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 treatment\(^3\)), 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 effective 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.\(^6,7\)

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 CBT\(^8\) 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-
Depression Study14-16 (TADS). TADS is a randomized con-
of sustained improvement during continuation and main-
insurance policies may be to facilitate continued improve-
ance did not associated with less depression recurrence
among recovered patients (27% recurrence among booster
patients vs 8% among assessment-only controls; P < .05).
This study suggests that an important function of post-
acute treatments may be to facilitate continued improve-
ment among partial responders.

The goal of the present study was to examine the rates
of sustained improvement during continuation and main-
inance in TADS, we compared whether treatment modali-
ties 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 attend-
ance. 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 at-
tend postacute treatment. Although we are unable to
evaluate the degree to which patients complied with con-
tinuation and maintenance therapies in TADS, we com-
pared whether treatment attendance varied across

The TADS design has been extensively documented in previ-
ous publications13-16 and will be only briefly reviewed herein.

STAGE 1 PARTICIPANTS AND PROCEDURES

Between 2000 and 2003, 439 adolescents at 13 sites were en-
rolled. Both adolescents and parents provided written in-
formed 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 pri-
mary 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 mea-
sure of depression severity in the past week, and (2) re-
ponder status on the 7-point Clinical Global Impression–
Improvement (CGI-I).20

Inclusion criteria were (1) 12 to 17 years of age, (2) diag-
nosis of current DSM-IV MDD, (3) CDRS-R total score of 43
or higher, (4) stable mood symptoms for at least 6 weeks, and
(5) impairment in at least 2 settings. Exclusion criteria in-
cluded (1) psychiatric disorders requiring out-of-protocol treat-
ments, (2) 1 failed CBT trial or 2 failed selective serotonin re-
uptake inhibitor trials for depression, (3) current psychiatric
treatment (other than stable dose of stimulant medication
for attention-deficit/hyperactivity disorder), (4) non-English speak-
ing, (5) confounding medical condition, (6) previous toler-
ance to FLX, (7) pregnant or sexually active while refusing ac-
ceptable 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-
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–Improvement20 assessments completed for 242 cases at weeks 18 and 36.

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 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.
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 \( r = 0.81, 0.80, \) 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 assumptions 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 (22.3% vs 3.8%; \( P < .01 \)); 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
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.

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

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>No. (%) of Patients Who Had Not Achieved Sustained Response by Week 12</th>
<th>Weeks 18 and 36 Sustained Response Status</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMB (n=86)</td>
<td>25 (29.1)</td>
<td>Sustained response</td>
<td>15 (60.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Possible sustained response</td>
<td>5 (20.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nonsustained response</td>
<td>5 (20.0)</td>
</tr>
<tr>
<td>FLX (n=80)</td>
<td>26 (32.5)</td>
<td>Sustained response</td>
<td>12 (46.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Possible sustained response</td>
<td>4 (15.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nonsustained response</td>
<td>5 (20.0)</td>
</tr>
<tr>
<td>CBT (n=76)</td>
<td>44 (57.9)</td>
<td>Sustained response</td>
<td>25 (56.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Possible sustained response</td>
<td>9 (20.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nonsustained response</td>
<td>10 (22.7)</td>
</tr>
<tr>
<td>All Active Treatments (n=242)</td>
<td>95 (39.3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

*The “Weeks 18 and 36 Sustained Response Status” column indicates whether the patient achieved sustained response at any point during 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**

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

Abbreviations: See Table 1.

*Patients 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).*
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 colleagues 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, 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 outcome during additional psychosocial 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 colleagues 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, 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.
management reported by Emslie et al. 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, 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.” 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. 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, although patients received only 6 sessions of CBT on average. As noted earlier, Clarke et al 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, treatment conditions did not predict recurrence. Conversely, in the study with adults with depression that most closely parallels the TADS design, Hollon et al 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 assigned 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. 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. 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.

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. 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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Disclaimer: The opinions and assertions contained in this report are the private views of the authors and are not to be construed as official or as reflecting the views of the National Institute of Mental Health, the National Institutes of Health, or the Department of Health and Human Services.

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


