Moderators and Mediators of Fluoxetine Treatment for Pediatric Depression and Co-Morbid Substance Use

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ABSTRACT

Objectives: To examine treatment response patterns in adolescents suffering from both a depressive disorder and a co-morbid substance abuse disorder that were administered either fluoxetine or placebo under the auspices of a clinical trial.

Methods: Adolescents aged 12-17 years meeting DSM-IV criteria for a depressive disorder and co-morbid substance abuse disorder received either placebo or fluoxetine as part of an 8-week, double-blind, randomized, controlled study. The primary outcome measure was the Children's Depression Rating Scale-Revised. Moderators considered included depression severity, hopelessness severity, and whether or not the participant had received prior non-pharmacological treatment. Mediators considered included amount of alcohol and the amount of marijuana used per day.

Results: The clinical trial was stopped for futility after 34 youths (16 placebo, 18 fluoxetine) were enrolled and received study medication based on the results of an interim analysis. The subjects' mean age was 16.5 years. The mean baseline CDRS-R was 53.4. Most youths were abusing alcohol (85%) and/or marijuana (56%). The mean baseline CDRS-R was 53.4. Greater depression severity (p= 0.04) and lower alcohol use (p= 0.04) was found to be associated with greater response to fluoxetine.

Conclusion: More severe depression and lower alcohol consumption was associated with greater fluoxetine response.

BACKGROUND AND OBJECTIVE

Depression during adolescence is a common and serious psychiatric condition associated with substantive psychosocial dysfunction and increased risk for suicide attempts and completed suicide (Lewinsohn et al, 1994). Moreover, an estimated 20-30% of youths with substance use disorders (SUD) also suffer from co-morbid depression (Riggs et al, 1997). This combination of depression and substance abuse appears to be a particularly malignant combination which further elevates the risk for future pediatric depression and completed suicide (Lewinsohn et al, 1994). A previous open-label study of pediatric depression and co-morbid SUD found fluoxetine superior to placebo in decreasing depressive symptoms (Cornelius et al., 2001). However, a recent double-blind study of pediatric depression and co-morbid SUD performed at this center did not find fluoxetine superior to placebo in decreasing depression symptoms (Findling et al, under review). The disparity in depression outcome research suggests that the efficacy of pediatric antidepressant pharmacotherapy is altered by moderating and mediating conditions. The goal of this exploratory analysis was to examine potential moderating and mediating effects on depression outcomes.

METHODS

STUDY SUBJECTS

- The study enrolled outpatient youths aged 12-17 with current major depressive disorder or dysthymic disorder according to K-SADS-PL and a CDRS-R total score of greater than or equal to 40. Additionally, youths with current DSM-IV substance-related disorder (primarily alcohol or marijuana) or who met criteria within 4 weeks prior to enrollment.
- Exclusion criteria included clinically significant medical or neurological conditions, mental retardation, pervasive developmental disorders, a diagnosis of any of the following DSM-IV defined disorders: bipolar I or II disorder, psychotic disorder (history), obsessive-compulsive disorder (current), panic disorder (current), and eating disorder (current). Additionally, subjects with a history of non-response or intolerance to fluoxetine or failed 4-weeks of treatment with a non-TCA, non MAOI antidepressant during the current depressive episode. Furthermore, youths who were actively suicidal or required pharmacological detoxification were excluded from participation.

STUDY INTERVENTION

- Subjects were randomly assigned to fluoxetine versus matching placebo for 8 weeks of treatment. The active intervention (10 mg of fluoxetine for the first 4 weeks of treatment, 10-20 mg of fluoxetine for the latter 4 weeks of treatment per physician discretion) was carefully monitored 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 Children's Depression Rating Scale-Revised (CDRS-R), and the secondary outcome measure was the Clinical Global Impressions Scale-Severity (CGI-S). Outcome scores compared between treatment groups across time using a random effects mixed model for repeated measurements.
- Initially, a planned sample size of 30 subjects per arm was to be enrolled into this trial. A single interim analysis was performed after 50% of patients per treatment group had ended study participation. This interim analysis pre-specified that the study would be stopped for futility at t=0.5 if $CP_{t(0.5)} <= 0.3$. Based on the results of this futility analysis, study enrollment was halted.
- Study moderators were assessed pre-randomization. The following moderators were assessed: receipt of adjunct therapy; above threshold on the Beck Hopelessness Scale (BHS +/9); and depression severity based upon type and length of depressive episode
- Study mediators included alcohol and marijuana consumption levels during the trial period. Substance use levels were charted retrospectively at baseline (prior 30 days), and assessed prospectively at study weeks 1, 2, 3, 4, 6, and 8. Daily alcohol and substance use was quantified using a combination of the Time Line Follow-Back (TLFB) measure and NIMH Daily Life Charting Method. Consumption was quantified and then converted to an average severity score based on a scale of 0 (no use) to 3 (heavy, 8-12 beers/3+ joint/day).

DATA ANALYSIS

- Random effect regression models were conducted to evaluate the superiority of fluoxetine versus placebo in greater decline of depressive symptoms among 4 subgroups of youth: severe versus moderate depression; high versus low anxiety; prior adjunct therapy versus none; mild versus moderate/heavy substance use.
- Average weekly consumption of alcohol and marijuana was modeled as a binary time-varying covariate, controlling for pre-randomization consumption levels. Prior work indicated that a linear model was adequate.
- Due to the complexity of the model, subgroup covariates (main effect, subgroup X treatment interaction effect) were examined in 4 separate models for each depression outcome.
- The analysis assumed a within-subject autocorrelation for outcome scores across time, the most restrictive assumption possible. Due to the exploratory nature of this secondary analysis, two-tailed tests with alpha level of p<.05 were considered significant. Analyses were performed using SAS version 8.2.

RESULTS

Patient Disposition

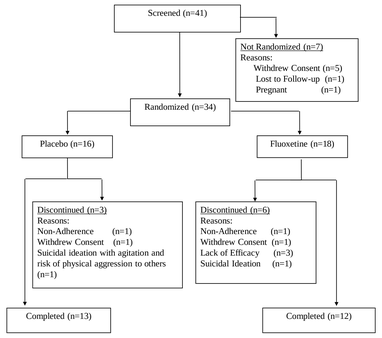


Table 1 Baseline Demographic Characteristics of Sample

Patient Characteristic	
Fluoxetine	18 (53%)
Placebo	16 (47%)
Ethnicity, n (%)	
White	25 (74%)
African American	6 (18%)
Other	3 (9%)
Age (years), mean ± SD	16.46 ± 1.08
Gender, n (%)	
Female	5 (15%)
Male	29 (85%)
Current Depressive Disorder	
Recurrent MDD[a]	11 (32%)
Other MDD[b]	23 (68%)
Age at onset of depression, mean ± SD	12.28 (3.23)
Duration of current episode (months)	42.84 (38.46)
Baseline CDRS-R Score, mean ± SD	53.44 (9.69)
Baseline CGI-S Score, mean ± SD	4.32 (0.63)
Current SUD[c,d]	
Alcohol	13 (38.2%)
Alcohol Abuse	10 (29.4%)
Alcohol Dependence	3 (2.9%)
Cannabis	30 (88.2%)
Cannabis Abuse	16 (47.1%)
Cannabis Dependence	14 (41.2%)
Polysubstance	1 (2.4%)
Age at onset of SUD[c], mean ± SD	13.7 (1.2)

[a]Major Depressive Disorder
[b]Specific numbers for all MDD types: 3 Dysthymic Disorder, 3 patients had Depression Not Otherwise Specified, 11 MDD Recurrent, 17 MDD
[c]Substance Use Disorder
[d]4 patients had multiple substance use disorders: cannabis, alcohol (N=3), cannabis, polysubstance use (N=1)

Table 2. Baseline Moderators/Mediators by Treatment Group

Moderator		Total 34 (100%)	Fluoxetine[a] 18 (53%)	Placebo[b] 16 (47%)	p*
Prior Non-pharmaceutical Treatment	No	29 (85%)	14 (78%)	15 (94%)	.34
	Yes	5(15%)	4 (22%)	1 (16%)	
Beck Hopelessness Scale	Non-Case (<9)	29 (91%)	16 (94%)	13 (87%	.59
	Case (9+)	3 (9%)	1 (6%)	2 (13%)	
	M (SD)	7.01 (1.26)	6.78 (1.27)	7.28 (1.23)	.27
Depressive Disorder Severity	Moderate	29 (85%)	16 (89%)	13 (87%)	.65
	Severe	5 (15%)	2 (11%)	3 (19%)	
Mediator					
Drinks/per Drinking Day	Not Heavy	22 (65%)	11 (61%)	11 (69%)	.73
	Heavy	12 (35%)	7 (39%)	5 (31%)	
Marijuana/per Using Day	Not Heavy	6 (18%)	3 (17%)	3 (19%)	1.0
	Heavy	28 (82%)	15 (83%)	13 (81%)	

*Fisher's Exact Test
[a]Fluoxetine: for Beck Hopelessness Scale, n =17.
[b]Placebo: for Beck Hopelessness Scale, n =15.

Table 3. Treatment by mediator and moderator conditions on depression outcome

Independent Variable	Measure	Subgroup (pos vs. neg state of moderator)	Treatment Main Effect (F,P)	Condition Effect (F,P)	Interaction (F,P)
Prior Non-pharmaceutical Treatment	CGI	Yes vs. No	1.23, 0.27	2.44, 0.12	1.99, 0.16
	CDRS-R	Yes vs. No	1.4, 0.24	0.60, 0.44	2.07, 0.15
Hopelessness	CGI	Case vs. NonCase	1.23, 0.27	6.84, 0.01*	1.25, 0.27
	CDRS-R	Case vs. NonCase	0.13, 0.72	3.03, 0.08	0.11, 0.74
Depression Severity	CGI	Transient vs. Chronic	2.97, 0.09	0.45, 0.50	8.10, 0.01
	CDRS-R	Transient vs. Chronic	1.91, 0.17	0.15, 0.70	3.68, 0.04
Alcohol Use Severity	CGI	Mild vs. Heavy Use	0.26, 0.61	0.04, 0.84	4.79, 0.03
	CDRS-R	Mild vs. Heavy Use	0.09, 0.77	0.76, 0.39	3.88, 0.04
Marijuana Use Severity	CGI	Mild vs. Heavy Use	0.05, 0.82	1.47, 0.23	2.42, 0.10
	CDRS-R	Mild vs. Heavy Use	0.02, 0.88	0.07, 0.79	0.25, 0.61

*p<0.05 'p<0.10

Figure 1: Treatment by depression severity interaction for depression outcome measures

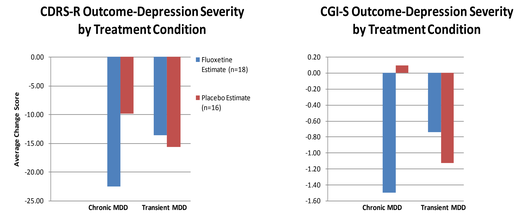
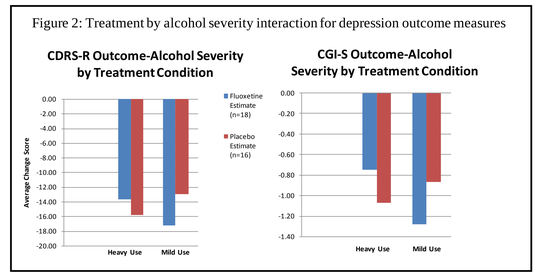


Figure 2: Treatment by alcohol severity interaction for depression outcome measures



- For both outcome measures, a greater decline in depressive symptoms was observed among more depressed youth treated with fluoxetine (CGI, p=0.01; CDRS-R, p=0.04). Less alcohol (0-1 drinks per drinking day) was also associated with greater fluoxetine response (CGI, p=.03; CDRS-R, p=.04).
- Post hoc analyses of the overlap between significant subgroup conditions at baseline found twice as many severely depressed youth with low alcohol use assigned to fluoxetine versus placebo treatment (X2=10.88, p=.001).

CONCLUSION

More severe depression and lower alcohol consumption was associated with greater fluoxetine response.

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DISCLOSURE

Dr. Findling receives or has received research support, acted as a consultant and/or served on a speaker's bureau for Abbott, Addrenex, AstraZeneca, Bristol-Myers Squibb, Forest, GlaxoSmithKline, Johnson & Johnson, Lilly, Neuropharm, Novartis, Organon, Otsuka, Pfizer, Sanofi-Aventis, Sepracore, Shire, Solvay, Supernus Pharmaceuticals, and Wyeth.

ACKNOWLEDGEMENTS

This study was primarily supported by the American Foundation for Suicide Prevention and the St. Luke's Foundation of Cleveland, OH; Study medications were provided, in part, by Lilly.