

# Sleep and Autism Spectrum Disorders

Ann M. Reynolds, MD<sup>a,\*</sup>, Beth A. Malow, MD, MS<sup>b</sup>

## KEYWORDS

- Autism spectrum disorders • Sleep • Neurodevelopment
- Quality of life

Autism spectrum disorders (ASD) are neurodevelopmental disorders characterized by dysfunction in social interaction and communication, as well as the presence of restricted interests or repetitive behaviors. ASD include autistic disorder, Asperger syndrome, and pervasive developmental disorder, not otherwise specified. Sleep problems are common in children with ASD and have a significant effect on the quality of life of children with ASD and their families.

## NEUROBIOLOGY OF SLEEP AND WAKEFULNESS IN CHILDREN WITH ASD

Although a detailed examination of neurobiological alterations in the regulation of the sleep-wake cycle in children with ASD compared with that in typically developing children is beyond the scope of this review, some discussion of potential factors that may be related to abnormal sleep patterns in these children is warranted. Several neurotransmitters involved in these systems have also been implicated in the cause of ASD and include  $\gamma$ -aminobutyric acid (GABA), serotonin, and melatonin. In autism, GABAergic interneurons seem to be disrupted<sup>1</sup> and a genetic susceptibility region has been identified on chromosome 15q that contains GABA-related genes.<sup>2</sup> Abnormal expression of GABA may interfere with its inhibitory function, which may in turn interfere with sleep. Melatonin, a sleep-promoting substance that is inhibited by light and released by the pineal gland,<sup>3</sup> is synthesized from serotonin.<sup>4</sup> There are reports of abnormal platelet serotonin levels in children with autism.<sup>5</sup> The relationship between hyperserotonemia and sleep requires further study<sup>6</sup>; however, melatonin secretion has also been noted to be low in individuals with ASD,<sup>7-10</sup> and in one study, the level of the major metabolite of melatonin (6-sulfoxy melatonin) was directly related to the level of deep sleep in children with ASD.<sup>11</sup> Jonsson and colleagues<sup>12</sup> found mutations in regulatory regions in 3 genes in the melatonin pathway: acetylserotonin-O-methyltransferase (ASMT), melatonin receptor 1A, and melatonin receptor

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<sup>a</sup> Department of Pediatrics, The Children's Hospital, University of Colorado Denver School of Medicine, 13123 East 16th Avenue, B-140, Aurora, CO 80045, USA

<sup>b</sup> Department of Neurology, Vanderbilt University Medical Center, 1161 21st Avenue South, Room A-0106 MCN, Nashville, TN 37232-2551, USA

\* Corresponding author.

E-mail address: [reynolds.ann@tchden.org](mailto:reynolds.ann@tchden.org)

1B in children with ASD, whereas Cai and colleagues<sup>13</sup> found a higher rate of abnormalities in ASMT in children with ASD compared with controls. Melke and colleagues<sup>8</sup> also found ASMT polymorphisms and lower levels of ASMT activity in children with ASD. In contrast, Toma and colleagues<sup>14</sup> examined ASMT variants in Finnish, Italian, and multiplex European families and found no differences from controls. Nonetheless, these findings are provocative and suggest that ASMT variability contributes to abnormalities in the synthesis of serotonin to melatonin. Treatment with melatonin has also been found to be helpful in treating insomnia in children with ASD (see later discussion). Other genes worthy of study in children with autism and insomnia include clock genes that regulate sleep phase (eg, *Per 3* is associated with delayed sleep phase) or sleep duration (eg, *BMAL* and *CRY* are associated with short sleep duration); however, the function of these genes on sleep is still being explored.<sup>15</sup> It is expected that a better understanding of these genetic variations and their effects on sleep will lead to better treatments in the future.

### PREVALENCE OF SLEEP PROBLEMS IN ASD

Sleep problems are common in children with ASD, with prevalence rates of approximately 50% to 80% compared with 9% to 50% in children with typical development.<sup>16–19</sup> Children with ASDs are also reported to have sleep problems more frequently than children with other developmental disabilities.<sup>20,21</sup> Although children with developmental disorders in general have a high rate of sleep problems, children with autism differ within that group. Although lower cognitive level and younger age are associated with the presence of higher rates of sleep problems in other developmental disorders, these associations are not necessarily seen in ASD.<sup>17,22,23</sup> Cognitive level and age do not always predict severity of sleep problems in ASD because children with high-functioning autism and Asperger syndrome have a high rate of sleep disturbance as well.<sup>24</sup> In one series, parents of younger children (<8 years) reported more severe sleep concerns than parents of older children.<sup>25</sup> However, a larger series comparing children younger and older than 8 years found no age differences, with the exception that behavioral sleep problems, including limit-setting sleep disorder and sleep-onset association disorder, were more common in the younger group. These discrepancies may reflect differences in methodology and the heterogeneity in this population.

### EFFECTS OF SLEEP PROBLEMS IN CHILDREN WITH ASD

Sleep disturbances may contribute to stress in families of children with ASD and developmental disabilities. Parents of children with ASD who report sleep problems in their children also report more frequent daily stress and more intense hassles.<sup>26</sup> Quine<sup>27</sup> found a correlation between sleep problems in children with developmental disorders and maternal stress and parental sleep disruption. Sleep problems may worsen daytime behavior in individuals with developmental disabilities<sup>28</sup> and in children with epilepsy.<sup>29</sup> Behavioral issues such as inattention and hyperactivity may be worsened by the presence of sleep disorders such as sleep disordered breathing.<sup>30,31</sup> In ASD, short sleep duration has been associated with higher rates of stereotypic behavior, as well as higher overall autism severity scores and social skills deficits.<sup>32</sup> Sleep problems have been associated with increased repetitive behaviors and need for sameness on the Repetitive Behavior Scale<sup>33</sup>; however, the relationship may also have been moderated by level of cognitive ability in that particular study. It is critical to identify and address sleep problems in children with ASD because of the effect on health and quality of life in both the children and their parents.

## TYPES OF SLEEP DISORDERS IN CHILDREN WITH ASD

### *Insomnia*

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Symptoms of insomnia, defined as difficulty initiating or maintaining sleep, are the major sleep concerns reported by parents of children with ASD. Questionnaires and sleep diaries completed by parents have shown that children with ASD are more likely to exhibit insomnia with prolonged sleep latency (time to fall asleep), bedtime resistance, decreased sleep efficiency (decreased time asleep in relation to time in bed), decreased sleep duration and continuity, and increased awakenings.<sup>16,17,22,34</sup> Overall, sleep-onset insomnia (difficulty falling asleep) is more prevalent, compared with sleep maintenance insomnia (difficulty staying asleep),<sup>17,34</sup> although children with ASD frequently experience aspects of both.

Insomnia is a symptom with many causes, and the causes of insomnia in ASD are multifactorial. They include neurobiological factors such as aberrations in neurotransmitter systems that promote sleep and establish a regular sleep-wake cycle (eg, melatonin) and medical disorders that disrupt sleep continuity (eg, neurologic conditions such as epilepsy, gastrointestinal disorders such as reflux, and primary sleep disorders such as sleep apnea). Psychiatric comorbidities, including anxiety/depression, attention-deficit/hyperactivity disorder (ADHD), and obsessive/repetitive behavior, can also contribute to insomnia and may also be exacerbated by insomnia. Medications used to treat seizures and psychiatric conditions can also disrupt sleep. The core behavioral deficits associated with ASD may also impede the establishment of sound bedtime behaviors and routines. For example, children with ASD may have difficulty with emotional regulation (eg, ability to calm self) or transitioning from preferred or stimulating activities to sleep. Children with ASD can also perseverate on an activity or thought that can interfere with settling for sleep. Because of deficits in communication skills, children with ASD may not readily understand the expectations of parents related to going to bed and falling asleep. Sorting out the cause of insomnia in children with ASD can be challenging, especially because multiple issues may be contributing to the sleep problems simultaneously.

### *Sleep Disordered Breathing*

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Sleep disordered breathing encompasses disorders related to airway obstruction and includes obstructive sleep apnea (OSA). Although not necessarily more common in autism, sleep disordered breathing is common in the general pediatric population and can adversely affect daytime behavior, contributing to sleepiness or ADHD symptoms, with improvement after adenotonsillectomy.<sup>31,35,36</sup> Hypotonia, which can be seen in children with ASD and other developmental disorders, can also contribute to sleep disordered breathing. Therefore, it is important to recognize sleep disordered breathing in this population. In one report, treatment of OSA in a child with ASD improved daytime behaviors.<sup>37</sup>

### *Parasomnias*

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#### ***Non-rapid eye movement arousal disorders***

The non-rapid eye movement (NREM) arousal disorders, such as night terrors, sleep walking, and confusional arousals, usually occur in the first half of the night and during deeper levels of NREM (ie, deep, slow wave, or  $\delta$ ) sleep. Although they have not been extensively studied in children with ASD, some (but not all) studies report more parasomnias in individuals with ASD than in comparison groups.<sup>20,24,25,38</sup>

### ***Rapid eye movement–associated sleep abnormalities***

In one study that performed 1 night of polysomnography (PSG), rapid eye movement (REM) sleep percentage was noted to be lower in children with ASD compared with children with typical development and children with developmental disorders, 14.5% versus 22.6% and 25% respectively ( $P < .001$ ).<sup>39</sup> Another group of investigators found that REM sleep percentage was lower on night 1 but not night 2 of PSG, with the difference between nights attributable to a first-night effect (sleep is more disrupted on the first night in the sleep laboratory than on subsequent nights).<sup>8</sup> The significance of these potential differences in REM percentage is not fully understood, but may reflect underlying central nervous system dysregulation in these children.

REM sleep behavior disorder (RBD), in which individuals act out their dreams because of the absence of the normal physiologic generalized muscle paralysis during REM sleep, has been reported in one case series of children with ASD who were studied with PSG.<sup>40</sup> However, a larger polysomnographic study that excluded children on psychotropic medication did not document REM sleep without atonia or RBD.<sup>23</sup> REM sleep behavior disorder can occur in association with psychotropic medications that affect REM sleep, such as the selective serotonin reuptake inhibitors,<sup>41</sup> which are frequently used in children with ASD.

### ***Sleep-related Movement Disorders***

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#### ***Rhythmical movement disorder***

Rhythmical movement disorder is characterized by repetitive motion of the head (including head banging), trunk, or limbs, usually during the transition from wakefulness to sleep.<sup>42</sup> It may also arise during sustained sleep. Although the condition most often affects infants and toddlers with typical development in a transient and self-limited fashion, it may be more persistent and increased in intensity in children with autism and other developmental disabilities. Padding the sleeping environment can be helpful.

**Restless legs syndrome/periodic limb movements in sleep/periodic limb movement disorder** Restless legs syndrome (RLS) is a sensorimotor disorder that involves an urge to move the legs and that typically occurs at bedtime, is worse at rest, and is relieved by movement. An accompanying uncomfortable sensory component or dysesthesias in the lower extremities is common and may be expressed as growing pains. Periodic limb movements in sleep (PLMS) are defined by repetitive stereotypic movements of the limbs during sleep. Periodic limb movement disorder (PLMD) includes both repetitive stereotypic movements but also is associated with insomnia or daytime sleepiness. Although most patients with PLMD do not report symptoms of RLS, approximately 63% to 74% of pediatric patients with RLS have PLMS.<sup>43</sup>

Diagnosing RLS is difficult even in typically developing children less than 5 years of age, because of their inability to fully communicate symptoms.<sup>43</sup> Because difficulty communicating is a core feature of ASD, the diagnosis of RLS is even more challenging in children with ASD. Also, because PLMS on PSG may be helpful in corroborating the diagnosis of RLS in children who are nonverbal or who do not meet classic criteria,<sup>43</sup> making a diagnosis in children with ASD is further complicated because they are often unable to tolerate PSG because of tactile sensitivities or anxiety in novel situations.

### **ADDITIONAL CONSIDERATIONS**

#### ***Medical and Psychiatric Issues***

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Insomnia may result from coexisting medical conditions that disrupt sleep. Addressing medical issues that have an effect on sleep is paramount to successful treatment of

sleep disorders. Co-occurring disorders that cause pain or discomfort must be addressed; these include, but are not limited to, reflux esophagitis, constipation, dental issues, reactive airway disease, eczema, or oversensitivity to the environment (discomfort caused by diaper or pajamas). For example, if a child has severe eczema accompanied by pruritus and is uncomfortable at night, then sleep hygiene is unlikely to be successful until the eczema is addressed. Identifying these issues may be particularly challenging in children with ASD who often have difficulty communicating pain or discomfort.

Potential causes of sleep-onset and maintenance insomnia in children with ASD include primary sleep disorders such as sleep disordered breathing and restless leg syndrome. One potential risk factor for sleep disorders is nutritional deficiency, which is common in children with ASD and often related to issues such as severely restricted diets, food neophobia, and mealtime rituals<sup>32,44</sup>; as many as 70% to 90% of children with ASD have atypical feeding behaviors.<sup>45–48</sup> In particular, both RLS and PLMD are associated with iron deficiency; specifically, a serum ferritin level of less than 50 ng/ml.<sup>43,49</sup> There is 1 small study that reported a high rate of iron deficiency in children with ASD,<sup>50</sup> and another small study that reported low ferritin, a marker of iron deficiency, in children with ASD who also had restless sleep.<sup>49</sup> Both the ferritin levels and restless sleep responded to iron treatment in that small, open-label study.<sup>49</sup>

Psychiatric conditions such as ADHD, anxiety, or depression can interfere with sleep, as can the psychotropic medications often used to treat these conditions. Depression may be manifested by early morning waking, and bipolar disorder by decreased need for sleep. Anxiety, which is particularly common in children with Asperger syndrome, may lead to difficulty falling asleep alone, obsessive-compulsive disorder may result in prolonged sleep latency caused by excessive bedtime rituals, and sensory hypersensitivities (eg, to extraneous noises) may be an unrecognized cause of difficulty falling asleep. Coexisting epilepsy or its treatment may also disrupt sleep and, if there is a concern for sleep-related seizures, referral for PSG with electroencephalogram may be appropriate.<sup>51</sup>

## EVALUATION AND TREATMENT OF SLEEP DISORDERS IN ASD

As with any child, it is important to take a comprehensive sleep history and refer for appropriate work-up as indicated. Sleep problems in children with ASD may be overlooked because daytime behavioral issues often take precedence. The sleep history should include bedtime, waking time, napping during the day, and any waking during the night, with estimated durations and associated behaviors. Daytime functioning should be assessed, including hyperactivity as well as sleepiness, because daytime sleepiness may manifest as hyperactivity in children. Parents should be encouraged to keep a sleep diary to assess sleep latency, total sleep time, night waking, and response to treatment. A sleep questionnaire, such as the Children's Sleep Habits Questionnaire,<sup>52</sup> is a useful adjunctive tool to assess multiple domains of sleep problems including sleep-related breathing disorders, sleep anxiety, bedtime resistance, and daytime sleepiness. The Family Inventory of Sleep Habits (FISH) is a parentally completed instrument that provides a quantitative measure of sleep habits, including bedtime routine, sleep environment, and parental interactions.<sup>53</sup> A behavioral rating scale such as the Child Behavior Checklist<sup>54</sup> can screen other behavioral domains including anxiety, aggression, and hyperactivity that may affect sleep. When appropriate, a psychiatric evaluation to assess for bipolar disorder, depression, or anxiety disorder should be obtained, because all of these conditions can affect sleep.

The presence of symptoms of and risk factors for treatable primary sleep disorders such as sleep-related breathing disorders, RLS, seizures, or narcolepsy should be assessed. Although PSG is the gold standard for measuring sleep in children with autism, including the detection of sleep apnea, seizures, interictal epileptiform discharges, parasomnias, and periodic limb movements, it does have limitations in terms of child tolerance, timely availability, and expense. However, desensitization therapy before PSG can work well for many children with ASD. Actigraphy, a methodology that measures sleep and wake patterns based on limb movement, represents an alternative to PSG for documenting sleep patterns in children with autism. It is especially helpful in insomnia. Actigraphy is performed in the child's home environment, and may be especially helpful in those with tactile sensitivities or anxiety in novel environments such as a hospital sleep laboratory.

Addressing sleep issues in children with ASD is a priority of the Autism Treatment Network (ATN), which is a group of 17 sites across the United States and Canada that have been funded by Autism Speaks to address medical conditions in children with ASD. The ATN is currently developing an algorithm and a behavioral sleep medicine toolkit for the evaluation and treatment of insomnia in children with ASD. The algorithm emphasizes screening for sleep problems in children with ASD, followed by identification and treatment of associated medical comorbidities that may affect sleep (**Box 1** and **Fig. 1**). Implementation of sleep education and behavioral strategies are then considered the first-line treatment.

### TREATMENT OF INSOMNIA IN ASD

Once treatable medical and psychiatric disorders are addressed, the treatment of insomnia in children with ASD should include an approach that includes attention to the sleep environment, good sleep hygiene, establishment of a bedtime routine, and other educational and behavioral interventions. When a family is unable to implement these educational and behavioral interventions, or these interventions are not successful, consultation with a sleep specialist may be warranted. In these cases,

#### Box 1

##### Causes of sleep disturbance in autism

Poor sleep habits

Hypersensitivity to environmental stimuli

Hyperarousal/difficulty with self regulation

Medical concerns that may cause pain, discomfort, or sleep disruption (eg, constipation, gastroesophageal reflux, eczema, tooth pain, coughing/asthma)

Repetitive thoughts or behaviors that interfere with settling

Inability to benefit from communication/social cues regarding sleep

Co-occurring psychiatric conditions (eg, anxiety, depression)

Psychotropic medications

Coexisting epilepsy

OSA

RLS/periodic limb movements of sleep

Circadian rhythm abnormalities

**Screening Checklist for Medical Comorbidities Associated with Sleep Problems**  
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**Gastrointestinal**

1. Does your child have a history of reflux?  Yes  No  
If yes, when did it resolve? \_\_\_\_\_
2. Are there any ongoing symptoms?  Yes  No  
If yes, list: \_\_\_\_\_
3. Does your child have constipation?  Yes  No  
If yes, is it controlled?  Yes  No  
What medication(s) is used for control? \_\_\_\_\_
4. Does your child have abdominal pain?  Yes  No
5. Does abdominal pain occur at night?  Yes  No  
How often does this occur? \_\_\_\_\_

**Seizures and Other Nighttime Events**

1. Does your child have seizures?  Yes  No  
If yes, does your child have seizures that happen multiple times a night?  Yes  No
2. Does our child have unusual events (behaviors or movements) during the night?  Yes  No  
If yes, is the event similar every time (suggests seizure)?  Yes  No

**Sleep Disordered Breathing**

1. Does your child snore/breathe loudly?  Yes  No
2. Does your child gasp for breath or stop breathing (if no, child may still have sleep disordered breathing)  Yes  No
3. Does your child have allergies/nasal congestion?  Yes  No

**Asthma/Sinusitis**

1. Does your child cough at night?  Yes  No

**Pain/Itching/Discomfort**

1. Does your child see a dentist regularly?  Yes  No
2. Could your child have any tooth pain?  Yes  No
3. Does your child have eczema?  Yes  No  
If yes, is it currently well controlled?  
What medication is used for this? \_\_\_\_\_  
When is this medication used (i.e. daily, as needed?) \_\_\_\_\_  
Do you think that the eczema causes your child to be itchy or have pain?  Yes  No
4. Could your child be hungry at night?  Yes  No
5. Is your child overly sensitive to light, sounds, or textures of clothing?
6. Can you think of anything that may be causing your child pain or discomfort?  Yes  No  
If yes, explain: \_\_\_\_\_

**Nutrition**

1. Does your child eat at least 1 – 2 ounces of meat per day?  Yes  No
2. If not, does your child take a multivitamin with iron?  Yes  No  
How often? \_\_\_\_\_

**Restless Sleep**

1. Does your child have restless sleep?  Yes  No
2. Does your child have leg pains/"growing pains"?  Yes  No
3. Does your child experience frequent leg movements during sleep or complain of unusual feelings involving the legs when in bed?

**Medication**

1. Is your child on medication?  Yes  No  
What is the name of the medication? \_\_\_\_\_

**Physical Exam**

1. Does child have large tonsils?  Yes  No
2. Is child hypotonic?  Yes  No
3. Does child have nasal congestion or signs of allergic rhinitis?  Yes  No
4. Dental issues?  Yes  No
5. Wheezing?  Yes  No
6. Significant eczema/dry itchy skin?  Yes  No

**Fig. 1.** Screening checklist for medical comorbidities associated with sleep problems. This checklist was developed by the Autism Treatment Network to screen for medical issues that might have a negative effect on sleep. Intended for use by clinicians when interviewing families. (Courtesy of Ann M. Reynolds, MD and Beth A. Malow, MD.)

melatonin or other medications may be effective in promoting sleep and may sometimes allow for the successful implementation of educational/behavioral interventions.

### ***Good Sleep Practices and Sleep Education***

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Despite parents of children with ASD facing many stressors and multiple priorities, a sleep education program is considered an important component for treatment of insomnia in children with ASD. Healthy sleep practices (sleep hygiene) can be divided into the following categories: daytime habits, evening habits, sleep environment, and bedtime routines. Daytime habits should include adequate exercise and exposure to light, limiting caffeine, and limiting naps. Evening habits should include decreasing stimulation, decreasing light, decreasing exposure to electronics, and a good bedtime routine. The sleep environment should be cool with minimal light and sound. Children with ASD may be hypersensitive to stimuli in their environment such as light and sound. A continual noise machine may be helpful for some children. Textures can also present a challenge, such as pajamas, sheets, or diapers. Children with ASD may respond more favorably to deep pressure than a light touch. A study of use of a weighted blanket is underway in England (Lucy Wiggs, personal communication, November 2010). A bedtime routine should include a series of bedtime tasks or activities that occur at the same time and place every night. The routine should be simple enough to occur nightly. Clinicians and families may benefit from completing a sleep habits checklist that identifies potential areas of concern that can be targeted for improvement.<sup>55</sup> For a more in-depth review of sleep hygiene in children with neurodevelopmental disabilities please see Jan and colleagues.<sup>56</sup>

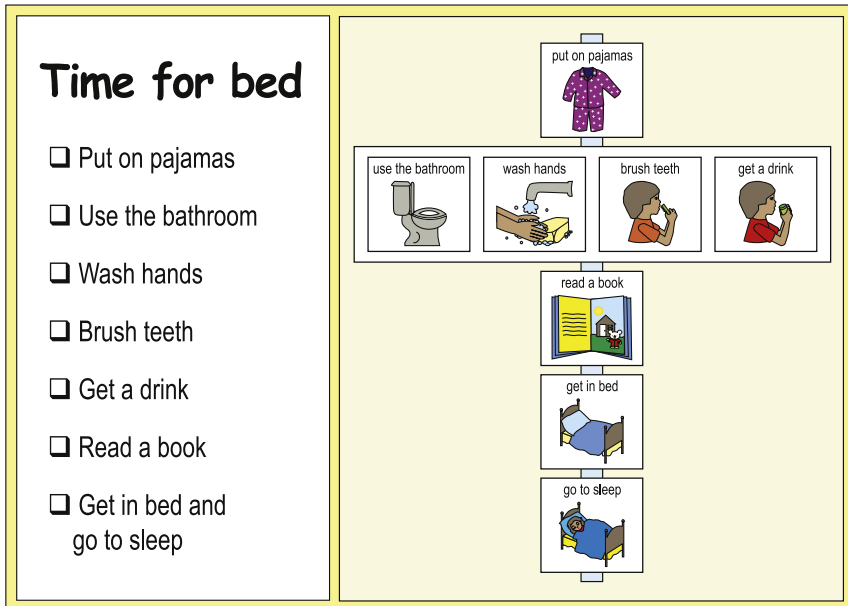
### ***Behavioral Treatment***

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Behavioral treatment of sleep problems in children with intellectual disabilities reduces parental stress, increases parents' satisfaction with their own sleep and their child's sleep, and heightens their sense of control and ability to cope with their child's sleep.<sup>57</sup> Behavioral sleep interventions must be tailored to meet the needs of the child and family but generally adhere to strategies that are successful for children with typical development. Until recently, case studies<sup>58,59</sup> have mainly been reported regarding the effectiveness of behavioral interventions for sleep in children with ASD. Reed and colleagues<sup>53</sup> showed subjective and objective (actigraphy) improvements in insomnia as well as aspects of daytime behavior and parental stress<sup>53</sup> after a group intervention program for parents of children with ASD that included both parental education and behavioral strategies. Moon and colleagues<sup>60</sup> reported improvement in sleep with a controlled trial of behavioral intervention. Studies determining the most effective methods for delivering sleep behavioral interventions are underway at several sites in the United States, Canada, and United Kingdom.

Children with ASD typically respond well to visual cues and routines once established. A visual schedule can be helpful for children with ASD. It should include pictures of each step of the bedtime routine (**Fig. 2**). The child should be trained to follow the visual schedule after a cue from parents, which may be accomplished using physical prompts. Back-to-bed reminders on the door also communicate parental expectations to the child. Stories that describe other children going to sleep and their struggles can also be helpful for communicating expectations for sleep to a child with adequate language to understand the story. Sleep restriction (decreasing total hours expected to sleep) and fading (move bedtime to a later time, often the time that the child usually falls asleep, and then gradually moving the bedtime to an earlier time once the child is in the habit of falling asleep more quickly) may also be helpful, especially for children who do not seem sleepy at bedtime.





**Fig. 2.** Picture schedule. Picture schedules can be particularly helpful for children with ASD who respond better to visual stimuli than to auditory stimuli.

It is important for children to learn to fall asleep on their own. Fears and/or unhelpful rituals must also be addressed. If the child has anxiety about falling asleep alone, parents may temporarily set up a bed or rocking chair next to the child's bed. No physical contact or eye contact should be made during this phase of treatment. The rocking chair can be gradually moved closer to the door on successive nights until it is through the door. This transition may need to be done slowly.

The Bedtime Pass developed by Friman,<sup>61</sup> which limits nighttime waking, can also be helpful for children, especially those with comorbid anxiety, who can understand actions and consequences. The child may use the pass for 1 curtain call or opportunity to check in. If the child has not used the pass during the night, then the child can turn in the pass for a reinforcer in the morning. If the pass is the picture of a favorite toy or character, then keeping the pass may be its own reinforcer.

### ***Melatonin for Insomnia and Circadian Rhythm Sleep Disorders***

Whether the sleep problem primarily involves sleep initiation or a circadian phase shift, a combination of sleep hygiene and melatonin may be useful before considering other medications. Synthetic melatonin is available as a dietary supplement. Although studies have not been shown to support the use of melatonin to treat sleep disorders in children with typical development, a meta-analysis that included studies of children with ASD<sup>62</sup> found that melatonin seems to be safe and effective in the short term in individuals with an intellectual disability. There have also been some studies that evaluated the use of melatonin specifically in children with ASD. A retrospective open-label study of 107 children with ASD that included long-term follow-up<sup>63</sup> and several small open-label or randomized trials found improvement in sleep latency with melatonin and minimal adverse effects.<sup>64–67</sup> Although there is the need for larger placebo

controlled trials, there seems to be enough evidence to consider use of melatonin in children with ASD who have significant issues with sleep-onset latency.

In the studies referenced earlier, and in practice, melatonin is generally used as a hypnotic with doses of 1 mg or higher given 30 minutes before bedtime. Doses may be rapidly titrated up to 3 mg if needed; rarely, 6 mg or more is needed. Melatonin may also be used as a chronobiotic, to shift or advance timing of sleep onset. In this latter case, melatonin is usually given in lower doses (300  $\mu$ g), 3 to 5 hours before bedtime. Once a sleep cycle is established for 6 weeks or more, the melatonin may be discontinued, although long-term use is often necessary to maintain sleep patterns.<sup>66</sup> The use of melatonin for sleep maintenance is less well studied and less likely to be efficacious given that the half-life of melatonin is less than 1 hour. Extended-release preparations may be helpful in those circumstances.<sup>66,68</sup> Although generally regarded as a low-risk alternative, melatonin has not been rigorously tested for safety or efficacy in either adults or children; however, no serious long-term adverse effects have been reported with this widely used supplement.

### ***Other Pharmacologic Treatments***

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When behavioral therapies and melatonin are ineffective, pharmacologic treatment can be considered. Although many different medications have been used in clinical practice, including clonidine, trazodone and other sedating antidepressants, and atypical antipsychotics,<sup>69</sup> there are few data to guide the use of psychotropic medications in children with ASD. One open-label, retrospective case series of clonidine use in children with ASD found that all children with difficulty with sleep initiation had a reduction in sleep-onset time by parent report, and 16 of 17 with night waking had improvement in the frequency of night waking.<sup>70</sup>

A helpful principle for prescribing sleep medications in children with coexisting neurologic or psychiatric disorders is to consider the overlapping neurologic systems that are affected. Wherever possible, prescribe a medication for the coexisting condition that also assists with sleep, and avoid those that cause insomnia. For example, in children with coexisting epilepsy or bipolar disorder, mood stabilizers with sedating properties, such as atypical antipsychotics or anticonvulsants, may be a reasonable choice. The antiepileptic regimen can be adjusted to administer a bedtime dose of medication that provides sedation and promotes sleep. Children with comorbid bipolar disorder, extreme mood irritability, aggression, or self-injurious behavior may benefit from treatment with the sedating atypical neuroleptics (eg, risperidol, olanzapine). The dosages of these medications can be adjusted to give the higher dose at bedtime. In children with anxiety or depression, antidepressants that promote sleep, such as mirtazepine, may be considered.

For a review of pharmacologic treatment of pediatric insomnia see Owens and Moturi.<sup>71</sup>

### **SUMMARY**

Sleep disorders are common in children with ASD and have a significant effect on daytime function and parental stress. The cornerstone of treatment is to establish the cause of the sleep concern, which is often multifactorial. Identifying and treating sleep disorders may result not only in more consolidated sleep, more rapid time to fall asleep, and avoidance of night waking but also favorably affect daytime behavior and parental stress. Targeting effective treatment strategies is dependent on understanding the underlying cause/causes of sleep problems in children with ASD, therefore further research is paramount.

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