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Predictors and Moderators of Relapse in Children and Adolescents With Major Depressive Disorder

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Abstract

Objective: To identify predictors and moderators of relapse during continuation treatment among depressed youth randomly assigned to fluoxetine or placebo.

Methods: Potential predictors and moderators of relapse that were identified by a literature review were examined in 102 youth (aged 7–18 years), diagnosed with major depressive disorder as defined by *DSM-IV* criteria, who were considered responders after 12 weeks of fluoxetine treatment (acute phase). This randomized controlled trial was conducted from June 2000 through October 2005. Each candidate predictor and moderator was evaluated with a multiple logistic regression model to examine the main and interaction effects of 12 weeks of continuation treatment on relapse status (at week 24) while controlling for age, sex, and depression severity. Relapse was defined as a Children's Depression Rating Scale–Revised total score ≥ 40 with worsening of depressive symptoms for at least 2 weeks.

Results: Youth with comorbid dysthymia (adjusted odds ratio [OR] = 2.88, $P = .03$) and low levels of family leadership (adjusted OR = 1.39, $P = .006$) at baseline are more likely to relapse than their counterparts. Higher levels of depression (OR = 1.21, $P = .003$) and higher levels of residual sleep disturbance (insomnia) (OR = 6.74, $P = .006$) and irritability (OR = 7.40, $P = .01$) at the end of acute treatment (12 weeks) increased the odds of relapse. Higher levels of depressive symptoms at baseline in youth who remained on fluoxetine for continuation treatment were associated with increased odds of relapse (adjusted OR = 1.14, $P = .03$). Females who

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remained on fluoxetine for the duration of continuation treatment were almost 9 times more likely to relapse than males (adjusted OR = 8.86, $P = .007$).

Conclusions: This is the first large continuation study for treatment of depression in youth to examine predictors and moderators of relapse. Youth with greater improvement by the end of 3 months of treatment were less likely to relapse than those with continued depressive symptoms. In addition, youth with comorbid dysthymia had 3 times greater risk of relapse that those without. Targeting residual symptoms, particularly sleep disturbance and irritability, earlier in treatment may reduce relapse rates.

Trial Registration: ClinicalTrials.gov identifier: NCT00332787

Large samples of depressed youth have been examined in acute phase psychopharmacologic and psychosocial treatments, leading to increased evidence that certain clinical characteristics are related to improved outcomes. Emslie and colleagues[1] reviewed the results of 3 large studies examining psychosocial and psychopharmacologic interventions in depressed youth to identify predictors and moderators of treatment outcome. Lower baseline depression severity and suicidality, better functioning, shorter duration of illness, and lower rates of comorbid psychiatric conditions (especially anxiety) were common predictors of improved outcome. Psychosocial factors such as lower levels of family stress or conflict and less hopelessness or negative cognitions were also predictive of improved outcome. One of the strongest predictors identified in this review was improvement in depression severity early on in treatment.[1]

Although this review provides us with evidence of a certain clinical profile of depressed youth that is more likely to improve with acute phase treatment, it is important to note that early-onset depression is often chronic, leading to high rates of relapse. In fact, 20% to 60% of youth will experience a relapse of depression within 1 to 2 years of remission.[2–5]

Current guidelines for antidepressant treatment in youth recommend continuing treatment for at least 6 to 9 months to prevent relapse and promote a longer period of time spent “well” (minimal or no depressive symptoms). However, to date, only 1 double-blind, placebo-controlled study has examined continuation treatment for youth with depression.[3] Youth who had responded to 12 weeks of fluoxetine were randomly assigned to continue fluoxetine or switch to placebo for 6 months. Continued antidepressant treatment led to reduced relapse rates compared with placebo (42% vs 69%, respectively). Of note, relapse was still high even for those remaining on medication.[3] As such, it is of great clinical importance to investigate the predictors and moderators of relapse. Predictors are variables that are present prior to treatment, can be independent of treatment group or assignment, and relate to some outcome. Predictors can tell us which patient characteristics, regardless of type of treatment, relate to the outcome variable. Moderators are also variables present prior to treatment, but they interact with the treatment condition and thus can tell us which treatment outcomes depend on a given moderator variable.[6]

There are limited extant findings on predicting who will relapse. A recent long-term study of the Treatment for Adolescents With Depression Study (TADS) sample indicates that females are more likely to relapse than males, and adolescents with more robust responses to acute

treatment were less likely to relapse than those with less robust responses.[7] In Treatment of Resistant Depression in Adolescents (TORDIA), similar variables that predicted remission also predicted relapse, with higher depression severity after acute treatment being the best predictor of relapse.[4,8] To date, no placebo-controlled study has examined the predictors and moderators of relapse. This article examines the predictors and moderators of relapse in youth with depression who responded to 12 weeks of fluoxetine and were then randomly assigned to continue fluoxetine or switch to placebo for 6 more months.

METHOD

The current study is based on an extant single-site study, funded by the National Institute of Mental Health, which compared fluoxetine and placebo during 6 months of continuation treatment in youth with major depressive disorder (MDD) who had responded to 12 weeks of fluoxetine treatment (Determining Optimal Continuation Treatment Duration for Depressed Children and Adolescents [NCT00332787]).

A detailed description of the full methodology and outcomes has been previously reported.[3] The study was approved by the University of Texas Southwestern Medical Center Institutional Review Board, and all participants and their parents provided written informed consent and assent prior to entering the study.

Participants

Participants were 7 to 18 years of age with at least 4 weeks of MDD and had a Children's Depression Rating Scale–Revised (CDRS-R)[9] total score ≥ 40 and Clinical Global Impression–Severity Scale (CGI-S)[10] score ≥ 4 (moderately to extremely ill). Participants were excluded for lifetime history of psychotic depression or bipolar disorder and alcohol or substance abuse or dependence within the past 6 months. Treatment with other psychotropic medications or specific psychotherapy was not allowed, with the exception of stimulant treatment for attention-deficit/hyperactivity disorder. Of 168 youth who initiated fluoxetine, 102 responded to treatment (≥ 50% decrease on the CDRS-R from baseline) and were randomly allocated for continuation treatment.

Procedures and Measures

Study methods have been previously described.[3] Youth underwent a 2-week diagnostic evaluation using the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version.[11] At baseline, youth who continued to meet entry criteria began fluoxetine 10 mg/d, increasing to 20 mg at week 1. Dose could be titrated to 30 to 40 mg after 6 weeks if clinically indicated. After 12 weeks, responders were randomly assigned to fluoxetine (n = 50) or placebo (n = 52). Randomization eligibility required participants to be either remitted (defined as a CGI Improvement score of very much or much improved [score = 1 or 2] and a CDRS-R score ≤ 28) or showing an adequate clinical response (defined as a CGI Improvement score of 1 or 2 and a decrease of 50% or more in the CDRS-R total score). Visits during continuation were biweekly for 1 month, then monthly until the end of the study. Depression rating scales were rated at each visit by the treating psychiatrist.

Outcome Variable

For the proposed analyses, relapse was defined as a CDRS-R total score ≥ 40 with worsening of depressive symptoms for at least 2 weeks. In the original study, relapse was defined using strict criteria (CDRS-R ≥ 40), as well as clinical deterioration of depression not yet reaching full threshold of depression.[3] The differences between active treatment and placebo were driven by the stricter definition of relapse. Thus, for the current study and analyses, we chose to go with the strict relapse criteria to allow for greater opportunity to identify predictors and moderators of relapse.

Predictors and Moderators

Available pharmacologic research of early-onset MDD was reviewed, with particular attention to the recent large randomized clinical trials (TADS, TORDIA, and ADAPT [Adolescent Depression Antidepressants and Psychotherapy Trial]); reviewed in Emslie et al).[1] Based on results from these trials, we explored unadjusted means and prevalence rates of a large number of variables to identify potential differences between youth who relapsed ("relapsers") and those who did not ("nonrelapsers"), both across treatment groups and within treatment groups. We then selected a set of variables pertaining to demographic characteristics, illness characteristics, comorbid conditions, family characteristics, and symptom change during acute treatment as potential predictors and moderators for further analysis.

Demographic characteristics.—Among demographic characteristics, age group (children vs adolescents), sex (female vs male), and race (non-Caucasian vs Caucasian) were examined. Although socioeconomic status appeared to influence outcome in TADS,[12] socioeconomic status was not available for the present study.

Illness characteristics.—Presence of recurrent depression, length of episode, depression severity at baseline (CDRS-R), and presence of insomnia (sleep disturbance) were included. Suicidal ideation at baseline did not predict relapse in the aforementioned research studies, and it was not statistically different between relapsers and nonrelapsers in the current study, so it was not included in these analyses.

Comorbid conditions and cognitive measures.—Presence of dysthymia or an anxiety disorder at baseline (week 0), as well as the total score of the Multidimensional Anxiety Scale for Children[13] at baseline (week 0) and randomization (week 12) were included in the current analyses. In the current sample, variables such as other comorbid conditions, prior trauma, hopelessness, and quality of life were similar between relapsers and nonrelapsers; therefore, these variables were not included in the present analyses.

Family characteristics.—The Self-Report Family Inventory (SFI-II)[14] subscales (administered at baseline) were explored, and only the leadership subscale, which measures whether there is parental leadership within the family unit, was included in the predictor/moderator analyses. Lower scores represent positive qualities reflecting strong and consistent patterns of adult leadership within the family.

Symptom change during acute treatment.—Depression severity (CDRS-R) at weeks 6 and 12, presence of residual insomnia at week 12 (based on a score of 3 or greater on the CDRS-R item 4), and presence of residual irritability at week 12 (based on a score of 3 or greater on the CDRS-R item 8) were examined. Other residual depressive symptoms occurred in very low rates, and no further analysis of these variables was warranted.

Statistical Analysis

Demographic and clinical characteristics for relapsers and nonrelapsers were described using the sample mean and standard deviation (continuous variables) and the frequency and percentage (categorical variables). These characteristics were compared between groups using the 2–independent sample *t* test with the Satterthwaite method for unequal variances (continuous outcomes) and the χ^2 test or, when appropriate, Fisher exact test (categorical variables). Note that control variables (covariates for adjustment) were not part of the inferential comparison (test) of the 2 groups (relapsers vs nonrelapsers) on these characteristics via the *t* test, χ^2 test, or Fisher exact test, as presented in Tables 1 and 3.

Multiple logistic regression was used to estimate the odds of relapse from each predictor variable in a separate model while controlling for treatment (fluoxetine vs placebo), age, sex, and depression severity after 12 weeks of treatment. To assess a moderator effect, a separate multiple logistic regression model was used to estimate the odds of relapse (while controlling for age, sex, and depression severity at randomization [week 12]) and included the main effects and the 2-way interaction effects (incorporating treatment and the moderator variable). For each moderator variable that interacted with treatment, the odds of relapsing for fluoxetine versus placebo were estimated either at each level of the binary moderator or at the mean level of the continuously measured moderator. We note that a separate logistic regression model was used to evaluate each candidate predictor and moderator on the outcome of relapse status. The 95% Wald CIs were calculated for each adjusted odds ratio (OR), and the Wald χ^2 statistic (associated with the joint test) was used to test for a significant association between each effect and relapse status.

All statistical analyses were performed using SAS software, version 9.3 (SAS Institute, Inc, Cary, North Carolina). The level of significance for all tests was set at $\alpha = .05$ (2-tailed) and, because this is an exploratory report, we did not correct *P* values for multiple testing.

RESULTS

Participant Characteristics

Among the randomized sample, the mean age was 11.5 ± 2.8 years, and most of the patients were Caucasian (70.6%). Males represented a slightly larger portion of the sample (55.9%). The mean CDRS-R total score at baseline was 57.7 ± 7.6, and most were in their first depressive episode (72.5%). At the time of randomization (week 12), the mean CDRS-R score was 22.8 ± 4.2.

Full relapse occurred in 35.3% of participants, with fewer relapses among those remaining on fluoxetine compared with placebo (22.0% vs 48.1%; $P = .007$). Table 1 provides the

demographic, clinical, family, and symptom change characteristics between relapsers and nonrelapsers.

Predictors

Demographic and illness characteristics.—No baseline demographic or illness characteristics were predictive of relapse (Table 2).

Comorbid conditions.—Among those who relapsed, 47.2% had dysthymia at baseline, compared with only 25.8% of those who did not relapse (Table 1). After controlling for treatment status, age, sex, and CDRS-R score at the time of randomization (week 12), the predicted odds of relapsing for those who had dysthymia were 2.88 times the odds for those who had no dysthymia (adjusted OR = 2.88, $P = .03$). Anxiety was not predictive of relapse (Table 2).

Family characteristics.—Independent of treatment assignment, the only baseline family variable that predicted relapse was the youth's and parent's perception of poor leadership in the family unit (SFI-II; Tables 1 and 2). After controlling for treatment status, age, sex, and CDRS-R total score at the time of randomization (week 12), we found that a 1-unit increase in the baseline child rating of perceived poor family leadership was associated with 1.39 times (or 39% increase in) the predicted odds of relapsing (adjusted OR = 1.39, $P = .006$). Moreover, after controlling for treatment status, age, sex, and CDRS-R total at randomization (week 12), we found that a 1-unit increase in the baseline parent rating of perceived poor family leadership was associated with 1.24 times (or 24% increase in) the predicted odds of relapsing (adjusted OR = 1.24, $P = .06$), albeit not statistically significant.

Symptom change.—Symptom change following 12 weeks of treatment yielded several positive findings. CDRS-R total scores at weeks 6 and 12 were significantly lower among youth with no relapse than among those who experienced a relapse of depression during follow-up (Table 1). Higher depression severity at randomization (week 12) was associated with 1.21 times (or a 21% increase in) the predicted odds of relapse (OR = 1.21, $P = .003$), even when controlling for treatment, age, and sex (Table 2). However, week 6 depression severity did not predict relapse (Table 2).

In addition, youth who relapsed were more likely to have residual symptoms than those who did not relapse (69.4% vs 43.9%; $P = .01$). Having 1 or more residual symptom was associated with relapse, but after controlling for treatment status, age, sex, and CDRS-R total score at randomization (week 12) this was no longer statistically significant (OR = 2.46, $P = .21$; Table 2). Youth with residual sleep disturbance at randomization (week 12) had 6.74 times the predicted odds of relapse of those without residual sleep disturbance (OR = 6.74, $P = .006$), and youth with residual irritability (assessed at week 12) had 7.40 times the predicted odds of relapse compared with those with no residual irritability (OR = 7.40, $P = .01$).

Moderators

Table 3 details the descriptive statistics on patient characteristics between relapsers and nonrelapsers by treatment assignment. Results of the moderators of treatment relapse from the interaction-effects multiple logistic regression models are shown in Table 4.

Demographic characteristics.—While controlling for age and CDRS-R total score at randomization (week 12), a significant main effect of treatment (fluoxetine vs placebo, $P = .0004$) and a significant treatment × sex interaction effect ($P = .01$) were found. For those who took fluoxetine, the predicted odds of relapse for females were 8.86 times the odds for males (adjusted OR = 8.86; 95% CI, 1.83–42.78; $P = .007$). No significant sex effect was observed at the level of placebo, suggesting that both males and females were at similar risk of relapse upon discontinuing medication following 3 months of acute treatment. Moreover, after controlling for age and CDRS-R total score at randomization (week 12), the effect of medication treatment at the level of sex suggests that males who received fluoxetine had 0.07 times (or 93.0% decrease in) the predicted odds of relapsing of males who received placebo (adjusted OR = 0.07; 95% CI, 0.01–0.31; $P = .006$). No significant medication effect was observed at the level of female sex. Age and race did not moderate treatment relapse (Table 4).

Illness characteristics.—While controlling for age, sex, and CDRS-R total score at randomization (week 12), a significant main effect of treatment (fluoxetine vs placebo, $P = .01$) and a significant treatment × baseline CDRS-R total interaction effect ($P = .03$) were found. The effect of medication at the level of the average CDRS-R total score at baseline (57.74) suggests that those who received fluoxetine had 0.193 times (or 80.7% decrease in) the predicted odds of relapsing of those who received placebo (adjusted OR = 0.193; 95% CI, 0.07–0.54; $P = .02$). The effect of baseline CDRS-R total at levels of medication suggests that, for those who took fluoxetine, a 1-unit increase in the baseline CDRS-R total score was associated with 1.14 times (or 14% increase in) the predicted odds of relapsing (adjusted OR = 1.14; 95% CI, 1.01–1.31; $P = .03$). No significant effect was observed at the level of placebo. Other illness characteristics did not moderate treatment relapse (Table 4).

Comorbid conditions.—Among youth with dysthymia, 4 of 17 (23.5%) relapsed on fluoxetine, whereas 13 of 17 (76.5%) relapsed on placebo. Despite these differences, presence of dysthymia did not moderate treatment relapse based on the multiple logistic regression model (Table 4). Presence of an anxiety disorder at baseline and baseline anxiety severity also did not moderate relapse (Table 4). After controlling for CDRS-R total at randomization (week 12), sex, and age in a multiple logistic regression model, we observed a significant main effect of treatment (fluoxetine vs placebo, $P = .006$) but no significant treatment × anxiety score interaction effect ($P = .06$). Upon examining the pattern of adjusted ORs, to interpret a moderator effect of randomization (week 12) anxiety score, we found that the effect of medication at the mean level of anxiety score (40.06) suggests that those who received fluoxetine had 0.19 times (or 81.0% decrease in) the predicted odds of relapsing of those who received placebo (adjusted OR = 0.19; 95% CI, 0.07–0.53; $P = .002$).

Family leadership.—Family leadership did not moderate relapse (Table 4).

Symptom change.—Depression severity at week 6 did not moderate relapse (Table 4), although within the fluoxetine group, CDRS-R total score at randomization (week 12) was lower among those who did not relapse compared with those who relapsed (26.0 ± 7.0 vs 32.2 ± 11.9; $P = .03$; Table 3). As shown in Table 4, depression severity after 12 weeks of treatment did moderate treatment relapse. After controlling for sex and age, the effect of medication at the mean level of CDRS-R total score at randomization (week 12; 22.83) revealed that those who received fluoxetine had 0.125 times (or 87.5% decrease in) the predicted odds of relapsing of those who received placebo (adjusted OR = 0.12: 95% CI, 0.03–0.44; $P = .001$). The effect of randomization (week 12) CDRS-R total score at levels of medication suggests that, for those who took fluoxetine, a 1-unit increase in CDRS-R total score at randomization (week 12) was associated with 1.56 times (or 56% increase in) the predicted odds of relapsing (adjusted OR = 1.56; 95% CI, 1.18–2.06; $P = .02$). Depression severity at randomization (week 12), however, did not significantly moderate the predicted odds of relapse for those receiving placebo.

Among youth with no residual symptoms who were randomly assigned to fluoxetine, there were no relapses. However, among those with no residual symptoms who were randomly assigned to placebo, 39.3% (11/28) relapsed. For youth with any residual symptoms at randomization (week 12), 36.7% relapsed on fluoxetine compared with 58.3% on placebo. However, after controlling for age, sex, and CDRS-R total score at randomization (week 12), presence of residual symptoms was not a moderator of relapse.

We further examined specific residual symptoms of insomnia and irritability at week 12. After controlling for age, sex, and randomization (week 12) CDRS-R total score (minus the sleep item), in a multiple logistic regression, we observed a significant main effect of treatment (fluoxetine vs placebo, $P = .0004$) but no significant treatment × residual insomnia interaction effect ($P = .08$). When we examined the pattern of adjusted ORs to interpret a moderator effect of residual insomnia at randomization (week 12), we found that the effect of medication at each level of residual insomnia revealed that youth on fluoxetine who had no residual insomnia had 0.116 times (or 88.4% decrease in) the predicted odds of relapsing of those who received placebo and who had no residual insomnia (OR = 0.12; 95% CI, 0.03–0.38; $P = .006$). No significant medication effect was observed at the level of those who had residual insomnia at randomization (week 12). Residual irritability did not moderate treatment relapse (Table 4).

DISCUSSION

Although acute phase treatments for youth with depression have proven effective, relapse rates are high, even with continued treatment. Determining predictors of relapse, as well as factors that may interact with specific treatments to affect probability of relapse, is an important area of investigation. Knowing which youth are at greater risk may inform follow-up care, as well as identify possible risk factors to target for further treatment.

In this study, we examined predictors, which are defined as factors that are independent of treatment assignment and present at baseline. In this study, we did not find evidence of demographic factors as predictors of relapse. Examination of baseline clinical variables

identified that comorbid dysthymia leads to greater risk for relapse, almost 3 times greater than those without dysthymia. No other baseline illness variables were predictive of relapse. However, those individuals who had higher levels of depression at the end of acute treatment (12 weeks) were at greater risk of relapse. Similarly, youth with residual sleep disturbance and irritability at randomization (week 12) were about 7 times more likely to relapse than those without these residual symptoms. Taken together, these findings point to illness severity, both at baseline (severity and comorbidity) and at end of treatment (residual symptoms), as a predictor of relapse.

Factors that interacted with treatment assignment, or moderators, to influence relapse were also examined. Females who remained on fluoxetine after randomization (week 12) were almost 9 times more likely to relapse than males on fluoxetine; males who remained on fluoxetine were about 93% less likely to relapse than males on placebo. No other demographic factors moderated treatment outcome, and no family factors moderated treatment outcome. The influence of sex on treatment outcomes has been mixed. However, in a naturalistic follow-up study of adolescent depression, the most robust predictor of recurrence of depression was female sex.[7] Similarly, in a community study of young adults aged 19 to 23, women were more likely to experience recurrence of depression than men.[15]

Other moderators that were found also point to severity and comorbidity affecting outcome. Higher levels of depressive symptoms at baseline in those remaining on fluoxetine increased the odds of relapse. Other studies have found depression severity to be associated with recurrence.[7] Also, youth on fluoxetine after 12 weeks who had lower levels of insomnia were shown to be less likely to relapse. Insomnia has been associated with poor treatment outcomes.[16]

We acknowledge that this study has several limitations, including a small sample size. Given that this is a secondary analysis of the original study, the study was not powered for moderator analyses. In addition, although there were 2 treatment conditions, one of these was placebo and limits the generalizability of the findings, given that a placebo condition is limited to research settings and not real-world practice.

Identifying risk factors for relapse is important both for providing psychoeducation about course of illness to youth with depression and their families and for tailoring treatments to specifically target these risk factors. For example, after acute treatment, for youth with levels of residual symptoms, such as sleep disturbance, irritability, and anxiety, clinicians may recommend continuing treatment for extended periods or may recommend specific interventions to reduce these residual symptoms. Furthermore, clinicians are encouraged to monitor closely youth at increased risk for relapse (eg, females and youth with continued high levels of depressive symptoms) for early signs of relapse even while they remain on medication.

Our findings provide important directors for future research. In an era of improving individualized treatment strategies for patients with mental health concerns, it is important to identify characteristics that may predict treatment outcomes. Whereas many studies focus on predicting outcomes for acute treatments, this study identifies predictors and moderators

of depression relapse. Specifically, knowing which patients respond to which treatments is essential in improving outcomes and reducing rates of relapse. Moderator analyses require large sample sizes. Depression registries and collaborative databases should be used to afford access to more information on matching treatments to individuals based on their characteristics and course of treatment. Additional research is needed, however, in the area of personalized treatments adapted based on patient characteristics.

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Potential conflicts of interest:

Dr Emslie receives research support from BioMarin, Duke University, Forest, and Mylan and is a consultant for Alkermes, Allergan, NCS Pearson (previously Biobehavioral Diagnostics Company), Bristol-Myers Squibb, Eli Lilly, INC Research Inc, Lundbeck, Merck, and Pfizer. **Drs Kennard** and **Nakonezny** and **Mss Mayes**, **Chahal**, and **Moorehead** report no competing interests.

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Clinical Points

- With high rates of relapse in youth treated for depression, identifying factors related to relapse is important in personalizing treatment to specific patient characteristics.
- Patients who have comorbid dysthymia and higher levels of residual symptoms after acute treatment are at risk for relapse and may need closer monitoring and possible treatment augmentation strategies.
- Females receiving fluoxetine treatment may be at higher risk for relapse than males receiving fluoxetine.

Table 1.

Characteristics of Youth With Major Depressive Disorder Who Did and Who Did Not Relapse After Antidepressant Treatment[a,b]

	Relapse (n = 36)	No Relapse (n = 66)	*P*
Demographic characteristics			
Age, mean (SD)	11.4 (2.7)	11.5 (2.8)	.86
Male, n (%)	20 (55.6)	45 (68.2)	.28
Female, n (%)	16 (44.4)	21 (31.8)	
Caucasian, n (%)[c]	25 (69.4)	47 (71.2)	.99
Non-Caucasian, n (%)[c]	11 (30.6)	19 (28.8)	
Illness characteristics			
Length of episode, mean (SD), wk	28.0 (24.3)	22.1 (16.8)	.15
Recurrent depression, n (%)	11 (30.6)	17 (25.8)	.61
CDRS-R total at baseline, mean (SD)	58.9 (7.3)	57.1 (7.7)	.24
Comorbid conditions			
Presence of dysthymia, n (%)	17 (47.2)	17 (25.8)*	.03
Presence of anxiety, n (%)	8 (22.2)	18 (27.3)	.57
MASC at baseline (anxiety), mean (SD)	56.9 (18.2)	53.1 (19.7)	.34
MASC at week 12 (anxiety), mean (SD)	40.6 (16.6)	39.7 (16.7)	.79
Family characteristics			
SFI-II leadership (patient) at baseline, mean (SD)	8.1 (2.5)	6.7 (1.9)**	.004
SFI-II leadership (parent) at baseline, mean (SD)	7.6 (2.0)	6.4 (2.2)**	.007
Depressive symptoms during treatment			
CDRS-R total at week 6, mean (SD)	30.1 (9.4)	26.5 (7.6)*	.04
CDRS-R total at week 12, mean (SD)	24.3 (4.1)	22.1 (4.0)**	.009
Residual symptoms (≥ 1) at week 12, n (%)	25 (69.4)	29 (43.9)*	.01
Residual insomnia at week 12, n (%)	9 (25.0)	5 (7.6)*	.01
Residual irritability at week 12, n (%)	8 (22.2)	4 (6.1)*	.01

[a]Demographic and clinical characteristics were compared between relapsers and nonrelapsers using the 2–independent sample *t* test with the Satterthwaite method for unequal variances (continuous outcomes) and the χ^2 test or, when appropriate, Fisher exact test (categorical variables). Note that control variables (covariates for adjustment) were not part of the inferential comparison (test) of the 2 groups (relapsers vs nonrelapsers) on these characteristics via the *t* test, χ^2 test, or Fisher exact test.

[b]Randomization was at week 12; baseline was at week 0.

[c]Race was operationally defined as Caucasian (n = 72, 70.6%) and non-Caucasian: African American (n = 9, 8.8%), Hispanic (n = 15, 14.7%), and other (n = 6, 5.9%).

*$P < .05$.

**$P < .01$.

Abbreviations: CDRS-R = Children's Depression Rating Scale–Revised, MASC = Multidimensional Anxiety Scale for Children, SFI = Self-Report Family Inventory.

Table 2.

Odds Ratios With 95% Confidence Intervals for Each Predictor of Treatment Relapse From the Main-Effects Multiple Logistic Regression Models[a,b]

	OR[c]	95% CI for OR[d]	χ^2 (*P* Value)[e]
Demographic characteristics			
Age group (children vs adolescents)	1.45	0.55–3.83	0.57 (.45)
Sex (female vs male)	2.09	0.82–5.31	2.42 (.12)
Race (non-Caucasian vs Caucasian)[f]	1.16	0.43–3.13	0.08 (.77)
Illness characteristics			
Baseline CDRS-R total	1.01	0.95–1.08	0.28 (.59)
Length of episode (weeks)	1.01	0.98–1.03	0.68 (.41)
Recurrent depression (yes vs no)	1.31	0.48–3.56	0.28 (.59)
Sleep disturbance (insomnia) at baseline (yes vs no)[g]	2.14	0.78–5.88	2.19 (.13)
Comorbid conditions			
Presence of dysthymia (yes vs no)	2.88	1.09–7.64	4.54 (.03)
Presence of anxiety (yes vs no)	0.92	0.30–2.81	0.02 (.88)
Baseline anxiety score	1.02	0.99–1.04	1.67 (.19)
Week 12 anxiety score	1.01	0.97–1.03	0.12 (.72)
Family characteristics			
Baseline child leadership score	1.39	1.09–1.76	7.40 (.006)
Baseline parent leadership score	1.24	0.99–1.55	3.68 (.05)
Depressive symptoms during treatment			
Week 6 depression severity (CDRS-R total score)[h]	1.01	0.94–1.07	0.06 (.80)
Week 12 depression severity (CDRS-R total score)[i]	1.21	1.06–1.36	8.92 (.003)
Residual symptoms at week 12 (yes vs no)	2.46	0.61–9.94	1.60 (.21)
Residual insomnia at week 12 (yes vs no)[g]	6.74	1.71–26.58	7.44 (.006)
Residual irritability symptoms at week 12 (yes vs no)[j]	7.40	1.56–34.96	6.38 (.01)

[a]Relapse status was a binary outcome variable operationally defined as “relapse” or “nonrelapse” to treatment outcome. The probability of relapsing was modeled. A separate main-effects multiple logistic regression model was conducted for each predictor of relapse status.

[b]Randomization was at week 12; baseline was at week 0.

[c]Adjusted ORs were estimated for each predictor of relapse, while controlling for the effect of treatment (fluoxetine vs placebo), age, sex, and randomization (week 12) CDRS-R total (unless otherwise noted below).

[d]Wald CI for ORs.

[e]Wald χ^2 statistic for the type 3 analysis of effects.

[f]Race was operationally defined as Caucasian (n = 72, 70.6%) and non-Caucasian = African American (n = 9, 8.8%), Hispanic (n = 15, 14.7%), and other (n = 6, 5.9%).

[g]Adjusted OR was estimated for residual sleep and relapse, while controlling for the effect of treatment, age, sex, and randomization (week 12) CDRS-R Total minus sleep item.

[h] Controlled for treatment (fluoxetine vs placebo), age, sex, and randomization (week 12) CDRS-R Total.

[i] Controlled for treatment (fluoxetine vs placebo), age, and sex.

[j] Adjusted OR was estimated for residual irritability and relapse, while controlling for the effect of treatment, age, sex, and randomization (week 12) CDRS-R Total minus irritability item.

Abbreviations: CDRS-R = Children's Depression Rating Scale–Revised, OR = odds ratio.

Table 3.

Differences in Relapsers and Nonrelapsers by Treatment Group[a,b]

	Fluoxetine			Placebo		
	Relapse (n = 11)	**No Relapse (n = 39)**	***P***	**Relapse (n = 25)**	**No Relapse (n = 27)**	***P***
Demographic characteristics						
Age, mean (SD)	11.55 (2.62)	11.1 (2.7)	.61	11.36 (2.80)	12.15 (2.98)	.33
Male, n (%)	3 (27.3)	29 (74.4)	.01	17 (68.0)	16 (59.3)	.57
Female, n (%)	8 (72.7)	10 (25.6)		8 (32.0)	11 (40.7)	
Caucasian, n (%)[c]	7 (63.6)	27 (69.2)	.72	18 (72.0)	20 (74.1)	.98
Non-Caucasian, n (%)[c]	4 (36.4)	12 (30.8)		7 (28.0)	7 (25.9)	
Illness characteristics						
Length of episode, mean (SD), wk	31.1 (30.9)	20.4 (13.0)	.09	26.6 (21.4)	24.6 (21.2)	.73
Recurrent depression, n (%)	3 (27.3)	10 (25.6)	.91	8 (32.0)	7 (25.9)	.63
CDRS total at baseline, mean (SD)	62.73 (8.13)	56.03 (5.99)	.004	57.28 (6.45)	58.63 (9.51)	.55
Comorbid conditions						
Presence of anxiety, n (%)	4 (36.4)	14 (35.9)	.97	4 (16.0)	4 (14.8)	.91
Presence of dysthymia, n (%)	4 (36.4)	13 (33.3)	.85	13 (52.0)	4 (14.8)	.005
MASC at baseline, mean (SD)	65.36 (16.74)	53.85 (17.6)	.06	53.24 (17.8)	52.11 (22.6)	.84
MASC at week 12, mean (SD)	49.55 (12.14)	39.15 (16.9)	.06	36.72 (17.0)	40.59 (16.7)	.41
Family characteristics						
SFI-II leadership (patient) at baseline, mean (SD)	8.4 (2.3)	6.7 (1.7)	.009	8.0 (2.6)	6.6 (2.2)	.04
SFI-II leadership (parent) at baseline, mean (SD)	7.5 (1.7)	6.1 (2.0)	.04	7.7 (2.2)	6.9 (2.4)	.22
Depressive symptoms during treatment						
CDRS-R total at week 6, mean (SD)	32.2 (11.9)	26.0 (7.0)	.03	29.2 (8.2)	27.3 (8.4)	.41
CDRS-R total at week 12, mean (SD)	26.9 (2.7)	22.3 (3.5)	.0002	23.1 (4.1)	21.74 (4.7)	.26
Any residual symptoms at week 12, n (%)						
No	0 (0)	20 (51.3)	.002	11 (44.0)	17 (63.0)	.26
Yes	11 (100)	19 (48.7)		14 (56.0)	10 (37.0)	
Residual insomnia at week 12, n (%)	6 (54.5)	3 (7.7)	.0004	3 (12.0)	2 (7.4)	.57
Residual irritability at week 12, n (%)	7 (63.6)	3 (7.7)	.0001	1 (4.0)	1 (3.7)	.95

[a] Characteristics were compared between relapsers and nonrelapsers within each treatment group using the 2–independent sample *t* test with the Satterthwaite method for unequal variances (continuous outcomes) and the χ^2 test or, when appropriate, Fisher exact test (categorical variables). Note that control variables (covariates for adjustment) were not part of the inferential comparison (test) of the 2 groups (relapsers vs nonrelapsers) on these characteristics via the *t* test, χ^2 test, or Fisher exact test.

[b] Randomization was at week 12; baseline was at week 0.

[c] Race was operationally defined as Caucasian (n = 72, 70.6%) and non-Caucasian = African American (n = 9, 8.8%), Hispanic (n = 15, 14.7%), and other (n = 6, 5.9%).

Abbreviations: CDRS-R = Children's Depression Rating Scale–Revised, MASC = Multidimensional Anxiety Scale for Children, SFI = Self-Report Family Inventory.

Table 4.

Moderators of Treatment Relapse From the Interaction-Effects Multiple Logistic Regression Models[a,b]

	Relapse Status		
	Treatment	Variable	Treatment × Variable
Variable	**χ^2 (*P* Value)[c]**	**χ^2 (*P* Value)[c]**	**χ^2 (*P* Value)[c]**
Demographic characteristics			
Age group (children vs adolescents)	2.55 (.11)	1.18 (.27)	0.64 (.42)
Sex (female vs male)	12.51 (.0004)	0.14 (.70)	5.71 (.01)
Race (non-Caucasian vs Caucasian)[d]	7.45 (.006)	0.0001 (.99)	0.09 (.75)
Illness characteristics			
Length of episode (wk)	6.64 (.01)	0.004 (.95)	0.82 (.36)
Recurrent depression (yes vs no)	5.74 (.01)	0.62 (.43)	0.34 (.55)
Sleep disturbance (insomnia) at acute baseline (yes vs no)[e]	4.97 (.02)	0.31 (.57)	0.94 (.33)
Baseline CDRS-R total	5.93 (.01)	0.76 (.38)	4.60 (.03)
Comorbid and cognitive variables			
Dysthymia (yes vs no)	2.76 (.09)	6.35 (.01)	2.44 (.11)
Presence of anxiety (yes vs no)	6.97 (.008)	0.02 (.87)	0.007 (.93)
Baseline anxiety score	4.99 (.02)	0.10 (.75)	1.83 (.17)
Week 12 anxiety score	7.52 (.006)	1.25 (.26)	3.39 (.06)
Family characteristics			
Baseline child leadership score	2.18 (.14)	3.66 (.05)	0.60 (.43)
Baseline parent leadership score	2.09 (.14)	1.40 (.23)	0.53 (.46)
Depressive symptoms during treatment			
Week 6 depression severity (CDRS-R total score)[e]	3.81 (.05)	0.35 (.55)	1.29 (.25)
Week 12 depression severity (CDRS-R total score)[f]	6.55 (.01)	2.06 (.15)	5.07 (.02)
Residual symptoms at week 12 (yes vs no)	0.005 (.94)	0.06 (.80)	0.005 (.94)
Residual insomnia at week 12 (yes vs no)[g]	12.56 (.0004)	0.23 (.63)	2.94 (.08)
Residual irritability symptoms at week 12 (yes vs no)[h]	12.64 (.0004)	0.002 (.96)	2.30 (.13)

[a] Relapse status was a binary outcome variable operationally defined as “relapse” or “nonrelapse” to treatment outcome. We modeled the probability of relapsing. A separate interaction-effects multiple logistic regression model was conducted for each moderator variable of relapse status, with the main effects of treatment (fluoxetine vs placebo) and variable and the variable × treatment interaction effect included in the model, while controlling for age, sex, and randomization (week 12) CDRS-R total (unless otherwise noted below).

[b] Randomization was at week 12; baseline was at week 0.

[c] Wald χ^2 statistic for the type 3 analysis of effects.

[d] Race was operationally defined as Caucasian (n = 72, 70.6%) and non-Caucasian = African American (n = 9, 8.8%), Hispanic (n = 15, 14.7%), and other (n = 6, 5.9%).

[e] Controlled for age, sex, and randomization (week 12) CDRS-R total.

[f] Controlled for age and sex.

[g] Controlled for age, sex, and randomization (week 12) CDRS-R total minus sleep item.

[h] Controlled for age, sex, and randomization (week 12) CDRS-R total minus irritability item.

Abbreviation: CDRS-R = Children’s Depression Rating Scale–Revised.