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


Ashura Williams Buckley (1), Deborah Hirtz (2), Maryam Oskoui (3), Carolyn Bridgemohan (4), Daniel Coury (5), Diane Donley (6), Robert Findling (7), David Gloss (8), Gary Gronseth (9), Shannon Merillat (10) David Michelson (12), Judith Owens (13), Tamara Pringsheim (14), Lin Sikich (15), Aubyn Stahmer (16), Roberto Tuchman (17), Zachary Warren (18), Amy Wetherby (19), Max Wiznitzer (20), Stephen Ashwal (21), Anshu Batra (22), Geraldine Dawson (14), Thomas Gaughan (1), Audrey Thurm (1)

Additional authors who contributed: Melissa Armstrong (20)

1. National Institute of Mental Health
2. University of Vermont
3. McGill University, Montréal, Québec, Canada
4. Boston Children’s Hospital
5. The Ohio State University College of Medicine
6. Northern Michigan Neurology
7. Case Western Reserve University School of Medicine
8. Barrow Neurologic Institute
9. Kansas University Medical Center
10. American Academy of Neurology
11. Beth Israel Deaconess Medical Center
12. Boston Children’s Hospital
13. University of Calgary
14. University North Carolina- Chapel Hill
15. UC San Diego and Rady Children's Hospital
16. Miami Children’s Hospital
17. Vanderbilt Kennedy Center
18. College of Medicine at Florida State University
19. Rainbow Babies & Children’s Hospital, Ohio
20. University of Florida
21. Loma Linda University School of Medicine
22. Developmental Pediatrics in Los Angeles, California

Address correspondence and reprint requests to

American Academy of Neurology:

guidelines@aan.com
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D. Coury has nothing to disclose.

G. Dawson serves on the NIH Interagency Autism Coordinating Committee, NIMH Board of Scientific Advisors, NICHD Strategic Planning Working Group, Integragen, Inc. Autism Speaks Scientific Advisory Board and Autism Speaks Treatment Network Scientific Advisory Board; receives funding for travel from the NIH Interagency Autism Coordinating Committee, NIMH Board of Scientific Advisors, NICHD Strategic Planning Working Group, Integragen, Inc. Autism Speaks Advisory Board and Autism Speaks Treatment Network Scientific Advisory Board, McGill University, Harvard University, University of Pittsburgh, Brown University, Texas Autism Research Center, NIH, American College of Neuropsychopharmacology, Cold Spring Harbor Laboratories (Banbury Conference), Simons Foundation, Alexandria Summit, Association for Psychological Science, Roche-Nature Medicine, and Fudan University; serves as Associate Editor for *Development and Psychopathology* and on the Editorial boards of *Autism Research, Autism Research and Treatment, Clinical Psychological Science*, and the *Journal of Neurodevelopmental Disorders*; receives royalties from several books on autism published by Guilford Press, Inc; received honoraria from the NIH interagency Autism Coordinating
Committee, NIMH Board of Scientific Advisors, Integragen, Inc., McGill University, University of Pittsburgh, Brown University, Texas Autism Research Center, NIH, American College of Neuropsychopharmacology, and Fudan University; serves as Chief Science Officer for Autism Speaks; serves as Advisor for Guidepoint Expert Advisors, Inc.; spends 1% of her clinical efforts on clinical diagnostic evaluations and early intervention for young children with autism spectrum disorder; and has given testimony to the US Senate Committee on Armed Services, Subcommittee on Personnel in support of programs and policies to support military families with special needs.

D. Donley reviews child neurology cases for Physicians Review Organization of Michigan and her husband, Bradley Evans, MD, reviews adult neurology PROM (an independent company, related to Michigan State Medical Society that performs independent reviews of hospitalizations at various Michigan facilities) cases; she reads pediatric electroencephalograms, and her husband reads adult electroencephalograms that are done at Munson Medical Center; her husband is PI at their site for multi-center clinical drug trials, phase 2-4, for multiple sclerosis (MS), Alzheimer disease, Parkinson, and she serves as blinded rater for these trials, for which Sanofi has sponsored two MS trials in which patients were paid for participation.


receives publishing royalties from Sage, Johns Hopkins University Press, and American Psychiatric Press; receives consulting fees for serving on the advisory boards of Alexza, AstraZeneca, Biovail, Bristol-Myers Squibb, Forest, GlaxoSmithKline, Johnson & Johnson, KemPharm, Lilly, Lundbeck, Merck, Novartis, Noven, Oranon, Otsuka, Pfizer, Roche, Sanofi-
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T. Gaughan has nothing to disclose.

D. Gloss serves as an evidence-based medicine consultant for the American Academy of Neurology and as an associate editor (risk of bias classification) for Neurology.

G. Gronseth has received funding for travel to meetings from the AAN; serves as associate editor of Neurology; and has received honoraria for presentations at the AAN Annual Meeting.

S. Merillat has nothing to disclose.

D. Michelson has nothing to disclose.

J. Owens serves on the Narcolepsy Advisory Board for Jazz Pharmaceuticals; has received funding for travel for presentations at meetings; has served as an editor of Behavioral Sleep Medicine, Sleep Medicine Reviews, and the Journal of Developmental and Behavioral Pediatrics; serves on the speakers bureau of Shionogi, Inc.; serves as a consultant for UCB, Takeda Pharmaceutical Company Limited, Purdue Pharma, and Transcept Pharmaceuticals Inc.; and received research support from UCB and the National Cancer Institute.

T. Pringsheim has nothing to disclose.
L. Sikich participated in positive studies of the use of aripiprazole in people with autism spectrum disorder and authored one of the papers, in negative trials of amantadine, fluoxetine and citalopram, and in ongoing trials of memantine, ar-baclofen, oxytocin; serves on the editorial board of the *Journal of Child and Adolescent Psychopharmacology*; receives publishing royalties for *Pediatric Psychopharmacology, 2nd Edition* (chapter on early onset psychosis); and has received honoraria from the North Carolina Psychiatric Association, the King’s Daughter’s Children’s Hospital, Virginia Child Psychiatry Council, NIH Study Sections, Autism Speaks Grant Reviews, Duke University Community Education Meeting, University of Iowa Department of Psychiatry, TENETS DSMB (Research Foundation for Mental Hygiene).

A. Stahmer serves on the advisory board of; has received funding for travel to scientific meetings from the NIH and Institute of Education Sciences (IES) and travel to Denmark from the Danish Ministry of Education; has received publishing royalties from Guilford Press; has received honoraria from Autism Speaks Grant Reviews; received payment to conduct training in behavioral interventions for autism spectrum disorder; dedicates 20% of clinical efforts to behavioral parent training; and has received research support from the NIH and the IES.

A. Thum works for the NIH Intramural Research Program.

R. Tuchman serves on the Autism Speaks Scientific Advisory Committee and expends 10% of his clinical efforts performing electroencephalography and video electroencephalography.

Z. Warren serves on the editorial Board for *Autism: International Journal of Research and Practice*; has received honoraria from Autism Speaks (grant review honorarium, Agency for Healthcare Research & Quality (AHRQ) (Medicaid Medical Director's Learning Collaborative CME Honorarium), East Tennessee State University (CME speaker honorarium), Pri-Med
(education, CME honorarium); expends 20% of his clinical efforts performing diagnostic assessments for children at risk of autism spectrum disorder; receives payment from the Center for Psychological Consultation as an external consultant on a NIMH SBIR grant, developing computer-based parent training interventions for young children with autism spectrum disorder. Hua’s wife is a paid historical preservation consultant for property Tax Adjusters LLC, in Miami FL; received grant support from AHRQ, Autism Speaks, HRSA, MCHB, NIMH, NICHD, NSF, and Simons Foundation; has received financial compensation from the following academic medical centers for presenting ASD specific CME trainings: OUHSC, MUSC, CHOP, IUPUI, Greenville Children's Hospital.

A. Wetherby serves on the editorial advisory board for the Journal of Autism and Developmental Disorders; performs grant review for the NIH; receives publishing royalties from Brookes Publishing Company for *Communication and Symbolic Behavior Scales and the SCERTS Model: A comprehensive Educational Approach for Children with Autism Spectrum Disorders*; and received financial support from the NIH/NIMH, NIH/NICHD, NIH/NIDCD, CDC, U.S. Department of Education.

M. Wiznitzer serves on the editorial boards of *Lancet Neurology* and the *Journal of Child Neurology*; received honoraria as a speaker for AAN and AAP meetings; has given expert testimony for medical malpractice proceedings and the Vaccine Injury Compensation Program—Expert Witness for Department of Health and Human Service (written opinions and hearing testimony); and prepared an affidavit for a medical malpractice case.

S. Ashwal serves on the Medical Advisory Board of the Tuberous Sclerosis Association; receives publishing royalties as coeditor of *Pediatric Neurology: Principles and Practice, 6th edition*;
serves on the Executive Board of the Pediatric Epilepsy Research Foundation; and is a paid staff member at Loma Linda University School of Medicine, Department of Pediatrics.
ABBREVIATIONS LIST

ABC: Aberrant Behavior Checklist
ADI-R: Autism Diagnostic Interview-Revised
ADOS: Autism Diagnostic Observation Schedule
ASD: autism spectrum disorders
CAM: complementary and alternative medicine
CBT: cognitive behavioral therapy
CSHQ: Children’s Sleep Habit Questionnaire
CSHQ-BR: Children’s Sleep Habit Questionnaire-Bed Resistance
DBC: Developmental Behavior Checklist
PSG: polysomnography
SE: Sleep efficiency
SOL: sleep onset latency
TST: time to sleep
WASO: wake after sleep onset
INTRODUCTION

Sleep disturbances, including difficulties initiating and maintaining sleep, irregular sleep-wake patterns, and early morning waking comprise some of the most common and challenging difficulties faced by individuals with autism spectrum disorders (ASD) and their families (Richdale et al, 1999). Between 44% and 83% of children and adolescents with ASD reported sleep abnormalities as a comorbidity, adversely affecting daily functioning. (Reynolds et al, 2011). Although many typically developing children and adolescents (up to 40%) have sleep problems, these problems often tend to lessen with age. In children and adolescents with ASD, the pattern is usually different, and although subtypes of symptoms may vary, sleep problems often persist (Hodge D et al 2014). Sleep disturbance severity is associated with both poor physical health and poor psychosocial quality of life (Delahaye J 2014). Poor quality of sleep or insufficient night time sleep or both exacerbate core and associated features of ASD, contributing to negative effects on mood and emotional regulation, behavior, and cognitive functioning. Children and adolescents with intellectual disabilities and severe autistic symptoms are at especially high risk of sleep problems. Sleep disorders are disruptive to not only the child or adolescent who has them but the entire family, with negative impacts on caregivers’ sleep and quality of life (Meltzer, 2008).

Most of the information available concerning sleep disturbances in children and adolescents with ASD comes from subjective parental reports (surveys and sleep logs) and objective measures, including recordings from actigraphy and polysomnography (PSG). Actigraphy is a diagnostic procedure in which a compact, lightweight, wristwatch-like device records and stores...
information about body movements during a specific period. Activity and inactivity, respectively, are used as a proxy for wake and sleep. PSG is a diagnostic test, usually performed in a laboratory, that gives information about the distribution and percentage of sleep stages, cardiorespiratory function during sleep, body movements, and arousals from sleep. Results from studies indicate that insomnia (defined as trouble initiating or maintaining sleep, frequent and prolonged night awakenings), irregular sleep–wake cycles, short sleep duration, and early morning wake times are the major sleep issues in children and adolescents with ASD. The causes are likely to be multifactorial. For example, dysregulation of melatonin synthesis; altered secretion patterns of melatonin, including inverse patterns, (Kulman et al., 2000; Melke et al., 2008 Tordjman et al., 2005); anomalies in circadian clock genes (Veatch 2016); greater sensitivity in photoperiod (time during the day when light is received); and decreased awareness of or attention to the social and environmental clues that help to habituate sleep-wake cycles are all possible contributors to circadian rhythm misalignment. Abnormalities in neurotransmission intrinsic to ASD, including γ-aminobutyric acid, glutamate, serotonergic and dopaminergic systems also have been proposed. In some children and adolescents with ASD, medical (eg, seizures and gastrointestinal disturbances) or psychiatric (eg, anxiety and obsessive–compulsive symptoms) comorbidities may contribute to sleep problems. However, in other children and adolescents with ASD, core and co-occurring symptoms (eg, sensory integration deficits, ritualistic or self-injurious behaviors, poor communication skills, and limited responsiveness to social cues which can interfere with sleep training and may exacerbate and prolong sleep problems.
Studies in typically developing children show an association between disordered sleep and daytime behavioral disturbances (Gottlieb et al., 2003; Patzold, et al., 1998; Schreck, Mulick, and Smith, 2004), including, an increased risk of injury (Koulouglioti, Cole, & Kitzman, 2008; Schwebel & Brezausek, 2008), obesity (Lumeng et al., 2007) and poor academic performance (Fallone, Acebo, Seifer, & Carskadon, 2005; Owens, Belon, & Moss, 2010; Perez-Chada et al., 2007). Sleep-related exacerbations of autism symptoms, consistently associate poor sleep quality with externalizing behavior in children with ASD (Cohen et al, Journal of Neurodevelopmental Disorders 2014). For example, in a 2012 study (Tudor et al) of 109 children and adolescents between the ages of 3 years and 18 years, it was reported that sleep onset latency (SOL) and shortened sleep time were the strongest predictors of communication deficits and stereotypies. In a similar study of 166 children and adolescents with ASD (Park et al, 2012) between the ages of 4 years and 15 years, sleep problems were associated with communication deficits and restrictive and repetitive behaviors (Cohen et al, 2014).

While it is unclear whether the behavioral abnormalities are a manifestation of poor sleep quality or both the aberrant behavior and the sleep disturbances stem from the same root cause, evidence from studies of typically developing children and adolescents with sleep disorders indicates that therapeutic interventions result in improved behavior. For example, results from a randomized trial of school-aged children (n= 62) with sleep-onset insomnia indicated significant improvement in general health indices after 4 weeks of treatment in the group treated with 5 mg/d of melatonin, taken at bedtime (Smits et al, 2003).
Exogenous melatonin is a synthetic form of endogenous melatonin, a hormone that is the primary biomarker for the circadian rhythm process of sleep regulation. Endogenous melatonin is synthesized from the amino acid tryptophan and produced in the pineal gland, retina, and intestinal tract (Dement). Melatonin release is suppressed by light (especially blue spectrum light) and follows a normal secretory pattern of increasing at dusk, peaking in the middle of the night, and decreasing in the morning. The hormone has both a chronobiologic (circadian) function and a hypnotic effect. Exogenous melatonin’s effect is largely on sleep initiation.

Children and adolescents with ASD and sleep disturbances receive combinations of treatments for their sleep disturbances. These treatments vary over time and may include pharmacotherapy, behavioral and educational therapies, and complementary and alternative medicine (CAM). Behavioral therapies are the mainstay of treatment and first therapeutic choice for pediatric insomnias (Meltzer and Mindell, 2004). For younger children (typically aged 5 years and younger), behavioral therapies may include 1) unmodified extinction, in which parents impose a set bed time and wake up time and ignore protest behavior that occurs after the bed time and before the wake up time, 2) graduated extinction in which parents ignore bedtime resistance for specified periods that are fixed or progressively longer and then respond without reinforcing the resistant behavior (ie, brief and boring verbal reassurance), 3) positive routines whereby set regular pre-bed calming rituals are developed and adhered to strictly by the parents, and 4) bedtime fading in which parents put their child to bed close to the time the child begins falling asleep and then adjust the bedtime earlier each successive night until the agreed-upon target bedtime has been reached (AASM, Casebook Sleep Medicine).
Older children and adolescents may respond to cognitive behavioral therapies (CBT) that have been adapted from adult paradigms (Bootzin & Stevens, 2005; Perfect & Elkins, 2010). Cognitive behavioral sleep interventions are short-term, multicomponent, goal-oriented psychotherapeutic treatments that aim to modify the patterns of thinking and behavior that frequently perpetuate insomnia, such as irregular sleep-wake schedules, poor sleep hygiene, and maladaptive sleep-related cognitions. However, there is currently no consensus on the appropriate age to begin CBT, and reliable tools for the measurement of insomnia severity in children and adolescents have yet to be developed.

Despite these limitations, there are a handful of empirical studies with results that indicate the appropriate first approach for pediatric insomnia is behavioral modification. For example, in a 4-year longitudinal study of 509 children with a mean age of 7.5 years at study onset, the authors discovered that younger children had a good response to extinction-based therapies, and older children responded well to CBT (Byars and Simon, 2014). The authors of another study reported improvements in sleep latency, wake after sleep onset, and sleep efficiency (SE) in 42 9-year-old children after they received 6 months of CBT (Paine and Gradisar, 2011). In a randomized controlled trial of the use of CBT for insomnia in adolescents in group therapy, guided Internet therapy, and a waiting list, insomnia was improved in both treatment conditions compared with the waitlist group (De Bruin et al, 2015). In addition, results from a larger study (n=142) indicated improvement in sleep-related behaviors in school-aged children who received CBT for insomnia versus waitlist (Schlarb et al, 2016).
In this guideline, we review the current literature on available treatment for common sleep disturbances in children and adolescents with ASD and address the following therapeutic questions:

In children and adolescents with ASD, which pharmacologic, behavioral, and CAM interventions are more effective than no treatment for improving:

1. bedtime resistance?
2. SOL?
3. sleep continuity?
4. total sleep time?
5. daytime behavior?

DESCRIPTION OF THE ANALYTIC PROCESS

The American Academy of Neurology (AAN) Guideline Development Dissemination Implementation (GDDI) Subcommittee convened an expert development panel composed of subcommittee members and methodologists on August 1, 2012. After review of potential panel members’ conflict of interest statements and expertise, the AAN Guideline Development Subcommittee (GDDI) approved a multidisciplinary panel of expert authors, including child neurologists (AB, SA, DH, MO, MW, RT, DM, DD), child psychiatrists (RF, LS), child neuropsychologists (GD, AS, AT, AW, ZW), developmental pediatricians (CB, DC, AB, JO) and evidence-based methodologists (GG, TP, DG, TG). All panel members were required to submit online conflict of interest (COI) forms and copies of their curriculum vitae (CV). The panel leadership, consisting of the lead author (AB), the AAN methodologist (DG), and the AAN staff
persons (SM), reviewed the COI forms and CV for financial and intellectual COI. These documents were specifically screened to exclude not only individuals with a clear financial conflict but also those whose professional and intellectual biases might diminish the perceived credibility of the review. In accordance with AAN policy, the lead author (AB) has no COI. One of the 24 authors were determined to have COI, which were judged to be not significant enough to preclude them from authorship (RF). All authors determined to have COI were not permitted to review or rate the evidence. These individuals were involved in an advisory capacity to help validate key questions, assess the scope of the literature search, identify seminal articles to validate the literature search, and participate in the recommendation development process. AAN GDDI leadership provided final approval of author panel composition. This panel was solely responsible for decisions concerning the design, analysis, and reporting of the proposed systematic review, which was then submitted for approval to the AAN GDDI.

This practice guideline follows the methodologies described in the 2011 edition of the AAN’s guideline development process manual, as amended to include an updated classification scheme for therapeutic studies and a change in the order of steps for the external (peer) review process (Van Geijlskijk, 2010). The guideline panelists summarize the process here and provide a detailed description in the appendices referenced later. This process is compliant with Institute of Medicine (IOM) recommendations for guideline development; IOM recommendations were specifically reviewed and adhered to during the process of guideline development.
An initial search was performed using the following keywords to find relevant systematic reviews: autism, autistic, Asperger, PDD, and pervasive. Autism spectrum disorder is the current diagnostic term, defined by the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5). However, many of the studies used to support these guidelines were conducted before DSM-5 was published. Some of these studies include references to diagnostic terms, such as Autism or Asperger syndrome, that were defined in a previous edition of the DSM. For historical accuracy, we retain the former terms when we address the studies that used them. However, in general context, in the summaries, and in the recommendations, we use the most recent and inclusive term, ASD.

Medline, The Cochrane database CENTRAL, EMBASE, and Web of Science were searched. The panel intended to identify and grade relevant articles cited within these systematic reviews. See Appendix e-1 for the search strategy that was used. There were 900 articles cited in the 66 systematic reviews that met inclusion criteria (Appendix e-1).

Initially, the guideline was to be developed as a pilot for a potential new process for creating systematic reviews of systematic reviews written by other authors and organizations. After reviewing these articles, due to the fact that the reviews did not include a consistent level of information on individual studies, the content experts did not feel that this method of identifying and reviewing articles was helpful without looking at the individual studies included and rating their risk of bias. A post hoc decision was made to grade the individual studies included in each
systematic review and to use the standard AAN development process. Two authors graded the studies independent of each other according to the amended 2011 manual.

An updated literature search was performed in April 2016 by a medical research librarian. Of the 765 abstracts retrieved in the search and reviewed by two panel members, 127 met inclusion criteria. Appendix e-1 presents the comprehensive search strategy. Two nonconflicted panel members rated the class of evidence for each review according to the AAN scheme for classification of therapeutic articles. Disagreements were resolved by a third panel member. Outcome data from the reviews that were included were extracted by a panel member with training in therapeutic studies and verified by a guideline methodologist.

Through responses to a survey, members of the author panel determined the clinically important differences between treatments according to various measures, which were applied to results from PSG or actigraphy or from patient entries in sleep diaries or responses to standardized questionnaires. For SOL, an improvement of 20 min or more was considered clinically important, an improvement between 10 min and 20 min was considered of uncertain clinical significance and a difference of 10 min or less was considered clinically unimportant for all metrics (ie. PSG, actigraphy, diary entry, and questionnaire results). For the risk difference in achieving SOL of less than 30 min or a reduction of 50% or greater in SOL, a risk difference of 10% or greater was considered clinically important and a risk difference of 5% or less was considered clinically unimportant. For SE measured by PSG or actigraphy, a difference of 5% or greater was considered clinically meaningful and a difference of 2% or less was considered
clinically unimportant. For the risk difference in achieving a SE greater than 85%, a risk difference of 10% or greater was considered clinically important, a risk difference between 5% and 10% was considered of uncertain clinical significance, and a risk difference of 5% or less was considered clinically unimportant. An improvement of 15 min or more in wake after sleep onset (WASO) time as measured by PSG or actigraphy was considered to be clinically important, improvement between 15 min and 5 min was considered to be of uncertain clinical significance, and an improvement of 5 min or less was considered clinically unimportant. A decrease in night awakenings of three or more was considered clinically important, a decrease of between one and three night awakenings was considered to be of uncertain clinical significance, and a decrease in night awakenings of one or fewer was considered clinically unimportant. An improvement in total sleep time of 30 min or greater was considered clinically important, an improvement in total sleep time between 15 min and 30 min was considered to be of uncertain clinical significance, and an improvement in total sleep time of less than 15 min was considered clinically unimportant. The Children’s Sleep Habit Questionnaire (CSHQ) is a parent-rated questionnaire composed of 33 items. Each item is scored on a 3-point scale. The questionnaire increasingly is used in pediatric sleep research to capture parental perspectives. Changes captured on the CSHQ, were not weighed against clinically important changes, and statistically significant changes were accepted without downgrading or upgrading for magnitude of effect.

This manuscript is arranged by clinical symptom. The results were analyzed by intervention–outcome pairs (ie, treatments for sleep-onset insomnia found to be most effective in children and adolescents with ASD). Outcome-intervention pairs that did not surpass a very low confidence in evidence after Grading of Recommendations Assessment, Development and Evaluation
(GRADE) was applied are not described in detail in this manuscript. We used a modified GRADE process to develop conclusions (Guyatt 2011, AAN guideline process manual 2011). In this process, the evidence was analyzed according to a variety of parameters of risk of bias (multiple types), consistency, directness, precision, and publication bias. Using this process, modification of the class of evidence up or down was transparent (Guyatt 2011).

The panel formulated practice recommendations based on the strength of evidence and other factors, including axiomatic principles of care; the magnitude of anticipated health benefits relative to harms, financial burden, availability of interventions, and patient preferences. The panel assigned levels of obligation (A, B, C, U) to the recommendations using a modified Delphi process. The development panel formulated a rationale for recommendations that was based on the evidence that was systematically reviewed; stipulated axiomatic principles of care; and, when evidence directly related to the treatment of ASD was unavailable, strong evidence derived from the non–autism-related literature. We explain the rationale in a section labeled “Clinical Context,” which precedes each set of recommendations. Using this rationale, we determined corresponding actionable recommendations. To reduce the risk of bias from individual development panel members, the final recommendation for each question was assigned using a modified Delphi process that considered the following prespecified domains: the confidence in the evidence systematically reviewed, the acceptability of axiomatic principles of care, the strength of indirect evidence, and the relative value of the benefit as compared with the risk of harm. Additional factors that could modify each recommendation were explicitly considered by the development panel. These factors included judgments about the importance of outcomes, cost of recommendation compliance relative to its benefit, the availability of the intervention, and
anticipated variations in patient preferences. Considerations for future research and recommendations for future studies were also developed during the guideline development process.

**ANALYSIS OF EVIDENCE**

A total of 18 articles were selected for full-text review; six studies were class III or higher. All trials were conducted in either the United States or Europe and included children and adolescents with ASD who were between the ages of 0 years and 18 years. The time frame of each study varied from 2 weeks to 12 weeks.

I. In children and adolescents with ASD, which pharmacologic, behavioral, and CAM interventions are effective at improving bedtime resistance when compared with either no treatment or when compared with other treatments?

Bedtime resistance is a behavioral phenomenon that often manifests as refusal to go to bed, stalling behavior at bedtime, and the requirement of a parent or caretaker’s presence at bedtime and sleep onset.

A. pharmacologic and B. behavioral interventions:
Melatonin alone or in combination with cognitive behavioral therapy (CBT):

One class II study was identified (Cortesi 2012). In this placebo-controlled study with four primary outcomes, children aged 4 to 10 years who have ASD (Diagnostic and Statistical Manual of Mental Disorders [Fourth Edition, Text Revision] criteria confirmed by Autism Diagnostic Interview-Revised [ADI-R] and Autism Diagnostic Observation Schedule [ADOS]) and concurrent sleep onset or maintenance insomnia or both, were randomized to one of four arms: 1) patients who received 3 mg/d of controlled-release melatonin, taken at 9:00 PM, for 12 weeks (N=34); 2) patients who received four 50-minute sessions of CBT per week for 12 weeks (N=33); 3) patients who received 3 mg/d of controlled-release melatonin, taken at 9:00 PM, for 12 weeks and four 50-minute sessions of CBT per week for 12 weeks (N=35); and 4) patients who received placebo (N=32). The melatonin used in this study was of high purity (99.9%) and formulated to release 1 mg immediately and the remaining 2 mg at a controlled rate throughout a 6-hour period. Children with significant emotional or behavioral disorders, determined by the Child Behavior Checklist, were excluded from the study, as were children with serious medical, psychiatric, or neurologic conditions. Bedtime resistance was measured on the CSHQ-bed resistance (CSHQ-BR) subscale as a secondary outcome (Owens 2000) at baseline and after 12 weeks. Children in the melatonin-alone arm and children in the CBT-alone arm had a greater improvement on this measure compared with children in the placebo arm (mean difference in the melatonin-alone arm -3.60 [95% confidence interval (CI), -4.60 to -2.60]; mean difference in CBT-alone arm -2.48 [95% CI, -3.49 to -1.47). Children in the combined therapy arm showed the greatest improvement when compared with the children in the placebo arm (mean difference
Melatonin was well tolerated; no adverse events were reported, and no children had to discontinue participation in the study because of adverse effects.

C. CAM interventions:

There were no CAM interventions with higher than a very low confidence in evidence and therefore none were included in this manuscript.

II. In children and adolescents with ASD, which pharmacologic, behavioral, and CAM interventions are effective at decreasing SOL compared with no treatment or compared with other treatments?

Sleep-onset latency refers to the amount of time (in minutes) after lights are turned off until the onset of any stage of sleep. Delayed sleep onset may or may not be accompanied by restlessness, nighttime awakenings, or short sleep duration.

A. Pharmacologic and B. Behavioral Therapy

Melatonin alone or in combination with CBT:
Two class II studies were identified. In the previously described class II placebo-controlled study in children aged 4 to 10 years with ASD and mixed sleep-onset insomnia and maintenance, who were randomized to controlled-release melatonin (N=34), CBT (N=33), controlled-release melatonin and CBT (N=35), or placebo (N=32) (Cortesi 2012), SOL was one of the four primary outcomes. The treatment goal was SOL of less than 30 min or reduction in SOL by at least 50% after 12 weeks. The authors considered a mean reduction in SOL of 15 min to be clinically relevant. SOL was measured in minutes by actigraphy and by the CSHQ-SOD subscale. By both measurements, controlled-release melatonin in combination with CBT had the greatest effect in decreasing SOL compared with placebo (mean difference by actigraphy was -45.91 min [95% CI, -57.93 to -33.98]; mean difference by CSHQ-SOD subscale was -1.24 [95% CI, -1.50 to -0.98]). Controlled-release melatonin alone also showed a meaningful improvement compared with placebo (mean difference by actigraphy was -34.39 min [95% CI -47.91 to -20.88]) while CBT alone was less effective (mean difference by actigraphy was -20.47 min [95% CI, -34.98 to -5.96]). The proportion of children achieving the treatment goal was greatest in the combination group (84.6% compared with 0% in placebo group, odds ratio [OR] 358.4 [95% CI, 28.69 to 3880.41]; risk difference 0.85 [95% CI, 0.66 to 0.93]), but also important in the melatonin-alone arm (39.29%, risk difference 0.39 [95% CI, 0.21 to 0.56]), and not seen in the CBT group (10.34%, risk difference 0.10 [95% CI, -0.02 to 0.26]). In another class II (3 primary outcomes), 3-month, crossover study of the use of 2 mg/d of melatonin (standard release, from one manufacturer, modal dose is 7 mg), which could be increased up to 10 mg/d to achieve optimal response, for 12 weeks in children and adolescents aged 3 to 16 years with ASD and sleeplessness (N=17), SOL was measured by sleep diaries. The authors determined that the sleep diaries had a good correlation with actigraphy (Wright 2011). To be included in this study,
children and adolescents had to have excessive sleep latencies, defined as greater than 30 min, and have failed an attempt at behavioral management. The mean difference for improvement in SOL between the melatonin and placebo group was -46.7 min (95% CI, -78.50 to -14.90). Melatonin was well tolerated, no adverse events were reported, and no one had to discontinue participation because due to side effects.

A. Behavioral therapy

Parent Based Sleep Education:

One class II study and two class III studies used parent workshops to educate parents about sleep schedules and hygiene. In a class II study, children aged 2 to 10 years were randomized to have a parent receive an educational pamphlet (N=19) or nothing (N=17) (Adkins 2012). The four-page pamphlet covered six areas promoting sleep in children with ASD: providing a comfortable sleep setting, establishing regular bedtime habits, keeping a regular schedule, teaching your child to fall asleep alone, avoiding naps, and encouraging daytime activities that promote a better sleep-wake schedule. After two weeks, SOL was measured by actigraphy and a sleep diary. Children whose parents received the pamphlet were no more likely to improve on SOL than those whose parents received no instruction (raw mean difference -11.8 min, 95% CI -37.16 to 13.56). In a class III placebo controlled study (>80% lost for the actigraphic outcome, 4 primary outcomes, no allocation concealment) in children with an average age of 3.5 years, parents were randomized to receive either sleep specific behavioral training (N=20) or non-sleep-related
parent education (N=20) (Johnson 2013). The study consisted of 5 sessions over 8 weeks for both arms. The sleep changes were measured by actigraphy and available in 27 children.

Children whose parents received sleep focused education were not more likely to improve on SOL after 8 weeks than those whose parents received non-sleep related parent education (raw mean difference 4.0 (95% CI -14.24 to 22.24). In the previously described class III study comparing individual versus a group sleep education program (Malow 2014), SOL was measured by actigraphy. Children whose parents received individual training were not more likely to improve on SOL than those whose parents received group training (raw mean difference -0.2, 95% CI –9.79 to 9.39).

B. CAM therapy

Weighted blankets:

One class I study was identified and was a two-week cross over trial in children aged 5 to 16 years with ASD (autism, Asperger syndrome, or pervasive developmental disorder NOS diagnosed by a multidisciplinary team using standardized tools not specified in the study), SOL was measured by actigraphy for weighted blanket (N= 54) compared to a regular blanket (N= 57) and by a sleep diary for weighted (N=67) versus regular blanket (N=67) (Gringras 2014).
Children had to have had at least a 5-month history of sleep complaints in the absence of obstructive sleep apnea, night terrors, or other sleep disorders. Children with a weighted blanket were no more likely than those using a regular blanket to improve on SOL measured by actigraphy (mean difference weighted-control 2.1 min, 95% CI -5.30 to 9.50) or sleep diary (mean difference weighted-control -1.6 min, 95% CI -6.61 to 3.41).

III. In individuals with ASD, which pharmacologic, behavioral, or CAM interventions are effective at improving sleep continuity compared with no treatment or compared with other treatment?

Sleep continuity is the amount of consolidated sleep that is attained over a sleep period. Continuity can be reported using various measurements, including SE (expressed as a percentage of sleep), total sleep time (TST)/time in bed) X 100, total WASO, and number of nighttime awakenings.

Sleep Efficiency

A. Pharmacologic and B. Behavioral therapy

Melatonin alone or in combination with cognitive behavioral therapy (CBT):
One class II study was identified. In the previously described class II placebo controlled study, children aged 4 to 10 years with ASD and mixed sleep onset and maintenance insomnia randomized to receive either 3 mg of controlled release melatonin (N=34), taken at 9pm, 4 weekly 50-minute sessions of CBT (N=33), melatonin + CBT (N=35) or placebo (N=32) (Cortesi 2012). SE was measured by actigraphy after 12 weeks of treatment, with SE >85% considered optimal. Children in the melatonin alone group were more likely than children in the placebo group to achieve this optimal outcome (46.43% versus 0% in placebo, Risk Difference 0.41, 95% CI 0.22 to 0.58). Children in the CBT group alone also were more likely than children in the placebo group to achieve this optimal outcome not reaching statistical significance (10.34%, risk difference 0.11, 95% CI -0.02 to 0.27). Children in the combined therapy group showed the greatest improvement compared to placebo (63.38% achieving optimal SE%, risk difference 0.64, 95% CI 0.44 to 0.78). Children in the melatonin alone group had a greater improvement than children in the placebo group (raw mean difference in SE% 10.78%, 95% CI 8.69 to 12.87).

Children in the CBT group alone had a greater improvement than children in the placebo group (raw mean difference in SE% 7.65%, 95% CI 6.78 to 9.52). Children in the combined therapy group showed the greatest improvement compared to placebo (raw mean difference 12.53%, 95% CI 10.40 to 14.66). Melatonin was well tolerated, no adverse events were reported, and no children had to discontinue the study due to side effects.

B. Behavioral therapy
Parent-based sleep education:

Three previously described (one class II and two class III) studies used parent workshops to educate parents about sleep schedules and hygiene. In the class II study comparing an educational pamphlet promoting sleep in ASD (N=19) or treatment as usual (N=17) (Adkins 2012), after two weeks, SE % was measured by actigraphy. Children whose parents received the pamphlet did not have a greater improvement on SE than those whose parents received no instruction (mean difference 2.70, 95% CI -1.78 to 7.18). The class III placebo controlled study comparing sleep specific behavioral training (N=13) or non–sleep-related parent education (N=14) (Johnson 2013) over 8 weeks, actigraphy was available on < 80% of children. The group of children whose parents received sleep-focused parent training was not more likely than the group who received general training to improve (raw mean difference 3.0, 95% CI -2.01 to 8.01).

The class III study comparing individual instruction to the group parent sleep education program (Malow 2014) measured SE% by actigraphy. The children whose parents were in individual classes did not have a greater improvement than the children whose parents were in group sessions (raw mean difference in SE% -1.10%, 95% CI -3.61 to 1.41).

Weighted blankets:
One previously described class I study was identified. In this crossover trial, SE was measured by actigraphy to compare children and adolescents who slept with a weighted blanket (N= 59) with children and adolescents who slept with a regular blanket (N= 59) (Gringras 2014). Children and adolescents who slept with a weighted blanket did not have a greater improvement in SE than children and adolescents who slept with a regular blanket (mean difference in SE weighted-control -0.3% [95% CI, -1.41 to 0.81]). When SE was measured by sleep diary, there was no advantage to using the weighted blanket (mean difference weighted-control 1.9% [95% CI -2.71 to 6.51]).

Night awakenings

A. Pharmacologic and B. Behavioral therapy

Melatonin alone or in combination with CBT:

Two previously described class II studies were identified. The class II placebo-controlled study compared the uses of melatonin alone, CBT alone, and a combination of melatonin and CBT with placebo (Cortesi 2012) and used actigraphy to measure WASO and the CSHQ-NW subscale (secondary outcome). Children in the melatonin-only group had a greater improvement in WASO time compared with the placebo group (raw mean difference -27.94 min [95% CI, -44.55 to -11.33]). Children in the CBT-only group did not have a greater improvement according to the WASO time measure when compared with the placebo group (raw mean difference -8.98 min.
Children in the combined therapy group experienced the greatest improvement compared with the placebo group (raw mean difference -40.46 [95% CI -55.89 to -25.03]) represented by a decrease in the average WASO time from almost 70 min to just under 30 min. Secondary measurements on the CSHQ-NW scale revealed that the combination therapy group had a greater improvement than the placebo group (raw mean difference -3.44 [95% CI, -3.85 to -3.03]). The melatonin-only group also had a greater improvement according to the CSHQ-NW scale than the placebo group (mean difference -2.83 [95% CI, -3.29 to -2.37]). The children in the CBT-only group did not have a greater improvement than the children in the placebo group according to the CSHQ-NW scale (mean difference -0.80 [95% CI, -1.26 to -0.34]). In the class II 3-month crossover study of children who received 2-10 mg/d of melatonin (modal dose was 7 mg/d) compared with children and adolescents who received placebo, the number of night awakenings after sleep onset was recorded by parents in sleep diaries (Wright 2011). The children and adolescents who received melatonin did not have a greater improvement in night awakenings than those who received placebo (mean difference 0.1 [95% CI, -0.06 to 0.26]).

B. Behavioral therapy

Parent-based sleep education:

One class II study and one class III study previously described used parent workshops to educate parents about sleep schedules and hygiene. In the class II study that compared children of parents
who were provided an educational pamphlet about how to help promote sleep in individuals with
ASD compared with children of parents who were not provided the pamphlet (Adkins 2012),
WASO was measured by actigraphy and by questionnaires completed by the parents. Children
whose parents received the pamphlet did not have a greater improvement in WASO than those
whose parents did not receive it (mean difference 0.5 min [95% CI, -17.96 to 18.96]). In the class
III study that compared children whose parents received individual sleep education with children
whose parents received group sleep education (Malow 2014), WASO was measured by
actigraphy and the CSHQ-NW subscale. The children whose parents received individual
education did not have a greater improvement in WASO, measured by actigraphy, than the
children whose parents received education in group sessions (raw mean difference 1 [95% CI, -
10.24 to 12.24). The CSHQ-NW data were not provided but were described as not being
different between the two groups.

C. CAM

Weighted blankets:

One previously described class I crossover study was identified in which sleep discontinuity was
measured four different ways: 1) number of times the child and adolescents awoke, measured by
actigraphy; 2) the amount of WASO time in minutes, measured by actigraphy; 3) proportion of
nights per week that children and adolescents awoke, as measured by sleep diary; and 4) the
average WASO time, measured by sleep diary. Wake-after-sleep-onset time and night
awakenings were measured by actigraphy (children and adolescents who slept with weighted
blankets [N=54] compared with children and adolescents who slept with regular blankets [N=
57] and by sleep diary (children and adolescents who slept with weighted blankets [N=67]
compared with children and adolescents who slept with regular blankets [N=67] (Gringras 2014).

Actigraphy measurement revealed that children and adolescents who slept with weighted
blankets did not have a greater reduction in the amount of WASO time (mean difference
weighted-control -2.5 minutes [95% CI, -9.49 to 4.49]) or fewer discrete awakenings (mean
difference weighted-control -0.2 [95% CI, -1.05 to 0.65]) than children and adolescents who
slept with regular blankets. Sleep diaries revealed that children and adolescents who slept with
weighted blankets did not have a greater improvement in night awakenings per week (mean
difference weighted-control -0.01 [95% CI -0.05 to 0.03]) or average time awake (mean
difference weighted-control 0.01[95% CI -1.41 to 1.43]) than children and adolescents who slept
with regular blankets.

IV. In children and adolescents with ASD, which pharmacologic, behavioral, and CAM
interventions are effective at improving total sleep time compared with no treatment
or compared with other treatment?

Shortened sleep time, often accompanied by early morning wake times, is a consistently reported
phenomenon that contributes to reduced quality of life for families and caretakers of people with
ASD. Total sleep time may refer to total nocturnal sleep duration for children adolescents who
do not take daytime naps or total sleep duration during a 24-hour period for children and adolescents who do take daytime naps. Reduced TST may be related to prolonged SOL, frequent or prolonged night awakenings or both, and early morning waking. The following studies typically compare posttreatment TST with baseline TST in treatment groups as opposed to using an a priori definition of shortened sleep at baseline compared with age-specific sleep duration recommendations.

A. Pharmacologic and B. Behavioral therapy:

Melatonin alone or in combination with CBT:

Two class II studies previously described were identified. In the class II placebo-controlled study that compared children who received only melatonin, children who received only CBT, and children who received both melatonin and CBT with children who received placebo (Cortesi 2012), TST was measured by actigraphy and by the CSHQ-sleep duration (CSHQ-SD) subscale. Children in the melatonin-only group had a greater improvement in TST compared with children who received placebo (mean difference 64.87 min [95% CI, 46.10 to 83.64]). Children in the CBT-only group did not have a greater improvement in TST compared with children who received placebo (28.90 [95% CI, 6.53 to 51.27], \( P=0.01 \) not significant after Bonferroni adjustment \( [0.05/6=0.008] \)). Children in the combined therapy group experienced the greatest improvement compared with children receiving placebo (mean difference 88.78 min, [95% CI, 70.30 to 107.26]), represented by an average extension of TST by 22% (or about 90 min).
Secondary measurements on the CSHQ-SD subscale revealed the same pattern, with both the melatonin-only group (mean difference -1.58 [95% CI, -2.13 to -1.03]) and the combination therapy group having the greatest improvement (mean difference -2.02 [95% CI, -2.58 to -1.46]). The children in the CBT-only group did not have greater improvement than the children in the placebo group as measured on the CSHQ-SD subscale (mean difference 0.28 [95% CI, -0.32 to 0.88]). In the class II crossover study of children and adolescents who received 2-10 mg/d of melatonin (modal dose was 7 mg/d) compared with children and adolescents who received placebo, TST was measured according to sleep diaries completed by parents (Wright 2011). The children and adolescents who received melatonin had a greater improvement in TST than those who received placebo (mean difference 52.3 min [95% CI 26.11 to 78.49]).

A. Behavioral therapy

Parent Based Sleep Education:

One class II study and two class III studies previously described used parent workshops to educate parents about sleep schedules and hygiene. In the class II study that compared children of parents who received an educational pamphlet with information about promoting sleep in children with ASD with children whose parents did not receive the pamphlet (Adkins 2012), TST was measured by actigraphy and by responses to a questionnaire completed by the parents. Children whose parents were given the pamphlet did not have a greater improvement in TST than children whose parents were given no information (raw mean difference 12.2 min [95% CI, 0.0 to 24.5]).
-22.6 to 47 min, lack precision). In the class III placebo-controlled study comparing children whose parents received sleep-specific behavioral training with children of parents who received non–sleep-related parent education (Johnson 2013), sleep changes were measured by actigraphy. Children whose parents attended the sleep education sessions did not have a greater improvement in TST than children whose parents had non-sleep education (raw mean difference -26.0 minutes, 95% CI -83.33 to 31.33, lack precision). In the class III study that compared children whose parents received individual sleep education with children whose parents received sleep education in a group program (Malow 2014), TST was measured by actigraphy and by CSHQ-SD. Children whose parents received individual instruction did not have a greater improvement in TST compared with children whose parents received group instruction, as measured by actigraphy (raw mean difference -7.2 min [95% CI, 29.44 to 15.04]) or by the CSHQ-SD scale (data not provided).

C.CAM

Weighted blankets:

One previously described class I study was identified. In this crossover trial of children who slept with weighted blankets compared with children and adolescents who slept with regular blankets, sleep outcomes were measured by actigraphy and entries in sleep diaries (Gringras 2014). Children and adolescents who slept with weighted blankets did not have a greater improvement in TST than children and adolescents who slept with regular blankets, as measured by actigraphy.
(primary outcome, mean difference weighted-control -4.2 min [95% CI, -13.40 to 5.00]) or by sleep diary entries (mean difference weighted-control 15.9 min [95% CI, -6.37 to 38.17]).

V. In children and adolescents with ASD, which sleep-targeted pharmacologic, behavioral, and CAM interventions are effective at improving daytime behavior compared with no treatment or compared with other treatments?

A. Pharmacologic therapy

Melatonin:

One class II study previously described was identified. In this class II crossover study of children and adolescents who received 2-10 mg/d of melatonin (modal dose was 7 mg) compared with children and adolescents who received placebo, behavioral changes were measured as a secondary endpoint, using the Developmental Behavior Checklist (DBC) (Wright 2011). The DBC contains 96 items on a broad range of behavioral and emotional disturbances in children and adolescents with intellectual and developmental disability, each item is rated on a 3-point scale (0, 1, 2). The total score, as well as the score for all five subscales, did not illustrate an improvement over baseline (after Bonferroni adjustment, with no crossover effects [disruptive behavior, self-absorption, communicative difficulties, anxiety and social relating]) in treated children and adolescents who received melatonin compared children and adolescents who received placebo. The mean differences in scores are listed as follows: DBC Total, 6.0 (95% CI,
0.87 to 11.13); DBC-disruptive, 1.3 (95% CI, -1.08 to 3.68); DBC-self-absorption, 0.9 (95% CI, -0.57 to 2.37); DBC-communication, 1.6 [95% CI, 0.08 to 3.12], P=0.045 was not significant after Bonferroni adjustment for five subscales 0.05/5=0.01 set as significant level); DBC-anxiety 0.1 (95% CI, -0.80 to 1.00); and DBC-social relating 1.3 (95% CI, 0.06 to 2.54).

B Behavioral therapy

There were no studies at a level of other than very low confidence in evidence that evaluated behavioral therapy for improving daytime behavior.

C. CAM

Weighted blankets:

One class I study previously described was identified. In this class I crossover trial, changes in mood and behavior were measured as a secondary endpoint by the Aberrant Behavior Checklist (ABC) in children and adolescents who slept with weighted blankets compared with children and adolescents who slept with regular blankets (Gringras 2014). The ABC contains 58 items on a broad range of behavioral disturbances. Children and adolescents who slept with weighted blankets did not have greater improvement on the total score or any of the subscales compared with children and adolescents who slept with regular blankets, with no crossover effects. The mean differences in scores are listed as follows: ABC-total, -2.3 (95% CI, -5.31 to 0.71); ABC-irritability agitation crying, -0.9 (95% CI, -2.03 to 0.23); ABC-lethargy social withdrawal, -0.7
(95% CI, 1.48 to 0.08); ABC-stereotypic behavior, -0.2 (95% CI, -0.7 to 0.3); ABC-hyperactivity noncompliance, -1.0 (95% CI, -2.3 to 0.3); and ABC-inappropriate speech, -0.1 (95% CI, -0.44 to 0.24).
CONCLUSIONS (EVIDENCE SYNTHESIS)

In school-aged children and adolescents with ASD and sleep dysregulation:

1. Bedtime Resistance

   Weak Evidence

   3 mg/d of controlled-release melatonin, taken at 9 PM; four individual 50-minute sessions of CBT per week; or a combination of both treatments is possibly no more effective than placebo for improving bedtime resistance (low level of confidence in evidence, one class II study).

   Insufficient Evidence

   There is insufficient evidence to determine the efficacy of individualized parent sleep education compared with group parent sleep education at improving bedtime resistance (very low confidence in evidence, one class III study).

2. SOL

   Strong Evidence
In children who have not responded to behavioral therapy, 2–10 mg/d of controlled-release melatonin taken at bedtime for 12 weeks, is more effective than placebo in reducing SOL (pooled mean difference: -36.27 [95% CI -48.71 to -14.9], I²=0) (high level of confidence in evidence, two class II studies, upgraded for magnitude of effect).

**Moderately Strong Evidence**

a. 3 mg/d of controlled-release melatonin, taken at bedtime for 12 weeks is probably more effective than placebo at normalizing SOL (reducing SOL to less than 30 min or reducing SOL by more than 50%) (risk difference 0.39 [95% CI, 0.21 to 0.56]) (moderate level of confidence in evidence, one class II study, upgraded for magnitude of effect).

b. A combination of 3 mg/d of controlled-release melatonin, taken at bedtime, for 12 weeks and four 50-minute sessions of CBT per week for 12 weeks is probably more effective than placebo at normalizing SOL (reducing SOL to less than 30 min or reducing SOL by more than 50%) (risk difference 0.85 [95% CI, 0.66 to 0.93]) and in reducing SOL (mean difference -45.91 min [95% CI, -57.93 to -33.89]) (moderate level of confidence in evidence, one class II study, upgraded for magnitude of effect).

**Weak Evidence**
Four 50-minute sessions of CBT per week for 12 weeks is possibly no more effective than placebo in reducing SOL (mean difference -20.47 [95% CI, -34.98 to -5.96]) and is not likely to be more effective than placebo at normalizing SOL (reducing SOL to less than 30 min or reducing SOL by more than 50%), (low level of confidence in evidence, one class II study).

**Insufficient Evidence**

a. There is insufficient evidence to determine the efficacy of 2 weeks of sleep education via an informational pamphlet compared with no intervention at improving SOL (very low level of confidence, one class II study, downgraded for lack of precision).

b. There is insufficient evidence to determine the efficacy of behavioral parent-based sleep education compared with non-sleep parent education in improving SOL (very low level of confidence in evidence, one class III study).

c. There is insufficient evidence to determine the efficacy of individualized parent sleep education compared with group parent sleep education at improving SOL (very low confidence in evidence, one class III study).

3. **Sleep Continuity**

**Moderately Strong Evidence**
a. 3 mg/d of controlled-release melatonin, taken at bedtime for 12 weeks is probably more effective than placebo at improving SE (mean difference 10.78% [95% CI, 8.69 to 12.87]) and at achieving SE greater than 85% (risk difference 41% [95% CI, 22% to 58%]) (moderate level of confidence in evidence, one class II study, each upgraded for magnitude of effect)

b. The combination of 3 mg/d of controlled-release melatonin, taken at bedtime, for 12 weeks and four 50-minute sessions of CBT per week for 12 weeks is probably more effective than placebo at achieving SE greater than 85% (risk difference 64% [95% CI, 44% to 78%]), in improving WASO time (mean difference -40.46 min [95% CI, -55.89 to -25.03]), and reducing the number of night awakenings as measured by the CSHQ-NW (-3.44 [95% CI -3.85 to -3.03]), (moderate level of confidence in evidence, one class II study, upgraded for magnitude of effect).

c. Weighted blankets are probably no more effective than regular blankets at improving SE, number of night awakenings, WASO, proportion of nights with at least one awakening, average time awake or total sleep time (moderate level of confidence, one class I study).

**Weak Evidence**

- Combined therapy of 3 mg/d of controlled-release melatonin, taken at bedtime for 12 weeks and four 50-minute sessions of CBT per week for 12 weeks is possibly no
more effective than placebo in improving SE (low level of confidence in evidence, one class II study, mean difference 12.53% [95% CI, 10.40 to 14.66]).

- 3 mg/d of controlled-release melatonin, taken at bedtime for 12 weeks is possibly no more effective than placebo in improving WASO time (mean difference -27.94 min [95% CI, -44.55 to -11.33) and number of night awakenings, as measured by the CSHQ-NW scale (mean difference -2.83 [95% CI -3.29 to -2.37]) (low level of confidence in evidence, one class II study).

- In children who have not responded to behavioral therapy, 2–10 mg of controlled-release melatonin, taken at bedtime for 12 weeks is possibly no more effective than placebo at reducing the number of night awakenings, as measured by sleep diary entries (low confidence in evidence, one class II study).

a. Four 50-minute sessions of cognitive behavioral therapy per week for 12 weeks may be more effective than placebo at improving SE (mean difference 7.65 [95% CI, 5.78 to 9.52]) but may not be more effective than placebo at normalizing SE more than 85% (low level of confidence in evidence, one class II study).

**Insufficient Evidence**

a. There is insufficient evidence to determine the efficacy of four 50-minute sessions of CBT per week for 12 weeks compared with placebo in improving WASO time or number
of night awakenings on the CSHQ (very low level of confidence in evidence, one class II study, each downgraded for magnitude of effect).

b. There is insufficient evidence to determine the efficacy of 2 weeks of sleep education via information pamphlet compared with no intervention at improving SE or at improving WASO (very low level of confidence, one class II study, each downgraded for lack of precision).

c. There is insufficient evidence to determine the efficacy of individualized parent sleep education compared with group parent sleep education at improving SE or WASO (very low confidence in evidence, one class III study).

4. **Total sleep time**

   **Strong Evidence**

   In children who have not responded to behavioral therapy, 2–10 mg of controlled release melatonin taken at bedtime for 12 weeks is more effective than placebo in improving TST (pooled effect 60.6 minutes [95% CI, 45.35 to 75.86, I² 0]); (high level of confidence in evidence, two class II studies, upgraded for magnitude of effect).

   **Moderately strong evidence**
A combination of 3 mg/d of controlled-release melatonin, taken at bedtime for 12 weeks and four 50-minute sessions of CBT per week for 12 weeks is probably more effective than placebo at improving TST (mean difference 88.78 min [95% CI, 70.30 to 107.26]) (moderate level of confidence in evidence, one class II study, upgraded for magnitude of effect).

**Insufficient Evidence**

- There is insufficient evidence to determine the efficacy of behavioral parent-based sleep education compared with non-sleep parent education in improving TST (very low level of confidence in evidence, one class III study).
- There is insufficient evidence to determine the efficacy of four 50-minute sessions of CBT per week for 12 weeks compared with placebo at improving TST. (very low level of confidence in evidence, one class II study, each downgraded for magnitude of effect).
- There is insufficient evidence to determine the efficacy of 2 weeks of sleep education via information pamphlet compared with no intervention at improving TST (very low level of confidence, one class II study, each downgraded for lack of precision).
- There is insufficient evidence to determine the efficacy of behavioral parent-based sleep education compared with non-sleep parent education in improving TST (very level of confidence in evidence, one class III study).
• There is insufficient evidence to determine the efficacy of individual parent sleep education compared with group parent sleep education in improving TST (very low confidence in evidence, one class III study).

d. **Daytime Behavior**

**Moderately Strong Evidence**

The use of weighted blankets is probably not more effective than the use of regular blankets in improving disruptive daytime behaviors associated with sleep dysregulation (moderate level of confidence, one class I study).

**Weak Evidence**

2–10 mg of controlled-release melatonin, taken at bedtime for 12 weeks is possibly no more effective than placebo at improving disruptive daytime behaviors according to parent reports (low confidence in evidence, one class II study).
PUTTING THE EVIDENCE INTO CLINICAL CONTEXT

Treatment of sleep disorders in ASD is an important goal, as sleep disruption is associated with increased behavioral problems, daytime sleepiness, and overall poorer health (Medic G, et al 2017). In addition, people with ASD are at higher risk for primary sleep disorders, including obstructive sleep apnea, restless legs syndrome, and periodic limb movement disorder, which are not reviewed herein (Reynolds AM 2011, Veatch OJ 2015). They are also at higher risk of sleep disorders secondary to medical conditions, such as epilepsy and gastrointestinal reflux disease, and more likely to use of medications that disrupt normal sleep patterns, such as anticonvulsants and psychotropic medications. Co-occurring psychiatric disorders, especially anxiety, also contribute to sleep dysfunction in this population. Lastly, but equally as important, learned maladaptive sleep patterns, including lack of parental boundaries around sleep, may be more difficult to correct in children and adolescents with ASD than in typically developing children and adolescents. For this reason, behavioral strategies are likely to augment and perhaps outlast any short-term pharmacologic intervention. As a general tenant of pediatric practice, behavioral strategies are often the first option.

Our review reveals that there is a dearth of evidence-based treatments for sleep dysregulation in ASD. Only six studies were found to be class III or higher. The two best studies examined pharmacologic treatment with melatonin and used a formulation produced specifically for their study to overcome a limitation of unknown purity in over-the-counter formulations. Although there are no medications for insomnia or other sleep difficulties that are approved by the Food and Drug Administration for use in children, melatonin, which has both hypnotic (MT1) and
chronobiologic properties (MT2), is the most commonly dispensed hypnotic drug in children (Hartz 2012) and is available over the counter. In 2014, the European Consensus Conference (Bruni 2015) published a consensus guideline to address the widespread use of melatonin in children and adolescents in the absence of large-scale pediatric clinical trials. They allow that while few data in safety and tolerability in children are available, there is no evidence that short-term use of melatonin has any adverse effects (Hoebert 2011, van Geijlswijk 2010 and van Geiglswijk 2011). However, given that many children with ASD undergo long-term treatment with melatonin for months or years, the lack of data regarding the safety of long-term use is concerning. For example, melatonin affects the hypothalamic–gonadal axis (Shi, et al 2013), and therapeutic use of melatonin potentially has effects on pubertal development in children and adolescents. A recent study highlighted the vast differences in melatonin concentration in over-the-counter formulations, including some that were contaminated with other products, such as serotonin (Cerezo AB, et al 2016; Erland LA, et al 2017).

PRACTICE RECOMMENDATIONS

Recommendation 1

Rationale

Environment and family factors, including child-rearing practices and bedtime routines that are not conducive to good sleep, can contribute to sleep dysregulation in children with ASD
In children with neurodevelopmental disabilities, promotion of improved sleep habits or hygiene is considered first-line treatment (Richdale and Schreck, 2009, Henderson et al., 2011). As a general tenant of pediatric practice, behavioral strategies are often the preferred first option (Jan and Owens, 2008). When behavioral strategies fail, caregivers often turn to melatonin. It is the most commonly dispensed hypnotic drug in children (Hartz, 2012) and the only compound for sleep and ASD that had rigorous enough clinical trials to be included in this guideline. In the two research studies analyzed herein, pharmaceutical-grade preparations were used, and the exact amounts administered were ascertained. In one study, 3 mg of controlled-release melatonin taken at 9 PM was used and in the other study 2 mg of immediate-release melatonin was initiated, with titration to effect up to 10 mg and a modal dose of 7 mg. In practice, variable concentrations of melatonin may be found in over-the-counter preparations (REL). It is axiomatic of good pediatric care that use of any behavioral or medical treatment be periodically re-evaluated to make sure that there is continued benefit and no new side effects (PRIN). Given that many children with ASD undergo treatment with melatonin from many months to years, the lack of long-term safety data must be acknowledged. Although few data in safety and tolerability are available for children, there is no evidence that short-term use of melatonin has any adverse effects (Hoebert 2011, van Geijlswijk 2010 and van Geijlswijk 2011), and it is currently used as neuroprotection in infants who were born preterm (Biran et al, 2014). Its use in ASD must be weighed against the harm of persistently disordered sleep. Contributing to the complexities of treating insomnia in people with ASD, children with ASD are at increased risk of medical comorbidities that contribute to sleep dysregulation, such as sleep apnea, epilepsy, gastrointestinal reflux disease, depression, anxiety, and attention deficit
hyperactivity disorder [RELA], and each presentation must be factored into the decision to begin therapy with melatonin.

Statement 1a

Clinicians seeking to improve any metric of sleep function in children with autism should counsel parents or guardians of patients about improved sleep habits, with behavioral strategies as a first line treatment approach (Level B).

Statement 1b

Clinicians should offer melatonin if behavioral strategies have not been helpful and all co-occurring medical conditions have been addressed. Clinicians should start by prescribing low doses (1–3 mg/d), to be taken 30 minutes before bedtime, and titrate to effect (Level B).

Statement 1c

For parents and guardians who elect the use of melatonin, clinicians should recommend a high-purity pharmaceutical grade of melatonin, initially prescribing a dose lower than that recommended by the manufacturer, and gradually increasing the dose as needed (Level B).
Statement 1d

Clinicians should consider the use of melatonin as a short-term, adjunctive treatment that is tailored to the individual and revisit the need for such treatment on a regular basis (Level B).

Statement 1e

Clinicians seeking to improve sleep function in children with ASD should evaluate these patients for coexisting medical conditions and appropriately manage these conditions in conjunction with optimizing sleep practices (Level B).

Recommendation 2

Rationale

Our review has identified several treatment approaches for minimizing SOL in children with ASD, lending support for treatment with melatonin, CBT, and a combination of melatonin and CBT [EVID]. There is substantial evidence of the efficacy of both melatonin and CBT in reducing SOL in other populations, including patients with insomnia and attention-deficit/hyperactivity disorder as well as in nonclinical populations [RELA].
Clinicians seeking to improve SOL in children with ASD may offer behavioral strategies (Level C).

Clinicians seeking to improve SOL in children with ASD should offer melatonin, to be taken one-half hour before bedtime, for those who have not responded to behavioral strategies (Level B).

Clinicians seeking to improve bedtime resistance in children with ASD should offer behavioral strategies (Level B).

Recommendation 3

Rationale
Children with ASD are at increased risk of disordered sleep including increased total WASO time and increased number of awakenings during the night [RELA] (Reynolds, 2011). These disruptions result in a decrease of SE defined as TST divided by the amount of time in bed. For some people with ASD, it is these sleep interruptions and not sleep onset that is the difficulty. There is a moderate level of confidence that 3 mg/d of controlled-release melatonin, taken at bedtime, for 12 weeks is more effective than placebo at improving SE [EVID]. There is also a moderate level of evidence that controlled-release melatonin used together with behavioral therapy is more effective than placebo at achieving SE greater than 85%, in improving both WASO time and number of night awakenings as per parent report [EVID]. In children who have failed behavioral therapy initiated for decreased SE, there is a low level of confidence in the evidence that controlled-release melatonin, (2–10 mg/d), taken at bedtime, for 12 weeks, is any more effective than placebo at reducing the number of night awakenings, as documented by sleep diary. Although behavioral strategies are often the first line of treatment for pediatric care, there is not persuasive evidence to suggest that behavioral strategies alone can increase SE [EVID]. There is moderate confidence in the evidence that the use of weighted blankets is no better than placebo at increasing [SE].

Statement 3a

Clinicians seeking to improve sleep continuity in children with ASD may offer behavioral strategies (Level C).
Clinicians seeking to improve sleep continuity in children with ASD may offer controlled-release melatonin alone or in conjunction with behavioral therapy (Level C).

Clinicians seeking to improve sleep continuity in children with ASD may not offer the use of weighted blankets (Level C).

Disturbances in sleep are likely to adversely affect various daytime behaviors in children with ASD, although evidence from studies of the use of either weighted blankets or melatonin that were reviewed for this guideline does not support a benefit in improving daytime behaviors [PRIN]. In typically developing children, sleep disorders have been associated with difficult and disruptive daytime behaviors, such as hyperactivity, inattention, aggressiveness, and daytime
sleepiness (Gottlieb 2003, Schrek 2004, Cohen 2011) [RELA]. Disruptive sleep and reduced TST are associated with impaired attention and both internalizing and externalizing behaviors in children with ASD [RELA] Sikora 2012). Improving sleep quality may result in improved daytime behaviors in this population [INFER]. Poor sleep patterns, sleep habits, and lack of sleep in children with ASD may adversely affect their quality of life (Reynolds 2011, Delahaye 2014 [RELA] and the quality of life in their households.

Statement 4a

Clinicians should counsel parents and guardians of children with ASD that treatments of sleep disturbances may not improve difficult and disruptive daytime behaviors (Level B).

Statement 4b

Clinicians should review healthy sleep habits with parents and guardians and promote these habits to improve daytime behaviors (Level B).

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Conflict of Interest Statement

The AAN’s Conflict of Interest Policy Implementation for AAN Guidelines is available at [web link]. All AAN guideline authors must meet the stipulations outlined in the policy in order to participate on a guideline development panel. This policy is further described in the 2017 AAN
Clinical Practice Guideline Development Manual, available at
## Appendix e-1: Search Strategies

### Updated search strategy

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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
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20 15 or 18 or 19 5834 Advanced
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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

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

18 and (19 or 20) 588 Advanced

18 and (meta-analysis/ or systematic review/) 66 Advanced

21 22 23 not (case report/ or note.pt. or comment.pt. or letter.pt.) 579 Advanced

24 remove duplicates from 24 560

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
exp epilepsy/ or exp anticonvulsive drugs/ 26441 Advanced
1
2 9 1 and 8395 Advanced
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4 10 exp behavior analysis/ 10992 Advanced
5
6 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
7 Advanced
8
9 12 exp communications skills/ or exp group intervention/ or intervention/ or family intervention/ or early intervention/ or exp school based intervention/ 71474 Advanced
10 13 and (10 or 11 or 12 or treatment effectiveness evaluation/) 4485 Advanced
11
12 14 exp ATTENTION DEFICIT DISORDER/ or exp ATTENTION/ or exp ATTENTION DEFICIT DISORDER WITH HYPERACTIVITY/ 68794 Advanced
13
14 15 exp behavior problems/ 21782 Advanced
15
16 16 behavior problems/ or exp behavior disorders/ or exp conduct disorder/ or exp rebelliousness/ 148028 Advanced
17
18 17 obsessive compulsive disorder/ or exp hoarding behavior/ or exp hoarding disorder/ or exp neurosis/ or exp obsessive compulsive personality disorder/ 14275 Advanced
19 18 exp Major Depression/ 103691 Advanced
20
21 19 irritability/ 635 Advanced
22
23 20 exp Anxiety Disorders/ 64017 Advanced
24
25 21 or/14-20 363735 Advanced
26
27 22 1 and 21 3478 Advanced
28
29 23 3 or 5 or 7 or 9 or 13 or 22 8653 Advanced
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31 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
32 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
limit 26 to (all journals and English language and yr="2012 - 2016") 2125
Advanced

*autism spectrum disorders/ and 27 1882 Advanced

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

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

PsychINFO 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
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3 exp Complementary Therapies/ 163375 Advanced
4 2 and 3 152 Advanced
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6 child development disorders, pervasive/dt, dh, th or exp autistic disorder/dt, dh, th 3155 Advanced
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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
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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

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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

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Embase 1988 to 2013 Week 03 # Searches Results Search Type

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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
References


Lumeng, J C, 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(5):1020–1029.


