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RESEARCH ARTICLE

The Assessment and Treatment of Sleep Abnormalities in Children and Adolescents with Autism Spectrum Disorder: A Review

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Abstract

Objective: To summarize causes, evaluation methods, and treatment of sleep disturbance in children and adolescents with autism spectrum disorder (ASD)**. Methods:** A narrative literature and synthesis approach was used. **Results/Discussion:** Sleep disturbances in this population are common and include insomnia, parasomnias, circadian rhythm disorders, and sleep-related movement disorders. Multiple factors may contribute to the higher rates of sleep disturbances in persons with ASD. Unfortunately, there are not evidence-based guidelines specific for the management of these sleep disorders in this population. There is also a lack of controlled clinical studies. Nevertheless, assessment of sleep problems using both subjective and objective methods are recommended to develop an individualized approach. Behavioural interventions are preferred first line treatment for insomnia. As adjunctive measures, pharmacotherapy may be warranted and choice should be guided based on accompanying symptoms. The most commonly used pharmacotherapy for sleep disturbance, primarily insomnia, include melatonin and alpha agonists. Not all currently used medications are approved for use for children and adolescents.

Key Words: *melatonin, autism spectrum disorder, sleep disturbance, evaluation*

Résumé

Objectif: Résumer les causes, les méthodes d'évaluation et de traitement des troubles du sommeil chez les enfants et les adolescents souffrant du trouble du spectre de l'autisme (TSA). **Méthodes:** une littérature narrative et une approche de synthèse ont été utilisées. **Résultats/Discussion:** les troubles du sommeil dans cette population sont communs et comprennent l'insomnie, la parasomnie, les perturbations du rythme circadien, et le trouble du mouvement lié au sommeil. De multiples facteurs peuvent contribuer aux taux élevés de troubles du sommeil chez les personnes souffrant du TSA. Malheureusement il n'existe pas de directives fondées sur des données probantes pour la prise en charge de ces troubles du sommeil dans cette population. Il manque également des études cliniques contrôlées. Néanmoins, l'évaluation des troubles de sommeil à l'aide de méthodes tant subjectives qu'objectives est recommandée pour développer une approche individualisée. Les interventions comportementales sont le traitement de première intention préféré pour l'insomnie. La pharmacothérapie des mesures d'appoint peut être justifiée et le choix devrait être basé sur les symptômes accompagnateurs. La pharmacothérapie la plus utilisée pour les troubles du sommeil, surtout l'insomnie, comprend la mélatonine et les alpha- agonistes. Les médicaments couramment en usage ne sont pas tous approuvés à utiliser pour les enfants et les adolescents.

Mots clés: *mélatonine, trouble du spectre de l'autisme, évaluation des troubles du sommeil*

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Introduction

Autism spectrum disorder (ASD) is characterized by deficits in social interactions, language development and communication, as well as restricted stereotyped behavioural patterns or interests (American Psychiatric Association, 2013). Compared with age-matched typically developing peers, children with ASD are more likely to experience sleep problems, with an estimated prevalence between 50% to 80% compared with 11% to 37% of children without ASD (Polimeni, Richdale, & Francis, 2005; Kotagal & Broomall, 2012; Souders et al., 2017).

A longitudinal study conducted in 5,151 children with ASD at 1.5, 3, 6, and 9 years of age showed that sleep problems co-occur with autistic traits in early childhood and worsen over time in children with ASD (Verhoeff et al., 2018). Humpreys et al. (2014) reported that children with ASD have reduced total sleep duration compared with contemporary controls. This aspect is most pronounced between 18 and 42 months and persists until adolescence (Humphreys et al., 2014). Parents of children with ASD most commonly report sleep onset and maintenance insomnia, early morning awakenings, and poor sleep routines (Schreck & Mulick, 2000; Honomichl, Goodlin-Jones, Burnham, Gaylor, & Anders, 2002). Other reported sleep problems include daytime sleepiness, parasomnias, sleep-related rhythmic movement disorder and circadian rhythm disorders as listed in Table 1 (Richdale & Schreck, 2009).

The extent of sleep disturbance in children and adolescents with ASD was previously believed to correlate with their level of functional and cognitive ability. Recently published studies, however, have shown that children with ASD at all levels of functional and cognitive ability have increased rates of sleep disturbances, further impacting this population (Herrmann, 2016; Baker, Richdale, Short, & Gradisar, 2013). Furthermore the severity of sleep problems, especially insomnia, is significantly correlated with problematic behaviours in preschoolers with ASD (Christensen et al., 2016).

This review summarizes causes, evaluation methods and treatment of sleep disturbance in children and adolescents with ASD.

1. Hypotheses for the High Prevalence of Sleep Disorders in Children and Adolescents with ASD

Given that the causes of ASD are poorly understood, it is not surprising that the origin of sleep disturbance in children with ASD is also unclear. It is hypothesized, however, that disordered sleep is intrinsic to the pathophysiology of ASD (Verhoeff et al., 2018). Sleep problems in ASD may have behavioural, medical, neurobiological mechanisms and in any given child its cause appears to be multifactorial.

A. Behavioural Causes of Sleep Disturbance

Behavioural factors (e.g., poor sleep hygiene, bedtime stalling, refusal behaviours) are some of the most common causes of insomnia in children with or without ASD (Souders et al., 2009; Souders et al., 2017; Mindell & Meltzer, 2008). These challenges are further exacerbated in children with ASD owing to communication challenges, understanding parental expectations, over-responsiveness to environmental stimuli, and self-stimulatory behaviours (Mazurek & Petroski, 2015a). These core behavioural difficulties interfere with the establishment of optimal and consistent bedtime behaviours and routines.

B. Medical Causes of Sleep Disturbance

A higher prevalence of obstructive sleep apnea and periodic leg movements of sleep (PLMS) associated with low serum ferritin levels have been found in children with ASD. These disorders eventually lead to sleep fragmentation (Youssef et al., 2013). Children and adolescents with ASD are reported to have increased gastrointestinal symptoms, including gastroesophageal reflux disease, diarrhea, constipation, and abdominal pain, which could impact sleep efficiency (McElhanon, McCracken, Karpen, & Sharp, 2014; Klukowski, Wasilewska, & Lebensztejn, 2015).

Table 1: Sleep Problems in Children with Autism Spectrum Disorder

Problem	Reported as
Insomnia	Difficulty falling sleep, staying sleep, early morning awakenings, inappropriate bed time routine, day time hyperactivity and sleepiness
Parasomnia	Nightmares, night terrors, vocalizations during sleep, sleep walking
Sleep Related Movement Disorders	Head banging, body rocking, restless around bed time, restless sleep, teeth grinding
Circadian Rhythm Disorders	Persistent difficulty with initiating sleep, sleep inertia, sleep onset and wake times progressively delayed

Epilepsy is common in children with ASD, reportedly occurring in one-third of patients (Spence & Schneider, 2009). Rates as high as 60% of epileptiform discharges have been reported in children with autism who have no history of seizures or epilepsy. These discharges are most commonly noted during sleep and include diffuse or generalized, multi-focal, and focal discharges, unilateral or bilateral, and localized to many different brain areas possibly resulting in sleep fragmentation (Chez et al., 2000; Spence & Schneider, 2009). Medications, e.g., stimulants, stimulating antidepressants, and antiepileptics, can also affect sleep.

C. Anxiety, Hyperarousal, Attention-Deficit Hyperactivity Disorder, and Sleep Disturbance in ASD

Anxiety and attention-deficit hyperactivity disorder (ADHD) are high arousal disorders prevalent in children and adolescents with ASD (Yerys et al., 2009; Kerns et al., 2014; Wiggs & Stores, 2004). Positive correlation between anxiety and various sleep problems, including bedtime resistance, sleep onset delay, and night wakenings have been reported in children with ASD (Mazurek & Petroski, 2015).

D. Abnormal Melatonin and Serotonin Secretion

Abnormal melatonin levels might play a role in insomnia in children with ASD. Melatonin is synthesized in the pineal gland and is received in the suprachiasmatic nucleus, the master clock of the brain, by receptors MTNR1A and MTNR1B, which are involved with multiple functions, including sleep induction, circadian and seasonal rhythm regulation, and immune function (Souders et al., 2017). Low levels of melatonin have been demonstrated in the urine, serum, or plasma of individuals with ASD (Tordjman, Anderson, Pichard, Charbuy, & Touitou, 2005; Melke et al., 2008). These findings suggest that circadian dysfunction may be the genesis of sleep-onset delay in some patients with ASD, while in others it might be multifactorial as suggested by patients' variable clinical responses to supplemental melatonin.

E. *Genes Involved in the Control of Circadian Rhythm*

Although genetic studies in ASD are currently an area of research interest, there have been few studies on genes that might be relevant to sleep disorders. Mutations in circadian-relevant genes, including *PER1*, *PER2*, *NPAS2, MTNR1A*, and *MTNR1B* appear to be more frequent in patients with ASD and sleep disorders (Yang et al., 2016; Glickman, 2010). Left unsettled is whether children and adolescents with ASD have an altered inherent circadian rhythm that regulates the sleep-wake cycle.

F. *Organization and Maturation of Brain Waves in ASD*

Support for differences in total rapid eye movement sleep by objective data has been inconsistent. Buckley et al. demonstrated a significantly reduced total sleep time, increased proportion of slow-wave sleep and reduced rapid eye movement (REM) sleep in the ASD group (Buckley et al., 2010). These results have been replicated in adults with ASD (Limoges et al., 2005). In a study of 21 children with ASD and ten controls, the REM sleep percentage was lower on night one but not on night two, suggesting a first-night effect (Malow et al., 2006). This study is limited by the small number of subjects; however, if differences in REM sleep do occur, it is possible this can affect neuroplasticity and ultimately sleep.

2. Clinical Evaluation of Children and Adolescents with ASD and Sleep Disorders

It is essential to screen for sleep problems at an early stage during routine visits (Moore, Evans, Hanvey, & Johnson, 2017; Katz et al., 2018). Identifying the presence of sleep disturbance should lead to further subjective and objective assessment measures (Malow et al., 2012). Depending on resources, availability, and the nature of the sleep problem, assessment approaches include sleep logs, actigraphy, and polysomnography. Sleep medicine specialist referral should be considered when necessary.

An initial clinical assessment of sleep disturbance is critical and often overlooked. It is essential for assessing sleep disturbance and should include inquiry regarding:

- A detailed history of the child or adolescent's sleep habits, bedtime, and wake-up routines and naps
- Behavioural factors, such as difficulty understanding parental expectations secondary to communication problems
- Sleep disorders, including sleep apnea, restless leg syndrome, sleep-related movements, nightmares, night terrors, and sleepwalking. Children with the capacity to verbalize may use terms, such as 'owwies,' 'ouchies,' 'tickles,' or 'bugs crawling on my legs' to describe the sensory discomfort associated with bedtime restless leg syndrome (Moore et al., 2017).
- Comorbid psychiatric disorders, such as anxiety or attention deficit hyperactivity disorder

Table 2. Subjective assessment methods for the evaluation of sleep abnormalities in children and adolescents with autism spectrum disorder (ASD)

Subjective Method	Patient Group	Age Range (years)	Components of the Subjective Assessment
Sleep diaries (Wiggs & Stores, 2004)	Patients with sleep disorders, including ASD.	All age groups	A record of times of going to sleep, waking up, night waking, daytime naps, and behavioral changes.
The Children's Sleep Habit Questionnaire (CSHQ). (Johnson, Turner, Foldes, Malow, & Wiggs, 2012)	A modified version is used for children with ASD.	4–10	Duration of sleep, resistance in going to bed, sleep anxiety, night waking, parasomnia, daytime sleepiness, sleep disordered breathing.
The Family Inventory of Sleep Habits (FISH). (Malow et al, 2009)	Children with ASD.	3–10	Child and parental behavior around bedtime, sleep routine, sleep environment, habits before bedtime.
The Modified Simmonds and Parraga Sleep Questionnaire (MSPSQ).(Malow et al., 2009)	A modified version is used for children with ASD and other developmental abnormalities.	5–18	Part 1 consists of the assessment of sleep quality and quantity. Part 2 consists of sleep disorders, including sleep anxiety, altered breathing patterns, delayed sleep onset, parasomnia, and daytime sleepiness.

- Medical disorders, including seizures, gastrointestinal reflux disease, nocturia, night cough, eczema, and pain.
- Prescription and over-the-counter medications

Before adding medications or other interventions for sleep, it is important to first identify and determine the cause of the sleep disorder and treat the underlying medical condition.

The British Association for Psychopharmacology has published consensus guidelines on the assessment and treatment of ASD; however, it contains limited recommendations on sleep disorders in children and adolescents (Howes et al., 2018). Similarly, a recently published set of practice parameters for the assessment and treatment of children and adolescents with ASD, lacks details on the assessment and treatment of sleep disorders in this population (Volkmar et al., 2014). Thus, there is a lack of recent evidence-based guidelines specifically for the evaluation of sleep disorders in children and adolescents with ASD.

A. Subjective Methods for Evaluating Sleep in Children and Adolescents with ASD

Owing to limitations in social communication and development in children, subjective methods used to evaluate sleep disorders often require responses from parents, guardians, or other family members via questionnaires or a sleep diary record (Malow et al., 2009; Simonds & Parraga, 1982; Owens, Spirito, & McGuinn, 2000). The main subjective assessment methods for the evaluation of sleep disorders in ASD are summarized in Table 2. Such measures have inherent limitations. They may be time-consuming, may not accurately capture the time of sleep onset or night awakenings, and may not distinguish true sleep from silence or being awake with closed eyes (Johnson, Turner, Foldes, Malow, & Wiggs, 2012; Johnson et al., 2016).

B. Objective Methods for Evaluating Sleep in Children and Adolescents with ASD

Subjective screening methods are useful in detecting sleep disturbances in children and adolescents with ASD, but diagnostic or laboratory methods provide objective assessment for problems, such as obstructive sleep apnea, nocturnal seizures, and excessive leg movements, and can also provide a tool for monitoring responses to treatment (Moore et al., 2017). Primary diagnostic assessment methods include polysomnography and actigraphy (Miano et al., 2007; Morgenthaler et al., 2007). These objective methods are summarized in Table 3.

Polysomnography (PSG) is an objective method that must be performed in a sleep laboratory (Miano et al., 2007). It is considered the gold standard for assessing sleep disorders, as it records multiple physiological sleep parameters, including brain waves, eye movements, leg muscle activity, heart rate, and respiratory rate. Consequently, the PSG can identify sleep disorders, including sleep-disordered breathing, nocturnal seizures, PLMS, and sleep fragmentation, that might be less reliably detected by other methods (Miano et al., 2007).

PSG has several limitations, including the cost, the need to remove the child or adolescent from their own home and bed, and attaching several electrodes to the scalp and

Table 3. Objective assessment methods for the evaluation of sleep abnormalities in children and adolescents with autism spectrum disorder (ASD)

Objective Method	Practical Method of Use	Components of the Objective Assessment
Polysomnography (Miano et al., 2007)	Both portable and laboratory method that uses electrodes applied to the face and scalp during sleep.	Total duration of sleep, sleep interruption, sleep latency, narcolepsy, periodic leg movements of sleep and breathing pattern disorders.
Actigraphy (Morgenthaler et al., 2007)	Detection of limb movement using a device strapped to the wrist or ankle to monitor movement, with data evaluation using age-adjusted algorithms.	Sleep onset, waking, sleep duration, frequency of sleep disturbance and length of sleep disturbance, circadian rhythm disorders.

face during sleep. All of this may be difficult in patients with ASD who have behavioural and sensory difficulties (Moore et al., 2017). Systematic desensitization to monitoring equipment can allow for the successful completion of this test.

The actigraph is a portable accelerometer device that can be worn on the wrist or ankle. It records limb and body movements over extended periods of time (Morgenthaler et al., 2007). The data collected by the actigraph is analyzed by computer software that incorporates age-based algorithms. The actigraph measures muscle activity to determine if an individual is awake or asleep at a given time. It also measures several sleep variables, including time of sleep onset, total sleep time, morning waking time, and the frequency of nighttime waking. Results should be matched with simultaneously maintained sleep logs.

The use of actigraphy in children and adolescents with ASD has proved effective with minimal data loss (Morgenthaler et al., 2007). The limitations associated with actigraphs include cost, potential malfunction, the small size of the device (similar to a wristwatch) subjecting it to being lost or damaged, or the inability of the patient to tolerate the device, and the lack of standardization of the hardware, software and scoring algorithms (Wiggs & Stores, 2004b). A further significant limitation of actigraphy is that it evaluates limb movement, thus possibly underestimating sleep onset latency if the child or adolescent remains awake but is physically inactive.

3. Treatment of Sleep Disorders in Children and Adolescents with ASD

Treatment approaches vary depending on the particular sleep problem. For insomnia, treatment usually involves behavioural interventions, lifestyle modifications, and pharmacological treatments. Patients with obstructive sleep apnea should be referred to otolaryngology for further treatment that is beyond the scope of this paper.

In 2017, Cuomo and colleagues performed a systematic review of the literature and meta-analysis of controlled clinical studies on the effectiveness of sleep-based interventions for children with ASD (Cuomo et al., 2017a). This meta-analysis identified eight review publications for five treatment groups: (1) pharmacological treatment; (2) melatonin treatment; (3) psychological and behavioural therapy; (4) parent education and training; and (5) complementary and alternative therapies. The authors of this recent review used the Effective Public Health Practice Project Quality Assessment Tool to rate the quality of each study and concluded that further and better quality research is needed on the treatment of sleep disorders in children and adolescents in ASD, including better designed controlled clinical studies (Armijo-Olivo et al., 2012). The secondary aim of the meta-analysis was to synthesize the study finding and to provide a reference table for clinicians with initial treatment advice for families who observe sleep problems in a child with ASD.

There remains a lack of recent evidence-based guidelines specifically for the management of sleep disorders in children and adolescents with ASD owing to the lack of controlled clinical studies.

A. Behavioural Therapy

Good sleep habits and behavioural interventions are recommended as first-line treatment for pediatric insomnia; however, implementing such interventions in children with ASD can be challenging. A systematic review of behavioural sleep interventions and the management of insomnia in children with a range of neurodevelopmental disorders showed that the most common behavioural interventions include the use of healthy sleep practices, reinforcement, graduated extinction, and faded bedtime (Rigney et al., 2018). All studies reported at least one behavioural

treatment component as effective, but no conclusions were made for specific behavioural interventions in children and adolescents with ASD (Rigney et al., 2018). Commonly used behavioural interventions are listed in Table 4. Behavioural parent training (BPT) was assessed as part of a small randomized study in children with ASD and sleep disturbances. In this eight-week study, sleep was assessed subjectively by parent reporting and objectively by actigraphy. Sleep outcome by parent report improved significantly in the BPT group compared with the non-BPT group, but the benefit was not seen on actigraphy. The authors of this study concluded that parent training to improve sleep in children with ASD requires further large-scale controlled studies (Johnson et al., 2013)

Currently, no firm evidence-based conclusions can be drawn regarding behavioural treatment protocols for children with ASD (Turner & Johnson, 2013; Vriend, Corkum, Moon, & Smith, 2011).

B. Pharmacological Treatment

In an analysis of 1,518 children aged 4 to 10 years enrolled in the Autism Speaks Autism Treatment Network Registry, Malow and colleagues report that medications for sleep were prescribed in 46% who had been diagnosed with a sleep disorder (Malow et al., 2016). Unfortunately, medications can have a deleterious effect on children's daytime behaviour and quality of life. Before starting a new medication, it is important to consider the following (Bruni et al., 2018):

- Review medications, prescription and over-the-counter, that a child may be taking. Abrupt discontinuation of sleep medications should be avoided.
- Proper choice of sleep-enhancing medications. As there is a lack of sufficient scientific evidence for sleep-enhancing medications, the choice should be made based on the main sleep complaint and any associated symptoms.
- Age of the child and clinical history with associated medical conditions
- Treatment goals. These should be established with parents and should be realistic and measurable. Potential side effects, such as daytime sedation and tolerance, should be discussed.

The following is a summary of the evidence for insomnia medications commonly used in this patient population. Further details on use, dosing and adverse effects are summarized elsewhere (e.g., Blackmer & Feinstein, 2016; Elbe et al., 2018).

i) Melatonin

Melatonin is an indolamine secreted by the pineal gland that has a key role in regulating circadian rhythm. In 2015, the European Pediatric Neurology Society convened a consensus meeting and established treatment guidelines (Bruni et al., 2015). The consensus panel agreed that based on best evidence, melatonin treatment reduced sleep onset insomnia and improved delayed sleep phase syndrome. As a sleep inductor, doses between 1-5 mg can be used 30 minutes before bedtime. For delayed sleep phase syndrome doses between 0.2-0.5 mg were most effective when given 6 to 8 hours before the desired sleep time. Melatonin decreased sleep onset latency and increased total sleep time but did not decrease nighttime wakening. The panel did not identify any serious adverse effects arising from melatonin treatment.

A recent meta-analysis found strong supporting evidence for the efficacy of supplemental melatonin, including the melatonin receptor agonist, ramelteon 4-8 mg, but limited evidence for the use of other pharmacological treatments used for sleep disorders in children with ASD (Cuomo et al., 2017a). Based on findings using study questionnaires, melatonin treatment in children with ASD was found to be more efficacious and safer than sedative and hypnotic drugs. Dual therapy for insomnia in ASD with the use of melatonin and behavioural techniques is also gaining support (Miano & Ferri, 2010).

By contrast, another randomized, placebo-controlled phase III trial to assess the safety and efficacy of a range of immediate-release melatonin doses (0.5-12 mg) in treating severe sleep problems in children with neurodevelopmental disorders showed that melatonin treatment resulted in little additional sleep and no improvement in behavioural outcomes (Gringras et al., 2012).

Limitations to studies that evaluate melatonin efficacy include the small size of study cohorts, confounding factors related to co-morbid neurodevelopmental disabilities, lack of precision in distinguishing different aspects of sleep, variability in the drug doses used, the lack of long-term follow-up data, and lack of a placebo group (Cuomo et al., 2017a).

ii) Alpha 2 agonists

A case series of six children with neurodevelopmental disorders found clonidine (75-125 mcg) for severe and intractable sleep problems a valuable alternative to melatonin (Ingrassia & Turk, 2005). It was reported as effective in dealing with settling problems but had less of an impact on recurrent nighttime and early morning wakenings. An open labeled retrospective study of clonidine for the treatment of

Table 4. Behavioral interventions commonly used for Insomnia in Autism Spectrum Disorder (Turner & Johnson, 2013)

Sleep Environment
• Dark, cool, quiet, non-stimulating, electronic devices turned off
Sleep Hygiene
• Consistent bed time routine with similar bed time and wake up time
• Avoiding naps, at least 4 hours prior to bed time
• Self-soothing skills that allows child to manage night awakenings
Faded Bedtime
• Bedtime close to when child naturally falls sleep, with gradual advancement of bed time until desired bed time is met
Promoting Positive Thoughts
• Through visual stimuli and story telling
Extinction
• Planned ignoring of undesired sleep behaviors as crying and fussing
Chronotherapy
• Resetting circadian rhythm using graduated delay of bed time and wake times
Stimulus Fading
• Gradual distancing of the parent from the child's bed
Scheduled Awakenings
• To reduce fearful behaviours

insomnia, and/or hyperactivity, inattention, mood disorder, and aggressive behaviours in a cohort of 19 children with ASD showed that clonidine was effective in reducing sleep initiation latency and nighttime awakening. It was less effective in improving attention deficit hyperactivity, mood instability, and aggressiveness in this population. The side effects were largely tolerable (Ming et al., 2008). Limitations include a lack of placebo- controlled double-blind clinical trials that could provide more insight into the clinical efficacy and safety of the medication in ASD.

iii) Antipsychotics/Antidepressants/Anticonvulsants

Atypical antipsychotics, such as aripiprazole, risperidone, quetiapine, and olanzapine are used in children with neurodevelopmental disabilities with disruptive behaviours. Risperidone was the first antipsychotic to receive approval by the US Food and Drug administration for irritability in ASD. A study examining acute and long-term safety and tolerability of risperidone in children with autism reported that two problems were significantly less common in the risperidone group: difficulty falling asleep and anxiety (Aman et al., 2005). The side effect profile of these medications can be problematic and include weight gain, hyperglycemia, or hyperprolactinemia, among others. Atypical antipsychotics, in particular risperidone, should not be used solely to manage sleep disorders; however, in patients with additional problems such as irritability, aggression, and self-injurious behaviours, sleep problems may be mitigated.

Despite being commonly used in clinical practice for insomnia, only a few case reports have reported some benefit with trazodone (Parker & Hartman, 2002). An open-label study examined the efficacy and tolerability of mirtazapine (dosage range 7.5-45 mg/day) in the treatment of associated symptoms of ASD (Posey et al., 2001). Nine of the 26 participants (34.6%) were judged to be responders ('much improved' or 'very much improved' on the Clinical Global Impression-Improvement Scale) based on the improvement of a variety of symptoms, including aggression, self-injury, irritability, hyperactivity, anxiety, depression, and insomnia (Posey et al., 2001). There are no data to support the use of amitriptyline or trimipramine in children with ASD; however, amitriptyline has been used in children with neurodevelopmental disabilities in doses from 5-50 mg.

Successful use of gabapentin was reported in 23 children, 87% of whom had a neurodevelopmental disorder (Blackmer & Feinstein, 2016). Gabapentin (3-7.5 mg/kg, maximum of 15 mg/kg) 30 to 45 minutes before bedtime resulted in improved sleep in 18 of 23 (78%) children (Blackmer & Feinstein, 2016). Adverse effects, including agitated nighttime awakenings and feeling weird were reported; however, gabapentin is not frequently used as a first-line agent (Blackmer & Feinstein, 2016). It might, however, be beneficial for children and adolescents with ASD who also have comorbid restless leg syndrome symptoms or excessive periodic leg movements of sleep or nighttime seizures.

iv) Benzodiazepines

Gamma-amino butyric acid (GABA) is a major neurotransmitter in the brain. Benzodiazepines exhibit inhibitory effects through GABA receptors. In a case series of 11 children with ASD, treatment of sleep-related REM behavioural disorder was reported as successful in 75% of children with 0.5-1 mg of clonazepam (Thirumalai et al., 2002). It may be a treatment option for children with parasomnias. Limitation for the use of clonazepam include concerns about its tolerability profile, potential for drug dependence, and the lack of evidence-based data in the pediatric population.

v) Non-Benzodiazepine Sedative-Hypnotics

Non-benzodiazepine receptor agonists (Z drugs) bind preferentially to the alpha 1 subunit of GABA receptor. Few studies have been conducted in children and none in children with ASD. Pediatric studies using zolpidem up to 10 mg in ADHD associated with insomnia were ineffective and associated with significant side effects, such as dizziness and hallucinations (Blumer et al., 2009). Eszopiclone also failed to demonstrate efficacy in ADHD-related insomnia in children and adolescents. About 70% of patients in this group had adverse events, including headache, dysgeusia, and dizziness (Sangal et al., 2014). Sleep walking and complex behaviours have been reported with zaleplon overdose in a 14-year-old boy (Liskow & Pikalov, 2004). Owing to poor efficacy and a high rate of adverse reactions, these agents have limited utility in practice and should be avoided in this population unless all other options have failed. However, they may be considered for patients who are in late adolescent/early adulthood.

vi) Suvorexant

Suvorexant is a dual orexin receptor agonist that selectively binds to orexin-1 and -2 receptors, thus inactivating wakefulness. Kawabe and colleagues evaluated the tolerability, efficacy, and safety of suvorexant (20 mg/kg) in insomnia in 30 adolescents about 6 months after initiation. Of these patients, seven had ASD. Seventeen of thirty (56.7%) patients continued taking suvorexant with a significant decrease on the Clinical Global Impression-Severity Scale and overall improvement in sleep quality. This study is limited by its small number and lack of control population. Nonetheless, this study suggests that suvorexant may be considered a treatment option for adolescents with insomnia and perhaps with ASD (Kawabe et al., 2017).

vii) Iron

Iron is a cofactor for tyrosine hydroxylase, the enzyme responsible for the conversion of amino acid tyrosine to dopamine. Low serum ferritin is common in children with ASD. An 8-week open-label treatment trial with supplemental oral iron in 33 children with ASD and restless sleep reported significant improvement in sleep quality. Baseline mean ferritin was 15.72 mcg/L (4.2-39.0 mcg/L). Posttreatment mean ferritin was 28.8 mcg/L (6.6-103 mcg/L) suggesting a relationship between sleep disturbance and iron deficiency in children with ASD (Dosman et al., 2007). This study was limited by its small number and lack of controls

Another retrospective chart review demonstrated an increased incidence of PLMS (47%) in children with ASD compared with controls (8%). Median ferritin levels in ASD patients was less than 31 ng/mL and was associated with sleep fragmentation and poor sleep efficiency compared with controls.

Questions for restless sleep should be asked when poor sleep is reported in children with ASD. Parents should be asked for a family history of restless leg syndrome and hemochromatosis and patients' serum ferritin level should be monitored. If ferritin levels are less than 30-50 mcg/L, 3-5 mg/kg/day of elemental iron should be considered; however, it is to be noted that the normative range of serum ferritin concentrations differ through the pediatric literature and a definitive goal has not been established owing to a lack of robust data.

In summary, behavioural interventions should be used first-line as monotherapy and may be combined with pharmacotherapy as required. Selection of the most effective pharmacological agent requires assessment on a case by case basis depending on the presence of additional comorbidities. It is important to note that none of the above-mentioned agents are FDA-approved for children.

C. Complementary and Alternative Treatments

Some children and adolescents with ASD are managed with both pharmacologic treatments and with complementary-alternative medicine (CAM). Complementary and alternative treatments include aromatherapy, massage therapy, multivitamin supplementation, and yoga therapy (Cuomo et al., 2017b); however, there have been few published studies that have investigated the effects of either CAM treatments alone or in combination with pharmacological treatments for sleep disorders in children with ASD. One retrospective study of 115 children, adolescents and young adults with ASD, found no significant benefits from the use of CAMs (Huffman et al., 2011) Lacking scientific research, regulation on accuracy of techniques, effective dosages of substances, CAM approaches for disturbed sleep patterns are currently unestablished.

Conclusions

Sleep disorders are common in children and adolescents with ASD. The origin of sleep disturbance in these children is unclear. Disordered sleep co-occurs with autistic traits and is likely multifactorial. Recent studies have shown that sleep problems, particularly insomnia, are associated with worsening behavioural problems, particularly in preschool children. Therefore, it is important that all caregivers of children with ASD, including primary care providers, pediatric specialists, therapists, and school personal, be aware of the frequency and significance of the issues to facilitate early identification and initiation of effective treatment.

Before treatment can be started, it is important to assess sleep problems in this patient population using both subjective and objective methods to provide an individualized approach to evaluation and management with the goal to improve the quality of life of patients and their families. Treatments must be individualized, as there is no single answer. Behavioural interventions are preferred as first-line therapy for insomnia; however, such interventions may be limited by the core features of ASD, especially communication difficulties. Most medications for the treatment of insomnia in children and adolescents with ASD are used off label. The decision to initiate pharmacotherapy should be done in concert with practitioners who are familiar with managing sleep in this population, or in consultation with a clinical pharmacist who can carefully review drug-drug interactions, overlapping toxicities, and recommend doses and monitor and manage drug-disease interactions. Medications may be helpful, but their use must be carefully monitored.

Future randomized controlled studies are needed to elucidate the effectiveness of pharmacological agents that can be used in young children and to study their potential side effects and drug-drug interactions. It will further be worthwhile looking into shared genetic factors between sleep problems and autistic traits. Molecular and proteomic studies may lead to the development of novel drug targets for ASD, including specific genes or proteins associated with abnormal circadian rhythms in this patient population. Future studies should underscore bedtime routines and family regularity when evaluating children with ASD who have disturbed sleep patterns.

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Conflicts of Interest

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