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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attention-deficit/hyperactivity disorder, long-term safety of antipsychotic use, biomarkers in ASD, oxytocin in ASD, and treatment of antipsychotic medication–associated weight gain in children; and receives publishing royalties for *Pediatric Psychopharmacology*, 2nd edition. A. Stahmer serves as an editor for *Autism: International Journal of Research and Practice* and on the editorial board for the *Journal of Early Intervention*; has received funding for travel to scientific meetings and research support from the NIH National Institute of Mental Health (NIMH), HRSA, and Institute of Education Sciences (IES); has received speaking honoraria; has received publishing royalties from Guilford Press; has received honoraria from Autism Speaks and NIMH for grant reviews; received payment to conduct training in behavioral interventions for ASD; dedicates 10% of clinical efforts to behavioral parent training; and has received research support from the NIMH, HRSA, and the IES.

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GLOSSARY

ABC: Aberrant Behavior Checklist

ASD: autism spectrum disorder

ADHD: attention-deficit/hyperactivity disorder

AEs: adverse events

BR: bedtime resistance

CAM: complementary and alternative medicine

CBT: cognitive behavioral therapy

CSHQ: Children's Sleep Habit Questionnaire

CSHQ-BR: Children's Sleep Habit Questionnaire-Bed Resistance

CSHQ-SOD: Children's Sleep Habit Questionnaire-Sleep Onset Delay

DBC: Developmental Behavior Checklist

FDA: Food and Drug Administration

GERD: gastroesophageal reflux disease

OSA: obstructive sleep apnea

OTC: over the counter

RMD: raw mean difference

SE: sleep efficiency

SOL: sleep onset latency

STS: Sound-to-Sleep

TST: time to sleep

WASO: wake after sleep onset

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ABSTRACT

Objective: To review pharmacologic and nonpharmacologic strategies for treating sleep disturbances in children and adolescents with autistic 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.

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INTRODUCTION

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 (BR), (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 (GDDI) Subcommittee approved initiation of autism treatment guidelines in 2012 (appendices e-1 and e-2). 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 COI which were not significant enough to preclude participation. Restrictions on their roles reflect AAN policy.[24] The lead author had no COI.

Studies used various strategies for defining ASD, particularly because some were conducted before the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition,[25] publication. 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 articles from SRs for inclusion. A medical research librarian performed updated literature searches using a comprehensive search strategy (6/24/2016, 12/21/2017; appendix e-3). Of 1,087 additional 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 e-1 [available upon request]). 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). 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); four 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 (CSHQ-BR) 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

Sleep onset latency 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 min, 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 min [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 min [95% CI -47.91 to -20.88], CSHQ-SOD -0.83 [95% CI -1.07 to -0.59]; CBT: actigraphy -20.47 min [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 min) and an unsuccessful behavioral management trial. The RMD for SOL reduction between weeks receiving melatonin vs placebo was -46.7 min (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 min (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 one 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 min, 95% CI -37.16 to 13.56; difference in mean change between baseline and 2 weeks: -16.4 min, 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 min, 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 one 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-, 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 min, SD 27) than the behavioral training group (35 min, 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 min, 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). Sleep onset latency was no shorter during weeks weighted blankets were used than during weeks regular blankets were used (mean change difference: actigraphy 2.1 min, 95% CI -5.30 to 9.50; sleep diary -1.6 min, 95% CI -6.61 to 3.41).

Sound-to-Sleep Mattress Technology

One randomized crossover trial investigated the use of Sound-to-Sleep (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 min) or on (14.11 min) condition as measured by actigraphy in the 38 children completing the study (RMD -4.09 min, 95% CI -11.2 to 3.0).

Sleep continuity: sleep efficiency

Sleep continuity is the amount of consolidated sleep attained over a sleep period. Continuity is reported using sleep efficiency (SE), TST, wake after sleep onset (WASO), and number of nighttime awakenings. Sleep efficiency 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 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

Wake after sleep onset 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 min, 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 biggest 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 min, 95% CI -44.55 to -11.33). No difference in WASO was seen for CBT alone vs placebo (RMD -8.98 min, 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 min, 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 min, 95% CI -17.96 to 18.96; difference in mean change: -8.2 min, 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 children whose parents received individual sessions vs group sessions (RMD at 4 weeks: 1.00 min, 95% CI, -10.24 to 12.24; difference in mean change: -2.4 min, 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 that 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 min, 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 one awakening (RMD -0.01, 95% CI -0.05 to 0.03) or average time awake (RMD 0.01 min, 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 min with technology off, 17.85 min with technology on; RMD -0.94 min, 95% CI -1.912 to 0.032) or sleep diary (off: 0.13 min, on: 0.12 min; RMD -0.01 min, 95% CI -0.043 to 0.023).[37]

Total sleep time

Total sleep time signifies sleep duration over 24 hours (including naps). 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 min, 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 min, 95% CI 70.30–107.26; melatonin-only group: RMD 64.87 min, 95% CI 46.10–83.64); CBT-only group: 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 weeks they received placebo (RMD 52.3 min, 95% CI 19.3–85.47).[32] A random-effects meta-analysis resulted in an estimated increased TST of 52.63 min (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 min, 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 the 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 e-2 and table e-3). Evidence for other interventions is largely 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-4). Evidence is insufficient to determine the effect of parental sleep-specific behavioral training based on the basis of one Class III study.[35] Evidence

profile tables (appendix e-4) and evidence synthesis tables (appendix e-5) 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 harder to correct in children and adolescents with ASD than in 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, alpha 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, 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/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; tables summarize recommendation statements (tables e-5 through e–7). Rationale profile tables are available online (appendix e-6).

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:

- 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]

In addition, 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.

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 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.

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 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. Adverse events 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 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.

Figure e-1—Available Upon Request

Table e-1. Consensus-based clinically important and unimportant differences on sleep measures

Outcome	Relevant outcome measure(s)	Clinically important difference	Uncertain clinical significance	Clinically unimportant
SOL	PSG, actigraphy, diary entry, questionnaire results	20 min or more	More than 10 min to less than 20 min	10 min or less
Risk difference in achieving SOL of less than 30 min or a reduction of 50% or greater in SOL	PSG, actigraphy, diary entry, questionnaire results	10% or greater	More than 5% to less than 10%	5% or less
SE	PSG or actigraphy	5% or greater	More than 2% to less than 5%	2% or less
Risk difference in achieving an SE greater than 85%	PSG or actigraphy	10% or greater	More than 5% to less than 10%	5% or less
WASO	PSG or actigraphy	15 min or more	More than 5 min to less than 15 min	5 min or less
Decrease in night awakenings		3 or more	More than 1 to fewer than 3	1 or fewer
Improvement in total sleep time		30 min or greater	More than 15 min to less than 30 min	15 min or less

Abbreviations: PSG: polysomnography; SE: sleep efficiency; SOL: sleep onset latency; WASO: wake after sleep onset.

Table e-2. 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*	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 (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

[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 of the full-length guideline, available from the AAN, 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.

Text presented in italics signifies other outcomes for this intervention and this sleep category show either no benefit or have insufficient evidence.
Abbreviations: CBT: cognitive behavioral therapy, CR: controlled release; STS: Sound-to-Sleep, WASO: wake after sleep onset.

Table e-3. Evidence synthesis of interventions showing benefit for insomnia and disrupted sleep behavior in children and adolescents with autism spectrum disorder (ASD)

Outcome	Intervention	Conclusion
Bedtime resistance	Controlled-release melatonin 3 mg with or without CBT	Children with ASD (aged 4–10 y) with sleep onset insomnia and impaired sleep maintenance taking controlled-release melatonin 3 mg at 9 PM or taking controlled-release melatonin at 9 PM in conjunction with CBT probably have lower bedtime resistance at 12 wk compared with those taking placebo (moderate confidence; one Class II study with increased confidence in the evidence due to effect size, Cortesi 2012).
	CBT alone	Children with ASD (aged 4–10 y) with sleep onset insomnia and impaired sleep maintenance using CBT alone possibly have lower bedtime resistance at 12 wk compared with those taking placebo (low confidence; one Class II study, Cortesi 2012).
Sleep onset latency	Melatonin (any form – meta-analysis)	Children with ASD and sleep disturbance taking various forms of melatonin probably have lower SOL as measured by different approaches compared with those taking placebo (moderate confidence; raw mean difference -33.1, 95% CI -43.5 to -22.6, meta-analysis of one Class I study and 2 Class II studies, Cortesi 2012, Wright 2011, Gringas 2017).
	Controlled-release melatonin 3 mg with CBT	Children with ASD (aged 4–10 y) with sleep onset insomnia and impaired sleep maintenance taking controlled-release melatonin at 9 PM in conjunction with CBT possibly have lower SOL at 12 wk as measured by actigraphy compared with those taking placebo (low confidence; one Class II study, Cortesi 2012). Children with ASD (aged 4–10 y) with sleep onset insomnia and impaired sleep maintenance taking controlled-release melatonin at 9 PM in conjunction with CBT probably have an increased likelihood of achieving SOL less than 30 min at 12 wk as measured by actigraphy compared with those taking placebo (moderate confidence; one Class II study, Cortesi 2012, with increased confidence due to magnitude of effect). Children with ASD (aged 4–10 y) with sleep onset insomnia and impaired sleep maintenance taking controlled-release melatonin at 9 PM in conjunction with CBT probably have lower SOL at 12 wk as measured by the CSHQ subscale score compared with those taking placebo (moderate confidence; one Class II study with increased confidence in the evidence due to effect size, Cortesi 2012).

	Controlled-release melatonin 3 mg alone	Children with ASD (aged 4–10 y) with sleep onset insomnia and impaired sleep maintenance taking controlled-release melatonin at 9 PM (without CBT) probably have an increased likelihood of achieving SOL less than 30 min at 12 wk as measured by actigraphy compared with those taking placebo (moderate confidence; one Class II study, Cortesi 2012, with increased confidence due to magnitude of effect).
	CBT alone	Children with ASD (aged 4–10 y) with sleep onset insomnia and impaired sleep maintenance doing CBT alone possibly have lower SOL at 12 wk as measured by actigraphy and as measured by the CSHQ subscale score compared with those taking placebo (low confidence; one Class II study, Cortesi 2012). However, there is insufficient evidence to determine whether children with ASD (aged 4–10 y) with sleep onset insomnia and impaired sleep maintenance doing CBT alone are more or less likely than children taking placebo to achieve SOL less than 30 min at 12 wk as measured by actigraphy (very low confidence; one Class II study, Cortesi 2012, with decreased confidence in the evidence due to precision).
Sleep continuity: sleep efficiency	Controlled-release melatonin 3 mg with CBT	Children with ASD (aged 4–10 y) with sleep onset insomnia and impaired sleep maintenance taking controlled-release melatonin at 9 PM in conjunction with CBT probably have higher sleep efficiency at 12 ws as measured by actigraphy compared with those taking placebo (moderate confidence; one Class II study, Cortesi 2012, with increased confidence in the evidence due to magnitude of effect). Children with ASD (aged 4–10 y) with sleep onset insomnia and impaired sleep maintenance taking controlled-release melatonin at 9 PM in conjunction with CBT probably have a higher likelihood of achieving >85% SE at 12 wk compared with those taking placebo (moderate confidence; one Class II study with increased confidence in the evidence due to magnitude of effect, Cortesi 2012).
	Controlled-release melatonin 3 mg alone	Children with ASD (aged 4–10 y) with sleep onset insomnia and impaired sleep maintenance taking controlled-release melatonin at 9 PM (without CBT) possibly have higher sleep efficiency at 12 wk as measured by actigraphy compared with those taking placebo (low confidence; one Class II study, Cortesi 2012). Children with ASD (aged 4–10 y) with sleep onset insomnia and impaired sleep maintenance taking controlled-release melatonin at 9 PM probably have a higher likelihood of achieving >85% SE at 12 wk compared with those taking

		placebo (moderate confidence; one Class II study with increased confidence in the evidence due to magnitude of effect, Cortesi 2012).
	CBT alone	Children with ASD (aged 4–10 y) with sleep onset insomnia and impaired sleep maintenance doing CBT alone possibly have higher sleep efficiency at 12 wk as measured by actigraphy compared with those taking placebo (low confidence; one Class II study, Cortesi 2012). However, there is insufficient evidence to determine whether children with ASD (aged 4–10 y) with sleep onset insomnia and impaired sleep maintenance doing CBT alone are more or less likely than children taking placebo to achieve >85% SE at 12 wk as measured by actigraphy (very low confidence; one Class II study, Cortesi 2012, with decreased confidence in the evidence due to precision).
	Parent educational pamphlet	Children with ASD (aged 2–10 y) and a mean sleep latency of 30 min whose parents receive an educational pamphlet are possibly more likely than children of parents receiving no pamphlet to have improved SE between baseline and 2 wk (low confidence; one Class II study, Adkins 2012). However, children with ASD (aged 2–10 y) and a mean sleep latency of 30 min whose parents receive an educational pamphlet are possibly no more likely than children of parents receiving no pamphlet to have higher SE at 2 wk (low confidence; one Class II study, Adkins 2012).
	STS mattress technology (vs regular mattress)	Children with ASD and sleep difficulties are possibly more likely to have higher SE (as measured by actigraphy over 2 wk) when using the STS mattress technology turned on compared with when using the mattress with the technology turned off (low confidence in the evidence; 1 Class II study, Frazier 2017).
Sleep continuity – WASO, night awakenings	Controlled-release melatonin 3 mg with CBT	Children with ASD (aged 4–10 y) with sleep onset insomnia and impaired sleep maintenance taking controlled-release melatonin at 9 PM in conjunction with CBT possibly have lower WASO at 12 wk as measured by actigraphy compared with those taking placebo (low confidence; one Class II study, Cortesi 2012). Children with ASD (aged 4–10 y) with sleep onset insomnia and impaired sleep maintenance taking controlled-release melatonin at 9 PM in conjunction with CBT probably have lower scores on the CSHQ-Night Wakings subscale at 12 wk compared with those taking placebo (moderate confidence; one Class II study, Cortesi 2012, with increased confidence due to magnitude of effect).

	Controlled-release melatonin 3 mg	Children with ASD (aged 4–10 y) with sleep onset insomnia and impaired sleep maintenance taking controlled-release melatonin at 9 PM probably have lower scores on the CSHQ-Night Wakings subscale at 12 wk compared with those taking placebo (moderate confidence; one Class II study, Cortesi 2012, with increased confidence due to magnitude of effect).
	CBT	Children with ASD (aged 4–10 y) with sleep onset insomnia and impaired sleep maintenance participating in CBT possibly have lower scores on the CSHQ-Night Wakings subscale at 12 wk compared with those taking placebo (low confidence; one Class II study, Cortesi 2012).
Total sleep time	Melatonin (any form – meta-analysis)	Children with ASD and sleep disturbance taking various forms of melatonin probably have longer TST as measured by different approaches compared with those taking placebo (moderate confidence; mean difference 52.63 min, 95% CI 33.10 – 72.16, I^2 39%, meta-analysis of one Class I and study 2 Class II studies, Cortesi 2012, Wright 2011, Gringas 2017).
	Controlled-release melatonin 3 mg with CBT	Children with ASD (aged 4–10 y) with sleep onset insomnia and impaired sleep maintenance taking controlled-release melatonin at 9 PM in conjunction with CBT probably have longer TST at 12 wk as measured by actigraphy compared with those taking placebo (moderate confidence; one Class II study, Cortesi 2012, with increased confidence in the evidence due to magnitude of effect). Children with ASD (aged 4–10 y) with sleep onset insomnia and impaired sleep maintenance taking controlled-release melatonin at 9 PM in conjunction with CBT probably have lower scores on the CSHQ Sleep Duration subscore at 12 wk compared with those taking placebo (moderate confidence; one Class II study with increased confidence in the evidence due to magnitude of effect, Cortesi 2012).
	Controlled-release melatonin 3 mg alone	Children with ASD (aged 4–10 y) with sleep onset insomnia and impaired sleep maintenance taking controlled-release melatonin at 9 PM (without CBT) possibly have lower scores on the CSHQ Sleep Duration subscore at 12 wk compared with those taking placebo (low confidence; one Class II study, Cortesi 2012).
	CBT alone	Children with ASD (aged 4–10 y) with sleep onset insomnia and impaired sleep maintenance doing CBT alone possibly have longer TST at 12 wk as measured by actigraphy compared with those taking placebo (low confidence; one Class II study, Cortesi 2012).

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Abbreviations: CBT: cognitive behavioral therapy; CSHQ: Children's Sleep Habit Questionnaire; SE: sleep efficiency; SOL: sleep onset latency; STS: Sound-to-Sleep; TST: total sleep time; WASO: wake after sleep onset.

Table e-4. Evidence synthesis of interventions showing no benefit for insomnia and disrupted sleep behavior in children and adolescents with autism spectrum disorder (ASD) or for which there is insufficient evidence

Outcome	Intervention	Conclusion
Sleep onset latency	Parent educational pamphlet	Children with ASD (aged 2–10 y) and a mean sleep latency of 30 min whose parents receive an educational pamphlet are possibly no more likely than children of parents receiving no pamphlet to have a reduction in SOL at 2 wk (low confidence; one Class II study, Adkins 2012).
	Parental sleep-specific behavioral training	There is insufficient evidence to determine whether children with ASD and at least one sleep disturbance whose parents receive a sleep-specific behavioral training are more or less likely than children of parents receiving education unrelated to sleep to have lower SOL at 8 wk (very low confidence; one Class III study, Johnson 2013).
	Individual parental sleep education (vs group parental sleep education)	Children with ASD (aged 2–10 y) and prolonged sleep latency whose parents receive individual sleep training are possibly no more likely than children of parents receiving group sleep education to have a reduction in SOL at 4 wk (low confidence; one Class II study, Malow 2015).
	Weighted blankets (vs usual weight blankets)	Children with ASD and 5 mo of sleep concerns are possibly no more likely to have improved SOL (as measured by actigraphy) when using a weighted blanket compared with when using a regular weight blanket (low confidence in the evidence; one Class II study, Gringras 2014).
	STS mattress technology (vs regular mattress)	Children with ASD and sleep difficulties are possibly no more likely to have lower SOL (as measured by actigraphy over 2 wk) when using the STS mattress technology turned on compared with when using the mattress with the technology turned off (low confidence in the evidence; one Class II study, Frazier 2017).
Sleep continuity – sleep efficiency	Parent educational pamphlet	Children with ASD (aged 2–10 y) and a mean sleep latency of 30 min whose parents receive an educational pamphlet are possibly no more likely than children of parents receiving no pamphlet to have higher sleep efficiency at 2 wk (low confidence; one Class II study, Adkins 2012).
	Parental sleep-specific behavioral training	There is insufficient evidence to determine whether children with ASD and at least one sleep disturbance whose parents receive a sleep-specific behavioral training are more or less likely than children of parents receiving education unrelated to sleep to have better sleep efficiency at 8 wk (very low confidence; one Class III study, Johnson 2013).
	Individual parental sleep education (vs	Children with ASD (aged 2–10 y) and prolonged sleep latency whose parents receive individual sleep training are possibly no more likely than children of parents receiving

	group parental sleep education)	group sleep education to have higher SE at 4 wk (low confidence; one Class II study, Malow 2015).
	Weighted blankets (vs usual weight blankets)	Children with ASD and 5 mo of sleep concerns are possibly no more likely to have improved SE (as measured by actigraphy) when using a weighted blanket compared with when using a regular weight blanket (low confidence in the evidence; one Class II study, Gringras 2014).
Sleep continuity – WASO, night awakenings	Melatonin (any form – meta-analysis)	There is insufficient evidence to determine wither children with ASD and sleep disturbance taking various forms of melatonin have lower WASO as measured by different approaches compared with those taking placebo (very low confidence; raw mean difference -12.95, 95% CI -40.17 to 14.28, I^2 89%, meta-analysis of one Class I study and one Class II study, Cortesi 2012, Gringas 2017). Children with ASD and sleep disturbance taking various forms of melatonin are probably no more likely than those taking placebo to have a reduction in night awakenings (moderate confidence; raw mean difference -0.097, 95% CI -2.33 to 0.038, I^2 0%, meta-analysis of one Class I [Gringas 2017] and one Class II study [Wright 2011]).
	CBT alone	Children with ASD (aged 4–10 y) with sleep onset insomnia and impaired sleep maintenance doing CBT alone are possibly no more likely to have lower WASO at 12 wk than children taking placebo (low confidence; one Class II study, Cortesi 2012).
	Parent educational pamphlet	Children with ASD (aged 2–10 y) and a mean sleep latency of 30 min whose parents receive an educational pamphlet are possibly no more likely than children of parents receiving no pamphlet to have lower WASO at 2 weeks (low confidence; one Class II study, Adkins 2012). Children with ASD (aged 2–10 y) and a mean sleep latency of 30 min whose parents receive an educational pamphlet possibly have no greater reduction in WASO from baseline to 2 wk than children of parents receiving no pamphlet (low confidence; one Class II study, Adkins 2012).
	Individual parental sleep education (vs group parental sleep education)	Children with ASD (aged 2–10 y) and prolonged sleep latency whose parents receive individual sleep training are possibly no more likely than children of parents receiving group sleep education to have lower WASO at 4 wk (low confidence; one Class II study, Malow 2015). Children with ASD (aged 2–10 y) and prolonged sleep latency whose parents receive individual sleep training are possibly no more likely than children of parents receiving

		group sleep education to have a greater reduction in WASO from baseline to 4 weeks (low confidence; one Class II study, Malow 2015).
	Weighted blankets (vs usual weight blankets)	Children with ASD and 5 mo of sleep concerns are possibly no more likely to have decreased WASO (as measured by actigraphy) when using a weighted blanket compared with when using a regular weight blanket (low confidence in the evidence; one Class II study, Gringras 2014). Children with ASD and 5 mo of sleep concerns are possibly no more likely to have a greater reduction in the number of night wakings (as measured by actigraphy) when using a weighted blanket compared with when using a regular weight blanket (low confidence in the evidence; one Class II study, Gringras 2014).
	STS mattress technology (vs regular mattress)	Children with ASD and sleep difficulties are possibly no more likely to have lower WASO (as measured by actigraphy over 2 weeks) when using the STS mattress technology turned on compared with when using the mattress with the technology turned off (low confidence in the evidence; one Class II study, Frazier 2017).
Total sleep time	CBT alone	Children with ASD (aged 4–10 y) with sleep onset insomnia and impaired sleep maintenance doing CBT alone are possibly are no more likely to have lower scores on the CSHQ sleep duration subscore at 12 wk than children taking placebo (low confidence; one Class II study, Cortesi 2012).
	Parent educational pamphlet	Children with ASD (aged 2–10 y) and a mean sleep latency of 30 min whose parents receive an educational pamphlet are possibly no more likely than children of parents receiving no pamphlet to have longer TST at 2 weeks (low confidence; one Class II study, Adkins 2012). Children with ASD (aged 2–10 y) and a mean sleep latency of 30 min whose parents receive an educational pamphlet possibly have no greater improvement in TST from baseline to 2 wk than children of parents receiving no pamphlet (low confidence; one Class II study, Adkins 2012).
	Individual parental sleep education (vs group parental sleep education)	Children with ASD (aged 2–10 y) and prolonged sleep latency whose parents receive individual sleep training are possibly no more likely than children of parents receiving group sleep education to have longer TST at 4 wk (low confidence; one Class II study, Malow 2015). Children with ASD (aged 2–10 y) and prolonged sleep latency whose parents receive individual sleep training are possibly no more likely than children of parents receiving

		group sleep education to have a greater increase in TST from baseline to 4 wk (low confidence; one Class II study, Malow 2015).
	Parental sleep-specific behavioral training	There is insufficient evidence to determine whether children with ASD and at least one sleep disturbance whose parents receive a sleep-specific behavioral training are more or less likely than children of parents receiving education unrelated to sleep to have longer TST at 8 weeks (very low confidence; one Class III study, Johnson 2013).
	Weighted blankets (vs usual weight blankets)	Children with ASD and 5 mo of sleep concerns are possibly no more likely to have increased TST as measured by actigraphy when using a weighted blanket compared to when using a regular weight blanket (low confidence in the evidence; one Class II study, Gringras 2014).
	STS mattress technology (vs regular mattress)	Children with ASD and sleep difficulties are possibly no more likely to have longer TST (as measured by actigraphy over 2 wk) when using the STS mattress technology turned on compared with when using the mattress with the technology turned off (low confidence in the evidence; one Class II study, Frazier 2017).
Daytime behavior	Controlled-release melatonin	Children with ASD and sleep problems are possibly no more likely to have improved daytime behavior as measured by the Developmental Behavior Checklist after receiving controlled-release melatonin 2–10 mg nightly compared with when receiving placebo (low confidence in the evidence; one Class II study, Wright 2011).
	Weighted blankets (vs usual weight blankets)	Children with ASD and 5 mo of sleep concerns are possibly no more likely to have improved daytime behavior as measured by the Aberrant Behavior Checklist when using a weighted blanket compared with when using a regular weight blanket (low confidence in the evidence; one Class II study, Gringras 2014).
	STS mattress technology (vs regular mattress)	There is insufficient evidence to support or refute whether children with ASD and sleep difficulties are more or less likely to have improved daytime behavior when using the STS mattress technology turned on compared with when using the mattress with the technology turned off (very low confidence in the evidence; one Class III study [for questionnaire outcomes], Frazier 2017).

Abbreviations: CBT: Cognitive behavioral therapy; CSHQ: Children's Sleep Habit Questionnaire; SE: sleep efficiency; SOL: sleep onset latency; STS: Sound-to-Sleep; TST: total sleep time; WASO: wake after sleep onset.

Table e-5. 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 e-6. 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 AEs of melatonin use and the lack of long-term safety data (Level B).

Table e-7. Recommendation statements for care of children and adolescents with 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 AEs 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.

DISCLAIMER

Practice guidelines, practice advisories, comprehensive systematic reviews and other guidance published by the American Academy of Neurology and its affiliates are assessments of current scientific and clinical information provided as an educational service. The information: 1) should not be considered inclusive of all proper treatments, methods of care, or as a statement of the standard of care; 2) is not continually updated and may not reflect the most recent evidence (new evidence may emerge between the time information is developed and when it is published or read); 3) addresses only the question(s) specifically identified; 4) does not mandate any particular course of medical care; and 5) is not intended to substitute for the independent professional judgment of the treating provider, as the information does not account for individual variation among patients. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. AAN provides this information on an "as is" basis, and makes no warranty, expressed or implied, regarding the information. AAN specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. AAN assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information or for any errors or omissions.

Drs. Buckley and Thurm provided scientific expertise to this paper and these recommendations in no way represent a position from the National Institute of Mental Health or the NIH.

CONFLICT OF INTEREST STATEMENT

The American Academy of Neurology (AAN) is committed to producing independent, critical, and trustworthy clinical practice guidelines (CPGs) 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 www.aan.com.[24]

ACKNOWLEDGMENT

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1

APPENDICES

Appendix e-1. AAN GDDI mission

The mission of the GDDI is to develop, disseminate, and implement evidence-based systematic reviews and clinical practice guidelines related to the causation, diagnosis, treatment, and prognosis of neurologic disorders.

The GDDI is committed to using the most rigorous methods available within its budget, in collaboration with other available AAN resources, to most efficiently accomplish this mission.

Appendix e-2. 2017–2019 AAN GDDI Subcommittee members

The AAN has structured its subcommittee overseeing guideline development in several ways in recent years. The GDDI was first formed in 2014; it existed under a previous name and structure when this guideline project was inaugurated. At the time this guideline was approved to advance beyond subcommittee development, the subcommittee was constituted as below.

Cynthia Harden, MD (Chair); Steven R. Messé, MD (Co-Vice-Chair); Sonja Potrebic, MD, PhD (Co-Vice-Chair); Stephen Ashwal, MD; Lori L. Billinghurst, MD; Brian Callaghan, MD; Gregory S. Day, MD, MSc; Diane Donley, MD; Richard M. Dubinsky, MD, MPH; Jeffrey Fletcher, MD; Gary S. Gronseth, MD (Senior Evidence-based Medicine Methodology Expert); Michael Haboubi, DO; John J. Halperin, MD; Yolanda Holler-Managan, MD; Annette M. Langer-Gould, MD, PhD; Nicole Licking, DO; Mia T. Minen, MD; Pushpa Narayanaswami, MBBS, DM; Maryam Oskoui, MD; Alejandro A. Rabinstein, MD; Alexander Rae-Grant, MD; Kevin Sheth, MD; Kelly Sullivan, PhD; Eric J. Ashman, MD (Ex-Officio); Jacqueline French, MD (Ex-Officio, Guideline Process Historian)

Appendix e-3: Complete search strategies

Updated search strategy

Ovid MEDLINE

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present

#	Searches	Results	Type
1	child development disorders, pervasive.mp. or exp autistic disorder/ [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	23451	Advanced
2	child development disorders, pervasive/dt, dh, th, px or exp autistic disorder/dt, dh, th, px	10035	Advanced
3	exp complementary therapies/	194402	Advanced
4	2 and 3	381	Advanced
5	(complementary or alternative or "mind body").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	563213	Advanced
6	2 and 5	303	Advanced
7	4 or 6	598	Advanced
8	(exp dietary supplements/ or exp vitamins/ or diet*.mp.) and 2 [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	252	Advanced
9	2 and nutrition*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	92	Advanced
10	8 or 9	287	Advanced
11	exp Behavior Therapy/ or exp Psychotherapy/	168950	Advanced
12	2 and 11	1370	Advanced
13	2 and parents/	653	Advanced
14	2 and (skill* or training or intervention*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	2811	Advanced
15	7 or 10 or 12 or 13 or 14	4208	Advanced
16	attention*.mp. or exp "attention deficit and disruptive behavior disorders"/ or adhd.mp. or "attention deficit disorder with hyperactivity"/ or conduct disorder/ or "obsessive-compulsive*".mp. or hoarding.mp. or "irritable mood*".mp. or exp anxiety disorders/ or anxiety*.mp. [mp=title, abstract, original title, name of substance word, subject heading word,		

keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 539842 Advanced

17 (panic* or phobia* or phobic* or anxious* or neurotic or neuroses or depress* or aggress*).mp. or exp depressive disorders/ [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 484915 Advanced

18 2 and (16 or 17) 2509 Advanced

19 2 and (defiance or defiant or oppositional or disrupt*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 318 Advanced

20 15 or 18 or 19 5834 Advanced

21 limit 20 to (English language and yr="2012 - 2016")1849 Advanced

22 limit 21 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or evaluation studies or meta analysis or multicenter study or observational study or pragmatic clinical trial or randomized controlled trial or "review" or systematic reviews or validation studies) 654 Advanced

23 exp case-control studies/ or exp cohort studies/ or exp cross-sectional studies/ or exp feasibility studies/ or exp intervention studies/ 1932689 Advanced

24 21 and 23 392 Advanced

25 22 or 24 945 Advanced

26 25 not (letter or note or editorial).pt. 940 Advanced

27 remove duplicates from 26 889

Cochrane CENTRAL

Cochrane CENTRAL – same strategy = 97

Embase

Embase 1988 to 2016 Week 25

#	Searches	Results	Type
1	exp autism/dm, dt, pc, rh, th [Disease Management, Drug Therapy, Prevention, Rehabilitation, Therapy]	5852	Advanced
2	exp *autism/dm, dt, pc, rh, th	4593	Advanced
3	exp alternative medicine/	38802	Advanced
4	exp diet therapy/	259883	Advanced
5	exp psychotherapy/	161404	Advanced
6	exp attention deficit disorder/ or attention/	97824	Advanced
7	behavior disorder/ or abnormal behavior/ or attention deficit disorder/ or disruptive behavior/ or exp impulse control disorder/ or oppositional defiant disorder/	90729	Advanced
8	conduct disorder/	5436	Advanced
9	obsessive compulsive disorder/	17349	Advanced
10	irritability/	17852	Advanced

11 anxiety disorder/ or anxiety neurosis/ or "mixed anxiety and depression"/ or exp obsessive compulsive disorder/ or exp panic/ or exp phobia/103749 Advanced
12 exp depression/ 329867 Advanced
13 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 911732 Advanced
14 2 and 13 2385 Advanced
15 limit 14 to (English language and yr="2012 - 2016")819 Advanced
16 2 and (skill* or parent* or intervention*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 2208 Advanced
17 limit 16 to (English language and yr="2012 - 2016")804 Advanced
18 15 or 17 1139 Advanced
19 exp comparative study/ or exp controlled study/ or exp feasibility study/ or exp observational study/ or exp pilot study/ or exp quasi experimental study/ 5813877 Advanced
20 exp case control study/ or exp case study/ or exp clinical trial/ or exp "clinical trial (topic)"/ or exp intervention study/ or exp longitudinal study/ or exp major clinical study/ or exp prospective study/ or exp retrospective study/ 3469522 Advanced
21 18 and (19 or 20) 588 Advanced
22 18 and (meta-analysis/ or systematic review/) 66 Advanced
23 21 or 22 613 Advanced
24 23 not (case report/ or note.pt. or comment.pt. or letter.pt.) 579 Advanced
25 remove duplicates from 24 560

PsycINFO

PsycINFO 1987 to June Week 3 2016

#	Searches	Results	Type
1	autism spectrum disorders/	30137	Advanced
2	alternative medicine/ or acupuncture/ or aromatherapy/ or faith healing/ or fold medicine/ or biofeedback training/ or dietary supplements/ or holistic health/ or exp hypnotherapy/ or exp massage/ or exp "medicinal herbs and plants"/ or exp meditation/ or exp mind body therapy/	16886	Advanced
3	1 and 2124		Advanced
4	exp Drug Therapy/	111225	Advanced
5	1 and 41122		Advanced
6	exp sleep disorders/ or exp sleep/	24817	Advanced
7	1 and 6264		Advanced
8	exp epilepsy/ or exp anticonvulsive drugs/	26441	Advanced
9	1 and 8395		Advanced
10	exp behavior analysis/	10992	Advanced
11	exp cognitive therapy/ or exp cognitive behavior therapy/ or exp group psychotherapy/ or parent training/ or exp treatment outcomes/ or social skills training.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]	73120	Advanced
12	exp communications skills/ or exp group intervention/ or intervention/ or family intervention/ or early intervention/ or exp school based intervention/	71474	Advanced

13 1 and (10 or 11 or 12 or treatment effectiveness evaluation/) 4485 Advanced
14 exp ATTENTION DEFICIT DISORDER/ or exp ATTENTION/ or exp ATTENTION DEFICIT DISORDER WITH HYPERACTIVITY/ 68794 Advanced
15 exp behavior problems/ 21782 Advanced
16 behavior problems/ or exp behavior disorders/ or exp conduct disorder/ or exp rebelliousness/ 148028 Advanced
17 obsessive compulsive disorder/ or exp hoarding behavior/ or exp hoarding disorder/ or exp neurosis/ or exp obsessive compulsive personality disorder/ 14275 Advanced
18 exp Major Depression/ 103691 Advanced
19 irritability/ 635 Advanced
20 exp Anxiety Disorders/ 64017 Advanced
21 or/14-20 363735 Advanced
22 1 and 21 3478 Advanced
23 3 or 5 or 7 or 9 or 13 or 22 8653 Advanced
24 23 and ("evidence based" or trial* or meta-analysis or "systematic review").mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] 1328 Advanced
25 limit 23 to ("0430 followup study" or "0450 longitudinal study" or "0451 prospective study" or "0453 retrospective study" or "0600 field study" or "0700 interview" or "0800 literature review" or "0830 systematic review" or 1200 meta analysis or 1600 qualitative study or 1800 quantitative study or "2000 treatment outcome/clinical trial") 4997 Advanced

26 24 or 25 5481 Advanced
27 limit 26 to (all journals and English language and yr="2012 - 2016") 2125 Advanced
28 *autism spectrum disorders/ and 27 1882 Advanced
29 exp *Drug Therapy/ or (exp *sleep disorders/ or exp *sleep/) or (exp *epilepsy/ or exp *anticonvulsive drugs/) or exp *behavior analysis/ or (exp *cognitive therapy/ or exp *cognitive behavior therapy/ or exp *group psychotherapy/ or *parent training/ or exp *treatment outcomes/ or *social skills training/) or (exp *communications skills/ or exp *group intervention/ or *intervention/ or *family intervention/ or *early intervention/ or exp *school based intervention/) or (exp *ATTENTION DEFICIT DISORDER/ or exp *ATTENTION/ or exp *ATTENTION DEFICIT DISORDER WITH HYPERACTIVITY/) or exp *behavior problems/ or (*behavior problems/ or exp *behavior disorders/ or exp *conduct disorder/ or exp *rebelliousness/) or (*obsessive compulsive disorder/ or exp *hoarding behavior/ or exp *hoarding disorder/ or exp *neurosis/ or exp *obsessive compulsive personality disorder/) or exp *Major Depression/ or *irritability/ or exp *Anxiety Disorders/ 499096 Advanced
30 28 and 29 1490

Original search strategy

Cochrane Central

EBM Reviews - Cochrane Central Register of Controlled Trials December 2012 # Searches Results Search Type
1 (autism or autistic* or Asperger*).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] 591 Advanced
2 limit 1 to yr="2002 - 2012" 317 Advanced
3 *autistic disorder/DT, th, pc, px or autia*.ti. 478 Advanced
4 2 and 3 256

PsychInfo

PsycINFO 1987 to January Week 3 2013 # Searches Results Search Type
1 autism/ or pervasive developmental disorders/ or aspergers syndrome/ 20537 Advanced
2 alternative medicine/ or acupuncture/ or aromatherapy/ or faith healing/ or folk medicine/ or biofeedback training/ or dietary supplements/ or holistic health/ or exp hypnotherapy/ or exp massage/ or exp "medicinal herbs and plants"/ or exp meditation/ or exp mind body therapy/ 13546 Advanced
3 1 and 2 92 Advanced
4 drug therapy/ 83456 Advanced
5 1 and 4 838 Advanced
6 sleep disorders/ or exp sleep/ 15262 Advanced
7 1 and 6 164 Advanced
8 exp epilepsy/ or exp anticonvulsive drugs/ 19864 Advanced
9 1 and 8 271 Advanced
10 exp behavior analysis/ 8278 Advanced
11 1 and 10 495 Advanced
12 exp cognitive therapy/ or exp cognitive behavior therapy/ or exp group psychotherapy/ or parent training/ or exp treatment outcomes/ or social skills training.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] 57508 Advanced
13 exp communications skills/ or exp group intervention/ or intervention/ or family intervention/ or early intervention/ or exp school based intervention/ 43253 Advanced
14 1 and (12 or 13 or treatment effectiveness evaluation/) 2449 Advanced
15 3 or 5 or 7 or 9 or 11 or 14 3977 Advanced
16 limit 15 to (all journals and English language and yr="2000 - 2012") 2390 Advanced
17 (*autism/ or *pervasive developmental disorders/ or *aspergers syndrome/) and 16 2199 Advanced
18 17 and (evidence adj based).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] 97 Advanced
19 17 and (trial* or meta-analysis or "systematic review").mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] 361 Advanced
20 limit 17 to ("0430 followup study" or "0450 longitudinal study" or "0451 prospective study" or "0453 retrospective study" or "0600 field study" or "0700 interview" or "0800 literature review" or "0830 systematic review" or 1200 meta analysis or 1600 qualitative study or 1800 quantitative study or "2000 treatment outcome/randomized clinical trial") 1380 Advanced
21 18 or 19 or 20 1522

Ovid MEDLINE

Ovid MEDLINE(R) 1946 to January Week 2 2013 # Searches Results Search Type

1 child development disorders, pervasive/ or exp autistic disorder/ 17031 Advanced
2 *child development disorders, pervasive/dt, th or exp *autistic disorder/dt, th 2083 Advanced
3 exp Complementary Therapies/ 163375 Advanced
4 2 and 3 152 Advanced
5 exp Dietary Supplements/ or exp Vitamins/ 53550 Advanced
6 child development disorders, pervasive/dt, dh, th or exp autistic disorder/dt, dh, th 3155 Advanced
7 5 and 6 56 Advanced
8 4 or 7 199 Advanced
9 *child development disorders, pervasive/dt, th, px, pc or exp *autistic disorder/dt, th, px, pc 4613 Advanced
10 *child development disorders, pervasive/dt or exp *autistic disorder/dt 804 Advanced
11 exp Psychotherapy/ 140916 Advanced
12 parents/ and 9 285 Advanced
13 9 and (skill* or training or intervention*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] 1346 Advanced
14 8 or 10 or 12 or 13 2293 Advanced
15 limit 14 to (English language and yr="2000 - 2012") 1567 Advanced
16 limit 15 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or evaluation studies or meta analysis or multicenter study or randomized controlled trial or "review" or systematic reviews or validation studies) 718 Advanced
17 exp case-control studies/ or exp cohort studies/ or exp cross-sectional studies/ or exp feasibility studies/ or exp intervention studies/ 1480198 Advanced
18 15 and 17 274 Advanced
19 16 or 18 873 Advanced
20 19 not (letter or editorial).pt. 860 Advanced
21 remove duplicates from 20 851

Embase

Embase 1988 to 2013 Week 03 # Searches Results Search Type

1 child development disorders, pervasive/ or exp autistic disorder/ 28064 Advanced
2 *child development disorders, pervasive/dt, th or exp *autistic disorder/dt, th 3093 Advanced
3 exp Complementary Therapies/ 29886 Advanced
4 2 and 3 70 Advanced
5 exp Dietary Supplements/ or exp Vitamins/ 367785 Advanced
6 *child development disorders, pervasive/dt or exp *autistic disorder/dt 1331 Advanced
7 exp Psychotherapy/ 127816 Advanced
8 exp case-control studies/ or exp cohort studies/ or exp cross-sectional studies/ or exp feasibility studies/ or exp intervention studies/ 346539 Advanced
9 exp behavior therapy/ 29177 Advanced

10 *child development disorders, pervasive/dt, dm, th, rh or exp *autistic disorder/dt, dm, th, rh 3496 Advanced

11 (7 or 9) and 10 1039 Advanced

12 10 and (skill* or parent* or intervention*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 1637 Advanced

13 4 or 6 or 11 or 12 2898 Advanced

14 limit 13 to (English language and yr="2000 - 2012") 2207 Advanced

15 exp comparative study/ or exp controlled study/ or exp feasibility study/ or exp observational study/ or exp pilot study/ or exp quasi experimental study/ 4598280 Advanced

16 exp case control study/ or exp case study/ or exp clinical trial/ or exp "clinical trial (topic)"/ or exp intervention study/ or exp longitudinal study/ or exp major clinical study/ or exp prospective study/ or exp retrospective study/ 2595366 Advanced

17 14 and (15 or 16) 1043 Advanced

18 14 and (meta-analysis/ or systematic review/) 89 Advanced

19 17 or 18 1069 Advanced

20 limit 19 to embase 907 Advanced

21 remove duplicates from 20 903

Scopus ((TITLE-ABS-KEY((**autism** OR **autistic** OR **asperger*** OR (**pdd** AND **pervasive**))) AND TITLE-ABS-KEY(**skill*** OR **train*** OR **intervention*** OR **therapy** OR **aba** OR **"behavioral analysis"** OR **"behavioural analysis"**))) AND (**outcome*** OR **effective*** OR **followup**) AND NOT (PMID(**1*** OR **2*** OR **3*** OR **4*** OR **5*** OR **6*** OR **7*** OR **8*** OR **9***)) AND (LIMIT-TO(PUBYEAR, **2013**) OR LIMIT-TO(PUBYEAR, **2012**) OR LIMIT-TO(PUBYEAR, **2011**) OR LIMIT-TO(PUBYEAR, **2010**) OR LIMIT-TO(PUBYEAR, **2009**) OR LIMIT-TO(PUBYEAR, **2008**) OR LIMIT-TO(PUBYEAR, **2007**) OR LIMIT-TO(PUBYEAR, **2006**) OR LIMIT-TO(PUBYEAR, **2005**) OR LIMIT-TO(PUBYEAR, **2004**) OR LIMIT-TO(PUBYEAR, **2003**) OR LIMIT-TO(PUBYEAR, **2002**) OR LIMIT-TO(PUBYEAR, **2001**) OR LIMIT-TO(PUBYEAR, **2000**)) AND (LIMIT-TO(LANGUAGE, **"English"**)) AND (EXCLUDE(DOCTYPE, **"ip"**)) 1952

1

Appendix e-4. Evidence profile tables

The evidence profile tables are available from the AAN, by request.

Appendix e-5. Evidence synthesis tables

The evidence synthesis tables are available from the AAN, by request.

Appendix e-6. Rationale of factors considered in developing the practice recommendations

In this appendix, *EVID* refers to evidence systematically reviewed; *RELA* to strong evidence derived from related conditions; *PRIN* to axiomatic principles of care; and *INFER* to inferences made from one or more statements in the recommendation rationale.

In the tables that follow, consensus is considered to have been reached if 80% or more of the guideline panel agree on the strength of a given domain. For nonpremise domains, intensity of shading corresponds to the number of panel members who were in agreement (shading of greater intensity indicates a larger number of panel members who reached agreement). The strength of the recommendation is anchored to the strength of the inference. The recommendation strength can be downgraded for any modifier; it can be upgraded only by one level for a moderate to large benefit relative to harm. In addition, domains include the premises and factors on which the recommendations are based.

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 (PRIN). 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 (PRIN).

Statement 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).

Statement 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).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in Inference (and evidence)	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 1	Benefit >> harm 2	Benefit >>> harm 14	Yes
Importance of outcomes	Not important or 0	Mildly 1	Very 9	Critically important 7	Yes
Variation in preferences	Large 0	Moderate 1	Modest 5	Minimal 11	Yes
Feasible	Rarely 0	Occasionally 3	Usually 6	Always 8	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 4	Small 13	Yes
Strength of recommendation	R/U	C	B	A	

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in Inference (and evidence)	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 1	Benefit >> harm 1	Benefit >>> harm 15	Yes
Importance of outcomes	Not important or 0	Mildly 1	Very 6	Critically important 10	Yes
Variation in preferences	Large 0	Moderate 2	Modest 4	Minimal 11	Yes
Feasible	Rarely 0	Occasionally 1	Usually 4	Always 12	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 2	Small 15	Yes
Strength of recommendation	**R/U**	**C**	**B**	**A**	

Statement 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).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in Inference (and evidence)	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 1	Benefit >> harm 2	Benefit >>> harm 14	Yes
Importance of outcomes	Not important or 0	Mildly 1	Very 9	Critically important 7	Yes
Variation in preferences	Large 0	Moderate 2	Modest 9	Minimal 6	Yes
Feasible	Rarely 0	Occasionally 3	Usually 10	Always 4	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 14	Small 3	Yes
Strength of recommendation	R/U	C	B	A	

x

Statement 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).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in Inference (and evidence)	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 1	Benefit >> harm 6	Benefit >>> harm 10	Yes
Importance of outcomes	Not important or 0	Mildly 1	Very 9	Critically important 7	Yes
Variation in preferences	Large 0	Moderate 3	Modest 10	Minimal 4	Yes
Feasible	Rarely 0	Occasionally 2	Usually 9	Always 6	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 10	Small 7	Yes
Strength of recommendation	R/U	C	B	A	

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]

In addition, this systematic review shown that family-based CBT with or without melatonin improves several aspects of sleep (EVID). 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 (PRIN). 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 (INFER).

Statement 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).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference (and evidence)	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 3	Benefit >>> harm 13	Yes
Importance of outcomes	Not important or 0	Mildly 0	Very 12	Critically 4	Yes
Variation in preferences	Large 0	Moderate 4	Modest 10	Minimal 2	Yes
Feasible	Rarely 0	Occasionally 2	Usually 12	Always 2	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 9	Small 7	Yes
Strength of recommendation	R/U	C	B	A	

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 (PRIN). There is low to moderate confidence that melatonin improves various aspects of sleep in children and adolescents with ASD (EVID). In the studies included in the systematic review, pharmaceutical-grade melatonin preparations were used and the exact administration amounts ascertained (EVID). One study used prolonged-release melatonin up to 10 mg/d, one used 3 mg of prolonged-release melatonin, and one started 2 mg of immediate-release melatonin with titration to effect up to 10 mg (modal dose 7 mg).[29, 31, 32] 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 (INFER). Melatonin is generally administered 30–60 minutes before bedtime (RELA).[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 (PRIN).

No study in the systematic review reported serious AEs (EVID). Adverse events reported with melatonin include morning drowsiness, increased enuresis, headache, dizziness, diarrhea, rash, and hypothermia (RELA).[44-47] Melatonin is currently used safely as neuroprotection in preterm infants (RELA),[51] suggesting that it may also be safe in other pediatric populations (INFER), 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 (RELA).[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 (PRIN). 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 (PRIN).

Statement 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).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference (and evidence)	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 6	Benefit >>> harm 10	Yes
Importance of outcomes	Not important or 0	Mildly 0	Very 11	Critically 5	Yes
Variation in preferences	Large 0	Moderate 1	Modest 8	Minimal 7	Yes
Feasible	Rarely 0	Occasionally 1	Usually 9	Always 6	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 10	Small 6	Yes
Strength of recommendation	R/U	C	B	A	

Statement 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).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference (and evidence)	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 1	Benefit > harm 1	Benefit >> harm 7	Benefit >>> harm 7	Yes
Importance of outcomes	Not important or 2	Mildly 0	Very 11	Critically 3	Yes
Variation in preferences	Large 0	Moderate 2	Modest 7	Minimal 7	Yes
Feasible	Rarely 0	Occasionally 3	Usually 11	Always 2	Yes
Cost relative to net benefit	Very large 0	Large 1	Moderate 11	Small 4	Yes
Strength of recommendation	R/U	C	B	A	

Statement 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)

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference (and evidence)	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 1	Benefit > harm 0	Benefit >> harm 3	Benefit >>> harm 12	Yes
Importance of outcomes	Not important or 1	Mildly 0	Very 9	Critically 6	Yes
Variation in preferences	Large 0	Moderate 1	Modest 6	Minimal 9	Yes
Feasible	Rarely 0	Occasionally 1	Usually 8	Always 7	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 9	Small 7	Yes
Strength of recommendation	R/U	C	B	A	

Statement 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 AEs of melatonin use and the lack of long-term safety data (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference (and evidence)	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 2	Benefit >>> harm 14	Yes
Importance of outcomes	Not important or 0	Mildly 0	Very 7	Critically 9	Yes
Variation in preferences	Large 0	Moderate 0	Modest 5	Minimal 11	Yes
Feasible	Rarely 0	Occasionally 0	Usually 1	Always 15	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 2	Small 14	Yes
Strength of recommendation	R/U	C	B	A	

Recommendation 4: CAM Approaches

Rationale

Families of children and adolescents with ASD are often interested in CAM approaches (PRIN). The systematic review identified that STS mattress technology possibly results in higher SE over 2 weeks but possibly fails to improve SOL, WASO, or TST (EVID). Weighted blankets possibly fail to improve SOL, SE, WASO, night awakenings, TST, and daytime behavior over 2 weeks (EVID). No high-quality studies of other CAM approaches were identified (EVID). Adverse events 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 (EVID). Weighted blankets vary in approach to production (PRIN); 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 (EVID).

Statement 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).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in Inference (and evidence)	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 1	Benefit >> harm 5	Benefit >>> harm 10	Yes
Importance of outcomes	Not important or 0	Mildly 2	Very 11	Critically 3	Yes
Variation in preferences	Large 0	Moderate 2	Modest 12	Minimal 2	Yes
Feasible	Rarely 0	Occasionally 2	Usually 6	Always 8	Yes
Cost relative to net benefit	Very large 0	Large 1	Moderate 5	Small 10	Yes
Strength of recommendation	R/U	C	B	A	

Statement 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 AEs with blanket use and that blankets could be a reasonable nonpharmacologic approach to try for some individuals (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in Inference (and evidence)	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 1	Benefit > harm 1	Benefit >> harm 10	Benefit >>> harm 4	Yes
Importance of outcomes	Not important or 1	Mildly 4	Very 9	Critically 2	Yes
Variation in preferences	Large 1	Moderate 4	Modest 6	Minimal 5	No
Feasible	Rarely 0	Occasionally 3	Usually 9	Always 4	Yes
Cost relative to net benefit	Very large 1	Large 4	Moderate 8	Small 3	No
Strength of recommendation	R/U	C	B	A	

REFERENCES

1. Richdale AL. Sleep problems in autism: prevalence, cause, and intervention. Dev Med Child Neurol 1999;41:60-66.
2. Reynolds AM, Malow BA. Sleep and autism spectrum disorders. Pediatr Clin North Am 2011;58:685-698.
3. Hodge D, Carollo TM, Lewin M, Hoffman CD, Sweeney DP. Sleep patterns in children with and without autism spectrum disorders: developmental comparisons. Res Dev Disabil 2014;35:1631-1638.
4. Delahaye J, Kovacs, E., Sikora, D., Hall, T., Orlich, F., Clemons, T., van der Weerd, E., Glick, L., Kuhlthau, K. The relationship between Health-Related Quality of Life and sleep problems in children with Autism Spectrum Disorders. Research in Autism Spectrum Disorders 2014;8:292-303.
5. Cohen S, Conduit R, Lockley SW, Rajaratnam SM, Cornish KM. The relationship between sleep and behavior in autism spectrum disorder (ASD): a review. J Neurodev Disord 2014;6:44.
6. Goldman SE, Richdale AL, Clemons T, Malow BA. Parental sleep concerns in autism spectrum disorders: variations from childhood to adolescence. J Autism Dev Disord 2012;42:531-538.
7. Robinson AM, Richdale AL. Sleep problems in children with an intellectual disability: parental perceptions of sleep problems, and views of treatment effectiveness. Child Care Health Dev 2004;30:139-150.
8. Park JH, An H, Jang ES, Chung S. The influence of personality and dysfunctional sleep-related cognitions on the severity of insomnia. Psychiatry Res 2012;197:275-279.
9. Tudor ME, Hoffman, C. D., & Sweeney, D. P. . Children With Autism: Sleep Problems and Symptom Severity. Focus on Autism and Other Developmental Disabilities 2012;27:254–262.
10. Meltzer LJ. Brief report: sleep in parents of children with autism spectrum disorders. J Pediatr Psychol 2008;33:380-386.
11. Patzold LM, Richdale AL, Tonge BJ. An investigation into sleep characteristics of children with autism and Asperger's Disorder. J Paediatr Child Health 1998;34:528-533.
12. Gottlieb DJ, Vezina RM, Chase C, et al. Symptoms of sleep-disordered breathing in 5-year-old children are associated with sleepiness and problem behaviors. Pediatrics 2003;112:870-877.
13. Schreck KA, Mulick JA, Smith AF. Sleep problems as possible predictors of intensified symptoms of autism. Res Dev Disabil 2004;25:57-66.
14. Schwebel DC, Brezausek CM. Nocturnal awakenings and pediatric injury risk. J Pediatr Psychol 2008;33:323-332.
15. Koulouglioti C, Cole R, Kitzman H. Inadequate sleep and unintentional injuries in young children. Public Health Nurs 2008;25:106-114.
16. Lumeng JC, Somashekar D, Appugliese D, Kaciroti N, Corwyn RF, Bradley RH. Shorter sleep duration is associated with increased risk for being overweight at ages 9 to 12 years. Pediatrics 2007;120:1020-1029.
17. Perez-Chada D, Perez-Lloret S, Videla AJ, et al. Sleep disordered breathing and daytime sleepiness are associated with poor academic performance in teenagers. A study using the Pediatric Daytime Sleepiness Scale (PDSS). Sleep 2007;30:1698-1703.

18. Fallone G, Acebo C, Seifer R, Carskadon MA. Experimental restriction of sleep opportunity in children: effects on teacher ratings. Sleep 2005;28:1561-1567.
19. Owens JA, Belon K, Moss P. Impact of delaying school start time on adolescent sleep, mood, and behavior. Arch Pediatr Adolesc Med 2010;164:608-614.
20. Carmassi C, Palagini L, Caruso D, et al. Systematic Review of Sleep Disturbances and Circadian Sleep Desynchronization in Autism Spectrum Disorder: Toward an Integrative Model of a Self-Reinforcing Loop. Front Psychiatry 2019;10:366.
21. Medicine AAoS. Case Book of Sleep Medicine, 2nd ed. . Darien, IL: American Academy of Sleep Medicine, 2015.
22. Bootzin RR, Stevens SJ. Adolescents, substance abuse, and the treatment of insomnia and daytime sleepiness. Clin Psychol Rev 2005;25:629-644.
23. Perfect MM, Elkins GR. Cognitive-behavioral therapy and hypnotic relaxation to treat sleep problems in an adolescent with diabetes. J Clin Psychol 2010;66:1205-1215.
24. Neurology) AAAo. Clinical Practice Guideline Process Manual. St. Paul, MN: American Academy of Neurology, 2011.
25. Association AP. Diagnostic and Statistical Manual of Mental Disorders (5th ed., text rev.), 5th edition ed. Arlington, VA: American Psychiatric Publishing, 2013.
26. Owens JA, Spirito A, McGuinn M. The Children's Sleep Habits Questionnaire (CSHQ): psychometric properties of a survey instrument for school-aged children. Sleep 2000;23:1043-1051.
27. Einfeld SL, & Tonge, B. J. . Manual for the Developmental Behaviour Checklist: Primary Carer Version (DBC-P) & Teacher Version (DBC-T) (2nd. ed.), 2nd ed. Clayton, Melbourne, Austrailia: Monash University Centre for Developmental Psychiatry and Psychology, 2002.
28. Aman MG, Singh NN, Stewart AW, Field CJ. The aberrant behavior checklist: a behavior rating scale for the assessment of treatment effects. Am J Ment Defic 1985;89:485-491.
29. Cortesi F, Giannotti F, Sebastiani T, Panunzi S, Valente D. Controlled-release melatonin, singly and combined with cognitive behavioural therapy, for persistent insomnia in children with autism spectrum disorders: a randomized placebo-controlled trial. J Sleep Res 2012;21:700-709.
30. Association AP. Diagnostic and statistical manual of mental disorders (4th ed., text rev.). Washington, DC: American Psychiatric Publishing, 2000.
31. Gringras P, Nir T, Breddy J, Frydman-Marom A, Findling RL. Efficacy and Safety of Pediatric Prolonged-Release Melatonin for Insomnia in Children With Autism Spectrum Disorder. J Am Acad Child Adolesc Psychiatry 2017;56:948-957.e944.
32. Wright B, Sims D, Smart S, et al. Melatonin versus placebo in children with autism spectrum conditions and severe sleep problems not amenable to behaviour management strategies: a randomised controlled crossover trial. J Autism Dev Disord 2011;41:175-184.
33. Adkins KW, Molloy C, Weiss SK, et al. Effects of a standardized pamphlet on insomnia in children with autism spectrum disorders. Pediatrics 2012;130 Suppl 2:S139-144.
34. Malow BA, Adkins KW, Reynolds A, et al. Parent-based sleep education for children with autism spectrum disorders. J Autism Dev Disord 2014;44:216-228.
35. Johnson CR, Turner KS, Foldes E, Brooks MM, Kronk R, Wiggs L. Behavioral parent training to address sleep disturbances in young children with autism spectrum disorder: a pilot trial. Sleep Med 2013;14:995-1004.
36. Gringras P, Green D, Wright B, et al. Weighted blankets and sleep in autistic children--a randomized controlled trial. Pediatrics 2014;134:298-306.

37. Frazier TW, Krishna J, Klingemier E, Beukemann M, Nawabit R, Ibrahim S. A randomized, crossover trial of a novel sound-to-sleep mattress technology in children with autism and sleep difficulties. Journal of clinical sleep medicine 2017;13:95-104.
38. Medic G, Wille M, Hemels ME. Short- and long-term health consequences of sleep disruption. Nat Sci Sleep 2017;9:151-161.
39. Veatch OJ, Maxwell-Horn AC, Malow BA. Sleep in Autism Spectrum Disorders. Curr Sleep Med Rep 2015;1:131-140.
40. Malow BA, Byars K, Johnson K, et al. A practice pathway for the identification, evaluation, and management of insomnia in children and adolescents with autism spectrum disorders. Pediatrics 2012;130 Suppl 2:S106-124.
41. Hartz I, Furu K, Bratlid T, Handal M, Skurtveit S. Hypnotic drug use among 0-17 year olds during 2004-2011: a nationwide prescription database study. Scand J Public Health 2012;40:704-711.
42. Cerezo AB LA, Alvarez-Fernandez MA, Hornedo-Ortega R, Troncoso, AM, Garcia-Parrilla MC Quality control and determination of melatonin in food supplements. Journal of Food Composition and Analysis
2016;45:80-86.
43. Erland LA, Saxena PK. Melatonin Natural Health Products and Supplements: Presence of Serotonin and Significant Variability of Melatonin Content. J Clin Sleep Med 2017;13:275-281.
44. Bruni O, Alonso-Alconada D, Besag F, et al. Current role of melatonin in pediatric neurology: clinical recommendations. Eur J Paediatr Neurol 2015;19:122-133.
45. Hoebert M, van der Heijden KB, van Geijlswijk IM, Smits MG. Long-term follow-up of melatonin treatment in children with ADHD and chronic sleep onset insomnia. J Pineal Res 2009;47:1-7.
46. van Geijlswijk IM, Mol RH, Egberts TC, Smits MG. Evaluation of sleep, puberty and mental health in children with long-term melatonin treatment for chronic idiopathic childhood sleep onset insomnia. Psychopharmacology (Berl) 2011;216:111-120.
47. van Geijlswijk IM, van der Heijden KB, Egberts AC, Korzilius HP, Smits MG. Dose finding of melatonin for chronic idiopathic childhood sleep onset insomnia: an RCT. Psychopharmacology (Berl) 2010;212:379-391.
48. Shi L, Li N, Bo L, Xu Z. Melatonin and hypothalamic-pituitary-gonadal axis. Curr Med Chem 2013;20:2017-2031.
49. Henderson K. Policies and practices used by states to serve children with autism spectrum disorders. Journal of Disability Policy Studies 2011;22:106-115.
50. Cummings C, Canadian Paediatric Society CPC. Melatonin for the management of sleep disorders in children and adolescents. Paediatr Child Health 2012;17:331-336.
51. Biran V, Phan Duy A, Decobert F, Bednarek N, Alberti C, Baud O. Is melatonin ready to be used in preterm infants as a neuroprotectant? Dev Med Child Neurol 2014;56:717-723.
52. Kennaway DJ. Potential safety issues in the use of the hormone melatonin in paediatrics. J Paediatr Child Health 2015;51:584-589.