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Remission and Recovery in the Treatment for Adolescents with Depression Study (TADS): Acute and Long-term Outcomes

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Abstract

Objective—We examine remission rate probabilities, recovery rates, and residual symptoms across 36 weeks in the Treatment for Adolescents with Depression Study (TADS).

Method—TADS, a multisite clinical trial, randomized 439 adolescents with major depressive disorder (MDD) to 12 weeks of treatment to fluoxetine (FLX), cognitive behavioral therapy (CBT), their combination (COMB), or pill placebo (PBO). The PBO group, treated openly after week 12, was not included in the subsequent analyses. Treatment differences in remission rates and probabilities of remission over time are compared. Recovery rates in remitters at week 12 (acute phase remitters) and week 18 (continuation phase remitters) are summarized. We also examined whether residual symptoms at the end of 12 weeks of acute treatment predicted later remission.

Results—At Week 36, the estimated remission rates for intention-to-treat cases were: COMB: 60%, FLX: 55%; CBT: 64%; overall: 60%. Paired comparisons reveal that at week 24 all active treatments converge on remission outcomes. The recovery rate at Week 36 was 65% for acute phase remitters and 71% for continuation phase remitters, with no significant between-treatment differences in recovery rates. Residual symptoms at the end of acute treatment predicted failure to achieve remission at weeks 18 and 36.

Conclusions—The majority of depressed adolescents in all three treatment modalities achieved remission at the end of nine months of treatment.

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Keywords

adolescent depression; remission; residual symptoms; recovery

Introduction

In recent years, our understanding of acute treatment outcomes in pediatric depression has increased; however, much less is known about the long-term outcomes following acute treatment. Guidelines on continuation and maintenance phase treatments in youth have been proposed, but few studies have specifically investigated the effectiveness of interventions in these phases of treatment, particularly with respect to remission and recovery.[1–2] Most of the reports on later outcomes in treatment in this age group are from naturalistic follow-up studies. The Treatment for Adolescents with Depression Study (TADS) included an acute phase of treatment (Stage I, 0 −12 weeks) followed by a continuation phase (Stage II, 12 to 18 weeks) and a maintenance phase component (Stage III, weeks 18 to 36). In this paper we evaluate the remission and recovery rates through week 36 in the TADS sample.

Few reports of remission rates after acute treatment in pediatric depression are available. The most common efficacy outcome in clinical trials is response, typically defined as a clinician rating of improvement. Remission, a more stringent outcome, is defined as a return to a symptom free or near symptom free status. Brent and colleagues reported a remission rate of 64.7% (defined as absence of MDD on the K-SADS-P/E and 3 consecutive weekly scores on the Beck Depression Inventory, BDI, of < 9).3 Birmaher and colleagues, in a 12- to 16- week psychotherapy trial, reported a remission rate of 64% at the end of acute treatment.4 Remission rates in antidepressant trials in youth range from 23% to 63%.5–6 Recently the TADS reported on remission rates, defined as the attainment of a Childhood Depression Rating Scale-Revised (CDRS-R)7 score of ≤ 28 at the end of acute treatment.6 The remission rate across treatment groups was only 23% after twelve weeks of acute treatment. Although the rate of remission for the combination treatment of fluoxetine and cognitive behavioral therapy (CBT) was the highest of the four treatment arms, at 37%, it is clearly a less than optimal rate given that this represents the most intensive and effective treatment available to date for adolescent depression.8

Reports of remission outcomes during the continuation phase of treatment in children with depression are rare. Birmaher and colleagues report a cumulative remission rate of 83.7% over a 2-year period.[4] In adult studies of continuation treatment for depression, rates of remission in continuation treatment ("late remitters") range from 30–53%.[9–11]

Relatively little is known about sustained remission or recovery in continuation care. A recent ACNP task force recommended that recovery be defined as the achievement of remission which is sustained by a well period of at least four months.[12] Much of the adult literature to date uses terms of sustained remission, or maintained remission. The rates of maintenance of remission in adults effectively treated for depression range from 67 to 86%.[9–11] Combination treatment appears to have higher rates of remission maintenance compared to those who received either monotherapy.[11]

There have been more investigations of longer-term outcomes in recovery. Clarke and colleagues examined continuation phase recovery rates in adolescents after acute phase group CBT with or without parent group.[13] Continuation phase recovery rates at one year were: 100% (5/5) for booster sessions and 50% (6/12) in the two assessment conditions ($p < .05$). While booster sessions were associated with better continuation phase outcomes, the study was limited by its small sample size. In addition, Birmaher and colleagues found an 80% recovery

rate at the 2-year follow-up of an acute psychotherapy trial.[4] Finally, naturalistic follow-up studies of pediatric depression have found that the average rates of recovery from first-episode MDD range from nine to twelve months.14–15

In adult depressed patients, reaching remission in acute care resulted in better follow-up outcomes than merely achieving responder status.[12] Regardless of response status, the presence of residual symptoms after acute treatment for major depressive disorder (MDD) has been found to increase the risk of relapse in adults.[16–18] Similarly, partial remission was related to poor outcomes in both medication and CBT trials.[17,19–23] In the TADS trial, among patients having an adequate treatment response (defined as very much improved or much improved on the Clinical Global Impressions-Improvement scale, CGI-I),[24] 50% had one or more residual symptoms at the end of acute treatment.6 While few studies have investigated whether the presence of residual symptoms in youth is associated with poorer outcomes, a recent report suggests that, similar to adults, youth with residual symptoms at the end of acute treatment are at a high risk for relapse.25 In addition, having subsyndromal depressive symptoms in adolescence places youth at risk for slower recovery, subsequent major depression, and other negative outcomes such as substance abuse.[26–28]

TADS was a controlled clinical trial of pharmacotherapy with fluoxetine (FLX), CBT, their combination (COMB), or clinical management with pill placebo (PBO) in adolescents with MDD. The rationale, design, and methods for the study are presented in previous reports.[29–30] In addition, the primary outcome results from the acute treatment phase and the long-term outcomes of the study have been reported.31–32 The initial report of 36 week outcomes demonstrates that all three active treatments converged with respect to clinical response, with over 80% showing response in each group. In this report, we present the continuation and maintenance phase outcomes on remission and recovery, which typically are considered to be more stringent outcomes than response or sustained improvement.

Method

Study Participants

The methods for the TADS have been described in prior publications.[29,31,33] The original TADS sample was comprised of 439 adolescents who met DSM-IV criteria for MDD and had a CDRS-R score of 45 or greater at study entry. The demographic and clinical characteristics of the TADS sample are presented in a prior report.[33] Study participants were randomized to one of the four treatment conditions: COMB (n=107), FLX (n=109), CBT (n=111), and PBO (n=112).

All 439 teenagers randomized to treatment were encouraged to continue assessments throughout the 36-week period regardless of treatment compliance, termination of randomized treatment, or use of concomitant treatments. The two blinded conditions (PBO and FLX) were unveiled and the PBO arm was discontinued at the end of the 12-week acute treatment phase (Stage I), regardless of treatment response. PBO-treated patients who were partial or non responders at the end of Stage I were followed in open treatment by TADS clinicians. PBO responders were offered phone follow-up and their choice of the three active TADS treatments upon relapse. Only those youth randomized to active treatment (COMB, FLX, and CBT) who were a full responder or partial responder at the end of Stage I continued in their randomized treatment arm during the subsequent six-week consolidation phase (Stage II) which was followed an 18 week maintenance phase (Stage III). Full response was defined by the clinician as CGI-I score of 1 (very much improved) or 2 (much improved) at the end of Stage I, while partial response was indicated by a CGI-I score of 3 (minimally improved).

Treatment

During Stage I, participants in a medication arm (i.e., FLX, COMB, and PBO) received an initial 60-minute visit, followed by 20- to 30-minute visits with the study psychiatrist over the 12 weeks of treatment. The initial visit included an education component, and all visits consisted of assessment of patient status and side effects monitoring. Both PBO and FLX began with one week of 10 mg/day, followed by an increase to 20 mg/day. From week 4 through the remainder of acute treatment, dose increases (10 mg/day increments) were based on response and tolerability to a maximum of 40 mg/day. Beginning with the week 12 visit, the dose could be increased up to a maximum of 60 mg/day in partial responders and the dose for the full-responders was continued for those adolescents in the COMB and FLX arms. In Stage II, full responders had two office visits and partial responders had four office visits. In Stage III, the medication dose remained constant unless adverse events required a dose reduction and patients were followed at 6-week intervals.

TADS CBT in Stage I consisted of 15 60-minute sessions. COMB and CBT participants determined by the clinician to be partial responders at week 12 received six additional weekly sessions in Stage II. Stage I full responders received biweekly CBT session in stage II. In the 18-week Stage III maintenance phase participants had three "booster" sessions, each 6 weeks apart. COMB participants received all the components of medication management and CBT.

Measures

Participants were assessed by a blinded Independent Evaluator (IE) at baseline, as well as weeks 6, 12 (end of Stage I acute treatment), 18 (end of Stage II), 24, 30, and 36 (end of Stage III). The IE provided the ratings for the measures described below.

The CDRS-R,[7] a 17-item clinician-rated measure of depression severity with each item rated on a scale of 1 to 5 or 1 to 7, was completed at each IE assessment. The total score was based on the synthesis of information from interviews with the adolescent and the parent. Interrater reliability on the CDRS-R at baseline (intraclass correlation coefficient of .95) and week 12 (intraclass correlation coefficient of .98) was high.[33]

The CGI-I measures the clinician's impression of improvement rated relative to baseline severity.[24] This seven–point Likert scale was completed by the IE. Responder status was defined by an end of acute treatment score of "very much improved" or "much improved" (i.e., 1 or 2 respectively) and partial response was defined as a CGI-I of 3. Treatment dosing and continuation, however, was determined by the treating clinician's CGI-I ratings.

The Schedule for Affective Disorders and Schizophrenia for School-Age Children--Present and Lifetime version (K-SADS-PL)[34] was completed at baseline and then repeated at week 12 (end of acute treatment) to determine the presence of residual symptoms. A depressive symptom was rated as present or not present, with the threshold for presence being defined as a score of at least 3.

Concomitant treatment and medication logs, as well as a modified version of the Child and Adolescent Services Assessment (CASA)[35] documented mental health treatment received outside of TADS. The CASA assesses mental health service utilization (defined as inpatient or outpatient services for emotional, behavioral or substance problems).

Definition of Remission, Recovery, and Residual symptoms

Remission for the analyses in this manuscript is defined as CDRS-R $\leq$ 28. This definition is consistent with previous definitions of remission in the child and adolescent psychiatry literature.[6,36–38] Recovery was determined using two subsamples: 1) remitters at week 12

(acute phase remitters) and 2) remitters at week 18 (continuation phase remitters, i.e. those not remitted at week 12). In acute phase remitters, participants were defined as recovered if they retained remission status at weeks 18, 24, 30, and 36. For the continuation phase remitters, recovery was defined as retaining remission at weeks 24, 30, and 36. A residual symptom was defined as the presence of a score of at least one affective symptom on the K-SADS-PL at week 12.

Data Analysis

The primary analyses of remission rates, recovery rates, and impact of residual symptoms were conducted using an "intention-to-treat" (ITT) approach in which the analysis included all participants randomized to treatment regardless of protocol adherence and/or treatment completion. Analyses were conducted to examine remission rates (a) during the 12-week acute treatment phase in the four treatment conditions (Stage I) and (b) across the 36-week treatment period in those youth randomized to one of the three active treatment arms (Stages I–III). Because the PBO condition was discontinued at the end of Stage I, this arm was excluded from the Stage I–III analyses.

For Stage I, the ITT analysis (N=439) included the data from all participants randomized to treatment For Stages I–III, the ITT analysis focused on the youths randomized to COMB, FLX, and CBT arms at the beginning of Stage I (N=327).

A longitudinal data analysis approach was employed and were designed to examine remission rates in the treatment arms during the post-randomization period. Generalized linear mixed models (GLMM) for binary outcomes applying a Generalized Estimating Equations (GEE) method with a logit link function for a binomial distribution were used to compare treatment differences in remission rates across time and estimate the probabilities of remission over time for the treatment arms. These hierarchical mixed model tested for fixed effects of site, treatment, time, and the treatment-by-time interactions and the random effects of patient and patient-by-time. The initial models included site and its two-and three-way interactions. Because the site interactions were not statistically significant ($p > .05$), these interactions were omitted from the final analytic models while retaining the main effect of site since treatments were nested within clinical site. The original 13 clinical sites were collapsed into ten sites[32–33] so as to adjust for three low enrolling sites which were affecting the stability of the analytic models. More specifically, each low enrolling site was combined with another site with similar baseline demographics and treatment effects to form one site. For the 28 adolescents who dropped out of the study before completing the first post-baseline assessment, their week 6 score was set to 0 (no remission) given that all patients met criteria for major depression and a CDRS-R total of 45 or greater at baseline.

Chi-square tests were used to determine whether residual symptoms at Week 12 are associated remission at weeks 18 and 36. All analyses were conducted using SAS 8.2® and the level of significance was set at 0.05 for each statistical test. *A posteriori* paired comparisons were conducted only if the omnibus test was significant at the 0.05 level for treatment or treatment-by-time effects.

Results

Baseline Characteristics

Table 1 presents the baseline demographic and clinical characteristics for adolescents included in the Stage (N=439) and Stages I–III (N=327) ITT analyses. There were no statistically significant differences between treatment groups on any of the baseline measures for any of the analysis samples.

Stage I Remission Rates for the Four Treatment Conditions

The remission rates, using predicted scores from the GEE method, for Stage I cases at the end of acute treatment were: COMB: 39%; FLX: 24%; CBT: 19%, PBO: 19%. With the PBO arm included, the overall rate was 26% for the ITT cases. Although the treatment-by-time interaction was not significant ($\chi^2 = 7.54$, df = 3, $p < .06$), the main effects for treatment ($\chi^2 = 24.26$, df = 3, $p < .0001$) and time ($\chi^2 = 32.87$, df = 1, $p < .0001$) were significant. Site was a significant covariate ($p = .0029$). Because the main effect of treatment was statistically significant, we conducted paired contrasts at week 12. COMB had a significantly higher remission probability at week 12 compared to FLX ($\chi^2 = 4.64$, df = 1, $p = .0313$), CBT ($\chi^2 = 8.52$, df = 1, $p = .0035$), and PBO ($\chi^2 = 8.77$, df = 1, p=.0031). These results are consistent with the week 12 findings reported by Kennard et al (2006) using a logistic regression model controlling for site and applying a last observation carried forward imputation method.

Stages I–III Remission Rates for the Three Active Treatment Conditions

Figure 1 presents estimated remission rates based on the predicted probabilities of remission derived from the GEE method for the three active treatment arms across assessments. The overall estimated remission rate for the 327 cases in the three active treatment arms was 27% at week 12, 40% at week 18, and 60% at week 36. The analysis indicated that the main effects of treatment ($\chi^2 = 10.95$, df = 2, $p = .0042$) and time ($\chi^2 = 127.43$, df = 5, $p < .0001$) were significant, as were the treatment-by-time interactions ($\chi^2 = 32.96$, df = 10, $p = .0003$). Site was also a significant predictor ($p = .0022$).

Paired comparisons revealed that at week 24 all active treatments converged on remission outcomes (Table 2). COMB and FLX were superior to CBT at Week 6 (COMB vs CBT, $p = .0001$; COMB vs FLX, $p = .0068$), while COMB was superior to both monotherapies at Weeks 12 (COMB vs CBT, $p = .0033$; COMB vs FLX, $p = .0261$) and 18 (COMB vs CBT, $p = .0002$; COMB vs FLX, $p = .0087$). The estimated remission rates, Stage I – III, for the COMB, FLX and CBT groups were 39%, 24% and 19%, respectively at week 12, while the estimated remission rates at week 18 were 56%, 37%, and 27%, respectively. At week 36, the estimated remission rates were: COMB: 60%, FLX: 55%; CBT: 64%; overall: 60%.

Recovery Rates in Acute and Continuation Phase Remitters

Table 3 summarizes recovery rates, defined as maintaining remission once achieved, at subsequent assessments for patients who were: (a) remitters at end of Week 12 (acute phase remitters) and (b) remitters at the end of Week 18 (continuation phase remitters). The recovery rate at Week 36 was 65% for the acute phase remitters and 71% for the continuation phase remitters. Chi-square analyses indicated no significant between-treatment differences in recovery rates at each subsequent assessment for the acute and continuation phase remitters.

Stage I Residual Symptoms and Remission

Residual symptoms were defined by the nine MDD items from the K-SADS-PL Week 12 assessments. For Stages I–III analyses that include youths randomized to one of the three active treatment arms, the total number of residual symptoms at Week 12 in remitters was 0.28 ± 0.62 and in non-remitters was 3.24 ± 2.23. Total number of residual symptoms at week 12 was significantly correlated with remission status at Weeks 18 ($r = -0.52$, $p < .0001$) and 36 ($r = -0.37$; $p < .0001$), with a greater number of symptoms at week 12 associated with non-remission status at both weeks 18 and 36.

Treatment within and outside of the TADS Study

Table 4 presents descriptive data on participants receiving treatment within and outside of TADS for each treatment stage of the study. Overall these findings demonstrate that in Stages

I and II, most of the combination participants remained in their assigned treatment arm, while many in monotherapy did not (between 34 to 46%). Furthermore, those initially assigned to monotherapy, in Stages II and III frequently added the monotherapy that they were not already receiving (FLX added psychosocial treatment, and CBT added an antidepressant medication).

Discussion

In this study, we report on later remission rates in pediatric depression. Earlier we reported on acute remission outcomes for the TADS sample,[6] with 23% of patients having achieved remission. Although this rate was relatively low, the present report found that later remission rates are considerably better. By week 36 the overall estimated remission rate is around 60%, more than doubling the rate found at week 12. This remission rate is comparable to the overall cumulative remission rate found in the STAR*D trial, which was 67%.[39] These findings highlight the importance of continuation and maintenance phase treatments, as the rates of remission improve with time and continued treatment. While the outcome for the majority of patients who continue in treatment is promising, it is important to recognize that a substantial number of patients who undergo nine months of treatment fail to achieve remission.

Combination treatment and fluoxetine monotherapy achieved significantly higher rates of remission early in treatment (Week 6), compared to CBT (only 4%). The combination of fluoxetine and CBT was superior to both monotherapies at weeks 12 and 18. By week 24 all active treatment conditions converged on rates of remission. The superiority of combination treatment over both monotherapies at week 18 is especially important to note, as all treatment conditions were open label beginning at week 12. Thus, selecting a monotherapy treatment could mean a delay of remission for a substantial number of depressed adolescent patients by two to three months. These findings mirrored the longer-term outcomes recently reported on response rates.[32]

Between 65 and 72% of adolescents who reached remission during acute treatment maintained it through continuation and maintenance therapies. Thus, these adolescents had recovered from their depression as defined by the ACNP definition of recovery, which is sustained remission for four months.12 No differences were found on rates of recovery across treatment groups. This recovery rate was similar to the rates of sustained remission as reported in the adult literature (67 – 86%).9¯11 While not statistically significant, it does appear that those remitters who received CBT monotherapy had slightly higher rates of recovery (ranging from 77.8 to 87.5%), which is consistent with findings in the adult depression CBT outcome literature.40

Conversely, one third of patients achieving remission did not maintain remission during continuation and maintenance treatments. This finding has important clinical implications, as it highlights the need to continue to monitor patients even after they have reached remission status. Furthermore, the loss of remission status in one third of patients may have methodological implications in future studies of remission. For example, a last observation carried forward (LOCF) approach to this missing data in analyses of remission may be misleading, as it may not capture variations in remission rates over time.

The presence of residual symptoms provided important prognostic information on later remission achievement. Greater numbers of symptoms remaining at the end of 12 weeks of treatment were predictive of later remission status. This was true at both 18 and 36 weeks.

Finally, participants assigned to combination treatment tended to stay in TADS COMB. However, those assigned to a TADS monotherapy tended to augment with either medication (in the case of CBT) and with psychosocial treatment (in the case of FLX) in later stages of treatment. It is unclear if this was based on a clinician decision or a patient decision, but it suggests that there is a belief that combination treatment is preferable.

These findings should be evaluated in light of the adopted definitions of remission and recovery, possible influence of mere passage of time, and experimental sample size. An accepted definition of remission, based on normative data (i.e., CDRS-R ≤ 28) was used for these analyses; however a different definition might result in different findings. In addition, we were restricted to measuring remission according to a set assessment schedule, and thus were not able to capture or properly analyze timing of remission.

Although we found that remission rates improved over time and concluded that this was related to continued treatment, it is possible that the mere passage of time contributed partially or fully to higher remission rates. Studies of depressed youth which include long term follow-up assessments frequently find that experimental groups and control groups converge on later outcomes.41 Furthermore, Kovacs has reported that the length of an episode is typically 9 months with most youth having recovered by one year.14–15 It is possible, that at 36 weeks, our patients were out of their episode as a result of time and not treatment. However, the mean episode duration in the study was greater than one year and more than half the sample had received prior treatment, yet these participants continued to meet criteria for depression (i.e., had not recovered).[33] Thus, in our sample, spontaneous remission is unlikely, due to the illness severity of these patients and past treatment of this sample.33

Our study is also limited by the design in which all participants were in open treatment after week 12. For ethical reasons, we could not create and follow an untreated group of depressed adolescents for nine months. To truly evaluate the effects on continuation treatment, one would need to conduct an RCT of continuation care versus a control condition, such that of Emslie and colleagues.[25] Finally, the smaller sample sizes at subsequent weeks due to attrition and removal of the PBO arm may have limited our ability to adequately investigate questions of treatment group differences and their impact on the achievement and maintenance of remission.

Despite the early low remission rates, the majority of depressed adolescents go on to achieve remission after nine months of treatment. Methods of achieving higher or more rapid remission rates are still needed. A better understanding of which remitted patients will fail to maintain their recovery and how to better assist them is also necessary. Clinicians should be particularly attentive to the presence of residual symptoms remaining after initial treatment response.

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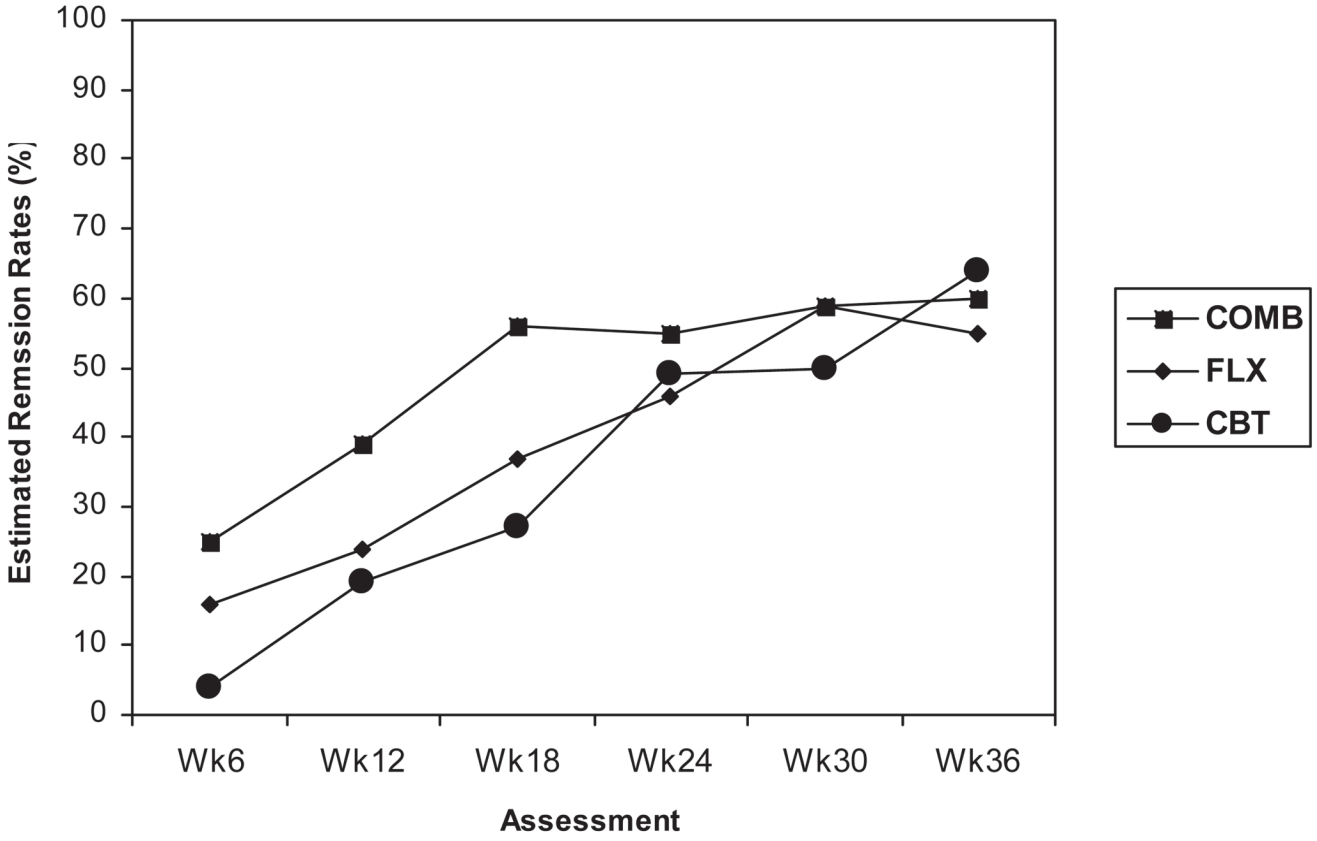

Figure 1.
Estimated Remission Rates Across 36 Weeks for the Active Treatments Groups

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Table 1

Baseline Characteristics

	COMB		FLX		CBT		PBO		Stage I ITT		Stage I–III ITT	
Baseline Characteristic	**n**	**Mean ± SD**	**n**	**Mean ± SD**	**n**	**Mean ± SD**	**n**	**Mean ± SD**	**n**	**Mean ± SD**	**n**	**Mean ± SD**
Age	107	14.60 ± 1.48	109	14.50 ± 1.57	111	14.62 ± 1.50	112	14.51 ± 1.62	439	14.56 ± 1.54	327	14.57 ± 1.51
CDRS-R Total Score	107	60.75 ± 11.58	109	58.96 ± 10.16	111	59.58 ± 9.21	112	61.11 ± 10.50	439	60.10 ± 10.39	327	59.76 ± 10.34
CGI-S Rating	107	4.79 ± 0.85	109	4.66 ± 0.85	111	4.77 ± 0.76	112	4.84 ± 0.84	439	4.77 ± 0.83	327	4.74 ± 0.82
CGAS Rating	107	49.95 ± 7.52	109	49.49 ± 7.26	111	50.01 ± 7.58	112	49.13 ± 7.59	439	49.64 ± 7.47	327	49.82 ± 7.43
Duration of Current MDE (weeks)	107	83.07 ± 94.00	109	70.92 ± 94.33	111	71.71 ± 70.14	112	61.16 ± 67.45	439	71.59 ± 82.35	327	75.16 ± 86.67
Number of Current Co-morbidities	106	0.77 ± 0.98	109	0.77 ± 1.19	111	0.77 ± 0.96	111	0.79 ± 1.03	437	0.78 ± 1.04	326	0.77 ± 1.05
	N	**n (%)**	**N**	**n (%)**	**N**	**n (%)**	**N**	**n (%)**	**N**	**n (%)**	**N**	**n (%)**
Females	107	60 (56.1%)	109	59 (54.1%)	111	61 (55.0%)	112	59 (52.7%)	439	239 (54.4%)	327	180 (55.1%)
First MDE	103	93 (90.3%)	107	91 (85.1%)	109	92 (84.4%)	110	93 (84.6%)	429	369 (86.0%)	319	276 (86.5%)
Current Dysthymia	107	11 (10.3%)	109	6 (5.5%)	110	17 (15.5%)	112	12 (10.7%)	438	46 (10.5%)	326	34 (10.4%)
Current ADHD Diagnosis	107	14 (13.1%)	109	13 (11.9%)	111	14 (12.6%)	112	19 (17.0%)	439	60 (13.7%)	327	41 (12.5%)
Current Anxiety Disorders	107	30 (28.0%)	109	26 (23.9%)	111	36 (32.4%)		28 (25.2%)	438	120 (27.4%)	327	92 (28.1%)
Current Disruptive Behavior Disorders	107	23 (21.5%)	109	25 (22.9%)	111	27 (24.3%)	112	28 (25.0%)	439	103 (23.5%)	327	75 (22.9%)

Attention-Deficit/Hyperactivity Disorder (ADHD) Diagnosis: K-SADS-PL diagnosis, rated by blinded Independent Evaluator

Anxiety Disorder: K-SADS-PL diagnosis of panic disorder, separation anxiety disorder, specific phobia, social phobia, agoraphobia, generalized anxiety disorder, posttraumatic stress disorder, or acute stress disorder, rated by blinded Independent Evaluator

Disruptive Behavior Disorder: K-SADS-PL diagnosis of ADHD, conduct disorder, or oppositional defiant disorder, rated by blinded Independent Evaluator

CBT: Cognitive Behavioral Therapy alone

Children's Depression Rating Scale-Revised (CDRS-R): total score, rated by a blinded Independent Evaluator.

Clinical Global Impression – Severity (CGI-S): rated by blinded Independent Evaluator
Children's Global Assessment Scale (CGAS): rated by blinded Independent valuator
COMB: combination of fluoxetine and cognitive behavior therapy
FLX: Fluoxetine therapy alone
Major Depressive Episode (MDE): K-SADS-PL diagnosis, rated by blinded Independent Evaluator
Number of current co-morbidities: Number of current DSM-IV comorbidities, including dysthymia
PBO: Placebo

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Table 2

Remission Rates Paired Contrasts for the Three Active Treatment Arms

Assessment	Contrasts	DF	χ^2	*p*-Value	Odds Ratio	95% CI Lower Limit	95% CI Upper Limit
Week 6	COMB vs CBT	1	14.54	0.0001	9.43	2.98	29.87
	COMB vs FLX	1	2.72	0.0992	1.81	0.89	3.69
	FLX vs CBT	1	7.31	0.0068	5.20	1.57	17.15
Week 12	COMB vs CBT	1	8.62	0.0033	2.77	1.40	5.46
	COMB vs FLX	1	4.95	0.0261	2.04	1.09	3.81
	FLX vs CBT	1	0.73	0.3917	1.36	0.67	2.73
Week 18	COMB vs CBT	1	14.23	0.0002	3.46	1.82	6.59
	COMB vs FLX	1	6.88	0.0087	2.34	1.24	4.42
	FLX vs CBT	1	1.29	0.2552	1.48	0.75	2.90
Week 24	COMB vs CBT	1	0.43	0.5123	1.22	0.67	2.21
	COMB vs FLX	1	1.39	0.2377	1.46	0.78	2.73
	FLX vs CBT	1	0.31	0.5796	0.84	0.45	1.57
Week 30	COMB vs CBT	1	0.88	0.3490	1.35	0.72	2.53
	COMB vs FLX	1	0.02	0.8757	0.95	0.49	1.85
	FLX vs CBT	1	1.09	0.2974	1.42	0.73	2.77
Week 36	COMB vs CBT	1	0.58	0.4452	0.78	0.40	1.49
	COMB vs FLX	1	0.27	0.6044	1.18	0.63	2.23
	FLX vs CBT	1	1.57	0.2101	0.66	0.34	1.27

ITT = Cases in the Stages I-II Intent-to-treat analysis
CBT: Cognitive Behavioral Therapy alone
COMB: Combination of fluoxetine and cognitive behavior therapy
FLX: Fluoxetine therapy alone

Table 3

Subsequent Recovery Rates by Treatment Arm in Remitters at the End of the Acute Treatment Phase (Week 12) and Continuation of Treatment Phase (Week 18)

Analysis	Remitter Subgroup	Treatment	Week 12	Week 18	Week 36
Stage I–III ITT	Acute Phase Remitters	COMB	40	34	25 (62.5%)
		FLX	25	20	15 (60.0%)
		CBT	18	16	14 (77.8%)
		All	83	70	54 (65.1%)
	Continuation Phase Remitters	COMB		54	38 (70.4%)
		FLX		36	24 (66.7%)
		CBT		25	20 (80.0%)
		All		115	82 (71.3%)

ITT = Cases in the Stages I–II Intent-to-treat. Recovery was determined using two subsamples: 1) remitters at week 12 (acute phase remitters) and 2) remitters at week 18 (continuation phase remitters). In acute phase remitters, participants were determined to have recovered if they retained remission status at weeks 18, 24, 30, and 36. For the continuation phase remitters, recovery is defined as retaining remission at weeks 24, 30, and 36. Percents are relative to number of youth in the remission on subgroup.

CBT: Cognitive Behavioral Therapy alone

COMB: Combination of fluoxetine and cognitive behavior therapy

FLX: Fluoxetine therapy alone

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Table 4

Treatment Interventions Received

Treatment Interventions Received Within TADS				
Randomized Treatment	**N**	**Stage 1 Acute Treatment**	**Stage 2 Continuation Treatment**	**Stage 3 Maintenance Treatment**
COMB	107			
COMB intervention		107 (100.0%)	78 (72.9%)	75 (70.1%)
FLX alone intervention		0 (0.0%)	2 (1.9%)	5 (4.7%)
CBT alone intervention		0 (0.0%)	7 (6.5%)	5 (4.7%)
No TADS intervention		0 (0.0%)	20 (18.7%)	22 (20.6%)
FLX	109			
COMB intervention		0 (0.0%)	0 (0.0%)	0 (0.0%)
FLX alone intervention		107 (98.2%)	75 (68.8%)	63 (57.8%)
CBT alone intervention		0 (0.0%)	0 (0.0%)	0 (0.0%)
No TADS intervention		2 (1.8%)	34 (31.2%)	46 (42.2%)
CBT	111			
COMB intervention		0 (0.0%)	0 (0.0%)	0 (0.0%)
FLX alone intervention		0 (0.0%)	0 (0.0%)	0 (0.0%)
CBT alone intervention		110 (99.1%)	77 (69.4%)	65 (58.6%)
No TADS intervention		1 (0.9%)	34 (30.6%)	46 (41.4%)
Psychiatric Interventions Received Outside of TADS				
Randomized Treatment	**N**	**Stage 1 Acute Treatment**	**Stage 2 Continuation Treatment**	**Stage 3 Maintenance Treatment**
COMB	107			
SSRI		4 (3.7%)	4 (3.7%)	5 (4.7%)
Other anti-depressant		4 (3.7%)	4 (3.7%)	5 (4.7%)
Mood stabilizer		1 (0.9%)	0 (0.0%)	0 (0.0%)
Anti-anxiety medication		0 (0.0%)	0 (0.0%)	0 (0.0%)
Psychostimulant		5 (4.7%)	6 (5.6%)	6 (5.6%)
CBT		0 (0.0%)	0 (0.0%)	2 (1.9%)
Other psychosocial therapy		1 (0.9%)	1 (0.9%)	8 (7.5%)
FLX	109			
SSRI		6 (5.5%)	7 (6.4%)	7 (6.4%)
Other anti-depressant		7 (6.4%)	8 (7.3%)	7 (6.4%)
Mood stabilizer		0 (0.0%)	1 (0.9%)	3 (2.8%)
Anti-anxiety medication		0 (0.0%)	3 (2.8%)	2 (1.8%)
Psychostimulant		5 (4.6%)	4 (3.7%)	5 (4.6%)
CBT		2 (1.8%)	5 (4.6%)	6 (5.5%)
Other psychosocial therapy		9 (8.3%)	15 (13.8%)	18 (16.5%)
CBT	111			
SSRI		13 (11.7%)	16 (14.4%)	21 (18.9%)

Treatment Interventions Received Within TADS				
Randomized Treatment	**N**	**Stage 1 Acute Treatment**	**Stage 2 Continuation Treatment**	**Stage 3 Maintenance Treatment**
Other anti-depressant		14 (12.6%)	17 (15.3%)	22 (19.8%)
Mood stabilizer		1 (0.9%)	0 (0.0%)	1 (0.9%)
Anti-anxiety medication		0 (0.0%)	1 (0.9%)	1 (0.9%)
Psychostimulant		0 (0.0%)	1 (0.9%)	0 (0.0%)
CBT		1 (0.9%)	1 (0.9%)	4 (3.6%)
Other psychosocial therapy		4 (3.6%)	5 (4.5%)	10 (9.0%)

As per protocol, randomized treatment was continued at the end of acute treatment stage only if the youth was determined by the treating clinician to be a full or partial treatment responder as defined by a CGI-I score of 1 (very much improved) or 2 (much improved) or 3 (minimally improved).
CBT: Cognitive Behavioral Therapy alone
COMB: Combination of fluoxetine and cognitive behavior therapy
FLX: Fluoxetine therapy alone