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Recovery and Recurrence Following Treatment for Adolescent Major Depression

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Context: Major depressive disorder in adolescents is common and impairing. Efficacious treatments have been developed, but little is known about longer-term outcomes, including recurrence.

Objectives: To determine whether adolescents who responded to short-term treatments or who received the most efficacious short-term treatment would have lower recurrence rates, and to identify predictors of recovery and recurrence.

Design: Naturalistic follow-up study.

Setting: Twelve academic sites in the United States.

Participants: One hundred ninety-six adolescents (86 males and 110 females) randomized to 1 of 4 short-term interventions (fluoxetine hydrochloride treatment, cognitive behavioral therapy, their combination, or placebo) in the Treatment for Adolescents With Depression Study were followed up for 5 years after study entry (44.6% of the original Treatment for Adolescents With Depression Study sample).

Main Outcome Measures: Recovery was defined as absence of clinically significant major depressive disorder symptoms on the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version interview for at least 8 weeks, and recurrence was defined as a new episode of major depressive disorder following recovery.

Results: Almost all participants (96.4%) recovered from their index episode of major depressive disorder during the follow-up period. Recovery by 2 years was significantly more likely for short-term treatment responders (96.2%) than for partial responders or nonresponders (79.1%) ($P<.001$) but was not associated with having received the most efficacious short-term treatment (the combination of fluoxetine and cognitive behavioral therapy). Of the 189 participants who recovered, 88 (46.6%) had a recurrence. Recurrence was not predicted by full short-term treatment response or by original treatment. However, full or partial responders were less likely to have a recurrence (42.9%) than were nonresponders (67.6%) ($P=.03$). Sex predicted recurrence (57.0% among females vs 32.9% among males; $P=.02$).

Conclusions: Almost all depressed adolescents recovered. However, recurrence occurs in almost half of recovered adolescents, with higher probability in females in this age range. Further research should identify and address the vulnerabilities to recurrence that are more common among young women.

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MAJOR DEPRESSIVE DISORder (MDD) is one of the most prevalent psychiatric disorders among adolescents, with rates of approximately 5.9% among females and 4.6% among males.[1] It is associated with functional impairment, risk of suicide, and risk of adult depression.[2-4] Thus, it is important to investigate not only the efficacy of adolescent MDD treatments but also whether they reduce risk of subsequent negative outcomes, especially depression recurrence.

The episodic nature of adolescent MDD is evident across community and clinical samples. In community samples, approximately 75% of MDD episodes end within 6 to 15 months.[5-7] However, recurrence rates reach 45% in 6 years.[4] In clinical samples, recovery rates 1 year after treatment onset range from 81% to 98%,[8,9] but recurrence rates range from 54% in 3 years among outpatients[8] to more than 60% in 1 year for inpatients.[9]

Treatment studies usually report outcomes of response (clinically significant improvement) and remission (no or very few remaining symptoms).[10,11] Three clinical trials have also reported rates of recovery (maintenance of remission for an ex-

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Table 1. Potential Predictors of Recovery or Recurrence

Baseline	End of Short-term Treatment
Age[a,b,c]	
Sex	
Family income[d]	
Minority ethnicity[c]	
Clinic referral[e]	
Interviewer-rated depression[a,c,d,f]	Interviewer-rated depression[f]
Self-reported depression[c,f]	Self-reported depression[f]
	Residual major depressive disorder symptoms[g]
Index episode duration[b]	
Melancholic features[b]	
Global functioning[b]	Global functioning[f]
Suicidal ideation[b,c]	
Hopelessness[b]	Hopelessness[f]
Cognitive distortions[d]	Cognitive distortions[d]
Comorbid anxiety disorder[b]	
No. of comorbid disorders[a,b]	
Expectations for improvement[b]	
Parent-adolescent conflict[a]	Parent-adolescent conflict[e]

[a] Predicted recovery following medication trial.[12]
[b] Predicted short-term outcome in the Treatment for Adolescents With Depression Study.[20]
[c] Predicted recurrence following inpatient treatment.[9]
[d] Moderated short-term outcome in the Treatment for Adolescents With Depression Study.[20]
[e] Predicted recurrence following psychotherapy trial.[14]
[f] Predicted recovery following psychotherapy trial.[14]
[g] Predicted remission after maintenance treatment in the Treatment for Adolescents With Depression Study.[17]

tended period) and recurrence (a new episode following recovery). Emslie et al[12] assessed 87 child and adolescent outpatients with MDD 1 year after treatment with fluoxetine hydrochloride or placebo. Eighty-five percent had recovered, but 39% of recovered patients experienced a recurrence. Rates were not reported by initial randomized treatment. Clarke et al[13] followed up 64 depressed adolescents treated with cognitive behavioral therapy (CBT). Over 2 years, almost all recovered; however, 22% of recovered adolescents experienced a recurrence. Birmaher et al[14] followed up 107 depressed adolescents 2 years after treatment with 1 of 3 psychotherapies. Eighty percent recovered, with no differences among treatments. However, 30% of recovered adolescents had 1 recurrence and 8% had 2 recurrences. Thus, even effective treatments can be followed by recurrence rates of 30% to 40% within 1 to 2 years, with no treatment yet surpassing others in preventing recurrence.

In this study, we investigated recovery from and recurrence of MDD during an extended naturalistic follow-up of participants in the Treatment for Adolescents With Depression Study (TADS). We first described recovery rates over 5 years from TADS baseline, and to facilitate comparison with previous research,[14] we tested predictors of recovery by 2 years. Second, we described recurrence rates over the 5-year period and tested predictors of recurrence. Third, we investigated long-term effects of initial treatment and short-term response on recovery or recurrence. Finally, because about 8% to 20% of depressed adolescents are at risk for developing bipolar disorder,[8] we described the rate of this outcome in our sample.

The Treatment for Adolescents With Depression Study compared fluoxetine, CBT, and their combination and included a placebo condition. The combination of fluoxetine and CBT was the most efficacious short-term treatment.[15] Active treatment groups did not differ in rates of sustained response (75%-88%) or remission (55%-60%) at 9 months following maintenance treatment[16,17] or in rates of remission (68%) 1 year later.[18] Among adolescents randomized to placebo followed by open treatment, 48% were in remission at 9 months.[19]

To investigate longer-term recovery and recurrence, we first identified baseline or post–short-term treatment predictors found in 3 studies of recovery following a fluoxetine trial,[12] recurrence following inpatient treatment,[9] or recovery and recurrence following a psychotherapy trial.[14] We included all predictors from these studies except psychotic features,[9] an exclusion criterion in TADS. Second, we included variables that had predicted or moderated short-term TADS outcome.[20] Third, we included residual symptoms following short-term TADS treatment, which had predicted nonremission after maintenance treatment.[17] Finally, because of sex differences in MDD prevalence, we included sex. Potential predictors are shown in **Table 1**.

Although it is not ethically possible to test long-term treatment effects by withholding treatment from a control group, it is possible to compare groups who responded more or less successfully to short-term treatment.[21] We hypothesized that favorable response to short-term treatment would predict higher rates of recovery and lower rates of recurrence. Following the study by Birmaher et al,[14] we also tested the hypotheses that treatment with the most efficacious short-term intervention would predict higher rates of recovery and lower rates of recurrence than treatment with other interventions.

METHODS

RELATIONSHIP OF TADS TO PRESENT STUDY

The Treatment for Adolescents With Depression Study compared fluoxetine, CBT, and their combination with one another across short-term (12 weeks), continuation (6 weeks), and maintenance (18 weeks) treatment and with short-term placebo. Participants (N=439) were randomized to fluoxetine, CBT, their combination, or placebo. Following short-term treatment, placebo partial responders, nonresponders, or responders who relapsed were offered their TADS treatment of choice. Following maintenance treatment, adolescents were followed up openly for 1 year.[18] The present study, Survey of Outcomes Following Treatment for Adolescent Depression (SOFTAD), was an open follow-up extending an additional 3.5 years after the TADS follow-up year. The TADS-SOFTAD period spanned 63 months (21 months of TADS and 42 months of SOFTAD), with diagnostic interviews administered according to the schedule shown in **Table 2**.

The design, sample characteristics, and outcomes of TADS have been described previously.[15,22,23] Treatment response was defined as an independent evaluator rating of 1 (very much improved) or 2 (much improved), partial response was defined as a rating of 3 (minimally improved), and nonresponse was defined as a rating of 4 or higher on the 7-point Clinical Global Impressions–Improvement scale.[24] During TADS, remission was defined as a normalized score (<29) on the Children's Depression Rating Scale–Revised (CDRS-R).[25]

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Participants in SOFTAD were recruited from among all 439 adolescents who had been randomized in TADS. The TADS participants were recruited between spring 2000 and summer 2003. The SOFTAD recruitment occurred from March 8, 2004, to December 20, 2006, with the final assessment completed on December 4, 2008. Recruitment involved recontacting TADS early completers and dropouts and, after March 8, 2004, asking TADS completers to participate. For minors, written parental consent and adolescent assent were obtained. For adults, written consent was obtained from them and from their parents, since parents completed some measures. The Duke University Medical Center and site institutional review boards approved this study.

Initial SOFTAD assessment optimally occurred 27 months after TADS baseline, but participants began assessments at whatever assessment point corresponded most closely to the time of their recruitment. At most, participants could complete 7 SOFTAD assessments at 6-month intervals, of which 5 assessments included diagnostic interviews.

Table 2. Schedule of Diagnostic Interview Assessments During the Treatment for Adolescents With Depression Study and the Survey of Outcomes Following Treatment for Adolescent Depression[a]

TADS Period	SOFTAD Period
Baseline	
3 mo (end of stage 1)	
9 mo (end of stage 3)	
15 mo	
21 mo (end of stage 4)	
	27 mo
	33 mo
	39 mo
	51 mo
	63 mo

Abbreviations: SOFTAD, Survey of Outcomes Following Treatment for Adolescent Depression; TADS, Treatment for Adolescents With Depression Study.

[a] All months are in time since TADS baseline.

SOFTAD PARTICIPANTS

The SOFTAD participants included 196 adolescents (44.6% of youths randomized in TADS), representing 12 of 13 TADS sites. One site was unable to recruit participants. The sample included 110 females (56.1%). The mean (SD) age at SOFTAD entry was 18 (1.8) years (range, 14-22 years). The sample was 78.6% white, 9.2% Latino, 8.2% African American, and 4.1% other ethnicity. Points of entry into SOFTAD by months since TADS baseline were as follows: month 27 (33.7%), month 33 (21.9%), month 39 (13.8%), month 45 (10.7%), month 51 (9.7%), month 57 (8.2%), and month 63 (2.0%). The modal number of completed SOFTAD assessments was 5, with a mean (SD) of 3.5 (1.5) completed SOFTAD assessments.

CRITERION MEASURES

Diagnoses

The Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (K-SADS-PL)[26] was administered at 5 SOFTAD assessment points (Table 2). The Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS) was used in TADS and by Birmaher et al[14] and assessed mood, anxiety, behavior, eating, substance use, psychotic disorders, and tic disorders using *DSM-IV* criteria[27] for the time since the last TADS or SOFTAD assessment and current MDD episode.

Episodes of MDD

When the K-SADS-PL indicated MDD at any point since the last interview, the interviewer inquired about episode onset (time when the participant met full diagnostic criteria) and, if relevant, offset (time when the participant had no remaining clinically significant MDD symptoms for ≥2 weeks). We used the absence of MDD symptoms on the K-SADS-PL rather than a normalized CDRS-R score to define remission in SOFTAD to facilitate comparison with previous research[14] and because participants exceeded CDRS-R age limits.

Definition of Recovery and Recurrence

Consistent with adult criteria and prior adolescent research,[14,28] we defined recovery as remission lasting at least 8 weeks, with the exception noted later for recovery during the TADS period. Following recovery, time of MDD recurrence was estimated as the month when 5 or more symptoms again became present.

Although SOFTAD interviews inquired about the time since the preceding TADS or SOFTAD interview, TADS interviews had only inquired about current symptoms. To deal with this limitation, we assumed that an index episode of MDD during the TADS period was in remission if no symptoms were reported on a K-SADS-PL assessment and in recovery if no symptoms were reported at 2 consecutive TADS assessments.

Interviewer Training

The SOFTAD evaluators met the same educational and experience criteria as the TADS evaluators. Certification following didactic training required the following: (1) rating a videotaped standard patient interview, with agreement on presence or absence of MDD, 80.0% agreement on the full MDD criterion set, and agreement on other classes of disorders (eg, anxiety disorder); and (2) rating a site-based interview, subsequently rated at the coordinating center with acceptable reliability, using these same criteria.

Evaluators had monthly conference calls and annually rated a standard patient interview. On these, there was complete agreement between evaluators and coordinating center ratings for diagnosis of MDD since the last interview and 95.6% agreement on current MDD; 91.3% of evaluator ratings exceeded 80.0% agreement on diagnostic criteria.

PREDICTORS OF RECOVERY OR RECURRENCE

The following predictors of recovery and recurrence were measured at TADS baseline. Age, ethnicity, sex, family income, and referral source were reported by participants or parents. Income was dichotomized at $75 000 and ethnicity as white or nonwhite for comparison with previous findings.[9,20] For duration of index episode and depression severity, an independent evaluator estimated the duration of the index major depressive episode (MDE) and completed the CDRS-R[25] for severity. Adolescents completed the Reynolds Adolescent Depression Scale (RADS).[29] For global functioning, the evaluator assigned a rating on the Children's Global Assessment Scale.[30] To measure suicidal ideation, adolescents completed the Suicide Ideation Questionnaire–Junior High Version.[31] The index for melancholic features included 5 CDRS-R items: anhedonia, insomnia, appetite disturbance, guilt, and psychomotor retardation. Comorbid diagnoses

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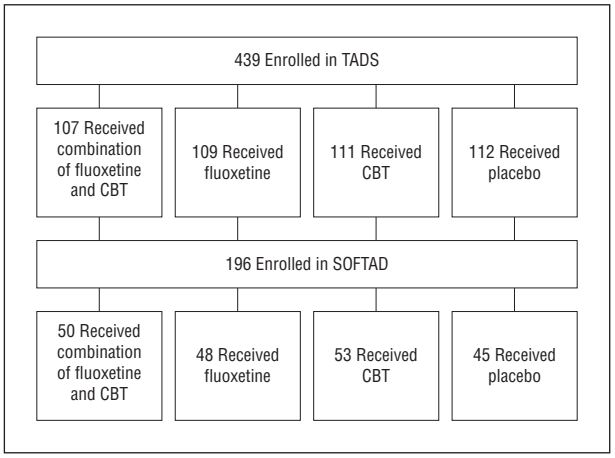

Figure 1. Survey of Outcomes Following Treatment for Adolescent Depression (SOFTAD) patient flow. TADS indicates Treatment for Adolescents With Depression Study; CBT, cognitive behavioral therapy.

were yielded by the K-SADS-PL. To measure hopelessness, cognitive distortions, and treatment expectancy, adolescents completed the Beck Hopelessness Scale,[32] completed the Children's Negative Cognitive Errors Questionnaire,[33] and rated their expectations for improvement with fluoxetine, CBT, or their combination. To determine parent-adolescent conflict, adolescents and parents completed the Conflict Behavior Questionnaire.[34]

The following predictors of recovery were assessed at the end of TADS short-term treatment: CDRS-R scores, RADS scores, Children's Negative Cognitive Errors Questionnaire scores, Beck Hopelessness Scale scores, Children's Global Assessment Scale scores, residual K-SADS MDD symptoms, and Conflict Behavior Questionnaire scores. The latter two were also investigated as predictors of recurrence.

TREATMENT DURING SOFTAD

At each SOFTAD assessment, participants were asked what services they had received (if any) for emotional, behavioral, or substance abuse problems. As part of this review of services, they reported whether they had received psychotherapy or antidepressant medication.

STATISTICAL ANALYSIS

Baseline characteristics of TADS participants who enrolled in SOFTAD (n=196) were compared with those who did not (n=243) using general linear models for continuous measures and χ^2 test for binary outcomes. Fisher exact test and nonparametric median test were alternatively performed as needed.

Because recovery during the TADS period was estimated on the basis of 2 consecutive symptom-free interviews separated by 3 or 6 months and not, as in SOFTAD, on the basis of a specific month of recovery, we reported the cumulative percentages of recovered subjects in 6-month intervals from TADS baseline. Participants were subdivided into 3 groups: (1) those with persistent depression (baseline MDE never resolved); (2) those with recovery from baseline MDE without recurrence; and (3) those with recovery with recurrence. For comparison with previous research,[14] we examined recovery by 2-year follow-up, testing its predictors with logistic regression. Among those who recovered at any point, we examined predictors of recurrence over the 63-month period using logistic regression and reported mean and median time from recovery to recurrence.

All analyses were conducted with SAS version 9.2 statistical software (SAS Institute, Inc, Cary, North Carolina). Nondirectional hypotheses were tested, with the significance level set at .05 for each test. The α was not adjusted for multiple outcomes or tests owing to the exploratory nature of the investigation.

RESULTS

PRELIMINARY ANALYSES

To determine whether SOFTAD participants represented the full TADS sample, we compared them with TADS participants not in SOFTAD on the variables related to hypothesis testing. Participants and nonparticipants did not differ on percentage of short-term treatment responders (53.6% vs 51.0%, respectively; χ^2_1=0.28; P=.60) or initial treatment condition (χ^2_3=1.54; P=.67). **Figure 1** depicts the number of SOFTAD participants from each condition.

Demographic and clinical comparisons are shown in **Table 3**. There were few differences. The SOFTAD participants were younger (P=.006), included fewer minority adolescents (P=.04), were more likely to be experiencing their initial episode (P=.02), had fewer total comorbid disorders (P=.04), and had fewer anxiety disorders (P=.04).

RECOVERY

The vast majority of SOFTAD participants recovered from their index MDE during the 63 months (**Figure 2**). Specifically, 189 (96.4%) recovered and 7 (3.6%) did not. Cumulative recovery rates were as follows: 29.6% at 6 months, 66.3% at 12 months, 84.7% at 18 months, 88.3% at 24 months, 92.3% at 30 months, 94.8% at 36 months, and 96.4% at 42 months. Among the 189 adolescents who recovered, 68.8% had recovered by 1 year after baseline and 91.5% had recovered within 2 years.

PREDICTION OF RECOVERY BY 2 YEARS

As hypothesized, recovery by 2 years was significantly more likely for those who were short-term treatment responders (96.2%) than for others (79.1%) (χ^2_1=11.02; $P<.001$). However, it was not associated with the combination of fluoxetine and CBT, any particular treatment, or any baseline variables. Among post–short-term treatment variables, recovery was significantly predicted by less severe evaluator-rated depression (CDRS-R score; χ^2_1=12.54; $P<.001$) and higher global functioning (Children's Global Assessment Scale score; χ^2_1=5.48; P=.02). There were trends for lower parent-reported conflict (Conflict Behavior Questionnaire score; χ^2_1=3.70; P=.05) and more cognitive distortions (Children's Negative Cognitive Errors Questionnaire score; χ^2_1=3.00; P=.08) to predict recovery by year 2. Self-reported depression (RADS score), hopelessness (Beck Hopelessness Scale score), and adolescent-reported conflict (Conflict Behavior Questionnaire score) with the mother or father were not significant predictors (all $P>.15$).

For 186 participants with complete K-SADS symptom ratings after short-term treatment, any of 7 MDD

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Table 3. Treatment for Adolescents With Depression Study Baseline Characteristics of Participants and Nonparticipants in the Survey of Outcomes Following Treatment for Adolescent Depression

Characteristic	Participants (n=196)	Nonparticipants (n=243)	Statistic	*P* Value
Female, %	56.1	53.1	0.40[a]	.53
Age, mean (SD), y	14.3 (1.5)	14.7 (1.6)	7.78[b]	.006
Minority ethnicity, %	21.5	30.0	4.16[a]	.04
Income >$75 000/y, %	23.7	26.7	0.46[a]	.50
Clinic referral, %	29.6	35.4	1.66[a]	.20
Duration at TADS baseline of index MDE, median, wk	37	42	−0.70[c]	.48
First MDE, %	90.2	82.6	5.00[a]	.02
CDRS-R score, mean (SD)	59.6 (10.2)	60.6 (10.5)	1.05[b]	.31
RADS score, mean (SD)	78.5 (15.4)	79.9 (13.4)	1.00[b]	.32
SIQ-Jr score, median	15.0	17.5	−1.57[c]	.12
CGAS score, mean (SD)	50.2 (7.8)	49.2 (7.2)	2.06[b]	.15
Comorbid diagnoses, median, No.	0.0	1.0	−2.00[c]	.04
Dysthymia, %	7.7	12.8	2.95[a]	.08
SUD, %	1.0	2.1	NA[d]	.47
Anxiety, %	22.5	31.4	4.37[a]	.04
DBD, %	21.9	24.7	0.46[a]	.50
OCD or tic disorder, %	2.6	2.9	0.04[a]	.83

Abbreviations: CDRS-R, Children's Depression Rating Scale–Revised; CGAS, Children's Global Assessment Scale; DBD, disruptive behavior disorder; MDE, major depressive episode; NA, not applicable; OCD, obsessive-compulsive disorder; RADS, Reynolds Adolescent Depression Scale; SIQ-Jr, Suicide Ideation Questionnaire–Junior High Version; SUD, substance use disorder; TADS, Treatment for Adolescents With Depression Study.

[a] From χ^2 test.

[b] From general linear model *F* test, with *df* of 1,437 for all except RADS, which has *df* of 1,426.

[c] Median test *z* value.

[d] From Fisher exact test.

symptoms (excluding psychomotor or concentration disturbance) was associated with lower probability of recovery in 2 years. With all 7 MDD symptoms in a multivariable logistic regression, the significant predictors were appetite or weight disturbance (χ^2_1=1.13; *P*=.03) and sleep disturbance (χ^2_1=1.11; *P*=.03).

RECURRENCE

Of 189 participants who recovered, 101 (53.4%) remained well throughout the SOFTAD period and 88 (46.6%) had MDD recurrence. Most had 1 recurrence (n=74), but 12 had 2 recurrences and 2 had 3 recurrences. Figure 2 shows the rate of first recurrence across time. Among all recovered participants, cumulative recurrence rates for years 1 through 4 were 1.6%, 12.2%, 29.6%, and 38.1%, respectively. One year after TADS baseline, only 3.4% of the 88 recurrences had occurred. Corresponding rates for years 2, 3, and 4 were 26.1%, 63.6%, and 81.8%, respectively.

For those with recurrence, the mean (SD) time from recovery to the first recurrence was 22.3 (13.9) months (median, 20.3 months). Time from recovery to recurrence ranged from 2 to 55 months, with cumulative rates as follows: 12.5% at 6 months, 26.1% at 12 months, 40.9% at 18 months, 61.3% at 24 months, 77.3% at 30 months, and 84.9% at 36 months.

PREDICTION OF RECURRENCE

Within the SOFTAD sample of 196 participants, 105 (53.6%) had been full responders to short-term treatment, whereas 91 (46.4%) had not been (54 partial responders and 37 nonresponders). For the 189 participants who recovered, the full response rate was 55.6% and the partial response or nonresponse rate was 44.4%.

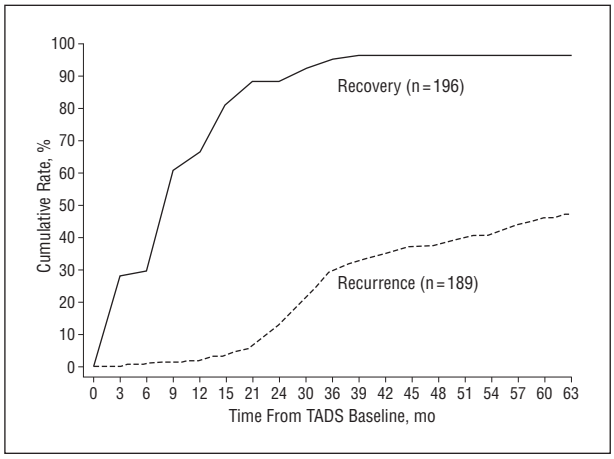

Figure 2. Cumulative recovery and recurrence rates. TADS indicates Treatment for Adolescents With Depression Study.

Contrary to our hypothesis, the recurrence rate for full responders (45.7%) was not significantly lower than for others (47.6%) (χ^2_1=0.07; *P*=.79). We explored whether the combined group of full and partial responders had a lower recurrence rate than nonresponders. Recurrence rates were 42.9% for full or partial responders and 67.6% for nonresponders, which was a significant difference (χ^2_1=4.68; *P*=.03).

Also contrary to our hypothesis, the recurrence rate for participants receiving the combination of fluoxetine and CBT (49.0%) did not differ from that of others (45.7%) (χ^2_1=0.16; *P*=.69). There were no treatment condition differences in recurrence rates (χ^2_3=1.91; *P*=.59).

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ADDITIONAL PREDICTORS OF RECURRENCE

In individual regression models, 4 baseline variables predicted recurrence: sex (χ^2_1=10.58; P=.001), self-reported depression (RADS score; χ^2_1=6.16; P=.01), suicidal ideation (Suicide Ideation Questionnaire–Junior High Version score; χ^2_1=6.88; P=.009), and comorbid anxiety disorder (χ^2_1=4.98; P=.03). Among females, 57.0% experienced recurrence, compared with 32.9% of males. Among those with anxiety disorder, 61.9% experienced recurrence compared with 42.2% of others. Participants with recurrence compared with those without recurrence had higher mean (SD) RADS and Suicide Ideation Questionnaire–Junior High Version scores (RADS: 81.5 [14.6] vs 75.7 [15.8], respectively; Suicide Ideation Questionnaire–Junior High Version: 25.4 [21.1] vs 17.4 [18.4], respectively).

In a multivariable regression including these 4 predictors, only female sex remained significant (χ^2_1=5.04; P=.02). Anxiety disorder approached significance (χ^2_1=3.35; P=.07).

BIPOLAR DISORDER

The emergence of bipolar disorder was relatively rare. Twelve participants (6.1%; 3 males, 9 females) were diagnosed with bipolar I disorder (n=5), bipolar II disorder (n=4), or, if the duration was 1 day shorter than the criterion, bipolar disorder not otherwise specified (n=3). Bipolar outcome was unrelated to treatment condition, but most of these participants (n=9) had not responded to short-term treatment. One never recovered from the index MDE; the other 11 recovered but had recurrence. In each case, bipolar disorder emerged after the end of the TADS period, at a mean (SD) age of 18.0 (1.4) years. Given the small number, we did not conduct further statistical comparisons.

TREATMENT DURING SOFTAD

During SOFTAD, 83 participants (42.3%) received psychotherapy and 88 (44.9%) received antidepressant medication, each unrelated to TADS treatment condition ($P>.05$). Each treatment was more likely among participants who had not recovered by 2 years (psychotherapy: χ^2_1=5.23; P=.02; medication: χ^2_1=4.13; P=.04) and among those with recurrence (psychotherapy: χ^2_1=13.77; $P<.001$; medication: χ^2_1=16.00; $P<.001$) than among those with recovery and no recurrence.

COMMENT

We followed up 196 adolescent participants in TADS, the largest treatment follow-up sample of depressed adolescents to date. Rate of recovery from the index MDE over 5 years from TADS baseline was very high (96.4%), and 88.3% of participants recovered within 2 years. As hypothesized, full short-term treatment response was associated with recovery by 2 years, as were other post–short-term treatment variables: less severe depression, absence of sleep or appetite disturbance, and better functioning. Contrary to our hypothesis, treatment with a combination of fluoxetine and CBT did not predict recovery in 2 years.

Slightly fewer than half of recovered adolescents (46.6%) experienced a recurrence by 5 years after baseline. Contrary to our hypotheses, neither full response to short-term treatment nor treatment with a combination of fluoxetine and CBT reduced the risk of recurrence. However, short-term treatment nonresponders were more likely to experience recurrence than full and partial responders. Females were significantly more likely to have a recurrence than males.

The SOFTAD 2-year recovery rate of 88.3% is comparable to the previously reported rate of 80%.[14] Comparisons with previous TADS findings[17,18] indicate that remission rates increase and that progress toward recovery continues after treatment ends, consistent with other studies.[12,14] This is the second study to indicate that longer-term recovery rates are not superior for adolescents receiving the most efficacious short-term treatment.[14] Such findings may be attributed to the episodic nature of depressive disorder and limited variance in 2-year recovery as a comparative index.

The SOFTAD recurrence rate reached 29.6% 3 years after baseline, whereas it had reached this rate 2 years after a previous psychotherapy trial.[14] Although sample differences cannot be ruled out, it is possible that incorporating continuation and maintenance treatment within TADS slowed the pace of recurrence. The lower rate of recurrence in TADS is consistent with the previous finding that TADS treatment gains were generally maintained during the first year of follow-up.[18] Unfortunately, no treatment has yet been identified that reduces adolescent recurrence rates.

The most robust predictor of recurrence was female sex. Females are more likely than males to experience MDD after approximately age 14 years,[35] but to our knowledge this is the first study documenting higher recurrence rates among treated adolescent females. Adult studies do not show a sex difference in recurrence.[36] One adolescent community study did show such a difference[37] from ages 19 to 23 years. This age range overlaps ours, suggesting that female vulnerability to recurrence may be age related. Factors implicated as potential causes of higher depression rates among postpubertal women include sex steroids,[38] long-term environmental stressors, low perceived mastery, and ruminative response style.[39] Further research should investigate whether more frequent MDD recurrence among young women is confirmed and, if so, what variables are associated with it.

Anxiety disorder was an individual predictor of recurrence. Anxiety disorders were more frequent among females (28.2%) than among males (15.1%) (χ^2_1=4.73; P=.03), likely accounting for the elimination of anxiety disorder as a predictor when considering sex simultaneously. Anxiety disorders also predicted poorer short-term outcome in TADS.[20] In depressed adults, anxiety mitigates the effectiveness of antidepressant treatment[40] and slows response time to CBT.[41] These findings suggest that adolescent MDD with anxiety requires further treatment development.

The rate of bipolar outcome in our sample was lower than in adolescent inpatient samples but similar to rates

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found among outpatients.[8] Our rate likely reflects TADS exclusion of participants for whom a placebo-controlled outpatient study was inappropriate (eg, those with psychotic depression or short-term suicidal risk).

CLINICAL IMPLICATIONS

Our results reinforce the importance of modifying a short-term treatment that leads to partial response or nonresponse because these were associated with less likelihood of recovery in 2 years. A study of adolescent selective serotonin reuptake inhibitor nonresponders showed that augmentation with CBT improved response rates.[42] To our knowledge, no parallel study has been completed investigating medication augmentation for incomplete CBT response, but treatment algorithms recommend such augmentation.[43] The finding that recurrence rates increased significantly from 2 to 3 years after baseline suggests that recurrence prevention efforts, such as symptom or medication monitoring or CBT booster sessions, may be of value beyond the maintenance period included in TADS.

LIMITATIONS

The most significant limitation of this study is that slightly fewer than half of the TADS participants took part. This likely reflects the difficulty maintaining a sample of adolescents during a period when many are moving away from home. Indeed, SOFTAD participants were somewhat younger than nonparticipants. Nevertheless, they did not differ on most measures, including depression characteristics, initial treatment, short-term treatment response rates, or sex. Participants had fewer anxiety disorders, suggesting that recurrence rates may have been higher if all TADS adolescents had participated.

Two other limitations should be noted. First, there was not a no-treatment condition in TADS. Second, most participants receiving placebo eventually received a TADS treatment,[19] and access to treatment was not controlled during SOFTAD. Thus, findings do not reflect the naturalistic course of untreated depression. In a separate report, we will describe participants' treatment utilization in more detail.

In summary, all predictors of recovery by 2 years were associated with clinical status after short-term treatment. Female sex was the most robust predictor of recurrence, indicating the importance of understanding and reducing the vulnerabilities of female adolescents to recurrent episodes.

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