ORIGINAL ARTICLE

The Treatment for Adolescents With Depression Study (TADS)

Long-term Effectiveness and Safety Outcomes

The TADS Team

Context: The Treatment for Adolescents With Depression Study evaluates the effectiveness of fluoxetine hydrochloride therapy, cognitive behavior therapy (CBT), and their combination in adolescents with major depressive disorder.

Objective: To report effectiveness outcomes across 36 weeks of randomized treatment.

Design and Setting: Randomized, controlled trial conducted in 13 academic and community sites in the United States. Cognitive behavior and combination therapies were not masked, whereas administration of placebo and fluoxetine was double-blind through 12 weeks, after which treatments were unblinded. Patients assigned to placebo were treated openly after week 12, and the placebo group is not included in these analyses by design.

Participants: Three hundred twenty-seven patients aged 12 to 17 years with a primary *DSM-IV* diagnosis of major depressive disorder.

Interventions: All treatments were administered per protocol.

Main Outcome Measures: The primary dependent measures rated blind to treatment status by an independent evaluator were the Children's Depression Rating Scale–Revised total score and the response rate, defined as a Clinical Global Impressions–Improvement score of much or very much improved.

Results: Intention-to-treat analyses on the Children's Depression Rating Scale–Revised identified a significant time × treatment interaction ($P < .001$). Rates of response were 73% for combination therapy, 62% for fluoxetine therapy, and 48% for CBT at week 12; 85% for combination therapy, 69% for fluoxetine therapy, and 65% for CBT at week 18; and 86% for combination therapy, 81% for fluoxetine therapy, and 81% for CBT at week 36. Suicidal ideation decreased with treatment, but less so with fluoxetine therapy than with combination therapy or CBT. Suicidal events were more common in patients receiving fluoxetine therapy (14.7%) than combination therapy (8.4%) or CBT (6.3%).

Conclusions: In adolescents with moderate to severe depression, treatment with fluoxetine alone or in combination with CBT accelerates the response. Adding CBT to medication enhances the safety of medication. Taking benefits and harms into account, combined treatment appears superior to either monotherapy as a treatment for major depression in adolescents.

Trial Registration: clinicaltrials.gov Identifier: NCT00006286

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MAJOR DEPRESSIVE DISORDER (MDD), which has a point prevalence of 5% in adolescents, is associated with significant morbidity and family burden[1,2] as well as suicidal behavior and completed suicide.[3,4] Hence, improvements in the treatment of MDD in adolescents should be of significant public health value. To this end, the National Institute of Mental Health (NIMH) in 1999 funded the Treatment for Adolescents With Depression Study (TADS).[5] The TADS is a randomized controlled trial that is intended to evaluate the short- (0-12 weeks) and long-term (0-36 weeks) effectiveness of the following 3 active treatments for adolescents with MDD: clinical management with fluoxetine hydrochloride therapy, cognitive behavior therapy (CBT), their combination (fluoxetine therapy plus CBT) and, in the short term only, clinical management with pill placebo as a control condition.

Previous publications from the TADS described the study aims, rationale, and design[5]; the sample characteristics[6]; and the results of short-term treatment.[7] Short-term treatment (12 weeks) outcomes showed that combination therapy and fluoxetine therapy produced the greatest improvement in symptoms of MDD.[7] Cog-

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nitive behavior therapy alone was less effective than combination therapy or fluoxetine therapy alone and was not significantly more effective than placebo.

Almost 30% of the TADS participants exhibited clinically significant suicidal ideation at baseline, with 2% reporting high-intensity suicidal ideation. Suicidal ideation decreased significantly during 12 weeks in all treatment groups and showed the greatest improvement with the combination of fluoxetine therapy and CBT. Consistent with recent findings showing a slightly elevated risk of treatment-emergent suicidality in patients receiving antidepressants,[8] harm-related events were more common in patients receiving fluoxetine.[7] In a secondary analysis that used the Columbia coding scheme for suicidal events,[9] 24 suicidal events occurred during the 12-week short-term treatment period, including 5 of 107 patients (4.7%) receiving combination therapy, 10 of 109 (9.2%) receiving fluoxetine therapy, 5 of 111 (4.5%) receiving CBT, and 3 of 112 (2.7%) receiving placebo. Statistically, only fluoxetine therapy was associated with more suicidal events than placebo ($P = .04$; odds ratio [OR], 3.7; 95% confidence interval, 1.00-13.7).

Before study inception, we hypothesized that combination therapy would show a larger, more rapid short-term treatment benefit than fluoxetine therapy or CBT. We additionally hypothesized that the advantage for combination therapy relative to fluoxetine therapy and CBT would be evident across 9 months of randomized treatment.[5] In a test of this hypothesis, we now report effectiveness outcomes for combination therapy, fluoxetine therapy, and CBT across the full 36 weeks of randomized treatment. For ethical and feasibility reasons, patients assigned to placebo were treated openly after week 12, and the placebo group is not included in these analyses by design. Reflecting the paramount public health importance of suicidality,[10] we also report rates of clinically significant suicidal ideation and treatment-emergent suicidal events.

METHODS

The TADS methods have been extensively documented in previous publications,[5-7,11-18] and only those aspects of the study that are directly relevant to the weeks 0 to 36 analyses will be presented herein. All participants and at least 1 parent for each participant provided informed consent/assent. The institutional review board at each site approved and monitored the protocol. Safety monitoring was performed quarterly by the NIMH Data Safety and Monitoring Board.

Participants and all study staff remained masked in the "pills-only" conditions (fluoxetine therapy and placebo) until the end of stage 1 (week 12). Patients and treatment providers in the combination and CBT conditions were aware of treatment assignment. Cognitive behavior therapy, fluoxetine therapy, and combination therapy responders or partial responders (minimally improved or better on a clinician-assigned Clinical Global Impressions–Improvement [CGI-I] score) entered stage 2, a 6-week maintenance/consolidation phase, followed by stage 3, an 18-week maintenance phase. For ethical reasons, to maintain the sample, and to protect the ecological validity of the fluoxetine therapy condition during long-term treatment, placebo and fluoxetine treatments were unmasked at the end of stage 1. Placebo-treated patients who were deemed partial or nonresponders at the end of stage 1 were treated openly by the TADS team; placebo responders were offered telephone follow-up and, if they relapsed, their choice of open fluoxetine therapy, CBT, or combination therapy. Results past 12 weeks for placebo-treated patients will be reported separately.

Medication management in fluoxetine therapy and combination therapy included monitoring patient status and medication effects during 20- to 30-minute visits across 36 weeks of treatment and general encouragement about the effectiveness of pharmacotherapy for MDD. Dosages of fluoxetine hydrochloride began at 10 mg/d, and were increased if necessary to 40 mg/d at week 6. At the week 12 visit, the dosage was increased to a maximum of 60 mg/d in partial responders. In stages 2 and 3, the dosage of fluoxetine was held constant unless adverse events required a reduction, and the visit schedule was switched to maintenance visits every 6 weeks after week 18. Cognitive behavior therapy in the TADS included fifteen 1-hour sessions during the first 12 weeks of treatment. Partial responders were then given 6 additional weeks of weekly CBT; full responders were given biweekly CBT during the same interval (stage 2). After week 18, CBT was provided every 6 weeks on a maintenance visit schedule (stage 3). Combination therapy consisted of all the components of the medication management and CBT protocols plus limited interaction between the CBT therapist and the pharmacotherapist.

The TADS used the following 2 primary outcome measures assessed at baseline and weeks 6, 12, 18, 24, 30, and 36 by an independent evaluator who was blind to the treatment condition: (1) the scalar Children's Depression Rating Scale–Revised (CDRS-R) total score[19] and (2) responder status (defined as much or very much improved) on the CGI-I.[20] Data from the adolescent self-report, the Reynolds Adolescent Depression Scale,[21] was included because of the prominent place accorded adolescent self-report in the CBT literature.[22] Psychometric properties and intercorrelations for all measures were acceptable.[6]

To ascertain suicidal ideation, we used a "flag" score of 31 or greater on the Suicidal Ideation Questionnaire–Junior High School Version (SIQ-Jr),[23] which denotes suicidal ideation of sufficient severity to warrant prompt clinical evaluation. To identify prospectively assessed treatment-emergent suicidal events, we used the Columbia University classification scheme of the US Food and Drug Administration analyses of antidepressant-associated suicidal events.[8] In the Columbia coding scheme, classification as a suicidal event requires a suicide attempt, preparatory action toward suicidal behavior, or suicidal ideation. Self-harm without suicidal ideation or intent, such as cutting or other forms of self-mutilation, are not included in this definition. All suicidal events met the TADS adverse event reporting threshold of functional impairment or seeking medical attention. Coding of treatment-emergent suicidal events was completed with the evaluator blinded to treatment assignment and course using the Columbia Suicidality Classification Group.

The primary effectiveness and safety analyses were conducted using an intention-to-treat (ITT) principle in which the analysis included all patients randomized to treatment regardless of adherence to study treatment or procedures. To minimize confounding, we also conducted supplementary observed cases (OCs) analyses that included only those data elements for which the patient was still in his or her assigned treatment arm at the time of the assessment. A teenager was considered an observed case if any of the following did not occur before the assessment or event date: investigator-initiated provision of out-of-protocol treatment administered under the adjunctive services and attrition prevention provisions of the protocol (termed *premature termination*), study dropout, or discontinuation of assigned treatment based on treatment nonresponse at the end of stage 1.

Statistical analyses on the primary scalar outcome measures were conducted using random coefficients regression (RR) models.[24] Specifically, the influence of treatment on outcome was modeled as a function of fixed effects for treatment (with time defined as the natural logarithm of days since randomization) and clinical site (and their 2- and 3-way interaction terms), as well as the random effects for patient and patient × time interactions. The final model included linear and quadratic time effects and their significant interactions. Site was retained but its interactions were omitted from the final model owing to statistical nonsignificance. Generalized estimating equations (GEEs) for binary outcomes were used to compare the probability of treatment response over time in the 3 treatment arms. The model included treatment, time, treatment × time, and site. The time effect was linear and, thus, it was not necessary to include a quadratic term in the GEE model. For this analysis, the original 13 sites were collapsed into 10 sites to improve the stability of the model (low enrolling sites were combined into a single site). The RR and GEE models are tolerant to data missing at random in the dependent variable; accordingly, no imputation methods were used.

General linear models and tests for differences in proportions (χ^2 tests) were performed to evaluate differences across treatment groups at baseline. The rate of clinically significant suicidality on the SIQ-Jr and of treatment-emergent suicidal events in each treatment arm was compared using χ^2 and Fisher exact tests. For treatment-emergent suicidal events, Wald ORs and 95% confidence intervals were calculated to provide an indicator of the risk of active treatments relative to each other.

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 3 treatment arms. If the treatment or a treatment × time (linear or quadratic) interaction term was significant, then pairwise comparisons were conducted using a closed test procedure with an α of .05 for each test. In the event of a nonsignificant omnibus result, a sequential rejective approach[25] was planned (but not needed) in all but the safety analyses for which the samples sizes were deemed too small to warrant the more stringent procedure.

To evaluate the magnitude of the influence of combination therapy and fluoxetine therapy relative to CBT, we calculated the effect size and the number needed to treat (NNT) for the primary scalar and binary outcomes, respectively. Effect sizes (Hedges *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 standard deviations from within both groups.[26] The NNT was calculated according to methods outlined by Sackett and colleagues.[27]

Analyses were conducted using SAS statistical software (version 8.2; SAS Institute, Cary, North Carolina), with PROC MIXED used for RR and PROC GENMOD used for GEE and treatment response analyses.

RESULTS

PATIENT CHARACTERISTICS

The full TADS sample (N=439) has been extensively described and compared with clinical and epidemiological samples.[6]

The clinical and demographic characteristics of the 327 adolescents assigned to an active treatment arm (fluoxetine therapy, CBT, or combination therapy) follow. The mean (SD) age was 14.6 (1.5) years; 45.0% are male; 74.0% are non-Hispanic white; 11.3% are African American; and 9.8% are Hispanic. With a range of mild to severe depression (CDRS-R total raw score, 45-98), the mean (SD) CDRS-R raw score at entry was 59.8 (10.3). Translated to a normed T score (standardized to a mean of 50 and SD of 10) of 75.3 (6.5), on average the TADS sample shows moderate to moderately severe MDD. This level of depression is consistent with mean (SD) Clinical Global Impressions Severity Scale[20] and Clinical Global Assessment Scale scores of 4.7 (0.8) and 49.8 (7.4), respectively. This was the first episode of depression for 86.5% of the TADS patients, with a mean (SD) duration of 75.1 (86.7) weeks. On the CDRS-R suicide item, 28.1% of patients were defined as having at least minimal suicidal ideation (CDRS-R item 13 score of ≥2), with 1.2% endorsing severe depression (CDRS-R item 13 score of ≥6). Including dysthymia, more than half of the sample (52.0%) was comorbid for at least 1 other psychiatric disorder. Forty-one of 327 patients (12.5%) met *DSM-IV* criteria for attention-deficit/hyperactivity disorder and, of these, 9 of 41 (22.0%) were taking a psychostimulant at study entry. The modal family income was $50 000 to $74 000, with a range of less than $5000 to more than $200 000; 41.7% lived in a single-parent home; and 26.7% had been suspended or expelled from school. No statistically significant differences among the 3 treatment groups on any of the specified baseline characteristics were noted.

PATIENT DISPOSITION

As shown in **Figure 1**, 2804 patients were screened by telephone (gate A). Of these, 1088 signed consent for evaluation of inclusion and exclusion criteria (gate B) and 439 completed the baseline assessment and were subsequently randomized to treatment (gate C). This report concerns only the 327 patients randomized to 1 of the 3 active treatment conditions: combination therapy (n=107), fluoxetine therapy (n=109), and CBT (n=111). Of these, 270 (82.6%) continued in their assigned randomized treatment across the 12-week short-term treatment period. By the end of stage 1, 23 of 327 patients (7.0%) prematurely terminated, 34 of 327 (10.4%) exited owing to withdrawal of consent or loss to follow-up, and 28 of 327 (8.6%) were referred to open treatment owing to nonresponse at the end of stage 1. Two hundred forty-three of 327 patients (74.3%) remained in the study at week 36. Of the 327 patients, 178 (54.4%) remained in the treatment condition to which they initially had been randomized (n=68 for combination therapy, n=55 for fluoxetine therapy, and n=55 for CBT). Eighty-four of 327 (25.7%) exited the study because of loss to follow-up or withdrawal of consent (n=21 for combination therapy [19.6%], n=32 for fluoxetine therapy [29.4%], and n=31 for CBT [27.9%]). Ninety-six of 327 patients (29.4%) discontinued their randomized treatment before week 36 owing to premature termination or nonresponse at the end of stage 1 (n=25 for combination therapy [23.4%], n=39 for fluoxetine therapy [35.8%], and n=32 for CBT [28.8%]), with only combination therapy vs fluoxetine therapy proving statistically significant (*P*=.046; OR, 1.8; 95% confidence interval, 1.0-3.3). Among the 149 patients who discontinued randomized treatment across the 36 weeks, the pri-

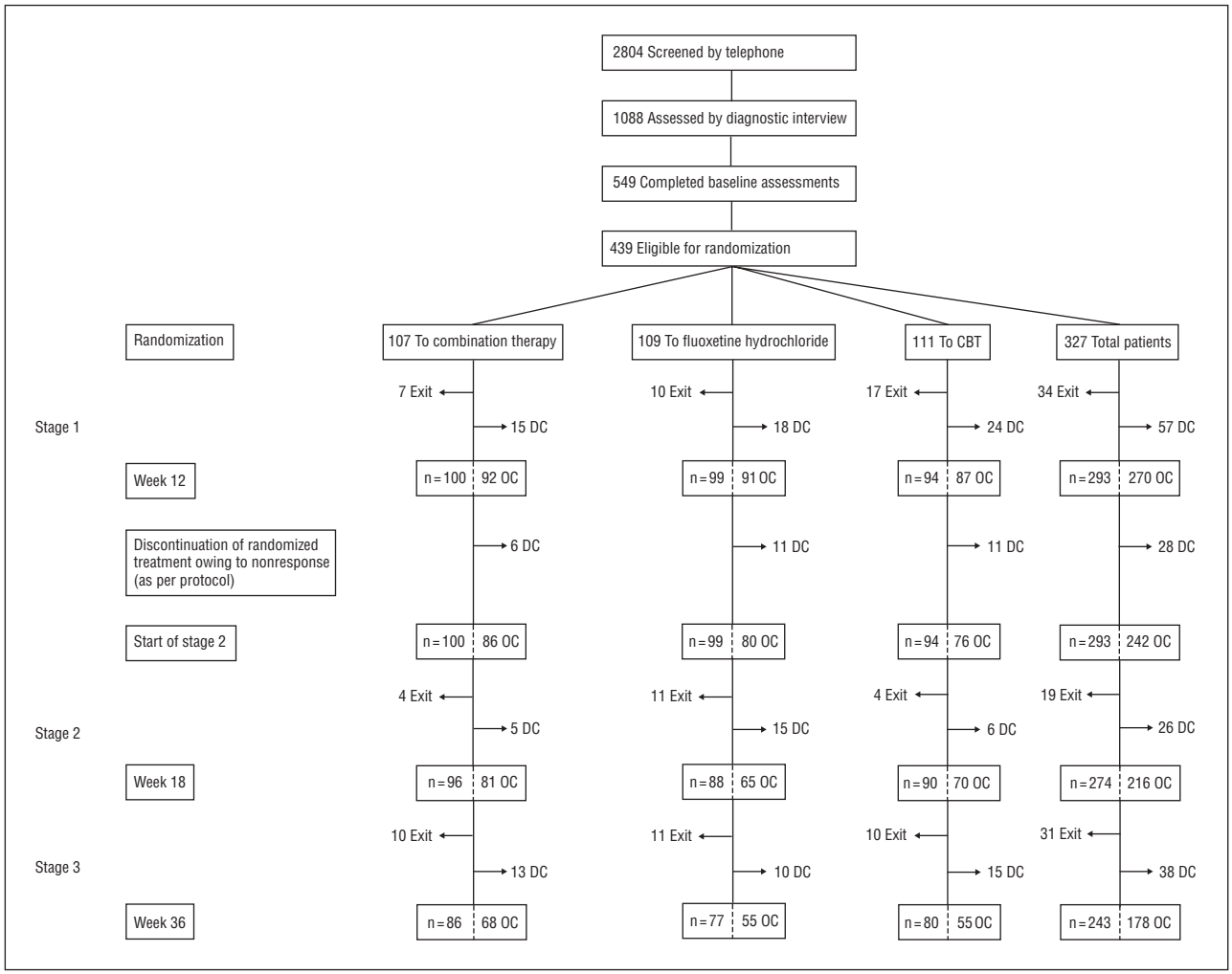

Figure 1. Flow diagram for the Treatment for Adolescents With Depression Study. Reasons for discontinuation before randomization have been previously reported.[7] All 112 patients assigned to the placebo condition discontinued randomized treatment at the end of stage 1 as per protocol and are not included in the current randomization through week 36 analysis. Observed cases (OCs) are cases in a randomized treatment arm at the assessment point. CBT indicates cognitive behavior therapy; DC, discontinuation of treatment owing to premature termination, nonresponse at the end of stage 1, or study exit; Exit, exit from the study owing to withdrawal of consent or loss to follow-up.

mary reason for termination was clinician-initiated discontinuation of treatment (n=96 [64.4%]) or departure from the study without prior termination of treatment (n=53 [35.6%]).

BENEFITS

Table 1 presents the ITT and OC adjusted means and standard deviations for the CDRS-R and Reynolds Adolescent Depression Scale, as well as the adjusted CGI-I response probabilities broken out for each treatment group by assessment point. **Table 2** presents planned contrasts by treatment week for each treatment arm. **Figure 2** graphs the ITT and OC trajectories on the CDRS-R for the 3 active treatments across 36 weeks.

Intention-to-treat RR analyses on CDRS-R total score across time identified a statistically significant linear time effect ($F_{1,296}=46.2$; $P<.001$), time × treatment interaction ($F_{2,296}=15.4$; $P<.001$), quadratic time effect ($F_{1,287}=12.8$; $P<.001$), and quadratic time × treatment interaction ($F_{2,287}=13.0$; $P<.001$). The fixed effect of site was significant ($F_{12,311}=2.0$; $P=.02$). Planned contrasts at weeks 6, 12, 18, 24, 30, and 36 identified early superiority for combination therapy and fluoxetine therapy relative to CBT at 6 and 12 weeks, whereas combination therapy and fluoxetine therapy did not separate, thereby replicating previously published results.[7] Combination therapy and fluoxetine therapy retained superiority relative to CBT at week 18, and combination therapy remained superior to CBT at week 24; all 3 treatments converged at weeks 30 and 36. The OC analyses matched the ITT results, with planned contrasts showing that fluoxetine therapy retained superiority over CBT to week 24 and combination therapy retained superiority over CBT to week 30.

With a positive response defined as a CGI-I of 1 (very much improved) or 2 (much improved) as the dependent variable, GEE analyses indicated that, for the ITT cases, the effect of treatment was statistically significant ($\chi^2_2=8.8$; $P=.01$), as was time ($\chi^2_5=72.0$; $P<.001$) and treatment × time ($\chi^2_{10}=19.6$; $P=.03$); the effect of site was nonsignificant ($\chi^2_9=10.7$; $P=.30$). Adjusted response rates (adjusted for site) at 12 weeks were 73% for combination therapy, 62% for fluoxetine therapy, and 48% for CBT. These GEE estimated responses rates are similar to the pre-

Table 1. Adjusted Mean CDRS-R and RADS Total Score and CGI-I Response Probabilities[a]

Cases/Treatment	Measure	Mean ± SD Score						
		Baseline	Week 6	Week 12	Week 18	Week 24	Week 30	Week 36
ITT/combination	CDRS-R	60.79 ± 6.18	37.79 ± 9.87	33.65 ± 8.62	30.86 ± 8.03	29.98 ± 8.10	28.51 ± 8.02	27.62 ± 8.00
	RADS	79.97 ± 9.59	61.24 ± 13.37	57.12 ± 12.88	54.56 ± 12.78	54.03 ± 12.77	52.55 ± 13.07	51.51 ± 13.38
	CGI-I	NA	0.68 ± 0.07	0.73 ± 0.06	0.85 ± 0.04	0.81 ± 0.05	0.80 ± 0.05	0.86 ± 0.04
ITT/FLX	CDRS-R	58.94 ± 5.10	39.96 ± 8.95	35.98 ± 8.15	32.64 ± 7.86	30.86 ± 7.39	29.39 ± 7.20	28.44 ± 7.53
	RADS	77.06 ± 9.96	63.79 ± 14.26	59.86 ± 13.13	57.90 ± 12.53	55.86 ± 12.58	54.46 ± 12.36	54.37 ± 13.01
	CGI-I	NA	0.57 ± 0.07	0.62 ± 0.07	0.69 ± 0.06	0.69 ± 0.06	0.82 ± 0.04	0.81 ± 0.04
ITT/CBT	CDRS-R	59.55 ± 5.49	45.76 ± 10.00	40.33 ± 9.07	36.73 ± 8.53	33.08 ± 8.42	30.03 ± 8.51	28.49 ± 8.77
	RADS	78.86 ± 10.73	70.57 ± 15.16	66.09 ± 14.20	62.85 ± 12.87	59.18 ± 13.30	57.37 ± 13.20	56.20 ± 13.92
	CGI-I	NA	0.35 ± 0.07	0.48 ± 0.08	0.65 ± 0.07	0.77 ± 0.06	0.82 ± 0.04	0.81 ± 0.05
ITT/all	CDRS-R	59.75 ± 5.64	41.15 ± 10.15	36.59 ± 9.01	33.40 ± 8.49	31.27 ± 8.07	29.28 ± 7.93	28.17 ± 8.10
	RADS	78.62 ± 10.15	65.21 ± 14.76	61.01 ± 13.87	58.36 ± 13.14	56.33 ± 13.02	54.65 ± 12.99	53.98 ± 13.53
	CGI-I	NA	0.53 ± 0.16	0.61 ± 0.12	0.73 ± 0.10	0.76 ± 0.07	0.81 ± 0.05	0.83 ± 0.05
OC/combination	CDRS-R	60.78 ± 6.78	37.21 ± 9.17	32.97 ± 8.01	30.21 ± 7.33	28.89 ± 7.19	27.40 ± 7.00	26.51 ± 7.28
	RADS	79.96 ± 9.99	60.77 ± 12.87	56.74 ± 12.49	53.87 ± 11.89	52.49 ± 11.93	50.30 ± 12.24	48.69 ± 12.23
	CGI-I	NA	0.70 ± 0.05	0.76 ± 0.05	0.89 ± 0.03	0.84 ± 0.03	0.82 ± 0.04	0.88 ± 0.03
OC/FLX	CDRS-R	58.96 ± 5.77	39.71 ± 8.83	35.80 ± 8.25	31.24 ± 7.23	29.12 ± 7.14	27.85 ± 7.03	26.86 ± 7.69
	RADS	77.06 ± 10.47	63.88 ± 14.18	59.74 ± 13.56	56.74 ± 13.27	55.08 ± 12.95	54.17 ± 12.38	53.26 ± 13.11
	CGI-I	NA	0.60 ± 0.06	0.65 ± 0.05	0.72 ± 0.05	0.72 ± 0.05	0.85 ± 0.03	0.83 ± 0.03
OC/CBT	CDRS-R	59.57 ± 5.90	45.29 ± 9.86	40.34 ± 9.06	36.25 ± 7.83	33.08 ± 8.47	29.67 ± 8.30	27.84 ± 8.40
	RADS	78.87 ± 11.20	70.04 ± 15.01	65.80 ± 14.47	61.83 ± 12.45	57.72 ± 12.98	55.43 ± 12.61	53.11 ± 12.88
	CGI-I	NA	0.39 ± 0.07	0.50 ± 0.07	0.65 ± 0.06	0.78 ± 0.05	0.81 ± 0.04	0.80 ± 0.04
OC/all	CDRS-R	59.76 ± 6.19	40.78 ± 9.88	36.30 ± 8.93	32.47 ± 7.88	30.30 ± 7.81	28.24 ± 7.46	27.03 ± 7.74
	RADS	78.62 ± 10.61	64.98 ± 14.54	60.74 ± 13.99	57.28 ± 12.88	54.94 ± 12.70	53.03 ± 12.53	51.51 ± 12.83
	CGI-I	NA	0.56 ± 0.14	0.64 ± 0.12	0.76 ± 0.11	0.79 ± 0.07	0.83 ± 0.04	0.84 ± 0.05

Abbreviations: CBT, cognitive behavior therapy; CDRS-R, Children's Depression Rating Scale–Revised; CGI-I, Clinical Global Impressions–Improvement; FLX, fluoxetine hydrochloride therapy; ITT, intention-to-treat; NA, not applicable; OCs, observed cases; RADS, Reynolds Adolescent Depression Scale.

[a]For CDRS-R, the total score was rated by blinded clinical evaluator; for CGI-I, estimated response probability was from ratings by a blinded clinical evaluator; and for RADS, the total score was rated by the patient. All means are adjusted for fixed and random effects as specified in the analytic models.

viously published week 12 response rates (71% for combination therapy, 61% for fluoxetine therapy, and 43% for CBT), in which the last-observation-carried-forward method was used to impute missing data in a logistic regression analysis.[7] Adjusted response rates at week 18 were 85% for combination therapy, 69% for fluoxetine therapy, and 65% for CBT for the ITT cases. At week 18, combination therapy maintained statistical superiority relative to fluoxetine therapy and CBT, which did not differ from each other. By week 24, all 3 treatments converged and remained so to 36 weeks. Adjusted response rates at week 36 were 86% for combination therapy, 81% for fluoxetine therapy, and 81% for CBT. Observed cases analyses indicated that combination therapy maintained superiority over fluoxetine therapy and CBT at week 18, whereas fluoxetine therapy did not differ from CBT after week 12.

Intention-to-treat RR analyses on longitudinal Reynolds Adolescent Depression Scale scores identified a statistically significant linear time effect ($F_{1,276}=14.9$; $P=.001$), time × treatment interaction ($F_{2,276=}$ 9.9; $P<.001$), quadratic time effect ($F_{1,265}=10.4$; $P=.001$), and quadratic time × treatment interaction ($F_{2,265}=6.7$; $P=.002$). The fixed effect of site was significant ($F_{12,314}=3.0$; $P=.003$). As shown in Table 2, planned contrasts at weeks 6, 12, 18, 24, 30, and 36 identified early superiority for combination therapy and fluoxetine therapy relative to CBT at 6 and 12 weeks, thereby replicating previously published results.[7] Combination therapy and fluoxetine therapy did not differ. Fluoxetine therapy retained statistical superiority relative to CBT through week 18. Combination therapy maintained superiority relative to CBT at weeks 24 and 30. The OC results matched the ITT results, with planned contrasts indicating that combination therapy retained superiority relative to CBT to week 36, whereas CBT and fluoxetine therapy were not statistically different from week 18 onward.

The magnitude and, hence, clinical significance of the influence of combination therapy and fluoxetine therapy relative to CBT was evaluated by calculating effect sizes (Hedges *g*) using the CDRS-R and Reynolds Adolescent Depression Scale adjusted scores and by calculating the NNT using adjusted response rates. An effect size of 0.2 is small, 0.5 is moderate, and 0.8 is large; corresponding values for the NNT are 10, 5, and 2. As shown in **Table 3**, the magnitude of the treatment effect for combination therapy and fluoxetine therapy relative to CBT decreased across time for the ITT and OC samples, with combination therapy but not fluoxetine therapy maintaining a numerically significant, if at times clinically modest, advantage over CBT at all time points. The advantage of combination therapy over fluoxetine therapy relative to CBT is most evident on adolescent self-report and OC analyses.

SUICIDAL IDEATION AND EVENTS

With respect to clinically significant suicidal ideation, 97 of 320 patients with an SIQ-Jr (30.3%) met the SIQ-Jr suicidality flag criterion at baseline, including 42 of 106 (39.6%) for combination therapy, 28 of 107 (26.2%) for

Table 2. Planned Contrasts for the CDRS-R and RADS Total Scores and CGI-I Response Probabilities

Week	Contrast	ITT			OC		
		F	*df*	*P* Value	*F*	*df*	*P* Value
		CDRS-R					
6	Combination-CBT	23.55	1, 301	<.001	25.57	1, 288	<.001
	Combination-FLX	2.34	1, 296	.13	2.63	1, 283	.11
	FLX-CBT	11.17	1, 299	<.001	11.62	1, 287	<.001
12	Combination-CBT	18.94	1, 294	<.001	24.29	1, 279	<.001
	Combination-FLX	2.31	1, 292	.13	2.72	1, 276	.10
	FLX-CBT	8.09	1, 295	.005	10.50	1, 281	.001
18	Combination-CBT	11.23	1, 282	<.001	17.45	1, 251	<.001
	Combination-FLX	1.69	1, 284	.19	2.06	1, 249	.15
	FLX-CBT	4.18	1, 287	.04	7.18	1, 258	.008
24	Combination-CBT	5.09	1, 269	.02	10.59	1, 223	.001
	Combination-FLX	1.02	1, 273	.31	1.32	1, 222	.25
	FLX-CBT	1.53	1, 276	.22	4.16	1, 232	.04
30	Combination-CBT	1.44	1, 258	.23	5.45	1, 206	.02
	Combination-FLX	0.49	1, 262	.48	0.72	1, 205	.40
	FLX-CBT	0.24	1, 265	.63	2.04	1, 214	.15
36	Combination-CBT	0.14	1, 252	.70	2.60	1, 197	.11
	Combination-FLX	0.21	1, 256	.65	0.37	1, 196	.54
	FLX-CBT	0.01	1, 259	.94	0.92	1, 205	.34
		RADS					
6	Combination-CBT	15.62	1, 310	<.001	16.49	1, 297	<.001
	Combination-FLX	1.16	1, 304	.28	1.45	1, 293	.23
	FLX-CBT	8.52	1, 305	.004	8.28	1, 296	.004
12	Combination-CBT	14.73	1, 301	<.001	16.40	1, 286	<.001
	Combination-FLX	1.66	1, 298	.20	2.61	1, 283	.11
	FLX-CBT	6.66	1, 300	.01	5.97	1, 287	.02
18	Combination-CBT	11.46	1, 291	<.001	13.61	1, 268	<.001
	Combination-FLX	1.75	1, 292	.19	3.20	1, 267	.07
	FLX-CBT	4.30	1, 295	.04	3.57	1, 275	.06
24	Combination-CBT	8.10	1, 283	.005	10.50	1, 252	.001
	Combination-FLX	1.61	1, 287	.21	3.35	1, 252	.07
	FLX-CBT	2.48	1, 291	.12	1.92	1, 263	.17
30	Combination-CBT	5.20	1, 277	.02	7.62	1, 238	.006
	Combination-FLX	1.37	1, 282	.24	3.25	1, 239	.07
	FLX-CBT	1.21	1, 286	.27	0.87	1, 250	.35
36	Combination-CBT	3.24	1, 273	.07	5.51	1, 229	.02
	Combination-FLX	1.14	1, 278	.29	3.05	1, 229	.09
	FLX-CBT	0.52	1, 281	.47	0.33	1, 240	.56

Week	Contrast	ITT			OC		
		χ^2 Test	*P* Value	OR	χ^2 Test	*P* Value	OR
		CGI-I TR					
6	Combination-CBT	22.7	<.001	4.1	18.2	<.001	3.7
	Combination-FLX	2.5	.11	1.6	2.1	.14	1.6
	FLX-CBT	10.9	<.001	2.6	8.2	.004	2.4
12	Combination-CBT	11.8	<.001	2.9	11.7	<.001	3.1
	Combination-FLX	2.4	.12	1.6	2.4	.13	1.7
	FLX-CBT	3.8	.052	1.8	3.8	.050	1.9
18	Combination-CBT	9.5	.002	3.1	11.1	<.001	4.3
	Combination-FLX	6.2	.01	2.5	6.1	.01	3.0
	FLX-CBT	0.3	.56	1.2	0.9	.34	1.4
24	Combination-CBT	0.5	.47	1.3	1.1	.30	1.6
	Combination-FLX	2.9	.09	1.9	3.1	.08	2.1
	FLX-CBT	0.9	.33	0.7	0.5	.47	0.8
30	Combination-CBT	0.1	.83	0.9	0.0	.87	1.1
	Combination-FLX	0.1	.71	0.9	0.3	.56	0.8
	FLX-CBT	0.0	.88	1.1	0.6	.45	1.4
36	Combination-CBT	1.0	.32	1.5	1.6	.20	1.8
	Combination-FLX	1.1	.30	1.6	0.7	.41	1.5
	FLX-CBT	0.0	.96	1.0	0.2	.63	1.2

Abbreviations: CBT, cognitive behavior therapy; CDRS-R, Children's Depression Rating Scale–Revised; CGI-I, Clinical Global Impressions–Improvement; CGI-I TR, CGI-I predicted probabilities of treatment response; FLX, fluoxetine hydrochloride therapy; ITT, intention to treat; NA, not applicable; OCs, observed cases; OR, odds ratio; RADS, Reynolds Adolescent Depression Scale.

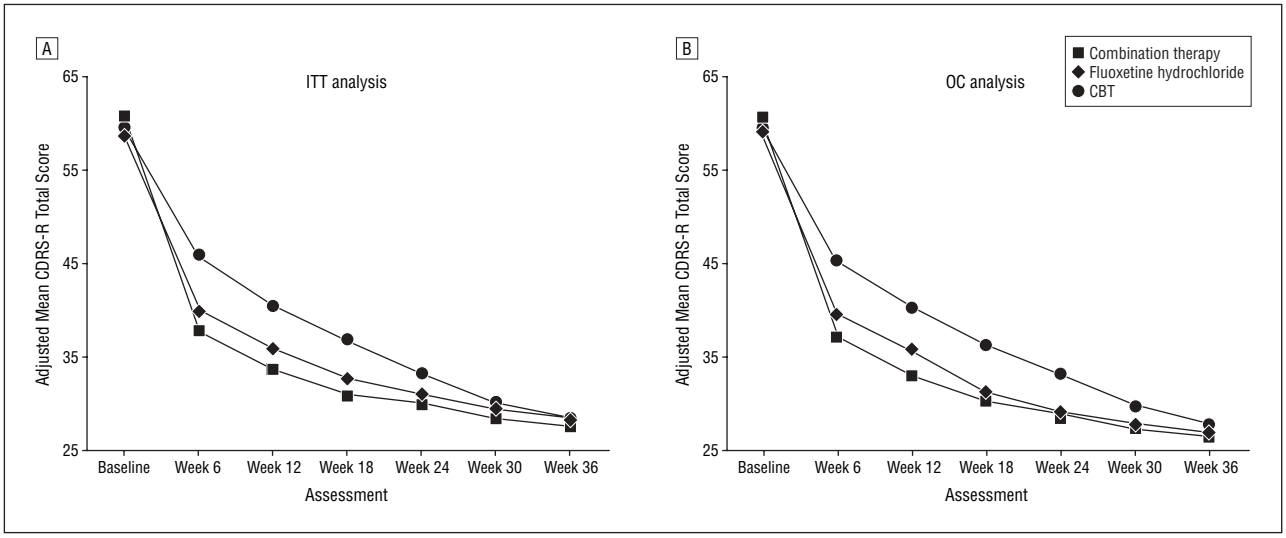

Figure 2. Adjusted mean Children's Depression Rating Scale–Revised (CDRS-R) total scores. A, intention-to-treat (ITT) analysis. B, and observed case (OC) (B) analyses. CBT indicates cognitive behavior therapy.

Table 3. Magnitude of the Effect of Combination Therapy and Fluoxetine Relative to CBT

		ITT Population			OC Population		
		Effect Size, Hedges *g*			Effect Size, Hedges *g*		
Week	Contrast	CDRS-R	RADS	CGI-I, NNT	CDRS-R	RADS	CGI-I, NNT
12	Combination-CBT	0.71	0.59	4	0.81	0.63	4
	FLX-CBT	0.48	0.39	7.0	0.49	0.38	7
18	Combination-CBT	0.55	0.52	5	0.71	0.61	4
	FLX-CBT	0.38	0.33	25	0.57	0.30	14
36	Combination-CBT	0.07	0.31	20	0.17	0.34	13
	FLX-CBT	–0.01	0.12	>100	0.12	–0.01	33

Abbreviations: CBT, cognitive behavior therapy; CDRS-R, Children's Depression Rating Scale–Revised; CGI-I, Clinical Global Impressions–Improvement; FLX, fluoxetine hydrochloride therapy; ITT, intention-to-treat; NNT, number needed to treat; OCs, observed cases; RADS, Reynolds Adolescent Depression Scale.

fluoxetine therapy, and 27 of 107 (25.2%) for CBT. Pairwise comparisons indicated that combination therapy had an excess of suicidal ideation at baseline relative to fluoxetine therapy ($P=.04$) and CBT ($P=.02$). At week 12, 31 of 278 patients who completed the questionnaire met the SIQ-Jr flag criterion (11.2%), including 8 of 90 (8.9%) for combination therapy, 18 of 97 (18.6%) for fluoxetine therapy, and 5 of 91 (5.5%) for CBT. For the observed cases, 24 of 257 (9.3%) met the SIQ-Jr flag criterion at week 12, including 5 of 84 (6.0%) for combination therapy, 14 of 89 (15.7%) for fluoxetine therapy, and 5 of 84 (6.0%) for CBT. Thus, by week 12, patients treated with fluoxetine continued to show more clinically significant suicidal ideation than those treated with CBT ($P<.01$) or, as a trend, with combination therapy ($P=.06$). Among the observed cases, fluoxetine therapy was significantly different from CBT ($P=.04$) and combination therapy ($P=.04$), which did not differ. At week 36, 15 of 228 patients (6.6%) who completed an SIQ-Jr met the SIQ-Jr flag criterion, including 2 of 79 (2.5%) for combination therapy, 10 of 73 (13.7%) for fluoxetine therapy, and 3 of 76 (3.9%) for CBT. For the observed cases, 10 of 171 (5.8%) met the SIQ-Jr flag criterion, including 0 of 63 for combination therapy, 8 of 55 (14.5%) for fluoxetine therapy, and 2 of 53 (3.8%) for CBT. Fluoxetine therapy showed higher rates of suicidal risk compared with CBT ($P=.04$) and combination therapy ($P=.01$), whereas combination therapy and CBT did not differ. Among the observed cases, fluoxetine therapy showed elevated rates compared with combination therapy ($P=.002$) and a trend toward elevated rates compared with CBT ($P=.09$), whereas combination therapy and CBT did not differ.

Table 4 presents rates and **Table 5** presents planned contrasts and ORs for treatment-emergent suicidal events by treatment group for the ITT and OC samples. During stage 1, 6.7% of ITT and 6.1% of OC patients had a suicidal event. From 0 to 36 weeks of treatment, 9.8% of ITT and 8.0% of OC patients experienced a suicidal event. Of these, 22 of 32 ITT events (69%) and 20 of 26 OC events (77%) occurred during the first 12 weeks of treatment. Across 12 weeks of treatment, suicidal events were more common in patients treated with fluoxetine alone in the ITT sample (11.0%, compared with 4.7% for combination therapy and 4.5% for CBT) and in the OC sample (9.2%, compared with 4.7% for combination therapy and

4.5% for CBT). Likewise, across 36 weeks of treatment, suicidal events were more common in patients treated with fluoxetine alone in the ITT sample (14.7%, compared with 8.4% for combination therapy and 6.3% for CBT) and in the OC sample (11.0%, compared with 7.5% for combination therapy and 5.4% for CBT). Although only the 0- to 36-week fluoxetine therapy vs CBT contrast proved statistically significant (OR, 2.6; $P=.04$), ORs at 12 and 36 weeks indicate approximately twice the risk of a treatment-emergent suicidal event in patients treated with fluoxetine therapy than in patients treated with CBT or combination therapy. There were no completed suicides in the TADS.

Table 4. Patients With Suicidal Events[a]

Treatment	No. of Patients	No. (%) of Patients	
		ITT Population	OC Population
Stage 1			
Combination	107	5 (4.7)	5 (4.7)
FLX	109	12 (11.0)	10 (9.2)
CBT	111	5 (4.5)	5 (4.5)
Total	**327**	**22** (6.7)	**20** (6.1)
Stages 1-3			
Combination	107	9 (8.4)	8 (7.5)
FLX	109	16 (14.7)	12 (11.0)
CBT	111	7 (6.3)	6 (5.4)
Total	**327**	**32** (9.8)	26 (8.0)

Abbreviations: CBT, cognitive behavior therapy; FLX, fluoxetine hydrochloride therapy; ITT, intention-to-treat; OCs, observed cases.
[a] Suicidal events include suicide attempt, preparatory action toward suicidal behavior, or suicidal ideation as adjudicated by the Columbia Suicidality Classification Group. Youths with multiple suicide-related events are counted only once and the most severe code is represented.

COMMENT

Relative to our previous report at 12 weeks,[7] data on the benefits and harms during 36 weeks of randomized treatment provide important new information. First, clinically meaningful improvement occurred in all 3 active treatment conditions, with convergence on most end points by week 36. Second, treatment with fluoxetine alone or in combination with CBT produced more rapid improvement in MDD symptoms than did CBT alone. Third, although rarely statistically superior, combination therapy proved numerically superior to fluoxetine therapy on most end points, with the advantage for combination therapy most apparent on the OC analyses and on adolescent self-report. Fourth, CBT catches up to fluoxetine therapy at the midpoint of treatment and to combination therapy toward the end of treatment. Fifth, clinically significant suicidal ideation persists in a minority of patients and is significantly more common in patients treated with fluoxetine alone than with combination therapy or CBT. Sixth, despite state-of-the-art treatment and notable improvement in depression, treatment-emergent suicidal events occurred in 10% of TADS patients during 9 months of treatment, with most of these occurring early in treatment. Patients treated with fluoxetine alone were twice as likely as patients treated with combination therapy or CBT to experience a suicidal event, indicating that CBT may protect against treatment-emergent suicidal events in patients taking fluoxetine. After taking benefit and risk into account, we conclude that the combination of fluoxetine and CBT appears superior to either monotherapy as a long-term treatment strategy for MDD in adolescents.

GENERALIZABILITY

Although the TADS sample spans the range from mild to severe depression, most patients (97%) fell in the moderate to severe range of illness as characterized by a mean CDRS-R score 2.5 SD above the mean (98th percentile), high rates of comorbidity, and a strikingly prolonged median (42 weeks) and mean (75 weeks) current episode duration. Given a mix of younger and older teenagers of both sexes, minority representation roughly proportionate to US population values, and wide variability in socioeconomic circumstances,[6] the results should be broadly applicable to those obviously ill depressed adolescents who few would disagree ought to receive evaluation and treatment as a part of routine clinical practice.[28]

COMBINATION THERAPY

Overall, combination therapy in the TADS proved robustly superior to CBT and modestly and inconsistently better than fluoxetine therapy. Secondary analyses of outcomes at 12 weeks show that the combination of CBT and fluoxetine but not fluoxetine alone proved superior to CBT and placebo with respect to probability of remission,[29] function and quality of life,[30] and multiple measures of acceptability, tolerability, and safety, including suicidality.[9] Of the 16 possible week 12 end points examined so far, combination therapy proved superior to CBT and placebo on greater than 90% of the week 12 end points and to fluoxetine therapy half the time, whereas fluoxetine therapy was superior to CBT and placebo in just under half.[31] Although the reasons for the advantage of combination therapy relative to fluoxetine therapy are unclear, it is clear that the TADS was underpowered to detect the identified 10% difference between combination therapy and fluoxetine therapy at week 12 or 18 on the primary categorical outcome. This difference (NNT=10), although at the margin of clinical detection, is nonetheless of considerable public health relevance.

Given the difference in the sampling frame and CBT intervention strategies, it is difficult to directly compare the TADS findings with those of the few other trials in depressed youth that included a combined treatment condition. One methodologically flawed and severely underpowered study by Melvin and colleagues[32] showed no advantage for combined treatment over medication or CBT, but it did show an advantage for CBT over sertraline hydrochloride. Another study comparing CBT combined with medication vs medication alone in a mildly ill population showed a weak and inconsistent CBT

Table 5. ORs and Treatment Contrasts for Suicidal Events

Planned Contrast	ITT Population			OC Population		
	χ^2 Test	*P* Value[a]	OR (95% CI)	χ^2 Test	*P* Value[a]	OR (95% CI)
Stage 1						
Combination-CBT[b]	0.0	> .99	1.0 (0.3-3.7)	0.0	> .99	1.0 (0.3-3.7)
FLX-CBT	3.3	.07	2.6 (0.9-7.7)	1.9	.17	2.1 (0.7-6.5)
FLX-combination	3.0	.08	2.5 (0.9-7.4)	1.7	.19	2.1 (0.7-6.2)
Stages 1-3						
Combination-CBT	0.4	.55	1.4 (0.5-3.8)	0.4	.53	1.4 (0.5-4.2)
FLX-CBT	4.1	.04	2.6 (1.0-6.5)	2.3	.13	2.2 (0.8-6.0)
FLX-combination	2.1	.15	1.9 (0.8-4.4)	0.8	.37	1.5 (0.6-3.9)

Abbreviations: CBT, cognitive behavior therapy; CI, confidence interval; FLX, fluoxetine hydrochloride therapy; ITT, intention-to-treat; OCs, observed cases; OR, odds ratio.

[a] Unless otherwise indicated, *P* values were calculated using 2×2 χ^2 test results.

[b] Fisher exact test was used to calculate the *P* value owing to 25% of the cells having expected counts less than 5.

effect.[33] A report from the randomized controlled trial most like the TADS—the British Adolescent Depression Antidepressant and Psychotherapy Trial—is slated for publication in late 2007. By intention, the Adolescent Depression Antidepressant and Psychotherapy Trial and the TADS both include the Health of the Nation Outcome Scales for Children and Adolescents. At 12 weeks, the TADS showed a robust advantage for combined treatment on this measure[34]; combined data set analyses, which were built into the structure of both trials, should amplify and extend the results of the individual studies. Future analyses of the TADS also should shed light on who is likely to respond to combined treatment or to 1 of the 2 monotherapies and whether adherence to treatment mediates these differences. These future analyses are expected to generate hypotheses that will inform future studies in this area.

WHAT IS THE ROLE OF CBT?

In short-term studies of CBT, one-third of depressed youth do not respond.[35,36] In the TADS CBT condition, which blended the best available elements of cognitive, behavioral, and family treatments,[11,15,16] more than half of the patients did not respond at 12 weeks, which represents a substantially larger proportion of patients with an inadequate response compared with other CBT trials and well below the hypothesized 60% response rate. In the CBT literature, it is conventional to argue that treatment should continue longer than 12 weeks to maximize the probability of a response and to minimize the possibility of a relapse.[37] Given that the TADS patients also were more severely ill than most patients in published CBT trials,[6] 12 weeks of CBT may not have been long enough to allow CBT to separate from placebo in the short term.[5,38] In support of this proposition, which replicates and extends previous results in the CBT literature where 16 to 20 weeks of treatment is the norm,[39] the response rate for CBT improved from 48% to 65% at week 18, whereas the response rate for fluoxetine therapy moved from 62% to 69%. Although causal interpretations are limited by the absence of a placebo control beyond week 12, the data show that CBT caught up with fluoxetine therapy by weeks 18 to 24 and to combination therapy by weeks 30 to 36. Thus, although some have speculated that CBT was poorly constructed or implemented,[38] the long-term outcomes presented herein make it more likely that the severity of illness simply delayed the onset of benefit for CBT relative to combination therapy and fluoxetine therapy, a finding that is widely acknowledged in adult studies of CBT relative to medication.[40] Given that a recent meta-analysis of the CBT literature for depressed youth showed a relatively small effect size (0.34),[41] efforts to understand the mechanisms by which CBT alters the course of MDD and in turn to revise CBT protocols so as to increase their effect are in order.

FLUOXETINE THERAPY

In contrast to the unenthusiastic view of medications held by some,[42,43] we and others[7,28,44,45] concluded from the short-term treatment data that the benefits of including fluoxetine (we make no claims about other antidepressants) in the short-term treatment of adolescent MDD were readily apparent and clinically meaningful. In secondary analyses at 12 weeks, we have now shown that fluoxetine alone or in combination with CBT accelerates response relative to CBT and to placebo.[46] Thus, when considered in light of 2 other positive randomized controlled trials for fluoxetine therapy in pediatric MDD,[47,48] short- and long-term data from the TADS unequivocally confirm that fluoxetine is an effective treatment for adolescents with moderate to severe MDD.

SUICIDALITY

Although the absolute magnitude of the medication-attributable risk is low (number needed to harm, 50), treatment-emergent suicidal events are an important public health concern in children and adolescents treated with antidepressants.[8,10] Findings from the TADS across 9 months of treatment confirm and extend results at 12 weeks[7] showing that patients treated with fluoxetine alone are more likely than patients treated with combination therapy or CBT to show clinically significant suicidal ideation (on the SIQ-Jr) and treatment-emergent suicidal

events (on the adverse event report). As an effectiveness trial for which suicidal events were not a primary end point, the TADS was not structured properly to segment risk or to establish the mechanism by which fluoxetine therapy may enhance risk or that CBT may exert a protective effect. The increased risk of a suicidal event with fluoxetine therapy cannot simply be due to improvement because (1) combination therapy, which began with statistically higher suicidal ideation, improved as much as or more than fluoxetine therapy while patients receiving combination therapy had a rate of suicidal events that approximated CBT alone and (2) suicidality did not increase in the CBT group during the 12- to 24-week interval, when a large portion of the CBT benefit occurred. Recalling that medication and CBT were administered in a coordinated fashion,[12] the mean dose of fluoxetine hydrochloride in combination therapy (28 mg) was lower than that for fluoxetine hydrochloride alone (32 mg) at 12 weeks.[7] Although there is no evidence from the TADS to suggest that fluoxetine induces mania or "behavioral activation," patients treated with combination therapy show fewer psychiatric and nonpsychiatric adverse events than patients treated with fluoxetine alone.[9] Thus, it is at least possible if not likely that the added risk associated with fluoxetine monotherapy was dose related. More likely, CBT alone or in combination with fluoxetine mitigates suicidality, perhaps by minimizing the probability that ideation will lead to an attempt, decreasing the likelihood or improving the management of stressful psychosocial events, decreasing family conflict and enhancing family problem solving ability, or providing skills to manage negative affects, agitation, irritability, or disinhibition.[4,49]

LIMITATIONS

We discuss design challenges and controversies in detail elsewhere[5,31] and restrict our comments herein to 3 areas of concern: (1) the absence of a placebo group after week 12, (2) expectancy effects, and (3) the influence of time and attention.

We readily acknowledge that it is impossible to conclude that patients would not have reached equivalent week 36 outcomes simply because of the passage of time without a placebo group or, better, an untreated control group, both of which were considered unfeasible for ethical and practical reasons.[50] Thirty percent to 70% of youth with MDD recover during the first year of illness, although 30% subsequently relapse.[51] Naturalistic follow-up of randomized controlled trials of psychotherapy[52] and placebo-substitution trials of fluoxetine therapy[37] also show a high rate of relapse, even against a background of substantial improvement. In the only trial of maintenance psychotherapy in depressed teens, CBT booster sessions did not reduce the rate of recurrence but did appear to accelerate recovery among participants who were still depressed at the end of the short-term phase.[53] The mean episode duration was longer than 1 year, and more than half the TADS sample had received previous treatment within the current episode.[6] Secondary analyses at week 12 also showed that shorter episode duration predicted a better outcome at 12 weeks, which is the opposite of what would be predicted if episodes were spontaneously remitting.[34] Thus, it is unlikely that improvement within 36 weeks primarily reflected spontaneous remission. It is more likely that a reduction in relapse coupled with gradual improvement in MDD symptoms with continued treatment was responsible for the observed overall improvement rate of approximately 85%.

In comparative treatment trials that include medication and psychotherapy, double-blind administration of the medication therapy but not the psychosocial treatment conditions is possible. This is a design choice, not a design flaw,[43,54] which constrains the question to an effectiveness (primarily information for clinical decision makers) rather than efficacy (dismantling treatment elements) aim.[5,7,31] In the absence of a CBT-placebo group and a fluoxetine therapy–nonsupportive psychotherapy comparison group, it is not possible to conclusively claim the superiority of combination therapy relative to CBT or combination therapy relative to fluoxetine therapy, respectively. Similarly, in the absence of an active psychotherapy comparison group, it is not possible to claim that the benefits of TADS CBT are unique to CBT compared with a different type of psychosocial treatment. However, 3 lines of evidence suggest that the advantage shown by combined treatment is not artifactual. First, low expectation of benefit predicted a poorer outcome at 12 weeks; however, expectancy did not differentially moderate outcomes,[34] suggesting that expectancy alone cannot account for the advantage of combined treatment. Second, if expectancy effects accounted for all the advantage of combination therapy over fluoxetine therapy, one might expect that unblinding the fluoxetine condition at 12 weeks should reduce the superiority of combination therapy over fluoxetine therapy at 18 weeks. Instead, the numerical superiority of combination therapy over fluoxetine therapy increases once unblinding takes place, and combination therapy remains superior to CBT longer than fluoxetine therapy does. Third, combined treatment is robust to differences in patients, therapists, and settings across all the outcomes examined so far,[31,34] suggesting that rater bias is not playing a substantive role in the effect of combined treatment.

Finally, patients assigned to combined treatment experienced somewhat greater contact time than did patients assigned to fluoxetine therapy or CBT alone. As pointed out earlier, the TADS did not include the proper control conditions to disentangle time and attention from the other active components of treatment. Although analyses of the influence of treatment adherence on outcome may help decompose the extra benefit associated with combined treatment, the TADS was never intended to ask questions involving the mechanism of treatment benefit. Rather, it was designed to ask the simple question of whether combined treatment was advantageous relative to CBT and fluoxetine therapy because they would be delivered in clinical practice: the answer to this question is an unequivocal yes.

CONCLUSIONS

The 2 central findings from the TADS are that (1) fluoxetine alone or in combination with CBT accelerates im-

provement of depression relative to CBT alone and (2) adding CBT to fluoxetine therapy minimizes persistent suicidal ideation and treatment-emergent suicidal events. This leads us to make 4 key recommendations for health care decision makers at all levels of the health care system. First, identification and provision of evidence-based treatment to adolescents with moderate to severe depression would likely have a positive public health benefit and should be encouraged. Second, because accelerating symptom reduction by using medication is an important clinical outcome in psychiatry, as it is in other areas of medicine, use of fluoxetine should be made widely available, not discouraged. Third, given equivalent if delayed results for CBT monotherapy and increased protection from suicidality, CBT or other evidence-based psychosocial treatments[55] should be made readily available as part of comprehensive treatment for depressed adolescents. Because most adolescents with depression receive no or unproved psychosocial treatments, which oddly enough are sometimes sanctioned by expert guidelines,[56] conforming to this recommendation will require a significant shift in current practice.[57] Until this occurs, fluoxetine monotherapy, delivered in the context of regular clinical management and careful clinical monitoring, will remain an important stop-gap measure in patients for whom the earliest possible response is deemed clinically meaningful. Fourth, although not yet at the level of evidence necessary to mandate a standard of care, we believe that the literature on evidence-based treatment for adolescent MDD has reached sufficient maturity that it should fall within the realm of informed consent.[50]

Future reports from the TADS will address secondary outcomes; moderators and mediators, including adherence to treatment; remission, relapse, and recovery during randomized treatment and during a year-long naturalistic follow-up period; the nature and use of ancillary treatments; and short- and long-term cost-effectiveness, among other topics of interest to decision makers at all levels of the health care system. Although TADS manuals and procedures were designed to be clinically applicable, additional research will be necessary to better understand how to disseminate the TADS findings and to explore topics, such as sequential treatment, not addressed in the TADS.

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Additional Information: The TADS protocol and all of the TADS manuals are available on the Internet at https://trialweb.dcri.duke.edu/tads/index.html.

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Correction

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