Placebo Response in Pediatric Depression Trials

A review examined 12 pediatric randomized controlled antidepressant trials. Patient age (i.e., child vs adolescent) and other factors, such as numbers of patients and study sites, and the duration and severity of depression were analyzed.

The strongest predictor of placebo response was the number of sites participating in a study (p=0.007). Less severe depression at baseline also predicted placebo response, but the association was not statistically significant after controlling for the number of study sites. Younger patients had higher placebo response rates than adolescents, but the difference was not significant. More recent studies also had higher placebo response rates, which appeared to be driven by an increase over time in the number of sites per study. No associations were found between treatment or illness duration, study location, race, or gender.


Stimulants Did Not Cause Cytogenetic Damage

Because cytogenetic changes in lymphocytes are associated with increased cancer risk, there was much concern when these changes were reported in 12 children receiving methylphenidate. Single-dose studies in humans and mice as well as a small prospective study were prompted by that report, but they found no evidence of chromosomal aberrations. A recent larger prospective study has also found that methylphenidate and mixed amphetamine salts do not cause genetic damage.

After baseline physical evaluations including an electrocardiogram and blood sampling, 63 stimulant-naïve children aged 6–12 years were randomly assigned to receive methylphenidate or mixed amphetamine salts for 3 months. The specific preparations used were Concerta, Ritalin LA, Adderall, and Adderall XR. Treatment decisions, including which agent to use within the assigned medication class and dose adjustments, were made on an individual patient
basis. Patients with a recent x-ray were excluded because of the possibility for related chromosomal damage. Repeat blood sampling at 3 months in 47 of the patients found no change from baseline in indicators of chromosomal damage. In addition, there were no differences between patients treated with methylphenidate and mixed amphetamine salts.

Although this is not definitive proof of the long-term safety of ADHD medications, these results add to the evidence suggesting therapeutic levels of methylphenidate and mixed amphetamine salts do not cause cytogenetic damage.


### Antiepileptics and Autism

Preliminary results from a prospective cohort study suggest in utero exposure to valproic acid may be associated with the development of autism spectrum disorders.

**Methods:** Women (n=620) were recruited from antenatal clinics by members of the Liverpool and Manchester Neurodevelopment Group, and information was collected on 632 of their children. Follow-ups, which included medical and neuropsychological examinations, were scheduled for 1, 3, and 6 years. A sample of 336 children who were not exposed to antiepileptics in utero and whose mothers did not have epilepsy were also included.

**Results:** Of the 632 children born, 296 had mothers with epilepsy, 249 of whom took antiepileptic drugs during pregnancy. Within this group, 64 children had been exposed in utero to valproate, 44 to lamotrigine, 76 to carbamazepine, and 65 to other monotherapy or to multiple medications.

Nine of the children have received a diagnosis of either Asperger’s disorder or autism and another child has symptoms suggestive of autism. Of these 10 children, 7 were exposed in utero to antiepileptic drugs, most commonly valproate. Incidence rates for autism spectrum disorders ranged from <1% in control children to 2% with lamotrigine monotherapy and 6% with valproate monotherapy. No child exposed to carbamazepine in utero has an autism spectrum disorder.

**Discussion:** Conclusions cannot be drawn about all antiepileptics from these data because the absolute number of autism spectrum disorders diagnosed among patients exposed to some agents (e.g., phenytoin, lamotrigine) is small. However, there seems to be a clear increase in risk with valproate exposure. It should be noted that 32% of this cohort is still under the age of 6 years and autism and other disorders may not yet have been detected.


**Drug Trade Names:** carbamazepine—Epitol, Tegretol; lamotrigine—Lamictal; phenytoin—Dilantin; valproate—Depakene, Depakote

### Pediatric Use of Ziprasidone

A review of ziprasidone (Geodon) suggests it can be used as second- or third-line treatment for a limited range of indications.

There are only 2 randomized controlled trials, 5 open-label studies, and 12 case reports of ziprasidone use in children and adolescents. The controlled trials included patients with bipolar
disorder (n=238) or Tourette’s or other tics disorders (n=28). These studies showed about two-thirds of pediatric ziprasidone-treated patients with bipolar disorder achieved a ≥50% decrease in manic symptom scores and that tic severity was also significantly improved by about 40%.

In the open studies, 15 of the 24 patients (63%) with autism were judged to be at least “much improved” after treatment, and Brief Psychiatric Rating Scale and Young Mania Rating Scale scores were improved in all ziprasidone treatment groups. Case reports suggest ziprasidone may also be useful in disruptive behavior disorders, obsessive-compulsive disorder, and acute agitation or aggression.

Although it is less likely to cause extrapyramidal symptoms than other atypical antipsychotics, ziprasidone does have a greater propensity to cause QT prolongation and other cardiac effects. Galactorrhea and mild transient prolactin elevations have been reported in treated adolescent females. There has been 1 reported case of possible ziprasidone-associated mania. Weight gain is generally similar to placebo.

Because of the cardiac risks and the limited evidence available, the authors support ziprasidone use in pediatric patients with Tourette’s disorder, autism, or bipolar disorder only after they have been unresponsive to at least 1 “standard” therapy or when weight gain or metabolic changes are of particular concern. Although the product labeling does not mandate an electrocardiogram (ECG) before treatment initiation, the authors suggest ECG monitoring may be warranted.

Elbe D, Carandang C: Focus on ziprasidone: a review of its use in child and adolescent psychiatry. Journal of the Canadian Academy of Child and Adolescent Psychiatry 2008;17 (November):220–229. From BC Children’s Hospital, Vancouver, Canada; and other institutions. The authors have no financial relationships to disclose.

Cardiac Arrest with Methylphenidate

Concern has been raised about the cardiac effects of stimulant treatment for ADHD and in 2006 a label warning was added regarding cardiac risk, particularly in patients with underlying cardiac abnormalities.1 In addition, the American Heart Association has recommended more intensive screening for cardiac defects, including electrocardiograms for patients with findings suggestive of disease, before starting stimulants for ADHD.2 A case of cardiac arrest in an otherwise healthy adolescent with no indication of cardiac defect suggests patients may still be at risk despite an apparently comprehensive evaluation.3

A 17-year-old male with ADHD had been receiving methylphenidate (Concerta) for 18 months. Treatment had been started at 18 mg/day and increased over 3 months to 36 mg/day. He had recently complained of chest pain and burning, but had not sought medical attention.

The patient experienced cardiac arrest with pulseless electrical activity; resuscitation efforts were successful, but he had been pulseless for approximately 22 minutes. Initial laboratory evaluations revealed elevated creatine kinase-myocardial band (CK-MB) isoenzyme and myoglobin levels. Metabolic profile and blood counts were unremarkable, and toxicology studies were negative except for methylphenidate. The patient took no other prescription medications and overdose was ruled out. Evaluation in the cardiac catheterization laboratory found wall motion abnormalities without coronary lesions and an ejection fraction near 40%.

A childhood heart murmur had been detected in the patient at the age of 6 years. An echocardiogram at age 13 years was negative for structural defects, although a holosystolic murmur was heard. Re-evaluation of the echocardiogram after the cardiac event confirmed
the initial findings. Although cardiac function was recovered, anoxic brain encephalopathy persisted and the patient sustained severe mental deficiencies. Methylphenidate, which had been stopped on hospital admission, was not restarted and the patient had no further cardiac events during 2 years of follow-up. According to the Naranjo Probability Scale*, an association between methylphenidate and the cardiac arrest was probable.


*Reference Guide Item.

Predicting Depression Remission

The magnitude of improvement seen in the first 4 weeks of antidepressant therapy seems to be the best predictor of future remission.

Methods: A 12-week study included patients aged 7–18 years (n=168) with nonpsychotic major depressive disorder. All had a Clinical Global Impression-Severity (CGI-S) rating of at least “moderately ill” and a Children’s Depression Rating Scale-Revised (CDRS-R) score of ≥40. All patients received 10–40 mg/day fluoxetine for 12 weeks. Remission was defined as a CDRS-R score of ≤28. Age, gender, ethnicity, number of depressive episodes, duration of illness, family history, and other factors were examined as possible predictors of depression remission. Analysis of 145 patients who completed 8 weeks of treatment identified the percentage of CDRS-R improvement that predicted remission.

Results: As early as week 1, symptom reductions were significantly greater in patients who ultimately remitted than in those who did not (23% decrease in CDRS-R vs 16%; p=0.01). However, percent of improvement at 4-week evaluation was found to be the best predictor of remission. Overall, a ≥58% reduction in CDRS-R score at 4 weeks had a positive predictive value* of 89% and a negative predictive value* of 46%. The odds for achieving remission at 12 weeks were 6.5 times higher among patients with a ≥58% symptom reduction at week 4. In a subgroup analysis by age, the cutoff was slightly higher for children vs adolescents (64% vs 55%).

The only baseline factor significantly associated with remission in pediatric major depression was a family history of depression. Patients with this history were 3 times more likely to achieve remission than those without (p=0.01).

Discussion: Current treatment guidelines recommend a treatment change at 6–8 weeks if improvement is insufficient. The results of this study suggest a <50% improvement by 4 weeks of treatment may be cause for a treatment change, as those who do not yet show improvement of this magnitude are unlikely to achieve remission.


*Reference Guide Item.
Treatment with lithium had a large positive effect on aggression in children and adolescents with conduct disorder.

**Methods:** Clinical records were reviewed for 60 consecutive patients (mean age, 14 years) with conduct disorder who were treated with lithium at a tertiary-care university hospital. Both inpatients (n=44) and outpatients (n=16) were included and followed for 6–12 months. Patients whose symptoms were not adequately controlled with lithium monotherapy (n=37) received adjunctive risperidone or olanzapine. Psychosocial treatments were not part of the protocol, but 36 patients (60%) participated in them outside the study. Outcomes were assessed using the Modified Overt Aggression Scale (MOAS) and the Clinical Global Impression Improvement (CGI-I) and Severity (CGI-S) scales. The MOAS measures 4 domains: verbal aggression; physical aggression against objects; physical aggression against people; and self-aggression. Patients with a ≥50% decrease in MOAS score in addition to a CGI-I rating of “much improved” or “very much improved” and a CGI-S rating of “mildly ill” or better at 3 consecutive visits were judged to be responders.

**Results:** All MOAS measures of aggression improved significantly with lithium treatment (p<0.001) and the effect size* for total MOAS score was 1.03. Self-aggression showed the smallest improvement. Results were similar in patients who required adjunctive antipsychotics who also showed significant improvement on all MOAS items and an effect size of 1 for total score. These patients showed greater improvement in self-aggression than those on lithium monotherapy.

At the end of follow-up, 29 patients (48%) met full response criteria. Of these, 10 achieved response with lithium monotherapy and 19 with combined lithium and an antipsychotic. Although they did not meet full response criteria, 13 patients had moderate improvement with lithium monotherapy and were judged to be clinically manageable. Thus, 70% of patients were successfully treated either with lithium monotherapy or with lithium plus an atypical antipsychotic.

Patients who met response criteria were less severely impaired at baseline, and serum lithium concentrations did not appear to affect response. Comorbid substance abuse was more common among nonresponders, but other comorbidities (e.g., ADHD, obsessive-compulsive disorder, bipolar disorder) did not differ between responders and nonresponders.

Adverse effects were reported by about one-third of patients, but they were seldom severe. Two patients discontinued treatment because of adverse effects (i.e., persistent vomiting, thyroid dysfunction). GI complaints were the most common adverse effects (27%), followed by polydipsia and increased urinary frequency (17%). Tremors developed in 8 patients (13%) and were associated with high serum lithium levels. Weight gain averaged <3 lbs with lithium monotherapy and >9 lbs with adjunctive antipsychotics.


**Drug Trade Names:** olanzapine—Zyprexa; risperidone—Risperdal

*Reference Guide Item.
Reference Guide

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.

Naranjo Probability Scale: A 10-point scale used to determine the likelihood that an adverse reaction is caused by an implicated medication. Based on scores, associations are considered doubtful, possible, probable, or highly probable.

Negative Predictive Value: The proportion of patients with negative test results who are correctly diagnosed.

Positive Predictive Value: The proportion of patients with positive test results who are correctly diagnosed.

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