Switching to Another SSRI or to Venlafaxine With or Without Cognitive Behavioral Therapy for Adolescents With SSRI-Resistant Depression
The TORDIA Randomized Controlled Trial

David Brent, MD
Graham Emslie, MD
Greg Clarke, PhD
Karen Dineen Wagner, MD, PhD
Joan Rosenbaum Asarnow, PhD
Marty Keller, MD
Benedetto Vitiello, MD
Louise Ritz, MBA
Satish Iyengar, PhD
Kaleab Abebe, MA
Boris Birmaher, MD
Neal Ryan, MD
Betsy Kennard, PsyD
Carroll Hughes, PhD
Lynn DeBar, PhD
James McCracken, MD
Michael Strober, PhD
Anthony Spirito, PhD
Henrietta Leonard, MD†
Nadine Melhem, PhD
Giovanna Porta, MS
Matthew Onorato, LCSW
Jamie Zelazny, MPH, RN

Context Only about 60% of adolescents with depression will show an adequate clinical response to an initial treatment trial with a selective serotonin reuptake inhibitor (SSRI). There are no data to guide clinicians on subsequent treatment strategy.

Objective To evaluate the relative efficacy of 4 treatment strategies in adolescents who continued to have depression despite adequate initial treatment with an SSRI.

Design, Setting, and Participants Randomized controlled trial of a clinical sample of 334 patients aged 12 to 18 years with a primary diagnosis of major depressive disorder that had not responded to a 2-month initial treatment with an SSRI, conducted at 6 US academic and community clinics from 2000-2006.

Interventions Twelve weeks of: (1) switch to a second, different SSRI (paroxetine, citalopram, or fluoxetine, 20-40 mg); (2) switch to a different SSRI plus cognitive behavioral therapy; (3) switch to venlafaxine (150-225 mg); or (4) switch to venlafaxine plus cognitive behavioral therapy.

Main Outcome Measures Clinical Global Impressions-Improvement score of 2 or less (much or very much improved) and a decrease of at least 50% in the Children’s Depression Rating Scale-Revised (CDRS-R); and change in CDRS-R over time.

Results Cognitive behavioral therapy plus a switch to either medication regimen showed a higher response rate (54.8%; 95% confidence interval [CI], 47%-62%) than a medication switch alone (40.5%; 95% CI, 33%-48%; \( P \)=.009), but there was no difference in response rate between venlafaxine and a second SSRI (48.2%; 95% CI, 41%-56% vs 47.0%; 95% CI, 40%-55%; \( P \)=.83). There were no differential treatment effects on change in the CDRS-R, self-rated depressive symptoms, suicidal ideation, or on the rate of harm-related or any other adverse events. There was a greater increase in diastolic blood pressure and pulse and more frequent occurrence of skin problems during venlafaxine than SSRI treatment.

Conclusions For adolescents with depression not responding to an adequate initial treatment with an SSRI, the combination of cognitive behavioral therapy and a switch to another antidepressant resulted in a higher rate of clinical response than did a medication switch alone. However, a switch to another SSRI was just as efficacious as a switch to venlafaxine and resulted in fewer adverse effects.

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Author Affiliations: University of Pittsburgh, Pittsburgh, Pennsylvania (Drs Brent, Iyengar, Birmaher, Ryan, and Melhem, Messrs Abebe and Onorato, and Miss Porta and Zelazny); University of Texas Southwestern Medical Center at Dallas (Drs Emile, Kennard, and Hughes); Kaiser Permanente Center for Health Research, Portland, Oregon (Drs Clarke and DeBar); The University of Texas Medical Branch, Galveston (Dr Wagner); University of California, Los Angeles (Drs Rosenbaum Asarnow, McCracken, Strober, and Suddath); Brown University, Providence, Rhode Island (Drs Keller, Spirito, and Leonard); and National Institute of Mental Health, Bethesda, Maryland (Dr Vitello and Ms Ritz); Mr Onorato is now with Nationwide Children’s Hospital, Columbus, Ohio.†Deceased.

Corresponding Author: David Brent, MD, Western Psychiatric Institute and Clinic, 3811 O’Hara St, Room 315 Bellefield Towers, Pittsburgh, PA 15213 (brentda@upmc.edu).

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switches the risk for suicidal behavior and completed suicide. Therefore, the proper treatment of adolescent depression has profound public health implications for youth in this critical stage of development.

Clinical guidelines for the acute management of adolescent depression recommend the prescribing of selective serotonin reuptake inhibitor (SSRI) medications, psychotherapy, or both, with the best-studied psychotherapy being cognitive behavioral therapy (CBT). While these treatments alone or in combination have been shown to be efficacious, at least 40% of adolescents with depression do not show an adequate clinical response to these interventions, and only one-third show complete symptomatic remission to acute treatment. Despite the high frequency of nonresponse and the serious consequences of persistent depression in this age group (12-18 years), there are no empirical studies to guide clinicians regarding the management adolescents with depression not responsive to an initial treatment with an SSRI. To address the clinical management of this clinically important population, we developed a 6-site, National Institute of Mental Health–funded study, the Treatment of SSRI-Resistant Depression in Adolescents (TORDIA) trial, in which adolescents with depression that did not respond to an adequate course of an initial SSRI were randomized to 1 of 4 treatments in a 2 × 2 factorial design: (1) switch to a second, different SSRI; (2) switch to venlafaxine; (3) switch to second SSRI plus CBT; or (4) switch to venlafaxine plus CBT.

This study focuses on nonresponse to SSRI medications rather than on nonresponse to psychotherapy, because SSRI medications have been the predominant method of treatment for adolescent depression for at least the past decade. Switch to another SSRI is compared with switch to venlafaxine, a selective serotonin and noradrenergic reuptake inhibitor, because the former strategy is recommended in clinical guidelines, whereas venlafaxine has been shown to be superior to an SSRI in the management of treatment-refractory adult depression in some but not all studies. The efficacy of adding CBT to a medication switch was studied because the combination of antidepressant medication and CBT has been shown to be beneficial in acute, residual, and chronic depression in adults and in some, but not all, studies of adolescents with depression. The addition of CBT would be superior to a medication switch alone.

METHODS
Participants
Participants were adolescents aged 12 to 18 years, in active treatment for major depressive disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), with a clinically significant depression (Children’s Depression Rating Scale-Revised [CDRS-R]; total score of at least 40 and a Clinical Global Impressions-Severity subscale of at least 4 (at least moderate severity)), despite being in treatment with an SSRI regimen for at least 8 weeks, the last 4 of which were at a dosage of at least 40 mg per day of fluoxetine or its equivalent (eg, 40 mg paroxetine, 40 mg citalopram, 20 mg s-citalopram, or 150 mg sertraline). We also included participants who, after attempting a dosage comparable to 40 mg of fluoxetine, could only tolerate a dose that was the equivalent of 20 mg of fluoxetine for at least 4 weeks (19/334 participants; 5.7%). Excluded were participants with 2 or more adequate trials of an SSRI, a history of nonresponse to venlafaxine (at least 4 weeks at a dosage of ≥150 mg), or to CBT (≥7 sessions). Participants currently receiving CBT were also excluded, whereas those with past or current exposure to other forms of individual psychotherapy were eligible to participate. Potential participants taking medications with psychoactive properties were excluded, with the exception of those who were prescribed stable doses (≥12 weeks) of stimulants, hypnnotics (trazodone, zolpidem, zaleplon), or antianxiety agents (clonazepam, lorazepam). Other exclusionary criteria were diagnoses of bipolar spectrum disorder, psychosis, pervasive developmental disorder or autism, eating disorders, substance abuse or dependence, or hypertension (diastolic blood pressure >90 mm Hg), and for females: pregnancy, breastfeeding, or having unprotected sex.

This study was approved by each site’s local institutional review board. All participants gave written informed assent (and consent after they turned age 18), and parents gave written informed consent in accordance with local institutional review board regulations. Recruitment, outcomes, and adverse effects were monitored quarterly by a National Institute of Mental Health–constituted data and safety monitoring board.

Intake and Enrollment
Participants were assessed with a diagnostic interview (Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version), interview ratings of depression (CDRS-R) and of clinical severity (Clinical Global Impressions-Severity subscale), and laboratory tests (eg, electrocardiogram, liver function, thyroid, electrolytes, urine drug screen). Those with abnormal laboratory test results were enrolled only if medically cleared. Participants then continued on the same prestudy treatment regimen (ie, initial SSRI at equivalent of 40 mg of fluoxetine) for another 2 weeks and were reassessed. At the second assessment, which served as the study baseline, the difference between the 2 CDRS-R ratings was calculated. For participants in whom the CDRS-R decreased less than 30% and who still had significant depressive symptoms (CDRS-R ≥40), enrollment into the study was offered. The majority (79.9%) of participants came from clinical sources, and the remainder (20.1%) from advertisements.
Figure. Study Participants From Prescreening Through Analysis

3258 Adolescents prescreened

- 2776 Excluded
  - 2722 Did not meet criteria
  - 45 Not interested
  - 9 Unable to contact

- 482 Assessed by diagnostic interview and medical record review

- 97 Excluded
  - 52 Did not meet criteria (32 had CDRS-R ≤ 30)
  - 37 Withdrew consent
  - 8 Other

- 385 Underwent baseline assessment

- 51 Excluded
  - 25 Had a change in CDRS-R (≥ 30% or CDRS-R ≤ 40)
  - 11 Refused to continue
  - 9 Had exclusion criteria
  - 2 Had abnormal laboratory test results
  - 4 Other

334 Randomized

- 83 Randomized to receive venlafaxine alone
  - 33 Received adjunctive treatment
    - 12 Received sleep medication
    - 3 Received anxiolytic medication
    - 7 Received individual therapy

- 83 Randomized to receive venlafaxine with CBT
  - 25 received adjunctive treatment
    - 11 received sleep medication
    - 9 received anxiolytic medication
    - 7 received individual therapy

- 85 Randomized to receive SSRI alone
  - 31 received adjunctive treatment
    - 19 received sleep medication
    - 11 received anxiolytic medication
    - 5 received individual therapy

- 83 Randomized to receive SSRI with CBT
  - 34 received adjunctive treatment
    - 16 received sleep medication
    - 9 received anxiolytic medication
    - 8 received individual therapy

- 83 Randomized to receive fluoxetine
  - 25 received adjunctive treatment
    - 19 received sleep medication
    - 11 received anxiolytic medication
    - 5 received individual therapy

- 42 Randomized to receive paroxetine
  - 25 received adjunctive treatment
    - 16 received sleep medication
    - 9 received anxiolytic medication
    - 8 received individual therapy

- 42 Randomized to receive citalopram
  - 18 received adjunctive treatment
    - 12 received sleep medication
    - 9 received anxiolytic medication
    - 4 received individual therapy

618 Excluded

- 385 Underwent baseline assessment

- 334 Randomized

- 22 Withdrew from treatment
  - 6 Serious adverse events
  - 3 Adverse events
  - 4 Nonadherence
  - 2 Withdrew consent
  - 2 Lost to follow-up
  - 3 Worsening depression
  - 1 Ancillary treatment–comorbidity
  - 1 Hypomania

- 61 Completed treatment protocol
  - 74 Completed 6-wk assessment
  - 71 Completed 12-wk assessment
  - 83 Included in analysis

- 53 Completed treatment protocol
  - 4 Completed < 2 CBT sessions
  - 68 Completed 6-wk assessment
  - 72 Completed 12-wk assessment
  - 83 Included in analysis

- 60 Completed treatment protocol
  - 77 Completed 6-wk assessment
  - 76 Completed 12-wk assessment
  - 85 Included in analysis

- 57 Completed treatment protocol
  - 73 Completed 6-wk assessment
  - 68 Completed 12-wk assessment
  - 83 Included in analysis

CBT indicates cognitive behavioral therapy; CDRS-R, Children’s Depression Rating Scale-Revised; SSRI, selective serotonin reuptake inhibitor. Numbers may not sum within boxes because participants could receive more than one adjunctive treatment.

4Participants were taking paroxetine at the time of the 2003 UK reports concerning paroxetine use,40 were unblinded, and tapered off of the medication.

5Participant was withdrawn from the study and unblinded after providing disclosure of having alcohol dependence, an exclusionary criterion. Participant later withdrew the claim.
Randomization
Participants were randomly assigned to 1 of 4 treatment regimens (FIGURE) in a 2 × 2 factorial design: change to second SSRI, change to venlafaxine, change to a second SSRI plus CBT, or change to venlafaxine plus CBT. Randomization was balanced both within and across sites with respect to incoming treatment medication, comorbid anxiety, chronic depression (duration ≥24 months), and suicidal ideation (Beck Depression Inventory item 9 ≥2), using a variation of Efron’s biased coin toss.39 Participants in the SSRI switch groups who were initially treated with citalopram, sertraline, or fluvoxamine were randomized to receive either fluoxetine or paroxetine. If they were initially treated with fluoxetine, they were switched to receive paroxetine and vice versa.

Change in Study Medication
Midway through the study (after 181/334 participants had been enrolled), due to concerns about the efficacy and safety of paroxetine, 1 of the treatment options in the SSRI group was changed from paroxetine to citalopram.40,41 Of the 50 participants who were assigned to receive paroxetine, only 3 were in active treatment at the time of this change. These participants assigned to paroxetine were unblinded and removed from the study and 2 of the 3 were subsequently lost to follow-up. The clinical and demographic characteristics of participants were similar before and after the announcement about paroxetine.

Blinding Procedure
The intent was for study participants, clinicians, and independent evaluators to be blinded to medication treatment assignment and for independent evaluators to be blinded to CBT assignment. Blinding for medication was maintained by use of 3 encapsulated pills daily for all prescriptions, some of which might be placebo to mask drug type and dose. The blinding to CBT for independent evaluators was maintained by scheduling the independent evaluators’ assessments at a time not contiguous with CBT sessions and by asking participants and staff not to discuss CBT treatment assignment when the independent evaluator was present. The pharmacotherapists’ accuracy in guessing medication assignment was less accurate than chance (44.2%; χ² = 5.14, P = .03), whereas the independent evaluators guessed CBT assignment at a rate slightly higher than chance (58.3%; χ² = 5.14, P = .02). In 64 cases, the blinding of the independent evaluator was compromised, most commonly because of participant disclosure of receiving CBT.

Interventions
Medication Taper. Participants were tapered to discontinuation from their initial medication by decreasing dosages over a period of 2 weeks, except for those who entered the study taking fluoxetine, for whom the medication was simply discontinued due to fluoxetine’s long half-life.

Pharmacotherapy. Pharmacotherapists were either psychiatrists or master’s degree–prepared nurses working with the supervision of a psychiatrist. The study psychiatrist examined participants at entry, 6 weeks, and 12 weeks.

Medication sessions were 30 to 60 minutes in duration and included assessment of vital signs, adverse effects, safety, and symptomatic response, and occurred weekly for the first 4 weeks and every other week thereafter during acute treatment. The dosage schedule for SSRI intake was 10 mg per day for the first week and 20 mg per day for weeks 2 to 6, with an option to increase to 40 mg per day if there was insufficient clinical improvement (Clinical Global Impressions–Severity subscale ≥3). The venlafaxine dosages for weeks 1 to 4 were 37.5, 75, 112.5, and 150 mg, respectively, with an option to increase to 225 mg at week 6. If intolerable adverse effects developed after a medication increase, the participant’s dosage was lowered to either 20 mg of an SSRI or to 150 mg of venlafaxine. By 12 weeks, the mean doses of SSRI were 33.8 mg (95% CI, 32.0-35.6), and for venlafaxine were 205.4 mg (95% CI, 199.0-211.7).

Family Psychoeducation. All parents of participants, regardless of treatment group, received family psychoeducation, which consisted of meeting with a nurse-clinician or psychiatrist who reviewed the symptoms of depression, its causes, treatments, possible adverse effects, and informed parents about how to cope with having a mood-disordered child.42,43 Across all treatment groups, clinicians met with families at intake, at the 6-week midpoint, and at 12 weeks—the end of acute treatment.

Cognitive Behavioral Therapy. Therapists who facilitated CBT earned at least a master’s degree in a mental health field, with prior experience in CBT. CBT drew upon the manuals that emphasize cognitive restructuring and behavior activation, emotion regulation, social skills, and problem solving for participants, and that also emphasize parent-child sessions to decrease criticism and to improve support, family communication, and problem solving.44-49 These different modules were flexibly applied on the basis of the clinical needs of the participant and family, with input from on-site and external supervisors, and review of case formulations during a CBT conference call every other week.

The protocol called for as many as 12 sessions (60-90 minutes each) of CBT during the first 12 weeks, 3 to 6 of which were to be family sessions. During 6 instances when judged clinically necessary, therapists “borrowed” as many as 3 sessions from their bank of sessions ordinarily reserved for continuation treatment. The mean and median number of CBT sessions attended in the first 12 weeks was 8.3 and 9 (interquartile range, 5), respectively, with no differences between medication groups or across sites.

Treatment Fidelity. All therapists underwent a 2-day training at the beginning and at midpoint in the study. Pharmacotherapy session audiotapes were reviewed by the coordinating center (153 tapes), using the 16-item Pharmacotherapy Rating Scale derived from the Clinical Management Scale50 to ensure coverage of assessment, safety issues, and distinctness from CBT, with 92.8% being of acceptable quality. CBT session audiotapes were reviewed using the Cognitive Therapy Rating Scale51 by on-site supervisors (277 tapes), 2 CBT supervisors in Pittsburgh.
Pennsylvania (351 tapes), and 1 external consultant who has served as a trainer for the Beck Cognitive Therapy Center, Philadelphia, Pennsylvania (49 tapes), with 94.9%, 94.0%, and 93.9% rated as acceptable, respectively.

**Adjunctive Treatments.** Adjunctive medications were prescribed for sleep (diphenhydramine, 25-50 mg; zaleplon, 5-20 mg; zolpidem, 5-10 mg; or trazodone [for females, 25-50 mg]), and for anxiety (clonazepam, 0.25 mg twice daily; or lorazepam, 0.5 mg 3 times/day). Participants who were involved in ongoing supportive treatment (≥3 months with no family or cognitive component) were allowed to continue no more frequently than every other week. These interventions occurred in a minority of participants (4%-21.5%) and were evenly distributed across treatment groups (Figure; χ² < 2.2; P > .14).

**Protocol Deviations.** Twelve participants (3.6%) were allowed into the protocol despite meeting exclusionary criteria, if consensus of the investigators was that such an exception was warranted (eg, participant who was 1 week younger than 12 years, pubertal, and cognitively mature). In addition, 11 participants (3.3%), after they had been enrolled and treated, were found to have had a shorter than required duration of initial treatment with an SSRI, and 12 (3.6%) were found to have had a response to the initial treatment better than allowed for entry. Results were unchanged when analyses were rerun excluding these participants.

**Assessments**

**Diagnostic and Primary Outcome Assessments.** The Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version, a widely used semi-structured interview, was used to determine DSM-IV diagnoses. Overall clinical improvement was rated by the Clinical Global Impressions-Improvement Subscale, which ranges from 1 (very much improved) to 7 (very much worse). Depressive symptoms were rated by the CDRS-R, a 17-item interview that ranges from 17 to 113, with a score of 40 or greater considered consistent with clinically significant depression. Both the Clinical Global Impressions-Improvement Subscale and the CDRS-R have been widely used in pediatric treatment trials of depression. These outcomes were rated by independent evaluators, who had attained or were completing a master's degree in a mental health field, with at least 3 years of clinical experience and who were trained to at least 80% interrater reliability on these assessments.

**Primary Outcomes.** The study had 2 declared primary outcomes. The first, “adequate clinical response,” was defined as a Clinical Global Impressions-Improvement Scale score of 2 or less and an improvement in the CDRS-R score of at least 50% in order to capture both global and symptomatic improvement. The second primary outcome was the trajectory of the CDRS-R over time.

**Interrater Reliability.** Interrater reliability was monitored throughout the study and remained high for diagnosis of depression and dysthymia (κ=0.70; 95% CI, 0.49-0.89; N=150), for CDRS-R (intraclass correlation coefficient=0.85; 95% CI, 0.80-0.89; N=324), and for both the Clinical Global Impressions-Severity Subscale and Clinical Global Impressions-Improvement Subscale (intraclass correlation coefficient=0.84; 95% CI, 0.74-0.89; N=176) for each.

**Secondary Outcomes.** Self-reported depression and suicide-related symptoms were assessed by the Beck Depression Inventory and the Suicide Ideation Questionnaire-Jr. Functional status was assessed using the Children's Global Adjustment Scale, a 1- to 100-point scale, with scoring of at least 70 being indicative of adequate functioning.

**Follow-up Assessment Visits During Acute Phase.** The previously noted interview and self-rated assessments of symptoms and adaptive functioning were obtained at baseline and at weeks 6 and 12, regardless of treatment status and response.

**Safety Assessment.** Safety assessments were completed during all pharmacotherapy visits and included a 4-item Kiddie Schedule for Affective Disorders and Schizophrenia for School-age Children mania screen. Any positive response resulted in the administration of the full 14-item Mania Rating Scale. Adverse effects were assessed using the Side Effects Form for Children and Adolescents. Treatment-emergent adverse events were defined as new-onset or worsening symptoms and were reviewed during weekly conference calls. Serious adverse events were those that resulted in significant disability, threat to life, or emergency care. After the concerns about the safety of antidepressants were raised, the remaining 153 participants were monitored weekly by clinicians for suicidal ideation, suicidal behavior, and adverse effects of antidepressants that might be related to suicidality (eg, hostility, irritability, lability).

**Statistical and Power Analyses**

All primary analyses were based on a 2 × 2 balanced factorial design, were of intent-to-treat format, and in the case of those using dichotomous outcomes, the last observation carried forward unless stated otherwise. Similar results were found using multiple imputation with the assumption of data missing at random, and therefore, this study reports only on last observation carried forward. Analyses were conducted using SPSS 14.0 (SPSS Inc, Chicago, Illinois) and STATA 9.2 (StataCorp, College Station, Texas). Differences in response were assessed using χ² and logistic regression, testing for effects of CBT (vs not), medication (switch to an SSRI vs venlafaxine), and their interaction. Unless noted otherwise, contrasts were planned, df=1, and tests were 2-sided. Logistic regression was used to assess the main effects of treatment after adjusting for baseline differences and interactions with treatment, followed by backward stepping to identify the best-fitting, most parsimonious model. The effect of treatment on the trajectory of the CDRS and other scalar measures was assessed by random effects linear regression, using a logarithmic transformation of time, testing for effects of time, CBT, medication, site, and their respective interactions on the scalar outcome. Effect sizes were calculated using Hedges g.
The study was designed to have a sample size of 400 and was powered to detect a 10% difference between groups at power of 80%, with \( P = .05 \). This study did not meet that target because at midpoint, concerns and warnings about SSRI use in pediatric populations led to a decline in use, making recruitment more difficult.64 For the actual sample of 334 participants and group sizes of 167, an effect size of \( d = 0.31 \) could be detected at 80% power, \( P = .05 \), which corresponds to a 15% difference between groups for dichotomous outcomes, with ability to detect slightly larger effect sizes (\( d = 0.34 \); 16.5% risk difference) for the sample with complete follow-up data (n = 287).

### RESULTS

#### Patient Disposition

Of 334 participants who were randomized to treatment (Figure), 292 (87.4%) had at least 1 postbaseline assessment point, 287 (85.9%) were assessed from baseline through week 12, and 231 (69.2%) completed the treatment protocol through week 12. The remaining participants (30.8%) left or were withdrawn from the protocol prematurely, most commonly due to adverse effects (n = 41); nonadherence, loss to follow-up, or withdrawal of consent (n = 31); need for out-of-protocol treatment for depression or other conditions (n = 20); or development of exclusionary criteria (n = 7). There were no differences in the completion rates across the 2 factorial variables (CBT [66.3%; 95% CI, 59%-74%] vs not [72.0%; 95% CI, 65%-79%]; \( \chi^2 = 1.30; P = .26 \); and venlafaxine [68.7%; 95% CI, 62%-76%] vs SSRI [69.6%; 95% CI, 63%-77%]; \( \chi^2 = 0.04; P = .85 \)).

#### Demographic and Clinical Characteristics

The treatment groups were very similar with regard to demographic and clinical baseline characteristics (Table 1) except that the venlafaxine group had a lower Beck Depression Inventory score (\( P = .03 \)) and lower rates of posttraumatic stress disorder (\( P = .04 \)) at baseline. As race and ethnicity can influence treatment response, these
were assessed based on participants’ reports.63,66 The sample was approximately 16 years of age, 70% female, 82% white, with a median household income of $61,000. Participants had moderately severe (CDRS-R = 59; 95% CI, 58-60 and Children’s Global Adjustment Scale = 51; 95% CI, 50-51) and chronic depression (56.3% had duration ≥2 years; median duration, 17 months; interquartile range, 22.3 months), mostly in their first episode (73.9%). Treatment duration prior to study entry was a median of 17 weeks of SSRI pharmacotherapy (interquartile range, 16.5 weeks), and a median of 8 sessions of psychotherapy in the previous 12 weeks (interquartile range, 5 sessions). A high proportion of participants showed clinically significant suicidal ideation (58.5%, Suicide Ideation Questionnaire-Jr score ≥31), and at least 1 additional comorbid disorder (51.7%). There were substantial site differences with regard to demographic and clinical baseline variables, although for the most part, the balance of these characteristics across treatments was maintained within each site as well.

**Clinical Response**

A higher proportion of participants treated with CBT showed an adequate clinical response (54.8% of participants [95% CI, 47%-62%]; Clinical Global Impressions-Improvement Subscale = 2 and a CDRS-R decline ≥50%) vs not (40.5% of participants [95% CI, 33%-48%]; risk difference = 14.3% [95% CI, 3.7%-24.9%]; χ² = 6.89; P = .009; Hedges g = 0.29 [95% CI, 0.07-0.51]; number needed to treat = 7 [95% CI, 4-27]), but there was no difference between medication groups (48.2% prescribed venlafaxine [95% CI, 41%-56%]; vs 47.0% prescribed SSRI [95% CI, 40%-55%]; risk difference = 1.2% [95% CI, 9.5-11.9]; χ² = 0.046; P = .83). The results were similar for each of the 2 components of response score (Clinical Global Impressions-Improvement Subscale; and a change in CDRS-R ≥50%) and also if the analyses were restricted to completers (Table 2). There was a significant difference in CBT response by site (χ² = 13.3; P < .001), but no site differences with regard to response to SSRI (χ² = 3.62; P = .061) or to venlafaxine (χ² = 7.22; P = .01). These findings with regard to CBT response were robust to sensitivity analyses that removed 1 site at a time (risk difference ranged from 8.8%-20.6%; median 13.3%) and that removed one-sixth (n = 56) of participants at random (risk difference from 11.4%-17.5%; median 13.4%).

Post hoc, there were no significant differences among the 3 SSRI medications with regard to clinical response (paroxetine, 19/50 [38.0%; 95% CI, 25%-52%]; fluoxetine, 41/84 [48.8%; 95% CI, 38%-60%]; citalopram, 19/34 [55.9%; 95% CI, 39%-73%]; χ² = 2.81; P = .25). Logistic regression with the outcome of clinical response showed that there was a main effect for CBT (P = .03), but not for medication type (P = .66), nor was there a medication by CBT interaction with regard to clinical response (P = .67; TABLE 3, model 1). The main effect for CBT (P = .002) persisted after controlling for baseline differences in the Beck Depression Inventory (P < .001) and posttraumatic stress disorder (P = .15; Table 3, model 2). Also, the main effect for CBT (P = .01) was still significant after controlling for the main effects of site (P = .02), baseline Beck Depression Inventory (P = .001), and a site by CBT interaction (P = .003; Table 3, model 3).

**CDRS-R Trajectory**

With regard to change in the CDRS-R (Table 4), there was a significant effect for time (z = −7.18; P < .001), but not for medication, CBT, site, or any 2- or 3-way interaction.

**Self-reported Depression and Suicidal Ideation**

There were significant effects on the Beck Depression Inventory for time (Table 4, z = −4.92; P < .001) and site (z = 2.82; P = .005). For the Suicide Ideation Questionnaire-Jr, there was an effect of time (z = −3.45; P = .001). No other main effects or interactions were detected for either measure.

**Global Functioning and Rating of Severity**

There were significant effects of time on the Children's Global Adjustment Scale (Table 4, z = −4.31; P < .001) and on the Clinical Global Impressions-Severity Subscale (z = −5.68; P < .001), but no other main effects or interactions were detected for either measure.
Relationship of Response and Continuous Outcomes

Participants who showed an adequate clinical response, compared with nonresponders, showed more rapid decline on the CDRS, Beck Depression Inventory, Suicide Ideation Questionnaire-Jr, Children’s Global Adjustment Scale, and Clinical Global Impressions Severity-Subscale (response × time; z scores = −14.33 to −4.71; all P values < .001).

Table 3. Logistic Regressions of Clinical Response, Adjusting for Baseline and Site Differences

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<th>Model</th>
<th>β</th>
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<th>Wald χ²</th>
<th>df</th>
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<td>.06</td>
<td>1</td>
<td>0.94 (0.60-1.49)</td>
<td>.80</td>
</tr>
<tr>
<td>CBT</td>
<td>.74</td>
<td>.23</td>
<td>9.99</td>
<td>1</td>
<td>2.10 (1.32-3.31)</td>
<td>.002</td>
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<td>Site</td>
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<tr>
<td>Site C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline Beck Depression Inventory</td>
<td>−.04</td>
<td>.01</td>
<td>12.54</td>
<td>1</td>
<td>0.96 (0.94-0.98)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Baseline posttraumatic stress disorder</td>
<td>.68</td>
<td>.48</td>
<td>2.06</td>
<td>1</td>
<td>1.98 (0.78-5.04)</td>
<td>.15</td>
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<tr>
<td>Model 3</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBT</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Site</td>
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<tr>
<td>Site C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline Beck Depression Inventory</td>
<td>−.04</td>
<td>.01</td>
<td>10.40</td>
<td>1</td>
<td>0.97 (0.95-0.99)</td>
<td>.001</td>
</tr>
</tbody>
</table>

Abbreviations: CBT, cognitive behavioral therapy; CI, confidence interval; OR, odds ratio; PTSD, posttraumatic stress disorder.

Table 4. Changes in Total Scores During a 12-Week Treatment Period

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline</th>
<th>Week 6</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRI</td>
<td>59.8 (10.6) [58.3-61.5]</td>
<td>42.3 (14.0) [40.1-44.6]</td>
<td>37.9 (13.7) [35.7-40.1]</td>
</tr>
<tr>
<td>Beck Depression Inventory</td>
<td>21.9 (12.0) [20.1-23.8]</td>
<td>13.2 (11.4) [11.4-15.1]</td>
<td>11.5 (10.9) [9.7-13.3]</td>
</tr>
<tr>
<td>Suicidal Ideation Questionnaire</td>
<td>42.6 (22.0) [39.5-46.2]</td>
<td>33.3 (20.8) [30.0-36.6]</td>
<td>31.6 (17.9) [28.6-34.6]</td>
</tr>
<tr>
<td>Clinical Global Impressions-Sever-ity Scores</td>
<td>4.5 (0.6) [4.4-4.6]</td>
<td>3.5 (1.0) [3.3-3.6]</td>
<td>2.9 (1.2) [2.7-3.1]</td>
</tr>
<tr>
<td>Children’s Global Assessment Scale</td>
<td>50.3 (7.8) [49.1-51.5]</td>
<td>58.9 (11.5) [57.1-60.8]</td>
<td>63.3 (11.9) [61.3-65.2]</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>57.8 (10.1) [56.2-59.3]</td>
<td>42.6 (13.2) [40.4-44.8]</td>
<td>37.0 (13.1) [34.9-39.2]</td>
</tr>
<tr>
<td>Beck Depression Inventory</td>
<td>19.1 (12.0) [17.2-20.9]</td>
<td>13.2 (12.2) [11.3-15.3]</td>
<td>9.9 (10.5) [8.2-11.6]</td>
</tr>
<tr>
<td>Suicidal Ideation Questionnaire</td>
<td>40.4 (22.6) [36.9-43.8]</td>
<td>35.1 (21.9) [31.5-38.7]</td>
<td>31.4 (19.7) [28.2-34.7]</td>
</tr>
<tr>
<td>Clinical Global Impressions-Sever-ity Scores</td>
<td>4.4 (0.7) [4.4-4.6]</td>
<td>3.4 (1.1) [3.3-3.6]</td>
<td>2.8 (1.2) [2.6-3.0]</td>
</tr>
<tr>
<td>Children’s Global Assessment Scale</td>
<td>50.9 (7.6) [49.7-52.1]</td>
<td>59.7 (9.7) [58.1-61.3]</td>
<td>64.8 (11.1) [62.9-66.6]</td>
</tr>
<tr>
<td>No CBT</td>
<td>58.4 (9.7) [57.0-59.9]</td>
<td>41.6 (13.4) [39.5-43.7]</td>
<td>38.1 (12.9) [36.0-40.1]</td>
</tr>
<tr>
<td>Beck Depression Inventory</td>
<td>19.6 (11.5) [17.9-21.4]</td>
<td>12.3 (10.8) [10.6-14.1]</td>
<td>10.5 (9.8) [8.9-12.1]</td>
</tr>
<tr>
<td>Suicidal Ideation Questionnaire</td>
<td>41.9 (21.1) [38.7-45.1]</td>
<td>34.5 (20.5) [31.0-37.7]</td>
<td>31.4 (17.5) [28.6-34.2]</td>
</tr>
<tr>
<td>Clinical Global Impressions-Sever-ity Scores</td>
<td>4.5 (0.6) [4.4-4.6]</td>
<td>3.4 (1.0) [3.3-3.6]</td>
<td>3.0 (1.1) [2.8-3.2]</td>
</tr>
<tr>
<td>Children’s Global Assessment Scale</td>
<td>50.6 (7.7) [49.4-51.8]</td>
<td>59.3 (10.7) [57.6-61.0]</td>
<td>63.0 (11.2) [61.2-64.8]</td>
</tr>
<tr>
<td>CBT</td>
<td>59.2 (11.0) [57.5-60.9]</td>
<td>43.4 (13.9) [41.1-45.7]</td>
<td>36.9 (13.9) [34.6-39.2]</td>
</tr>
<tr>
<td>Beck Depression Inventory</td>
<td>21.4 (12.6) [19.5-23.4]</td>
<td>14.2 (12.7) [12.1-16.2]</td>
<td>11.0 (11.5) [9.0-12.9]</td>
</tr>
<tr>
<td>Suicidal Ideation Questionnaire</td>
<td>41.3 (23.5) [37.7-44.9]</td>
<td>33.9 (21.7) [30.4-37.5]</td>
<td>31.7 (20.2) [28.3-35.1]</td>
</tr>
<tr>
<td>Clinical Global Impressions-Sever-ity Scores</td>
<td>4.5 (0.7) [4.4-4.6]</td>
<td>3.5 (1.0) [3.3-3.6]</td>
<td>2.7 (1.2) [2.5-2.9]</td>
</tr>
<tr>
<td>Children’s Global Assessment Scale</td>
<td>50.6 (7.7) [49.4-51.8]</td>
<td>59.4 (10.7) [57.6-61.1]</td>
<td>65.1 (11.8) [63.1-67.0]</td>
</tr>
</tbody>
</table>

Abbreviations: CBT, cognitive behavioral therapy; CI, confidence interval; SSRI, selective serotonin reuptake inhibitor.

Post Hoc Sensitivity Analyses

Post hoc, we stratified our analyses of treatment response on several variables that might have influenced it (TABLE 5). The response rates overall and within each treatment were similar before and after the safety warnings and the US Food and Drug Administration Antidepressant Black Box Warning. Response rates showed a nonsignificant trend toward being higher in the unblinded participants overall (P = .07) and within CBT (P < .06). Using logistic regression, the effects of CBT (odds ratio [OR], 1.70 [95% CI, 1.09-2.64]; P = .02) on response persisted, even after controlling for the effect of unblinding (OR, 1.49 [95% CI, 0.85-2.62]; P = .16; Hosmer-Lemeshow χ² = 1.87; P = .39). Participants who received adjunctive medication for sleep had a lower response rate overall (P = .01), as well as within SSRI (P = .01) and CBT treatments (P = .004). Overall results were similar with and without participants with ad-
junctive sleep medications. There was no relationship between outcome and the use of anxiolytics, stimulants, adjunctive supportive therapy, or the presence of comorbid attention-deficit/hyperactivity disorder.

**Adverse Events**

There were no differences between treatments with regard to the frequency of serious adverse events, adverse events, or the frequency of removal from the study for such events (Figure; Table 6). There were also no differences by treatment group with respect to the frequency of self-harm adverse events or related categories (increased suicidal ideation, self-injurious behavior, or suicide attempts), either when restricted to those within their treatment group (Table 6), or based on intent-to-treat analyses. There were 18 suicide attempts among 17 participants, but none of the participants completed suicide. Sleep difficulties and irritability were the only psychiatric adverse effects that occurred in at least 5% of participants. There was only 1 instance of hypomania during the first 12 weeks.

With regard to nonpsychiatric adverse events that occurred in at least 5% of participants, only skin problems were more common in venlafaxine vs those who were prescribed SSRI medications ($P = .01$; Table 6). The Side Effects Form for Children and Adolescents showed a similar pattern, with 31.7% of skin problems (mostly itching and rash) reported in the venlafaxine group (95% CI, 25%-39%) compared with 16.9% in the SSRI groups (95% CI, 11%-23%; $\chi^2 = 9.78; P = .002$).

Four participants (2.4% [95% CI, 0%-5%]) assigned to venlafaxine were removed from the study for cardiovascular events, vs 1 who was assigned to SSRI medications (0.6% [95% CI, 0.6%-2%]; Fisher, $P = .21$); these events were prolonged corrected QT interval in 1 participant, increased blood pressure in 2 participants, and increased heart rate. Venlafaxine resulted in greater increases in diastolic blood pressure ($P = .004$) and pulse ($P = .001$; Table 7), although these adverse effects were rarely of clinical impact. There were no medication effects on weight, systolic blood pressure, or the corrected QT interval.

**Comment**

Summary

In this study of adolescents with moderately severe and chronic depression who had not responded to an adequate course of treatment with an SSRI antidepressant, switching to a combination of CBT and another antidepressant resulted in a higher rate of clinical response than switching to another medication without CBT. There was no differential effect between switching to another SSRI or to venlafaxine. Although there were considerable site differences in CBT treatment response, the effects of CBT on outcome were robust to sensitivity analyses and persisted after controlling for site effects. There were no differential treatment effects on scalar measures of depression, suicidal ideation, and functioning, nor were there treatment effects on suicide attempts, or self-harm–related adverse events in 2 participants.

**Limitations**

We did not control for the greater contact and attention that participants in the combined treatment received (eg, by offering supportive therapy in the non-CBT groups. However, prior to entry, these participants had not responded to a fairly intense regimen of treatment, consisting of a median of 17 weeks of pharmacotherapy and 8 sessions of psychotherapy over the previous 12 weeks. Also, 2 characteristics of this sample, namely high rates of chronicity and clinically significant suicidality, have previously been shown to

---

**Table 5. Post Hoc Sensitivity Analyses of the Impact of Different Study Conditions on Treatment Response**

<table>
<thead>
<tr>
<th>Stratification Variable</th>
<th>Overall (95% CI)</th>
<th>Venlafaxine (95% CI)</th>
<th>SSRI (95% CI)</th>
<th>CBT (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No sleep medication</td>
<td>No. RR (% 95% CI)</td>
<td>No. RR (% 95% CI)</td>
<td>No. RR (% 95% CI)</td>
<td>No. RR (% 95% CI)</td>
</tr>
<tr>
<td>Before warning</td>
<td>181 47.5 (40-55)</td>
<td>89 50.6 (40-61)</td>
<td>92 44.6 (34-55)</td>
<td>90 56.7 (46-67)</td>
</tr>
<tr>
<td>After warning</td>
<td>153 47.7 (40-56)</td>
<td>77 45.5 (34-57)</td>
<td>76 50.0 (39-61)</td>
<td>76 52.6 (41-64)</td>
</tr>
<tr>
<td>Blinded</td>
<td>270 45.2 (39-51)</td>
<td>127 44.9 (36-54)</td>
<td>143 45.5 (37-54)</td>
<td>123 50.4 (42-59)</td>
</tr>
<tr>
<td>Unblinded</td>
<td>64 57.8 (46-70)</td>
<td>39 59.0 (44-74)</td>
<td>25 56.0 (37-76)</td>
<td>43 67.4 (53-81)</td>
</tr>
<tr>
<td>Sleep medication</td>
<td>58 32.8 (21-45)</td>
<td>23 39.1 (19-59)</td>
<td>28.6 (16-45)</td>
<td>27 29.6 (15-48)</td>
</tr>
<tr>
<td>No sleep medication</td>
<td>276 50.7 (45-57)</td>
<td>143 49.7 (42-58)</td>
<td>133 51.9 (43-60)</td>
<td>139 59.7 (52-68)</td>
</tr>
<tr>
<td>Anxiolytic medication</td>
<td>12 50.0 (22-78)</td>
<td>7 28.6 (6-65)</td>
<td>80.0 (37-98)</td>
<td>7 57.1 (23-86)</td>
</tr>
<tr>
<td>No anxiolytic medication</td>
<td>322 47.5 (42-53)</td>
<td>159 49.1 (41-57)</td>
<td>163 46.0 (38-54)</td>
<td>159 54.7 (47-63)</td>
</tr>
<tr>
<td>Stimulant medication</td>
<td>43 46.5 (32-61)</td>
<td>23 52.2 (32-73)</td>
<td>20 40.0 (19-62)</td>
<td>18 61.1 (38-81)</td>
</tr>
<tr>
<td>No stimulant medication</td>
<td>291 47.8 (42-54)</td>
<td>143 47.6 (39-56)</td>
<td>148 48.0 (40-56)</td>
<td>148 54.1 (46-62)</td>
</tr>
<tr>
<td>Supportive therapy</td>
<td>27 51.9 (34-70)</td>
<td>14 64.3 (38-85)</td>
<td>13 38.5 (16-65)</td>
<td>15 53.3 (29-76)</td>
</tr>
<tr>
<td>No supportive therapy</td>
<td>307 47.2 (42-53)</td>
<td>152 46.7 (39-55)</td>
<td>155 47.7 (40-56)</td>
<td>151 55.0 (47-63)</td>
</tr>
<tr>
<td>ADHD</td>
<td>52 51.9 (39-65)</td>
<td>26 61.5 (42-78)</td>
<td>26 42.3 (25-61)</td>
<td>29 69.0 (51-83)</td>
</tr>
<tr>
<td>No ADHD</td>
<td>279 46.2 (40-52)</td>
<td>140 45.7 (38-54)</td>
<td>139 46.8 (39-55)</td>
<td>135 51.1 (43-59)</td>
</tr>
</tbody>
</table>

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CBT, cognitive behavioral therapy; CI, confidence interval; RR, response rate; SSRI, selective serotonin reuptake inhibitor.

*P < .05; sleep medication: $\chi^2 = 6.20, P = .01$.

*Blind: $\chi^2 = 3.31, P < .07$; sleep medication: $\chi^2 = 6.04, P = .01$.

*Blind: $\chi^2 = 3.73, P < .06$; sleep medication: $\chi^2 = 8.26, P = .004$; ADHD: $\chi^2 = 3.01, P = .08$.  

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predict a poor response to supportive therapy in adolescents with depression. Second, the blinding with regard to CBT was compromised in about one-fifth of the sample, but since the effects of CBT persisted even after statistically controlling for the effect of unblinding, the compromise in the blinding alone does not explain our findings. Third, due to our design, we cannot determine whether the addition of CBT would have been beneficial even without making a change in medication. In the Sequenced Treatment Alternatives to Relieve Depression study, adult patients with depression who did not respond to citalopram showed response to augmentation with CBT comparable to a switch in medication. However, only one-third of the available participants agreed to a randomization that included this condition, consistent with our concern that recruitment for this treatment option would have been challenging. Fourth, our sample was not ethnically diverse (17% minority), limiting our ability to test for ethnic differences in response. Finally, there are several other treatment strategies used in clinical practice that were not evaluated, such as a switch to bupropion or augmentation with bupropion, lithium, thymoxine, or atypical antipsychotics. While most of these strategies were tested in adults with depression enrolled in the Sequenced Treatment Alternatives to Relieve Depression study, none of these strategies has ever been evaluated in children or adolescents with depression.

**Strengths**

This is the first clinical trial to encompass adolescents with depression who were not responding to a current, evidence-based treatment. Consequently, while the severity of depression was comparable with other studies, the sample had higher rates of 2 additional predictors of poor clinical response: chronic depression and clinically significant suicidal ideation. Previous clinical trials of antidepressants in adolescents with depression have routinely excluded participants with active suicidal ideation, which belies community practice insofar as suicidal behavior is one of the most common reasons for initiating antidepressant treatment for an adolescent with depression. We have demonstrated that it is possible to manage these participants in the context of a clinical trial, given sufficient appropriate rescue procedures. Thus, our findings could be applicable to community samples, while often more ethnically diverse than our sample, have comparable clinical complexity.

**Combination Treatment**

The strategy of comparing a medication switch plus CBT to a medication switch alone has not been previously tested in treatment-resistant depression, but combination treatment for depression in adults, including adults with chronic depression, has been shown to be superior to either monotherapy. We obtained an effect at a relatively low “dose” of CBT (median, 9 sessions), as have some other positive clinical trials in adolescents and adults. It is

### Table 6. Proportion of Participants Who Experienced at Least 1 Adverse Event by Treatment Group

<table>
<thead>
<tr>
<th>No. (%)</th>
<th>SSRI</th>
<th>Venlafaxine</th>
<th>No CBT</th>
<th>CBT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No. of participants</td>
<td>168 166 168 166</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 1 Serious adverse event</td>
<td>18 (10.7) 19 (11.4) 14 (8.3) 23 (13.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 1 Adverse event</td>
<td>86 (51.2) 78 (47.0) 84 (50.0) 80 (48.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Event/problem</th>
<th>Harm-related</th>
<th>Sleep</th>
<th>Irritability</th>
<th>Flu-like</th>
<th>Aches</th>
<th>Accident/injury</th>
<th>Gastrointestinal</th>
<th>Skin</th>
<th>Musculoskeletal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>31 (18.5)</td>
<td>5 (3.0)</td>
<td>8 (4.8)</td>
<td>31 (18.5)</td>
<td>24 (14.3)</td>
<td>12 (7.1)</td>
<td>9 (5.4)</td>
<td>3 (1.8)</td>
<td>6 (3.6)</td>
</tr>
<tr>
<td></td>
<td>37 (22.3)</td>
<td>12 (7.2)</td>
<td>8 (4.8)</td>
<td>21 (12.7)</td>
<td>23 (13.9)</td>
<td>7 (4.2)</td>
<td>7 (4.2)</td>
<td>13 (7.8)</td>
<td>10 (6.0)</td>
</tr>
<tr>
<td></td>
<td>32 (19.0)</td>
<td>7 (4.2)</td>
<td>6 (3.6)</td>
<td>26 (15.5)</td>
<td>23 (13.7)</td>
<td>10 (6.0)</td>
<td>7 (4.2)</td>
<td>7 (4.2)</td>
<td>5 (3.0)</td>
</tr>
<tr>
<td></td>
<td>36 (21.7)</td>
<td>10 (6.0)</td>
<td>10 (6.0)</td>
<td>26 (15.7)</td>
<td>24 (14.5)</td>
<td>9 (5.4)</td>
<td>9 (5.4)</td>
<td>9 (5.4)</td>
<td>11 (6.6)</td>
</tr>
</tbody>
</table>

Abbreviations: CBT, cognitive behavioral therapy; SSRI, selective serotonin reuptake inhibitor.

### Table 7. Change in Weight, Blood Pressure, Heart Rate, and Corrected QT Interval by Medication

#### Baseline Week 12

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD) [95% Confidence Interval]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Venlafaxine</strong></td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>68.9 (19.7) [65.7-71.9]</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>67.0 (8.8) [65.6-68.4]</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>112.3 (14.0) [110.1-114.5]</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>76.3 (11.9) [74.4-78.1]</td>
</tr>
<tr>
<td>Corrected QT interval, ms</td>
<td>412.7 (21.4) [409.4-416.1]</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Selective serotonin reuptake inhibitor</strong></td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>69.5 (19.8) [66.3-72.5]</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>66.3 (9.1) [64.9-67.7]</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>111.1 (13.1) [109.0-113.1]</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>77.6 (12.4) [75.6-79.5]</td>
</tr>
<tr>
<td>Corrected QT interval, ms</td>
<td>413.9 (18.4) [411.1-416.8]</td>
</tr>
</tbody>
</table>

*Venlafaxine vs selective serotonin reuptake inhibitor; t = 2.88; P = .004.*
possible that with a higher dose, we might have been able to achieve a larger effect. The Treatment of Adolescent Depression Study found the strongest advantage for combined treatment over medication alone in less severe depression.\textsuperscript{70} Our results extend the Treatment of Adolescent Depression Study findings to a more chronically depressed, treatment-resistant population.

Different Results for Clinical Response and Random Effects Regression

While a greater proportion of participants who received CBT were rated as clinically improved, there were no parallel treatment effects found on any of the scalar measures of outcome. This is because CBT had a modest effect and did not affect the speed of improvement, which is what is being tested in random effects regression analyses of scalar measures. In one study of adults with chronic depression that delivered nearly twice the number of CBT sessions that participants received in TORDIA, a combination of psychotherapy and antidepressant administration did result in a more rapid decline in depressive symptoms.\textsuperscript{29}

Choice of a Second-Line Medication

Contrary to our hypothesis, venlafaxine was not superior to the option of switching to another SSRI. In the Sequenced Treatment Alternatives to Relieve Depression study, it was also found that participants who did not respond to citalopram were just as likely to remit with a switch to a second SSRI (sertraline, 17.6\%) as to a switch to venlafaxine (24.8\%).\textsuperscript{30} While earlier studies of treatment-resistant depression reported as much as a 19\% difference in response rate between venlafaxine and other antidepressants,\textsuperscript{23} more recent meta-analyses have found either no difference or very modest advantages (ie, 5\%-7\%) in response and remission rates over SSRI medications.\textsuperscript{23,24} Differences that are much smaller than could be reliably detected with our sample sizes.

The slightly higher rate of cardiovascular effects associated with venlafaxine and the relatively modest treatment effects of venlafaxine in adolescent depression (albeit at lower doses than used in TORDIA), support the choice of another SSRI over venlafaxine as a second-line antidepressant.\textsuperscript{73-77}

Sleep Medication and Clinical Response

The use of sleep medication was associated with a poorer response rate to treatment. It is unclear if this finding is attributable to clinical features of those who received hypnotics, incomplete treatment of sleep difficulties, or an interaction between hypnotic and antidepressant medications. Disrupted sleep predicts onset and recurrence of depression, and in one study, a poorer response to CBT.\textsuperscript{78,79} These results highlight the need to better assess and manage sleep difficulties in adolescents with depression.

Site Effects

The effect of CBT, while significant in the aggregate, was quite variable across sites. However, the overall effect of CBT was robust to sensitivity analyses and also persisted even after controlling for site and CBT by site interactions. In a separate manuscript, we plan to examine the sources of variability in CBT performance, both related to quality control and the substantial site differences in clinical variables that are likely to predict differential treatment outcomes (A.S., K.A., and S.I., unpublished data, 2007).\textsuperscript{67-69,70}

Effect on Suicidal Behavior

We found no advantage of the combination of CBT and medication over medication alone on the incidence of suicidal adverse events, findings which are similar to one other large study of combined treatment in adolescents with depression.\textsuperscript{31} In contrast, the Treatment of Adolescent Depression Study group found a trend toward the combination of CBT and medication being protective against the occurrence of suicidal events.\textsuperscript{80} Our results might diverge from Treatment of Adolescent Depression Study because in TORDIA, participants had higher suicidality at intake, experienced a greater number of suicidal events, and were subject to more intense and frequent safety monitoring. Other studies have also shown that reductions in depression and in suicidal behavior do not necessarily correlate, supporting the need for further treatment development that targets the prevention of suicidal behavior.\textsuperscript{81,82}

Clinical Implications

On the basis of these findings, CBT-naive adolescents with chronic, treatment-resistant depression will be more likely to respond to the combination of CBT and a switch in antidepressant medication than to a switch in medication alone. Even in participants who did not receive CBT, 40% improved after enduring an average of 2 years of unremitting depression. Assuming that approximately half of adolescents with depression will respond to an initial treatment, the rate of response in our study is consistent with the relatively high cumulative response rate reported in those adults with depression in the Sequenced Treatment Alternatives to Relieve Depression study, who continued to pursue additional treatment steps.\textsuperscript{26} Therefore, the clinician should convey hope to the adolescent with depression and his or her family that, despite a first unsuccessful treatment for depression, persistence with additional appropriate interventions can result in substantial clinical improvement.

Author Contributions:

Dr Brent had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Brent, Emslie, Clarke, Wagner, Asarnow, Keller, Iyengar, Birmaher, Ryan, Kennard, Hughes, DeBar, McCracken, Strober, Leonard. Acquisition of data: Brent, Emslie, Clarke, Wagner, Asarnow, Keller, Ritz, Birmaher, Ryan, Kennard, Hughes, McCracken, Strober, Suddath, Spinto, Leonard, Onorato, Zelazny. Analysis and interpretation of data: Brent, Emslie, Clarke, Wagner, Asarnow, Keller, Vitiello, Iyengar, Abebe, Ryan, Kennard, Hughes, Suddath, Leonard, Melhem, Porta. Drafting of the manuscript: Brent, Suddath, Spinto, Leonard, Porta. Critical revision of the manuscript for important intellectual content: Brent, Emslie, Clarke, Wagner, Asarnow, Keller, Vitiello, Ritz, Iyengar, Abebe, Ryan, Kennard, Hughes, Suddath, Leonard, Melhem, Porta.
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Birmacher, Ryan, Kennard, Hughes, DeBar, McCracken, Strecker, Leonard, Melhorn, Onorato, Zelazny.

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REFERENCES


