Antidepressant Tolerability in At-Risk Youth

In a prospective cohort study, antidepressant tolerance was poor in children and adolescents at familial risk for bipolar disorder. Adverse behavioral reactions were particularly likely in younger patients.

Methods: The study enrolled 118 patients, aged 9–20 years, who had at least 1 parent with bipolar I disorder. Patients mood symptoms were evaluated every 1–4 months, depending on baseline symptom severity, using the Longitudinal Interval Follow-up Evaluation. Treatment was naturalistic and provided by the investigators or by community care providers. The primary study outcome was an adverse reaction that led to withdrawal of antidepressants.

Results: Patients had a mean age of 14 years, and about half were girls. Antidepressants were prescribed for 21 patients either immediately before or during prospective follow-up. Of the 21 patients, 11 had received a diagnosis of depressive disorder, 8 an anxiety disorder, 4 a disruptive behavior disorder, and 9 ADHD. The mean follow-up was about 2 years (range, approximately 1–4 years). A total of 14 patients took an SSRI, 8 took bupropion, and 1 took duloxetine; 2 patients had >1 antidepressant trial.

A total of 12 patients (57%) had an adverse reaction that led to treatment discontinuation. The reactions were increased irritability in 7 patients; increased aggression in 5; psychosis and increased impulsivity each in 2 patients; and suicidal ideation, insomnia, and increased hyperactivity, each affecting 1 patient. Mean duration of antidepressant treatment in these patients was 17 weeks (range 2–57 weeks). There was not a statistically significant difference in discontinuation rates between bupropion and SSRIs (50% vs. 63%). Risk of adverse reaction increased markedly with younger age; for every decreasing year of age, the risk of adverse reaction increased by a factor of 1.8 (p=0.02). According to a mathematical model, the risk of adverse reaction may decrease from 97% in a 9-year-old to 4% in a 20-year-old.

Discussion: There are few existing data that address the risk of antidepressant treatment in young people with familial risk of bipolar disorder. Results from this and previous studies...
suggest that antidepressants are often used to treat depressive and anxiety disorders in high-risk youths. The investigators observed trends toward higher irritability and motor hyperactivity in patients who experienced an adverse reaction, which suggests that subsyndromal manic symptoms (or behavioral activation) predict a poor response. Psychotherapies for depression and anxiety should be considered as alternatives in high-risk young patients. Results of previous research suggest mood stabilizing drugs are not helpful, and antipsychotics are poorly tolerated. Additional research is needed to assess first-line treatments in this patient population.

Strawn J, Adler C, McNamara R, Welge J, et al: Antidepressant tolerability in anxious and depressed youth at high risk for bipolar disorder: a prospective naturalistic treatment study. Bipolar Disorders 2013; doi 10.1111/bdi.12113. From the University of Cincinnati College of Medicine, OH; and other institutions. Funded by the NIH; and other sources. Six of 11 study authors disclosed financial relationships with commercial sources and 2 with noncommercial sources; the remaining 3 declared no conflicts of interest.

Drug Trade Names: bupropion—Wellbutrin; duloxetine—Cymbalta

New Practice Parameter for Pediatric Schizophrenia

Knowledge about the treatment of schizophrenia in children and adolescents has advanced considerably since the last practice parameter of the American Academy of Child and Adolescent Psychiatry (AACAP) was published in 2001. The new AACAP guideline, based on a review of literature published between 2004 and 2010, contains a list of 10 recommendations, most of which are deemed clinical standards—i.e., supported by rigorous evidence and/or overwhelming clinical consensus.

• It is a clinical standard to include screening questions for psychosis in all psychiatric assessments of children and adolescents.

• Diagnosis of early-onset (or childhood-onset) schizophrenia should be based on the DSM-5 criteria for adults.

• Patients with suspected schizophrenia should be evaluated for comorbid conditions including suicidality; relevant comorbid conditions; substance abuse; developmental disabilities; psychosocial stressors; and general medical status.

• Antipsychotic medications are first-line treatment for schizophrenia spectrum disorders. Most atypical agents, except for clozapine, may be used to treat pediatric schizophrenia; first-generation agents appear equally effective and may be considered. Medications that have FDA approval for the treatment of schizophrenia in patients aged ≥13 years include risperidone; aripiprazole; quetiapine; paliperidone; olanzapine; and haloperidol. There are few studies directly comparing the efficacy of these drugs in young people, and safety and effectiveness data are limited to short-term studies. The metabolic effects of olanzapine may limit its use as first-line therapy. Ziprasidone was shown to be ineffective in adolescents.

• Ongoing medication is recommended to improve functioning and prevent relapse, using the lowest effective dose.

• Adjunctive medications are recommended for some youth, although the practice is supported by less rigorous evidence and is considered a clinical guideline rather than a clinical standard. These treatments may include antiparkinsonian agents, beta-blockers, antidepressants, anxiolytics, and mood stabilizers.

• A trial of clozapine should be considered for young people with treatment-resistant schizophrenia.
• Baseline and follow-up monitoring of symptoms, adverse effects, and laboratory tests is recommended, with a focus on metabolic effects, body mass, and cardiovascular risk factors. Patients should be advised about following a healthy lifestyle. Significant weight gain or metabolic syndrome should prompt a switch to a different antipsychotic or the addition of a drug like metformin.

• Concomitant psychotherapeutic interventions are recommended as a clinical guideline, because the evidence base is less substantial.

• ECT is a clinical option (i.e., based on emerging empirical evidence or clinical opinion, but lacking strong evidence) for severely impaired patients who do not respond to or cannot tolerate medication.


Drug Trade Names: aripiprazole—Abilify; clozapine—Clozaril; haloperidol—Haldol; metformin—Glucophage; olanzapine—Zyprexa and others; paliperidone—Invega; quetiapine—Seroquel and others; risperidone—Risperdal and others; ziprasidone—Geodon

Maternal Smoking and Conduct Problems

An association between prenatal tobacco exposure and behavioral problems has long been suspected, but it has been difficult to rule out several confounding factors. Results of a meta-analysis of studies that accounted for the potential contributions of genetics and parenting practices confirm that maternal smoking during pregnancy increases conduct problems in children.¹

Methods: Data for the study was pooled from 3 longitudinal studies that investigated the link between maternal smoking and conduct problems. The Christchurch Health and Development Study from New Zealand included 1088 children reared by biological mothers and 36 by nonbiological adoptive mothers. The Early Growth and Development Study, from the U.S., was based on 311 adopted children. The Cardiff IVF Study, conducted mostly at clinics in the U.K., included 636 mother-child pairs who were genetically related (with conception via sperm donation or homologous in vitro fertilization [IVF]) and 206 genetically unrelated pairs (egg and embryo donation). In all studies, behavior problems were assessed during childhood (between the ages of 4 and 10 years) using validated structured questionnaires, including the Child Behavior Checklist, the Strengths and Difficulties Questionnaire, and the Children’s Behavior Questionnaire Short Form. Smoking during pregnancy was reported by the mothers after childbirth. Parenting practices were assessed using different standardized instruments, with an emphasis on negative disciplinary behaviors.

Results: In the U.S. and New Zealand studies, about one-third to one-half of the study children reared by biological and adoptive mothers were born to mothers who smoked during pregnancy. Rates of smoking were lower in the IVF study: about 6% for children reared by genetically related mothers and 4% of those reared by genetically unrelated mothers.

Across all the studies, children of mothers who smoked during pregnancy had higher mean scores on measures of conduct problems. Children whose mothers smoked ≥10 cigarettes per day had the highest problem scores. The association of maternal smoking and conduct problems was attenuated after adjustment for potential confounding factors, which included child gender; birth weight; race/ethnicity; placement age; breastfeeding; maternal age and education; family breakdown; parenting practices; and family socioeconomic status. However, associations remained significant in both children reared by genetically related mothers (p=0.04) and adopted children (p=0.003).
Editorial: This definitive study follows decades of basic and clinical research on the effects of maternal smoking on fetal outcomes and, most recently, on long-term neurobehavioral damage. Research in animals has shown that at least 1 component of tobacco smoke, nicotine, is sufficient to disrupt brain development and cause behavioral abnormalities. Until now, it has been difficult to translate this observation to humans. The present study has many implications for reducing nicotine exposure during pregnancy. Among them, the use of transdermal nicotine patches for smoking cessation in pregnancy should be abandoned, because maintaining steady-state nicotine blood levels removes the protective effect of the placenta, which would otherwise delay fetal entry of sporadically inhaled tobacco.

1 Gaysina D, Fergusson D, Leve L, Horwood J, et al: Maternal smoking during pregnancy and offspring conduct problems: evidence from 3 independent genetically sensitive research designs. JAMA Psychiatry 2013;70 (September): 956–963. From the University of Leicester U.K.; and other institutions. Funded by the Health Research Council of New Zealand; and other sources. The authors declared no conflicts of interest.

2 Slotkin T: Maternal smoking and conduct disorder in the offspring [editorial]. JAMA Psychiatry 2013;70 (September): 901–902. From Duke University Medical Center, Durham, NC. The author disclosed financial relationships with commercial sources.

ADHD Treatment: Parent Preferences, Goals

Shared decision making is being emphasized increasingly in caring for patients with chronic illness, including ADHD. A structured questionnaire, the ADHD Preference and Goal Instrument (ADHD PGI), was designed to measure parental preferences and goals regarding ADHD treatment. Use of this instrument in clinical practice could ensure that both treatment options—medication and behavior therapy—are discussed; this may in turn improve patient outcomes.

The questionnaire was recently tested in 172 parents of 148 children, aged 6–12 years, with a diagnosis of ADHD who were receiving either medication or behavioral therapy (but not both) or no treatment. Responses on the ADHD PGI were compared with the initiation of treatment during the next 6 months and with a second administration of the questionnaire.

Parents’ goals for treatment of their child’s ADHD tended to direct treatment decisions. When parents’ main concern was academic performance, they were more than twice as likely to initiate medication. Parents more worried with behavioral issues tended to choose behavioral therapy as an initial treatment. After 6 months, parents of children who had initiated their treatment of choice had lower academic and behavioral goal scores, suggesting that initiated treatment was successful and goals were being attained.


Extended Escitalopram in Adolescent Depression

In adolescents with depression, extended treatment with escitalopram (Lexapro) following an 8-week acute treatment trial resulted in a modest improvement in efficacy. Extended treatment was well tolerated, but self-harm and suicidal behavior/ideation continued to occur with escitalopram and to a lesser extent with placebo.

Methods: The present study was a 16-week, placebo-controlled extension of an 8-week controlled trial that had a role in the FDA approval of escitalopram for adolescent depression. Regardless of their response in the acute phase, 165 study participants continued to receive double-blind treatment at the same dosage (10 or 20 mg/day escitalopram or placebo) as in the acute trial. The primary efficacy outcome measure was change from baseline of the acute treatment study on the Children’s Depression Rating Scale-Revised (CDRS-R). Suicidal behavior
was assessed using the clinician-rated Columbia-Suicide Severity Rating Scale (C-SSRS) and the patient-rated Suicidal Ideation Questionnaire-Junior High School version.

**Results:** Fewer than half of the 165 patients completed extension treatment. Of those who discontinued, 18 patients in the placebo group and 16 in the escitalopram group withdrew because of insufficient response. At the end of treatment, improvement in the mean CDRS-R score was modestly, but significantly greater in the patients who received escitalopram. Scores decreased from a baseline of 58 to 34 with escitalopram and from 56 to 38 with placebo (difference in change, p=0.005). Secondary outcome measures, such as the Clinical Global Impression score and the functional Child Global Assessment Scale, also favored escitalopram. Rates of response (defined as ≥50% decrease from baseline in the CDRS-R) were 64% with escitalopram and 47% with placebo.

Adverse events during the extension phase were generally mild-to-moderate and not unexpected. A total of 4 patients stopped taking escitalopram because of side effects: severe weight loss, self-cutting, fatigue, and insomnia. There were no adverse event withdrawals in the placebo group. Events suggestive of self-harm occurred in 8 patients during the double-blind extension phase: 3 with placebo, 5 with escitalopram. The majority were incidents of self-cutting that were not considered to be suicidal. The event was considered serious in 3 patients (2 placebo, 1 escitalopram). Emerging suicidal ideation during the extension phase was more common with escitalopram than placebo (7 patients vs. 1 patient).

1. Findling R, Robb A, Bose A: Escitalopram in the treatment of adolescent depression: a randomized, double-blind, placebo-controlled extension trial. *Journal of Child and Adolescent Psychopharmacology* 2013;23 (September):468–480. From Johns Hopkins University, Baltimore, MD; and other institutions. **Funded by Forest Research Institute.**


### Lisdexamfetamine vs. Atomoxetine

In a manufacturer-sponsored study, lisdexamfetamine dimesylate was associated with more frequent and rapid responses than atomoxetine in a group of patients with ADHD that had not adequately responded to methylphenidate.

**Methods:** This randomized, head-to-head comparison was conducted at 51 sites in the U.S., Canada, and Europe. Participants (n=267) were patients, aged 6–17 years, with ADHD of at least moderate severity who had experienced residual symptoms, insufficient duration of action, or variable symptom control (i.e., inadequate response) to previous methylphenidate treatment. Patients who had experienced intolerable adverse events with methylphenidate were not enrolled. After a 7-day washout, patients were randomly assigned to either lisdexamfetamine or atomoxetine, beginning with a 4-week, stepwise, dose-optimization stage. The primary efficacy endpoint of the 9-week study was the time to first clinical response, defined as a Clinical Global Impression–Improvement* (CGI-I) score of 1 or 2.

**Results:** The median baseline CGI-Severity score was 5, indicating most patients were moderately or markedly ill. The median time to first clinical response was 12 days for lisdexamfetamine and 21 days for atomoxetine (p=0.001). The rate of response over the entire study was higher for lisdexamfetamine: 82% vs. 64% for atomoxetine (p=0.001). By visit 9, patients who received lisdexamfetamine also had significantly greater reductions from baseline in ADHD Rating Scale IV score, with an effect size* of 0.56, as well as lower final total scores and inattentiveness and hyperactivity/impulsivity subscale scores.

Adverse effects of the 2 medications were consistent with their known safety profiles. The effects on heart rate, blood pressure, and ECG were similar. Lisdexamfetamine was associated
with an average weight loss of about 3 lbs, while weight changes with atomoxetine were minimal. The proportion of patients losing ≥7% of their initial weight was 27% with lisdexamfetamine and 4.5% with atomoxetine.

Discussion: The faster response to lisdexamfetamine than atomoxetine was expected as stimulants generally produce immediate effects, while the non-stimulant atomoxetine may take 4–6 weeks to reach maximum efficacy. However, secondary outcomes favored lisdexamfetamine and tolerability of the agents was similar. The study authors note that the once-daily dosing and relatively short treatment period may not have allowed atomoxetine to reach its maximum therapeutic potential. Additional studies appear to be warranted.

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

Dittmann R, Cardo E, Nagy P, Anderson C, et al: Efficacy and safety of lisdexamfetamine dimesylate and atomoxetine in the treatment of attention-deficit/hyperactivity disorder: a head-to-head, randomized, double-blind, phase IIIb study. CNS Drugs 2013; doi 10.1007/s40263-013-0104-8. From the University of Heidelberg, Mannheim, Germany; and other institutions, including divisions of Shire in the U.S., the U.K., and Switzerland. Funded by Shire. All 11 study authors disclosed relationships with commercial sources, including 7 who were employees of Shire.

Drug Trade Names: atomoxetine—Strattera; lisdexamfetamine dimesylate—Vyvanse; methylphenidate—Ritalin and others

*See Reference Guide.