SPECIAL ARTICLE   LEVEL OF RECOMMENDATION

Practice guideline: Treatment for insomnia and disrupted sleep behavior in children and adolescents with autism spectrum disorder

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

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Abstract

Objective

To review pharmacologic and nonpharmacologic strategies for treating sleep disturbances in children and adolescents with autism spectrum disorder (ASD) and to develop recommendations for addressing sleep disturbance in this population.

Methods

The guideline panel followed the American Academy of Neurology 2011 guideline development process, as amended. The systematic review included studies through December 2017. Recommendations were based on evidence, related evidence, principles of care, and inferences.

Major recommendations (Level B)

For children and adolescents with ASD and sleep disturbance, clinicians should assess for medications and coexisting conditions that could contribute to the sleep disturbance and should address identified issues. Clinicians should counsel parents regarding strategies for improved sleep habits with behavioral strategies as a first-line treatment approach for sleep disturbance either alone or in combination with pharmacologic or nutraceutical approaches. Clinicians should offer melatonin if behavioral strategies have not been helpful and contributing coexisting conditions and use of concomitant medications have been addressed, starting with a low dose. Clinicians should recommend using pharmaceutical-grade melatonin if available. Clinicians should counsel children, adolescents, and parents regarding potential adverse effects of melatonin use and the lack of long-term safety data. Clinicians should counsel that there is currently no evidence to support the routine use of weighted blankets or specialized mattress technology for improving disrupted sleep. If asked about weighted blankets, clinicians should counsel that the trial reported no serious adverse events with blanket use and that blankets could be a reasonable nonpharmacologic approach for some individuals.

Glossary

AAN = American Academy of Neurology; **ABC** = Aberrant Behavior Checklist; **ADHD** = attention-deficit/hyperactivity disorder; **AE** = adverse event; **ASD** = autism spectrum disorders; **CAM** = complementary and alternative medicine; **CBT** = cognitive-behavioral therapy; **CI** = confidence interval; **COI** = conflict of interest; **CSHQ** = Children's Sleep Habits Questionnaire; **CSHQ-NW** = CSHQ–Night Wakings; **CSHQ-SD** = CSHQ–Sleep Duration; **CSHQ-SOD** = Children's Sleep Habits Questionnaire–Sleep Onset Delay; **DBC** = Developmental Behavior Checklist; **DSM-5** = *Diagnostic and Statistical Manual of Mental Disorders, 5th edition*; **FDA** = Food and Drug Administration; **GDDI** = American Academy of Neurology Guideline Development, Dissemination, and Implementation Subcommittee; **GERD** = gastroesophageal reflux disorder; **OSA** = obstructive sleep apnea; **OTC** = over-the-counter; **RMD** = raw mean difference; **SE** = sleep efficiency; **SOL** = sleep onset latency; **SR** = systematic review; **STS** = Sound-to-Sleep; **TST** = total sleep time; **WASO** = wake after sleep onset.

Autism spectrum disorders (ASD) 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 with ASD, sleep problems often persist.[3] Sleep disturbance severity is associated with poor physical health and quality of life.[4] Poor sleep quality and insufficient nighttime sleep can exacerbate core and associated ASD features, contributing to negative effects on mood and emotional regulation, behavior, and cognitive functioning. Children and adolescents with intellectual disabilities and severe symptoms associated with ASD are at especially high risk for sleep problems.[5–7] Sleep disturbances are associated with communication deficits and restrictive and repetitive behaviors in ASD.[8,9] Sleep disorders negatively affect sleep and quality of life of affected individuals and their families.[10] Disordered sleep is 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.

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.

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] 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).

This guideline addresses the following question:

In children and adolescents with ASD, which pharmacologic, behavioral, and CAM interventions improve (1) bedtime resistance, (2) sleep onset latency (SOL), (3) sleep continuity, (4) total sleep time (TST), and (5) daytime behavior?

Description of the analytic process

This guideline follows the 2011 American Academy of Neurology (AAN) guideline development process manual, as amended.[24] The AAN Guideline Development, Dissemination, and Implementation Subcommittee (GDDI) approved initiation of autism treatment guidelines in 2012 (appendices e-1 and e-2; see full-length guideline at aan.com/Guidelines/home/GetGuidelineContent/1004 for appendices). Panel leadership reviewed conflict of interest (COI) forms and curriculum vitae of potential panel members, according to AAN COI policy.[24] The GDDI approved formation of

a multidisciplinary panel including child neurologists, psychiatrists, neuropsychologists, and developmental pediatricians. Evidence-based medicine methodologists supported the project. Six of the 26 authors had COIs that were not significant enough to preclude participation. Restrictions on their roles reflect AAN policy.[24] The lead author had no COIs.

Studies used various strategies for defining ASD, particularly because some were conducted before the publication of the DSM-5.[25] This guideline uses the most recently established and inclusive term: ASD. Readers should consult source publications for details regarding studies' diagnostic approaches.

The initial plan was to use previously published systematic reviews (SRs). However, identified reviews contained insufficient information for assessing the level of evidence of individual studies. The guideline panel thus rated studies included in each SR using standard AAN methodology. Panelists evaluated 900 abstracts of articles from SRs for inclusion. A medical research librarian performed updated literature searches (June 24, 2016, and December 21, 2017; comprehensive search strategy in appendix e-3, aan.com/Guidelines/home/GetGuidelineContent/1004), retrieving 1,087 additional abstracts. Of 1,987 abstracts, 139 were potentially relevant. Twelve articles met criteria for data extraction. Eight were rated Class III or higher and were included in the review (figure). Classification of evidence, evidence synthesis, and recommendation development followed AAN methodology.[24] The panel based practice recommendations on the evidence strength, axiomatic principles, strong related evidence, and inferences. Level of obligation was assigned through modified Delphi voting.[24]

There are no established clinically important differences for study outcomes. Panelists were surveyed to achieve consensus regarding clinically important and unimportant differences (e.g., for actigraphy) (table e-1; see full-length guideline for e-tables, aan.com/Guidelines/home/GetGuidelineContent/1004). Three questionnaires were used in included studies: the Children's Sleep Habits Questionnaire (CSHQ; 45 items, each graded 1–3),[26] the Developmental Behavior Checklist (DBC; 96 items, each graded 0–2),[27] and the Aberrant Behavior Checklist (ABC; 58 items, each graded 0–3).[28] Higher scores indicate greater symptom burden. A change of <1% was considered unimportant and a change of >10% was considered important when assessing questionnaire scores.

Analysis of evidence

All trials occurred in the United States or Europe and included children and adolescents with ASD and aged ≤18 years.

Bedtime resistance

Bedtime resistance is a behavioral phenomenon manifesting as refusing to go to bed, stalling, or requiring a parent's presence at sleep onset. One Class II study examined the use of melatonin and family-based CBT.[29] No other studies were identified.

Melatonin and CBT

The Class II study was placebo-controlled and had 4 primary outcomes.[29] Children (4–10 years old) with ASD and sleep onset insomnia or maintenance insomnia or both were randomized to one of 4 arms: 3 mg of prolonged-release melatonin, taken at 9 PM (n = 34); 4 weekly 50-minute sessions of family-based CBT followed by twice-monthly maintenance sessions (n = 33); melatonin plus CBT (n = 35); or placebo (n = 32).[30] The high-purity melatonin (99.9%) released 1 mg immediately and 2 mg over 6 hours. Bedtime resistance was measured with the CSHQ–Bedtime Resistance subscale (6–18 points).[26] Baseline and 12-week scores were reported, but information was insufficient to calculate mean change differences between groups with confidence intervals (CIs). Bedtime resistance scores were lower for children in each active treatment group vs placebo (raw mean difference [RMD] in 12-week scores vs placebo: combination therapy −5.64 [95% CI, −6.45 to −4.83]; melatonin −3.60 [95% CI, −4.60 to −2.60]; CBT −2.48 [95% CI, −3.49 to −1.47]). Melatonin was well-tolerated. No adverse events (AEs) were reported.

Sleep onset latency

SOL refers to the amount of time from lights turned off until the onset of any sleep stage.

Melatonin and CBT

One Class I study and 2 Class II studies were identified. In the Class I study, 125 children (2–17.5 years old) with ASD, sleep problems for ≥3 months, and no response to 4 weeks of behavioral therapy were randomized to prolonged-release melatonin 2–5 mg/d (titration up to 10 mg/d) or placebo after a 2-week, single-blind placebo run-in.[31] At 13 weeks, children receiving melatonin had a larger mean decrease in diary-reported SOL compared with those receiving placebo (−25.3 minutes; 95% CI, −44.7 to −5.9).

In the previously described Class II study,[29] SOL was measured by actigraphy and the CSHQ–Sleep Onset Delay (CSHQ-SOD) subscale (1–3 points).[26] Children receiving prolonged-release melatonin with family-based CBT had the lowest SOL at 12 weeks vs placebo (RMD: actigraphy −45.91 minutes [95% CI, −57.93 to −33.89], CSHQ-SOD: −1.24 [95% CI, −1.50 to −0.98]). Prolonged-release melatonin and CBT individually also resulted in lower 12-week SOL vs placebo (melatonin: actigraphy −34.39 minutes [95% CI, −47.91 to −20.88], CSHQ-SOD: −0.83 [95% CI, −1.07 to −0.59]; CBT: actigraphy −20.47 minutes [95% CI, −34.98 to −5.96], CSHQ-SOD −0.42 [95% CI, −0.63 to −0.21]).

A Class II (3 primary outcomes) crossover study using standard-release melatonin (up to 10 mg/d; modal dose 7 mg) for 12 weeks in children (3–16 years old) with ASD and sleeplessness (n = 17) measured SOL using sleep diaries.[32] Participants had excessive sleep latencies (>30 minutes) and an unsuccessful behavioral management trial. The RMD for SOL reduction between weeks receiving melatonin vs placebo

Figure Evidence review flow diagram
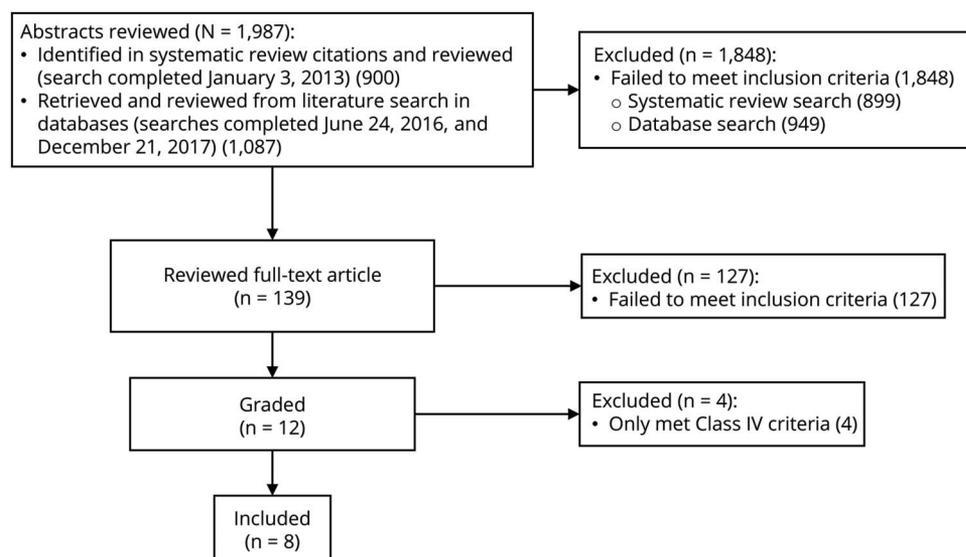
was −46.7 minutes (95% CI, −78.50 to −14.90). Melatonin was well-tolerated. No AEs were reported.

A random-effects meta-analysis was performed combining results from all 3 studies with the assumptions that (1) prolonged-release and standard melatonin forms were substantively similar, (2) SOL measurements from actigraphy vs diaries were similar, and (3) RMDs in 12-week SOL scores[29] were similar to differences in mean change in SOL[31,32] given similar baseline SOL in melatonin and placebo groups. This meta-analysis resulted in an estimated mean reduction in SOL of −33.1 minutes (95% CI, −43.5 to −22.6; $I^2 = 0\%$) for children with ASD and sleep disturbance treated with melatonin.

Parent-based sleep education
Two Class II studies[33,34] and 1 Class III study[35] used parental education about sleep schedules and hygiene. In one study (Class II for actigraphy outcomes), children (2–10 years old) with ASD and a mean SOL of ≥30 minutes were randomized to have a parent receive a 4-page educational pamphlet (n = 19) or nothing (n = 17).[33] The pamphlet described providing a comfortable sleep setting, establishing regular bedtime habits, keeping a regular schedule, teaching one's child to fall asleep alone, avoiding naps, and encouraging daytime activities promoting better sleep–wake schedules. There was no difference in SOL between children whose parents received the pamphlet and those whose parents received no instruction (RMD in SOL at 2 weeks: −11.8 minutes; 95% CI, −37.16 to 13.56; difference in mean change between baseline and 2 weeks: −16.4 minutes; 95% CI, −39.3 to 6.5).

A Class II study investigated the effect of parental sleep education for children (2–10 years old) with ASD and SOL of ≥30 minutes at least 3 nights weekly.[34] This study was Class IV for the full cohort (no comparison group) but Class II for comparing actigraphy outcomes after individual vs group education. Children whose parents received individual training were not more likely to have lower SOL at 4 weeks after intervention than those whose parents received group training (RMD: −0.2 minutes; 95% CI, −9.79 to 9.39).

In a Class III placebo-controlled study (>20% lost for actigraphy outcomes, 4 primary outcomes, no allocation concealment) in children with ASD and at least 1 sleep disturbance (average age 3.5 years), parents were randomized to receive either sleep-specific behavioral training (n = 20) or non–sleep-related education (n = 20).[35] Both arms received 5 sessions over 8 weeks. Sleep changes were measured by actigraphy (n = 27). Baseline, 4-week, and 8-week scores were reported, but information was insufficient for calculating mean change differences between groups with CIs. Baseline SOL was shorter in the control group (29 minutes, SD 27) than the behavioral training group (35 minutes, SD 31). Children whose parents received sleep-focused education were not more likely to have shorter SOL at 8 weeks than those whose parents received non–sleep-related education (RMD: 4.0 minutes; 95% CI, −14.24 to 22.24).

Weighted blankets
A 2-week crossover trial in children (5–16 years old) with ASD was Class II for actigraphy outcomes (74% of randomized participants included in analysis) and Class III for sleep diary outcomes.[36] Children had a ≥5-month history of sleep complaints in the absence of obstructive sleep apnea (OSA), night terrors, or other sleep disorders (n = 54–67, depending on arm). SOL was no shorter during weeks weighted blankets were used than during weeks regular blankets were used (mean

change difference: actigraphy: 2.1 minutes; 95% CI, −5.30 to 9.50; sleep diary: −1.6 minutes; 95% CI, −6.61 to 3.41).

Sound-to-Sleep (STS) mattress technology

One randomized crossover trial investigated the use of STS mattress technology in 45 children (2.5–12.9 years old) with ASD and significant sleep difficulties (CSHQ score ≥41).[37] The STS mattress embeds vibrations corresponding to a chosen sound source into the mattress. The study was Class II for actigraphy and Class III for diary results. There were no baseline actigraphy data. No difference was seen in 2-week SOL between the off (18.2 minutes) and on (14.11 minutes) condition as measured by actigraphy in the 38 children completing the study (RMD: −4.09 minutes; 95% CI, −11.2 to 3.0).

Sleep continuity: sleep efficiency (SE)

Sleep continuity is the amount of consolidated sleep attained over a sleep period. Continuity is reported using SE, TST, wake after sleep onset (WASO), and number of nighttime awakenings. SE is the percentage of time spent asleep while in bed (including time in bed while falling asleep and time between waking and arising from bed).

Melatonin and CBT

In a previously described Class II study, mean actigraphy SE scores at 12 weeks were higher in children receiving prolonged-release melatonin plus family-based CBT (RMD: 12.53%; 95% CI, 10.40–14.66), prolonged-release melatonin (RMD: 10.78%; 95% CI, 8.69–12.87), and CBT (RMD: 7.65%; 95% CI, 5.78–9.52) vs placebo.

Parent-based sleep education

In the Class II educational pamphlet study, children whose parents received the pamphlet had greater improvement in actigraphy-measured SE at 12 weeks compared with those whose parents received no instruction (mean change +2.3% vs −1.7%; difference in mean change 4.0%; 95% CI, 0.18–7.82). However, the children did not have a statistically higher SE at 12 weeks (77.8% ± 7.0% vs 75.1% ± 6.7%; RMD: 2.70%; 95% CI, −1.78 to 7.18).[33] The Class II study comparing individual with group parent sleep education found no difference in actigraphy-measured SE at 4 weeks between children whose parents were in individual vs group sessions (78.7% vs 79.8%; RMD: −1.10%; 95% CI, −3.61 to 1.41).[34] In the Class III study comparing sleep-specific behavioral training with control parental education over 8 weeks, baseline SE was >80% in both groups. Actigraphy-measured SE was similar between groups at 8 weeks (SE 85% ± 6% in children whose parents received sleep-specific training vs 86% ± 10% in children whose parents received non–sleep-based education; RMD: −1.0%; 95% CI, −7.17 to 5.17).[35]

Weighted blankets

In a previously described Class II trial, SE was not different during weeks of weighted blanket use than during weeks of regular blanket use (RMD: −0.3%; 95% CI −1.41 to 0.81).[36]

STS mattress technology

In the STS mattress technology study (Class II for actigraphy), children had higher SE over 2 weeks of using the STS system turned on (78.27%) compared with 2 weeks with the technology off (75.45%) (RMD: 2.82%; 95% CI, 1.14–4.50).[37]

Sleep continuity: night awakenings

WASO describes the time individuals spend awake after sleep onset and before sleep offset. Night awakenings reference the number of complete awakenings occurring after sleep initiation.

Melatonin and CBT

In a previously described Class I study, children receiving prolonged-release melatonin had no difference in the duration of wake time (−0.08 minutes; 95% CI, −7.02 to 6.86) or number of awakenings (−0.09; 95% CI, −0.35 to 0.16) at 13 weeks vs children receiving placebo.[31] The Class II study including melatonin and family-based CBT used actigraphy to measure WASO and the CSHQ–Night Wakings (CSHQ-NW) subscale to measure night awakenings.[29] Children in the combined therapy group had the largest difference in WASO at 12 weeks vs placebo (RMD: −40.46; 95% CI, −55.89 to −25.03). Children in the melatonin-only group also had lower WASO vs the placebo group (RMD: −27.94 minutes; 95% CI, −44.55 to −11.33). No difference in WASO was seen for CBT alone vs placebo (RMD: −8.98 minutes; 95% CI, −26.78 to 8.82). On the CSHQ-NW (range 3–9), children in all 3 treatment groups had lower 12-week scores than children in the placebo group (RMD for combination group: −3.44; 95% CI, −3.85 to −3.03; melatonin-only group: −2.83; 95% CI, −3.29 to −2.37; CBT-only group: −0.80; 95% CI, −1.26 to −0.34). In the Class II crossover study using melatonin 2–10 mg/d, there was no difference in the number of diary-reported night awakenings after weeks participants received melatonin vs weeks they received placebo (RMD: −0.1; 95% CI, −0.26 to −0.06).[32]

Random-effects meta-analyses used the prior assumptions. There was no difference between melatonin and placebo for WASO (−12.95 minutes; 95% CI, −40.17 to 14.28; $I^2 = 89\%$)[29,32,36] and number of awakenings (−0.097; 95% CI, −2.33 to 0.038; $I^2 = 0\%$).[32,36]

Parent-based sleep education

In the Class II educational pamphlet study, there was no difference in actigraphy-measured WASO when parents received the pamphlet vs when parents did not (RMD in scores at 2 weeks: 0.5 minutes; 95% CI, −17.96 to 18.96; difference in mean change: −8.2 minutes; 95% CI, −21.30 to 4.90).[33] In the Class II study comparing individual and group sleep education, there was no difference in actigraphy-measured WASO when parents received individual sessions vs group sessions (RMD at 4 weeks: 1.00 minutes; 95% CI, −10.24 to 12.24; difference in mean change: −2.4 minutes; 95% CI, −7.65 to 2.85).[34]

Weighted blankets

In the weighted blanket crossover study (Class II for actigraphy, Class III for diary outcomes), sleep discontinuity was measured

4 ways: (1) number of times children awoke (actigraphy), (2) actigraphy-measured WASO, (3) proportion of nights weekly that children awoke (sleep diary), and (4) average WASO (sleep diary).[36] There was no difference in actigraphy-measured WASO (RMD: −2.5 minutes; 95% CI, −9.49 to 4.49) or awakenings (RMD: −0.2; 95% CI, −1.05 to 0.65) between weeks of weighted blanket use vs weeks of control blanket use. Sleep diaries showed no difference in the proportion of nights with at least 1 awakening (RMD: −0.01; 95% CI, −0.05 to 0.03) or average time awake (RMD: 0.01 minutes; 95% CI, −1.41 to 1.43) between conditions.

STS mattress technology
In the STS mattress technology crossover trial, WASO was not different when measured by actigraphy over 2 weeks (18.79 minutes with technology off, 17.85 minutes with technology on; RMD: −0.94 minutes; 95% CI, −1.912 to 0.032) or sleep diary (off: 0.13 minutes, on: 0.12 minutes; RMD: −0.01 minutes; 95% CI, −0.043 to 0.023).[37]

Total sleep time
TST refers to sleep duration during a given sleep period time (usually at night). Reduced TST relates to prolonged SOL, night awakenings, and early-morning waking. Included studies compare TST changes with treatment rather than referencing age-specific sleep duration recommendations.

Melatonin and CBT
In the Class I study, children receiving prolonged-release melatonin had a greater increase in diary-reported TST (baseline to 13 weeks, 32.43 minutes; 95% CI, 2.48–62.38).[31] In the Class II study using melatonin and family-based CBT, actigraphy-measured TST at 12 weeks was longer in treatment groups compared with placebo (combined therapy group: RMD: 88.78 minutes; 95% CI, 70.30–107.26; melatonin-only group: RMD: 64.87 minutes; 95% CI, 46.10–83.64; CBT-only group: RMD: 28.90; 95% CI, 6.53–51.27).[29] CSHQ–Sleep Duration (CSHQ-SD) subscale outcomes (score range 3–9) at 12 weeks in the melatonin groups revealed the same pattern vs placebo (combined therapy group: RMD: −2.02; 95% CI, −2.58 to −1.46; melatonin-only group: RMD: −1.58; 95% CI, −2.13 to −1.03). There was no difference on the CSHQ-SD between the CBT-only and placebo groups (RMD: 0.28; 95% CI, −0.32 to 0.88). In the Class II crossover study, diary-based TST improved more during weeks children and adolescents received melatonin than during weeks they received placebo (RMD: 52.3 minutes; 95% CI, 19.3–5.47).[32] A random-effects meta-analysis resulted in an estimated increased TST of 52.63 minutes (95% CI, 33.10–72.16; I^2 = 39%) for children with ASD and sleep disturbance treated with melatonin vs placebo.

Parent-based sleep education
Actigraphy-measured TST did not differ between children whose parents received the educational pamphlet vs no instruction (Class II study; RMD in TST at 2 weeks: 12.2 minutes; 95% CI, −22.6 to 47.0; difference in mean change between baseline and 2 weeks: 7.9 minutes; 95% CI, −18.03 to

33.8).[33] Change in actigraphy-measured TST also did not differ between baseline and 4 weeks for children whose parents received individual vs group instruction (Class II study; RMD at 4 weeks: −7.2 minutes; 95% CI, −29.44 to 15.04; difference in mean change: −11.7 minutes; 95% CI, −37.3 to 13.9).[34] In the Class III placebo-controlled study comparing sleep-specific behavioral training vs control education, actigraphy-measured TST at 8 weeks was not significantly different between children whose parents attended sleep education sessions and the control group (RMD: 26.0 minutes; 95% CI, −31.33 to 83.33).[35]

Weighted blankets
In the weighted blanket study (Class II for actigraphy, Class III for diary outcomes), there was no difference in actigraphy-measured TST during weeks of weighted blanket use vs weeks of regular blanket use (RMD weighted control: −4.2 minutes; 95% CI, −13.40 to 5.00).[36] Diary-based TST also did not differ (RMD weighted control: 15.9 minutes; 95% CI, −6.37 to 38.17).

STS mattress technology
In the STS mattress technology trial (Class II for actigraphy, Class III for diary results), actigraphy-measured TST was longer during the 2 weeks that the STS technology was on vs the 2 weeks it was off (on: 8.35 hours, off: 7.99 hours; RMD: 0.36 hours; 95% CI, 0.15–0.57).[37] There was no difference in diary-based TST (on: 9.78 hours, off: 9.66 hours; RMD: 0.12 hours; 95% CI, −0.18 to 0.42).

Daytime behavior

Melatonin
In the Class II crossover study using melatonin 2–10 mg/d vs placebo, total DBC scores were lower after weeks of melatonin use vs weeks of placebo use (RMD: −6.0; 95% CI, −12.0 to 0). The only statistically significant difference in subscale scores was for communication (RMD: −1.6; 95% CI, −3.16 to 0.04).[32]

Weighted blankets
In the Class II weighted blanket trial, total ABC score did not differ between periods of weighted blanket use vs periods of regular blanket use (−2.3; 95% CI, −5.75 to 1.15). There were also no differences on subscale scores.[36]

STS mattress technology
In the STS mattress technology crossover trial (Class III for questionnaire results), ABC scores did not differ at the end of the 2-week off-technology and on-technology periods (RMD: −6.8; 95% CI, −14.8 to 1.3).[37]

Conclusions (evidence synthesis)

Various forms of melatonin with or without CBT improve multiple sleep outcomes compared with placebo (table 1 and table e-3, aan.com/Guidelines/home/GetGuideline-Content/1004). Evidence for other interventions is largely

Table 1 Evidence summary for interventions targeting sleep disorders in children and adolescents with autism spectrum disorder (ASD)[a]

	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[b]	Melatonin plus CBT; melatonin alone	
Possibly effective	CBT alone	CBT alone[b]	CBT alone[b]; parent educational pamphlet[b]; STS mattress technology	CBT alone[b]	CBT alone[b]	
Possibly ineffective		Parent educational packet; individual (vs group) parent education; weighted blankets; STS mattress technology	Individual (vs group) parent education; weighted blankets	Parent educational packet; individual (vs group) parent education; weighted blankets; STS mattress technology	Parent educational pamphlet; individual (vs group) parent education; weighted blankets; STS mattress technology	Melatonin CR; weighted blankets
Insufficient evidence		Parental sleep-specific behavioral training	Parental sleep-specific behavioral training		Parental sleep-specific behavioral training	STS mattress technology

Abbreviations: CBT = cognitive behavioral therapy; CR = controlled release; STS = Sound-to-Sleep; WASO = wake after sleep onset.
[a] Specific conclusion details regarding the interventions (e.g., type of melatonin, dose), outcomes measured, and timing are available in the systematic review text and the full conclusions outlined in appendix e-4 (aan.com/Guidelines/home/GetGuidelineContent/1004) of the full-length guideline, available from the American Academy of Neurology, upon request; for interventions for which there are multiple conclusions for a single sleep category, conclusions with the highest degree of confidence and potential benefit are reflected here.
[b] Other outcomes for this intervention and this sleep category show either no benefit or have insufficient evidence.

lacking. It is possible that a parental educational pamphlet, individual vs group parental sleep education, weighted blankets, and STS mattress technology have no benefits for sleep outcomes (outcomes vary slightly by intervention; table e-3, aan.com/Guidelines/home/GetGuideline-Content/1004). Evidence is insufficient to determine the effect of parental sleep-specific behavioral training on the basis of 1 Class III study.[35] Evidence profile tables (appendix e-4, aan.com/Guidelines/home/GetGuidelineContent/1004) and evidence synthesis tables (appendix e-5, aan.com/Guidelines/home/GetGuidelineContent/1004) are available from the AAN, by request.

Putting the evidence into clinical context

Treatment of sleep disorders in ASD is an important goal, as sleep disruption is associated with behavioral problems, daytime sleepiness, and poorer health.[38] Individuals with ASD are at risk for primary sleep disorders, including OSA, restless legs syndrome, and periodic limb movement disorder (not reviewed).[2,39] They are also at risk for sleep disorders secondary to coexisting conditions (e.g., epilepsy, GERD, anxiety, depression, bipolar disorder, psychosis, or ADHD), and are more likely to use medications that disrupt normal sleep patterns (e.g., antiseizure medicines, psychotropic medications). 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, including lack of parental boundaries regarding sleep, may be more difficult to correct in children and adolescents with ASD than in their typically developing peers. For this reason, behavioral strategies might augment and outlast short-term pharmacologic interventions.

This review reveals a dearth of evidence-based treatments for sleep dysregulation in ASD. No identified studies examined pharmacologic approaches (e.g., antidepressants, α-adrenergic agonists, benzodiazepines, antiseizure medicines, or antipsychotics), and the identified literature could not inform what population might be most likely to respond to treatment (e.g., based on age or comorbid symptoms). 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. 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 (e.g., serotonin).[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 AEs.[44] The most frequently reported AEs are morning drowsiness, increased enuresis, headache, dizziness, diarrhea, rash, and hypothermia.[45–47] Given that many children with ASD use

melatonin for months or 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 rationales are presented and tables 2–4 summarize recommendation statements (n.neurology.org/content/91/10/450). Rationale profile tables are available online (appendix e-6, aan.com/Guidelines/home/GetGuidelineContent/1004).

Recommendation 1 rationale: addressing coexisting medical conditions and concomitant medications

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 antiseizure medicines, and psychotropic medications.

Recommendation 2 rationale: behavioral strategies

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 the following:

- 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
- Bedtime fading: parents put their child to bed close to the time the child begins to fall asleep[21]

In addition, this SR has shown that family-based CBT with or without melatonin may improve several aspects of sleep. In the study, families attended 4 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.

Recommendation 3 rationale: melatonin

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

Table 2 Recommendation statements[a] for care of children and adolescents with autism spectrum disorder (ASD) and sleep disturbance regarding coexisting medical conditions and concomitant medications

Recommendation number	Recommendation statement and level
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).
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).
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).[b]
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).
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).

[a] Level A is the strongest recommendation level and is denoted by use of the helping verb must. These recommendations are rare. Level B corresponds to the helping verb should. Such recommendations are more common, as the requirements are less stringent but are still associated with confidence in the rationale and a favorable benefit–risk profile. Level C corresponds to the helping verb may. These recommendations represent the lowest allowable recommendation level that the American Academy of Neurology considers useful within the scope of clinical practice and can accommodate the highest degree of practice variation.
[b] Level B based on feasibility and cost relative to net benefit.

Table 3 Recommendation statements for care of children and adolescents with autism spectrum disorder (ASD) and sleep disturbance regarding melatonin use

Recommendation number	Recommendation statement and level
3a	Clinicians should offer melatonin to children and adolescents with ASD if behavioral strategies have not been helpful and contributing coexisting conditions and use of concomitant medications have been addressed (Level B).
3b	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).
3c	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).
3d	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 adverse events of melatonin use and the lack of long-term safety data (Level B).

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. When used as a hypnotic, 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 for sleep maintenance.

No study in the SR reported serious AEs. AEs 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 should 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 that there is continued benefit and no new AEs.

Recommendation 4 rationale: CAM approaches

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. No high-quality studies of other CAM approaches were identified. 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.

Suggestions for future research

There are few well-designed studies of sleep-related treatments in ASD. Optimal outcome measures (e.g., questionnaires, polysomnography, actigraphy) 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

Table 4 Recommendation statements for care of children and adolescents with autism spectrum disorder (ASD) and sleep disturbance regarding complementary alternative medicine

Recommendation number	Recommendation statement and level
4a	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).[a]
4b	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 adverse events with blanket use and that blankets could be a reasonable nonpharmacologic approach to try for some individuals (Level B).

[a] Level B based on importance of outcomes, variation in preferences.

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. 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.

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Conflict of interest

The American Academy of Neurology (AAN) is committed to producing independent, critical, and trustworthy clinical practice guidelines and evidence-based documents. Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this evidence-based document. Management and disclosure of document developer relationships is conducted in compliance with the 2011 AAN process manual section titled "Revealing conflicts of interest," which can be viewed at aan.com.[24]

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Disclosure

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Ashura Williams Buckley, Deborah Hirtz, Maryam Oskoui, et al.

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