Placebo Effects in ADHD

Both psychological and physiological changes have been attributed to placebo in several mental health disorders. A review of studies that evaluated placebo in ADHD found little evidence that it significantly changes behavior or cognition in elementary school-age children. However, placebo effects were found in the adults who evaluated the children. Parents and teachers tended to give more positive evaluations to children they thought were medicated and they often attributed behavioral changes to medication, even when the child had not received active medication treatment. Subjective parent and teacher ratings are the primary outcome measures in most ADHD studies, but the objective measures that do not seem to be influenced by placebo administration may be more accurate assessments of change.


Adolescent Outcomes of MTA Participants

At 8-year follow-up, participants in a large ADHD study were not performing as well as a healthy comparison group in terms of behavioral, academic, and overall functioning.

The Multimodal Treatment Study of Children With Attention-Deficit/Hyperactivity Disorder is a large NIMH-funded evaluation of ADHD treatments in which medication management, behavioral therapy, combination medication and behavioral treatment, and community care were compared in patients aged 7–9 years with combined-type ADHD. Combination treatment and medication management were significantly more effective than the other treatments at the end of the 14-month acute phase, but these differences dissipated by 3 years. The 8-year follow-up analysis evaluates outcomes by initial treatment assignment and compares the MTA participants with a local normative comparison group chosen from the same schools to reflect the general non-ADHD population. Predictors of adolescent outcomes were also assessed.

Medication Treatment: At 8 years, 33% of the MTA participants were receiving medication treatment, usually with stimulants (83%). Most (75%) had been medicated at 14 months, indicating...
medication was typically continued rather than initiated later. Of the children who were medicated at 14 months, 62% had discontinued pharmacotherapy by 8 years.

**Behavioral Symptoms:** There were no significant differences on any outcome measure based on initial treatment assignment at the 8-year follow-up. While improvements seen at the end of acute treatment were generally maintained, MTA participants were not "normalized" at 8 years; 30% continued to meet diagnostic criteria for ADHD. Clinically significant antisocial behavior was present in 25–30% of MTA patients: 25% met criteria for oppositional defiant disorder or conduct disorder; 27% had been arrested at least 1 time; and 30% reportedly had moderate-to-serious delinquent behavior. Psychosis, mania, and hypomania were uncommon at 8 years (1–3%), contradicting the belief that stimulant treatment can precipitate these disorders, but MTA participants had more psychiatric hospitalizations than the comparison group.

**Academic Functioning:** Standardized achievement test scores, teacher ratings of academic performance, and grade point averages were substantially lower among the adolescents who had participated in the MTA study than in the comparison group. Effect sizes for these variables were in the medium range (0.45–0.66). MTA participants were twice as likely to have repeated a grade.

**Overall Functioning:** Parent ratings of social performance and overall functioning were significantly lower for the MTA group than the comparison group (p=0.0001). Effect sizes for these outcomes were large: 0.96 for overall functioning and 0.84 for social performance.

**Predicting Outcomes:** Neither the type nor the intensity of ADHD treatment in childhood predicted functioning at 8 years. Rather, the initial symptom severity, conduct problems, and strength of ADHD response, regardless of treatment assignment, were predictive of adolescent outcomes. Children who had the strongest response early in treatment had the best long-term outcomes. However, despite substantial improvement that was generally maintained, adolescents who had been treated for ADHD in the MTA study had poorer functioning than non-ADHD adolescents in several domains.


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**Zolpidem for Insomnia in ADHD**

In a multicenter controlled trial, zolpidem (*Ambien*) did not improve sleep in a group of patients with ADHD-related insomnia.

**Methods:** Changes in sleep latency were evaluated in 201 patients aged 6–17 years with ADHD who had polysomnographically confirmed latency of >30 minutes at baseline. Participants were randomized to receive 8 weeks of double-blind zolpidem at 0.25 mg/kg/day with a maximum dose of 10 mg (n=136) or placebo (n=65) administered 30 minutes before bedtime. The primary outcome was sleep latency measured at 3–6 weeks.

**Results:** Compared with placebo, zolpidem did not produce a significantly greater decrease in sleep-onset latency; reductions averaged 21 and 20 minutes in the groups, respectively. Secondary sleep measures including total sleep time and number of awakenings also did not improve with zolpidem treatment. Clinical Global Impression ratings of insomnia showed improvement in adolescents, but not in younger children. No next-day residual effects of zolpidem were seen, and sleep latency worsening after discontinuation of both active and placebo treatment was not significant. ADHD severity was not affected.
CNS and neuropsychiatric adverse events were common with zolpidem, particularly dizziness (24%), headache (13%), and hallucinations (7%). Ten patients discontinued zolpidem because of adverse effects, compared with none of the placebo-treated patients.

**Study Rating**—14 (82%): Neither the study limitations nor potential bias was discussed, and the funding source was not disclosed.

Blumer J, Findling R, Shih W, Soubrane C, et al: Controlled clinical trial of zolpidem for the treatment of insomnia associated with attention-deficit/hyperactivity disorder in children 6 to 17 years of age. *Pediatrics* 2009;123 (May): e770–e776. From Case Medical Center, Cleveland, Ohio; and other institutions. **Source of funding not stated.** All study authors disclosed financial arrangements with pharmaceutical-industry sources; and 1 author is employed by Sanofi-Aventis (manufacturer of Ambien). Zolpidem is not FDA approved for use in pediatric patients.

*Reference Guide Item.*

### Divalproex ER in Bipolar Disorder

Although not an FDA approved indication, divalproex is commonly used to treat pediatric bipolar disorder. A large amount of open-label data seems to support this off-label use. The first multicenter double-blind placebo-controlled trial of divalproex ER (*Depakote ER*) in this population does not support its use.

**Methods:** Outpatients aged 10–17 years with a mixed or manic episode of bipolar I disorder and a Young Mania Rating Scale (YMRS) score of ≥20 were enrolled in the study. After a washout of all antipsychotics, antidepressants, mood stabilizers, and atomoxetine, 150 patients received 4 weeks of randomized double-blind divalproex ER or placebo. Divalproex was started at 15 mg/kg/day and titrated to a target serum level of 80–125 mcg/mL. At the end of acute treatment patients could enter a 6-month open-label extension phase. The primary outcome measure was the YMRS, and the Clinical Global Impression (CGI) Severity and Improvement scales and other standardized measures were secondary outcomes. Efficacy results are based on an intent-to-treat population of 144 patients: 74 who received divalproex and 70 who received placebo. Six patients were excluded because they had no recorded YMRS scores.

**Results:** The mean baseline YMRS score was 31 in both the divalproex and placebo groups. At 4 weeks, both groups showed improvement, but the change was not clinically meaningful. Endpoint CGI-Improvement ratings indicated minimal improvement in each group. There was no significant difference between the groups in YMRS score change (9 and 8 points). Response (≥50% decrease in YMRS score) was achieved by 24% of patients treated with divalproex and 23% of patients treated with placebo. Remission (final YMRS score of <12) was achieved by 16% and 19% of the groups, respectively. Improvement did not appear to be affected by serum valproate concentration or patient age. Adverse event rates were similar with divalproex and placebo as were discontinuations because of them. Hyperammonemia is a concern with divalproex. Treatment significantly increased the mean serum ammonia level, but only 1 patient was symptomatic. Platelet count was also significantly decreased with divalproex. After 6 months of open label divalproex, the mean YMRS score was 2 points lower than baseline.

**Discussion:** Although these results do not support divalproex ER use in pediatric manic/mixed episodes of bipolar disorder, this is the only controlled trial that has been conducted, and the results need to be replicated or refuted in additional trials.

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


*Reference Guide Item.*
Early Bipolar Disorder Symptoms

Medical records were reviewed for 38 children and adolescents with bipolar disorder who were treated at a university-based clinic. The Schedule for Affective Disorders and Schizophrenia for School-Aged Children, Present and Lifetime Version (K-SADS-PL) was retrospectively applied to chart data and symptom profiles were examined.

Results: The median age at diagnosis was 14 years, but 75% of patients had experienced symptoms of bipolar disorder before age 12 years. The average diagnostic delay was 1.5 years, but 25% had a lapse of >3 years from first symptoms to diagnosis. The most common prediagnosis symptoms were severe irritability (95%); dysphoria (74%); depressed mood (66%); anhedonia (68%); distractibility (66%); poor concentration (61%); and psychomotor agitation (61%). The symptom profile was similar at diagnosis, except that depressed mood and anhedonia were less common. ADHD, oppositional defiant disorder (ODD), and conduct disorder symptoms were also common at diagnosis (ranging from 42% to 95%) and there were no significant differences in these symptoms before and at diagnosis.

The majority of patients (76%) had previously received a psychiatric diagnosis other than bipolar disorder, most commonly ADHD, major depression, and ODD. Nearly all (92%) had been treated with a psychotropic prior to bipolar diagnosis: 66% with an antidepressant; 34% with mood stabilizers; and 42% with antipsychotics.


Venlafaxine-Associated Complex Hallucinations

A 17-year-old male presented for treatment of major depressive disorder, social phobia, and generalized anxiety disorder. He was receiving eletriptan for migraines that seemed to co-occur with anxiety episodes. He had recently begun treatment with lamotrigine, which was being titrated to an effective dose, and he took diphenhydramine as needed for sleep.

A combination of fluoxetine and cognitive behavioral therapy was recommended. However, the patient’s neurologist strongly favored venlafaxine because, in addition to antidepressant and antianxiety efficacy, it has been suggested to help with migraines. The evidence for venlafaxine use in adolescents is not strong, and it is not FDA approved for pediatric use. However, it was considered an option for this patient because he was 17 years old and had reached an adult body weight.

Treatment was started with 37.5 mg/day immediate-release venlafaxine and was increased to b.i.d. dosing after 2 weeks of persisting symptoms. On the first night of b.i.d. dosing the patient took the venlafaxine with diphenhydramine and lamotrigine. After the following morning dose, he experienced visual and tactile hallucinations of bugs crawling on him, and he became disoriented. Symptoms resolved over a few hours. Rechallenge with venlafaxine in the morning and half of a 37.5 mg pill in the evening (taken with eletriptan and lamotrigine) produced hallucinations and extreme disorientation. He was referred to the emergency department where no physical causes for the symptoms were found and serotonin syndrome was ruled out. Symptoms resolved overnight and he did not take any additional venlafaxine.

Hallucinations were reported in about 1% of pediatric patients treated with venlafaxine in 2 recent trials, but the nature of the hallucinations was not specified. In adults, complex visual
hallucinations are often associated with serotonin syndrome or withdrawal of an SSRI or SNRI. It is possible that the concomitant administration of diphenhydramine during the first episode and eletriptan during the second contributed to the adverse reaction in this patient. Combining agents with serotonergic effects (venlafaxine, eletriptan) or using one with an agent that has anticholinergic effects (diphenhydramine) could alter serotonergic balance and precipitate the complex hallucinations as a probable episode of delirium.

1 Jacob M, Ash P: Venlafaxine-induced complex hallucinations in a 17-year-old boy. Journal of Clinical Psychiatry 2009;70 (April):601–603. From Emory University, Atlanta, Ga. The authors disclosed no financial or other relationships that were relevant to this material.


Drug Trade Names: diphenhydramine—Benadryl, and others; eletriptan—Relpax; fluoxetine—Prozac; lamotrigine—Lamictal; venlafaxine—Effexor

Fatty Acids Are Not Helpful in ADHD

According to a report by the Agency for Healthcare Research and Quality, children with ADHD have lower plasma levels of some fatty acids than healthy children.\(^1\) Open-label trials have shown supplementation to be beneficial in these children. Results of controlled trials have been mixed, but most showed no benefit over that of placebo. A recent study evaluated supplementation with short-chain fatty acids in this population because previous research used longer-chain fatty acids.\(^2\)

The 7-week randomized double-blind placebo-controlled trial enrolled 73 unmedicated patients (aged 7–13 years) with ADHD. Participants were randomized to receive either placebo supplements containing only vitamin C or fatty acid supplements containing alpha-linolenic acid, linoleic acid, mineral oil, and alpha-tocopherol. Parent and teacher symptom questionnaires as well as omission and commission errors on computerized continuous performance tests were used to measure the effects of treatment.

No significant between-group differences were found on any measure, suggesting short-chain fatty acid supplementation is no more effective than placebo in young patients with ADHD.


Sleep Duration Affects Behavior

Studies of sleep deprivation and behavior in children are few, but clinical observations suggest hyperactivity/impulsivity and inattention are associated with short sleep duration. In addition, children with ADHD often have sleep difficulties, and children with sleep apnea frequently have behavioral symptoms. A prospective study was undertaken to confirm if objectively measured sleep parameters are related to ADHD-like behavioral symptoms.

Methods: A cohort of >1000 healthy full-term infants born in Finland between March and November 1998 who participated in an unrelated study of maternal licorice use during pregnancy were followed for up to 8 years. From this cohort, 280 children with no neurological
conditions that could affect sleep or behavior participated in the sleep study. Sleep quality and duration were measured objectively using actigraphy, and parents were asked to keep logs of daily rise times and bedtimes. Parents also completed the Sleep Disturbance Scale for Children, which measures difficulties with sleep initiation and maintenance; sleep disordered breathing; arousal; sleep-wake transitions; excessive somnolence; and sleep hyperhydrosis. Behavioral symptoms were evaluated with the parent-rated ADHD Rating Scale IV (ADHD-RS-IV).

**Results:** Children with sleep difficulties (score of >39 on the Sleep Disturbance Scale) had higher ADHD-RS-IV scores than those without: 9 vs 7.5 points on the hyperactivity/impulsivity subscale; 8 vs 6 on the inattention subscale; and total scores were 16 vs 14. Differences in inattention and total scores reached statistical significance (p≤0.003), but hyperactivity/impulsivity scores did not. Effect sizes* were small. Of the individual Sleep Disturbance Scale items, only sleep disordered breathing and sleep hyperhydrosis were not associated with behavioral symptom increases. Based on average sleep times, short sleepers were defined as those who slept <7.7 hours, average sleepers were those who slept 7.7–9.4 hours, and long sleepers were those who slept >9.4 hours. ADHD-RS-IV scores decreased with increasing sleep time.


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**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.

**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.