Fluoxetine, Cognitive-Behavioral Therapy, and Their Combination for Adolescents With Depression

Treatment for Adolescents With Depression Study (TADS) Randomized Controlled Trial

Treatment for Adolescents With Depression Study (TADS) Team

Context Initial treatment of major depressive disorder in adolescents may include cognitive-behavioral therapy (CBT) or a selective serotonin reuptake inhibitor (SSRI). However, little is known about their relative or combined effectiveness.

Objective To evaluate the effectiveness of 4 treatments among adolescents with major depressive disorder.

Design, Setting, and Participants Randomized controlled trial of a volunteer sample of 439 patients between the ages of 12 to 17 years with a primary *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, diagnosis of major depressive disorder. The trial was conducted at 13 US academic and community clinics between spring 2000 and summer 2003.

Interventions Twelve weeks of (1) fluoxetine alone (10 to 40 mg/d), (2) CBT alone, (3) CBT with fluoxetine (10 to 40 mg/d), or (4) placebo (equivalent to 10 to 40 mg/d). Placebo and fluoxetine alone were administered double-blind; CBT alone and CBT with fluoxetine were administered unblinded.

Main Outcome Measures Children's Depression Rating Scale-Revised total score and, for responder analysis, a (dichotomized) Clinical Global Impressions improvement score.

Results Compared with placebo, the combination of fluoxetine with CBT was statistically significant ($P=.001$) on the Children's Depression Rating Scale-Revised. Compared with fluoxetine alone ($P=.02$) and CBT alone ($P=.01$), treatment of fluoxetine with CBT was superior. Fluoxetine alone is a superior treatment to CBT alone ($P=.01$). Rates of response for fluoxetine with CBT were 71.0% (95% confidence interval [CI], 62%-80%); fluoxetine alone, 60.6% (95% CI, 51%-70%); CBT alone, 43.2% (95% CI, 34%-52%); and placebo, 34.8% (95% CI, 26%-44%). On the Clinical Global Impressions improvement responder analysis, the 2 fluoxetine-containing conditions were statistically superior to CBT and to placebo. Clinically significant suicidal thinking, which was present in 29% of the sample at baseline, improved significantly in all 4 treatment groups. Fluoxetine with CBT showed the greatest reduction ($P=.02$). Seven (1.6%) of 439 patients attempted suicide; there were no completed suicides.

Conclusion The combination of fluoxetine with CBT offered the most favorable tradeoff between benefit and risk for adolescents with major depressive disorder.

JAMA. 2004;292:807-820 www.jama.com

MAJOR DEPRESSIVE DISORDER (MDD) in adolescence is common—the point prevalence is 1 in 20—and is associated with significant morbidity and family burden.[1,2] Depression also is an important contributor to adolescent suicidal behavior and to completed suicide,[3,4] which is the third leading cause of death among adolescents.[5] Furthermore, depression in adolescence is a major risk factor for MDD, suicide, and long-term psychosocial impairment in adulthood.[6] Thus, improvements in the treatment of MDD among adolescents should positively affect public health.

When the Treatment for Adolescents With Depression Study (TADS) was designed in 1998, empirical literature supported cognitive-behavioral therapy (CBT) as a treatment for MDD in youth,[7] with both behavioral[8] and cognitive[9] approaches well represented.[10] In contrast, Emslie et al's[11] randomized controlled trial comparing fluoxetine with placebo, along with the lack of favorable efficacy data for the tricyclic antidepressants,[12] formed the sole empirical basis for the TADS pharmacotherapy condition. Although the fluoxetine results were subsequently replicated,[13] which lead to approval from the Food and Drug Administration of fluoxetine for MDD in youth—the only medication so recognized—meta-analyses of antidepressant trials for MDD in children and adolescents tell a mixed story regarding benefits and risks of medica-

For editorial comment see p 861.

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tion management.[14,15] Given that antidepressants are widely used as first-line treatments for depressed youth,[16] it seemed critical then (and even more so now) that rapid replication of the efficacy studies of CBT and fluoxetine be performed in an effectiveness sample of depressed adolescents.

Response rates for CBT and medication in previous studies are approximately 60%, leaving substantial room for improvement in treatment outcomes. In adults, the combination of CBT with medication may lead to greater improvement in depression than monotherapy with either treatment.[17-19] Although combined treatment is frequently recommended by experts, especially for more severely ill patients,[20,21] the relative efficacy of CBT and medication, alone and in combination, for depressed adolescents is unknown. It also is not clear which patients might benefit most from combined treatment.

TADS is a multicenter, randomized, clinical trial designed to evaluate the effectiveness of treatments for adolescents with MDD.[22] Stage 1 compares randomly assigned groups receiving 12-week treatment with (1) fluoxetine alone, (2) CBT alone, (3) fluoxetine with CBT, or (4) placebo. Placebo and fluoxetine alone were administered double-blind, while CBT alone and fluoxetine with CBT were administered unblinded. Blinding for the primary dependent measures was maintained by means of an independent evaluator.

The specific aims of the study, the design, and the rationale for choices made, the required sample size calculations, and the methods used are detailed elsewhere.[22] The demographic and clinical characteristics of the sample and the external validity relative to epidemiological and treatment-seeking samples have also been published.[23] The intent-to-treat effectiveness and safety outcomes for stage 1 of TADS are presented herein.

METHODS

Participants

A volunteer sample of 439 patients with a primary *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*[24] *(DSM-IV)*, diagnosis of MDD entered the study between spring 2000 and summer 2003. Patients were recruited without regard to sex, race, or ethnicity from (1) clinics; (2) paid and public service advertisements in newspapers and on the radio and TV; (3) primary care physicians; (4) other mental health clinicians; and (5) schools and juvenile justice facilities at 13 academic and community clinics. All patients and at least one of their parents provided written informed consent. The Duke University Medical Center (Durham, NC) and the institutional review boards at each site approved and monitored the protocol; TADS was monitored quarterly by the data safety and monitoring board of the National Institute of Mental Health (Bethesda, Md).

Inclusion criterion were age of 12 to 17 years (inclusive); ability to receive care as an outpatient; a *DSM-IV* diagnosis of MDD at consent and again at baseline; a Children's Depression Rating Scale-Revised[25] (CDRS-R) total score of 45 or higher at baseline; a full-scale IQ of 80 or higher; and not taking antidepressant(s) prior to consent. Depressive mood had to have been present in at least 2 of 3 contexts (home, school, among peers) for at least 6 weeks prior to consent. Concurrent stable psychostimulant treatment (eg, methylphenidate or mixed amphetamine salts) for attention-deficit/hyperactivity disorder was permitted.

Exclusion criterion were current or past diagnosis of bipolar disorder, severe conduct disorder, current substance abuse or dependence, pervasive developmental disorder(s), thought disorder, concurrent treatment with psychotropic medication or psychotherapy outside the study, 2 failed selective serotonin reuptake inhibitor (SSRI) trials, a poor response to clinical treatment containing CBT for depression, intolerance to fluoxetine, confounding medical condition, non-English speaking patient or parent, and/or pregnancy or refusal to use birth control. No patients were asked or required to discontinue other forms of psychiatric treatment to enter the study.

Patients were excluded for dangerousness to self or others if they had been hospitalized for dangerousness within 3 months of consent or were deemed by a cross-site panel to be "high risk" because of a suicide attempt requiring medical attention within 6 months, clear intent or an active plan to commit suicide, or suicidal ideation with a disorganized family unable to guarantee adequate safety monitoring.

Randomization and Blinding

Eligible patients were randomly assigned to fluoxetine alone, CBT alone, fluoxetine with CBT, or placebo using a computerized stratified randomization, a 1:1:1:1 treatment allocation ratio, permuted blocking (first block size=4, with subsequent random block sizes of 4 and 8) within each stratum, and site and sex as stratification variables. Except in emergencies, participants and clinicians remained blind in the fluoxetine alone and placebo treatment groups. Patients and clinicians were aware that participants in the fluoxetine with CBT group received active medicine and that participants in the CBT alone group did not receive medication. As is necessary in efficacy studies comparing psychosocial and pharmacological interventions, masking was maintained for the primary dependent measures by means of independent evaluators blind to treatment assignment. Except at assessments, independent evaluators were physically isolated from patients, data, and treating clinicians. Specific instructions were provided to the parents, participants, and the independent evaluator not to disclose treatment assignment.

Interventions

Treatments were designed to meet best practice standards and were performed according to instruction manuals to allow ready dissemination (if warranted) in clinical practice at the conclusion of the trial.[22]

Patients had only one pharmacotherapist throughout the study. In ad-

dition to monitoring clinical status and medication effects during six 20- to 30-minute medication visits spread across 12 weeks of treatment, the pharmacotherapist offered general encouragement about the effectiveness of pharmacotherapy for MDD. Using a flexible dosing schedule dependent on pharmacotherapist-assigned Clinical Global Impressions[26] (CGI) severity score and the ascertainment of clinically significant adverse events, doses of placebo and fluoxetine began at a starting dose of 10 mg/d, which was then increased to 20 mg/d at week 1 and, if necessary, to a maximum of 40 mg/d by week 8.

In TADS, CBT is a skills-oriented treatment based on the assumption that depression is either caused by or maintained by depressive thought patterns and a lack of active, positively reinforcing behavioral patterns; treatment included 15 sessions, which lasted between 50 and 60 minutes, over the first 12 weeks.[27,28] In this context, the approach taken for CBT required skill-building and optional or modular sessions, which allowed flexible tailoring of the treatment to the adolescent's needs in a developmentally sensitive fashion and integrated parent and family sessions with individual sessions. The required aspects of treatment (weeks 1-6 or longer if necessary) included psychoeducation about depression and its causes, goal-setting with the adolescent, mood monitoring, increasing pleasant activities, social problem-solving, and cognitive restructuring. Subsequently, modules chosen jointly by the therapist and adolescent during weeks 7 through 12 addressed relevant social skill deficits of the adolescent, such as problems in social engagement, communication, negotiation, compromise, or assertion. Two parent-only sessions provided psychoeducation about depression and, depending on need, 1 to 3 conjoint parent and adolescent sessions focused on addressing parent and adolescent concerns.

Treatment combining fluoxetine with CBT contained all of the components from both the medication alone and CBT alone groups. To allow limited integration between CBT and medication management, CBT was functionally independent of medication management (ie, no decisions regarding the CBT protocol depended on decisions about medication management). Second, the protocols for administering medication and CBT were functionally independent for all medication increases other than those depending on the presence of partial response. Third, when partial response was present, the pharmacotherapist in consultation with the CBT therapist evaluated compliance with CBT, the overall change trajectory, and the adverse event profile when considering whether to adjust the dose of fluoxetine.

Diagnostic and Outcome Measures

The diagnosis of MDD and associated comorbidities at baseline were established using the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version,[29] which was administered by the same independent evaluator who rated the primary dependent measures.

Two primary outcome measures were chosen a priori: the scalar CDRS-R total score, which is based on a synthesis of information collected from interviewing both the adolescent and the parent,[25] and an end-of-treatment CGI improvement score[26] (defined as much improved or very much improved). Both outcome measures were assessed by the independent evaluator at baseline, week 6, and week 12. Data is also presented herein from the Reynolds Adolescent Depression Scale (RADS),[30] which is an adolescent self-report measure of depression that was included because of the prominent place accorded adolescent self-report in the CBT literature.[7] The Suicidal Ideation Questionnaire-Junior High School Version (SIQ-Jr),[31] which is a self-reported measure of suicidal ideation, also was included to clarify the ratio of benefit to harm. Psychometric properties and intercorrelations for all measures are presented elsewhere.[23]

Independent evaluators were clinicians with either master or doctorate degrees, with experience administering research-related structured clinical interviews with depressed patients or adolescent psychiatric patients or, in most cases, both. Quality assurance procedures and reliability of the baseline assessments are documented elsewhere.[22,23] For the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version diagnostic criteria of the *DSM-IV* for MDD, 94.1% of the reviewed interviews met the criterion of at least 80% agreement between the 2 raters. The intraclass correlation coefficient for the total number of MDD symptoms present was 0.80. The intraclass correlation coefficient for the 14-item CDRS-R total score at baseline was 0.95, suggesting excellent interrater reliability for both measures. The intraclass correlation coefficient for the 14-item CDRS-R total score during stage 1 of treatment was 0.95, again suggesting excellent interrater reliability on the primary dependent measure.

Safety Assessments

To ensure patient safety, evaluate the tolerability of treatment, and to minimize the potential for cross-site differences in protocol delivery, integrated procedures were used for adverse event monitoring and adjunctive services and attrition prevention.[22] An *adverse event* was defined as any unfavorable medical change occurring postrandomization that was accompanied by functional or clinical impairment. An adverse event may or may not be related to or caused by the study drug or CBT treatment. A functional threshold on adverse event reporting was imposed, specifying that an adverse event must (1) cause clinically significant interference with functioning, (2) require medical attention, or (3) be associated with any impairment in functioning and cause the patient to take a concomitant medication. A *harm-related adverse event* was defined as involving harm to self, which can include a nonsuicidal event, such as cutting for relief of dysphoric affects, worsening of suicidal ideation with-

out self-harm, or a suicide attempt of any lethality; or harm to others, which includes aggressive or violent ideation or action against another person or property. A *suicide-related adverse event* requires that the patient exhibit either worsening suicidal ideation or make a suicide attempt, or both. Harmful behaviors without suicidal ideation or intent, such as some instances of cutting, are not included in the definition of a suicide-related adverse event. Reporting of an adverse event does not include preexisting conditions or illnesses that do not worsen in severity or increase in frequency during the study period.

Sample Size and Power Estimates

The primary end point used in the sample size estimate was treatment response rate, which was defined as a CGI improvement score of 1 (very much improved) or 2 (much improved), assigned by the independent evaluator. Using a χ^2 statistic, power estimates for detecting differences in treatment response in the 4 groups were then computed using the following assumptions: (1) H_a: $P_{(fluoxetine)}=.60$, $P_{(CBT)}=.60$, $P_{(fluoxetine\ with\ CBT)}=.80$, and $P_{(placebo)}=.40$; (2) no adjustment for loss to follow-up; (3) no adjustment for multiple comparisons; and (4) α level of .05 for a 2-tailed test. Under these assumptions, 108 patients per treatment group (N=432) were needed to achieve 80% or greater power to detect a difference of .20 in response rates between any 2 treatment groups.

Statistical Methods

Data entry and verification, data transfer, confidentiality and security, back-up and storage, and data analyses were conducted under the direction of the principal investigator and the principal statistician. All effectiveness and safety analyses were conducted using an intent-to-treat principle in which the analysis included all randomized patients in the treatment groups to which they were randomly assigned, regardless of their protocol adherence, actual treatment received, and/or subsequent withdrawal from treatment, assessments, or deviations from protocol.[32]

Statistical analyses on the primary outcome measure using CDRS-R scores were conducted using a linear random coefficient regression model.[33-35] Consistent with an intent-to-treat approach, random regression permits estimation of changes in continuous repeated measures in the presence of missing data on both a population and participant-specific level without necessitating last observation carried forward or exclusion of participants with missing data.[33-35] Specifically, the impact of treatment on outcome was modeled as a linear function of fixed effects for treatment, time (defined as the natural log of days since baseline+1), and treatment-by-time interaction and random effects for participant and clinical site, including all 2- and 3-way interactions in the initial model. Clinical site and its interaction effects were fitted in the model as random effects. Although site was retained in the model, the site interaction terms were omitted because they accounted for a minimal amount of the overall variance and their omission did not alter the outcome.[35] Under the assumption of random intercepts and slopes for each patient, the overall and treatment group-specific rate of change for the 4 treatment groups for the primary CDRS-R outcome were examined. Pairwise comparisons on treatment slopes (linear trends with time) were then conducted. Supplemental between-treatment contrast analyses also were conducted on the adjusted week 12 means. Identical analyses were performed on secondary measures assessing self-reported adolescent depression (RADS) and suicidal ideation (SIQ-Jr).

Responder rates based on the dichotomized end-of-treatment CGI improvement score for each treatment group were compared using a logistic regression model for the last available assessment point (last observation carried forward) with site as a covariate. The Wald χ^2 test results and adjusted odds ratios (ORs) derived from the regression analysis provided pairwise comparisons of the treatment effects. Generalized linear models and tests for differences in proportions (χ^2 and Fisher exact tests) were performed to evaluate differences across treatment groups at baseline. The rate of harm- and suicide-related adverse events in each treatment group were compared using χ^2 and Fisher exact tests, with ORs calculated to provide an indicator of relative risk of active treatment to the placebo or a control condition.

For hypotheses stipulated in the statistical plan for the 2 primary outcomes, the nominal significance level was set a priori at a 2-tailed type I error rate of .05 for the omnibus tests designed to compare all 4 treatment groups. If the treatment or treatment-by-time interaction term was significant, then pairwise comparisons were conducted using a closed test procedure with an α level of .05 for each test. In the event of a nonsignificant omnibus result, a sequential rejective approach was planned to safeguard against type I error.[36] Because adverse events were rare and the study was not powered for their detection, the sequential rejective method was not applied to adverse event reporting.

To evaluate the clinical significance of the impact of treatment on outcome, effect sizes (Hedge g) were calculated as $M_E - M_C/SD_{pooled}$, where M_E represents the adjusted mean of experimental treatment, M_C represents the adjusted mean of the comparison treatment, and SD_{pooled} represents pooling of the SDs from within both groups.[37] The *number needed to treat* was defined as the number of patients who need to be treated to bring about one additional good outcome and was calculated according to methods outlined by Sackett et al.[38]

Analyses were conducted using SAS statistical software (version 8.2, SAS Institute Inc, Cary, NC) with PROC MIXED used for the random regression analyses.[39]

RESULTS

Patient Disposition

A total of 2804 patients were screened by telephone (FIGURE 1). Of these, 1088

signed consent for evaluation of inclusion and exclusion criteria and 439 were randomized to treatment and baseline assessment. Of those randomized, 56% learned of the study via an advertisement; the remainder were recruited via clinical or self-referral. The most frequent reasons for exclusion were prohibited psychotropic medication use (8.8%), did not meet criteria for MDD (17.5%), MDD not stable and pervasive (11.7%), or missed more than 25% of school days in previous 2 months (13.2%). Of those excluded, 1.6% had not improved with clinical treatment during a previous fluoxetine trial or were intolerant to fluoxetine; 1.1% had not improved with clinical treatment during 2 previous SSRI trials; and 0.8% had not improved with clinical treatment during of a CBT trial.

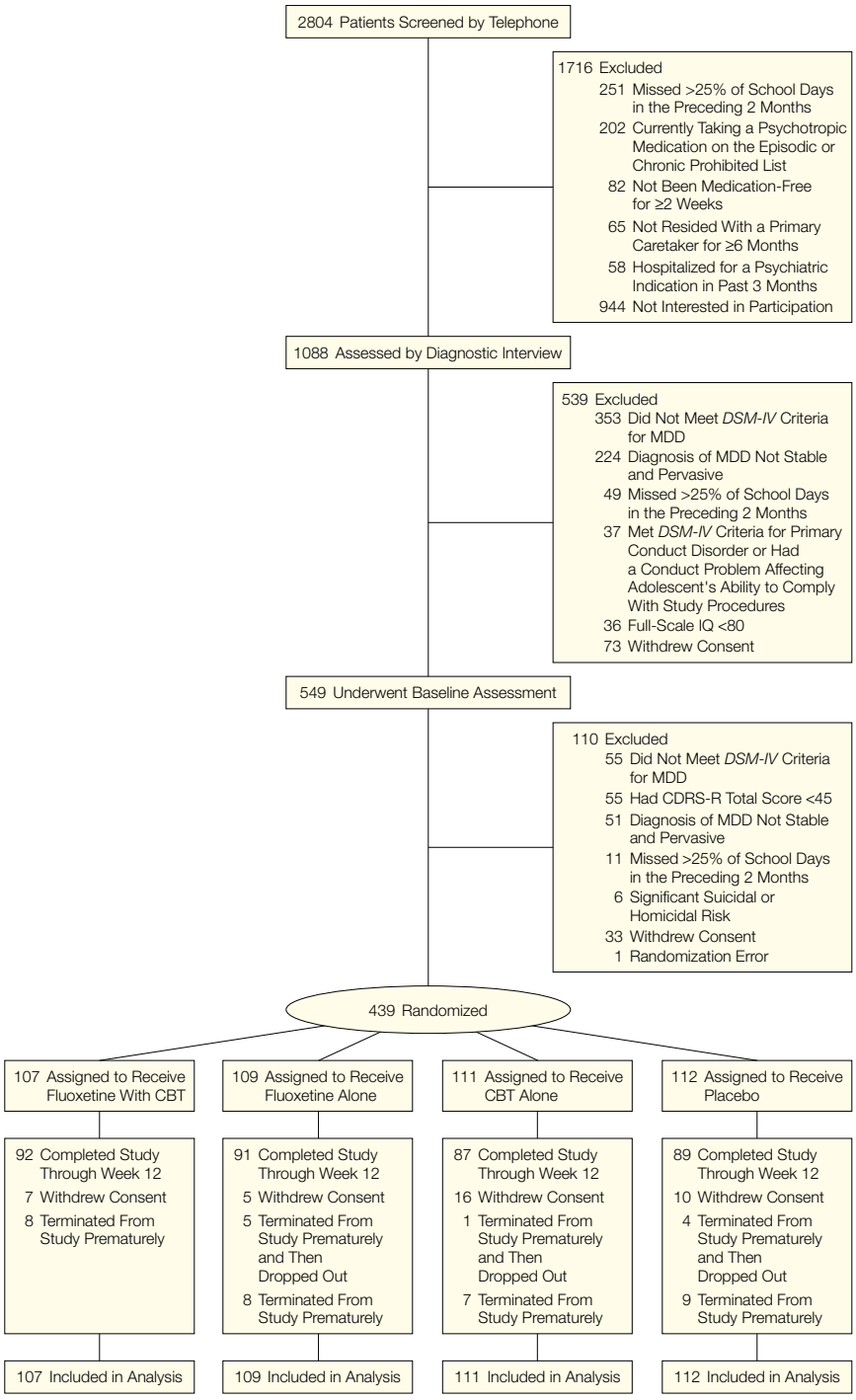
Of the 439 analyzable patients, 411 (94%) of the sample had at least 1 post-baseline CDRS-R data point. Forty-eight patients (10.9%) withdrew consent prior to week 12. Another 42 patients (9.6%) were terminated prematurely by the TADS team because they required an out-of-protocol treatment in place of or in addition to study treatment. Thus, 359 patients (82%) remained and 351 (80%) were assessed in their assigned treatment group at week 12. Treatment assignment did not influence the probability of dropping out ($P=.18$) or premature termination ($P=.50$).

Of the possible 15 sessions, the mean (median) number of completed CBT sessions was 11 (12) in both the in the CBT alone group and the CBT with fluoxetine group. The mean (SD) highest dose of fluoxetine was 28.4 (8.6) mg/d in the fluoxetine with CBT group; 33.3 (10.8) mg/d for the fluoxetine alone group; and 34.1 (9.5) mg/d for the placebo group.

Demographic and Clinical Characteristics

Participants resemble adolescents with MDD seen in general clinical practice (TABLE 1). The mean (SD) age was 14.6 (1.5) years; 45.6% of the sample was male; 73.8% was white; 12.5% was

Figure 1. Flow Diagram of Treatment for Adolescents With Depression Study



CBT indicates cognitive-behavioral therapy; CDRS-R, Children's Depression Rating Scale-Revised; *DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; MDD, major depressive disorder. The top 5 exclusionary reasons are listed for patients who were screened but were not assessed by diagnostic interview and for patients who underwent baseline assessment but were not randomized. Adolescents may have been included in more than one exclusionary category. The randomization error refers to a patient who was randomized but who should have been excluded according to the specified exclusionary criteria. This person was not included in the analysis, but was treated based on the recommendation by the TADS Scientific Advisory Board.

black; and 8.9% was Hispanic (includes black and white Hispanics). Race and ethnicity were self-classified. With a range of mild (CDRS-R total score of 45) to severe depression (CDRS-R total score of 98), the mean (SD) CDRS-R raw score at entry was 60 (10.4), which translates to a normed *t* score (standardized to a mean [SD] of 50 [10]) of 76 (6.43), indicating moderate to moderately severe MDD. This level of depression is consistent with a mean (SD) CGI severity score of 4.77 (0.83) and a CGAS score of 49.6 (7.5). Eighty-six percent of patients experienced only 1 episode of depression, with a median (range) duration of 40.0 (3-572) weeks. More than half the sample (52.1%) was comorbid for at least 1 other psychiatric disorder. Sixty (13.67%) of 439 patients met *DSM-IV* criteria for ADHD and, of these, 21 (4.8%) took an approved psychostimulant. The modal family income was between $50 000 and $74 000, with a range of less than $5000 to more than $200 000. Forty-one percent lived in a single-parent home; 27% had been suspended or expelled from school. No statistically significant differences between the 4 treatment groups on any baseline characteristic were noted.

Effectiveness Outcomes

TABLE 2 presents the intent-to-treat CDRS-R adjusted mean (SD) total scores by treatment group; CDRS-R adjusted mean scores for site are depicted graphically in FIGURE 2A. Random regression analyses on longitudinal CDRS-R score identified a statistically significant linear trend with time ($F_{1,382}=1066$; $P=.001$) and a time-by-treatment interaction ($F_{3,381}=9.08$; $P=.001$). Planned contrasts on the CDRS-R slope coefficients across 12 weeks of treatment produced a statistically significant ordering of outcomes. Specifically, fluoxetine with CBT ($P=.001$) was statistically significant compared with placebo, whereas treatment with fluoxetine alone ($P=.10$) and CBT alone ($P=.40$) were not. Fluoxetine with CBT was superior to fluoxetine alone ($P=.02$) and to CBT alone ($P=.001$). Despite failure to separate from placebo, fluoxetine alone also was superior to CBT alone ($P=.01$). Supportive contrasts performed on the week 12 adjusted means yielded a slightly different result. Specifically, fluoxetine with CBT ($P=.001$) and fluoxetine alone ($P=.002$) proved superior to placebo whereas CBT alone did not ($P=.97$). Fluoxetine with CBT was superior to CBT alone ($P=.001$), but not to fluoxetine alone ($P=.13$), whereas fluox-

Table 1. Baseline Values by Treatment Group

Variable	CBT With Fluoxetine	Fluoxetine Alone	CBT Alone	Placebo	Total	*P* Value
Characteristics for Depression, Suicidality, and Functioning[a]						
No. of persons randomized	107	109	111	112	439	
Children's Depression Rating Scale-Revised						
Raw score[b]	60.75 (11.58)	58.96 (10.16)	59.58 (9.21)	61.11 (10.50)	60.10 (10.39)	.38
T score[c]	75.67 (6.53)	74.73 (6.74)	75.37 (6.32)	76.14 (6.11)	75.48 (6.43)	.43
Clinical Global Impressions severity score[d]	4.79 (0.85)	4.66 (0.85)	4.77 (0.76)	4.84 (0.84)	4.77 (0.83)	.43
Children's Global Assessment Scale score[e]	49.95 (7.52)	49.49 (7.26)	50.01 (7.58)	49.13 (7.59)	49.64 (7.47)	.79
Reynolds Adolescent Depression Scale total score[f]	79.91 (13.68)	77.00 (14.67)	78.83 (14.97)	81.20 (13.94)	79.24 (14.35)	.18
Suicidal Ideation Questionnaire-Junior High School Version total score, median (range)[g]	17.5 (0-89)	17.0 (0-79)	15 (0-85)	16.5 (0-84)	16.0 (0-89)	.57[h]
Current major depressive episode duration, median (range), wk	48.0 (3-456)	38.0 (6-572)	52.0 (4-330)	35.5 (4-357)	40.0 (3-572)	.28[h]
Comorbidity at Baseline by Treatment Group[i]						
Comorbidity						
Any psychiatric, No. (%)[j]	59 (55.66)	47 (43.12)	64 (58.18)	57 (51.35)	227 (52.06)	.13
Amount, median (range)	1.0 (0-5)	0 (0-5)	1.0 (0-5)	1.0 (0-5)	1.0 (0-5)	.50[h]
Dysthymia, No. (%)	11 (10.28)	6 (5.50)	17 (15.45)	12 (10.71)	46 (10.50)	.12
Type of disorder, No. (%)						
Anxiety	30 (28.04)	26 (23.85)	36 (32.43)	28 (25.23)	120 (27.40)	.50
Disruptive behavior	23 (21.50)	25 (22.94)	27 (24.32)	28 (25.00)	103 (23.46)	.93
Obsessive-compulsive/tic	4 (3.74)	2 (1.83)	2 (1.80)	4 (3.57)	12 (2.73)	.73[k]
Substance use	3 (2.80)	3 (2.75)	1 (0.90)	0	7 (1.59)	.23[k]
Attention-deficit/hyperactivity	14 (13.08)	13 (11.93)	14 (12.61)	19 (16.96)	60 (13.67)	.70
Taking medications	4 (3.74)	3 (2.75)	4 (3.60)	10 (8.93)	21 (4.78)	.12[k]

Abbreviation: CBT, cognitive-behavioral therapy.
[a]Values are expressed as mean (SD) unless otherwise indicated. For mean (SD) data, *P* values are for 1-way analysis of variance using a general linear model unless otherwise indicated.
[b]The range for possible scores is 17 to 113.
[c]The range for possible scores is 30 to 85.
[d]The range for possible scores is 1 to 7.
[e]The range for possible scores is 1 to 100.
[f]The range for possible scores is 30 to 120.
[g]The range for possible scores is 0 to 90.
[h]Nonparametric Kruskal-Wallis test.
[i]Values are expressed as number (percentage) unless otherwise indicated. For number (percentage) data, *P* values are for the χ^2 test unless otherwise indicated.
[j]Refers to the presence of 1 or more coexisting psychiatric disorder, including dysthymia.
[k]Fisher exact test.

etine alone proved superior to CBT alone ($P=.001$).

With a positive response defined as a CGI improvement score of 1 (very much improved) or 2 (much improved), rates of response adjusted for clinical site were 71.0% (95% CI 62%-80%) for fluoxetine with CBT; 60.6% (95% CI, 51%-70%) for fluoxetine alone; 43.2% (95% CI, 34%-52%) for CBT alone; and 34.8% (95% CI, 26%-44%) for placebo. When clinical site and treatment were entered in the logistic regression model, the effect of the clinical site was nonsignificant (Wald $\chi^2=.14$; $P=.71$), whereas treatment was statistically significant (Wald $\chi^2=33.9$; $P=.001$). Planned pairwise contrasts indicated that fluoxetine with CBT ($P=.001$) and fluoxetine alone ($P=.001$) were superior to placebo whereas CBT alone was not ($P=.20$). Fluoxetine with CBT and fluoxetine alone did not differ statistically ($P=.11$). Both fluoxetine with CBT ($P=.001$) and fluoxetine alone ($P=.01$) proved superior to CBT alone.

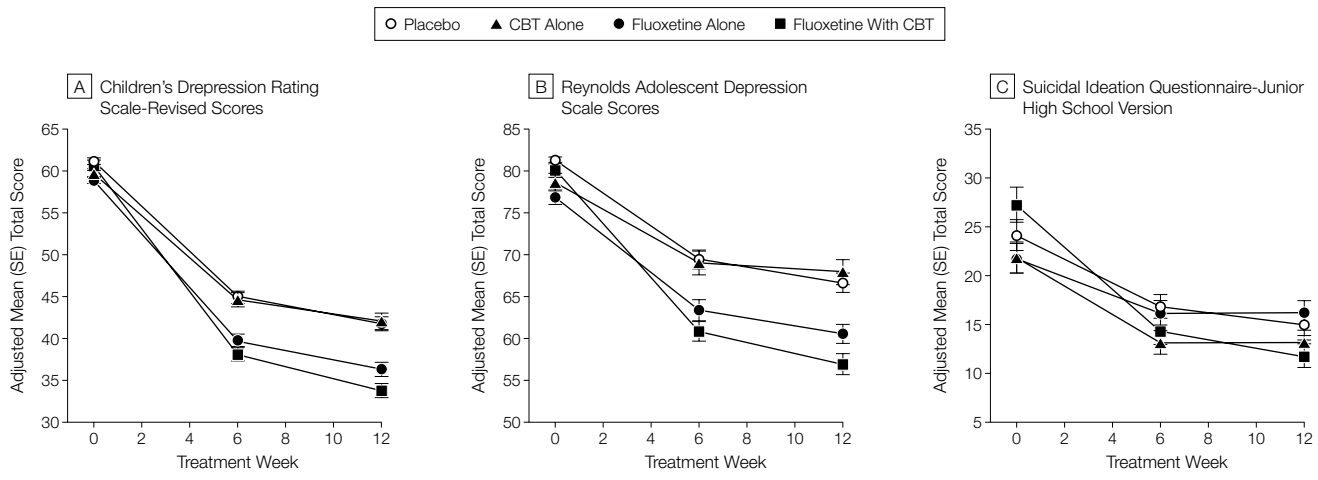
The adjusted mean (SD) total scores on the RADS for the intent-to-treat sample broken out by treatment group are presented in Table 2 and depicted graphically in Figure 2B. Random regression analyses on longitudinal RADS total score identified a statistically significant linear trend with time ($F_{1,380}=471.41$; $P=.001$) and a time-by-treatment interaction ($F_{3,380}=10.32$; $P=.001$). Planned contrasts on the RADS slope coefficients produced a statistically significant ordering of outcomes that was identical to that found on the CDRS-R. Specifically, fluoxetine with CBT ($P=.001$) proved statistically superior to placebo whereas fluoxetine alone ($P=.34$) and CBT alone

Table 2. Changes in Total Scores Across 12 Weeks of Treatment

	Adjusted Mean (SD)*		
	Baseline	Week 6	Week 12
CBT with fluoxetine			
Children's Depression Rating Scale-Revised clinician total score	60.79 (4.85)	38.10 (7.78)	33.79 (8.24)
Reynolds Adolescent Depression Scale total score	80.12 (9.23)	60.90 (11.59)	56.95 (12.24)
Suicidal Ideation Questionnaire-Junior High School Version total score	27.33 (18.51)	14.31 (12.58)	11.79 (11.69)
Fluoxetine alone			
Children's Depression Rating Scale-Revised clinician total score	58.94 (4.00)	39.80 (7.37)	36.30 (8.18)
Reynolds Adolescent Depression Scale total score	76.96 (9.57)	63.41 (12.44)	60.58 (13.07)
Suicidal Ideation Questionnaire-Junior High School Version total score	21.81 (15.68)	16.20 (12.42)	14.44 (11.13)
CBT alone			
Children's Depression Rating Scale-Revised clinician total score	59.64 (4.52)	44.63 (8.30)	42.06 (9.18)
Reynolds Adolescent Depression Scale total score	78.69 (10.59)	69.10 (13.59)	67.96 (14.18)
Suicidal Ideation Questionnaire-Junior High School Version total score	21.91 (16.28)	13.18 (11.34)	11.40 (10.44)
Placebo			
Children's Depression Rating Scale-Revised clinician total score	61.18 (4.27)	44.90 (7.32)	41.77 (7.99)
Reynolds Adolescent Depression Scale total score	81.26 (9.22)	69.43 (10.94)	66.68 (11.41)
Suicidal Ideation Questionnaire-Junior High School Version total score	24.20 (16.46)	16.85 (11.70)	15.01 (11.05)

Abbreviation: CBT, cognitive-behavioral therapy.
*Means are for predicted individual scores that have been adjusted for both fixed (treatment and time) and random (participant and site) effects derived from the linear random coefficient model.

Figure 2. Adjusted Mean (SE) Scale Scores for Participants in the Treatment for Adolescents With Depression Study



CBT indicates cognitive-behavioral therapy. Means are for predicted individual scores that have been adjusted for both fixed (treatment and time) and random (participant and site) effects derived from the linear random coefficient model.

(*P*=.21) did not. Fluoxetine with CBT was superior to fluoxetine alone (*P*=.002) and to CBT alone (*P*=.001). Despite failure to separate from placebo, fluoxetine alone also was superior to CBT alone (*P*=.03). Supportive contrasts performed on the week 12 adjusted means also followed the pattern established on the CDRS-R. Specifically, fluoxetine with CBT (*P*=.001) and fluoxetine alone (*P*=.003) proved superior to placebo whereas CBT alone did not (*P*=.94). Fluoxetine with CBT was superior to CBT alone (*P*=.001), but not to fluoxetine alone (*P*=.11), whereas fluoxetine alone again proved superior to CBT alone (*P*=.003).

The clinical significance (magnitude) of the impact of treatment on outcome was evaluated by calculating effect sizes (Hedge *g*) and the number needed to treat relative to placebo. The effect size on the CDRS-R was 0.98 for fluoxetine with CBT, 0.68 for fluoxetine alone, and –0.03 for CBT alone. Effect sizes derived from the OR for the dichotomized CGI improvement were 0.84 for fluoxetine with CBT, 0.58 for fluoxetine alone, and 0.20 for CBT alone. The number needed to treat for the dichotomized CGI improvement was 3 (95% CI, 2-4) for fluoxetine with CBT, 4 (95% CI, 3-8) for fluoxetine alone, and 12 (95% CI, 5-23) for CBT alone. Taken together, these scalar and categorical indicators of clinical magnitude indicate that combination of fluoxetine with CBT is better than fluoxetine alone, which is better than CBT alone, which is equal to placebo.

Suicidality

Despite the exclusion for high-risk suicidality, a substantial minority of patients endorsed at least some suicidal ideation at baseline. For CDRS-R suicide item No. 13, 27% of patients were defined as having at least minimal suicidal ideation (score of ≥2), with 2% endorsing severe ideation (score of ≥6). On the SIQ-Jr, 29% of patients attained a score of 31 or higher, which indicates a level of suicidality requiring prompt clinical attention. By the end of 12 weeks of treatment, the percentage of patients showing an elevated CDRS-R item No. 13 or a SIQ-Jr score had decreased to 9.4% and 10.3%, respectively.

The adjusted mean (SD) total scores on the SIQ-Jr for the intent-to-treat sample are presented in Table 2 and depicted graphically in Figure 2C. Random regression analyses on longitudinal SIQ-Jr total score identified a statistically significant linear trend with time ($F_{3,419}$=131.34; *P*=.001) and a time-by-treatment interaction ($F_{3,409}$=3.59; *P*=.01). Planned contrasts on the SIQ-Jr slope coefficients across 12 weeks of treatment produced a statistically significant ordering of outcomes different in direction from those identified on the CDRS-R and RADS. Specifically, fluoxetine with CBT (*P*=.02) proved statistically superior to placebo whereas fluoxetine (*P*=.36) alone and CBT alone (*P*=.76) did not. Fluoxetine with CBT was superior to fluoxetine alone (*P*=.002) and to CBT alone (*P*=.05) while fluoxetine alone was not significantly different from CBT alone (*P*=.22). Consistent with substantial improvement across all 4 treatment groups, none of the post-hoc week 12 contrasts was statistically significant. Effect sizes (Hedge *g*) on the week 12 SIQ-Jr adjusted means were 0.28 for fluoxetine with CBT, 0.33 for CBT alone, and 0.05 for fluoxetine alone, implying a discrete albeit small protective effect for CBT on suicidal ideation.

Table 3. Harm- and Suicide-Related Adverse Events

	Total No. of Patients	Intent-to-Treat Cases	
		Harm-Related	Suicide-Related
Active Treatment vs Placebo			
CBT with fluoxetine			
No. (%) of patients	107	9 (8.41)	6 (5.61)
OR (95% CI)		1.62 (0.56-4.72)	1.60 (0.44-5.85)
Fluoxetine alone			
No. (%) of patients	109	13 (11.93)	9 (8.26)
OR (95% CI)		2.39 (0.87-6.54)	2.43 (0.73-8.14)
CBT alone			
No. (%) of patients	111	5 (4.50)	5 (4.50)
OR (95% CI)		0.83 (0.25-2.81)	1.27 (0.33-4.87)
Placebo			
No. (%) of patients	112	6 (5.36)	4 (3.57)
SSRI vs No SSRI			
SSRI			
No. (%) of patients	216	22 (10.19)	15 (6.94)
OR (95% CI)		2.19 (1.03-4.62)	1.77 (0.76-4.15)
No SSRI			
No. (%) of patients	223	11 (4.93)	9 (4.04)
CBT vs No CBT			
CBT			
No. (%) of patients	218	14 (6.42)	11 (5.05)
OR (95% CI)		0.73 (0.36-1.49)	0.85 (0.37-1.94)
No CBT			
No. (%) of patients	221	19 (8.60)	13 (5.88)

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

Harm-Related Adverse Events

Counts, rates, and ORs (95% CI relative to placebo) for harm- and suicide-related adverse events are presented by treatment group in TABLE 3. Thirty-three (7.5%) of 439 patients experienced a harm-related adverse event. Of these, 23 (69.7%) met the Food and Drug Administrations's definition for a serious adverse event. Twenty-four (5.5%) of 439 patients experienced a suicide-related adverse event. Rates of harm-related adverse events by treat-

ment group were fluoxetine alone (11.9%), fluoxetine with CBT (8.4%), CBT alone (4.5%), and placebo (5.4%). For harm-related adverse events, an omnibus χ^2 test for differences across the 4 treatment groups was not statistically significant ($P=.15$). Inspection of the ORs indicated little or no increased risk (defined as OR ≤2) in the CBT alone group and intermediate risk for the fluoxetine and CBT combined group, suggesting a protective effect for CBT. However, the ORs (95% CIs) indicated a statistically significant elevated risk for harm-related adverse events only in SSRI-treated participants (fluoxetine alone and fluoxetine with CBT pooled) in contrast to non-SSRI treated patients (CBT only and placebo pooled) (OR, 2.19; 95% CI, 1.03-4.62). While the pattern is the same, none of the ORs for suicide-related events were statistically significant. Seven patients—too small a number (1.6% of the total sample) for statistical comparison—attempted suicide: 4 were assigned to fluoxetine with CBT, 2 to fluoxetine alone, and 1 to CBT alone. There were no completed suicides.

Psychiatric Adverse Events

TABLE 4 presents absolute rates for psychiatric-related adverse events, which reflect the broad construct of emotional and behavioral disinhibition. As expected, these adverse events were more common in patients receiving fluoxetine with CBT (16/107; 15%) and fluoxetine alone (23/109; 21%) compared with CBT alone (1/111; 1%) or placebo (11/112; 9.8%). Because overlapping adverse events can occur within the same patient, Table 4 also presents the total number of patients experiencing a psychiatric adverse event. Using the latter figure, the OR for active treatment vs placebo was 1.45 (95% CI, 0.58-3.58; 11.2%) for fluoxetine combined with CBT; 2.57 (95% CI, 1.11, 5.94; 18.5%) for fluoxetine alone; and 0.1 (95% CI, 0.01-0.84; 0.9%) for CBT alone. Thus, treatment with fluoxetine alone shows a statistically significant elevated risk for psychiatric adverse events; fluoxetine combined with CBT shows an intermediate risk between fluoxetine alone and CBT alone. Only 2 events met reporting requirements for a serious adverse event: worsening depression (fluoxetine) and mania (placebo). All patients with reported adverse events responded to dose reduction, treatment modification, addition of an out-of-protocol treatment, or treatment discontinuation.

Other Adverse Events

Rates of nonpsychiatric adverse events that occurred in at least 2% of patients and at least twice as often in one of the active treatment groups as in the placebo group appear in TABLE 5. Again, with the caveat that the rate of functionally impairing adverse events was low, they were more common in fluoxetine-treated patients. Headache was the only adverse event that occurred in at least 10% of patients in any single treatment group, but with little difference between fluoxetine combined with CBT (5.6%), fluoxetine alone (12%), and placebo (9%); no patients assigned to CBT alone reported headache or any other nonpsychiatric adverse event. As expected, gastrointestinal tract problems, seda-

Table 4. Psychiatric-Related Adverse Events*

Adverse Event	CBT With Fluoxetine	Fluoxetine Alone	CBT Alone	Placebo
Mania/hypomania				
Mania	0	1 (0.92)	0	1 (0.89)
Hypomania	1 (0.93)	2 (1.83)	0	1 (0.89)
Elevated mood	0	1 (0.92)	0	0
Irritable/depressed mood				
Hypersensitivity	0	2 (1.83)	0	0
Irritability	1 (0.93)	1 (0.92)	0	0
Anger	0	1 (0.92)	0	0
Worsening of depression	0	1 (0.92)	0	1 (0.89)
Crying	1 (0.93)	0	0	0
Agitation/restlessness				
Agitation	0	0	0	1 (0.89)
Akathisia	1 (0.93)	0	0	0
Nervousness	0	0	0	1 (0.89)
Restlessness	0	1 (0.92)	0	1 (0.89)
Hyperactivity	0	1 (0.92)	0	0
Anxiety/panic				
Panic attacks	0	1 (0.92)	1 (0.91)	0
Anxiety	0	1 (0.92)	0	0
Sleep				
Somnolence	1 (0.93)	0	0	1 (0.89)
Insomnia	5 (4.67)	3 (2.75)	0	1 (0.89)
Nightmare	1 (0.93)	0	0	0
Night sweats	0	1 (0.92)	0	0
Fatigue/sedation				
Sedation	1 (0.93)	3 (2.75)	0	0
Fatigue	2 (1.87)	1 (0.92)	0	2 (1.79)
Other				
Tremor	1 (0.93)	2 (1.83)	0	0
Behavior abnormal	0	0	0	1 (0.89)
Feeling abnormal	1 (0.93)	0	0	0
Total				
No. of events	16	23	1	11
No. of patients	12	20	1	9

Abbreviation: CBT, cognitive-behavioral therapy.
*Values are expressed as number (percentage) except for "total" values. A patient may experience multiple events, so total number of cases is presented. Events were defined as unique serious and nonserious events. Worsening of depression (fluoxetine) and mania (placebo) were reported as serious. Some patients have multiple unique events. Patients were defined as the number of patients with at least 1 event.

Table 5. Nonpsychiatric Adverse Events*

Adverse Event	Active Treatment Frequency (%)	Placebo Frequency (%)	Active to Placebo Ratio
Sedation			
Fluoxetine alone	3 (2.75)	0	3.00
Upper abdominal pain			
Fluoxetine alone	6 (5.50)	2 (1.79)	3.08
Diarrhea			
CBT with fluoxetine	2 (1.87)	1 (0.89)	2.09
Fluoxetine alone	2 (1.83)	1 (0.89)	2.06
Influenza			
Fluoxetine alone	2 (1.83)	1 (0.89)	2.06
Insomnia			
CBT with fluoxetine	5 (4.67)	1 (0.89)	5.23
Fluoxetine alone	3 (2.75)	1 (0.89)	3.08
Sinusitis			
Fluoxetine alone	4 (3.67)	2 (1.79)	2.06
Vomiting			
CBT with fluoxetine	4 (3.74)	1 (0.89)	4.19
Fluoxetine alone	2 (1.83)	1 (0.89)	2.06

Abbreviation: CBT, cognitive-behavioral therapy.
*Indicates events occurring in at least 2% of patients in at least 1 treatment group and with an incidence of at least 2 times greater than that seen in placebo-treated patients.

tion, and insomnia were the other most common complaints.

COMMENT

Focused on the initial treatment of MDD in adolescents, TADS was designed to answer clinically important questions concerning the benefit(s) of fluoxetine with CBT relative to medication management with fluoxetine alone or to CBT alone and the benefit(s) of CBT alone and fluoxetine alone relative to placebo. The effectiveness outcomes were clear and the clinical implications straightforward. The combination of fluoxetine with CBT produced the greatest improvement in symptoms of MDD. Fluoxetine alone was effective, but not as effective as fluoxetine with CBT. Treatment of CBT alone was less effective than fluoxetine alone and not significantly more effective than placebo. With respect to risk, suicidality decreased substantially with treatment. Improvement in suicidality was greatest for patients receiving fluoxetine with CBT and least for fluoxetine alone. While fluoxetine did not appear to increase suicidal ideation, harm-related adverse events may occur more frequently in fluoxetine-treated patients and CBT may protect against these events. Taking risks and benefits into account, the combination of fluoxetine with CBT appears superior as a short-term treatment for MDD in adolescents.

Generalizability

Patients exhibited the full range of mild-to-severe MDD, with a mean illness severity on the CDRS-R indicating moderate-to-moderately severe MDD. Given the tendency of industry-funded registration trials to exclude comorbid patients, it is especially noteworthy that more than 50% of the sample exhibited 1 or more comorbid disorders. Thus, while participants likely were more psychiatrically disturbed than participants in previous studies of medication and CBT monotherapy, TADS succeeded in recruiting a sample that includes the full range of treatment-seeking patients with MDD.[23] Accordingly, we conclude that the results of the study should be broadly applicable to youth with MDD seen in clinical practice.[23]

Treatment With Fluoxetine Alone

The response rates for fluoxetine monotherapy in TADS were consistent with those seen previously in pediatric fluoxetine trials. In the first placebo-controlled trial that demonstrated significantly positive effects of an antidepressant over placebo, the response rate for the fluoxetine group was 56% based on a CGI improvement score of 1 or 2.[11] In a multisite replication, fluoxetine had a 52% response rate based on a CGI improvement score of 1 or 2.[40] Thus, we conclude that the TADS response rate of 60.6% effectively replicates previous research demonstrating that fluoxetine monotherapy is an effective treatment for MDD in adolescents.

Treatment With CBT Alone

The 43% response rate for CBT alone in TADS is surprising given previous research showing that approximately 60% of depressed adolescents responded positively to CBT.[7,10] This lower absolute rate of response could be due to differences in the version of CBT and/or sample composition. Albeit modified for dissemination across multiple sites, the CBT used in TADS was based on models previously shown to be efficacious.[8,9,41] Although unlikely, it is possible that these modifications inadvertently weakened the intervention. Regarding sample composition, patients receiving CBT alone appear to have had more severe and chronic depression and higher rates of comorbidity than participants in previous CBT trials and thus may have faired more poorly with treatment. With respect to comparative effectiveness, it is important to note that this is the first adolescent depression study in which any psychotherapy has been compared with clinical management with either active medication or pill placebo. While it was not hypothesized that CBT monotherapy would fail to separate from pill placebo or prove inferior to fluoxetine monotherapy, CBT did show the specific effect of decreasing suicidality in both the CBT alone group and the CBT combined with fluoxetine group. Subsequent analyses regarding expectancy, treatment fidelity, mediational processes, and compliance with treatment should further explicate the pattern of findings. Finally, in all but one of the adult trials,[42] the comparative strength of CBT has been greater

in the follow-up phase than during acute treatment. Examination of post-acute treatment response and durability will be critical to a more nuanced understanding of the short- and long-term impact of CBT in this patient population.

Treatment With CBT Combined With Fluoxetine

The effectiveness of combined CBT and fluoxetine for treating clinically depressed youth has not been examined previously in a randomized controlled trial. As has generally been the case in studies of depressed adults,[18,19] CBT incrementally enhanced clinical management with fluoxetine leading to the highest response rate among all treatments. However, because the CBT plus placebo condition was not included in the design (it was deemed both too expensive and too artificial to have clinical relevance) it is not possible to determine whether this combined effect is additive (more is better) or synergistic (the 2 treatments enhance each other). Conversely, the divergent response patterns for depression and suicidality for participants who received fluoxetine with CBT suggests that the combination may exert a complimentary effect (targeting different domains) that enhances the overall outcome.

Placebo

Placebo response rates in TADS (34%) were consistent with the placebo rates in the 2 fluoxetine trials[11,40] (33% and 37%, respectively, based on CGI improvement score).[11,13] In the 2 earlier fluoxetine studies, the placebo response rates were lower than placebo response rates seen in other pediatric antidepressant trials. Because the response to active drug was comparable, it was the placebo response rate that generally determined the effect sizes and, hence, whether a trial was positive or negative.[14]

Why was there a low placebo response rate in TADS? From the point of view of experimental design, TADS was designed to minimize the placebo response rate. The inclusion criteria explicitly required stable depressed mood for at least 6 weeks in at least 2 of 3 contexts (home, school, among peers), making placebo-responsive mood fluctuations less likely. In addition, the primary outcome measures were rated by an independent evaluator blind to treatment assignment and to treatment course. Using an independent evaluator may have introduced a bias for interpreting improvement as being related to assignment to an active treatment.[43] Additionally, in contrast to other trials that included many small clincal sites with little research experience, all 3 fluoxetine studies used fewer clinical sites and the investigators were predominantly from clinical institutions with experience conducting treatment outcome studies with depressed adolescents.

The appropriateness of using a placebo group in randomized controlled trials with adolescent participants remains a subject of debate.[44] In this trial, symptomatic improvement, direct benefit from careful monitoring, high patient retention rate, and low adverse event rate all indicate that including a placebo group did not acutely place patients at unacceptable risk. Inclusion of a placebo group proved critical to documenting the effectiveness and safety outcomes reported herein. Thus, TADS supports the overall conclusion of a recent American Academy of Child and Adolescent Psychiatry report that including a placebo group in randomized controlled trials in pediatric psychopharmacology can be ethical and essential to the scientific aims of the study.[45]

Risk of Suicide

Approximately 500 000 adolescents in the United States attempt suicide each year; almost 2000, one half of whom suffer from major depression, die as a result.[3-5] While the rate of suicide attempts or completed suicide in (treated or untreated) adolescents with MDD is unknown, given the overall improvement in depression and suicidality in TADS it is likely that the rate of harm-related adverse events seen throughout the trial is below what might be expected in an untreated sample of depressed youth.

The separate question of whether SSRI medication is associated with an increased risk of developing suicidal ideation or facilitating suicidal behavior has been under intense scrutiny for years. Initial reports of adult patients developing intense suicidal ideation concurrent with fluoxetine treatment[46] led to investigations of clinical trial databases to assess the possibility of a causal connection.[47,48] In general, investigations with adult patients have failed to provide support for a specific causal association between antidepressant treatment and increased risk of suicidal ideation or behavior. Recently, controversy arose over similar issues among pediatric patients.[15] In June 2003, regulatory agencies in the United States and the United Kingdom issued safety warnings concerning the use of paroxetine in children and adolescents due to at least 1 study identifying increased risk of developing significant suicidality associated with paroxetine treatment. Further examination of this concern in a wide variety of second-generation antidepressants led the regulatory agency of the British Medicines and Healthcare to contraindicate all drugs in this class (except fluoxetine) for use in pediatric patients with MDD due to an unfavorable risk to benefit ratio.[49] The US Food and Drug Administration is continuing to study this issue and has made no definitive statements about risk enhancement specifically in pediatric patients. However, it has requested that stronger warnings be given to prescribing physicians about the need for close monitoring of all patients with second-generation antidepressants for worsening of depression or the development of acute suicidal thinking or behavior.[50]

Data from our study suggest a more complicated risk analysis. It is important to note at the outset that there were no deaths during the first 12 weeks of the study (and none to date of which

we are aware for any of the enrolled participants). The number of actual suicide attempts was too small to analyze statistically, and their lethality was low to moderate. The impact of treatment with fluoxetine on reduction of suicidal ideation was identical to that of placebo, suggesting that fluoxetine on average does not increase suicidal ideation. On the other hand, as expected in this population, suicidal crises and nonsuicidal self-harming behaviors were not uncommon and, with the caveat that the numbers were so small as to make statistical comparisons suspect,[51] seemed possibly to be associated with fluoxetine treatment. When considered in light of the SIQ-Jr results, which showed no exacerbation of suicidal ideation in fluoxetine-treated compared with placebo-treated patients, this finding may indicate that self-harm is not driven solely or even primarily by suicidal ideation. Recent research in this area suggests that the movement from ideation to attempt is facilitated by stressful psychosocial events, substance abuse, agitation, irritability, or disinhibition.[4,52] TADS findings are consistent with work suggesting that CBT has a specific beneficial effect on suicidal ideation[53] and, importantly, that CBT combined with fluoxetine may confer a protective effect not only against suicidal ideation, but also on harm-related behaviors.

Given the clear superiority of fluoxetine combined with CBT in reducing depression and suicidal ideation, the excess of suicide attempts in the fluoxetine with CBT group is perplexing. Reflecting a trend ($P = .06$) toward higher SIQ-Jr scores in the fluoxetine with CBT group, all but 1 of the 7 participants who attempted suicide met SIQ-Jr criteria for clinically significant suicidal ideation at baseline, suggesting that this finding might be related to an imbalance across treatment groups in risk for suicide at baseline. Of note, the TADS fluoxetine and placebo data will be included in the Food and Drug Administration reanalysis of suicide risk, which because of greater power associated with a much larger sample size should allow for stronger conclusions using a covariate-adjusted statistical model.

Other Adverse Events

The imposition of a functional impairment threshold presumably exerted a downward effect on the rates of adverse events. Nevertheless, with few patients ceasing treatment due to adverse events, treatment in TADS appeared to be reasonably well tolerated. As expected, gastrointestinal tract adverse events, sedation, and insomnia were more often reported in fluoxetine-treated patients. Mania/hypomania, irritability, agitation/restlessness, and anxiety, although more common in fluoxetine-treated patients, were rare and patients generally responded well to dose reduction or drug discontinuation. Mania was associated with a harm-related adverse event in only 1 of the 33 harm-related adverse events. Incident narratives indicate that irritability, agitation/restlessness, and anxiety were not commonly reported in association with harm-related adverse events, suggesting that other factors, such as substance use and psychosocial stressors, may be more important in mediating the risk of harm-related adverse events.

Limitations

The limitations of this study are inherent to the research questions, design, and methods that were selected. In the process of selecting the design, we discarded several alternatives, including a balanced fully factorial design, which was deemed better suited to a strict efficacy trial; a fifth placebo plus CBT group, which was not elected because of concerns about ecological validity and cost; psychosocial alternatives to a pill placebo group, such as educational support, which if credible are active and if truly inactive lack credibility; and a community-based treatment as a usual comparison group, which was discarded because of concerns about cross-site variability in quality of and access to treatment. In the end, there was unanimous agreement among the study investigators and the TADS Scientific Advisory Board that the final design represented the best compromise between scientific rigor and credibility, ethical considerations, stakeholder concerns, feasibility of implementation, and cost.

Three specific limitations merit comment. First, the patient's knowledge of the treatment he/she received varied across the 4 groups and across the 2 treatment modalities. Psychotherapeutic interventions cannot be masked at the participant level for experimental purposes, and the provision of CBT was not masked in any treatment group. Regarding pharmacotherapy, provision of fluoxetine was masked in 2 of the 4 groups. Blinding patients in the placebo and fluoxetine alone groups but not in the CBT alone group (participants knew they would not be receiving fluoxetine) and the fluoxetine combined with CBT group (participants knew that they would be receiving fluoxetine) may have interacted with expectancy effects regarding improvement and acceptability of treatment assignment. Second, contact time with the treatment clinicians and expectancy effects were not equated across treatment conditions, so the "active ingredient" in improvement cannot be specified. Third, patients deemed at high risk for suicidal behavior because of recent attempts or pervasive suicidal thoughts were excluded from this outpatient study. Given potentiation of suicidality among patients with substance abuse, exclusion for primary substance abuse or substance dependence also likely reduced the risk for self-harm among TADS patients. Methods for ascertaining suicidality, while more intensive than typical for industry trials, were less than ideal for a trial in which suicide is a primary end point. Specifically, suicide per se is too rare an event to be a primary end point in a 3-month effectiveness trial targeting MDD, and even suicide attempts are too rare to offer adequate statistical power in the TADS framework.

Conclusion

TADS is based on a best practice model that connects disorder (MDD), empiri-

cally supported treatment components (fluoxetine and CBT), and outcome (reduced MDD and collateral symptoms), which should make the treatment procedures widely applicable in a variety of mental health settings. In this context, the remarkably strong and consistent findings reported herein lead us to make the following recommendations for health care decision makers at all levels. First, given the high prevalence, morbidity, and significant mortality associated with MDD, the identification of depressed adolescents and provision of evidence-based treatment should be mandatory in health care systems. Second, despite calls to restrict access to medications, medical management of MDD with fluoxetine, including careful monitoring for adverse events, should be made widely available, not discouraged. Third, given incremental improvement in outcome when CBT is combined with medication and, as importantly, increased protection from suicidality, CBT also should be readily available as part of comprehensive treatment for depressed adolescents.

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Statistical analysis: March, Silva, McNulty, Severe.
Obtained funding: March.
Administrative, technical, or material support: March, Silva, Petrycki, Curry, Wells, Domino, Vitiello, Severe, Feeny, Stull, Amunategui, Robins, R. Weller, Jessani, Waslick, Sweeney, Kandel, Schoenholz, Walkup, Koo, Kratochvil, May, Harrington, Albano, Knibbs, Capili, Reinecke, Pathak, Wells, Arszman, Danielyan, Simons, Grimm, Nguyen, Emslie, Kennard, Ruberu, Rosenberg, Butkus, Bartoi.
Study supervision: March, Curry, Wells, Fairbank, Vitiello, Casat, Feeny, Findling, E. Weller, Robins, R. Weller, Jessani, Waslick, Sweeney, Walkup, Ginsburg, Kastelic, Kratochvil, LaGrone, Harrington, Albano, Hirsch, Knibbs, Reinecke, Leventhal, Pathak, Rohde, Grimm, Emslie, Kennard, Hughes, Butkus.

Financial Disclosures: Dr March has served on the speaker's bureau for Pfizer and Lilly and has received research support from Lilly, Pfizer, and Wyeth. Dr Findling has received research support from Bristol-Myers Squibb, Forest, GlaxoSmithKline, Lilly, Nature's Herbs, Organon, Pfizer, Solvay, Somerset, and Wyeth; been a consultant for Bristol-Myers Squibb, Forest, GlaxoSmithKline, Lilly, Pfizer, Somerset, and Wyeth; and served on the speaker's bureau for Bristol-Myers Squibb, GlaxoSmithKline, Lilly, and Wyeth. Dr Waslick has received research support from Lilly. Dr Walkup has received research support and honoraria from Lilly. Dr Kastelic has received honoraria from Pfizer. Dr Kratochvil has received reseach support from Lilly, Forest, and GlaxoSmithKline; been a consultant for Lilly; and served on the speaker's bureau for Lilly. Dr Harrington has received research support from Lilly, Pfizer, and Astra-Zeneca. Dr Leventhal has been a consultant, received research support, and served on the speaker's bureau for Lilly. Dr Emslie has received research support from Lilly, Organon, and RepliGen; been a consultant for Lilly, GlaxoSmithKline, Forest Laboratories, Pfizer, and Wyeth-Ayerst; and served on the speaker's bureau for McNeil.

Funding/Support: The research for this article was supported by contract RFP-NIH-NIMH 98-DS-0008 from the National Institute of Mental Health. Lilly Inc provided fluoxetine and matching placebo under an independent educational grant to Duke University.

Role of the Sponsor: National Institute of Mental Health program staff participated in the design and implementation, analysis of the data, and authorship of this manuscript. Lilly Inc had no role in the design and implementation, analysis of the data, or the authorship of this manuscript.

Acknowledgment: We are indebted to the TADS Scientific Advisory Board for their contributions to the design and methods of the study from Mount Sinai School of Medicine (Susan Essock, PhD), Washington University (Barbara Geller, MD), Carnegie Mellon University (Joel Greenhouse, PhD), New Jersey Medical School (Robert Johnson, MD), Yale University (James Leckman, MD), Depression and Bipolar Support Alliance (Lydia Lewis), Mount Sinai School of Medicine (Sue M. Marcus, PhD), and the University of Texas at Austin (Kevin Stark, PhD); to the members of the data and safety monitoring board of the National Institute of Mental Health for monitoring the progress of the study; and to consultants from Kaiser Permanente (Greg Clarke), University of Pittsburgh (David Brent), and Duke University Medical Center (James Rochon).

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