

Achievement and Maintenance of Sustained Response During the Treatment for Adolescents With Depression Study Continuation and Maintenance Therapy

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Context: The Treatment for Adolescents With Depression Study evaluated fluoxetine (FLX), cognitive behavioral therapy (CBT), and FLX/CBT combination (COMB) vs pill placebo in 439 adolescents with major depressive disorder. Treatment consisted of 3 stages: (1) acute (12 weeks), (2) continuation (6 weeks), and (3) maintenance (18 weeks).

Objective: To examine rates of achieving and maintaining sustained response during continuation and maintenance treatments.

Design: Randomized controlled trial. Response was determined by blinded independent evaluators.

Setting: Thirteen US sites.

Patients: Two hundred forty-two FLX, CBT, and COMB patients in their assigned treatment at the end of stage 1.

Interventions: Stage 2 treatment varied based on stage 1 response. Stage 3 consisted of 3 CBT and/or pharmacotherapy sessions and, if applicable, continued medication.

Main Outcome Measures: Sustained response was defined as 2 consecutive Clinical Global Impression-Improvement ratings of 1 or 2 ("full response"). Patients

achieving sustained response were classified on subsequent nonresponse status.

Results: Among 95 patients (39.3%) who had not achieved sustained response by week 12 (29.1% COMB, 32.5% FLX, and 57.9% CBT), sustained response rates during stages 2 and 3 were 80.0% COMB, 61.5% FLX, and 77.3% CBT (difference not significant). Among the remaining 147 patients (60.7%) who achieved sustained response by week 12, CBT patients were more likely than FLX patients to maintain sustained response through week 36 (96.9% vs 74.1%; $P = .007$; 88.5% of COMB patients maintained sustained response through week 36). Total rates of sustained response by week 36 were 88.4% COMB, 82.5% FLX, and 75.0% CBT.

Conclusions: Most adolescents with depression who had not achieved sustained response during acute treatment did achieve that level of improvement during continuation and maintenance therapies. The possibility that CBT may help the subset of adolescents with depression who achieve early sustained response maintain their response warrants further investigation.

Trial Registration: clinicaltrials.gov Identifier: NCT00006286.

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GIVEN THE HIGH PROBABILITY of relapse and recurrence following favorable response to treatment in adults and adolescents with depression,^{1,2} guidelines have been developed to extend beyond acute treatment. The goal of continuation treatment is to prevent relapse following remission (ie, the initial period during which the person has responded to treatment³), whereas the goal of maintenance treatment is to prevent recurrence following recovery (ie, once the person has been symptom-free long enough to consider the initial depressive episode over). Little is known concerning ef-

fective continuation and maintenance therapies for adolescents with depression, and practice guidelines for adolescents^{4,5} have been adopted from the larger body of guidelines for long-term treatment of adults with depression.⁶⁻⁹

Previous postacute treatment research with adolescents with depression is extremely limited. A 6-month course of cognitive behavioral therapy (CBT) continuation treatment in 17 patients (aged 11-17 years) following acute CBT¹⁰ was superior to no treatment in a historical control group of 12 patients, and fluoxetine (FLX) continuation treatment was superior to pill placebo (PBO) in reducing depression re-

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lapse among 40 patients (aged 8-18 years) who had responded to FLX acute treatment.¹¹ In the former study, the cumulative relapse risk was 20% among continuation CBT patients vs 50% among historical controls. In the latter study, relapse, which was defined as either a Children's Depression Rating Scale-Revised¹² (CDRS-R) score higher than 40 or physician opinion over a 32-week post-acute phase, occurred in 34% of patients who continued taking FLX vs 60% of those switched to PBO.

In the only study to our knowledge that evaluated a maintenance treatment for adolescent depression, Clarke and colleagues¹³ examined the degree to which an individual CBT booster intervention reduced depression recurrence. After an 8-week, 16-session group CBT intervention, one-third of the 54 adolescents (aged 14-18 years) who completed treatment (regardless of response status) were randomly assigned to individual boosters every 4 months over a 2-year follow-up. The booster condition was not associated with less depression recurrence among recovered patients (27% recurrence among booster patients vs 8% among assessment-only controls, results not significant) but did significantly improve the rate of recovery for adolescents who still had depression following acute treatment (100% recovery among booster patients vs 50% among assessment-only controls; $P < .05$). This study suggests that an important function of post-acute treatments may be to facilitate continued improvement among partial responders.

The goal of the present study was to examine the rates of sustained improvement during continuation and maintenance therapies in the Treatment for Adolescents With Depression Study¹⁴⁻¹⁶ (TADS). TADS is a randomized controlled trial that evaluated the effectiveness of 3 treatments for adolescents with major depressive disorder (MDD), FLX pharmacotherapy with clinical management, CBT, and the combination of FLX and CBT (COMB), relative to clinical management with PBO. TADS treatment was provided in 3 stages: (1) acute treatment lasting 12 weeks, (2) continuation treatment lasting 6 weeks and varying in intensity based on the patient's response to acute treatment, and (3) maintenance treatment lasting 18 weeks, in which patients met with their clinician(s) 3 times and, if applicable, continued taking medication. Previous publications reported that the COMB and FLX conditions had higher response rates than CBT or PBO during stage 1,¹⁴ and COMB performed better during stages 2 and 3 than either of the monotherapies, which had very similar response rates.¹⁷

Our outcome measure in the present study was sustained response, which is defined as 2 consecutive ratings of a full response in assessments conducted 6 weeks apart. TADS follow-up did not include the collection of weekly symptom ratings necessary to determine recovery and recurrence.^{3,18} Our creation of the sustained response variable provides an alternative outcome that answers important questions in clinical decision making that must be answered before a patient is considered recovered (eg, Is my patient responding to this treatment? Is this apparent response more than transitory? Should I augment treatment or change modalities?). Although it was not an original aim of TADS, data during TADS continuation and maintenance therapies provided a unique

and valuable opportunity to address 2 issues: (1) To what degree do patients who have not achieved sustained response during acute therapy subsequently achieve sustained response during continuation and maintenance therapies? (2) Among patients who achieved sustained response during acute therapy, how many maintain their sustained response through continuation and maintenance therapies? The present study extends the previous stage 3 TADS publication¹⁷ by requiring a maintained response rather than the one-time achievement of a positive response and by examining the degree to which sustained response is maintained once achieved. In addition, although data on treatment adherence and compliance following acute treatment were not available, we examine, as a secondary aim, whether treatment modalities differed in rates of attendance, which serves as one basic indicator of treatment use. Retaining the patient is a basic gauge of the perceived value of postacute care. In addition, differences in the rates of sustained response may be influenced by condition differences in attendance. One possible explanation for the nonsignificant recurrence prevention finding of the booster protocol in Clarke et al¹³ was that many adolescents assigned to booster therapy (perhaps more than half) failed to attend postacute treatment. Although we are unable to evaluate the degree to which patients complied with continuation and maintenance therapies in TADS, we compared whether treatment attendance varied across conditions.

METHODS

The TADS design has been extensively documented in previous publications¹⁴⁻¹⁶ and will be only briefly reviewed herein.

STAGE 1 PARTICIPANTS AND PROCEDURES

Between 2000 and 2003, 439 adolescents at 13 sites were enrolled. Both adolescents and parents provided written informed assent/consent. Institutional review boards at each site approved and monitored the protocol. Diagnoses 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.¹⁹ TADS used 2 primary measures of depression status assessed at baseline and weeks 6, 12, 18, 24, and 36 by an independent evaluator blind to condition: (1) the 17-item CDRS-R¹¹ as a continuous measure of depression severity in the past week, and (2) responder status on the 7-point Clinical Global Impression-Improvement (CGI-I).²⁰

Inclusion criteria were (1) 12 to 17 years of age, (2) diagnosis of current DSM-IV MDD, (3) CDRS-R total score of 45 or higher, (4) stable mood symptoms for at least 6 weeks, and (5) impairment in at least 2 settings. Exclusion criteria included (1) psychiatric disorders requiring out-of-protocol treatments, (2) 1 failed CBT trial or 2 failed selective serotonin reuptake inhibitor trials for depression, (3) current psychiatric treatment (other than stable dose of stimulant medication for attention-deficit/hyperactivity disorder), (4) non-English speaking, (5) confounding medical condition, (6) previous intolerance to FLX, (7) pregnant or sexually active while refusing acceptable birth control, or (8) danger to self or others.

Eligible participants were randomly assigned to FLX, CBT, COMB, or PBO using stratified randomization at the coordi-

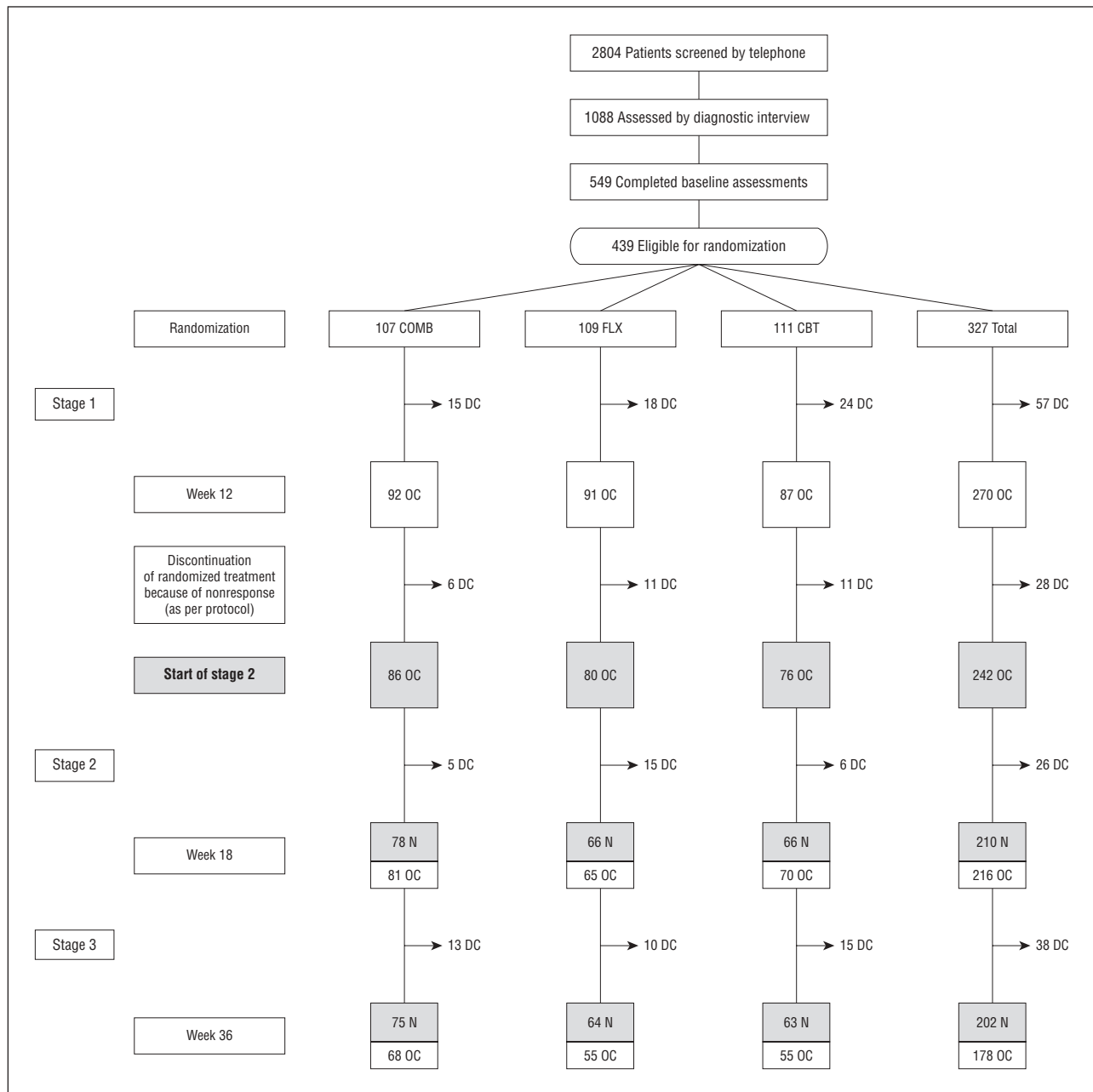


Figure. Treatment for Adolescents With Depression Study flow diagram for the 242 patients who continued randomized treatment after 12 weeks of acute treatment. Reasons for discontinuation prior to randomization have been previously reported.^{15(p811)} The 242 youths who started stage 2 as an observed case (OC) were evaluated in the current analysis. All 112 patients assigned to the placebo condition discontinued randomized treatment at the end of stage 1 as per protocol and are excluded from the current analysis. COMB indicates combination of fluoxetine (FLX) and cognitive behavioral therapy (CBT); DC, discontinuation of randomized treatment because of premature termination, nonresponse at the end of stage 1, or study exit; N, number of Clinical Global Impression–Improvement²⁰ assessments completed for 242 cases at weeks 18 and 36.

nating center. Patients and staff remained masked in the “pills only” conditions (FLX and PBO) until week 12, at which time patients and clinicians were unblinded. At the end of stage 1, PBO nonresponders were provided with the TADS treatment of their choice, and nonresponders to active treatment (6 in COMB, 11 in FLX, 11 in CBT) were withdrawn from treatment and provided with referrals for alternative care.

Given our focus on stages 2 and 3 in the present study, patients initially assigned to PBO were not included. Rates of participation at each project stage are shown in the CONSORT (Consolidated Standards of Reporting Trials) diagram (**Figure**). A total of 327 adolescents were randomized to an active treatment; 270 completed the study through week 12. The present

sample (n=242) consisted of observed cases (ie, adolescents in their randomized treatment arm with no treatment augmentation) at the start of stage 2. The sample had a mean (SD) age at intake of 14.6 (1.5) years and included 140 female adolescents (57.9%). One hundred ninety participants (78.5%) classified their race/ethnicity status as white; 21 (8.7%), African American; 17 (7.0%), Hispanic white; 4 (1.7%), Hispanic black; 3 (1.2%), Asian; and 7 (2.9%), other. Participants in the present study were compared on demographic factors (age, sex, race/ethnicity, income) and depression severity (CDRS-R and Clinical Global Impression–Severity [CGI-S] scores) with the 85 patients assigned to active treatment who had been excluded. Differences were nonsignificant, with one exception: retained

patients consisted of a higher proportion of white adolescents (78.5% vs 62.1%; $P = .002$). Data were available for 210 participants (86.8%) at the end of stage 2 and 202 (83.5%) at the end of stage 3.

INTERVENTIONS

Medication

Stage 1 medication management included monitoring status and medication effects during 20- to 30-minute visits. Doses began at 10 mg/d, titrated as necessary, up to 40 mg/d by week 8. At the week 12 visit, the dose was raised to 50 or 60 mg/d in patients rated by the clinician as partial responders (ie, CGI-I score = 3). Full responders at the end of stage 1 (CGI-I score = 1 or 2 by clinician rating) were maintained at the same FLX dose. In stage 2, full responders had 2 office visits; partial responders had 4 office visits. In stage 3, patients were followed up every 6 weeks with a 20- to 30-minute medication visit. Other than reductions because of major adverse effects, medication dose did not change without special approval from the conference call peer supervision group.

Cognitive Behavioral Therapy

TADS CBT in stage 1 included 15 sessions (a combination of adolescent only, parent psychoeducation, and conjoint). Patients rated by their clinician as partial responders at the end of stage 1 received 6 additional weeks of weekly CBT in stage 2, whereas stage 1 full responders shifted to biweekly CBT sessions. During stage 3, patients met with their therapist every 6 weeks for 3 CBT booster sessions.

Combination Treatment

Combination treatment consisted of all components from the medication management and CBT protocols.

DEFINITIONS OF DEPRESSION STATUS

Treatment Response

Treatment response status, relative to baseline, was determined at each assessment based on independent evaluator CGI-I scores. When a week 12 independent evaluator score was missing, last observation carried forward procedures were implemented. Adolescents with CGI-I scores of 1 ("very much improved") or 2 ("much improved") were considered full responders, those with a CGI-I score of 3 ("minimally improved") were considered partial responders, and those with a CGI-I score of 4 ("no change") and higher (indicating worsening) were considered nonresponders. Thirty-one adolescents rated by the independent evaluator as week 12 nonresponders were included in the present study because the patient had been rated by the clinician(s) as either a partial or full responder and had remained in his or her treatment arm without treatment augmentation. CGI-I ratings were made by the independent evaluator after the CDRS-R and scores between the 2 measures were highly correlated (ie, Spearman correlations between CGI-I and CDRS-R scores at weeks 12, 18, and 36 were $r = 0.81, 0.80, \text{ and } 0.73$, respectively; all $P < .001$).

Sustained Response Status

Sustained response status was based on the maintenance of independent evaluator CGI-I scores. The following 2 assump-

tions were applied when response status data were missing: (1) adolescents missing week 6 data were assumed to be nonresponders at week 6, and (2) when 1 or more consecutive assessments were missing, and response scores before and after the missing assessment(s) were identical, we assumed the same response status for the missed assessments.

Patients were categorized into 1 of 3 sustained response groups at each assessment. Sustained response was defined as 2 consecutive ratings of "full responder." Possible sustained response was defined as 1 rating of "full responder" followed by no additional stage 2 or 3 data. All other response patterns were defined as nonsustained response. At week 12, only 4 patients (1 COMB, 1 FLX, 2 CBT) were classified as possible sustained response. For ease of presentation, they were combined with the nonsustained response group at week 12.

Maintenance of Sustained Response

Once patients experienced sustained response, sustained response status at subsequent assessments was classified as (1) "failed to maintain," given a subsequent assessment of nonresponder or partial responder (CGI-I score = 3-7); (2) "maintained sustained response," given continued assessments of full responder; or (3) "unknown," if additional independent evaluator data following sustained response were not available.

STATISTICAL METHODS

Analyses were conducted by 2 of us (S.G.S. and S.T.T.). Fisher exact tests were conducted to test for between-treatment differences in rates. The level of significance was set at .05 for each 2-tailed statistical test.

Differences in the amount of missing data between the 3 conditions could have affected our ability to detect treatment effects. Differences in the amount of missing independent evaluator data across conditions and assessments were nonsignificant, with one exception: week 24, $P < .01$. Paired contrasts indicated more missing data for FLX compared with COMB patients (22.5% vs 5.8%; $P < .01$); CBT patients were intermediate (13.2% missing data) and did not differ from the other 2 groups. Given the lack of systematic differences across conditions in missing data, no adjustments were made.

RESULTS

SUSTAINED RESPONSE IN STAGE 1

Among the 242 participants, 147 (60.7%) were classified as having a sustained response by week 12: 70.9% COMB, 67.5% FLX, and 42.1% CBT. The overall difference was significant: $n = 147$; $\chi^2 = 16.35$; $P < .001$. Paired contrasts indicated that, compared with CBT, rates of sustained response by week 12 were significantly higher for COMB ($P < .001$) and FLX ($P = .001$) patients, whose rates did not differ.

SUSTAINED RESPONSE IN STAGES 2 AND 3 FOR PATIENTS WHO HAD NOT ACHIEVED SUSTAINED RESPONSE IN ACUTE TREATMENT

Ninety-five of the 242 participants (39.3%) were classified as having a nonsustained response by week 12: 29.1% COMB, 32.5% FLX, and 57.9% CBT. **Table 1** shows whether sustained response during weeks 18 and 36 was

Table 1. Sustained Response During Weeks 18 Through 36 for Patients Who Had Not Achieved Sustained Response by Week 12

Treatment Arm	No. (%) of Patients Who Had Not Achieved Sustained Response by Week 12	Weeks 18 and 36 Sustained Response Status ^a	No. (%)
COMB (n=86)	25 (29.1)	Sustained response	15 (60.0)
		Possible sustained response	5 (20.0)
		Nonsustained response	5 (20.0)
FLX (n=80)	26 (32.5)	Sustained response	12 (46.2)
		Possible sustained response	4 (15.4)
		Nonsustained response	10 (38.5)
CBT (n=76)	44 (57.9)	Sustained response	25 (56.8)
		Possible sustained response	9 (20.5)
		Nonsustained response	10 (22.7)
All Active Treatments (n=242)	95 (39.3)	Sustained response	52 (54.7)
		Possible sustained response	18 (18.9)
		Nonsustained response	25 (26.3)

Abbreviations: CBT, cognitive behavioral therapy; COMB, FLX/CBT combination; FLX, fluoxetine.

^aThe "Weeks 18 and 36 Sustained Response Status" column indicates whether the patient achieved sustained response at any point during the period. If the patient had multiple response classifications across the period, the best response status was counted. The clinical ordering of response status from best to worse is "sustained response" (ie, 2 consecutive ratings of "full responder," defined as a Clinical Global Impression–Improvement²⁰ score=1 or 2), "possible sustained response" (ie, 1 rating of "full responder" either at the end of stage 3 or followed by missing assessments only), and "nonsustained response" (all other responder patterns).

Table 2. Maintenance of Sustained Response During Weeks 18 Through 36 for Patients Who Achieved Sustained Response by Week 12^a

Treatment Arm	No. (%) of Patients Experiencing Sustained Response by Week 12	Weeks 18 and 36 Maintenance Status	No. (%)
COMB (n=86)	61 (70.9)	Failed to maintain	7 (11.5)
		Maintained sustained response	53 (86.9)
		Unknown	1 (1.6)
FLX (n=80)	54 (67.5)	Failed to maintain	14 (25.9)
		Maintained sustained response	38 (70.4)
		Unknown	2 (3.7)
CBT (n=76)	32 (42.1)	Failed to maintain	1 (3.1)
		Maintained sustained response	30 (93.8)
		Unknown	1 (3.1)
All Active Treatments (n=242)	147 (60.7)	Failed to maintain	22 (15.0)
		Maintained sustained response	121 (82.3)
		Unknown	4 (2.7)

Abbreviations: See Table 1.

^aPatients who experienced sustained response were classified on the degree to which they maintained their sustained response status for subsequent assessments. Maintenance status consisted of "failed to maintain" (ie, a subsequent assessment of "nonresponder" or "partial responder"; Clinical Global Impression–Improvement²⁰ score=1-3), "maintained sustained response" (ie, continued assessments of "full responder"), or "unknown" (ie, no assessment data were available following sustained response).

achieved for these patients as a function of condition. The majority of adolescents who had not achieved sustained response by week 12 achieved either definite or possible sustained response by week 36: 80.0% COMB, 61.5% FLX, and 77.3% CBT. Sustained response rates by week 18 are not presented in Table 1 but indicated that treatment response tended to occur slowly (48.0% COMB, 34.6% FLX, and 31.8% CBT). Differences in sustained response status across the 3 treatment conditions at both weeks 18 and 36 were nonsignificant.

MAINTENANCE OF SUSTAINED RESPONSE IN STAGES 2 AND 3 FOR PATIENTS WHO ACHIEVED SUSTAINED RESPONSE IN ACUTE TREATMENT

The next analyses examined whether the 147 patients who achieved sustained response by week 12 maintained that

status during TADS continuation and maintenance therapy. The maintenance of sustained response during weeks 18 and 36 for week 12 sustained responders is shown in **Table 2**. Among this subset of patients who responded well to acute therapy, the majority (82.3%) maintained their sustained response throughout stages 2 and 3 (ie, assessments at weeks 18, 24, 30, and 36). Fifteen percent, however, failed to maintain their sustained response, with rates differing as a function of treatment modality: 11.5% COMB, 25.9% FLX, and 3.1% CBT. The overall treatment by sustained response status effect was significant (Fisher exact $P = .01$). Paired contrasts indicated that the maintenance of sustained response was higher for CBT compared with FLX ($P = .007$) and approached significance in COMB compared with FLX ($P = .06$). Rates of maintaining sustained response in COMB vs CBT did not differ.

POTENTIAL DIFFERENCES IN DEPRESSIVE SEVERITY ASSOCIATED WITH SUSTAINED RESPONSE FOR DIFFERENT TREATMENT CONDITIONS

Given that a smaller proportion of CBT patients reached sustained response during stage 1 compared with COMB and FLX patients (42% vs 71% and 68%, respectively), it was possible that this subset of CBT patients had been less depressed at baseline than COMB and FLX patients who achieved sustained response during stage 1. CDRS-R scores at baseline for the COMB, FLX, and CBT patients who achieved sustained response by week 12 were compared and did not differ (baseline mean [SD] scores=60.4 [12.2], 59.2 [10.4], and 57.5 [7.9], respectively). Overall general linear model results were $F_{2,144}=0.77$; $P=.46$. As a secondary check, we compared the 3 groups of sustained responders on depression level at week 12. Differences between COMB, FLX, and CBT groups were nonsignificant (week 12 mean [SD] CDRS-R scores=28.3 [7.7], 29.7 [6.2], and 29.6 [6.5], respectively). Overall general linear model results were $F_{2,141}=0.67$; $P=.51$. Previously, Curry and colleagues²¹ identified 3 moderators of treatment condition, annual family income, severity of depression (CGI-S score), and cognitive distortions (Children's Negative Cognitive Errors Questionnaire²² score), and we compared sustained responders in the 3 conditions on baseline levels of these 3 moderators. Differences on family income and depression severity as per CGI-S score were nonsignificant, although group differences on cognitive distortions were present ($F_{2,144}=3.92$; $P=.22$), with higher cognitive distortions for COMB compared with FLX patients (mean [SD] scores=68.3 [19.3] vs 58.8 [19.0]; $P=.008$; CBT patients did not differ from either group, mean [SD] score=60.8 [17.3]).

TREATMENT ATTENDANCE IN STAGES 2 AND 3

Condition differences in the rates of maintaining sustained response may have been influenced by differential attendance. Because stage 2 treatment was designed to provide more treatment for partial responders compared with full responders, attendance was examined as a function of stage 1 response. Using the Wilcoxon rank sum test, all differences in attendance during stages 2 and 3 between conditions were nonsignificant. Full responders at week 12 ($n=161$) attended a mean (SD) 4.3 (2.0) of the 5 pharmacotherapy sessions and 4.9 (2.3) of the 6 CBT sessions. Week 12 partial responders ($n=50$) attended 4.3 (2.6) of the 6 pharmacotherapy sessions and 6.0 (2.2) of the 9 CBT sessions.

Treatment provided outside of TADS was infrequent (6.2% began taking non-TADS antidepressants; 12.0% began non-TADS psychotherapy during stages 2 and 3). Analyses examining the achievement and maintenance of sustained response were recomputed after deselecting the 34 patients who received adjunctive treatment and the pattern of results remained identical.

COMMENT

The purpose of this study was to describe the rates at which adolescents with depression in 3 treatment arms were able to achieve and maintain a sustained response during continuation and maintenance therapy as developed in TADS. Information on sustained response can be used by the clinician and the family to guide important decisions regarding the optimal course of treatment after the acute phase.

Rates of sustained response during acute therapy were significantly higher for the 2 conditions that included FLX compared with CBT monotherapy. Regarding the achievement of sustained response during continuation and maintenance therapies, 55% of adolescents with depression who had not reached sustained response by the end of acute treatment subsequently achieved this outcome during additional therapy, with an additional 19% possibly reaching this threshold. By the end of maintenance therapy, rates of sustained response across the 3 conditions were comparable, suggesting that CBT has a slower effect in treating depression. The findings suggest that approximately three-quarters of adolescents with depression who have not fully responded after 12 weeks of acute treatment will experience sustained response with further treatment. As noted earlier, Clarke and colleagues¹³ found that additional treatment produced further symptom reduction in those who were partially recovered during acute treatment. Also consistent with the present findings, from a study of 107 adolescents treated with various psychosocial interventions,²³ among the subset of 18 patients who had subsyndromal depression (ie, 2-3 MDD symptoms) at the end of acute treatment, 94% experienced recovery in the 2-year follow-up period, which included 2 to 4 booster sessions for all patients and open treatment for approximately half. In conclusion, these findings emphasize the value of ongoing treatment in facilitating the depression recovery process, even if psychosocial treatment occurs on a significantly less frequent basis. The findings also suggest that continuation and maintenance treatment guidelines explicitly recognize the value of "continued response among partial responders" as a stated goal.

The second method of evaluating continuation and maintenance therapies consisted of the degree to which patients who achieved sustained response during acute treatment were able to maintain that response through continuation and maintenance therapies. To our knowledge, TADS is the first study to contrast the impact of psychosocial and pharmacotherapy treatments on depression response in adolescents. Although the rate of sustained response improvement during acute treatment for patients receiving CBT was significantly lower than combination therapy or FLX monotherapy, among the subset of CBT patients who did achieve this measure of improvement by week 12, only 3.1% failed to maintain their sustained response during the following 24 weeks. This rate was significantly lower than that of patients receiving FLX (25.9%), a rate similar to the relapse rate of 34% over 32 weeks of continued FLX

management reported by Emslie et al.¹¹ This difference is the first TADS finding in which CBT monotherapy significantly outperformed the FLX monotherapy condition, although it only applied to the subset of patients still in their assigned treatment arm. The sustaining of response, which is consistent with findings from some adult studies,²⁴ is promising and warrants further investigation.

Although patients were assigned randomly to treatment modalities, the rate and degree to which patients across conditions achieved sustained response in acute therapy may have unbalanced the groups with respect to preexisting characteristics, a phenomenon that has been referred to as the "differential sieve effect."²⁵ Thus, while one interpretation of the present findings is that CBT improves the ability of adolescents with depression who respond to maintain their positive response to treatment, it is also possible that these results were due to other factors, such as patients who are at risk for relapse and recurrence being more likely to respond to pharmacotherapy compared with CBT. We examined 4 factors that might bias the results (ie, 2 measures of depression severity, family income, and cognitive distortions). We found no evidence suggesting that the group of CBT patients who achieved sustained response during stage 1 entered treatment less severely depressed than sustained responders in either the COMB or FLX conditions or differed on other variables previously found to moderate TADS treatment.²¹ Nonetheless, sustained responders across conditions could have differed on a number of other pretreatment factors and the phenomenon of a differential sieve effect needs to be carefully examined in future research.

Although quite limited, previous research with adolescents with depression has failed to detect a protective effect for CBT. For example, among 54 child/adolescent patients treated with either CBT or an expanded assessment procedure who were followed up for 2 years, 20% experienced recurrence with no differential treatment effects,²⁶ although patients received only 6 sessions of CBT on average. As noted earlier, Clarke et al¹³ found no effect for CBT booster sessions in the prevention of depression recurrence. In a follow-up study of the 3 psychosocial interventions evaluated by Birmaher and colleagues,²⁷ treatment conditions did not predict recurrence. Conversely, in the study with adults with depression that most closely parallels the TADS design, Hollon et al²⁸ compared relapse/recurrence rates for adult patients who remitted during cognitive therapy with patients who remitted while taking antidepressant medication and found that cognitive therapy continuation treatment at a greatly reduced dose (3 booster sessions over a 12-month period) was as effective as continued full-dosage pharmacotherapy in preventing relapse.

We also examined attendance rates in continuation and maintenance therapy as a basic aspect of treatment use. Both full and partial responders by week 12 appeared to find value in both continuation and maintenance treatments as designed by TADS and there was no indication that rates of sustained response were differentially impacted across treatments by attendance. In addition, attendance rates were comparable for patients as-

signed to combination therapy relative to either monotherapy, suggesting that patients engaged in 2 forms of treatment did not reduce their commitment to either monotherapy.

Several important limitations to the present study need to be acknowledged. First, our outcome measure of sustained response is related to, but not synonymous with, the criteria of recovery or recurrence. While the achievement of sustained response represents a significant reduction in depression severity, a subset of these adolescents were still experiencing persisting depressive symptoms or some degree of functional impairment. The TADS assessment battery did not track the week-by-week course of depression symptoms necessary to diagnose depression recovery, relapse, or recurrence with absolute confidence. Thus, comparison of the present findings with previous research is somewhat limited. Second, we had no PBO or untreated group following acute treatment. This design decision was made purposefully, for both scientific and ethical reasons, but it meant that we do not know how many patients would have achieved and maintained a sustained response with no postacute intervention. That said, given the lower rates of sustained response among CBT patients at the end of acute treatment and the higher rates of failure to maintain sustained response for patients receiving FLX monotherapy, the present findings clearly support the value of continuation and maintenance therapies. A third, and very important, limitation of the present study is the lack of data on treatment compliance or adherence for either CBT or pharmacotherapy in the continuation and maintenance phases of TADS. It is possible that adolescents receiving FLX discontinued or were more erratic with medication following the positive response, as the discontinuation of antidepressant therapy among adults is frequent.²⁹ We recognized that treatment attendance serves as a necessary but not sufficient factor in CBT and is not even required for adequate pharmacotherapy, if the patients continue to take their medication. A fourth limitation is that a small subset of TADS participants (n=28 [10%]) had been evaluated by the treatment provider to be clear nonresponders at the end of stage 1 acute treatment and were referred for treatment outside of TADS prior to stage 2. Thus, the present findings may be generalized to patients who have demonstrated at least a partial response to medications or CBT within 12 weeks. Lastly, some attrition had occurred during stage 1, which may have influenced the present findings. Although not significant across conditions, approximately 17% of TADS patients discontinued or augmented treatment during stage 1.

Given that a larger proportion of patients recover from FLX therapy than CBT but the sustained response may not be as enduring, one hypothesis for future research is that FLX monotherapy needs to be augmented once depression recovery has occurred, and CBT would seem to be a reasonable place to start. Continuation and maintenance treatments in TADS were designed to extend the acute treatment modality rather than to introduce new treatment modalities. While the issue of a stepped program of care has not, to our knowledge, been evaluated in adolescents with depres-

sion, there has been a recent shift toward the use of sequencing treatments to achieve remission in adults, as in the landmark study Sequenced Treatment Alternatives to Relieve Depression.³⁰ Stepped care protocols are based on the rationale of limiting the use of more expensive and time-consuming treatments, such as combination treatment, to the patients with more severe depression or treatment-resistant patients. Although much of the literature describes the sequencing of medication strategies, there is some support for the sequencing of pharmacotherapy and psychosocial treatments.^{31,32}

Another direction for future research consists of the adolescent's depressive course once treatment has ended. Adult patients who received cognitive therapy, with or without continuing clinical management, have been found to have significantly lower relapse and recurrence rates than medication patients, following withdrawal from medication.³³⁻³⁵ The rates of MDD recurrence in the 1-year open follow-up (stage 4) of TADS will be addressed in a subsequent report.

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

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