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Moderators of fluoxetine treatment response for children and adolescents with comorbid depression and substance use disorders

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Abstract

Our recent 8-week, randomized, placebo-controlled trial of fluoxetine in adolescents (ages 12–17 years) with comorbid depression and substance use disorder (SUD) did not detect a significant antidepressant treatment effect. The purpose of this secondary analysis was to explore moderators of the effect of fluoxetine in this sample. Static moderators measured at baseline were depression chronicity and hopelessness severity; time-varying moderators measured at baseline and weekly during the 8-week trial period were alcohol and marijuana use severity. Treatment effects on depression outcomes were examined among moderating subgroups in random effects regression models. Subjects assigned to fluoxetine treatment with chronic depression at baseline ($p = .04$) or no more than moderate alcohol use during the trial ($p = .04$) showed significantly greater decline in depression symptoms in comparison to placebo-assigned subgroups. The current analysis suggests that youth with chronic depression and no more than moderate alcohol consumption are likely to respond better to treatment with fluoxetine compared with placebo than youth with transient depression and heavy alcohol use.

Keywords

Depression; Dysthymia; Mediators; Moderators; Adolescents; Fluoxetine; Substance abuse; Alcohol; Marijuana

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1. Introduction

Adolescent-onset depression is a common and serious psychiatric condition associated with substantive psychosocial dysfunction, including increased risk for suicide attempts and completed suicide (Curry et al., 2006; Fordwood, Asarnow, Huizar, & Reise, 2007; Tuisku et al., 2006). Moreover, an estimated 20%–30% of youths presenting with substance use disorders (SUDs) also have comorbid depression (Chinet et al., 2006; Langenbach et al., 2010; Riggs, Baker, Mikulich, Young, & Crowley, 1995); and 15% of youths from a general population sample with depression are diagnosed with SUD (Keller et al., 1988). Among adolescents with SUD, comorbid depression or other mood disorders represents a significant risk factor for attempted suicide (Kelly, Cornelius, & Clark, 2004). Taken together, it is vital to enhance treatments for youths with comorbid depressive disorders and SUD.

Youths with comorbid depressive disorders and SUD comprise a heterogeneous group; therefore, treatment for both conditions may need to be tailored to the severity and type of co-occurring SUD and depressive disorders. In general, to improve pharmacological effectiveness for a psychiatric disorder, it is important to understand for whom and under what conditions treatment response is optimal. Although a treatment may not appear efficacious in a heterogeneous population, it may prove more effective for specific, clinically meaningful subgroups. One technique applied to address this issue is an analysis of moderating factors within clinical trials. In general, moderators specify for whom or under what conditions a given treatment works (e.g., gender, race, class; Kraemer, Wilson, Fairburn, & Agras, 2002).

Our randomized, placebo-controlled trial (RCT) of fluoxetine in adolescents with comorbid major depressive disorder (MDD) or a depressive disorder and SUD (alcohol or marijuana) found no significant between-group differences in depressive symptoms based on the Children's Depression Rating Scale–Revised (CDRS-R) scores and substance use as measured by positive drug urinalysis (Findling et al., 2009). However, a significant decline in depression symptoms was observed in both treatment arms. This study was terminated at its midpoint based on a priori futility analysis and therefore yielded a relatively small sample size of 34 subjects ($n = 16$, placebo; $n = 18$, fluoxetine). Despite the null findings of this original study, these data provide important clinical information. To avoid future negative investigations with vulnerable populations, investigators have an ethical responsibility to share negative trial findings with the scientific community (American Statistical Association, 1999). Furthermore, what can be learned from a negative trial extends to moderator subgroup analysis of treatment response, which can provide preliminary evidence for the planning of efficacy trials for targeted mental conditions.

Our null finding has been corroborated with other studies in this population. A previous RCT of fluoxetine in adolescents with comorbid MDD and alcohol abuse disorder found no significant between-group differences in depressive symptoms and in the amount of alcohol used (Cornelius et al., 2009). Likewise, another RCT comparing the treatment effects of combined fluoxetine and cognitive–behavioral therapy (CBT) for SUD versus placebo and CBT in adolescents with comorbid MDD, SUD, and lifetime conduct disorder found a significant decrease in depressive symptoms in the first group compared with the second (Riggs et al., 2007), suggesting efficacy of fluoxetine over placebo in this population. Results from these studies add complexity to our understanding of the effectiveness of fluoxetine, which has been shown to consistently have an antidepressant effect in adolescents without SUD (Emslie et al., 1997; Emslie et al., 1998; Emslie et al., 2002). These seemingly contradictory results raise a question: Are there subgroups of adolescents, based on baseline characteristics and experiences during treatment, who are more likely to

benefit from fluoxetine therapy? We chose to answer this question through an analysis of selected static and time-varying moderator variables in our RCT of fluoxetine in youths with MDD or a depressive disorder and SUD (Findling et al., 2009).

For this study, we chose a limited number of moderator variables a priori based on previous reports to minimize statistical testing. First, we chose severity of hopelessness and chronicity of depression as static moderators based on a previous a large-scale study of concomitant fluoxetine and CBT in adolescent depression in which less chronically depressed and less hopeless subjects were more likely to improve from combined therapy than their counterparts (Curry et al., 2006). To determine the criterion for chronic depression, we applied findings from Emslie et al. (1997), who explored the recurrence of MDD among children and adolescents treated for MDD with fluoxetine for up to 8 weeks. They found that 85% of the adolescents recovered from the episode within 12 months, but 39% of this recovered subgroup relapsed during the 12 months, with the majority during the first 6 months. Using these data, we determined that a duration of 9 months would capture participants with recurrent or chronic MDD versus remitting MDD. Second, we chose severity of daily alcohol and marijuana use as potential time-varying moderators of treatment effectiveness for two reasons: There is evidence to suggest a moderating effect of substance use during a trial on depression outcomes (Gual et al., 2003; Kranzler et al., 2006; Nunes & Levin, 2004; Riggs et al., 2007), and the limitation of SUD diagnostic criteria in assessing absolute levels of drinking or drug use (i.e., mild vs. heavy drinking), which can distinguish SUD subtypes not captured by abuse or dependency classification.

2. Materials and methods

2.1. Subjects and study design

As described in our previous report (Findling et al., 2009), this single-site, randomized, placebo-controlled study included male and female outpatients between the ages of 12 and 17 years with either a current MDD or a depressive disorder, comorbid SUD, and a CDRS-R score of 40 or higher. Exclusion criteria included the following: presence of a clinically significant general medical or neurological condition; presence of mental retardation; use of another psychotropic medication either during the study or within 2 weeks of receiving the blinded study medication; history of intolerance, allergy, or nonresponse to fluoxetine; failure of 4 weeks of treatment with a non-tricyclic antidepressant, non-monoamine oxidase inhibitor antidepressant during the current depressive episode; an abnormal screening laboratory; active suicidality; diagnosis of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*-defined Bipolar disorder I or II, psychotic disorder (history), obsessive–compulsive disorder (current), panic disorder (current), bulimia (current), or anorexia (current); females who were pregnant or breastfeeding; females who were sexually active and were not using medically accepted means of contraception; and requirement of pharmacological detoxification.

A total of 34 subjects with a mean ± standard deviation age of 16.46 ± 1.08 years were randomized to 8 weeks of treatment with fluoxetine ($n = 18$) or placebo ($n = 16$). Initially, the planned enrollment sample size was 30 subjects per arm. As described elsewhere (Findling et al., 2009), a single interim analysis was performed after 50% of patients per treatment group had ended study participation. Preserving an overall two-sided Type 1 error rate of .05, Lan–DeMets (Lan & DeMets, 1983) group sequential methods with the most conservative alpha spending function (O'Brien–Fleming) were used to reject the null hypothesis (efficacy boundary, if large treatment differences appear before the end of the study). Using results from the interim analysis, a conditional power (CP) computation for futility was also conducted using guidelines adapted from Lan and Wittes (1988). This interim analysis prespecified that the study would be stopped for futility at $t = 0.5$ if $CP_{D(0.5)}$

is 0.3 or less. Stated another way, the trial would be stopped after half of the subjects had completed the full 8 weeks if the spending function revealed that group differences were large enough at that time to conclude that subjects assigned to fluoxetine had significantly different changes in depression compared with subjects assigned to placebo. Based on the results of this futility analysis, study enrollment was halted. Of the 34 randomized patients, 25 completed the 8 weeks of treatment (12 fluoxetine, 13 placebo). Exploratory analyses of treatment response described here used data from all 34 randomized subjects.

The active intervention (10 mg of fluoxetine for the first 4 weeks of treatment and 10–20 mg of fluoxetine for the latter 4 weeks of treatment per physician discretion) was monitored at each study visit for treatment adherence throughout the trial period. Assessments were performed at baseline and at study Weeks 1, 2, 3, 4, 6, and 8. The primary outcome measure was the CDRS-R (Poznanski, Freeman,&Mokros, 1985), and the secondary outcome measure was the Clinical Global Impressions Scale-Severity (CGI-S; National Institute of Mental Health [NIMH], 1985). All procedures were approved by the University Hospitals Case Medical Center's Institutional Review Board for Human Investigation.

2.2. Measures

Pretreatment screening assessments were completed over two consecutive visits, which were 1 week apart. After receiving blinded study medication at the baseline visit, youths returned for assessments after 4 days and at the end of Weeks 1, 2, 3, 4, 6, and 8. The following measures were collected at baseline only: demographics variables, the Beck Hopelessness Scale (BHS), and the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (KSADS-PL). The CDRS-R, CGI-S, and consumption levels of illicit substances were collected at baseline and at each subsequent study visit.

2.2.1. Demographics—Variables collected included ethnicity, age, gender, diagnosis (current depressive disorder, current comorbid condition, and current SUD), age of onset of SUD, and length of SUD.

2.2.2. Moderator variables

2.2.2.1. Depression chronicity: Depression chronicity at baseline was assessed based on the duration of the most recent episode of MDD or depressive disorder, which was assessed using the KSADS-PL. We used duration of illness (chronicity) as an indicator of depression severity based on prior work highlighting current major depression episode as a key indicator of depression severity (Blom et al., 2007; Kessler et al., 2003). The cut score of 9 months' duration of a depressive episode was chosen based on statistical methods and findings in relevant literature. Following the model suggested byCurry et al. (2006), we chose a 9-month cutoff to define depression chronicity because it allowed for approximately balanced numbers of subjects per subgroup. Depression chronicity was also determined based on the recurrence of major depression episode. Those whose episodes lasted 9 months or longer were classified as having chronic depression, and those whose episodes lasted less than 9 months were classified as having transient depression.

2.2.2.2. Hopelessness: The BHS is a self-rating instrument composed of 20 items, with a score of 20 denoting the highest level of hopelessness (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961). For this analysis, a score of 9 was used as the cutoff to divide subjects into two hopelessness severity groups (case ≥9, noncase <9); this value is based on previous findings with the BHS (Beck, Brown, Berchick, Stewart, & Steer, 1990; Papakostas et al., 2007).

2.2.2.3. Substance use severity: The subjects' alcohol and marijuana use was gathered using a modified version of the calendar-assisted Time Line Follow Back (TLFB; Sobell, Sobell, Klajner, Pavan, & Basian, 1986). The TLFB provides a detailed account of a subject's substance consumption over a designated period. The TLFB has been used extensively with adult and youth populations with SUD (Donohue et al., 2004; Evans, Levin, Brooks, & Garawi, 2007), has demonstrated good psychometric properties with substance-dependent adults and adolescents (Donohue et al., 2004; Sobell & Sobell, 1992), and has shown greater accuracy with youth compared with parental report of alcohol and drug consumption (Fisher et al., 2006). At the baseline visit, subjects reported daily use of illicit substances for the month prior to enrollment; at each follow-up visit, subjects reported use since the last visit. All estimates of substance abuse and drinking were converted to standard drinking units and were then scored on a 4-point Likert scale: *no use* (0), *single use* (1), *moderate use* (2), or *heavy use* (3). We adapted the TLFB procedure for prospective alcohol and marijuana use using the NIMH Life Chart Method (Denicoff et al., 1997) to quantify daily substance use based on self-report. We divided subjects in this study into "moderate or less" (severity score ≤2) and "heavy" (severity score = 3) categories to allow for approximately balanced subgroups, the recommended method for subgroup hypothesis testing.

2.2.3. Outcome variables

2.2.3.1. Depression symptom severity: The CDRS-R is a 17-item scale that assesses the severity and presence of depressive symptoms in children and adolescents. Total scores range from 17 to 113, with a score 40 or higher indicative of clinical depression (Overholser, Brinkman, Lehnert, & Ricciardi, 1995; Poznanski et al., 1985).

2.2.3.2. Psychiatric illness severity: The CGI-S scale assesses severity of overall psychiatric illness throughout the duration of the study; items are rated from normal, not ill (1), to very, severely ill (7). The CGI-S was selected for these analyses because, like the CDRS-R, a pretreatment score is collected, and changes over time can be measured. The CGIS was intended to complement the data obtained by the CDRS-R by providing information about overall illness severity rather than just depressive symptom severity.

2.3. Statistical data analysis

Depending on the type of variables (continuous or discrete), analysis of variance or chi-square analyses were performed to evaluate demographic and clinical differences between subjects. Random effects regression models were constructed to explore subgroups differences in the effectiveness of fluoxetine on outcomes (i.e., CDRS-R, CGI-S); two static and two time-varying subgroups were analyzed separately for each outcome. Depression chronicity and hopelessness severity subgroups were modeled as static covariates (baseline assessment only); substance use severity subgroups were modeled as time-varying covariates using weekly interval ratings during the trial, controlling for baseline levels. Models included a random intercept, a time variable that indexed each study interval, treatment assignment, the subgroup variable, and a Treatment assignment × Subgroup interaction term. Preliminary analyses suggested that a linear model was adequate. To reduce potential collinearity (Aiken & West, 1991), continuous baseline variables were centered by subtracting the sample mean from each score. Analyses assumed a within-subject autocorrelation for scores across time points. Hypothesis testing was limited to eight random effect regression models to reduce potential Type I error. Because of the exploratory nature of this investigation, we report all two-tailed tests with alpha level of $p < .05$. The standardized mean difference (Hedges' g) was used to measure the relative effectiveness of fluoxetine over subgroup conditions for treating pediatric depression with comorbid SUD. Hedges's g has sound statistical properties in samples as small as 20 participants and

includes a correction for slight upward bias in estimated population effect (Hedges, 1994). Exploratory, post hoc analyses used Fisher's exact test to compare groups based on significant moderators at baseline. Fisher's exact test is regarded as the most stringent analytic method for dichotomous data when cell size counts are small. Statistical analyses were conducted with SAS version 8.0 (SAS Institute, Cary, NC).

3. Results

The majority of the sample (85%) was male and White (73%); the mean (standard deviation) age of subjects was 16.46 years (1.08 years). Eight-five percent met current *DSM-IV* criteria for MDD, and 15% met current *DSM-IV* criteria for either dysthymic disorder ($n = 4$) or depression not otherwise specified ($n = 3$). Most of the subjects (30/34 [88.2%]) reported marijuana use (marijuana dependence, 14/34 [41.2%]; marijuana abuse, 16/34 [47%]), whereas fewer (13/34 [38.2%]) had reported alcohol use (alcohol dependence, 3/34 [8.8%]; alcohol abuse, 10/34 [29.4%]); only 1 (2.9%) subject reported polysubstance use.

Moderator subgroups at baseline are presented in Table 1. When current MDD episode length was considered, 15% had chronic MDD, and 9% scored 9 or higher on the BHS, indicating high hopelessness. When recent substance use consumption levels were considered, 82% were heavy marijuana users and 35% were heavy alcohol users. At baseline, there were no significant differences between subjects randomly assigned to fluoxetine versus placebo treatment groups in terms of demographic characteristics, *DSM-IV* diagnoses, age of onset of depressive disorders, and SUD; and treatment groups were also well balanced across moderator subgroups at baseline. Other nonsignificant baseline comparisons between treatment assignment groups are detailed elsewhere (Findling et al., 2009).

Treatment response by moderator subgroups are presented in Table 2 Two significant interactions emerged between treatment assignment and depression chronicity (CGI: $F = 8.10$, $p = .01$; CDRS-R: $F = 3.68$, $p = .04$) and alcohol use severity (CGI: $F = 4.79$, $p = .03$; CDRS-R: $F = 3.88$, $p = .04$); the effect sizes for these interactions were moderate to large. These results indicate that differences in response to fluoxetine versus placebo were significant for subjects with chronic depression at baseline and for subjects with moderate or less alcohol use throughout the trial. Nonsignificant interactions were found between treatment condition and hopelessness severity (CGI: $F = 1.25$, $p = .27$; CDRS-R: $F = 0.11$, $p = .74$) and marijuana use severity (CGI: $F = 2.42$, $p = .10$; CDRS-R: $F = 0.25$, $p = .61$). Across conditions, a greater decline in depression score outcome was observed in subjects with less hopelessness at baseline (BHS scores≥9) compared with those with BHS scores less than 9 (CGI: $F = 6.84$, $p = 0.01$; CDRS-R: $F = 3.03$, $p = .08$).

A post hoc analysis was conducted to explore whether the treatment groups were well balanced by the subgroup combination of significant moderators (i.e., subjects who were chronically depressed and had moderate or less alcohol use in each treatment group). This analysis revealed nearly twice as many chronically depressed, moderate or less alcohol users assigned to fluoxetine versus placebo (11% vs. 6%, respectively; $\chi^2 = 10.88$, $p = .001$).

4. Discussion

Results of this secondary analysis showed that chronicity of depression at baseline and quantity of alcohol consumption over an 8-week period independently corresponded to significant differences in response to fluoxetine compared with placebo. Specifically, subjects with chronic (compared with transient) depression and those with no more than moderate (compared with heavy) alcohol use showed significantly greater response to

fluoxetine than to placebo. Our finding regarding the effect of depression chronicity prerandomization and differential treatment response is consistent with prior research conducted with adults and pediatric populations with depressive disorders. Meta-analyses of RCTs involving depressed adults (Fournier et al., 2010; Kirsch et al., 2008) and children and adolescents (Bridge, Birmaher, Iyengar, Barbe, & Brent, 2009) receiving antidepressants demonstrated that subjects who are more severely depressed at baseline showed greater treatment response to fluoxetine compared with placebo. Previous studies among adults (Papakostas et al., 2007) and adolescents (Curry et al., 2006) have found that lower self-rated levels of hopelessness predict lower depression severity scores after treatment with fluoxetine. Although our study examined the effect of hopelessness on the differential response to fluoxetine compared with placebo (rather than overall treatment response to fluoxetine), it is notable that we failed to find significantly greater treatment response to fluoxetine compared with placebo based on subjects' baseline level of hopelessness. In addition, we failed to find significantly greater treatment response to fluoxetine compared with placebo based on level of marijuana consumption during the trial.

There are several limitations of this study that warrant attention. First, the small sample size resulted in low statistical power to detect small to moderate effect size estimates of a significant interaction between treatment assignment and subgroup on end-point outcomes. However, there was more than 80% power to detect a large effect size estimate for our a priori subgroup hypotheses. Therefore, despite a limited sample size, our results indicate depression chronicity and alcohol use severity as two moderating influences of fluoxetine response. Second, findings from this study may not be generalizable to patients with mild depression or problems with drugs other than marijuana or alcohol. In addition, as with all self-report measures, assessments of substance use consumption in this study were subject to response bias. Although biomarkers of substance use provide objectivity, they do not measure quantity of substance use. Therefore, we used the gold standard nonbiomarker instrument for tracking substance use over time. Lastly, although treatment groups were well balanced across each of four subgroups at baseline, the post hoc analysis revealed that subgroup combinations of depression chronicity and alcohol consumption at baseline by treatment group (i.e., chronic depression/moderate or less alcohol use, chronic depression/heavy alcohol use, transient depression/moderate or less alcohol use, and transient depression/heavy alcohol use) were not. Specifically, there were more chronically depressed subjects who drank no more than moderately that were assigned to fluoxetine versus placebo. It is unlikely that this disparity can account for the differential treatment response on depression outcomes, given the similar proportions of chronically depressed youths with alcohol dependency were assigned to fluoxetine versus placebo. Nonetheless, in our original RCT, we failed to find an overall difference in the primary outcome of depression chronicity between the treatment groups. These results together suggest that moderate or less use of alcohol *during* treatment (not at baseline) differentiates treatment response to fluoxetine compared with placebo.

4.1. Conclusion

This study suggests that among adolescents with comorbid depressive and substance abuse disorders, chronic depression at baseline and no more than moderate alcohol consumption during therapy predicts greater relief from depression with fluoxetine compared with placebo. Given the limitations described above, these results should be interpreted for clinical implications with caution. Nonetheless, these results suggest that clinicians may be able to predict greater fluoxetine treatment response among adolescents with both chronic (vs. transient) depression at baseline and moderate or less (vs. heavy) alcohol consumption during treatment. Future studies including larger numbers of subjects are needed to validate these findings and confirm their clinical implications.

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Table 1

Subgroups at baseline by treatment condition

Subgroup	Categories	Total (*N* = 34, 100%)	Fluoxetine (*n* = 18, 53%)	Placebo (*n* = 16, 47%)	*p* [a]
Depression chronicity	Transient [b]	29 (85)	16 (89)	13 (87)	.65
	Chronic [b]	5 (15)	2 (11)	3 (19)	
Hopelessness severity [c]	Noncase [b]	29 (91)	16 (94)	13 (87)	.59
	Case [b]	3 (9)	1 (6)	2 (13)	
	M (*SD*)	7.0 (1.3)	6.8 (1.3)	7.3 (1.2)	.27
Alcohol consumption	Moderate or less [b]	22 (65)	11 (61)	11 (69)	.73
	Heavy [b]	12 (35)	7 (39)	5 (31)	
Marijuana consumption	Moderate or less [b]	6 (18)	3 (17)	3 (19)	1.0
	Heavy [b]	28 (82)	15 (83)	13 (81)	

[a] Fisher's exact test was used for categorical variables and independent sample *t* test for the continuous variable in comparing fluoxetine and placebo groups.

[b] Number (percentage).

[c] For fluoxetine, *n* = 17; for placebo, *n* = 15.

Table 2

Treatment response among subgroups

Subgroup	Measure	Condition effect [a] (*F*, *p*)	Subgroup effect [b] (*F*, *p*)	Interaction (*F*, *p*, *g*)
Chronic vs. transient depression	CGI-S	2.97, .09 †	0.45, .50	8.10, .01 *, 0.34
	CDRS-R	1.91, .17	0.15, .70	3.68, .04 *, 0.22
Hopelessness case vs. noncase	CGI-S	1.23, .27	6.84, .01 *	1.25, .27, 0.11
	CDRS-R	0.13, .72	3.03, .08 †	0.11, .74, 0.02
Moderate or less vs. heavy alcohol consumption	CGI-S	0.26, .61	0.04, .84	4.79, .03 *, 0.25
	CDRS-R	0.09, .77	0.76, .39	3.88, .04 *, 0.23
Moderate or less vs. heavy marijuana consumption	CGI-S	0.05, .82	1.47, .23	2.42, .10 †, 0.18
	CDRS-R	0.02, .88	0.07, .79	0.25, .61, 0.03

[a] Main effect of treatment condition (fluoxetine vs. placebo).

[b] Main effect of subgroup variable.

* $p < .05$.

† $p < .10$.