severity of all symptoms was noted in the investigators and parents' ratings. 80.9% of the patients experienced an improvement in dyssomnia and 70.4% of the patient's showed improvement in restlessness as well. No medication related adverse events were noted.

Lemon Balm (Melissa Officinalis)

Lemon balm has been known to have hypnotic properties though underlying mechanism of action is unclear. One RCT evaluated the efficacy of lemon balm alone and in combination with another herb Phytolacca decandra (pokeweed) in the treatment of possible sleep bruxism in children based on Visual Analogic Scale in 52 patients [66]. The study comprised a crossover design that included 4 phases of 30-day treatment, with a washout period of 15 days in-between treatments. Lemon balm showed promising results in the treatment of possible sleep bruxism in children, while the association of pokeweed did not improve the results. As discussed earlier, one RCT found the combination of valerian with lemon balm for management of dyssomnia and restlessness in 918 children to be safe and effective [65].

St. John's Wort (Hypericum Perforatum)

St. John's wort is used for a variety of clinical conditions, such as depression, anxiety, and sleep disorders. Mechanism of action is suspected to be via inhibition of the reuptake of serotonin, norepinephrine, dopamine, GABA, and L-glutamate [53]. Potential side effects include gastrointestinal complaints, dizziness, fatigue, anxiety, photosensitivity and headaches. The

primary concern related to its use is the possibility of severe drug interactions, mediated by the CYP450 and intestinal P-glycoprotein induction. Its serotonin-promoting effects may result in potential risk of serotonin syndrome when combined with serotonergic agents [53]. One study looked at the role of St. John's Wort in depressive symptoms in 101 children below the age of 12 [67]. The participants received doses ranging from 300 to 1800 mg/day for 4 weeks. Both physicians and parents reported improvement in symptoms. It was considered to be a safe and effective treatment for children with symptoms of depression. Another study evaluated the use of St John's wort in 33 children with depressive symptoms age 6 to 16 years in an open-label design for 8 weeks [68]. The dose range was 150 mg 3 times daily to 300 mg 3 times daily. 76% of the patients clinically improved and 93% continued therapy at the end of the study. To our knowledge, no published clinical trial has specifically investigated the effects of St. John's Wort on sleep disturbances.

Passiflora Incarnate (Passionflower)

Passionflower has been used for the treatment of anxiety and insomnia; exact mechanism of action is unclear [53]. One RCT demonstrated positive effects of Passionflower on objective sleep parameter of total sleep time on polysomnography in 110 adults with insomnia disorder [69]. One prospective observational study looked at the combination of Valerian, St. John's Wort and Passionflower in agitated depression [70]. 115 children between ages 6-12 were investigated over 2 years. Parent assessments showed an improvement in children who had attention problems, social withdrawal, and/or were anxious/depressed. Physicians' assessments showed 81.6-93.9% of the affected children had no or mild symptoms at the end of observation period. Therapeutic success was not influenced by additional medication/therapies and treatment was well-tolerated.

German Chamomile (Matricaria Recutita)

German chamomile is one of the popular ingredients in herbal teas and is the most widely used herbal product for sleep [71]. Despite lack of studies depicting efficacy and safety of chamomile in treatment of pediatric insomnia, it remains a commonly used herbal agent for sleep in children [7]. Mechanism of action is unknown, preclinical studies suggest sedative effects are secondary to modulation of GABA receptors. One RCT in 34 adults aged 18-65 years looked at the efficacy and safety of chamomile for improving subjective sleep and daytime symptoms [71]. Participants were randomized to receive 270 mg of chamomile twice daily or placebo for 28 days. Primary outcomes were total sleep time, sleep efficiency, sleep latency, wake after sleep onset, sleep quality, and number of awakenings. No significant differences were noted between groups except for modest improvement in daytime functioning.

Aromatherapy/ Massage therapy

Lavender is a commonly used essential oil that has been studied in recent years for its effects on anxiety and sleep in adults [53]. Adverse effects when consumed are mild to moderate gastrointestinal effects [53]. One small study looked at the effectiveness of massage with lavender on reducing sleep disturbances in infants [72]. 13 infants age 6-12 months received 30 minutes of massage for three consecutive days. Sleep Disturbances Scale in Children was used one day before and after the intervention. Statistical analysis depicted that massage with lavender was effective in reducing sleep disturbances in infants especially in starting and maintaining sleep, somnolence disorders, and interruption of wakefulness sleep transition dimension. Another small RCT looked at role of lavender aromatherapy massage on sleep of 12 children with ASD and learning difficulties (2 girls and 10 boys ages 12 to 15) in a residential school [73]. Repeated measures analysis revealed no differences in any of the sleep measures between the nights when the children received aromatherapy massage compared to nights without massage. Another RCT looked at the impact of Traditional Chinese Medicine (TCM) massage therapy on difficulty in falling asleep, waking during night and other sleep disorder of infants [74]. 51 participants between the ages 4 and 35 months were treated by basic and modified regimes of TCM massage 30 minutes every other day. The total Athens Insomnia Scale score was noted to be significantly low post-treatment as compared to pre-treatment. One review concluded that there is weak evidence on the effects of massage therapy on sleep of children with ASD [53].

Conclusions

Irrespective of the underlying cause, insomnia in children and adolescents leads to a multitude of psychological and physiological consequences. With improved understanding of the pathophysiology of insomnia, newer pharmacological and non-pharmacological treatment options are now available. In depth, knowledge about the unique properties of these options is helpful in guiding clinical decision-making for optimal management. However, there is paucity of safety and efficacy data for these highlighting the need for further research in this area.

References

1. Meltzer LJ, Johnson C, Crosette J, et al. Prevalence of diagnosed sleep disorders in pediatric primary care practices. Pediatrics. 2010; 125: e1410-e1418.
2. Owens JA, Mindell JA. Pediatric insomnia. Pediatr Clin North Am. 2011; 58: 555-569.
3. Gregory AM, Caspi A, Eley TC, et al. Prospective longitudinal associations between persistent sleep problems in childhood and anxiety and depression disorders in adulthood. J Abnorm Child Psychol. 2005;33: 157-163.
4. American Psychiatric Association. Sleep-Wake Disorders, Diagnostic and statistical manual of mental disorders. Fifth edition. 2013.
5. Mindell JA, Emslie G, Blumer J, et al. Pharmacologic management of insomnia in children and adolescents: consensus statement. Pediatrics. 2006; 117: e1223-e1232.
6. American Academy of Sleep Medicine. International classification of sleep disorders (ICSD). 3rd ed. 2014.
7. Ekambaram V, Owens J. Medications Used for Pediatric Insomnia. Child Adolesc Psychiatr Clin N Am. 2021; 30: 85-99.

8. Calhoun SL, Fernandez-Mendoza J, Vgontzas AN, et al. Prevalence of insomnia symptoms in a general population sample of young children and preadolescents: gender effects. Sleep Med. 2014; 15: 91-95.
9. Moturi S, Avis K. Assessment and treatment of common pediatric sleep disorders. Psychiatry (Edgmont). 2010; 7: 24-37.
10. Nunes ML, Bruni O. Insomnia in childhood and adolescence: clinical aspects, diagnosis, and therapeutic approach. J Pediatr (Rio J). 2015; 91: S26-S35.
11. Meltzer LJ. Clinical management of behavioral insomnia of childhood: treatment of bedtime problems and night wakings in young children. Behav Sleep Med. 2010; 8: 172-189.
12. Huhdanpää H, Klenberg L, Westerinen H, et al. Sleep and psychiatric symptoms in young child psychiatric outpatients. Clin Child Psychol Psychiatry. 2018; 23: 77-95.
13. Morgenthaler TI, Owens J, Alessi C, et al. Practice parameters for behavioral treatment of bedtime problems and night wakings in infants and young children. Sleep. 2006; 29: 1277-1281.
14. de Bruin EJ, Bögels SM, Oort FJ, et al. Efficacy of Cognitive Behavioral Therapy for Insomnia in Adolescents: A Randomized Controlled Trial with Internet Therapy, Group Therapy and A Waiting List Condition. Sleep. 2015; 38: 1913-1926.
15. De Bruin EJ, van Steensel FJ, Meijer AM. Cost-Effectiveness of Group and Internet Cognitive Behavioral Therapy for Insomnia in Adolescents: Results from a Randomized Controlled Trial. Sleep. 2016; 39: 1571-1581.
16. Hollway JA, Aman MG. Pharmacological treatment of sleep disturbance in developmental disabilities: a review of the literature. Res Dev Disabil. 2011; 32: 939-962.
17. Dujardin S, Pijpers A, Pevernagie D. Prescription Drugs Used in Insomnia. Sleep Med Clin. 2020; 15: 133-145.
18. Owens JA, Rosen CL, Mindell JA, et al. Use of pharmacotherapy for insomnia in child psychiatry practice: A national survey. Sleep Med. 2010; 11: 692-700.
19. Owens JA, Rosen CL, Mindell JA. Medication use in the treatment of pediatric insomnia: results of a survey of community-based pediatricians. Pediatrics. 2003; 111: e628-e635.
20. Owens JA, Moturi S. Pharmacologic treatment of pediatric insomnia. Child Adolesc Psychiatr Clin N Am. 2009; 18: 1001-1016.
21. Bruni O, Angriman M, Calisti F, et al. Practitioner Review: Treatment of chronic insomnia in children and adolescents with neurodevelopmental disabilities. J Child Psychol Psychiatry. 2018; 59: 489-508.
22. Parvataneni T, Srinivas S, Shah K, et al. Perspective on Melatonin Use for Sleep Problems in Autism and Attention-Deficit Hyperactivity Disorder: A Systematic Review of Randomized Clinical Trials. Cureus. 2020; 12: e8335.
23. Erland LA, Saxena PK. Melatonin natural health products and supplements: presence of serotonin and significant variability of melatonin content. J Clin Sleep Med. 2017; 13: 275-81.
24. Miyamoto A, Fukuda I, Tanaka H, et al. Treatment with ramelteon for sleep disturbance in severely disabled children and young adults. No To Hattatsu. 2013; 45: 440-444.
25. Stigler KA, Posey DJ, McDougle CJ. Ramelteon for insomnia in two youths with autistic disorder. J Child Adolesc Psychopharmacol. 2006; 16: 631-636.
26. Pharmacokinetic and Safety of Ramelteon Between Adolescents With Insomnia and Healthy Adults. clinicaltrials.gov. NCT00914862. 2012.
27. Salardini E, Zeinoddini A, Kohi A, et al. Agomelatine as a Treatment for Attention-Deficit/Hyperactivity Disorder in Children and Adolescents: A Double-Blind, Randomized Clinical Trial. J Child Adolesc Psychopharmacol. 2016; 26: 513-519.
28. Niederhofer H. Agomelatine treatment with adolescents with ADHD. J Atten Disord. 2012; 16: 530-532.
29. Fatouh AM, Elshafeey AH, Abdelbary A. Intranasal agomelatine solid lipid nanoparticles to enhance brain delivery: formulation, optimization and in vivo pharmacokinetics. Drug Des Devel Ther. 2017; 11: 1815-1825.
30. De Leersnyder H., Zisapel N., Laudon M. Prolonged-release melatonin for children with neurodevelopmental disorders. Pediatr Neurol. 2011; 45: 23-26.
31. Gringras P, Nir T, Breddy J, et al. Efficacy and Safety of Pediatric Prolonged-Release Melatonin for Insomnia in Children With Autism Spectrum Disorder. J Am Acad Child Adolesc Psychiatry. 2017; 56: 948-957.e4.
32. Malow BA, Findling RL, Schroder CM, et al. Sleep, Growth, and Puberty After 2 Years of Prolonged-Release Melatonin in Children With Autism Spectrum Disorder. J Am Acad Child Adolesc Psychiatry. 2021; 60: 252-261.e3.
33. Blumer JL, Findling RL, Shih WJ, et al. Controlled clinical trial of zolpidem for the treatment of insomnia associated with attention-deficit/ hyperactivity disorder in children 6 to 17 years of age. Pediatrics. 2009; 123: e770-e776.
34. Stockmann C, Gottschlich MM, Healy D, et al. Relationship between zolpidem concentrations and sleep parameters in pediatric burn patients. J Burn Care Res. 2015; 36: 137-144.
35. Liskow B., Pikalov A. Zaleplon overdose associated with sleepwalking and complex behavior. J Am Acad Child Adolesc Psychiatry. 2004; 43: 927-928.
36. Sein Anand J, Chodorowski Z, Hajduk A. Ostre zatrucie zaleplonem--opis przypadku [Acute intoxication with zaleplon--a case report]. Przegl Lek. 2007; 64: 310-311.
37. Sangal RB, Blumer JL, Lankford DA, et al. Eszopiclone for insomnia associated with attention-deficit/hyperactivity disorder. Pediatrics. 2014; 134: e1095-e1103.
38. Neubauer D. Lemborexant for Insomnia. Current Psychiatry. 2020; 19: 43-49.

39. Kawabe K, Horiuchi F, Ochi M, et al. Suvorexant for the Treatment of Insomnia in Adolescents. J Child Adolesc Psychopharmacol. 2017; 27: 792-795.
40. Robinson AA, Malow BA. Gabapentin shows promise in treating refractory insomnia in children. J Child Neurol. 2013; 28: 1618-1621.
41. Bruni O, Angriman M, Melegari MG, et al. Pharmacotherapeutic management of sleep disorders in children with neurodevelopmental disorders. Expert Opin Pharmacother. 2019; 20: 2257-2271.
42. Sullivan SS. Current treatment of selected pediatric sleep disorders. Neurotherapeutics. 2012; 9: 791-800.
43. Garcia-Borreguero D, Larrosa O, de la Llave Y, et al. Treatment of restless legs syndrome with gabapentin: a double -blind, cross -over study. Neurology. 2002; 59: 1573-1579.
44. Happe S, Sauter C, Klösch G, et al. Gabapentin versus ropinirole in the treatment of idiopathic restless legs syndrome. Neuropsychobiology. 2003; 48: 82-86.
45. de Leeuw TG, Mangiarini L, Lundin R, et al. Gabapentin as add-on to morphine for severe neuropathic or mixed pain in children from age 3 months to 18 years - evaluation of the safety, pharmacokinetics, and efficacy of a new gabapentin liquid formulation: study protocol for a randomized controlled trial. Trials. 2019; 20; 20: 49.
46. Cooper TE, Wiffen PJ, Heathcote LC, et al. Antiepileptic drugs for chronic non-cancer pain in children and adolescents. Cochrane Database Syst Rev. 2017; 8: CD012536.
47. Picchietti MA, Picchietti DL. Advances in pediatric restless legs syndrome: Iron, genetics, diagnosis and treatment. Sleep Med. 2010; 11: 643-651.
48. Reynolds AM, Connolly HV, Katz T, et al. Randomized, Placebo-Controlled Trial of Ferrous Sulfate to Treat insomnia in Children with Autism Spectrum Disorders. Pediatr Neurol. 2020; 104: 30-39.
49. Amos LB, Grekowicz ML, Kuhn EM, et al. Treatment of pediatric restless legs syndrome. Clin Pediatrics. 2014; 53: 331-336.
50. Montgomery P, Burton JR, Sewell RP, et al. Fatty acids and sleep in UK children: subjective and pilot objective sleep results from the DOLAB study--a randomized controlled trial. J Sleep Res. 2014; 23: 364-388.
51. Zaouali-Ajina M, Gharib A, Durand G, et al. Dietary docosahexaenoic acid-enriched phospholipids normalize urinary melatonin excretion in adult (n-3) polyunsaturated fatty acid-deficient rats. J Nutr. 1999; 129: 2074-2080.
52. Huss M, Völp A, Stauss-Grabo M. Supplementation of polyunsaturated fatty acids, magnesium and zinc in children seeking medical advice for attention-deficit/hyperactivity problems - an observational cohort study. Lipids Health Dis. 2010; 9: 105.
53. Esposito D, Belli A, Ferri R, et al. Sleeping without Prescription: Management of Sleep Disorders in Children with Autism with Non-Pharmacological Interventions and Over-the-Counter Treatments. Brain Sci. 2020; 10: 441.
54. Cubero J, Chanclón B, Sánchez S, et al. Improving the quality of infant sleep through the inclusion at supper of cereals enriched with tryptophan, adenosine-5'-phosphate, and uridine-5'-phosphate. Nutr Neurosci. 2009; 12: 272-280.
55. Bruni O, Ferri R, Miano S, et al, L -5-Hydroxytryptophan treatment of sleep terrors in children. Eur J Pediatr. 2004; 163: 402-407.
56. Van Zyl LT, Chung SA, Shahid A, et al. L-Tryptophan As Treatment for Pediatric Non-Rapid Eye Movement Parasomnia. J Child Adolesc Psychopharmacol. 2018; 28: 395-401.
57. Wali S, Alsafadi S, Abaalkhail B, et al. The Association Between Vitamin D Level and Restless Legs Syndrome: A Population-Based Case-Control Study. J Clin Sleep Med. 2018; 14: 557-564.
58. Deng Y, Wang G, Ye X, et al. The association between 25-hydroxyvitamin D levels and children's sleep-wake patterns: a prospective cohort study. Sleep Med. 2020; 67: 207-214.
59. Gong QH, Li SX, Li H, et al. 25-Hydroxyvitamin D Status and Its Association with Sleep Duration in Chinese Schoolchildren. Nutrients. 2018; 10: 1013.
60. Ozeki M, Juneja LR, Shirakawa S. The effects of theanine on sleep with the actigraph as physiological indicator. Jpn J Physiol Anthropol 2004; 9: 143-150.
61. Lyon MR, Kapoor MP, Juneja LR. The effects of L-theanine (Suntheanine®) on objective sleep quality in boys with attention deficit hyperactivity disorder (ADHD): a randomized, double-blind, placebo-controlled clinical trial. Altern Med Rev. 2011; 16: 348-354.
62. Cohen EM, Dossett ML, Mehta DH, et al. Factors associated with insomnia and complementary medicine use in children: results of a national survey. Sleep Med. 2018; 44: 82-88.
63. Feucht C, Patel DR. Herbal medicines in pediatric neuropsychiatry. Pediatr Clin North Am. 2011; 58: 33-54.
64. Francis AJ, Dempster RJ. Effect of valerian, Valeriana edulis, on sleep difficulties in children with intellectual deficits: randomised trial. Phytomedicine. 2002; 9: 273-279.
65. Müller SF, Klement S. A combination of valerian and lemon balm is effective in the treatment of restlessness and dyssomnia in children. Phytomedicine. 2006; 13: 383-387.
66. Tavares-Silva C, Holandino C, Homsani F, et al. Homeopathic medicine of Melissa officinalis combined or not with Phytolacca decandra in the treatment of possible sleep bruxism in children: A crossover randomized triple-blinded controlled clinical trial. Phytomedicine. 2019; 58: 152869.
67. Hübner WD, Kirste T. Experience with St John's Wort (Hypericum perforatum) in children under 12 years with symptoms of depression and psychovegetative disturbances. Phytother Res. 2001; 15: 367-370.
68. Findling R, McNamara N, O'Riordan M, et al. An open-label study of St. John's wort in juvenile depression. J Am Acad Child Adolesc Psychiatry 2003; 42: 908-914.

69. Lee J, Jung HY, Lee SI, et al. Effects of Passiflora incarnata Linnaeus on polysomnographic sleep parameters in subjects with insomnia disorder: a double-blind randomized placebo-controlled study. Int Clin Psychopharmacol. 2020; 35: 29-35.

70. Trompetter I, Krick B, Weiss G. Herbal triplet in treatment of nervous agitation in children. Wien Med Wochenschr. 2013; 163: 52-57.

71. Zick SM, Wright BD, Sen A, et al. Preliminary examination of the efficacy and safety of a standardized chamomile extract for chronic primary insomnia: a randomized placebo-controlled pilot study. BMC Complement Altern Med. 2011; 11: 78.

72. Arbianingsih A, Amal AA, Hidayah N, et al. Massage with lavender aromatherapy reduced sleep disturbances on infant. Enferm Clin. 2020; 30: 62-65.

73. Williams TI. Evaluating effects of aromatherapy massage on sleep in children with autism: a pilot study. Evid Based Complement Alternat Med. 2006; 3: 373-377.

74. Dong HY, Wang W. Clinical observations on curative effect of TCM massage on dyssomnia of infants. J Tradit Chin Med. 2010; 30: 299-301.