ARTICLE

A Randomized Controlled Trial of Fluoxetine and Cognitive Behavioral Therapy in Adolescents With Major Depression, Behavior Problems, and Substance Use Disorders

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Objective: To evaluate the effect of fluoxetine hydrochloride vs placebo on major depressive disorder, substance use disorder (SUD), and conduct disorder (CD) in adolescents receiving cognitive behavioral therapy (CBT) for SUD.

Design: Randomized controlled trial.

Setting: A single-site study conducted between May 2001 and August 2004.

Participants: One hundred twenty-six adolescents aged 13 to 19 years recruited from the community and meeting *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) diagnostic criteria for current major depressive disorder, lifetime CD, and at least 1 nontobacco SUD.

Interventions: Sixteen weeks of fluoxetine hydrochloride, 20 mg/d, or placebo, with CBT.

Main Outcome Measures: For depression, Childhood Depression Rating Scale–Revised and Clinical Global Impression Improvement; for SUD, self-reported nontobacco substance use and urine substance use screen results in the past 30 days; and for CD, self-reported symptoms in the past 30 days.

Results: Fluoxetine combined with CBT had greater efficacy than did placebo and CBT according to changes on the Childhood Depression Rating Scale–Revised (effect size, 0.78) but not on the Clinical Global Impression Improvement treatment response (76% and 67%, respectively; relative risk, 1.08). There was an overall decrease in self-reported substance use (4.31 days; 95% confidence interval, 2.12-6.50) and CD symptoms (relative risk, 1.20; 95% confidence interval, 0.82-1.59), but neither difference between groups was statistically significant. The proportion of substance-free weekly urine screen results was higher in the placebo-CBT group than in the fluoxetine-CBT group (mean difference, 2.10; 95% confidence interval, 0.37-4.15).

Conclusions: Fluoxetine and CBT had greater efficacy than did placebo and CBT on one but not both depression measures and was not associated with greater decline in self-reported substance use or CD symptoms. The CBT may have contributed to higher-than-expected treatment response and mixed efficacy findings, despite its focus on SUD.

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Adolescents with substance use disorders (SUDs) have higher rates of depression (15%-24%) than adolescents in the general population (2%-8%).[1] Comorbid depression is also associated with more severe substance abuse, poorer drug treatment outcomes, and higher relapse rates.[2-6] Three controlled trials have demonstrated the efficacy of fluoxetine hydrochloride—a selective serotonin reuptake inhibitor (SSRI)—for major depressive disorder (MDD) in adolescents without SUD, but none have yet been conducted in depressed adolescents with SUD, who are typically excluded from participating in pharmacotherapy trials.[7-9]

Given the paucity of research, clinicians are often reluctant to prescribe antidepressants for depressed adolescents with SUD. Such youths are commonly first referred to and expected to complete substance treatment and achieve a sustained period of abstinence before antidepressant medication is considered; however, successful treatment of SUD is less likely if MDD is not treated.[10] The lack of research on the safety and efficacy of medications for depression and other common co-occurring disorders contributes to this clinical conundrum. To address this

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research gap, we conducted a 16-week double-blind randomized controlled trial of fluoxetine vs placebo for MDD in 126 adolescents participating in weekly outpatient cognitive behavioral therapy (CBT) for SUD. Fluoxetine was selected as the study medication over other antidepressants (including other SSRIs) because of the larger body of empirical support for its efficacy in the treatment of MDD in adolescents without SUD.[7-9,11] The primary study hypotheses were (1) fluoxetine combined with CBT would have greater efficacy than placebo combined with CBT in reducing depression, (2) there would be a greater decline in substance use for patients receiving fluoxetine and CBT vs placebo and CBT, and (3) there would be a greater decline in conduct disorder (CD) symptoms in those receiving fluoxetine and CBT compared with placebo and CBT.

METHODS

PARTICIPANTS

Subjects were 126 adolescents recruited from the community and social and juvenile justice agencies. Prior approval of the protocol was obtained from the institutional review board of the University of Colorado School of Medicine, Denver. Written informed consent was obtained from all participants (as well as a parent or guardian if the participant was a minor) before conducting baseline assessments. Enrollment began in May 2001, and the last study visit occurred in August 2004.

Inclusion criteria were ages 13 to 19 years, willingness to participate in weekly CBT for SUD, *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) (*DSM-IV*)[12] criteria for current MDD, at least 1 nontobacco SUD, and lifetime CD.

Exclusion criteria were current or past diagnosis of a psychotic disorder or of bipolar disorder (type I or II), serious or unstable medical illness or pregnancy, current use of a psychotropic medication or participation in other concurrent substance or mental health treatment in the past month, and being considered at high risk for a suicide attempt during the trial in the clinical judgment of the study physician (P.D.R. or R.D.D.).

RANDOMIZATION AND BLINDING

A nonblinded research pharmacist assigned eligible participants to receive 20 mg of fluoxetine hydrochloride or matching placebo using a small block (6) randomization scheme of 20 blocks to achieve balance in treatment assignment. The protocol was amended to include as many as 10 additional subjects, and balance was similarly achieved with 1 block. Active medication and matching placebo were prepared by the research pharmacy at the University of Colorado at Denver and Health Sciences Center and then provided to clinical research staff in prerandomized and preblinded medication bottles. Research staff and participants remained blinded to medication status throughout the trial.

INTERVENTIONS

After randomization, all participants received a 20-mg fixed daily dose of fluoxetine hydrochloride or matching placebo and were monitored weekly for adherence to the medication regimen and adverse events (using the 56-item Side Effects for Children Assessment [SEFCA] Form).[13] Medication monitoring visits were conducted by 1 of 2 study research nurses (one of whom was M.L.) according to procedures adapted from the National Institute of Mental Health Treatment of Depression Collaborative Research Program, designed to enhance consistency of approach and to minimize overlap with the concurrent psychotherapy condition.[14] Adherence to the medication regimen was assessed by a combination of weekly pill counts, patient self-reports, and use of a medication event monitoring system (MEMS Smart Cap; APREX Corporation, Menlo Park, California). Discrepancies were reconciled by information gathered during weekly medication follow-up visits. Individual 1-hour CBT sessions were scheduled to precede or follow medication monitoring visits. The manual-standardized CBT was selected because of its empirical support as a treatment for adolescent SUD.[15,16] Study therapists were trained and certified by one of the manual's developers, who also provided ongoing therapist supervision and fidelity/adherence monitoring. The CBT sessions were videotaped and self-rated by each therapist (N = 1256 sessions). Thirty-two videotapes were randomly selected and independently rated for fidelity and adherence, by which neither therapist fell below preset fidelity/adherence standards at any point during the study. The treatment consists of weekly individual sessions, but could include 2 family sessions. Behavioral, cognitive behavioral, and motivational enhancement techniques are used to help adolescents reduce their drug use and improve their coping and decision-making skills related to substance use and relapse prevention. The manual-standardized therapy specifically focuses on the treatment of substance abuse, not depression; it includes a single module or session that helps adolescents identify, manage, and regulate negative mood states that often trigger substance use, such as dysphoria, anxiety, boredom, irritability, and anger. The CBT sessions were offered at no cost to all study participants; attendance was encouraged but not required.

DIAGNOSTIC AND OUTCOME MEASURES

Inclusion and exclusion criteria, including *DSM-IV* diagnoses of MDD, CD, and SUD, were determined by semistructured diagnostic interview administered at baseline by 1 of the 2 study physicians (P.D.R. and R.D.D.). Interrater reliability for physician diagnosis of MDD was established by 100% concurrence between both study physicians on 5 prestudy pilot cases. The MDD module of the Diagnostic Interview Schedule for Children–Version IV was administered to each adolescent and separately to the adolescent's parent or guardian.[17] The CD module was administered only to adolescents.

A primary outcome measure for depression was the Childhood Depression Rating Scale–Revised (CDRS-R), which was administered at baseline by a study physician and monthly thereafter via physician telephone interview.[18] The primary measure for assessment of the severity of suicidality was question 13 on the CDRS-R. The Clinical Global Impression (CGI) Severity rating was performed by the study physician (P.D.R. or R.D.D.), followed by CGI Improvement (CGI-I) ratings during monthly telephone follow-up interviews. The CGI-I item is a standard global assessment used as a repeated measure of change in depression referencing baseline severity of the target disorder.[19] Treatment response was defined a priori as a final CGI-I score of 1 (very much improved) or 2 (much improved). Remission of depression was defined a posteriori as a final CDRS-R raw score of 28 or lower to enhance comparability of study results to published rates of remission from controlled trials of fluoxetine in depressed adolescents without SUD.[8]

The *DSM-IV* diagnoses of substance abuse and dependence were determined by clinical interview and by the Comprehensive International Diagnostic Interview–Substance Abuse Mod-

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ule, a structured diagnostic interview assessing the following 11 drug categories: tobacco, alcohol, cannabis, cocaine, hallucinogens, inhalants, opiates, sedatives, phencyclidine, amphetamines, and club drugs (eg, [±]-3,4-methylenedioxymethamphetamine and flunitrazepam [street names, ecstasy or MDMA and rohypnol, respectively]).[20] A primary outcome measure for substance use was baseline and monthly self-reports of the number of days nontobacco drugs were used in the past 30 days (possible range, 0-30 days), assessed with timeline follow-back procedures.[21] Each day a substance was used counted as 1 toward the cumulative total, regardless of whether 1 or multiple substances were used on that day and regardless of the number of times a substance was used. Adolescent self-report of substance use ascertained by timeline follow-back procedures has been shown by numerous investigators to be a valid measure of alcohol and other drug use, especially under the confidentiality protection of a clinical trial.[22] Urine samples for substance use screening were collected weekly and evaluated for tetrahydrocannabinol, phencyclidine, barbiturates, benzodiazepines, opiates, amphetamines, cocaine, and alcohol. The number of negative (substance-free) urine screen results of a possible 16 was the secondary outcome measure for substance use. The primary outcome measure for CD was the number of self-reported *DSM-IV* symptoms in the past 30 days, assessed at baseline and monthly thereafter.

STATISTICAL METHODS

Data collection, entry, verification, transfer, confidentiality, security, storage, and analyses were conducted under the direction of the principal investigator (P.D.R.) and biostatistician (S.K.M.-G.). All analyses were intent-to-treat (including all randomized study participants; N=126) and were conducted using statistical software packages SPSS, version 14.0,[23] and SAS, version 8.2.[24(pp1363-1464; pp2083-2226)] Baseline comparisons between fluoxetine and placebo groups on demographic and key variables were assessed with χ^2 and independent *t* tests or nonparametric Mann-Whitney and Fisher exact tests when data distributions were nonnormal.

Analyses of dichotomous and continuous primary outcome measures over time used generalized estimating equation (GEE)[25] and likelihood-based methods, respectively. Both allow for estimates of changes in repeated measures in the presence of missing data, assuming those data were missing at random.[26,27] The pattern of missing data was evaluated with χ^2 tests comparing groups at each time point. Treatment responses (defined as a CGI-I score of 1 or 2) over time (weeks 4, 8, 12, and 16) between groups were compared using a GEE approach expedited by SAS PROC GENMOD, specifying a binary outcome and logit link.[24(pp1363-1464)] Logistic models evaluating linear and quadratic relationships with time were fit, and changes in deviance determined the best model.[27] Responder rates at the end of treatment (ie, 16 weeks) were compared between groups with a χ^2 test using multiple imputed values from the GEE approach for the missing data. The corresponding relative risk for response in the fluoxetine-CBT group compared with the placebo-CBT group was estimated. Secondarily, treatment response using the last available assessment was similarly compared between groups.

The continuous primary outcome variables for MDD, SUD, and CD were analyzed with mixed (random coefficient) models.[24(pp2083-2226)] Each outcome was assessed with the same mixed model design including a fixed treatment effect (fluoxetine and CBT vs placebo and CBT), a fixed time effect (baseline and monthly assessments measured as days from randomization), and a treatment × time interaction, estimating the average group-specific intercepts, rates of change over time, and group-specific differences in that rate, respectively. Specified random effects allowed the intercept and curve (eg, slope) of the lines to vary by subject. Linear, quadratic, and cubic relationships with time in the fixed and random effects were tested, and likelihood ratio tests and minimum values for the Akaike information criterion determined the best model.[28]

All comparisons used a 2-tailed, .05 significance level. Closed testing procedures with hierarchical evaluation were used in the following manner to provide some protection against multiple comparisons within the longitudinal analyses.[29] Overall treatment group curves (linear, quadratic, or cubic, depending on fit) were compared before conducting between-group comparisons at each time point. Only when curves were determined to differ significantly ($P<.05$) were comparisons between the estimated group means at each time point conducted. Effect sizes (Hedges *g*) were calculated as $(M_E-M_C)/SD$, where M_E represents the adjusted prerandomization-to-postrandomization mean change for the experimental group, M_C represents the adjusted prerandomization-to-postrandomization mean change for the comparison group, and SD represents the pooled standard deviation of each measure at baseline.[30]

Differences between treatment groups with regard to 56 adverse effects (SEFCA) and a subset of 12 SSRI-specific adverse effects (increased appetite, diarrhea, nausea, vomiting, difficulty falling asleep, drowsiness, sweating, irritability, outbursts of anger, nasal congestion, sexual dysfunction, and muscular cramps) were assessed with χ^2 and Fisher exact tests (for prevalence) and Mann-Whitney tests (for frequency). The SEFCA does not assess suicidality. Within-subject change in suicidality severity ratings were assessed by the monthly administration of the CDRS-R (question 13), and groups were compared over time with mixed model procedures[24(pp2083-2226)] as already described.

The unexpectedly high rate of treatment response and remission in the placebo and fluoxetine groups led us to conduct additional post hoc analyses comparing subjects who experienced remission (CDRS-R raw score ≤28) with those who did not (CDRS-R raw score >28), using linear mixed models for the continuous primary outcomes as described with the addition of fixed effects for remission status and the remission × medication group interaction. Similarly, 2-way analyses of variance were used to assess the effects of treatment group and remission status on urine screen data. Unless otherwise indicated, data are expressed as mean (SD).

RESULTS

PATIENT DISPOSITION

A total of 328 adolescents were screened by telephone (**Figure 1**). Of these, 143 signed the consent for evaluation of inclusion and exclusion criteria, of whom 126 (88.1%) were randomized to the fluoxetine-CBT (n=63) or the placebo-CBT (n=63) group and included in analyses. Reasons for exclusion of 17 of the 143 subjects (11.9%) and for study noncompletion by 11 (17.5%) in the fluoxetine-CBT group and 9 (14.3%) in the placebo-CBT group are noted in Figure 1.

DEMOGRAPHIC AND BASELINE CHARACTERISTICS

The mean age was 17.16 (1.66) years; 67.4% of the sample was male. Race and ethnicity were self-classified, including 48.4% white, 27.0% Hispanic, and 14.3% African

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American. The groups were not statistically significantly different on baseline demographics or primary outcome measures (**Table 1**).

The mean baseline CDRS-R raw score was 56.84 (13.42), which translates to a normed *t* score of 73.38 (8.09) (standardized to a mean of 50 [10]), indicating moderate to moderately severe depression consistent with the mean CGI-S score rating of 4.76 (0.84) (Table 1). The predominance of male study participants (85 of 126 [67.5%]) is consistent with higher rates of SUD and CD in adolescent boys compared with girls and also representative of sex differences in typical drug treatment programs. Twenty-six of the 126 subjects (20.6%) were assigned to drug treatment by court mandate; all others were self-referred or referred by a family member, a friend, another study participant, a school counselor, or a primary care or mental health care professional. Participants referred by court mandate were similar to participants referred by others on baseline characteristics and with respect to random assignment to treatment group.

EFFICACY OUTCOMES

Table 2 presents results from the intent-to-treat analyses of changes in measures of depression (CGI-I percentage responding with scores of 1 or 2 and CDRS-R *t* scores), substance use (number of self-reported days that nontobacco substances were used in the past 30 days and weekly urine screen results), and CD symptoms (number of self-reported symptoms in the past 30 days) by treatment group across the 16-week study. **Figure 2**A illustrates the longitudinal course of these measures over time for each group. The χ^2 test results supported the assumption that the pattern of missing data did not differ significantly between groups at any time. The logit model with a linear time effect was implemented using GEE and multiple imputation for missing data. There were high levels of treatment response, based on the CGI-I in the fluoxetine-CBT (84.1%) and placebo-CBT groups (77.8%), but the difference between groups was not statistically significant. The estimated risk ratio for fluoxetine responders relative to placebo responders based on the CGI-I was 1.08 (95% confidence interval [CI], 0.91-1.28). Thus, CGI-I treatment response rates based on the last available assessment were lower, or more conservative, than GEEs (fluoxetine, 76.3%; placebo, 66.7%) with an estimated relative risk of 1.14 (95% CI, 0.91-1.44). However, the difference between groups was not statistically significant with either analytic approach.

Likelihood-based criteria determined that the longitudinal course of the continuous outcomes followed a quadratic curve for MDD and SUD and a cubic curve for CD. All final models included random subject and linear time effects. Based on the decrease in CDRS-R *t* scores, the fluoxetine-CBT treatment (22.50 [1.59]) had greater efficacy compared with the placebo-CBT treatment (16.16 [1.58]). Significant separation between the curves began at week 12 (mean difference, 3.55; 95% CI, 0.50-6.60) continuing through week 16 (mean difference, 5.66; 95% CI, 1.45-9.87) (Table 2 and Figure 2B). On average, decreases in self-reported drug use in the past 30 days (4.31 [95% CI, 2.12-6.50] days) and CD symptoms (1.20 [95% CI, 0.82-1.59] symptoms) from baseline severity levels were observed, but the difference between treatment groups was not statistically significant (Table 2 and Figure 2C). However, the placebo-CBT group had a greater proportion of negative weekly urine screen results (6.14 [6.14]) compared with the fluoxetine-CBT group (4.05 [5.52]; mean difference, 2.10 [95% CI, 0.37-4.15] negative urine screen results).

The clinical significance of the effect of fluoxetine and CBT relative to placebo and CBT on depression, self-reported substance use, and CD outcomes was evaluated by calculating the effect sizes (Hedges *g*) relative to placebo and CBT, which was 0.78 for CDRS-R depression ratings, −0.07 for self-reported substance use, and −0.22 for self-reported CD symptoms (Table 2).

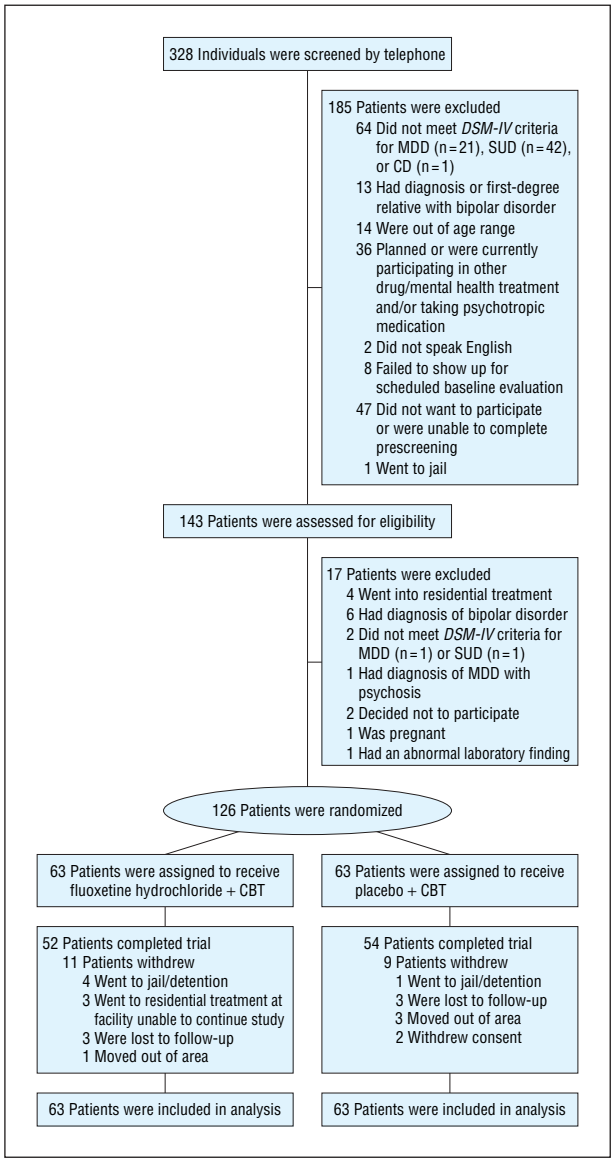

Figure 1. Flow diagram of treatment for depressed adolescents with substance use disorder (SUD). CBT indicates cognitive behavioral therapy; CD, conduct disorder; *DSM-IV, Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition); MDD, major depressive disorder.

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Table 1. Baseline Values by Treatment Group

Variable[a]	Treatment Group: Placebo With CBT (n = 63)	Treatment Group: Fluoxetine Hydrochloride With CBT (n = 63)	Total (N = 126)
Depression severity			
CDRS-R raw score[b]	55.87 (11.79)	57.81 (14.91)	56.84 (13.42)
CDRS-R *t* score[c]	73.03 (7.70)	73.74 (8.51)	73.38 (8.09)
CGI-S score[d]	4.68 (0.78)	4.84 (0.90)	4.76 (0.84)
Substance dependence severity			
No. of days nontobacco substance was used during the past 30 d	19.23 (10.51)	18.72 (10.35)	18.98 (10.39)
No. of abuse/dependence diagnoses including tobacco[e]	3.42 (1.84)	3.25 (1.98)	3.34 (1.91)
No. of abuse/dependence diagnoses without tobacco[e]	2.71 (1.71)	2.60 (1.78)	2.66 (1.74)
Positive urine screen results at baseline, No. (%)[f]	40 (65.6)	43 (68.3)	83 (66.9)
Abuse and dependence diagnoses by substance, No. (%)[e,g]			
Tobacco dependence	44 (71.0)	41 (65.1)	85 (68.0)
Alcohol abuse	8 (12.9)	8 (12.7)	16 (12.8)
Alcohol dependence	33 (53.2)	33 (52.4)	66 (52.8)
Cannabis abuse	20 (32.3)	15 (23.8)	35 (28.0)
Cannabis dependence	35 (56.5)	37 (58.7)	72 (57.6)
Cocaine abuse	6 (9.7)	6 (9.5)	12 (9.6)
Cocaine dependence	6 (9.7)	10 (15.9)	16 (12.8)
Amphetamine abuse	10 (16.1)	5 (7.9)	15 (12.0)
Amphetamine dependence	5 (8.1)	6 (9.5)	11 (8.8)
Hallucinogen abuse	6 (9.7)	3 (4.8)	9 (7.2)
Hallucinogen dependence	5 (8.1)	7 (11.1)	12 (9.6)
Inhalant abuse	1 (1.6)	1 (1.6)	2 (1.6)
Opiate abuse	5 (8.1)	4 (6.3)	9 (7.2)
Opiate dependence	1 (1.6)	4 (6.3)	5 (4.0)
Sedative abuse	4 (6.5)	3 (4.8)	7 (5.6)
Sedative dependence	1 (1.6)	1 (1.6)	2 (1.6)
Club drug abuse[h]	5 (8.1)	4 (6.3)	9 (7.2)
Club drug dependence	3 (4.8)	6 (9.5)	9 (7.2)
No. of CD symptoms reported during the past 30 d	3.17 (2.37)	2.54 (1.87)	2.86 (2.15)

Abbreviations: CBT, cognitive behavioral therapy; CD, conduct disorder; CDRS-R, Childhood Depression Rating Scale–Revised; CGI-S, Clinical Global Impression Severity.

[a] Values are expressed as mean (SD) unless otherwise indicated.

[b] The range of possible scores is 17 to 113.

[c] The range of possible scores is 30 to 85.

[d] The range of possible scores is 1 to 7.

[e] Calculated using the Composite International Diagnostic Interview–Substance Abuse Module (62 participants for placebo with CBT and 63 for fluoxetine with CBT [125 total]).

[f] The numbers of participants were 61 for placebo with CBT and 63 for fluoxetine with CBT (124 total).

[g] Inhalant dependence, phencyclidine abuse, and dependence are not reported as not endorsed.

[h] Club drugs included (±)-3,4-methylenedioxymethamphetamine (ecstasy or MDMA), γ-hydroxybutyric acid, ketamine, and flunitrazepam (rohypnol).

The groups were similar with regard to the proportion of treatment completers (fluoxetine-CBT group, 82.5% [95% CI, 73.1%-91.9%]; placebo-CBT group, 85.7% [95% CI, 77.1%-94.3%]). Treatment exposure was also similar between groups; the mean proportion of CBT sessions attended in the fluoxetine group was 0.72 (0.31) compared with 0.70 (0.29) in the placebo treatment group (mean difference, 0.01 [95% CI, –0.09 to 0.12]).

POST HOC ANALYSES

The higher-than-expected rate of treatment response and remission in both treatment groups led us to conduct post hoc analyses of the influence of remission on substance use and CD outcomes, regardless of medication group assignment. Because remission (CDRS-R raw score ≤28) trended somewhat higher in the fluoxetine-CBT (69.8% [95% CI, 58.5%-81.1%]) compared with the placebo-CBT (52.4% [95% CI, 40.1%-64.7%]) group (Fisher exact test, $P=.07$), we did not evaluate a main effect of remission on substance use (self-reported and urine screen results) or CD symptoms unless the interaction between medication group and remission status was not statistically significant, which was the case for each outcome measure. Those who experienced remission had a greater proportion of negative weekly urine screen results (5.92 [6.42]) compared with those without remission (3.80 [4.78]; mean difference, 2.13 [95% CI, 0.15-4.11] negative urine screen results) and greater reduction in self-reported days of drug use in the past month (5.77 [1.34]) compared with those without remission, whose substance use did not decrease significantly from baseline severity levels (0.68 [2.05]; mean difference, 5.09 [95% CI, 0.26-9.93] days). The average decrease in self-reported CD symptoms was about 1 symptom in those who experienced remission (1.31 [0.24]) and those who did not (1.04 [0.36]; mean difference, 0.26 [95% CI, –0.58 to 1.11]

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Table 2. Changes in Measures of MDD, SUD, and CD in 126 Patients in the Intent-to-Treat Sample by Treatment Group

Treatment Group	Change (95% CI)[a]				
	Week 0	Week 4	Week 8	Week 12	Week 16
Fluoxetine hydrochloride + CBT					
MDD					
CGI-I responders (score of 1 or 2), %[b]	NA	27.49 (18.51-38.76)	48.03 (37.63-58.60)	69.25 (57.36-79.04)	84.59 (72.83-91.84)
CDRS-R raw score	50.75 (48.04-53.45)	38.14 (35.85-40.42)	29.81 (27.73-31.88)	25.76 (23.78-27.73)	25.99 (23.10-28.88)
CDRS-R *t* score[c]	69.25 (67.53-70.98)	60.40 (58.72-62.09)	53.70 (51.82-55.58)	49.15 (47.00-51.31)	46.75 (43.77-49.74)
SUD					
No. of days substances were used[d]	17.18 (14.73-19.62)	15.66 (13.29-18.04)	14.51 (12.06-16.96)	13.70 (11.15-16.25)	13.24 (9.98-16.51)
CD					
No. of CD symptoms[e]	1.99 (1.58-2.40)	1.38 (1.00-1.76)	1.34 (1.01-1.68)	1.39 (1.03-1.74)	1.02 (0.52-1.52)
Placebo + CBT					
MDD					
CGI-I responders (score of 1 or 2), %[b]	NA	28.04 (18.93-39.40)	43.78 (33.93-54.14)	60.87 (49.55-71.13)	75.66 (62.72-85.17)
CDRS-R raw score	49.44 (46.74-52.14)	38.59 (36.31-40.88)	31.83 (29.76-33.91)	29.15 (27.18-31.12)	30.55 (27.69-33.42)
CDRS-R *t* score[c]	68.57 (66.86-70.29)	60.79 (59.10-62.48)	55.50 (53.62-57.38)	52.71 (50.55-54.86)	52.41 (49.44-55.38)
SUD					
No. of days substances were used[d]	17.10 (14.68-19.52)	13.69 (11.34-16.03)	11.77 (9.34-14.20)	11.35 (8.80-13.89)	12.41 (9.17-15.66)
CD					
No. of CD symptoms[e]	2.38 (1.97-2.80)	1.46 (1.09-1.83)	1.35 (1.02-1.69)	1.40 (1.05-1.76)	0.95 (0.45-1.44)

Abbreviations: CBT, cognitive behavioral therapy; CD, conduct disorder; CDRS-R, Childhood Depression Rating Scale–Revised; CGI-I, Clinical Global Impression Improvement; CI, confidence interval; MDD, major depressive disorder; NA, not available; SUD, substance use disorder.

[a] Change is expressed as percentage responding or as mean scores. Estimates of percentage responding are from a logistic linear model accounting for repeated measures on each subject using a generalized estimating equation approach. Means are used for predicted individual scores that have been adjusted for fixed and random effects derived from the polynomial (linear, quadratic, and cubic) random coefficient model selected for each variable from likelihood-based criteria.

[b] Relative risk (95% CI) at week 16 for fluoxetine responders compared with placebo responders was 1.08 (0.91-1.28).

[c] Treatment group difference in quadratic curves: $F_{3,192} = 2.83$ ($P = .04$); effect size, 0.78.

[d] Treatment group difference in quadratic curves: $F_{3,182} = 1.89$ ($P = .13$); effect size, –0.07.

[e] Treatment group difference in cubic curves: $F_{3,256} = 1.92$ ($P = .13$); effect size, –0.22.

symptoms). The effect size of remission relative to nonremission (after controlling for the treatment group) was 0.49 for a decrease in self-reported days of substance use in the past month and 0.12 for CD symptom reduction.

ADVERSE EVENTS

Rates of adverse events were generally mild and transient, and the difference between the fluoxetine-CBT and placebo-CBT groups, based on the 56-item SEFCA and a subset of SSRI-related adverse events, was not statistically significant. However, these results should be interpreted with caution given that the study was not specifically powered for safety. Also, the SEFCA does not contain items evaluating suicidality, which was assessed by CDRS-R at baseline and monthly thereafter. Adolescents with past, current, or intermittent suicidal ideation (39% at baseline) were not excluded from study participation unless suicidal ideation was severe or they were otherwise considered by the study physician and according to baseline CDRS-R ratings (question 13) to be at high risk for a suicide attempt during the trial. Likelihood-based criteria determined that the longitudinal course for suicidality followed a cubic curve with random subject and linear time effects. Both groups were similar ($F_{3,246}$=1.42; P=.24) with regard to an overall decrease in monthly suicide severity ratings (mean decrease, 0.84 [95% CI, 0.58-1.10]). There were no completed suicides or serious attempts during the trial. However, 5 participants (4 in the fluoxetine-CBT group and 1 in the placebo-CBT group) were evaluated in an emergency department or hospitalized for concerns of worsening suicidality during the study. Suicide severity ratings decreased during the first month of treatment for all 5, with worsening severity emerging during weeks 8 and 12 in all cases. Each of the 5 participants identified a specific psychosocial stressor as the perceived precipitant for worsening suicidality, and none had histories of escalating irritability, agitation/restlessness, anxiety, mania, or reduced need for sleep, based on weekly medication follow-up visits that included assessment of adverse events. Again, results should be interpreted with caution owing to the small sample size and the limitations of our measure of suicide severity in this study.

COMMENT

The combination of fluoxetine and CBT showed superior efficacy to that of placebo and CBT for MDD in adolescents with SUD on the CDRS-R but not according to the CGI-I treatment response (score of 1 or 2). In the context of other studies, the treatment response in the fluoxetine-CBT (76%) and placebo-CBT (67%) treatment groups (based on the more conservative last available assessment estimates) were higher than the treatment response for active fluoxetine (52% and 58%, respectively; also based on CGI-I ratings of 1 or 2) in the 2 previous placebo-controlled trials in depressed adolescents without SUD.[8,11] The effect size based on the CDRS-R score is 0.78, which is higher than the 0.68 effect size reported for fluoxetine

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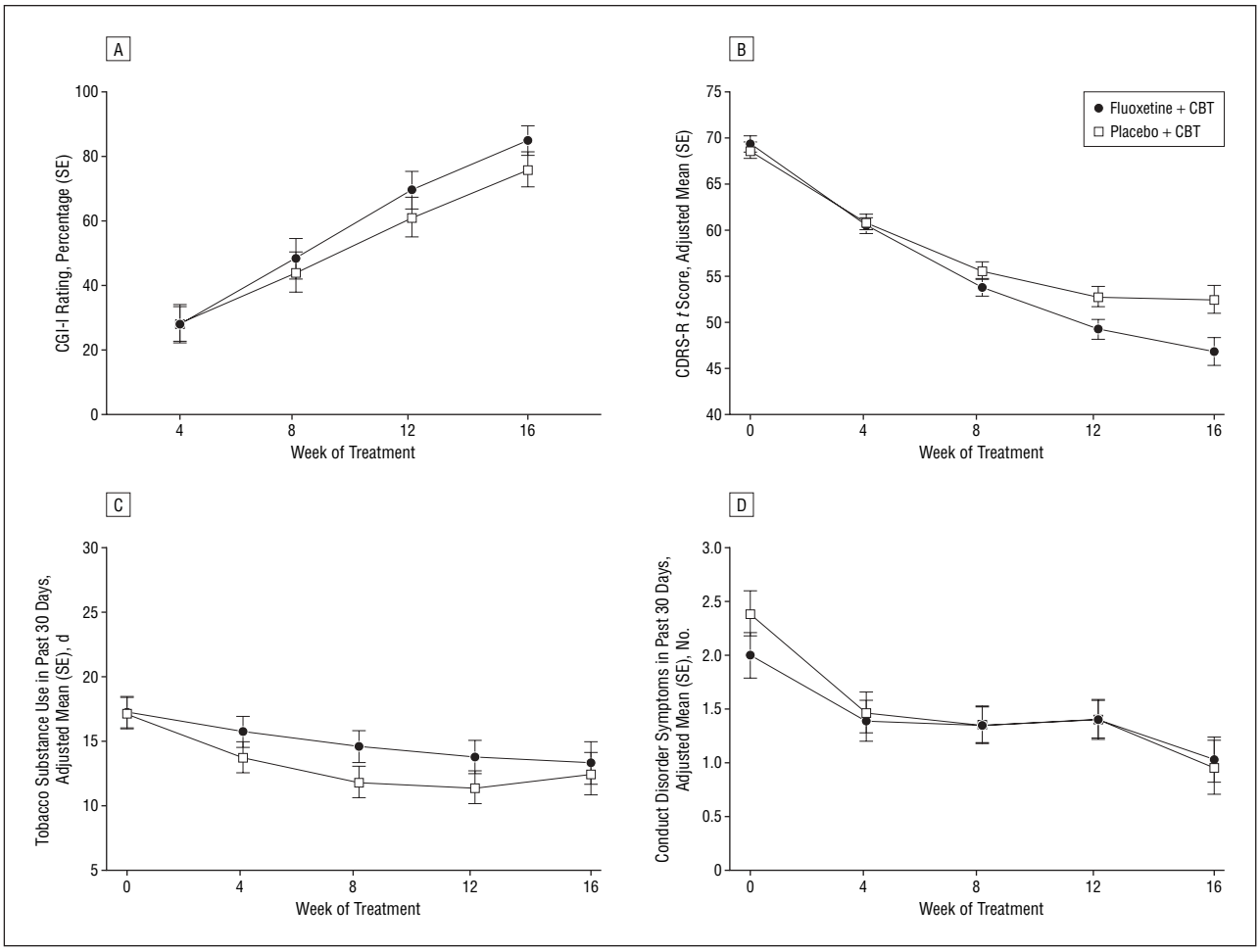

Figure 2. Adjusted change in the depression response indicated by Clinical Global Impression Improvement (CGI-I) rating (A), Childhood Depression Rating Scale–Revised (CDRS-R) *t* scores (B), number of days of nontobacco substance use in the past 30 days (C), and number of conduct disorder symptoms in the past 30 days (D). CBT indicates cognitive behavioral therapy. Estimates of percentages and means have been adjusted for fixed and random effects and are derived from the polynomial (linear, quadratic, and cubic) generalized estimating equation and random coefficient models selected for each variable based on deviance and likelihood-based criteria, respectively.

alone but lower than the 0.98 effect size (also based on the CDRS-R score) in a combined fluoxetine-CBT group (targeting depression) relative to placebo treatment alone in the 12-week multisite Treatment for Adolescents With Depression Study in adolescents without SUD.[9] The longer duration of this trial probably contributed to the higher-than-expected treatment response, especially in the active medication arm. However, the 67% placebo treatment response (most conservative estimate) is as high as or higher than that reported for the active medication arm in the aforementioned studies and more than double the average placebo response rate of 29% based on the same measure and definition of treatment response (CGI-I score of 1 or 2). This suggests that CBT may have contributed to the higher-than-expected depression treatment response and mixed efficacy results.[8,9,31] Because both groups in the present study received CBT, we are unable to evaluate the separate and combined effects of medication and CBT on treatment response. However, results from a meta-analysis[31] of 14 controlled medication trials (mostly of SSRIs) for depression in adults with SUD suggest that this is plausible. Nunes and Levin,[31] the authors of the meta-analysis, concluded that concurrent psychosocial treatment for SUD may have contributed to the higher-than-expected placebo-response rate in some studies (especially those using manual-standardized CBT) by exerting "substantial antidepressant effects, obscuring the effects of medication." The authors note that this could have been owing to a direct antidepressant effect or a more indirect effect on drug use. The former explanation may be more likely than the latter one given the relatively modest overall decline in drug use in this study. However, limitations inherent in our study design and sample size preclude meaningful analysis of the temporal relationships or directionality of the changes in depression and substance use. Larger studies are needed to evaluate these relationships, which are likely to be complex and highly variable across patients and to be affected by the severity, chronicity, and predominant class of substance used, as well as age, comorbidity, and other developmental factors.

LIMITATIONS

Self-reported drug use has been shown to be a reliable measure in adolescents when confidentiality is ensured and when participants know that self-reports will be cor-

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roborated by urine screen results.[22] However, the number of days of use of nontobacco substances in the past 30 days may not have been a sufficiently sensitive measure to capture clinically significant changes in substance use (eg, reduction in the number of times a substance was used per day). Although the lower proportion of substance-free urine screen results in the fluoxetine-CBT compared with the placebo-CBT group was statistically significant, the clinical significance of this finding (if replicated) is not clear until larger studies can address the issue.

Although standard procedures for maintaining the double-blind status were implemented, we did not systematically obtain clinician and participant guesses about which treatment was received, which could have provided useful information about the integrity of the blind. The relatively low prevalence and severity of adverse effects likely helped maintain the study blind. However, the lack of statistically significant differences between groups on adverse effects, including suicidality, should be interpreted with caution because the study was not specifically powered for safety. Overall, the severity of suicidal ideation decreased in both treatment groups, but worsened in 5 participants, 4 of whom were treated with fluoxetine. Thus, the possibility that some adolescents may have had a specific vulnerability to emergent or worsening suicidality while receiving fluoxetine cannot be excluded. It is important to highlight that the small sample sizes and the limitations inherent in our monthly measure of suicidality preclude meaningful analysis of the relationship between fluoxetine and suicidality.

In conclusion, the results of this study indicate that fluoxetine combined with CBT may have similar safety and efficacy for depression in adolescents with active SUD to that reported for depressed adolescents without SUD. However, the treatment was not associated with greater reduction in self-reported substance use and CD symptoms compared with placebo combined with CBT. Our results also indicate that, in the context of CBT (substance treatment), co-occurring depression may improve or remit without antidepressant pharmacotherapy. However, if depression does not appear to be improving early in the course of substance treatment, fluoxetine treatment should be considered, even if adolescents are not yet abstinent, with weekly monitoring of treatment adherence, substance use, adverse effects, and target symptom response.

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Author Contributions: Dr Riggs had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Riggs and Mikulich-Gilbertson. *Acquisition of data:* Riggs, Mikulich-Gilbertson, Davies, Lohman, Klein, and Stover. *Analysis and interpretation of data:* Riggs, Mikulich-Gilbertson, and Stover. *Drafting of the manuscript:* Riggs, Mikulich-Gilbertson, Davies, Klein, and Stover. *Critical revision of the manuscript for important intellectual content:* Riggs, Mikulich-Gilbertson, Davies, and Lohman. *Statistical analysis:* Riggs and Mikulich-Gilbertson. *Obtained funding:* Riggs. *Administrative, technical, and material support:* Riggs, Lohman, Klein, and Stover. *Study supervision:* Riggs, Mikulich-Gilbertson, Davies, and Lohman.
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Announcement

Submissions. The Editors welcome contributions to Picture of the Month. Submissions should describe common problems presenting uncommonly, rather than total zebras. Cases should be of interest to practicing pediatricians, highlighting problems that they are likely to at least occasionally encounter in the office or hospital setting. High-quality clinical images (in either 35-mm slide or electronic format) along with parent or patient permission to use these images must accompany the submission. The entire discussion should comprise no more than 750 words. Articles and photographs accepted for publication will bear the contributor's name. There is no charge for reproduction and printing of color illustrations. For details regarding electronic submission, please see: http://archpedi.ama-assn.org.

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