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Practice Guideline: Treatment for Insomnia and Disrupted Sleep Behavior in Children and Adolescents with Autism Spectrum Disorder

Report by:

Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology

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Practice Guideline Endorsement

This practice guideline was endorsed by the American Academy of Sleep Medicine, Autism Speaks, the Child Neurology Society, and the Society for Developmental and Behavioral Pediatrics.

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Presentation Objectives

- To present evidence regarding the effectiveness of pharmacologic and nonpharmacologic strategies for treating sleep disturbances in children and adolescents with autism spectrum disorder (ASD)
- To present practice recommendations for addressing sleep disturbance in children and adolescents with ASD

Overview

- Introduction
- Clinical questions
- AAN guideline process
- Methods
- Conclusions
- Practice recommendations

Introduction

- ASDs are complex neurodevelopmental disorders characterized by social interaction/communication challenges and restrictive, stereotyped behavior patterns.
- Sleep disturbances in ASD are common, including difficulties initiating and maintaining sleep, frequent and prolonged night awakenings, irregular sleep–wake patterns, short sleep duration, and early-morning waking.[1]
- Between 44% and 83% of children and adolescents with ASD report coexisting sleep abnormalities, adversely affecting daily functioning.[2]
- Although up to 40% of typically developing children and adolescents have sleep problems, these often lessen with age. In children and adolescents ASD, sleep problems often persist.[3]
- Sleep disturbance severity is associated with poor physical health and quality of life.[4]

Introduction

- Poor sleep quality and insufficient nighttime sleep can exacerbate core and associated ASD features.
- Children and adolescents with intellectual disabilities and severe symptoms associated with ASD are at especially high risk for sleep problems.[5–7]
- Sleep disorders:
  - Are associated with communication deficits and restrictive and repetitive behaviors in ASD[8,9]
  - Negatively affect sleep and quality of life of affected individuals and their families[10]
  - Are also associated with daytime behavioral disturbances,[11–13] increased injury risk,[14,15] obesity,[16] and poor academic performance[17–19] in general pediatric populations

Introduction

- Contributors to circadian rhythm misalignment potentially include dysregulated melatonin synthesis or altered melatonin secretion patterns, circadian clock gene anomalies,[20] and decreased awareness of social and environmental clues that help habituate sleep–wake cycles.
  - Abnormalities in GABAergic, glutamatergic, serotonergic, and dopaminergic systems in ASD are also possible contributors.
- Coexisting conditions such as epilepsy, nocturnal gastroesophageal reflux disorder (GERD), anxiety, depression, bipolar disorder, psychosis, and attention-deficit/hyperactivity disorder (ADHD) can further contribute to sleep problems.
  - Core or co-occurring ASD symptoms such as intellectual disability, sensory integration deficits, ritualistic or self-injurious behaviors, poor communication skills, and limited responsiveness to social cues can interfere with sleep training and exacerbate or prolong sleep problems.

Introduction

- Children and adolescents with ASD and sleep disturbances often receive combined medication, behavioral, and complementary and alternative medicine (CAM) treatments.
- Exogenous melatonin is a synthetic form of endogenous melatonin, a hormone that is the primary biomarker for circadian sleep regulation.
  - Melatonin has chronobiologic (circadian) functions and hypnotic effects. Over-the-counter (OTC) preparations are considered supplements and not subject to US Food and Drug Administration (FDA) purity regulations.
  - Pharmaceutical grade preparations are prescribed for exact dosing. Behavioral therapies for children aged ≤5 years include unmodified, graduated extinction; positive routines; and bedtime fading.[21]

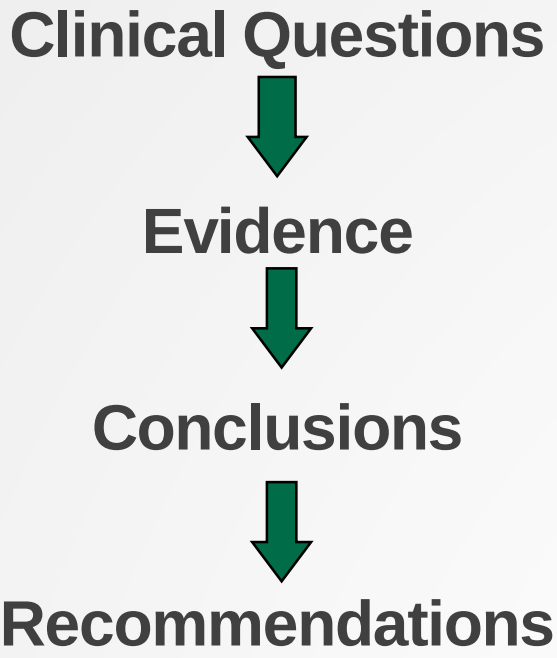
Introduction

- Older children and adolescents may respond to cognitive behavioral therapy (CBT) adapted from adult paradigms.[22,23]
  - These interventions are short-term, multicomponent, goal-oriented psychotherapeutic treatments aiming to modify thinking patterns and behaviors that perpetuate insomnia (e.g., irregular sleep–wake schedules, poor sleep hygiene, and maladaptive habits).

Clinical Question

- This guideline addresses the following question:
  - In children and adolescents with ASD, which pharmacologic, behavioral, and CAM interventions improve (1) bedtime resistance (BR), (2) sleep onset latency (SOL), (3) sleep continuity, (4) total sleep time (TST), and (5) daytime behavior?

AAN Guideline Process*



*Guideline developed using the 2011 *AAN Clinical Practice Guideline Process Manual*, as amended.

Literature Search/Review

Rigorous, Comprehensive, Transparent

Cochrane was searched for systematic reviews through January 3, 2013. MEDLINE, Embase, and PsychINFO were searched for studies through June 24, 2016 and December 21, 2017.

1,987 abstracts

8 included articles

Inclusion criteria:

- Randomized controlled trials (RCTs), evaluation studies, meta-analyses, multicenter studies, observational studies, pragmatic clinical trials, systematic reviews, or validation studies
- Studies published in the United States or Europe
- Studies of children and adolescents aged younger than 18 years who have an ASD diagnosis

Exclusion criteria:

- Studies in languages other than English
- Case reports and case series
- Studies of individuals aged 18 years or older

Class I

A clinical RCT of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent between treatment groups, or there is appropriate statistical adjustment for differences.

The following are also required:

a. Concealed allocation

b. No more than two primary outcomes specified

c. Exclusion/inclusion criteria clearly defined

d. Adequate accounting for dropouts (with at least 80% of enrolled subjects completing the study) and crossovers with numbers sufficiently low to have minimal potential for bias.

e. For noninferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following characteristics are also required*:

i. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or noninferiority.

ii. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g., for a drug, the mode of administration, dose, and dosage adjustments are similar to those previously shown to be effective).

iii. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment.

iv. The interpretation of the study results is based upon a per-protocol analysis that accounts for dropouts or crossovers.

f. For crossover trials, both period and carryover effects examined and statistical adjustments performed, if appropriate.

* Note that numbers i to iii in Class Ie are required for Class II in equivalence trials. If any one of the three is missing, the class is automatically downgraded to Class III.

Class II
An RCT of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criteria a–e (see Class I) or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets items b–e (see Class I).
(Alternatively, a randomized crossover trial missing one of the following two characteristics: period and carryover effects described or baseline characteristics of treatment order groups presented.)
All relevant baseline characteristics are presented and substantially equivalent among treatment groups, or there is appropriate statistical adjustment for differences.

AAN Classification of Evidence (2011)

Therapeutic Scheme

Class III

- All other controlled trials (including studies with external controls such as well-defined natural history controls).
- (Alternatively, a crossover trial missing both of the following two criteria: period and carryover effects described or baseline characteristics of treatment order groups presented.)
- A description of major confounding differences between treatment groups that could affect outcome.** Outcome assessment is masked, objective, or performed by someone who is not a member of the treatment team.

Class IV

- Studies that (1) did not include patients with the disease, (2) did not include patients receiving different interventions, (3) had undefined or unaccepted interventions or outcomes measures, or (4) had no measures of effectiveness or statistical precision presented or calculable.

**Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

Clinical Question

In children and adolescents with ASD, which pharmacologic, behavioral, and CAM interventions improve (1) BR, (2) SOL, (3) sleep continuity, (4) TST, and (5) daytime behavior?

Conclusions (Evidence Synthesis)

- Various forms of melatonin with or without CBT improve multiple sleep outcomes compared with placebo.

- Evidence for other interventions is largely lacking.
  - It is possible that a parental educational pamphlet, individual vs group parental sleep education, weighted blankets, and Sound-to-Sleep (STS) mattress technology have no benefits for sleep outcomes (outcomes vary slightly by intervention).
  - Evidence is insufficient to determine the effect of parental sleep-specific behavioral training based on the basis of one Class III study.[35]

Evidence Summary

	Bedtime resistance	Sleep onset latency	Sleep continuity: sleep efficiency	Sleep continuity: WASO, night awakenings	Total sleep time	Daytime behavior
Probably effective	Melatonin plus CBT Melatonin alone	Melatonin plus CBT Melatonin alone	Melatonin plus CBT Melatonin alone	Melatonin plus CBT *Melatonin alone*	Melatonin plus CBT Melatonin alone	—
Possibly effective	CBT alone	*CBT alone*	*CBT alone* *Parent educational pamphlet* STS mattress technology	*CBT alone*	*CBT alone*	—
Possibly ineffective	—	Parent educational packet Individual parent education Weighted blankets STS mattress technology	Individual parent education Weighted blankets	Parent educational packet Individual parent education Weighted blankets STS mattress technology	Parent educational pamphlet Individual parent education Weighted blankets STS mattress technology	Melatonin controlled-release Weighted blankets
Insufficient evidence	—	Parental sleep-specific behavioral training	Parental sleep-specific behavioral training	—	Parental sleep-specific behavioral training	STS mattress technology

Text presented in italics signifies other outcomes for this intervention and this sleep category show either no benefit or have insufficient evidence

Putting the Evidence into a Clinical Context

- Treatment of sleep disorders in ASD is an important goal.
- A practice pathway for identifying, evaluating, and managing insomnia in children and adolescents with ASD emphasized the importance of identifying and treating coexisting conditions.[40]
- Learned maladaptive sleep patterns may be harder to correct in children and adolescents with ASD than in typically developing peers. Thus, behavioral strategies might augment and outlast short-term pharmacologic interventions.

Putting the Evidence into a Clinical Context

- This review reveals a dearth of evidence-based treatments for sleep dysregulation in ASD.
  - No identified studies examined pharmacologic approaches, and the identified literature could not inform what population might be most likely to respond to treatment.
  - The best studies examined pharmacologic treatment with melatonin and used study-specific formulations to overcome limitations of unknown purity in OTC formulations. No medications for insomnia are FDA approved for pediatric use.

Putting the Evidence into a Clinical Context

- Melatonin is the most commonly dispensed hypnotic drug in children.[41]
  - However, melatonin concentrations in OTC formulations differ, and some formulations are contaminated with other products.[42,43]
- In 2014, the European Consensus Conference published consensus guidelines acknowledging that pediatric melatonin safety/tolerability trials are limited but there is no evidence that short-term melatonin use has serious adverse events (AEs).[44]
  - Given that many children with ASD use melatonin for months/years, the lack of long-term safety data is concerning.
  - Melatonin affects the hypothalamic–gonadal axis and can potentially influence pubertal development.[48]

Practice Recommendations

Recommendation 1: Addressing coexisting medical conditions and concomitant medications

Rationale

Children and adolescents with ASD are at increased risk of co-occurring conditions that contribute to sleep disturbance, such as intellectual disability, sleep apnea, epilepsy, gastrointestinal disturbances (including GERD), depression, anxiety, psychosis, bipolar disorder, and ADHD. Children and adolescents with ASD are also more likely to use medications that disrupt normal sleep patterns, such as stimulants, some anticonvulsants, and psychotropic medications.

Practice Recommendations

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Recommendation Statements 1a and 1b:

- **Recommendation 1a:** Clinicians seeking to improve sleep in children and adolescents with ASD should perform an assessment for coexisting conditions that could be contributing to sleep disturbance (**Level B**).
- **Recommendation 1b:** Clinicians seeking to improve sleep in children and adolescents with ASD should review concomitant medications that could be contributing to sleep disturbance (**Level B**).

Practice Recommendations

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Recommendation Statements 1c and 1d:

- **Recommendation 1c:** Clinicians seeking to improve sleep in children and adolescents with ASD who have a coexisting condition that is contributing to their sleep disturbance should ensure they receive appropriate treatment for their coexisting condition (**Level B**).*
- **Recommendation 1d:** Clinicians seeking to improve sleep in children and adolescents with ASD who have medications that could be contributing to sleep disturbance should address whether the potentially contributing medications can be stopped or adjusted (**Level B**).

* Level B based on feasibility and cost relative to net benefit

Practice Recommendations

Recommendation 2: Behavioral strategies

Rationale

- Environment and family factors, including child-rearing practices and bedtime routines that are not conducive to good sleep, contribute to sleep disturbance in children with ASD.[49] Although robust evidence for parental education and behavioral strategies to improve sleep in children and adolescents with ASD is lacking, suggested approaches include:
  - unmodified extinction: parents impose a set bedtime and wake-up time and ignore protest behavior that occurs after the bedtime and before the wake-up time
  - graduated extinction: parents ignore bedtime resistance for specified periods that are fixed or get progressively longer and then respond without reinforcing the resistant behavior (i.e., brief and boring verbal reassurance)
  - positive routines: parents develop and strictly adhere to regular pre-bed calming rituals, and
  - bedtime fading: parents put their child to bed close to the time the child begins to fall asleep.[21]

Practice Recommendations

Recommendation 2: Behavioral strategies

Rationale

- This SR has shown that family-based CBT with or without melatonin improves several aspects of sleep.
  - In the study, families attended four weekly 50-minute sessions of CBT, where parents/caregivers received education and instruction on how to modify behavior regarding sleep and were required to complete homework practicing strategies, and then twice-monthly maintenance sessions over the 12 study weeks.[29]
- As a general tenet of pediatric practice, behavioral strategies are the preferred first treatment option before initiation of pharmacologic approaches.
  - Successful application of behavioral approaches will require knowledgeable clinicians who can teach parents appropriate techniques and that parents implement the techniques consistently despite discomforts and challenges associated with behavioral modification.

Practice Recommendations

Recommendation Statement 2:

- **Recommendation 2:** Clinicians seeking to improve sleep function in children and adolescents with ASD should counsel parents or guardians regarding strategies for improved sleep habits, with behavioral strategies as a first-line treatment approach either alone or in combination with pharmacologic or nutraceutical approaches, depending on individual circumstances (**Level B**).

Practice Recommendations
Recommendation 3: Melatonin

Rationale

- When managing coexisting conditions and adopting behavioral strategies are unsuccessful at improving sleep of children and adolescents with ASD, pharmacologic strategies are an additional treatment approach.
  - There is low to moderate confidence that melatonin improves various aspects of sleep in children and adolescents with ASD.
  - In the studies included in the SR, pharmaceutical-grade melatonin preparations were used and the exact administration amounts ascertained.
    - One study used prolonged-release melatonin up to 10 mg/d,[32] one used 3 mg of prolonged-release melatonin,[29] and one started 2 mg of immediate-release melatonin with titration to effect up to 10 mg (modal dose 7 mg).[31]
  - In practice, variable concentrations of melatonin are found in OTC preparations,[43] such that melatonin obtained by prescription is more representative of what was used in studies than OTC forms.
  - Melatonin is generally administered 30–60 minutes before bedtime.[50]
  - Because immediate-release melatonin has a short half-life (40 minutes), it is assumed that the immediate-release formulations are more helpful for sleep onset insomnia and controlled-release forms more helpful for sleep maintenance.

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Practice Recommendations
Recommendation 3: Melatonin

Rationale

- No study in the SR reported serious AEs.
  - Adverse events reported with melatonin include morning drowsiness, increased enuresis, headache, dizziness, diarrhea, rash, and hypothermia.[44–47]
- Melatonin is currently used safely as neuroprotection in preterm infants,[51] suggesting that it may also be safe in other pediatric populations, but long-term safety data are lacking for all pediatric populations.
  - Possible long-term AEs are of particular concern given melatonin's ability to suppress the hypothalamic–gonadal axis and potentially initiate precocious puberty.[52]
- Risk associated with melatonin use in ASD must be weighed against the harms of persistently disordered sleep for individuals with ASD and their families.
- It is axiomatic of good care that use of any behavioral or medical treatment be periodically reevaluated to ensure there is continued benefit and no new AEs have occurred.

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Practice Recommendations

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Recommendation Statements 3a and 3b:

- Clinicians should offer melatonin to children and adolescents with ASD if behavioral if behavioral strategies have not been helpful and contributing coexisting conditions and use of concomitant medications have been addressed (**Level B**).
- Clinicians offering melatonin for sleep disturbance in children and adolescents with ASD should write a prescription for melatonin or recommend using a high-purity pharmaceutical grade of melatonin when available (**Level B**).

Practice Recommendations

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Recommendation Statements 3c and 3d:

- Clinicians offering melatonin for sleep dysregulation in children and adolescents with ASD should start by initiating a low dose (1–3 mg/d), 30–60 minutes before bedtime, and titrate to effect, not exceeding 10 mg/d (**Level B**).
- Clinicians offering melatonin for sleep disturbance in children and adolescents with ASD should counsel children and adolescents with ASD and sleep disturbance (as appropriate) and their parents regarding potential AEs of melatonin use and the lack of long-term safety data(**Level B**).

Practice Recommendations

Recommendation 4: CAM approaches

Rationale

- Families of children and adolescents with ASD are often interested in CAM approaches.
- The SR identified that:
  - STS mattress technology possibly results in higher SE over 2 weeks but possibly fails to improve SOL, WASO, or TST
  - Weighted blankets possibly fail to improve SOL, SE, WASO, night awakenings, TST, and daytime behavior over 2 weeks
  - AEs were not described in the STS mattress study
  - The only AE in the weighted blanket study was a 2-day skin rash on one child that might have been blanket related
  - Weighted blankets vary in approach to production; in the available study, weighted blankets were chosen to avoid extreme thickness and weighed 2.25 kg (small) or 4.5 kg (large) by using 3-mm steel shot pellets embedded evenly throughout the blanket
  - There were no high-quality studies of other CAM approaches

Practice Recommendations

Recommendation Statements 4a and 4b:

- Clinicians should counsel children and adolescents with ASD and sleep disturbance (as appropriate) and their parents that there is currently no evidence to support the routine use of weighted blankets or specialized mattress technology for improving disrupted sleep) (**Level B**).*
- Although evidence of efficacy is lacking, clinicians should counsel children and adolescents with ASD and sleep disturbance (as appropriate) and their parents asking about weighted blankets that the reviewed trial reported no serious AEs with blanket use and that blankets should be a reasonable nonpharmacologic approach to try for some individuals (**Level B**).

* Level B based on importance of outcomes, variation in preferences

Suggestions for Future Research

- There are few well-designed studies of sleep-related treatments in ASD.
- Optimal outcome measures that balance tolerability and accuracy are undefined, as are clinically important differences for most measures.
- Melatonin has the strongest evidence for use. Given melatonin's ability to suppress the hypothalamic–gonadal axis and potentially initiate precocious puberty, future directions should include the evaluation of long-term AEs with chronic melatonin use.
- Studies of individuals with ASD and concomitant mood disorders are also needed.
  - The bidirectional relationship between poor sleep and mood disorders is well documented.
  - Many people with ASD and mood disorders may also take medications that affect sleep disturbances.
- Finally, research tying the underlying neurobiology in early-life sleep disruption to behavior might help clinicians and researchers understand which treatments might work for which people with ASD.

References

References cited here can be found in the practice guideline article. To locate this material, please visit AAN.com/guidelines.

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Questions?