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Review Article

Current Pharmacological Treatment for Sleep Disorders in Children and Adolescents with Autism Spectrum Disorder

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ABSTRACT

Sleep disorders are very common in children and adolescents with Autism Spectrum Disorder (ASD) and can negatively impact their lives, mental health, developmental processes, families' lives, and emotional well-being. It is essential to determine the specific sleep disorder and its underlying cause in treatment planning. Currently, nonpharmacological and pharmacological interventions are the main treatments for improving sleep disorders in children and adolescents with ASD. If nonpharmacological strategies are unsuccessful or difficult to implement, medications should be considered and used in conjunction with them. Melatonin, behavioral interventions, and parent education are the most effective treatments to improve sleep, relative to other pharmacological treatments. Medications used to treat sleep disorders in these children are used off-label. Melatonin appearing to be safe and effective may be an evidence-based and efficacious first-line treatment for treating insomnia symptoms in children and adolescents with ASD. Antipsychotics (e.g.low dose quetiapine), antidepressants with strong sedative effects such as trazodone and mirtazapine, antihistamines (e.g.diphenhydramine, niaprazine), alpha-adrenergic drugs (e.g. clonidine), benzodiazepines (e.g.clonazepam) and other hypnotic drugs, anticonvulsants (e.g. gabapentin), Alzheimer's drugs (e..g donepezil), superoxide and iron treatment are other drugs used in pharmacological treatment. Depending on the type of sleep disorders and the presence of comorbidities, the most effective pharmacological treatment should be selected on a case-by-case basis.

Keywords: Autism Spectrum Disorder, Sleep, Sleep Initiation and Maintenance Disorders, Pharmacological Treatment, Melatonin

INTRODUCTION

Autism spectrum disorders (ASD) are neurodevelopmental disorders that cause difficulties with social interactions, communication, and stereotyped behavior patterns. ASD affects approximately one in 36 children [1]. It is common for individuals with ASD to have comorbid psychiatric disorders, including sleep disorders. Sleep is vital for a child's overall growth and well-being. It plays a vital role in regulating many biological functions in children such as metabolism, mood regulation, learning, and memory [2, 3]. Sleep disorders are very common in ASD. According to a recent review, children with ASD have a higher likelihood of experiencing sleep-related disorders, with a prevalence ranging from 50% to 80%, in contrast to 9% to 50% among typical children [4]. Insomnia is the most frequently

reported sleep problem. Sleep disorders such as parasomnias, sleep-disordered breathing, movement disorders during sleep, and excessive sleepiness during the day are also observed in children and adolescents with ASD [4, 5].

Studies show that children with ASD undergo more bedtime resistance, sleep onset delay, and difficulties maintaining sleep. They often wake up frequently at night and have irregular sleep patterns, a shorter sleep duration, and early morning awakening. Besides they suffer from sleep anxiety, excessive sleepiness during the day, parasomnias, and sleep-disordered breathing [5-10]. Sleep problems in children with ASD seem to be related to age. Younger children experience more difficulty going to bed, higher levels of bedtime resistance, bedtime anxiety, night wakings, and parasomnias. However, older children are more prone to sleeplessness [11].
Sleep problems in ASD children are commonly linked to conditions such as anxiety, attention problems, impulsivity, oppositional behavior, sensory sensitivities, digestive problems, and medication use [4, 12].

Sleep problems in children with ASD tend to last longer and endure when compared to typical children. Typical children's sleep problems typically fade with age [13]. As well as being prevalent and persistent, sleep issues have a significant impact on various aspects of children's and family's lives. Poor sleep has been shown to negatively affect ASD symptoms and their daytime functioning. Sleep problems can lead to difficulties in social communication, increased stereotypical behavior, more dysfunctional routines, lower cognitive and academic performance, lower learning capacities and memory, poorer quality of life, higher stress and mood disorders for family members. Insufficient sleep has also been associated with increased social, emotional/behavioral problems, such as tantrums, defiance, aggression, irritability, self-harm, low mood, anxiety, fluctuations in mood, attentional deficits, and hyperactivity. For this reason, it is very important to recognize and treat sleep problems in children with ASD [2, 7, 14-17].

Main Points:

- Sleep disorders, one of the most common comorbid disorders in children and adolescents with ASD, negatively affect the lives of both children and families in many ways.
- Melatonin appearing to be safe and effective may be an evidence-based and efficacious first-line treatment for insomnia in children and adolescents with ASD.
- Antipsychotics, antidepressants, antihistamines, alpha-adrenergic drugs, benzodiazepine and other hypnotic drugs, anticonvulsants, Alzheimer's drugs, superoxide and iron treatment are other drugs used in pharmacological treatment.
- Depending on the type of sleep disorders and the presence of comorbidities, the most effective pharmacological treatment should be selected on a case-by-case basis.

The causes of sleep problems in ASD have not yet been definitively established. Sleep disorder has been linked to biological factors, irregularities in circadian genes, abnormalities in the melatonin system, psychological, social and environmental factors, sensory hyperarousal, comorbid medical conditions, and medications [2, 4, 5, 17].

Clinical Assessment and Management of Sleep Disorders in ASD

The first clinical assessment of sleep problems is vital and frequently disregarded. Before using any medicines or other treatments for sleep problems, it is crucial to recognize and treat the underlying medical conditions causing them. To diagnose sleep disorders properly in ASD, Rana et al. 2021 advise following these steps: (1) taking a detailed history of sleep patterns, sleep times, wake-up times, and sleep schedules; (2) identifying any behavioral factors, such as struggling to understand affectionate expectancies ascribed to communication difficulties (3) screen for sleep disorders, such as nightmares, sleep apnea, night terrors, restless leg syndrome, sleep-related movements, and sleepwalking; (4) diagnosing psychiatric disorders that occur at the same time, like discomfort or notice attention deficiency hyperactivity disorder (ADHD); (5) diagnosing medical conditions that occur at the same time, such as seizures, nocturia, gastrointestinal reflux disease, eczema, night cough, and pain [5].

Currently, most treatments for improving sleep problems in children with ASD involve behavioral or pharmacological interventions. The National Institute for Health and Care Excellence (NICE) recommends that a behavioral sleep plan be developed in conjunction with parents or carers for individuals with ASD under 19 years old who have sleep problems. [18]. The evaluation should also consider any comorbidities, medication use, and environmental or psychological factors (like nearby

injury or bullying) that could be causing the sleep problem. It is suggested that drug treatments are only attempted if behavioral interventions have failed or if the impact on the child or their family is long-lasting. Similarly, in the recently published practice guideline of the American Academy of Neurology for sleep disturbance in children and adolescents with ASD, pharmacological treatments are recommended only when non-pharmacological treatments do not work and all relevant factors have been addressed [19].

Non-pharmacological treatments, which are the mainstay of treatment of sleep disorders, include establishing sleep routines, sleep training, and direct behavioral intervention. These methods are safer and can be just as efficient as drugs, mainly for mild or ordinary cases [4, 19].

Malow and colleagues [20] analyzed 1,518 children aged 4-10 and found that 46% of those diagnosed with a sleep disorder were prescribed sleep medications. To this day, the Food and Drug Administration (FDA) has not approved any medication for treating insomnia in children with ASD.

There are important conditions to keep in mind before starting a new medication in the treatment of sleep disorders in children with ASD [5, 20, 21]. (see Table 1).

Table 1. Important conditions to keep in mind before starting a new medication in the treatment of sleep disorders in children with ASD

- Prescription and non-prescription medications that the child may take should be reviewed.
- The child's age and clinical history, along with any associated medical conditions, should be evaluated in detail.
- The right choice of sleep-enhancing drugs should be made. Since there is insufficient scientific evidence for sleep-enhancing medications, the choice should be made based on the main sleep complaint and associated symptoms. Treatment approaches vary depending on the sleep problem.
- Sleep drugs should be started at the lowest effective dose, increased when necessary, and the side effects of the medications should be taken into account.
- To reduce the risk of rebound insomnia, drugs should be closely monitored and slowly reduced. Sudden discontinuation of sleeping medications should be avoided.
- Treatment goals should be determined together with parents and should be realistic and measurable. Potential side effects such as daytime sedation and tolerance should be discussed.
- It is important to screen adolescents for alcohol and drug use due to the additive impacts of sedative-hypnotic and entertaining drugs.
- Correct timing is vital when managing sleep disorders, as most hypnotic drugs take effect within half an hour and reach their highest point within one or two hours. Therefore, administering medication too soon or too late will result in reduced effectiveness

The Pharmacological Treatment of Insomnia and Disrupted Sleep Behavior

Melatonin is frequently used in the pharmacological treatment of sleep disorders in children with ASD. However, if behavioral and melatonin treatments are insufficient, other psychotropic drugs may be prescribed off-label. This includes drugs like antipsychotics, antidepressants with strong sedative effects such as trazodone and mirtazapine, antihistamines, alpha-adrenergic drugs like clonidine, benzodiazepines, and other hypnotic drugs, anticonvulsants such as gabapentin, Alzheimer's drugs like donepezil, superoxide and iron treatment [2, 4, 10, 20, 21]. Currently, there is not enough research on these medications and their clinical effectiveness and safety profile in treating sleep problems. However, surveys examining the effectiveness of psychotropic medication prescribed for various reasons on the sleep of individuals with ASD throughout their lifetime have been informative.

1. Melatonin

Melatonin is the most common pharmacological medication prescribed for insomnia and circadian rhythm sleep-wake disorders in ASD [10, 22]. Melatonin is a hormone synthesized principally in the pineal gland, has an important function in the regulation of circadian rhythm and core body temperature rhythms, and is regulated by the suprachiasmatic nucleus of the hypothalamus [23]. It is thought that melatonin may help relieve anxiety and improve overall health [24]. Several studies have been carried out on patients with ASD, demonstrating the effectiveness of melatonin. These studies encompassed open-label data, randomized controlled trials, uncontrolled trials, control trials, retrospective studies, and meta-analyses. The overall consensus is that melatonin decreases sleep onset latency (SoL), proceeds the sleep phase, and increases total sleep time (TST) while reducing night wakings [10, 20, 22, 25-27]. However, the reduction in night wakings has been reported to occur with sustained/prolonged-release melatonin formulations

rather than immediate-release melatonin [28]. A recent review reported that prolonged-release melatonin formulation treatment effectively improved both sleep onset, duration, and consolidation, and externalizing behaviors during the day in children and adolescents with ASD, as well as caregivers' quality of life and gratification with their children's sleep [22].

In a study of 125 children with ASD aged 2-17.5 years who had sleep problems for more than three months and did not benefit from behavioral intervention for four weeks, it was found that TST increased by 57.5 minutes and SoL decreased by 39.6 minutes after taking melatonin mini tablets at a dose of 2 to 5 mg for 13 weeks [26]. In a meta-analysis of 35 researchers, the findings show that melatonin increases TST by 73 minutes and reduces SoL by 66 minutes from the standard level. Unfortunately, the melatonin did not present any significant improvement in night wakings [29]. Open-label study determined the effectiveness of melatonin in 24 (aged 3 to 10 years) children using doses up to 9 mg. The research showed that reduced SoL (on average 21.3 minutes less, from 42.9 to 21.6 minutes), but there was no significant change in the TST, sleep quality, or night wakings after receiving therapy for 14 weeks. The study also displayed better behavior and less stereotypical and compulsive behavior [30]. A significant retrospective study investigating the use of melatonin with a dosage range of 3-6 mg in 107 participants aged 2-18 years demonstrated the absence of sleep concerns for around 25% of parents after 1.8 years of follow-up, based on objective evaluation [31]. In contrast, a different phase III trial, which was randomized and placebo-controlled, was carried out to evaluate a variety of immediate-release melatonin doses (0.5-12 mg) for the treatment of severe sleep problems in children with neurodevelopmental disorders. This study revealed that administering melatonin resulted in limited extra sleep (increase of 23 minutes in TST, decrease of 38 minutes in SoL, earlier waking times) and also did not improve behavioral outcomes and night wakings [32].

Generally, the application of melatonin is fairly well-tolerated and the side effects are rare and mild. Most published research studies have not disclosed any significant safety concerns. Commonly reported adverse effects of melatonin include headache, dizziness, hypothermia, increased enuresis, and morning drowsiness. A few children reported experiencing nightmares [17, 22, 25, 26, 29, 30]. In a recent study comprising 80 children and adolescents who were administered melatonin for 104 weeks, it was concluded that melatonin is safe with minor side effects such as fatigue (6.3%), daytime sleepiness (6.3%), and mood swings (4.2%) [28]. Long-term use of melatonin has been found to have no negative effects on height, body mass index, or pubertal development, as shown by the lack of evidence of delay or withdrawal effects [22]. Although there are concerns that long-term use of melatonin may cause a delay in pubertal development in children, the results are inconsistent and there are not enough studies on this subject according to some findings obtained from a small number of animal studies [33]. However, it is important to consider metabolic phenotypes and potential drug interactions that may increase the risk of side effects in individuals with ASD. Melatonin is metabolized via the hepatic microsomal P450 pathway. Drug interactions of melatonin are mostly with inhibitors and enhancers of CYP1A2, this condition is resulting in the increase or the decrease in melatonin bioavailability. There is a theoretical concern that antiepileptic drugs that act as enzyme inducers, such as phenobarbital, phenytoin, and carbamazepine, may accelerate the elimination of melatonin [34].

Melatonin is available in immediate, sustained, and prolonged-release oral tablets, intranasal spray, liquid, transdermal, and sublingual formulations that range from 1-10 milligrams. After oral administration, melatonin is absorbed rapidly, and peak plasma levels are observed after 40-60 minutes, which persists for up to 1.5 hours (depending on dosage) before declining [35]. It is presumed that the immediate release formulations are more helpful for sleep-onset insomnia and controlled-release forms for sleep maintenance, due to immediate-release melatonin has a short half-life (40 minutes) [19]. The generally recommended dose for administration 30-60 minutes before bedtime is 1-3 mg [19, 29]. The expert opinion of the European Society of Pediatric Neurology is that it can be administered at doses of 1-5 mg approximately 30 minutes before bedtime as sleep inductor, and it can be started at doses of 0.2-0.5 mg 3-4 hours before bedtime as kronobiyotic in delayed sleep phase syndrome. (It can be increased by 0.2-0.5 mg every week as needed until the effect is seen (maximum 3 mg; adolescents: 5 mg)) [36]. However, dose adjustments of up to 10 mg/day are possible for sleep disorders in ASD and age or weight is not related to an effective dose [19, 22].

As it is classified as a dietary supplement, the safety of melatonin has not been subject to thorough evaluation by the FDA. Although the use of melatonin is generally considered safe, there is a shortage of rigorous data supporting its use. In addition, recommendations concerning the usage of melatonin in children

and adolescents are inconsistent. The availability of various brands, combined with the lack of strict regulations imposed by the FDA on over-the-counter medications, raises concerns about the actual content of melatonin in different formulations. While melatonin has been demonstrated to be effective in treating ASD in children according to numerous studies, these studies are not without limitations. These limitations comprise small study sizes, comorbid neurodevelopmental disabilities confounding factors, imprecision in sleep aspects differentiation, varied drug dosages administered, lack of long-term monitoring data, and absence of a placebo group [5].

Melatonin receptor agonists, such as agomelatine and ramelteon, selectively act on MT1 and MT2 melatonin receptors and are utilized for treating sleep problems in children with ASD. Administering agomelatine (25 mg/day) for three months has resulted in a significant increase in TST and has improved the sleep phase and stability of sleep in ASD children [37]. Ramelteon (dose: 2-8 mg/day), a melatonin agonist administered to treat three ASD children, has been discovered to alleviate sleep problems, particularly insomnia, and lead to concurrent enhancements in behavior [38]. Ramelteon is the exclusive drug in this category that has received endorsement from the FDA for insomnia treatment in adults. Adverse effects primarily comprise dizziness and fatigue, and it is recommended to exercise caution when co-administering with Fluvoxamine.

Finally, pharmacological treatments for sleep disorders in children with ASD have revealed robust evidence supporting the effectiveness of melatonin supplementation, including the melatonin receptor agonist ramelteon. Nevertheless, there has been limited evidence for the use of other pharmacological treatments. Melatonin treatment for children with ASD has been discovered to be more effective and safer than sedatives and hypnotic medications [5].

2. Antipsychotics

Antipsychotic medication is commonly prescribed to address mood and behavioral comorbidities, such as aggression, irritability, and self-injurious behaviors found in individuals with ASD. These medications have a secondary benefit for sleep, although there is limited data on their efficacy and tolerability for treating insomnia in children. A study has demonstrated the efficacy of atypical antipsychotic drugs, specifically risperidone, in reducing SoL but not sleep duration. Nevertheless, considering the side effects and associated health risks related to risperidone treatment, it should not be prescribed for insomnia alone [39]. A six-month open-label extension study was conducted on 56 children and adolescents with ASD (ages 5 to 17), which revealed that those on higher doses of risperidone reported significant improvements in their sleep quality based on a sleep visual analog scale [40]. Children with ASD benefit from low-dose quetiapine to manage sleep disturbances and behavioral problems including aggression and irritability. During an 8-week open-label study involving 18 patients aged between 13-17 years old, quetiapine effectively alleviated their aggression and sleep problems [41]. Risperidone, quetiapine, and olanzapine are among the atypicals prescribed to treat sleep disorders in children [42]. However, it should be noted that while these drugs are often prescribed off-label to treat insomnia, they are not generally recommended as the first-line pharmacotherapeutic agent for this indication.

3. Antidepressants

There is limited data on the use and effectiveness of sedative antidepressants, selective serotonin reuptake inhibitors (SSRIs), and tricyclic antidepressants (TCAs) for sleep disorders in children with ASD. These medications have the potential to help with sleep problems, especially those associated with concomitant psychiatric conditions. Sedative antidepressants, mirtazapine, and trazodone may be advantageous for a child with concurrent symptoms of depression. SSRIs and TCAs may be prescribed in patients whose sleep onset is significantly impaired by obsessive thoughts and anxiety. These antidepressants promote sleep by counteracting wake-promoting neurotransmitters, like serotonin, noradrenaline, histamine, and acetylcholine. The majority of these antidepressants can cause suppression of REM sleep and daytime sedation [42]. An open-label trial investigated the effectiveness and tolerability of mirtazapine (at a dosage range of 7.5-45 mg/day) in adults with ASD suffering from related symptoms. Out of the 26 participants, nine individuals (34.6%) were deemed as responders (‘much improved’ or ‘very much improved’ on the Clinical Global Impression-Improvement Scale) following the alleviation of various symptoms, such as aggression, self-harm, depression, anxiety, hyperactivity, irritability, and insomnia [43]. Trazodone is a frequently utilized medication in psychiatric practice. While it is commonly prescribed for insomnia, only a small number of case reports have demonstrated its efficacy [44]. Its effectiveness has primarily been established in adults with psychiatric illness. Trazodone acts as a 5-HT2A/C antagonist and is among the most sedative antidepressants, which is accompanied by a notable morning hangover effect. Although there is currently no concrete evidence to support the use of

trazodone in children with ASD, it is prescribed to children and adolescents who struggle with sleep disorders [5, 42]. The TCAs, amitriptyline, imipramine, and doxepin are frequently prescribed for their sedative effects and are often used to treat insomnia in adults. [45]. No evidence supports the use of amitriptyline or trimipramine in children with ASD. Nevertheless, amitriptyline has been administered to children with neurodevelopmental impairments in doses ranging from 5 to 50 mg [5].

4. Antihistamines

Antihistamines are the primary non-prescription medicine for childhood sleep disorders. However, they carry a risk of adverse effects ranging from sedation to severe anticholinergic symptoms, which include blurred vision, constipation, urinary retention, dry mouth, tachycardia, fever, and confusion [10, 21]. Diphenhydramine, a first-generation antihistamine, is frequently used by practitioners to treat sleep problems (dosing range: 0.5 mg/kg up to a maximum of 25 mg per day). It functions as a histamine (H1) receptor antagonist in the peripheral and central nervous system resulting in a sedative and hypnotic effect [46]. In addition, Trimeprazine, another H1 receptor antagonist (dosing range: 45–90 mg per day), has been demonstrated to improve night wakings in children with chronic sleep disorders [47]. However, an open-label study has found niaprazine (an H1-receptor antagonist and piperazine derivative) to be effective in ameliorating sleep problems in children who had ASD and mild/moderate intellectual disability (dosage: 1 mg/kg/day, three times daily) [48]. Although antihistamines are widely used for patients with ASD, limited clinical trials have investigated their efficacy.

5. Alpha-2-adrenergic agonists

In cases of ASD, off-label use of the two main alpha agonists, Clonidine and Guanfacine, has increased despite the lack of any randomized controlled trial evidence of their effectiveness, particularly in anxiety and sleep disorders. In a case series of six cases with neurodevelopmental disorders, the findings showed that clonidine (dose range: 0.05-0.225 mg/day) effectively improves sleep onset and sleep maintenance in severe and unmanageable sleep problems. Hypotension, bradycardia, dry mouth, irritability, and REM suppression are potential side effects of clonidine and may lead to rebound hypertension and rebound REM if abruptly discontinued [49]. An open retrospective study investigated the efficacy of clonidine for treating insomnia, aggressive behaviors, hyperactivity, inattention, mood disorder, and in a cohort of 19 children with ASD. Oral clonidine was administered at 50 µg with a gradual increase up to 100 µg, 30 minutes before bedtime. Results showed that clonidine significantly reduced SoL and night waking, while its effectiveness in improving ADHD, mood instability, and aggression in this population has been limited. The adverse effects were generally tolerable [50].

Despite the frequent off-label use of immediate-release guanfacine (dosage range: 0.5–2 mg/day) to treat sleep problems in the young population, its efficacy has not been scientifically established [51]. A recent randomized placebo-controlled trial of extended-release guanfacine reported that it failed to significantly improve sleep patterns in individuals with ASD [52]. There is a shortage of placebo-controlled double-blind clinical trials that can offer a greater understanding of the clinical effectiveness and safety of these medications in ASD.

6. Benzodiazepines and non-benzodiazepine sedative-hypnotics

Benzodiazepines exhibit inhibitory actions through GABA receptors, leading to sedative, anxiolytic, and muscle-relaxing effects [53]. Although benzodiazepines are often prescribed for insomnia in adult patients, they are not frequently prescribed for the pediatric population due to their adverse effects such as headaches, cognitive impairment, dizziness, sedation, rebound insomnia, physical and behavioral dependence. Studies in children are limited, but they have shown the potential for benzodiazepines to improve sleep disorders [21].

Clonazepam is the only benzodiazepine that has been studied for sleep disorders in ASD. Clonazepam, an intermediate-acting benzodiazepine, demonstrated efficacy in managing parasomnias, periodic limb movement disorder (PLMD), nocturnal biting, and partial arousals in children with developmental disabilities. In a case series involving 11 children with ASD, 0.5-1 mg of clonazepam successfully resolved sleep-related REM behavioral disorder in 75% of the participants. The intervention has been generally well-tolerated among the participants. However, one child exhibited a paradoxical response, experiencing increased activity and agitation [54]. A study examining the use of clonazepam in children who had developmental disabilities revealed its efficacy in reducing nightmares and abnormal motor behavior during sleep [55]. However, limitations of clonazepam usage include concerns over its tolerability profile, potential for drug dependence, and lack of evidence-based data in the pediatric population.

The sedative-hypnotics, zaleplon, zolpidem, and eszopiclone, collectively referred to as the ‘Z-drugs’, have a pharmacology

similar to that of benzodiazepines but are not chemically related to them. They act by binding to the benzodiazepine-1 subtype within the GABA receptor complex and have a relatively short half-life. Unlike benzodiazepines, these drugs do not cause persistent sedation, cognitive or memory impairments throughout the day [56]. Additionally, these medications usually do not result in rebound insomnia (an increase in insomnia when a sleep aid is abruptly stopped), a negative consequence of benzodiazepines. Although zaleplon and zolpidem are used in children, information about eszopiclone is not extensive. There have been few studies on children, and there are no clinical trials available on the use of this type of medication for ASD. Clearance of non-benzodiazepine receptor agonist medications is three times higher in children than adults, resulting in drug inefficiency and potentially inducing frightening sleep states such as sleepwalking and sleep-related hallucinations [42]. Due to their low efficacy and high incidence of adverse reactions, these drugs have limited practical application and should only be considered for use in this population when all other options have been exhausted. However, they may be taken into consideration for patients who are in late adolescence or early adulthood.

7. Anticonvulsants

Concerning the treatment of insomnia in children, there is limited data on the effectiveness of anticonvulsants. Most studies have focused on examining aggression and irritability, and have reported improvements in these areas. Adverse events observed in these studies have ranged from insomnia to sedation. Sedation is typically dose-dependent, and tolerance is known to develop [42]. Gabapentin (3-7.5 mg/kg, maximum of 15 mg/kg) administered 30 to 45 minutes before bedtime has resulted in enhanced sleep among 18 out of 23 (78%) children. However, adverse effects, such as agitated night wakings and feeling peculiar, have been reported. Gabapentin is not commonly used as a first-line agent [57]. Nevertheless, it may have potential benefits for children. It could be advantageous for children and adolescents with ASD who have comorbid symptoms of restless leg syndrome (RLS), excessive PLMD, or nighttime seizures [5].

8. Alzheimer's medications

Donepezil is used to treat Alzheimer's disease, acting as a reversible acetylcholinesterase inhibitor and enhancing cholinergic transmission. A nonblinded study in a limited number of children with ASD demonstrated the effectiveness of donepezil in increasing REM sleep, improving related behavioral and attention problems, and reducing REM sleep onset latency [58]. However, the trial is impeded by its small sample size. Possible side effects of donepezil usage include hypotension, vivid dreams, insomnia, bradycardia, and gastrointestinal symptoms (nausea, vomiting, and diarrhea) [42]. There are no sufficient studies on the use of donepezil in sleep problems in children with ASD.

9. Suvorexant

Suvorexant is a dual orexin receptor agonist that binds selectively to orexin-1 and -2 receptors, leading to the inactivation of wakefulness. The tolerability, efficacy, and safety of suvorexant (20 mg/kg) in treating insomnia among 30 adolescents approximately 6 months after commencing treatment was assessed by Kawabe and colleagues. Of these patients, seven had ASD. Out of the thirty patients, seventeen (56.7%) have continued to take suvorexant, leading to a noteworthy decrease on the Clinical Global Impression-Severity Scale as well as an improvement in their overall sleep quality. The lack of a control group and the small sample size are important limitations of the study. Nevertheless, it indicates that suvorexant could be a viable treatment option for adolescents grappling with insomnia and conceivably ASD [59]. In a recent study of 3 children (2 with ASD) and 1 adult patient with neurodevelopmental disorders, has been reported one patient showed a strong improvement in sleep onset and maintenance, and another showed a significant improvement in insomnia symptoms in combination therapy with trazodone, and two patients have shown a slight benefit or no benefit from suvorexant treatment [60].

10. Oral Iron Supplement

Iron is a cofactor for tyrosine hydroxylase, the enzyme responsible for converting the amino acid tyrosine into dopamine. It is common for children with ASD to have low serum ferritin levels. In a treatment study of 33 children with ASD and RLS, iron supplementation (6 mg/kg/day, elemental iron) for 8 weeks reported a significant improvement in sleep quality. The baseline mean ferritin level was 15.72 mcg/L (4.2-39.0 mcg/L). The mean ferritin level after treatment was 28.8 mcg/L (6.6-103 mcg/L), indicating a correlation between iron deficiency and sleep disorder in children with ASD. This study is limited by a small sample size and a lack of controls. Oral iron supplementation has adverse effects such as vomiting, nausea, diarrhea, constipation, metallic taste, and black/green stools [61]. In a retrospective analysis of medical records from 9,791 children with ASD, the study has found significantly low levels of serum ferritin linked to various sleep disorders, such as PLMD (27 ng/mL), disrupted

sleep (24 ng/mL), and substandard sleep efficiency (7 ng/mL) [62]. Serum ferritin, which is an iron storage protein (level <50 ng/mL), was also linked with RLS. Iron therapy is recommended for ferritin levels below 50 ng/mL. Iron supplementation has been proven to be an effective treatment for low ferritin levels in individuals with sleep disorders [63].

The Pharmacological Treatment for Sleep-Disordered Breathing

In the treatment of sleep-disordered breathing, medical devices, and surgical interventions are primarily used. Adenotonsillectomy is typically the preferred first-line surgical treatment for pediatric obstructive sleep apnea (OSA). Some children may need continuous positive airway pressure (CPAP) or further surgical procedures following an adenotonsillectomy, particularly those who are obese or have underlying medical conditions like craniofacial anomalies. Focusing on reducing weight and utilizing positional therapy can also help alleviate obstructive sleep apnea in children [64]. Pharmacological treatment of OSA, particularly for mild OSA, may involve nasal corticosteroids, leukotriene antagonists, or a combination of both [64-66]. However, the primary course of treatment for OSA ought not to include medication, particularly for children with ASD due to limited evidence on the effectiveness of these treatments, which have been exclusively tested on typical children. Pharmacological treatment strategies for OSA in children with ASD require further research.

The Pharmacological Treatment for Sleep-Related Movement Disorders

Restless legs syndrome (RLS) and PLMD, both sleep-related movement disorders, have been linked to low levels of iron. Children with ASD may have idiosyncratic dietary preferences, causing iron deficiencies. Therefore, if ferritin levels are low (less than 50 ng/dl), replenishing iron is recommended, particularly if sleep is disrupted [61]. As well as iron supplements, gabapentin is sometimes used off-label to treat RLS that begins in childhood. A recent study has found that gabapentin is generally well-tolerated with no serious side effects and improves sleep quality or resolves insomnia in children with RLS [67]. Dopamine agonists are also medications used to treat RLS in older teens and adults [66]. The safety and efficacy of anticonvulsants and dopamine agonists have not been trialed in children with ASD.

The Pharmacological Treatment for Parasomnias

Parasomnias are unwanted events that occur during sleep, including sleepwalking, night terrors, confusional arousals, nightmares, REM sleep behavior disorder, and bruxism. When treating parasomnias, it is crucial to identify the primary diagnosis. Benzodiazepines and TCAs such as imipramine are generally used in the pharmacological treatment of parasomnias [66]. Clonazepam is a benzodiazepine that significantly suppresses third and fourth-stage NREM sleep. If sleep terrors (parasomnia) are frequent and severe or cause functional impairment such as fatigue, daytime sleepiness, and distress, clonazepam may be used briefly at bedtime. It is recommended to use clonazepam in the early hours of the night when sleep terrors predominate, at least 90 minutes before the child goes to sleep, for an effective drug level [68]. In a case series of children with ASD, it was reported that clonazepam could also be used in the REM sleep behavior disorder [54].

Limitations

In this review, many studies evaluating different medical treatments and differing methodologically in the treatment of sleep disorders in children with ASD have been examined. However, when these studies are evaluated in general; reasons such as small sample size, limited number of studies on specific sleep disorders, limited number of randomized placebo-controlled studies on medical treatments other than melatonin, differences in drug doses and methodological differences between treatment methods have made it difficult to establish a standard treatment protocol, in these population. Additionally, complementary and alternative treatments used by families were not evaluated in this review.

CONCLUSIONS

In summary, sleep disorders are very common in children and adolescents with ASD. Although sleep drugs are frequently prescribed, evidence regarding the use and effectiveness of drugs in these children is limited. No medications are approved by the FDA for sleep disorders in children who have ASD. Melatonin has shown good effectiveness in many studies. However, the long-term effects of melatonin still need to be studied extensively. Depending on the type of sleep disorders and the presence of comorbidities, the most effective pharmacological treatment should be selected on a case-by-case basis. Future randomized controlled trials are needed to elucidate the effectiveness of pharmacological drugs that can be used in young children and to examine possible side effects and drug-drug interactions for this population group.

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