A 16-year-old female with schizoaffective disorder that had been unresponsive to multiple adequate trials of antipsychotics and mood stabilizers was started on clozapine. Symptoms at presentation included auditory and visual hallucinations, disorganized speech and behavior, depressed mood, social withdrawal, and new-onset catatonic features with food and drink refusal. Her body mass index (BMI) at clozapine initiation was 29.

Psychiatric symptoms improved substantially over 6 months with 500 mg/day clozapine and 8 mg/day lorazepam for anxiety. Despite nutritional and exercise counseling, the patient’s weight increased by 50 lbs (BMI, 38). Topiramate and metformin were considered to curb the weight gain. Metformin was chosen because the patient had received topiramate for migraine during a previous trial of risperidone with no effect on body weight. Metformin was started at 250 mg b.i.d. and increased to 500 mg b.i.d. Six months later, the psychiatric symptoms remained fairly well controlled with fleeting episodes of auditory hallucinations and low mood. The patient experienced no further weight gain and was able to continue clozapine treatment. Laboratory evaluations showed no changes in lipid profile or other parameters. She never met criteria for impaired glucose tolerance during the course of treatment.

The present case supports the results of 2 previous studies suggesting metformin can attenuate weight gain in young patients receiving atypical antipsychotics.

1Weaver L, De Leon D, Borgmann-Winter K, Coffey B: Use of metformin to control clozapine-associated weight gain in an adolescent with schizoaffective disorder. Journal of Child and Adolescent Psychopharmacology 2010;20 (2):153–157. From the University of Pennsylvania School of Medicine, Philadelphia; and the NYU Child Study Center, New York, N.Y.


Drug Trade Names: clozapine—Clozaril; lorazepam—Ativan; metformin—Glucophage; risperidone—Risperdal; topiramate—Topamax
**Antidepressants and Suicide—Advancing Knowledge**

Previous analyses of antidepressant-related suicide generally evaluated risk associated with any antidepressant use and did not study risk with individual agents. A new cohort study found no clinically meaningful differences in risk between antidepressant classes or individual drugs.

**Background:** The FDA warning on suicide with antidepressants was based on a meta-analysis of studies with important limitations such as short trial durations, few suicide attempts and no completed suicides, nonstandardized definitions of suicidality, dosing variations, and heterogeneous patient populations. Nonrandomized studies have suggested increased suicide risk with antidepressant treatment, but these may have been underpowered or affected by prescribing bias. The present study addressed "whether the putative link between antidepressants and suicidality applies equally to all antidepressant classes, agents, and durations of use or whether there are particular regimens with safety advantages that should be prescribed preferentially in pediatric and adolescent populations."

**Methods:** A cohort of Canadian residents aged 10–18 years (n=20,906) who started antidepressant therapy for depression between 1997 and 2005 were identified from a national pharmacy database. Eighty percent of the patients were treatment-naïve, not having received antidepressants in the previous 3 years. Antidepressants were classified as SSRIs, SNRIs, TCAs, and other. Agents not included in the analysis were bupropion, because of its potential use for smoking cessation, and escitalopram and duloxetine because they were not marketed in Canada throughout the study period. Attempted and completed suicides were ascertained from hospital and vital statistics databases and then linked to prescription records. Patient follow-up was completed if they switched antidepressants or received augmentation. A propensity score-adjusted analysis* was undertaken to control for confounding by prescribing bias.

**Results:** Paroxetine (25%), citalopram (17%), and sertraline (17%) were the most used SSRI antidepressants. During the first year of treatment, 266 patients attempted suicide and another 3 completed the act (event rate, 27 per 1000 patient years). Most events occurred within the first 6 months of treatment. Compared with SSRIs, risk of completed or attempted suicide was not significantly increased with any of the other antidepressant classes. When individual SSRIs were compared, no clinically important variations in suicide risk were found. However, in patients with comorbid ADHD, sertraline appeared to increase suicide risk substantially (hazard ratio,* 4.7), but this finding must be interpreted cautiously because of the small number of events.

**Discussion:** A major strength of this study is the propensity-score analysis, which allowed the authors to rule out a relationship based on the likelihood that some antidepressants are prescribed more often for patients with greater suicide risk. These findings support the FDA decision regarding the class warning and suggest treatment decisions should be made based on efficacy rather than on suicide risk.

**Editor’s Note:** These authors applied the same research methods to a cohort of adult patients and obtained similar results. That article is covered in the current issue of *Psychiatry Drug Alerts* and is available at www.alertpubs.com.

Schneeweiss S, Patrick A, Solomon D, Dormuth C, et al: Comparative safety of antidepressant agents for children and adolescents regarding suicidal acts. *Pediatrics* 2010;125 (May):876–888. From Brigham and Women’s Hospital, Boston, Mass.; and other institutions. **Funded by the NIH. The authors disclosed no potential conflicts of interest.**

**Drug Trade Names:** bupropion—Wellbutrin, Zyban; citalopram—Celexa; duloxetine—Cymbalta; escitalopram—Lexapro; paroxetine—Paxil; sertraline—Zoloft

*See Reference Guide.
Cerebral Folate Deficiency

A 13-year-old male presented to a university children’s hospital for treatment of schizophrenia with catatonic features. Symptoms included hallucinations, severe motor instability, near total mutism, and resistance to passive movement. The patient had reportedly been a normally developing child who had achieved all developmental milestones. He had begun to experience hallucinations 17 months before presentation. Lorazepam and sertraline were started to treat the hallucinations and comorbid OCD. After 4 months the hallucinations persisted and paranoia developed. He was switched to aripiprazole. During the subsequent 8 months, symptoms worsened and he became increasingly withdrawn. He was switched to risperidone, but catatonia developed. On admission, no sensory or reflex abnormalities were found and initial brain MRI, ECG, and laboratory studies including cerebrospinal fluid analysis were unremarkable. However, results of repeat lumbar puncture (to investigate for neurotransmitter disease) and elevated titers of folate receptor blocking antibodies suggested cerebral folate deficiency. He was started on folic acid titrated to 1 mg/kg/day. Hallucinations resolved within 3 months, but catatonia did not improve over 9 months of follow-up. The patient’s parents would not consent to another lumbar puncture to measure the folate level.

Cerebral folate deficiency syndrome is a progressive neurodegenerative disease that can be caused by malnutrition, use of antifolate agents, amino acid biosynthesis disorders, or a recessive genetic polymorphism. Folate replacement usually results in marked neurological improvement if treatment is started soon after symptom onset. It is unclear if and why older patients require longer treatment to show improvement. The authors suggest poor adherence to the prescribed supplementation regimen might underlie the present patient’s lack of improvement.

Ho A, Michelson D, Aaen G, Ashwal S: Cerebral folate deficiency presenting as adolescent catatonic schizophrenia: a case report. Journal of Child Neurology. Published online May 5, 2010; doi 10.1177/0883073809343475. From Loma Linda University School of Medicine, Calif. The authors report no potential conflicts of interest.

Drug Trade Names: aripiprazole—Abilify; lorazepam—Ativan, and others; risperidone—Risperdal; sertraline—Zoloft

Methylphenidate for ADHD Plus Tics

Methylphenidate (Ritalin) did not affect comorbid anxiety symptoms or worsen tic severity in children with ADHD, tic disorders, and anxiety disorders.

Methods: The study enrolled 54 children, aged 6–12 years, with ADHD and either Tourette syndrome or chronic multiple tic disorder. The group included 17 patients with comorbid anxiety (12 with generalized anxiety disorder, 6 with separation anxiety disorder, and 1 with social phobia). Eleven of the anxious children also met criteria for a major depressive episode or dysthymia.

Patients received 2 weeks of placebo and methylphenidate at 0.1, 0.3, and 0.5 mg/kg in randomized order. Every 2 weeks, children were evaluated with self, parent, and teacher rating scales, and by direct observation in a simulated classroom. Tics were rated by the physician.

Results: Before treatment, children with comorbid anxiety appeared to have more severe tics and received higher parent ratings for ADHD, oppositional-defiant disorder, and peer aggression. Their laboratory measures of ADHD symptoms did not show greater severity than non-anxious children.

ADHD symptoms improved with methylphenidate to a comparable extent in children with and without anxiety. All 3 doses improved attention and work output in the simulated
classroom. Medication did not improve anxiety, depression, or emotional lability; however, teachers indicated a dose-related decrease in irritability. Methylphenidate did not exacerbate tics in children with anxiety; in fact, the teachers reported improvement in motor and vocal tic frequency.

**Discussion:** The present study is one of few in this population of patients with multiple comorbidities. The triad of tics, anxiety, and ADHD may represent a unique clinical entity characterized by cross-situational anxiety, more severe tics, depressive symptoms, oppositional behavior, and conflicts with other children. Methylphenidate appears to be highly effective at reducing ADHD symptoms in these children and somewhat less effective at reducing opposition and aggression.

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

Gadow K, Nolan E: Methylphenidate and comorbid anxiety disorder in children with both chronic multiple tic disorder and ADHD. *Journal of Attention Disorders.* Published online April 8, 2010; doi 10.1177/1087054709356405. From Stony Brook University, N.Y. Funded by the NIMH; and the Tourette Syndrome Association, Inc. Dr. Gadow disclosed a financial relationship with the publisher of the Child Symptom Inventory-4, which was used as a symptom measure in the study.

*See Reference Guide.

### Pharmacotherapy for PTSD

The current evidence for pharmacological treatment of PTSD in children and adolescents has been reviewed with each class or agent categorized by level of evidence.1

Although considered first-line therapy for PTSD in adults, the SSRIs paroxetine and sertraline are not approved for pediatric PTSD. Controlled trials showed adding sertraline to CBT had minimal benefits, and a direct comparison found it no better than placebo. No pediatric trials of paroxetine were identified in the literature. Fluoxetine was no more effective than imipramine or placebo in acute stress disorder, and other SSRIs have not been investigated in pediatric PTSD. There is limited evidence that nefazodone improves the 3 main PTSD symptoms clusters as well as anger and aggression. Evidence supports MAOI use in adult but not pediatric patients.

Antiadrenergic medications may be useful, as noradrenergic dysregulation has been documented in PTSD. Prazosin appears to be effective in adults, particularly in terms of intrusive thoughts. There have been 2 case reports of successful use in female adolescents. The authors suggest prazosin be started at 1 mg at bedtime and increased by 1 mg per week to a maximum of 4 mg (a substantially lower dose than that used for hypertension). Clonidine and to a lesser extent guanfacine have been useful in adult PTSD. Although no pediatric controlled trials have been conducted, clonidine has been shown to reduce reenactment symptoms in young patients and guanfacine may reduce nightmares. Clonidine should be initiated at 0.05 or 0.1 mg at bedtime and increased slowly to a maximum of 0.5 mg/day. Because of the short half-life multiple daily doses may be necessary. Heart rate and blood pressure should be monitored during treatment and alpha-agonists should not be discontinued abruptly. A small study recently found the beta-blocker propranolol ineffective at preventing PTSD following accidental trauma (e.g., automobile accident).

A meta-analysis of 7 controlled trials supports use of atypical antipsychotics in adult PTSD and notes they may be particularly useful for reducing intrusive symptoms. Risperidone was reportedly useful in an adolescent male with PTSD, but treatment was complicated by hyperprolactinemia. A small study found flexibly-dosed quetiapine improved PTSD symptom scores as well as anxiety, depression, and anger in adolescents treated for 6 weeks. Results of olanzapine
trials in adults have been mixed and it has not been investigated in youth. There are no reports of ziprasidone or aripiprazole use in pediatric PTSD. Although potentially useful, extrapyramidal symptoms, tardive dyskinesia, obesity, hyperlipidemia, and increases in prolactin level and QT interval can occur with pediatric atypical antipsychotic use.

In adults, some evidence supports the mood stabilizers lamotrigine, divalproex, topiramate, phenytoin, carbamazepine, levetiracetam, gabapentin, and pregabalin either as adjuncts to SSRI therapy or as monotherapy. Pediatric studies have supported carbamazepine and high-dose divalproex.

Conclusions: Very limited evidence suggests nefazodone, prazosin, clonidine, guanfacine, risperidone, and quetiapine may attenuate some symptoms of PTSD in young patients. However, randomized controlled trials are needed to confirm their efficacy. The American Academy of Child and Adolescent Psychiatry recommends that treatment of PTSD in young patients include psychoeducation, trauma-focused psychotherapy, and pharmacotherapy when necessary. Pharmacotherapy should generally be used to treat comorbid conditions and in combination with individual or group psychotherapy or CBT.

TMS Safety

Repetitive transcranial magnetic stimulation (rTMS) is approved for treatment of resistant depression in adults, but not young patients. The present review summarizes the evidence for efficacy and safety in children and adolescents.

There are 6 published reports (19 patients) of rTMS use at or above pulse frequency 1 Hz for psychiatric and nonpsychiatric conditions in patients aged ≤17 years. In 3 studies, adolescents received rTMS for major depressive disorder. Other studies investigated spastic cerebral palsy and epilepsy partialis continua. Of the 10 patients treated for depression, 7 improved. Mild headache was the only reported adverse effect. In the single report of spasticity, rTMS showed modest positive effects in 5 children (mean age, 10 years). Treatment was not effective in 3 of the 4 patients with epilepsy.

Safety considerations for rTMS in adults have been comprehensively reviewed, but safety data for children and adolescents is limited because few young patients have been treated. Seizure risk is the primary safety concern in adults. It increases when stimulation parameters are outside the recommended guidelines, and in patients predisposed to seizure either by concomitant conditions (e.g., epilepsy) or concurrent medications such as bupropion, clomipramine, maprotiline, and possibly methylphenidate. Seizure risk may be particularly important for young patients in whom the seizure threshold is lower.

Although there is some evidence that rTMS may be useful in bipolar disorder, manic or hypomanic switching is also a possibility. These episodes may be more common in young patients than in adults. Neurocardiogenic syncope has been reported in 2 adolescents who...
received single-pulse TMS. Both of these patients had previously experienced presyncope with venipuncture or micturition. TMS machines produce loud clicking noises, and temporary hearing loss and transient increases in auditory threshold have been reported mainly in patients not properly using ear protection. One adult patient with no ear protection suffered permanent hearing loss at 1 Hz. The effect of electromagnetic radiation on developing brains is a widespread concern. However the radiation pulses of rTMS are comparable to those of magnetic resonance imaging (MRI). Because MRI pulses are continuous, an imaging session likely delivers more radiation than an rTMS session.

**Discussion:** Based on extrapolation of adult data and the limited reports of use in children and adolescents, rTMS appears to be both generally effective and safe in young patients. The authors note that adverse events occur less frequently when rTMS is delivered within the published stimulation parameter recommendations and when subjects are prescreened for potential risk factors.

**Editor's Note:** As required, the study authors disclosed potential conflicts of interest. Several listed commercial relationships with Neuronetics and Brainsway, manufacturers of TMS devices. One author disclosed service as a consultant to Brainsway; however, he is named on their corporate website as medical director of the research and development team.

D'Agati D, Bloch Y, Levkovitz Y, Reti I: rTMS for adolescents: safety and efficacy considerations. Psychiatry Research. Published online April 8, 2010; doi 10.1016/j.psychres.2010.03.004. From Johns Hopkins University, Baltimore, Md.; and Shalvata Mental Health Center, Israel. **Funded by the Hope for Depression Research Foundation. Several study authors disclosed commercial relationships with TMS device manufacturers (see editor's note above).**

**Drug Trade Names:** bupropion—Wellbutrin; clomipramine—Anafranil; maprotiline—Ludiomil; methylphenidate—Ritalin, and others

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**Reference Guide**

**Hazard Ratio:** A measure of the risk of an event relative to exposure, or the probability of an event occurring in an exposed group versus a non-exposed group. A hazard ratio of 0.5 indicates that one group has half the risk of the other group.

**Propensity Score Analysis:** Selection bias can be problematic when using observational data, making causal relationships difficult to establish. Propensity score matching is a correction strategy used to reduce bias in nonexperimental settings where patients in the compared groups may not be similar or when patients must be compared across a high-dimensional set of pretreatment characteristics. Through matching and balancing samples, propensity scores help adjust for selection bias making it possible to obtain average treatment effects.

**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.