Autism Spectrum Disorder and Sleep

Kyle P. Johnson, MD*, Paria Zarrinnegar, MD

KEYWORDS

• Autism • Sleep • Melatonin • Behavioral • Insomnia • Pediatric • Children

KEY POINTS

- Children with autism spectrum disorder (ASD) frequently have sleep problems, most commonly insomnia.
- Sleep problems suffered by children with ASD are associated with daytime struggles.
- Parental education and behavioral interventions are effective in ameliorating the insomnia experienced by children with ASD.
- There is growing evidence that melatonin is an effective treatment of the insomnia suffered by children with ASD.

INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disability defined by developmental deficits in 2 domains: social interaction and communication; repetitive, restricted patterns of interests, behavior, or activities (American Psychiatric Association's The Diagnostic and Statistical Manual of Mental Disorders Fifth Edition).[1] The estimated prevalence rate of ASD in the United States is now estimated to range from 1 in 59 to 1 in 40, reflecting more than a double of prevalence between 2000 to 2002 and 2010 to 2012.[2,3] ASD is thought to result from altered early brain development and circuitry formation influenced by genetics and the prenatal environment.[4,5] The disorder can be associated with genetic conditions such as Angelman syndrome, intellectual disability, and other neuropsychiatric disorders, including epilepsy, mood disorders, anxiety disorders, and attention-deficit/hyperactivity disorder (ADHD). In approximately 20% to 30% of children, ASD becomes apparent after previously acquired skills are lost, a phenomenon known as "autistic regression."[6] The cause of early developmental regression remains unclear, with recent research

This article originally appeared in *Child and Adolescent Psychiatric Clinics*, Volume 30 Issue 1, January 2021.
Division of Child & Adolescent Psychiatry, Oregon Health & Science University, Mailcode: DC-7P, 3181 Southwest Sam Jackson Park Road, Portland, OR 97239, USA
* Corresponding author.
E-mail address: johnsoky@ohsu.edu

Psychiatr Clin N Am 47 (2024) 199–212
https://doi.org/10.1016/j.psc.2023.06.013 **psych.theclinics.com**
0193-953X/24/© 2023 Elsevier Inc. All rights reserved.

Descargado para Biblioteca Medica Hospital México (bibliomexico@gmail.com) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en marzo 19, 2024. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2024. Elsevier Inc. Todos los derechos reservados.

focusing on genetic and immunologic causes.[7] The brain regions and neurotransmitter systems thought to be involved in the development of ASD also regulate sleep and wake.[8] Sleep disturbances are one of the biggest challenges faced by youth with ASD and often by extension, the family members taking care of them. Approximately 50% to 80% of children and adolescents diagnosed with ASD suffer sleep problems.[9–14] The most common sleep problems experienced by this population include struggles initiating and maintaining sleep, frequent and often prolonged night awakenings, early morning waking, and irregular-sleep wake schedules.[15] Problems initiating and maintaining sleep rank as one the most common concurrent clinical disorders and are less likely to diminish with age compared with peers who do not have ASD.[16,17]

SUBJECTIVE AND OBJECTIVE FEATURES OF SLEEP PROBLEMS IN CHILDREN AND ADOLESCENTS WITH AUTISM SPECTRUM DISORDER

The high rates of sleep disturbances experienced by children with ASD initially documented in relatively small studies have been confirmed in larger studies. Malow and colleagues[18] investigated the prevalence of sleep difficulties in 1518 children aged 4 to 10 years diagnosed with ASD and enrolled in the Autism Speaks Autism Treatment Network Registry. The investigators found that 71% of the children experienced sleep disturbances although only 30% had been diagnosed with a sleep disorder. Another large study demonstrated that sleep problems that develop in early childhood often persist into adolescence although the types of sleep problems typically change with age.[19] In this study of parent-reported sleep disturbances, the younger children experienced bedtime resistance, frequent awakenings, parasomnias, and sleep anxiety, whereas the adolescents struggled with sleep onset insomnia, short sleep duration, and daytime sleepiness.

Objectively, compared with neurotypical subjects, individuals with ASD have abnormal sleep architecture as measured by polysomnography (PSG). Anomalies observed include prolonged sleep latency, reduced total sleep time, lower sleep efficiency, reductions in both rapid eye movement (REM) sleep and non-REM sleep, and a lower number of REMs during REM density.[20–22] A more recent study demonstrates that even children with ASD not complaining of sleep problems experience poor objective sleep.[23] Children with ASD who experienced regression with loss of previously acquired abilities experienced more severe alterations than those with nonregressed ASD.[24]

NEUROBIOLOGY OF AUTISM SPECTRUM DISORDER AND SLEEP

The neurobiological factors implicated in ASD and regulating sleep and wake overlap. This intersection involves the neurotransmitters gamma-aminobutyric acid (GABA) and serotonin as well as the neurohormone melatonin. Moreover, the disrupted sleep architecture noted in individuals with ASD suggests neurobiological anomalies.

GABA, a central nervous system inhibitory neurotransmitter, is involved in a sleep-promoting system with projections from the hypothalamus to the brainstem. GABA inhibits brainstem neurons active in arousal, which in turn facilitates sleep. Children with ASD show a disruption of GABA interneurons with some demonstrating a mutation in chromosome 15q, which contains GABA genes.[25,26] The identification of an autism-susceptibility region carrying GABA-related genes suggests that altered gene expression in this region could interfere in the inhibitory function of GABA resulting in hyperarousal and insomnia.[8]

Serotonin is a wake-promoting neurotransmitter, which also inhibits REM sleep. Elevated whole blood serotonin was the first biomarker identified in patients with

Descargado para Biblioteca Medica Hospital México (bibliomexico@gmail.com) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en marzo 19, 2024. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2024. Elsevier Inc. Todos los derechos reservados.

ASD. Hyperserotonemia is present in more than 25% of children with ASD and often their first-degree relatives.[27,28] ASD studies have also demonstrated genetic variations related to serotonin transport and degradation.[29,30] Abnormal serotonin function may negatively affect sleep through effects on melatonin.

Melatonin is a hormone produced by the pineal gland and is critical in regulating sleep-wake schedules. It is suppressed by bright light and released in response to darkness. Melatonin is synthesized from serotonin by means of the enzyme acetylserotonin O-methyltransferase (ASMT).

Melke and colleagues have postulated that melatonin may influence the synaptic plasticity contributing to the ASD phenotype (2008); this is intriguing in light of the evidence of abnormal melatonin regulation in ASD. Several early studies found lower levels of melatonin in children with ASD compared with controls but recent studies have not found such abnormalities.[31–35] Variations in melatonin have been observed in parents of children with ASD.[36,37] Given low to normal levels of melatonin in individuals with ASD despite elevated blood serotonin, the precursor to melatonin, attention has turned to the gene involved in ASMT production. In fact, polymorphisms in the ASMT gene are associated with low melatonin levels in subjects with ASD and autistic-like traits in a general population.[36,38] Genetic variation in ASMT and another melatonin pathway enzyme, cytochrome P450 1A2 (CYP1A2), were identified in individuals with ASD and comorbid sleep onset delay.[39] Differences in sleep architecture measured by PSG provide further evidence of biological roots to many of the sleep problems experienced by individuals with ASD.[15]

IMPACT OF SLEEP DISORDERS ON DAYTIME BEHAVIOR AND PARENTAL STRESS

It is now clear that poor sleep in children with ASD is associated with problematic daytime behavior. Children with ASD and poor sleep quality experience higher rates of aggression, self-injury, anxiety, hyperactivity, and inattention.[40–43] In addition, core symptoms of ASD such as repetitive behaviors and difficulty in social reciprocity are increased in poorly sleeping children with ASD.[44,45] Greater variation in sleep duration and timing have been found to predict subsequent disruptive, daytime behavior.[46] In another study, sleep disturbances at baseline predicted the later development of significant anxiety.[47] Sleep disturbances in children with ASD increase parenting burden and family stress, often directly affecting the parent's own sleep.[48,49] Addressing sleep problems in children with ASD may improve not only the child's daytime behavior but also parental functioning.

ASSESSMENT

Given the high rate of sleep problems, all youth with ASD should be screened for sleep disturbances by incorporating sleep questionnaires in the assessment process. The Modified Simonds and Parraga Sleep Questionnaire and the Children's Sleep Habits Questionnaire have been validated for youth with ASD.[50] A newer clinician-rated tool, the Pediatric Sleep Clinical Global Impressions Scale, shows promise in measuring insomnia and response to treatment in ASD.[51] It is critical that the questionnaire used screen for obstructive sleep apnea (OSA). If symptoms and signs of OSA are discovered, the youth should be referred to a sleep specialist, as an overnight PSG may be indicated. Although ASD in and of itself is not a risk factor for OSA, some children with ASD have other risk factors such as obesity, hypertrophy of the adenoids and tonsils, or craniofacial abnormalities. If restless legs syndrome (RLS) or excessive movements while asleep are suspected, one should consider referral to a sleep specialist while assessing for iron deficiency, given the association between this

Descargado para Biblioteca Medica Hospital México (bibliomexico@gmail.com) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en marzo 19, 2024. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2024. Elsevier Inc. Todos los derechos reservados.

condition and RLS (see DelRosso and colleagues' article, "Restless Legs Syndrome in Children and Adolescents," in this issue). Unusual behaviors that suggest a parasomnia such as sleep terrors or sleepwalking may also warrant a referral to a sleep specialist, particularly if the behavior is potentially dangerous to the child or disturbs the sleep of family members. Nocturnal seizures must be considered when a child with ASD engages in unusual behavior when asleep given the increased risk of epilepsy in ASD.

Insomnia will be the identified sleep problem in most of the cases. The clinician must obtain a complete history regarding the sleep environment, what occurs at sleep onset, and what family and child behaviors are engaged in after sustained, middle-of-the-night awakenings. This is necessary because insomnia is so often behavioral in origin even in ASD. Although the PSG is considered the gold standard for assessing sleep, it is not indicated when assessing uncomplicated insomnia. Sleep diaries and actigraphy are useful for this purpose.

A PSG is indicated when assessing for OSA, narcolepsy, and parasomnias not improving with supportive care. The assessment of narcolepsy requires a multiple sleep latency test following a PSG. However, these procedures are often difficult for children with ASD to tolerate, given their tactile sensitivity and anxiety in unfamiliar situations.

TREATMENT

The treatment of sleep problems experienced by youth with ASD is multidimensional given the multitude of causative factors at play. Environmental and behavioral causes are particularly relevant to insomnia. Several environmental challenges negatively affect the sleep of any child, not just those with ASD, whereas others are more specific to youth with ASD, including intrinsic factors, common comorbid psychiatric and medical conditions, and side effects of medicines used to treat problematic daytime behaviors. As demonstrated in a recent systematic review and meta-analysis, evidence-based, behavioral interventions are feasible and efficacious in ASD.[52]

Behavioral Interventions

Parent education in behavioral treatments is the first-line approach to improving the insomnia so commonly experienced by children and adolescents diagnosed with ASD.[53] The behavioral interventions to treat insomnia in children with ASD are essentially the same as those used to treat other children (**Table 1**). The techniques aim to correct problematic behaviors and promote good sleep habits. Positive bedtime routines and graduated extinction have been particularly helpful in combating tantrums associated with bedtime and night awakenings in young children with ASD.[54] Evidence from case series reveals that sleep restriction with bedtime fading (making bedtime gradually earlier as sleep consolidation improves) is also a powerful intervention.[55] A visual schedule of the bedtime routine is helpful for many children (**Fig. 1**).

Significant benefit comes from educating parents regarding sleep and instructing them how to institute behavioral interventions at home. Such parent training is effective whether provided in a group format or workshop.[56,57] Several randomized-controlled trials demonstrate the efficacy of parent training in ASD.[58,59] A recent systematic review of 11 studies using behavioral sleep interventions to treat sleep problems experienced by individuals with ASD and/or intellectual disability found trainings acceptable by parents who judged them to be beneficial.[60] An advantage of this model is the individualization of treatment, because parents can pick and choose which interventions may be most effective for their child and feasible in their home.

Descargado para Biblioteca Medica Hospital México (bibliomexico@gmail.com) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en marzo 19, 2024. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2024. Elsevier Inc. Todos los derechos reservados.

Table 1
Behavioral interventions to treat insomnia in children with autism spectrum disorder

Behavioral Intervention	Brief Description of the Intervention	Areas of Impact; Special Considerations
Parent education	Teaching parents the basics of childhood sleep, sleep hygiene, how to establish consistent and sleep-inducing bedtime, and how to implement behavioral interventions	Sleep latency, child and family functioning; individual, group, or workshop format
Positive bedtime routines	Implementation of consistent series of activities that help the child with transition to sleep (ie, clean up toys, brush teeth, go potty, put pajamas on, read books, get in bed, lights off)	Bedtime difficulties, settling problems; usually combined with other techniques
Extinction (planned ignoring)	*Standard* withholding rewards (such as TV) and ignoring sleep-disruptive behavior *Graduated* gradually increasing the time before the child is attended	Settling problems; "extinction burst," a temporary increase in target behaviors, is common with standard extinction
Gradual distancing (stimulus fading)	Parent gradually increases the distance to the child	Settling problems, night waking
Sleep restriction	Reducing total sleep time to 90% of average night-time sleep while keeping a consistent schedule. Once behaviors improve, fade back total amount of sleep to age-appropriate level	Bedtime disturbance, night waking
Bedtime fading	Bedtime is moved to 30 min after average sleep time at baseline. If a child falls asleep within 15–20 min of this new bedtime for 2 consecutive nights, bedtime is moved to 30 min earlier (fading). If the child does not initiate sleep within that interval, the bedtime is moved to 15 min later the subsequent night.	Bedtime disturbances and long sleep latency; can be combined with response cost (remove the child from bed if not falling asleep within the interval, keep them awake for a specified time and then return them to bed) and positive reinforcement
Scheduled awakening	Parents wake up the child 30 min before the time he/she usually awakens spontaneously	Night waking and night terrors
Chronotherapy	Moving bedtime and rise time later and later each day until the child is sleeping on a normal schedule	Circadian rhythm sleep-wake disorder (delayed phase type)

(*continued on next page*)

Descargado para Biblioteca Medica Hospital México (bibliomexico@gmail.com) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en marzo 19, 2024. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2024. Elsevier Inc. Todos los derechos reservados.

Table 1
(*continued*)

Behavioral Intervention	Brief Description of the Intervention	Areas of Impact; Special Considerations
Bed pass	The child is given a special card good for one free trip out of their room each night or one visit from a parent. Keep the bedtime consistent but making sure the pass is close at hand. When the child uses the pass, the card is surrendered for the rest of the night and if they leave the room again that night, they are walked back to their room with no words or attention. The child can trade unused passes for a reward at the end of the week.	Night waking; useful for verbal and higher functioning patients

Descargado para Biblioteca Medica Hospital México (bibliomexico@gmail.com) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en marzo 19, 2024. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2024. Elsevier Inc. Todos los derechos reservados.

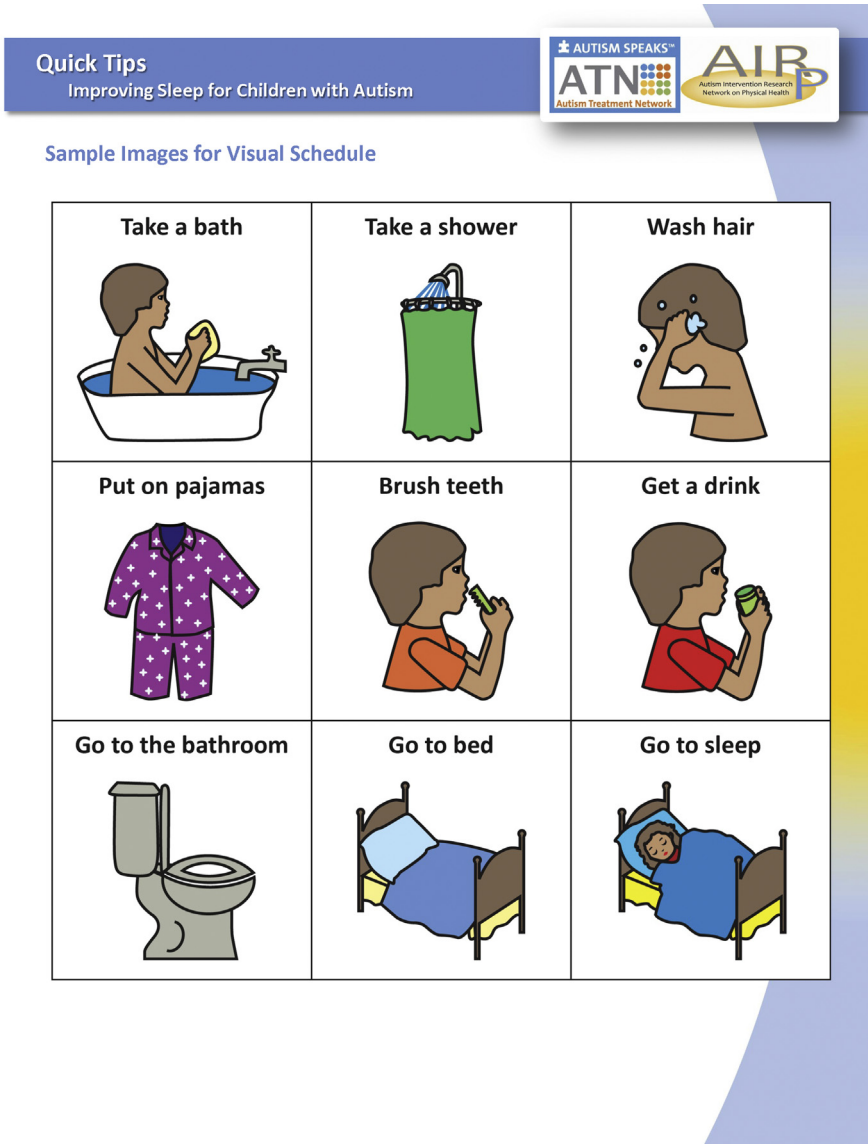

Fig. 1. Sample images for visual schedule. (*Courtesy of* Autism Treatment Network.)

Pharmacologic Interventions

In youth with ASD experiencing sleep disturbances, pharmacologic agents are often prescribed, especially when behavioral interventions have been ineffective. Medications are used to treat sleep initiation and/or maintenance insomnia resulting in longer sleep duration even though there are no Food and Drug Administration (FDA)-approved medicines for this indication in children and adolescents.[61,62] In the Autism Speaks Treatment Network Registry, medications for sleep were prescribed to 46% of 4- to 10-year-old children given a sleep diagnosis; melatonin was the most commonly used followed by alpha-agonists such as clonidine.[18]

Descargado para Biblioteca Medica Hospital México (bibliomexico@gmail.com) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en marzo 19, 2024. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2024. Elsevier Inc. Todos los derechos reservados.

The sleep disturbance must be well defined with potential causes considered before turning to medication treatment. This information and the presence or absence of comorbid conditions will inform the choice of medication used. Whenever possible, a medicine that treats the sleep disturbance while also improving the coexisting condition should be chosen with low doses initiated and titrated gradually while monitoring for side effects. This "start low and go slow" approach is important because children with autism are often sensitive to medications and have limited ability to communicate adverse effects.

A recent systematic review of pharmacologic treatments of sleep disorders in children found the evidence limited primarily to melatonin with little randomized control trial data for other drugs.[63] There is now considerable evidence that melatonin is effective in treating the insomnia often suffered by children with ASD. Melatonin is considered a nutritional supplement and is not regulated by the FDA. As a result, melatonin is readily available over the counter and relatively inexpensive. Related to sleep, melatonin has hypnotic and chronobiotic properties. When used solely as a chronobiotic, melatonin should be dosed 2 to 3 hours before the dim light melatonin onset or roughly 4 to 5 hours before habitual sleep onset time. Practically, melatonin is rarely used solely as a chronobiotic, especially for ASD. Instead, clinical trials of melatonin in ASD have dosed melatonin close to bedtime. Typically, melatonin is used as a hypnotic given about 30 to 45 minutes before desired sleep onset time.

In 2011, Rossignol and Frye published a systematic review and meta-analysis of 5 randomized, double-blind, placebo-controlled, crossover trials using melatonin to treat the insomnia experienced by children with ASD. This analysis demonstrated significant improvements in sleep-onset latency and sleep duration with melatonin treatment although night awakenings did not improve.[64] No significant adverse events were reported in these 5 trials. Following this initial evidence of efficacy, several randomized controlled trials (RCTs) have since been completed.

A multisite trial across England and Wales using immediate release melatonin (half-life of 40 minutes) demonstrated improvement in the sleep onset latency of subjects treated with melatonin compared with controls.[65] However, waking times became earlier with melatonin, negating an impact on sleep duration. As a result, the investigators recommended future trials of slow release melatonin. Cortesi and colleagues[66] studied 160 children with ASD, aged 4 to 10 years, struggling with sleep onset and sleep maintenance insomnia, randomly assigning them to 1 of 4 arms: combination of controlled-release melatonin, 3 mg, and cognitive behavioral therapy (CBT); controlled-release melatonin, 3 mg, alone; 4 sessions of CBT alone; or placebo drug treatment alone. The main outcome measures for this 12-week trial included actigraphically derived sleep latency, total sleep time, and number of awakenings, and wake after sleep onset. All active treatment groups improved, and the controlled release melatonin formulation was well tolerated with no adverse effects reported or observed.

A more recent study used pediatric-appropriate, prolonged-release melatonin formulated as easily swallowed, minitablets (PedPRM[67]; a total of 95 subjects completed the 13-week double-blind phase). Doses of PedPRM were from 2 to 5 mg/d. At the completion of 13 weeks, per sleep diaries completed by caregivers, children taking PedPRM slept on average 57.5 minutes longer compared with 9.4 minutes longer sleep in the placebo group ($P = .034$). Sleep latency also improved significantly ($P = .011$) in the PedPRM group (decreased 39.6 minutes on average compared with a decrease of 12.5 minutes in participants treated with placebo). These differences were significant as early as 3 weeks into the controlled trial. Children with and without comorbid ADHD benefited similarly to PedPRM. Headache and somnolence were more commonly reported in the PedPRM group. Daytime externalizing behaviors improved with melatonin treatment as did

Descargado para Biblioteca Medica Hospital México (bibliomexico@gmail.com) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en marzo 19, 2024. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2024. Elsevier Inc. Todos los derechos reservados.

caregivers' quality of life.[68] Compliance with the minitablet was excellent with no need to dissolve or crush the formulation. This RCT was followed by a 39-week, open-label study in which subjects took either 2 mg, 5 mg, or 10 mg doses of PedPRM.[69] The benefits of PedPRM observed in the RCT persisted, with the most common side effect being fatigue. After 2 years of treatment with PedPRM, no detrimental effects on children's growth or pubertal development was found, and the medicine was able to be discontinued without safety or withdrawal issues.[70]

Given these recent studies, melatonin is now considered a first-line treatment when a pharmacologic agent is deemed necessary. Melatonin is effective in improving insomnia and is well tolerated with limited side effects.

Although minimal data support their use, medicines beyond melatonin may be considered in the treatment of insomnia, particularly when safety is an issue. Children with insomnia comorbid with irritability, aggression, or self-injurious behavior may benefit from treatment with second-generation antipsychotics. Risperidone and aripiprazole are FDA approved for treating aggression and severe irritability in children and adolescents with ASD. Dosing these medicines in the evening or at least giving most a twice daily dose at night may treat the insomnia and disruptive daytime behaviors. Insomnia associated with a comorbid anxiety disorder or major depressive disorder may improve with treatment with a serotonin reuptake inhibitor. Alpha-agonists such as clonidine may be an option when there is comorbid ADHD or Tourette syndrome. A recent practical review of this issue suggested sedating antidepressants such as trazodone and mirtazapine as options while noting studies of safety and efficacy are needed.[71]

When patients with ASD have certain sleep disorders beyond insomnia, other medicines are options. Clonazepam and tricyclic antidepressants may be effective treatments of non-REM arousal disorders such as sleep terrors and sleep walking, although their use should be limited to situations where injury is a possibility. REM sleep behavior disorder may also respond to clonazepam. There are no FDA-approved medicines for pediatric RLS but this condition can be treated with dopaminergic agents, gabapentin, or clonidine. Given the association between iron deficiency and RLS, ferritin levels should be determined with iron supplementation prescribed if indicated. See Vijayabharathi Ekambaram and Judith Owens' article, "Medications Used for Pediatric Insomnia," in this issue.

SUMMARY

Youth diagnosed with ASD experience more sleep problems than their peers whether or not the peers have intellectual developmental disabilities. Although the most common sleep problem experienced by patients with ASD is insomnia, other sleep disturbances can also occur. Given the high prevalence of sleep problems and disorders in this population, all youth with ASD should be screened for sleep problems. Polysomnography is not indicated to assess uncomplicated insomnia but may be indicated when assessing unusual behaviors while sleeping, excessive movements in sleep, symptoms and signs that suggest OSA, and persistent daytime sleepiness. Behavioral treatments including parent training are effective in ASD. There is growing evidence for the utility of melatonin when treating insomnia refractory to behavioral interventions. There are no FDA-approved medicines to treat pediatric insomnia.

CLINICS CARE POINTS

- Most of the youth diagnosed with ASD experience significant sleep problems.

Descargado para Biblioteca Medica Hospital México (bibliomexico@gmail.com) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en marzo 19, 2024. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2024. Elsevier Inc. Todos los derechos reservados.

- Nighttime sleeping difficulties negatively affect daytime behavior and are associated with parental stress.
- All youth diagnosed with ASD should be screened for sleep problems and disorders.
- Behavioral interventions and parent training are the first line of treatment.
- Melatonin is the first-line pharmacologic agent to address insomnia in ASD, as its efficacy has been documented in multiple clinical trials.

DISCLOSURE

The authors have nothing to disclose.

REFERENCES

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th edition. Washington, DC: American Psychiatric Association; 2013.
2. Baio J, Wiggins L, Christensen DL, et al. Prevalence of autism spectrum disorder among children aged 8 years—autism and developmental disabilities monitoring network, 11 sites, United States, 2014. MMWR Surveill Summ 2018;67(6):1–23.
3. Kogan MD, Vladutiu LA, Schieve LA, et al. The prevalence of parent-reported autism spectrum disorder among US children. Pediatrics 2018;142(6): e20174161.
4. O'Reilly C, Lewis JD, Elsabbagh M. Is functional brain connectivity atypical in autism? A systematic review of EEG and MEG studies. PLoS One 2017; 12(5):1–28.
5. Muhle RA, Reed HE, Stratigos KA, et al. The emerging clinical neuroscience of autism spectrum disorder: a review. JAMA Psychiatry 2018;75(5):514–23.
6. Parr JR, Le Couteur A, Baird G, et al. Early developmental regression in autism spectrum disorder: evidence from an international multiplex sample. J Autism Dev Disord 2011;41:332–40.
7. Scott O, Shi D, Andriashek D, et al. Clinical clues for autoimmunity and neuroinflammation in patients with autistic regression. Dev Med Child Neurol 2017;59: 947–51.
8. Inui T, Kumagaya S, Myowa-Yamakoshi M. Neurodevelopmental hypothesis about the etiology of autism spectrum disorders. Front Hum Neurosci 2017; 11:354.
9. Polimeni MA, Richdale AL, Francis AJP. A survey of sleep problems in autism, Asperger's disorder and typically developing children. J Intellect Disabil Res 2005; 49(4):260–8.
10. Liu X, Hubbard JA, Fabes RA, et al. Sleep disturbances and correlates of children with autism spectrum disorders. Child Psychiatry Hum Dev 2006;37:179–91.
11. Malow BA, Marzec ML, McGrew SG, et al. Characterizing sleep in children with autism spectrum disorders: a multidimensional approach. Sleep 2006;29(12): 1563–71.
12. Richdale AL, Schreck KA. Sleep problems in autism spectrum disorders: prevalence, nature, & possible biopsychosocial aetiologies. Sleep Med Rev 2009; 13(6):403–11.
13. Fadini CC, Lamonica DA, Fett-Conte AC, et al. Influence of sleep disorders on the behavior of individuals with autism spectrum disorder. Front Hum Neurosci 2015; 9:347.

Descargado para Biblioteca Medica Hospital México (bibliomexico@gmail.com) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en marzo 19, 2024. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2024. Elsevier Inc. Todos los derechos reservados.

14. Elrod MG, Nylund CM, Susi AL, et al. Prevalence of diagnosed sleep disorders and related diagnostic and surgical procedures in children with autism spectrum disorders. J Dev Behav Pediatr 2016;37(5):377–84.
15. Buckley AW, Hirtz D, Oskoui M, et al. Practice guideline: treatment for insomnia and disrupted sleep behavior in children and adolescents with autism spectrum disorder. Neurology 2020;94(9):392–404.
16. Ming X, Brimacombe M, Chaaban J, et al. Autism spectrum disorders: concurrent clinical disorders. J Child Neurol 2008;23(1):6–13.
17. Hodge D, Carollo TM, Lewin M, et al. Sleep patterns in children with and without autism spectrum disorders: developmental comparisons. Res Dev Disabil 2014; 35:1631–8.
18. Malow BE, Katz T, Reynolds AM, et al. Sleep difficulties and medications in children with autism spectrum disorders: a registry study. Pediatrics 2016;137: S98–104.
19. Goldman SE, Richdale AL, Clemons T, Malow B A. Parental sleep concerns in autism spectrum disorders: variations from childhood to adolescence. J Autism Dev Disord 2012;42(4):531–8.
20. Lambert A, Tessier S, Chevrier E, et al. Sleep in children with high functioning autism: polysomnography, questionnaires and diaries in a non-complaining sample. Sleep Med 2013;14(suppl 1):e137–8.
21. Miano S, Bruni O, Elia M, et al. Sleep in children with autistic spectrum disorder: a questionnaire and polysomnographic study. Sleep Med 2007;9(1):64–70.
22. Goldman SE, Surdyka K, Cuevas R, et al. Defining the sleep phenotype in children with autism. Dev Neuropsychol 2009;34:560–73.
23. Lambert A, Tessier S, Rochette AC, et al. Poor sleep affects daytime functioning in typically developing and autistic children not complaining of sleep problems: a questionnaire-based and polysomnographic study. Res Autism Spectr Disord 2016;23:94–106.
24. Giannotti F, Cortesi F, Cerquiglini A, et al. Sleep in children with autism with and without regression. J Sleep Res 2011;20(2):338–47.
25. Nelson KB, Grether JK, Croen LA, et al. Neuropeptides and neurotrophins in neonatal blood of children with autism or mental retardation. Ann Neurol 2001; 49:597–606.
26. McCauley JL, Olson LM, Delahanty R, et al. A linkage disequilibrium may of the 1-Mb 15q12 GABA(A) receptor subunit cluster and association to autism. Am J Med Genet B Neuropsychiatr Genet 2004;131B(1):51–9.
27. Gabrielle S, Sacco R, Persico AM. Blood serotonin levels in autism spectrum disorder: a systematic review and meta-analysis. Eur Neuropsychopharmacol 2014; 24(6):919–29.
28. Piven J, Tsai GC, Nehme E, et al. Platelet serotonin, a possible marker for familial autism. J Autism Dev Disord 1991;21:51–9.
29. Prasad HC, Steiner JA, Sutcliffe JS, et al. Enhanced activity of human serotonin transporter variants associated with autism. Philos Trans R Soc Lond B Biol Sci 2009;364:163–73.
30. Verma D, Chakraborti B, Karmaker A, et al. Sexual dismorphic effect in the genetic association of monoamine oxidase A (MAOA) markers with autism spectrum disorder. Prog Neuropsychopharmacol Biol Psychiatry 2014;50:11–20.
31. Nir I, Meir D, Zilber N, et al. Brief report: Circadian melatonin, thyroid-stimulating hormone, prolactin, and cortisol levels in serum of young adults with autism. J Autism Dev Disord 1995;25:641–54.

Descargado para Biblioteca Medica Hospital México (bibliomexico@gmail.com) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en marzo 19, 2024. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2024. Elsevier Inc. Todos los derechos reservados.

32. Kulman G, Lissoni P, Rovelli, et al. Evidence of pineal endocrine hypofunction in autistic children. Neuro Endocrinol Lett 2000;21:31–4.
33. Tordjman S, Anderson GM, Pichard N, et al. Nocturnal excretion of 6-sulphatoxymelatonin in children and adolescents with autistic disorder. Biol Psychiatry 2005;57:134–8.
34. Goldman SE, Adkins KW, Calcutt MW, et al. Melatonin in children with autism spectrum disorders: Endogenous and pharmacokinetic profiles in relation to sleep. J Autism Dev Disord 2014;51:30–8.
35. Goldman SE, Alder ML, Burgess HJ, et al. Characterizing sleep in adolescents and adults with autism spectrum disorders. J Autism Dev Disord 2017;47:1682–95.
36. Melke J, Goubran Botros H, Chaste P, et al. Abnormal melatonin synthesis in autism spectrum disorders. Mol Psychiatry 2008;13:90–8.
37. Braam W, Ehrhart F, Maas A, et al. Low maternal melatonin level increases autism spectrum disorder risk in children. Res Dev Disabil 2018;82:79–89.
38. Jonsson L, Anckarsater H, Zettergren A, et al. Association between ASMT and autistic-like traits in children from a Swedish nationwide cohort. Psychiatr Genet 2014;24(1):21–7.
39. Veatch OJ, Pendergast JS, Allen MJ, et al. Genetic variation in melatonin pathway enzymes in children with autism spectrum disorder and comorbid sleep onset delay. J Autism Dev Disord 2015;45:100–10.
40. Goldman SE, McGrew S, Johnson KP, et al. Sleep is associated with problem behaviors in children and adolescents with autism spectrum disorders. Res Autism Spectr Disord 2011;5(3):1223–9.
41. Sikora DM, Johnson K, Clemons T, et al. The relationship between sleep problems and daytime behavior in children of different ages with autism spectrum disorders. Pediatrics 2012;130:S83–90.
42. Mazurek MO, Sohl K. Sleep and behavioral problems in children with autism spectrum disorder. J Autism Dev Disord 2016;46(6):1906–15.
43. Johnson CR, Smith T, DeMand A, et al. Exploring sleep quality of young children with autism spectrum disorder and disruptive behaviors. Sleep Med 2018;44:61–6.
44. Gabriels RL, Cuccaro ML, Hill DE, et al. Repetitive behaviors in autism: relationships with associated clinical features. Res Dev Disabil 2005;26(2):169–81.
45. Schreck KA, Mulick JA, Smith AF. Sleep problems as possible predictors of intensified symptoms of autism. Res Dev Disabil 2004;25(1):57–66.
46. Cohen S, Fulcher BD, Rajaratnam SMW, et al. Sleep patterns predictive of daytime challenging behavior in individuals with low-functioning autism. Autism Res 2018;11(2):391–403.
47. May T, Cornish K, Conduit R, et al. Sleep in high-functioning children with autism: longitudinal developmental change and associations with behavioral problems. Behav Sleep Med 2015;13(1):2–18.
48. Meltzer LJ. Brief report: sleep in parents of children with autism spectrum disorders. J Pediatr Psychol 2008;33(4):380–6.
49. Levin A, Scher A. Sleep problems in young children with autism spectrum disorders: a study of parenting stress, mothers' sleep-related cognitions, and bedtime behaviors. CNS Neurosci Ther 2016;22:921–7.
50. Johnson CR, Turner KS, Foldes EL, et al. Comparison of sleep questionnaires in the assessment of sleep disturbances in children with autism spectrum disorders. Sleep Med 2012;13:795–801.

Descargado para Biblioteca Medica Hospital México (bibliomexico@gmail.com) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en marzo 19, 2024. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2024. Elsevier Inc. Todos los derechos reservados.

51. Malow BA, Connolly HV, Weiss SK, et al. The Pediatric Sleep Clinical Global Impressions Scale – a new tool to measure pediatric insomnia in autism spectrum disorders. J Dev Behav Pediatr 2016;37(5):370–6.
52. Keogh S, Bridle C, Siriwardena NA, et al. Effectiveness of non-pharmacological interventions for insomnia in children with autism spectrum disorder: a systematic review and meta-analysis. PLoS One 2019;14(8):e0221428.
53. Malow BA, Byars K, Johnson K, et al. A practice pathway for the identification, evaluation, and management of insomnia in children and adolescents with autism spectrum disorders. Pediatrics 2012;130(Suppl 2):S106–24.
54. Knight RM, Johnson CM. Using a behavioral treatment package for sleep problems in children with autism spectrum disorders. Child Fam Behav Ther 2014;36:204–21.
55. Moon E, Corkhum P, Smith I. A case series evaluation of a behavioral sleep intervention for three children with autism and primary insomnia. J Pediatr Psychol 2011;36:47–54.
56. Reed H, McGrew S, Artibee K, et al. Parent-based sleep education workshops in autism. J Child Neurol 2009;24:936–45.
57. Malow BA, Adkins KW, Reynolds A, et al. Parent-based sleep education for children with autism spectrum disorders. J Autism Dev Disord 2014;44:216–28.
58. Johnson CR, Turner KS, Foldes E, et al. Behavioral parent training to address sleep disturbances in young children with autism spectrum disorder: a pilot trial. Sleep Med 2013;14:994–1004.
59. Papadopoulos N, Sciberras E, Hiscock H, et al. The efficacy of a brief behavioral sleep intervention in school-aged children with ADHD and comorbid autism spectrum disorder. J Atten Disord 2019;23(4):341–50.
60. Kirkpatrick B, Louw JS, Leader G. Efficacy of parent training incorporated in behavioral sleep interventions for children with autism spectrum disorder and/or intellectual disabilities: a systematic review. Sleep Med 2019;53:141–52.
61. Mindell JA, Emslie G, Blumer J, et al. Pharmacological management of insomnia in children and adolescents: Consensus statement. Pediatrics 2006;117:e1223–32.
62. Hollway JA, Aman MG. Pharmacological treatment of sleep disturbance in developmental disabilities: a review of the literature. Res Dev Disabil 2011;32:939–62.
63. McDonagh MS, Holmes R, Hsu F. Pharmacologic treatments for sleep disorders in children: a systematic review. J Child Neurol 2019;34(5):237–47.
64. Rossignol DA, Frye RE. Melatonin in autism spectrum disorders: a systematic review and meta-analysis. Dev Med Child Neurol 2011;53(9):783–92.
65. Gringras P, Gamble C, Jones AP, et al. Melatonin for sleep problems in children with neurodevelopmental disorders: randomized double masked placebo controlled trial. BMJ 2012;345:e6664.
66. Cortesi F, Giannotti F, Sebastiani T, et al. Controlled-release melatonin, singly or combined with cognitive behavioural therapy, for persistent insomnia in children with autism spectrum disorders: a randomized placebo-controlled trial. J Sleep Res 2012;21(6):700–9.
67. 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(11):948–57.
68. Schroder CM, Malow BA, Athanasios M, et al. Pediatric prolonged-release melatonin for sleep in children with autism spectrum disorder: impact on child behavior and caregivers' quality of life. J Autism Dev Disord 2019;49:3218–30.

Descargado para Biblioteca Medica Hospital México (bibliomexico@gmail.com) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en marzo 19, 2024. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2024. Elsevier Inc. Todos los derechos reservados.

69. Maras A, Schroder CM, Malow BA, et al. Long-term efficacy and safety of pediatric prolonged-release melatonin for insomnia in children with autism spectrum disorder. J Child Adolesc Psychopharmacol 2018;28(10):699–710.
70. 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 2020. https://doi.org/10.1016/j.jaac.2019.12.007.
71. 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(5):489–508.

Descargado para Biblioteca Medica Hospital México (bibliomexico@gmail.com) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en marzo 19, 2024. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2024. Elsevier Inc. Todos los derechos reservados.