Antidepressants: Self-Reported Efficacy

Meta-analyses of antidepressant treatment in young people have relied exclusively on clinician-rated measures of depressive symptoms. These symptom-based measures may not capture other important correlates of well-being, such as quality of life, functioning, global mental health or well-being, or self-reported depressive symptoms. Results of the present meta-analysis, based on 8 placebo-controlled studies of fluoxetine, citalopram, paroxetine, and sertraline, suggest antidepressants are not more effective than placebo in young patients.

Measures of quality of life, functioning, autonomy, and global mental health were infrequently reported as study outcomes. Of the studies that reported effects of treatment on well-being, only those conducted in adolescents showed a marginally significant influence of antidepressants (effect size,* 0.16; p=0.07). Effects in studies of younger children or mixed-age groups were negligible. Treatment effects on patient-rated depressive symptoms were small and not significant, although improvements in clinician-rated depressive symptoms in the same studies were statistically significant.

Spielmans G, Gerwig K: The efficacy of antidepressants on overall well-being and self-reported depression symptom severity in youth: a meta-analysis. *Psychotherapy and Psychosomatics* 2014;83 (May):158–164. From Metropolitan State University, St. Paul, MN; and the University of Wisconsin, Madison. Source of funding not stated. The authors did not include disclosure of potential conflicts of interest.

*Drug Trade Names:* citalopram—Celexa; fluoxetine—Prozac; paroxetine—Paxil; sertraline—Effexor

*See Reference Guide.*

High-Dose Antidepressants and Self-Harm

Risk of deliberate self-harm was twofold higher in young patients who started antidepressants at higher-than-average doses compared with those taking the standard dose, according to results of a large cohort study.¹

*Methods:* Investigators analyzed claims data for patients aged 10–65 years with a diagnosis of depression who started SSRI therapy after ≥1 year without antidepressant drug treatment.
Patients aged 10–24 years were analyzed separately from the older age group. The analysis was restricted to users of the 3 most common antidepressants (i.e., citalopram, sertraline, fluoxetine) which constitute two-thirds of all new antidepressant prescriptions. The modal, or most frequently prescribed, dosage was 20 mg/day for citalopram and fluoxetine and 50 mg/day for sertraline. The 24-and-under age group consisted of >32,500 patients taking the modal dose and >7000 taking higher doses. The analysis excluded >14,500 patients taking subtherapeutic dosages and the small percentage taking doses higher than the recommended maximum. Patients were followed for 1 year, or until treatment escalation, a drug switch, or they became unavailable for follow-up. Patients who took high-dose antidepressants were propensity-matched* to patients who received standard doses but who were similar in other ways that would influence dose selection, including baseline depression severity. Pretreatment suicidal ideation was not a factor in propensity matching, but the frequency of ideation was similar in modal-dose and high-dose cohorts.

**Results:** During follow-up, 142 patients in the 10–24-year age group engaged in deliberate self-harm. Of these, 68 had initiated an antidepressant at the modal dose, while 74 initiated at higher doses (15 vs. 32 events per 1000 person-years, respectively). The calculated frequency of deliberate self-harm in the first year of treatment was 1.5% with modal-dose therapy and 3.2% with high-dose therapy (adjusted hazard ratio,* 2.2). Although the rates remained proportional throughout the year, the majority of events occurred within the first 3 months of treatment. Rates of self-harm were lower in patients aged >24 years and did not differ according to antidepressant dose. The authors point out that because not all deliberate self-harm results in medical treatment, the reported frequency is likely an underestimate; but the relative hazard with high-dose therapy is probably not biased.

**Editorial.** An accompanying editorial highlights the many strengths of the study, particularly the use of suicidal behavior as the primary outcome, rather than suicidal ideation.2 Unanswered questions include why 18% of patients were started at high doses, counter to clinical guidelines, and whether such patients had unmeasured factors that put them at higher risk of a suicide attempt. However, rates of suicide attempts in the year prior to starting an SSRI were similar in both treatment groups at about 1.5%, yet only patients treated with high doses experienced an increase in deliberate self-harm.

**Study Rating*—14 (100%):** This study met all criteria for an observational study.

1Miller M, Swanson S, Azrael D, Pate V, et al: Antidepressant dose, age, and the risk of deliberate self-harm. *JAMA Internal Medicine* 2014; doi 10.1001/jamainternmed.2014.1053. From Harvard School of Public Health, Boston, MA; and University of North Carolina at Chapel Hill. **Funded by the NIMH; and other sources. One study author disclosed financial relationships with commercial sources.**

2Brent D, Gibbons R: Initial dose of antidepressant and suicidal behavior in youth: start low, go slow [editorial]. *JAMA Internal Medicine* 2014; doi 10.1001/jamainternmed.2014.1053. From the University of Pittsburgh School of Medicine, PA; and other institutions. **Both authors disclosed financial relationships with commercial sources.**

**Drug Trade Names:** citalopram—Celexa; fluoxetine—Prozac; sertraline—Zoloft

*See Reference Guide.

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**Family Accommodation in Anxiety Disorders and OCD**

According to results of a comparative study, family accommodation was highly prevalent among mothers of children with anxiety disorders and those with obsessive-compulsive disorder. Patterns of accommodation were similar in the 2 disorders.

**Methods:** Study participants were the mothers of children, aged 7–17 years, who met DSM-IV-TR criteria for a primary diagnosis of either OCD (n=26) or anxiety disorder (n=31). A comparison group of 30 children was free of any anxiety disorder or other psychiatric history. Average symptom scores in the OCD group were in the severe range. Among children with an
anxiety disorder, the most common diagnoses were generalized anxiety disorder (41%) and separation anxiety (31%). Two-thirds of the children with anxiety met criteria for multiple anxiety disorders.

Mothers of the children with OCD were interviewed using the Family Accommodation Scale (FAS), which is specific for this disorder. Mothers in the other groups completed the Family Accommodation Scale–Anxiety (FASA). Anxiety was assessed in all families with the Screen for Childhood Anxiety Related Emotional Disorders–Parent Report (SCARED–PR).

**Results:** A total of 61% of the mothers of children with anxiety disorders and 69% of the mothers of children with OCD reported accommodating behaviors. Daily modification of routines and schedules was reported by 19% and 27%, respectively, and 16% and 23% reported both daily modifications (e.g., reassuring the child, facilitating avoidance, or providing special items) and participation. Accommodation was reported by 23% of mothers in the comparison group, with low rates of daily participation and modification. Mothers of the children with a disorder reported greater distress resulting from accommodation and more negative consequences of not accommodating, compared with the control group. Family accommodation was correlated with the overall severity of anxiety symptoms in both clinical groups, but not in the healthy controls.

**Discussion:** Although well-intentioned, family adaptation has been linked by previous research to greater symptom severity, lower functioning, and poorer treatment outcomes. The results of this study suggest that if parents are less accommodating of their child's anxiety, the child may be less likely to develop clinically significant anxiety. The findings also highlight the role of factors that maintain the cycle of accommodation. Mothers of children in the clinical groups often reported that if they did not accommodate, the child became angry or abusive and anxiety symptoms worsened.

Parents may benefit from learning alternative ways to deal with a child's anxiety or from cognitive restructuring, and children may benefit from treatments that replace reliance on the parent's accommodation with self-reliance.

Lebowitz E, Scharfstein L, Jones J: Comparing family accommodation in pediatric obsessive-compulsive disorder, anxiety disorders, and nonanxious children. Depression and Anxiety 2014; doi 10.1002/da.22251. From the Yale Child Study Center, New Haven, CT; and the University of Texas, Austin. Source of funding not stated. The study authors did not include disclosure of potential conflicts of interest.

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**Metabolic Outcome After Stopping Risperidone**

Children who discontinued risperidone (*Risperdal*) after extended treatment lost the excessive age-inappropriate weight they had gained during treatment and showed improvement in treatment-associated metabolic abnormalities. Weight gains and metabolic alterations reached a new equilibrium in children who continued taking risperidone and continued to worsen in those switched to a different antipsychotic.

**Methods:** This analysis was conducted as part of an observational study of the adverse effects of long-term risperidone treatment. The study enrolled patients, aged 7–17 years, who had been taking risperidone for any indication for ≥6 months. At study entry, treatment with other psychotropic drugs was permitted, except for other antipsychotics. The study excluded patients with diabetes, dyslipidemia, or hypothyroidism and those using hormonal contraception. The analysis was based on body mass index (BMI) and metabolic measurements made at an 18-month follow-up visit.

**Results:** Of 151 patients enrolled in the study, 108 returned for the follow-up visit but 7 were excluded because of treatment non-adherence or new onset of diabetes or hypothyroidism. The
remaining patients included 74 who continued taking risperidone, 9 who switched to another second-generation antipsychotic (SGA), and 18 who discontinued antipsychotic therapy. There were no significant clinical differences among the 3 groups at study entry.

Patients in all groups continued to gain weight during treatment. Taking age-appropriate growth into account, BMI remained stable post-baseline in patients who continued on risperidone, who constituted the statistical comparison group. BMI continued to increase in patients who switched to a different SGA (p<0.003) and decreased to pre-risperidone levels in those who stopped all antipsychotics (p<0.004). This difference resulted in nearly triple the rate of obesity in the SGA continuation group (78%), compared with the risperidone continuation group (27%) and with patients who stopped all antipsychotics (17%). Change in age-specific BMI was correlated with changes in systolic and diastolic blood pressure; total insulin; insulin resistance (HOMA-IR); C-peptide; triglycerides; and total, HDL, and LDL cholesterol. Prolactin levels were elevated at follow-up in 47% of the group continuing risperidone and in no patients in the other 2 groups.

Discussion: Because children are given SGAs primarily for externalizing disorders, use of these agents in young patients tends to be time-limited. Placebo-controlled discontinuation studies suggest disruptive behavior can remain controlled in many children after treatment is withdrawn. The investigators could not identify any clinical characteristics that predicted which of their study subjects were able to discontinue antipsychotic therapy.

Study Rating*—14 (100%): This study met all criteria for an observational study.

*See Reference Guide.

Individual vs. Group CBT for Anxiety Disorders

In a randomized trial, individual and group cognitive behavioral therapies were equally effective in children and adolescents with anxiety disorders. However, remission rates in this community-based study were low compared with academic clinical trials, suggesting the need to further improve the efficacy and transportability of CBT.

Methods: Study subjects were 182 patients, aged 8–15 years, referred to 7 clinics in Norway and given a primary diagnosis of separation anxiety disorder, social phobia, or generalized anxiety disorder. Children and adolescents were stratified by age (with 12-year-olds assigned according to developmental maturity), and then randomly assigned to individual or group CBT or to a waitlist condition for 10 weeks. Both group and individual therapy were delivered according to the manualized FRIENDS for Life program, which could be individualized as long as the exposure tasks were included. After 10 weeks, the wait-listed group was randomly assigned to an active therapy. The primary outcome was percentage of patients who no longer met anxiety disorder diagnostic criteria at treatment end and 1 year.

Results: After treatment, 23% of participants in the CBT groups no longer met criteria for any of the 3 inclusion anxiety disorders, 35% no longer had their principal anxiety diagnosis, and 55% no longer met the criteria for at least 1 of their initial disorders. These results were significantly superior to the wait-listed group (p≤0.009 or better for these comparisons).

Data from the wait-listed controls who were eventually treated were pooled with the other groups for the between-treatment comparisons. Patients receiving individual or group CBT did not differ in the rate of resolution of all diagnoses (25% vs. 21%, respectively), the principal
diagnosis (35% in both groups), or any single diagnosis (51% vs. 63%). At 1-year follow-up, there were still no significant differences between the treatments. Effect sizes varied from small to large, depending on the rating instrument and other factors, and did not differ between the 2 treatments. Effect sizes tended to increase by the 1-year follow-up.

**Discussion:** Clinical trials report efficacy rates of about 50–60% for CBT in anxiety disorders. However, unlike the patients in the present study, who were from mostly upper- and middle-class families, children who participate in clinical trials of CBT for anxiety tend to come from single-parent or low-income families. They have complex needs that may be amenable to the greater flexibility of individual therapy. Group CBT offers different advantages, such as positive peer modeling, social support, and exposure to social situations.

**Study Rating**—15 (88%): This study met most criteria for a randomized controlled trial, but raters were not blinded to participants’ randomized treatment.

Wergeland G, Fjermestad K, Marin C, Haugland B, et al: An effectiveness study of individual vs. group cognitive behavioral therapy for anxiety disorders in youth. *Behaviour Research and Therapy* 2014; doi 10.1016/j.brat.2014.03.007. From Haukeland University Hospital, Bergen, Norway; and other institutions. **Funded by the Western Norway Regional Health Authority;** and other institutions. The authors did not include disclosure of potential conflicts of interest.

*See Reference Guide.

### D-cycloserine with CBT for Posttraumatic Stress Disorder

In a pilot study, D-cycloserine (*Seromycin*) had no effect as an adjunct to cognitive behavioral therapy in children and adolescents with PTSD.\(^1\)

**Background:** The partial NMDA receptor agonist D-cycloserine, an antibiotic introduced to treat tuberculosis half a decade ago, has been shown to have anxiolytic effects. Some research indicates the agent may be a useful adjunct to behavioral treatments for anxiety disorders and obsessive-compulsive disorder, producing faster improvement than adjunctive placebo. Results in child studies have been mixed. Adjunctive D-cycloserine does not appear to have been previously investigated in childhood PTSD.

**Methods:** Study participants, aged 7–18 years, had multiple PTSD symptoms following sexual abuse, a disaster, exposure to domestic violence, or other traumas. Patients received a manualized 12-session CBT program developed for this study. Either adjunctive D-cycloserine or placebo was randomly assigned in the 57 patients who remained in treatment at the fourth CBT session. D-cycloserine was administered as a 50-mg oral dose 1 hour before sessions 5–11. The primary study outcome measure was change from baseline on the Child PTSD Symptom Scale (CPSS).

**Results:** Study participants were an average age of 12 years and had experienced an average of 3 prior types of traumas, on multiple occasions. CPSS scores reflected marked improvement during the course of CBT. However, patients experienced the same degree of improvement with D-cycloserine and placebo (effect sizes,* 1.5 and 1.9, respectively). D-cycloserine was not associated with earlier improvement, greater improvement upon long-term follow-up, or differential results in any patient subgroup. Adverse effects with D-cycloserine were similar to those with placebo.

Study randomization was not stratified by baseline symptom severity, and by chance participants in the D-cycloserine group had significantly higher scores than the placebo group on both the primary and secondary efficacy measures. However, a secondary analysis eliminating the highest and lowest scoring patients in each group (thereby eliminating the significant difference) found similar nonsignificant between-group differences in outcome.
Editor’s Note: According to the package insert for Seromycin, severe anxiety is a contraindication to D-cycloserine use.²

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

1Scheeringa M, Weems C: Randomized placebo-controlled D-cycloserine with cognitive behavior therapy for pediatric posttraumatic stress. *Journal of Child and Adolescent Psychopharmacology* 2014;24 (March):69–77. From Tulane University School of Medicine and the University of New Orleans, LA. Funded by the NIMH; and the National Alliance for Research on Schizophrenia and Depression (NARSAD). The authors disclosed no competing interests. See related story in *Child & Adolescent Psychiatry Alerts* 2010;12 (September):52.


*See Reference Guide.

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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.

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 1 group has half the risk of the other group.

Propensity Matching: 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.

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