Melatonin for Insomnia in ADHD

Four studies of melatonin in children with ADHD and sleep onset insomnia were identified by Medline search. Participants were aged 6–14 years and melatonin dosages ranged from 3 to 6 mg/day administered shortly before bedtime. One small open-label study found sleep onset was significantly improved with melatonin, but delays recurred when a melatonin dose was missed and after it was withdrawn at study end. A larger double-blind controlled trial in unmedicated children with ADHD found significantly improved sleep parameters (e.g., onset, latency, total sleep time) but no improvements in behavior or cognition. A long-term follow-up of patients in that study found that sleep-onset delay recurred in 92% of children who took a "melatonin holiday," suggesting long-term therapy may be necessary. Finally, a small randomized cross-over trial measured sleep latency using actigraphy and other objective measures and found melatonin combined with sleep hygiene produced significant improvement. Adverse effects were mild in all studies.

All of these studies had important methodological limitations and larger, better designed trials are warranted. On the basis of the currently available evidence, the authors judge melatonin to be both safe and effective in the treatment of pediatric insomnia associated with ADHD.

**The Choking Game**

The "choking game" is similar to the well-described phenomenon of autoerotic asphyxia but without the erotic features. Game players attempt to get a "high" by applying pressure to the neck and temporarily depriving the brain of oxygen. Pressure sources can be another player’s hands, belts, ties, or other ligatures. The game can be life-threatening, particularly if the player is alone and can not remove the ligature. Nonfatal, but serious complications can include seizures, fractures, and brain injury. Common warning signs that an adolescent may be participating in the game include: unexplained bruises on the neck; headaches; bloodshot eyes, facial petechiae, disorientation after being alone; and ligatures left in unusual places.

**Bendz L, Scates A: Melatonin treatment for insomnia in pediatric patients with attention-deficit/hyperactivity disorder.** Annals of Pharmacotherapy. Published online December 22, 2009 at www.theannals.com; doi 10.1345/aph.1M365. From Duke University Hospital, Durham, N.C. The authors disclosed no potential conflicts of interest.
Surveys of adolescents indicate that nearly 70% know of the game, almost half know someone who has played, and 7–11% have tried it themselves. A recent survey of 163 clinicians treating adolescents in Ohio found most (68%) were aware of the game; more than half had learned of it through popular media. Less than 8% of survey respondents believed they had treated a patient who participated in the choking game. Although nearly two-thirds of the responding physicians felt the game should be included in anticipatory guidance for adolescents, only 2% of those aware of the game reported including it with their own patients. Briefly discussing the choking game with adolescents and their parents may increase parental awareness and help prevent game play in children.

McClave J, Russell P, Lyren A, O’Riordan M, et al: The choking game: physician perspectives. Pediatrics 2010;125 (January):82–87. From Case Western Reserve University, Cleveland, Ohio; and other institutions. Source of funding not stated. The authors indicate they have no commercial relationships relevant to this article.

Adjunctive Divalproex Improved Aggression in ADHD

Adding extended-release divalproex to optimized stimulant therapy improved aggression in children with ADHD.

**Methods:** Children (n=74) aged 6–13 years with ADHD, comorbid oppositional defiant disorder or conduct disorder, and significant aggression received behaviorally-oriented psychosocial treatments plus open-label stimulant monotherapy for an average of 5 weeks. All children were started on OROS methylphenidate titrated to a maximum of 90 mg/day. Those who could not tolerate the OROS formulation were switched to extended-release methylphenidate capsules at a maximum of 60 mg/day. Children with little or no improvement were switched to extended-release mixed amphetamine salts or to dextroamphetamine spansules.

Participants whose ADHD symptoms improved but who continued to have clinically significant aggression received randomized adjunctive divalproex (n=14) or placebo (n=13) for 8 weeks. Divalproex dosing was weight-based and titrated to a target dose of 20 mg/kg and a serum level of 80–100 mcg/mL. An unblinded clinician monitored serum divalproex levels and recommended dosage changes as well as sham changes in the placebo group to maintain the initial blind. Remission, defined as a Retrospective-Modified Overt Aggression Scale (MOAS) score of ≤10, was the primary outcome.

**Results:** Mean MOAS scores decreased in both groups after 8 weeks from 42 to 32 with divalproex, compared with from 53 to 36 with placebo. Significantly more patients treated with divalproex achieved remission of aggression: 8 of 14 (57%) vs 2 of 13 (15%). The odds ratio* for remission of aggression with divalproex was 7.3 (95% confidence interval* 1.2–46.2) and the number needed to treat* was 2.4. Serum divalproex levels did not appear to affect remission status and improvements in aggression were not driven by changes in ADHD symptoms.

**Discussion:** The mean serum divalproex level of 68 mcg/mL was lower than the target range, and the authors suggest higher dosages may have produced better remission rates. Because the study sample was small, the confidence interval for remission status was large, making the results tentative until they can be replicated in a larger trial. Despite its limitations, this study provides preliminary support for the use of adjunctive divalproex to control aggression not responsive to stimulant therapy in patients with ADHD.

**Editorial:** Despite a lack of empirical evidence, polypharmacy seems to be the rule rather than the exception for physicians providing clinical care. The present study suggests that combining activating (e.g., stimulants) and inhibiting (e.g., valproic acid) agents may control
main and downstream neurotransmitter effects and produce remission of aggressive symptoms in some patients with ADHD.

**Study Rating**—17 (100%): This study met all criteria for a randomized controlled trial.

1. Blader J, Schooler N, Jensen P, Pliszka S, et al: Adjunctive divalproex versus placebo for children with ADHD and aggression refractory to stimulant monotherapy. *American Journal of Psychiatry* 2009;166 (December):1392–1401. From Stony Brook University School of Medicine, N.Y.; and other institutions. **Funded by the NIH; the National Alliance for Research on Schizophrenia and Depression; and Abbott Laboratories.** The study authors disclosed commercial relationships with multiple pharmaceutical industry sources including Abbott Laboratories, the manufacturer of Depakote.

2. Steiner H, Karnik N: Integrated treatment of aggression in the context of ADHD in children refractory to stimulant monotherapy: a window into the future of child psychopharmacology [editorial]. *American Journal of Psychiatry* 2009; 166 (December):1315–1317. From Stanford University School of Medicine, Calif. Dr. Steiner disclosed a relationship with Eli Lilly but it was not found to influence this report. Dr. Karnik reports no commercial relationships.

**Drug Trade Names**: dextroamphetamine—Dexedrine; divalproex, extended-release—Depakote ER; methylphenidate, long-acting—Metadate CD; methylphenidate, OROS—Concerta; mixed amphetamine salts, extended release—Adderall XR

*Reference Guide Item.

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**Divalproex Improved Irritability in Autism**

A controlled trial was undertaken to confirm results of an open-label study that found divalproex (Depakote) reduced aggression and irritability in children with autism spectrum disorders.

**Methods**: Participants in the 12-week trial were children aged 5–17 years with autism and clinically significant irritability. Those who met minimum severity criteria of a Modified Overt Aggression Scale score of ≥13 or an Aberrant Behavior Checklist (ABC) irritability score of ≥18 were randomized to divalproex (n=16) or placebo (n=11). Divalproex was titrated to a therapeutic level of ≥50 mcg/mL and dosage changes were driven by recommendations from an unblinded physician who independently monitored blood levels. Irritability was evaluated at 2-week intervals, and the primary outcome measures were the Clinical Global Impression–Improvement (CGI-I) scale* and the ABC irritability subscale.

**Results**: Divalproex-treated patients showed a significantly greater decrease in mean ABC irritability score than the placebo group: from 22 at baseline to 14.5 at 12 weeks vs from 20 to 17.7 with placebo (p=0.03; effect size*, 0.44). Ten of 16 divalproex patients responded to treatment (CGI-I score of 1 or 2), compared with 1 of 11 placebo patients (63% vs 9%; p=0.008). Secondary outcomes including repetitive behaviors and adaptive function were unchanged in both groups. Divalproex was well tolerated with mainly mild-to-moderate adverse effects including insomnia, moderate weight gain, headache, rash, polyuria, and agitation.

Sleep-deprived electroencephalograms (EEGs) in 17 of the 27 study participants suggested that patients with abnormal epileptiform activity may be more likely to respond to divalproex than those with normal EEG records. Higher serum levels were also predictive of treatment response, and all patients with a level in the target range of 87–110 mcg/mL met CGI response criteria.

**Discussion**: Several mechanisms such as the GABA-enhancing effects or inhibition of kindling may underlie the positive effects of divalproex on irritability. It is also possible that treatment of an underlying epileptiform abnormality may be a contributing factor, although the data supporting this hypothesis is preliminary. Regardless of the mechanism, divalproex appears to be a safe and effective treatment for irritability in children with autism.

**Study Rating**—17 (100%): This study met all criteria for a randomized controlled trial.

Hollander E, Chaplin W, Soorya L, Wasserman S, et al: Divalproex sodium vs placebo for the treatment of irritability in children and adolescents with autism spectrum disorders. *Neuropsychopharmacology.* Published online December 9, 2009 at www.neuropsychopharmacology.org; doi 10.1038/npp.2009.202. From Montefiore Medical Center University Hospital for Albert Einstein College of Medicine, Bronx, N.Y.; and other institutions. **Funded by the National Institute of Neurological Disorders and Stroke; and the NIH.** Study medication was provided by Abbott Laboratories. The primary study author disclosed a commercial relationship with Abbott Laboratories, the manufacturer of Depakote.

*Reference Guide Item.
**Flexibly-Dosed Aripiprazole for Irritability**

A previous manufacturer-sponsored controlled trial showed fixed doses of aripiprazole (*Abilify*; 5, 10, and 15 mg/day) improved irritability in autism.1 In a similar but smaller study also supported by the manufacturer, the investigators found a flexible dosing schedule was also effective.2

**Methods:** Ninety-eight patients aged 6–17 years (mean age, 9.3 years) who had autism and at least moderately severe irritability received 8 weeks of randomized double-blind placebo (n=51) or aripiprazole (n=47) flexibly dosed in the target range of 5–15 mg/day; 2 mg/day was permitted if tolerability was an issue. Provided they were stable at study entry and unchanged during treatment, behavioral interventions were permitted, but not most other psychotropic medications. Use of benztropine for movement disorders, benzodiazepines for study-related anxiety, and sleep aids were permitted. The primary outcome measures were the Aberrant Behavior Checklist (ABC) irritability subscale and the Clinical Global Impression-Improvement (CGI-I) scale.

**Results:** During the last study week aripiprazole was dosed at 2 mg/day in 2 patients, 5 mg/day in 13 patients, 10 mg/day in 16 patients, and 15 mg/day in 8 patients. ABC irritability scores decreased from a baseline mean of 30 to 17 with aripiprazole and from 30 to 25 with placebo (p<0.001). Significantly more aripiprazole patients received a CGI-I rating of much or very much improved at 8 weeks: 67% vs 16% (p<0.001). At 8 weeks, response (ABC score decrease of ≥25% plus a CGI-I rating of much or very much improved) was achieved by 52% of the aripiprazole group, compared with 14% of the placebo group (p<0.001).

As with the previous study, most patients (72–92%) experienced adverse effects, but the rates did not differ significantly between the groups. Somnolence, sedation, vomiting, and fatigue were the most commonly associated with aripiprazole, affecting about 10–20% of patients. Extrapyramidal symptoms developed in 15% of the aripiprazole group. No clinically important changes in vital signs or ECG tracings occurred, but aripiprazole was associated with a mean 4-lb weight gain.

**Discussion:** These results confirm both the efficacy and safety findings of the previously reported study. Although patients treated with 15 mg/day aripiprazole in the earlier study showed the greatest improvements, the present results suggest many patients will respond to lower dosages. It should be noted that while aripiprazole did improve ABC irritability scores, the mean final score of 17 indicates residual symptoms persist in some patients.

**Study Rating*—17 (100%):** This study met all criteria for a randomized controlled trial.


2 Owen R, Sikich L, Marcus R, Corey-Lisle P, et al: Aripiprazole in the treatment of irritability in children and adolescents with autistic disorder. *Pediatrics* 2009;124 (December):1533–1540. From Bristol-Myers Squibb; the University of North Carolina at Chapel Hill; and other institutions. **Funded by Bristol-Myers Squibb; and Otsuka Pharmaceuticals. The authors disclosed commercial relationships with Bristol-Myers Squibb, Otsuka Pharmaceuticals, and other pharmaceutical industry sources that might pose conflicts of interest.**

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**The Early Start Denver Model for Autism**

Results of early behavioral interventions for toddlers with autism have been promising but few randomized controlled trials have been conducted. A methodologically rigorous study of the Early Start Denver Model (ESDM) found several aspects of autism were significantly improved.

**Methods:** Children aged 18–30 months with a DSM-IV diagnosis of autism or pervasive developmental disorder not otherwise specified (PDD-NOS) were recruited from pediatricians,
preschools, hospitals, and community programs. The 48 children enrolled in the study were randomly assigned to an ESDM group or to an assess-and-monitor group and followed for up to 2 years. Those in the latter group were assessed annually and given recommendations and referrals for community treatment. The ESDM intervention is individualized and focuses on teaching strategies to improve interpersonal skills, positive affect, and shared engagement. The strategies are consistent with applied behavioral analysis principles. The protocol comprised 20 hours/week of manual-based treatment provided by a trained therapist. Community services outside the study were permitted.

**Results:** ESDM participants received an average of 15 hours/week of therapist intervention and parents applied ESDM strategies for an average of 16 hours/week. Children in the assess-and-monitor group received an average of 9 hours/week each in individual therapy and in group interventions (e.g., developmental preschool).

After 1 year in the study, ESDM participants showed a significantly greater increase in IQ (15 vs 4 points). Improvement continued to the 2-year assessment. ESDM participants also had significantly improved receptive and expressive language skills, communication, activities of daily living, and motor skills. Although they remained behind their peers, adaptive behaviors progressed in the ESDM group at a similar pace to a normative sample of children without autism. In the assess-and-monitor group, adaptive skills, including socialization, continued to fall further behind the normative sample. Diagnostic status was also more likely to improve with ESDM: 7 children in this group (30%) compared with 1 in the assess-and-monitor group (5%) improved from a diagnosis of autism to PDD-NOS. Repetitive behaviors did not improve in either group.

**Study Rating*—16 (94%):** This study met all criteria for a randomized controlled trial except that there was no discussion of its limitations.


*Reference Guide Item.

### Prevalence of Auditory Vocal Hallucinations

Hearing voices in childhood may predict adult schizophrenia, but most children who hear voices do not progress to a clinical disorder. A cross-sectional study of 7 and 8 year old children assessed the prevalence of hearing voices and their characteristics, demographic associations, and developmental and behavioral problems.

**Methods:** During a routine school-based health screening 3870 children in the Netherlands were asked if in the past year they had heard voices no one else could hear. A structured interview to assess the auditory hallucinations was undertaken in children who answered positively. Parents of children whose hallucinations were confirmed during the interview were asked to complete the Child Behavior Checklist (CBCL), and data on pre- and perinatal influences and early development were extracted from Infant Health Service records. A matched control sample of children without hallucinations was also selected.

**Results:** Of the 3870 children, 347 (9%) screened positive for vocal hallucinations. There were no gender differences in prevalence, but among the children who did hear voices, 7-year-olds heard them more frequently than 8-year-olds. Children living in rural areas were about 4-times as likely to report hallucinations as those living in urban areas. However, urban children more frequently reported hearing 2 or more voices, often speaking simultaneously and for longer periods of time. The voices were associated with more thought interference in the urban children.
There were no associations between vocal hallucinations and most pre- and perinatal variables. Maternal infection during pregnancy had occurred nearly twice as frequently in the group reporting hallucinations as in controls. Children who reported voices appeared to have had some developmental delays in the first year of life. Current behavioral problems did not differ between the groups; CBCL scores indicated clinical psychopathology in 27% of children who heard voices and in 22% of those who did not. Children whose hallucinations were judged to be severe experienced more somatic symptoms than those with mild or no hallucinations.

Discussion: Although hearing voices appears to be relatively common during childhood, most children do not experience any subjective burden. However, there may be associations between more severe hallucinations (e.g., ≥ 2 voices) and behavioral problems. The children with severe hallucinations and clinical CBCL scores from the present study will be followed to adulthood to characterize the course of hallucinatory illness.


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Clinical Global Impression–Improvement (CGI-I) Scale: A 7-point rating of patient improvement. A score of 1 corresponds to a rating of very much improved; 2=much improved; 3=minimally improved; 4=no change; 5=minimally worse; 6=much worse; 7=very much worse.

Confidence Interval: The range in which the value of a variable in question is likely to fall, usually calculated at 95%. Confidence intervals indicate the reliability of an estimate, and a very wide interval may indicate that more data should be collected before making definite conclusions.

Effect Size: The effect size represents the amount of change in outcome that can be attributed to treatment, where 0.2 indicates a small effect, 0.5 a medium effect, and 0.8 a large effect. It is relatively independent of clinical significance, and large effect sizes do not ensure treatment efficacy.

Number Needed to Treat (NNT): Indicates how many patients need to be treated for 1 to benefit. The ideal NNT is 1, where everyone improves with treatment. The higher the NNT value, the less effective is the treatment.

Odds Ratio: A comparison of the probability of an event in two groups. An odds ratio of 1 implies that the event is equally likely in both groups. An odds ratio greater than 1 indicates that the event is more likely to occur in that group than in the comparison group.

Study Rating: A measure of how well a study conforms to quality standards. The study rating uses a checklist system based on the comprehensive Strength of Evidence Report from the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality (AHRQ). The rating checklists have been posted at www.alertpubs.com.