According to a follow-up study of children with anxiety disorders who participated in a randomized controlled trial, internet-delivered cognitive behavioral therapy produced lasting improvement.

Methods: Study participants were self-referred families with a child, aged 8–12 years, who had a primary diagnosis of generalized anxiety disorder, panic disorder, separation anxiety, social anxiety disorder, or a specific phobia. The study excluded children with a diagnosis of ADHD, autism, depression, or acute psychiatric conditions. Patients were randomly assigned to internet-delivered CBT or a wait-list control. Treatment consisted of a parent-led, exposure-based, 10-session program with online therapist support. Patients who still met diagnostic criteria in the control group were offered the active CBT at the end of the initial observation period. Treatment efficacy was measured at the end of therapy and at 3 and 12 months post-treatment using the Clinician Severity Rating, derived from the Anxiety Disorder Interview Schedule Child/Parent Version. An additional aim of the trial was to identify variables that might predict response. Potential moderators included comorbidity, depressive symptoms, and parental psychopathology. The 3-month evaluation was used to test the predictive factors, and the 12-month evaluation was the time point for the primary long-term efficacy comparison.

Results: A total of 84 children received internet-delivered CBT, either initially (46 children) or after crossing over from the control condition (38 children). At baseline, patients had an average of ≥3 anxiety-disorder diagnoses. Most had a principal diagnosis of separation anxiety or specific phobia, and about 20% had a principal diagnosis of generalized anxiety disorder. Of the families that started CBT, 83% completed ≥9 modules, including nearly all of the psycho-education components. Eight families sought additional help outside the study before the 12-month evaluation.

Internet-delivered CBT was associated with large improvements in anxiety-disorder symptoms at the end of treatment (effect size,* 1.33). Clinician Severity Rating scores decreased from 5.7 at
baseline to 4.2 post-treatment (p<0.001) and continued to decrease at the 3-month assessment (3.4; effect size vs post-treatment, 0.56) and 12-month assessment (2.8; effect size vs post-treatment, 0.42). At 3 months, 55% of the study children no longer met criteria for their principal diagnosis, and the rate increased to 73% at 12 months. One-third did not meet criteria for any anxiety disorder at 3 months, and 40% at 12 months. Secondary outcome measures, including global functioning and parent-rated anxiety, also showed improvement. A multivariate analysis identified only 1 factor that was predictive of treatment nonresponse: suspected autism spectrum disorder.

Discussion: Previous studies of internet-delivered CBT for childhood anxiety disorders have shown similar patterns of maintenance and even improvement of response. The finding that children with autism symptoms may be less likely to benefit from the therapy also replicates previous research.


2Vigerland S, Serlachius E, Thulin U, Andersson G, et al: Long-term outcomes and predictors of internet-delivered cognitive behavioral therapy for childhood anxiety disorders. Behavior Research and Therapy 2017;90 (March):67–75. From the Karolinska Institutet, Sweden; and other institutions. Funded by the Stockholm County Council; and other sources. The authors did not include disclosure of potential conflicts of interest.

Prazosin for Nightmares in PTSD

The blood pressure lowering medication prazosin (Minipress) appears to be an effective treatment for nightmares related to posttraumatic stress disorder in children and adolescents, according to a systematic review.

Background: Sleep disturbances are common in children and adolescents who have recently suffered a traumatic event. Currently there are no FDA-approved medications for treating PTSD-related nightmares in children. Prazosin has been shown to be effective in randomized trials in adults with PTSD. It is a lipid-soluble α1 adrenergic receptor antagonist and the only drug in its class that crosses the blood-brain barrier, where it decreases sympathetic activity in the brain. Nightmares and many of the other hyperarousal symptoms of PTSD are believed to arise from elevated noradrenergic responsiveness in the prefrontal cortex. In adults, symptoms of PTSD have been shown to improve significantly when sleep disturbance is treated.

Methods: A comprehensive literature search was undertaken to identify reports of prazosin use to treat PTSD-associated sleep disorders in children and adolescents. Bibliographic data from identified studies were also reviewed for additional publications.

Results: No reviews or clinical trials were identified in the search; the literature base comprised 6 case reports describing 7 patients, aged 7–16 years, who had experienced such traumas as abuse, parental neglect, sexual assault, and witnessing a friend’s violent death. In most cases, nightmares persisted despite treatments, including cognitive behavioral therapy, supportive psychotherapy, melatonin, and first- and second-generation antidepressants from several classes. In some cases, these treatments ameliorated other PTSD symptoms, but nightmares persisted. Prazosin was administered in 1–4 mg doses at bedtime. In each case, the child experienced a marked reduction in both nightmare frequency and intensity. Improvements in sleep quality and in hyperarousal and intrusive PTSD symptoms were also evident. The only reported adverse effect was weight gain and increased body mass index in a boy who received treatment for 11 months. Two other patients had increases in nightmares after prazosin was discontinued, accompanied in 1 case by an increase in aggressive behavior.
Discussion: The reports in children indicate promise but provide little guidance for clinicians who would like to use prazosin to treat PTSD-related nightmares. Large randomized trials appear to be warranted.


Single-Session Interventions

Up to 80% of young people with psychiatric disorders do not receive treatment. Among those who do, dropout rates are high. Single-session interventions are gaining attention as a way of increasing access to treatment. According to the results of a systematic literature review and meta-analysis of 50 randomized controlled trials, single-session interventions were associated with an overall mean effect size* of 0.32 relative to control conditions (p<0.001). Positive effects were largest for anxiety problems (effect size, 0.58) and conduct problems (effect size, 0.52). Effects were smaller but still significant for other problems such as low self-esteem or self-efficacy and for substance abuse. Effects were nonsignificant for depression and family relationship problems, in part because of small study samples. The effect for eating disorders was large but not statistically significant (effect size, 1.29).

The effects of single-session interventions did not differ according to whether the sample was clinically diagnosed or from the community, whether the intervention was for treatment or prevention, or whether the prevention was indicated, selective, or universal. Therapist-administered interventions had larger effects than self-administered ones (effect sizes, 0.33 and 0.21, respectively), although the difference was not statistically significant. Effects were largest when measured in the period immediately after the intervention to 2 weeks later and smallest when measured ≥13 weeks post intervention.

Study Rating*—89%: This study met most criteria for a systematic review/meta-analysis. However, the source of funding was not stated.


*See Reference Guide.

Amantadine for Aggressive Behavior

In a small series of hospitalized children, use of adjunctive amantadine reduced aggression and decreased the use of restraints and seclusion.

Background: Amantadine is an N-methyl-D-aspartate receptor antagonist that increases synaptic dopamine. According to previous reports, it has reduced aggression in children with neurodevelopmental disorders and has been used as an adjunct to risperidone in children with autism spectrum disorders and in patients with traumatic brain injury.

Methods: Charts from a single institution were retrospectively reviewed to identify psychiatrically-hospitalized children who had been started on amantadine for the management of aggressive behavior over a 2-year span. The 8 children (1 girl) ranged in age from 6 to 10 years. The most common primary diagnoses were ADHD, intermittent explosive disorder, oppositional defiant disorder, and bipolar disorder. Five children had borderline intellectual function or an unspecified cognitive disorder, and 4 had confirmed or suspected in-utero drug exposure. Previous or background medications included stimulants, second-generation
antipsychotics, mood stabilizers, alpha agonists, and antidepressants. Changes in aggressive behavior were evaluated by a child and adolescent psychiatrist using the Clinical Global Impression–Improvement (CGI-I) scale.

**Results:** The children were hospitalized for between 58 and 156 days (mean, 113 days) and received adjunctive amantadine for 20–92 days. On the CGI-I, 5 children were rated as "very much improved" and the other 3 as "much improved." Average seclusions per week were reduced from 1.8 at baseline to 0.25 during week 1 of treatment (p=0.01), and as-needed medications declined from 4 to 1.63 per week (p=0.02). In week 2, use of physical restraints was also significantly reduced from baseline (from 1.59 to 0 per week; p=0.04). During weeks 3 and 4, all 3 types of intervention were used fewer times per week than at baseline, but the differences were no longer statistically significant, possibly because of the small sample size. No patient was readmitted to the facility within 60 days following discharge, and only 1 was readmitted within 180 days. No adverse effects of amantadine were observed.

McGrane I, Loveland J, Zaluski H: Adjunctive amantadine treatment for aggressive behavior in children: a series of eight cases. *Journal of Child and Adolescent Psychopharmacology* 2016;26 (December):935–938. From Shodair Children's Hospital, Helena, MT; and the University of Montana Skaggs School of Pharmacy, Missoula. **This study was conducted without external funding.** The authors declared no competing interests.

**Common Drug Trade Names:** amantadine—Symmetrel; risperidone—Risperdal

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**Pathways to Major Depression in High-Risk Youth**

A British longitudinal study of children and adolescents at high familial risk for major depression identified 6 mechanisms contributing to a first depressive episode, including 2—irritability and fear/anxiety—that may be amenable to clinical intervention and 2 others—poverty and psychosocial adversity—that are possible targets for community-based interventions.1

**Methods:** Participating families were recruited from U.K. general practices and had 1 parent with ≥2 episodes of major depressive disorder. The youngest child between the ages of 9 and 17 years in each family was selected for follow-up. Parents and offspring were assessed on 3 occasions: at baseline, after about 16 months, and after another 12 months. The primary study outcome was the onset of major depressive disorder in the young person, measured using the Child and Adolescent Psychiatric Assessment (CAPA). Antecedent variables, assessed at baseline, were low mood (Mood and Feelings Questionnaire); fear/anxiety (Screen for Child Anxiety Related Emotional Disorders); irritability and disruptive behavior (subscales of the CAPA); familial risk of major depressive disorder (severity in the parent and occurrence in other family members); self-reports of stressful life events; and parent-reported household income.

**Results:** A total of 337 families participated, and nearly all parents with depression were mothers. Offspring had a mean age of 12 years at baseline, 140 were boys and 197 were girls. A total of 20 young people (including 14 girls) had a first episode of major depression during follow-up, with onset at a mean age of 14 years. Of the clinical antecedents, irritability and fear/anxiety were associated with depression onset (p=0.03 and p<0.001, respectively), but low mood and disruptive behavior were not. Both economic disadvantage and low socioeconomic status were directly associated with depression onset (p=0.02 and p<0.001), and both were also associated with the clinical antecedents.

**Discussion:** These results suggest that primary prevention of depression in young people with high familial risk should address irritability and fear/anxiety in the child and should also take social risk factors into account. Family-based programs may be indicated in this risk group, particularly in the U.S., where, according to an accompanying editorial,2 women of childbearing age...
age have higher rates of depression and a greater burden of disease than British women; rates of violence (an aspect of adversity) are higher; adolescent depression is associated with greater disability; and there is a 4-fold higher rate of lethal self-harm.


2Glowinski A, Rosen M: Prevention targets for child and adolescent depression [editorial]. *JAMA Psychiatry* 2016; doi 10.1001/jamapsychiatry.2016.3160. From Washington University School of Medicine, St. Louis, MO. The authors declared no financial relationships with commercial sources.

### Child Psychiatric Access Projects

Most children in need of behavioral health treatment do not receive care. This is due in part to a lack of available services, and as a result, primary care physicians are assuming more responsibility for the mental health care of their patients. Child psychiatric access projects, now in place in 31 states and the District of Columbia, connect pediatricians, family physicians, and other clinicians with psychiatrists or other behavioral health specialists who provide brief telephone consultations on a case-by-case basis. Despite the success of these programs, concerns remain about the effectiveness of communications between primary-care and specialist providers.

The Five S’s is a framework developed to provide a simple but comprehensive set of questions, to be reviewed by the primary care clinician before the specialist consultation. The framework does not require the primary care physician to reach a diagnosis before contacting the specialist. Rather, it is designed to help the physician collect the information that would be most useful to the mental health provider.

Harrison J, Wasserman K, Steinberg J, Platt R, et al: The Five S’s: a communication tool for child psychiatric access projects. *Current Problems in Pediatric and Adolescent Health Care* 2016; doi 10.1016/j.ccppeds.2016.11.006. From Johns Hopkins University School of Medicine, Baltimore, MD; and other institutions. Funded by the Maryland Department of Health and Mental Hygiene. The authors did not include disclosure of potential conflicts of interest.

### Deutetrabenazine for Tics

In a phase I pilot study, deutetrabenazine (SD-809), a modified form of tetrabenazine, reduced tic severity in adolescents with Tourette’s disorder.

**Background:** Tetrabenazine, a potential treatment for a variety of hyperkinetic movement disorders, works by depleting dopamine presynaptically. Although generally effective, it is associated with frequent and often intolerable adverse effects including somnolence, nausea, depression, insomnia, akathisia, and parkinsonism. Its active metabolites have short half-lives, requiring dosing ≥3 times a day. Deutetrabenazine provides a slower and more consistent metabolism, leading to a more benign side-effect profile and less frequent dosing. The starting dose is about half that of tetrabenazine.

**Methods:** This pilot study was carried out in 23 adolescents, aged 12–18 years, with Tourette’s disorder and motor and/or vocal tics of at least moderate severity. Following blinded genotyping for CYP2D6, which metabolizes the drug, participants received open-label
deutetrabenazine in a 6-week titration period, followed by 2 weeks on the stable final dosage. Deutetrabenazine was started at 6 mg/day, and was increased weekly by 6 mg, to a maximum of 36 mg/day. The primary outcome measure was the Yale Global Tic Severity Scale (YGTSS).

**Results:** The sample included no poor metabolizers and 3 ultra-rapid metabolizers, based on genotyping. A total of 18 patients were taking concomitant medications at baseline, including stimulants and antidepressants. At study end, 14 patients were taking the maximum daily deutetrabenazine dosage of 36 mg/day. This group included the 3 ultra-rapid metabolizers, which suggests this patient group may require a higher dose. Of the 23 patients enrolled, 3 did not complete the study, but none withdrew because of a treatment-related adverse event.

The mean YGTSS total tic score was 32 at baseline and was reduced to 21 after 8 weeks of treatment (a 37.6% decrease; p<0.0001). More than 60% of patients met criteria for clinically meaningful change (≥25% decrease in tic severity). Participants had statistically significant mean reductions in subscores for both motor and vocal tics (37% and 35%, respectively). Average YGTSS scores increased slightly in the week after the study drug was withdrawn. Secondary study outcomes also supported the efficacy of deutetrabenazine. A total of 86% of patients had a ≥1-point improvement in the Tourette Syndrome Clinical Global Impression (TS-CGI) scale. Average scores decreased from the moderate-to-severe range to the mild-to-moderate range.

Adverse events during treatment were mild to moderate in severity. The most frequent were fatigue and headache, each affecting 4 patients. Smaller numbers experienced irritability, somnolence, hyperhidrosis, diarrhea, and nasopharyngitis. One patient with a history of fluctuating mood had mild suicidal ideation, which resolved during continued treatment.

**Discussion:** Currently, haloperidol, pimozide, and aripiprazole are the only FDA-approved drugs for the treatment of Tourette’s disorder and their use is limited by frequent adverse effects including drowsiness, weight gain, and metabolic syndrome, as well as the potential to cause tardive dyskinesia. While the results of this study support the safety and efficacy of deutetrabenazine, they must be replicated in a stronger study. A larger double-blind, placebo-controlled trial with a longer duration is currently being planned.

Jankovic J, Jimenez-Shahed J, Budman C, Coffey B, et al: Deutetrabenazine in tics associated with Tourette syndrome. *Tremor and Other Hyperkinetic Movements* 2016; doi 10.7916/D8M32W3H. From Baylor College of Medicine, Houston, TX; and other institutions including Auspex, a subsidiary of Teva Pharmaceutical Industries, La Jolla, CA. **Funded by Auspex. All study authors declared financial relationships with commercial sources including Auspex/Teva.**

Common Drug Trade Names: aripiprazole—Abilify; haloperidol—Haldol; pimozide—Orap; tetrabenazine—Xenazine

**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.

**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 are posted at www.alertpubs.com.