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Double-Blind Placebo-Controlled Trial of Fluoxetine in Adolescents with Comorbid Major Depression and an Alcohol Use Disorder

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Abstract

Objective—This study compared the acute phase (12-week) efficacy of fluoxetine versus placebo for the treatment of the depressive symptoms and the drinking of adolescents with comorbid major depression (MDD) and an alcohol use disorder (AUD). We hypothesized that fluoxetine would demonstrate efficacy versus placebo for the treatment of both the depressive symptoms and the drinking of comorbid MDD/AUD adolescents.

Methods—We conducted the first double-blind placebo-controlled study of fluoxetine in adolescents with comorbid MDD/AUD. All participants in both treatment groups also received intensive manual-based cognitive behavioral therapy (CBT) and motivation enhancement therapy (MET).

Results—Fluoxetine was well tolerated in this treatment population. No significant group-by-time interactions were noted for any depression-related or drinking-related outcome variable. Subjects in both the fluoxetine group and the placebo group showed significant within-group improvement in both depressive symptoms and level of alcohol consumption. End-of-study levels of depression and drinking were low in both treatment groups.

Conclusions—The lack of a significant between-group difference in depressive symptoms and in drinking may reflect limited medication efficacy, or may result from limited sample size or from efficacy of the CBT/MET psychotherapy. Large multi-site studies are warranted to further clarify the efficacy of SSRI medications in this adolescent MDD/AUD population.

Keywords

Comorbid; Major depression; Alcohol use disorder; Antidepressants; Adolescents

1. Introduction

Adolescent-onset depression is associated with a higher level of comorbid alcohol and other substance use disorders than adult-onset depression (Bukstein, Glancy & Kaminer., 1992;

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Kessler & Walters, 1998; Blazer, Kessler, McGonagle & Swartz, 1994; Rohde, Lewinsohn & Seeley, 1991). Alcohol use disorders (AUD) are the most common group of substance use disorders (SUD) among adolescents (Young, Corley, Stallings, Rhee, Crowley & Hewitt, 2002). Most AUD start in adolescence, with prevalence of alcohol dependence peaking between the ages of 18 and 20 (Grant, Dawson, Stinson, Chou, Dufour & Pickering, 2004; Willenbring, 2006). Despite the widespread prevalence of this comorbid condition among adolescents, no previous double-blind, placebo-controlled studies have been conducted involving adolescents with comorbid major depressive disorder and an alcohol use disorder (Cornelius et al., 2001; Willenbring, 2006). However, multiple controlled trials have demonstrated the efficacy of fluoxetine for treating major depressive disorder in adolescents without an AUD or SUD (Emslie, et al., 1997; Emslie et al., 2002; March, et al., 2004; Treatment for Adolescents with Depression Study (TADS) Team, 2004; Treatment for Adolescents with Depression Study (TADS), 2007; Emslie et al., 2008). Also, a recent double-blind placebo-controlled study evaluated the efficacy of fluoxetine versus placebo for treating adolescents with major depression, conduct disorder, and at least one non-tobacco substance use disorder (not necessarily an alcohol use disorder). That study demonstrated efficacy for fluoxetine for treating one of two depressive measures among their adolescent participants, but demonstrated no efficacy for treating the substance use or conduct disorder symptoms of that population (Riggs, Mikulich-Gilbertson, Davies, Lohman, Klein, & Stover, 2007).

Our own research group completed the first double-blind, placebo-controlled study of fluoxetine in adults with comorbid major depressive disorder and alcohol dependence (Cornelius, Salloum, Ehler, Jarrett, Cornelius, Perel, Thase & Black, 1997). That study demonstrated efficacy for fluoxetine in decreasing both the depressive symptoms and the alcohol use of adult depressed alcoholics. A meta-analysis by Nunes & Levin (2004) found a pooled effect size of 0.38 in favor of antidepressant treatment for comorbid MDD/AUD-SUD. That same meta-analysis also demonstrated that the placebo response rate accounted for more than 70% of the variation in effect sizes on depression outcome across studies.

Our own research group also recently completed a pilot study involving open label fluoxetine in adolescents with comorbid AUD and MDD. That pilot study demonstrated within-group efficacy for fluoxetine for decreasing both the drinking and the depressive symptoms of that population, and suggested that fluoxetine is a safe medication in that population (Cornelius, Bukstein, Birmaher, Salloum, Lynch, Pollock, Gershon & Clark, 2001; Cornelius, Bukstein, Salloum, Kelly, Wood & Clark, 2004; Cornelius, Clark, Bukstein, Birmaher, Salloum & Brown, 2007). However, since no placebo group was involved in that pilot study, we cannot rule out the possibility that part or all of the therapeutic effect observed with fluoxetine was a placebo response. To date, no double-blind study of any SSRI medication has been conducted in adolescents with comorbid alcohol use disorder (AUD) and major depressive disorder (MDD). Because of the lack of studies involving adolescents with major depression in combination with an AUD, clinicians may be reluctant to prescribe antidepressant medication for that large youthful comorbid population.

In the current report, the first prospective double-blind, placebo-controlled study is described involving an SSRI medication (fluoxetine) versus placebo in the treatment of adolescents with comorbid major depressive disorder and an alcohol use disorder (AUD/MDD). All subjects in both treatment groups also received 9 sessions of manual-based intensive therapy, which consisted of Cognitive Behavioral Therapy (CBT) and Motivation Enhancement Therapy (MET). The primary goal of this study was to compare the acute phase (12 week) efficacy of the SSRI medication fluoxetine plus CBT and MET versus placebo plus CBT and MET therapy for the treatment of the depressive symptoms and the alcohol consumption of an adolescent sample with comorbid diagnoses of an alcohol use disorder (AUD) (alcohol dependence or alcohol abuse) plus major depressive disorder (MDD). We hypothesized that fluoxetine plus

CBT/MET therapy would demonstrate efficacy versus placebo plus CBT/MET therapy for the treatment of both the depressive symptoms and the alcohol consumption of comorbid MDD/AUD adolescents.

2. Method

2.1. Subjects

Before entry into this treatment protocol, the study was explained, and written informed consent was obtained from all subjects (as well as from a parent or guardian if the participant was a minor) after all procedures had been fully explained. The study was approved by the University of Pittsburgh Institutional Review Board, and was entered into the Clinical Trials Register (registration number NCT00027378). This study was conducted at the Western Psychiatric Institute and Clinic (WPIC) of the University of Pittsburgh Medical Center (UPMC). Subjects were recruited for participation in the treatment study through referrals from any of the WPIC treatment programs and by responding to newspaper, radio, and bus advertisements.

Study participants were required to be between 15 and 20 years of age at baseline to be included in the study. At the baseline assessment, participants were evaluated for the DSM-IV diagnoses of an alcohol use disorder (AUD) (alcohol abuse or alcohol dependence) and for major depressive disorder (MDD). The comorbid presence of both a current AUD and a current MDD was required for inclusion in the treatment study. Standardized diagnostic instruments were used to assess for current diagnoses of major depressive disorder and for alcohol abuse or dependence. The DSM-IV diagnosis of MDD was confirmed using the Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version (K-SADS-PL) (Kaufman, Birmaher, Brent, Rao, Flynn, Moreci, Williamson & Ryan, 1997; Puig-Antich, 1986). The DSM-IV diagnosis of an alcohol use disorder (alcohol abuse or dependence) was confirmed using the Substance Use Disorders Section of the Structured Clinical Interview for the DSM (SCID) (Spitzer, Williams & Gibbon, DSM-III; Martin, Pollock, Bukstein & Lynch, 2000). Faculty members from our alcohol research center have validated the SCID with adolescent substance abuse populations (Martin et al., 2000). In addition, minimum current levels of drinking and of depressive symptoms were also required for study inclusion, as noted on the Timeline Follow-back scale and the HAM-D-27, respectively. Minimum levels of drinking for study inclusion were defined as drinking at least 10 drinks over the month prior to baseline assessment, as demonstrated on the Timeline Follow-back scale. Minimum levels of depressive symptoms for study inclusion were defined as a HAM-D-27 score of greater than or equal to 15 at the baseline assessment.

Exclusion criteria included a DSM-IV diagnosis of bipolar disorder, schizoaffective disorder, or schizophrenia. Patients with hyper- or hypothyroidism, significant cardiac, neurological, or renal impairment, and those with significant liver disease (SGOT, SGPT, or gamma-GTP greater than 3 times normal levels) were also excluded from the study. Patients who had received antipsychotic or antidepressant medication in the month prior to baseline assessment were excluded. Persons with any substance abuse or dependence other than nicotine dependence or cannabis abuse or dependence were excluded from the study. Patients with any history of intravenous drug use were excluded from the study. Patients were recruited into the study regardless of race, ethnicity, or gender. Other exclusion criteria were pregnancy, inability or unwillingness to use contraceptive methods, and an inability to read or understand study forms.

All patients completed a comprehensive medical examination prior to entering the pharmacotherapy study. In addition, the medical health of all participants was assessed with standard laboratory tests, including CBC, differential blood count, electrolytes, SGOT, SGPT, gamma-GTP, TSH and an EKG. All female patients completed a urine pregnancy test prior to

participation in the pharmacotherapy study. All participants completed a urine drug screen and a breathalyzer prior to participation in the pharmacotherapy study.

2.2 Treatment and assessment

Following completion of the baseline assessment, participants were randomly assigned to receive fluoxetine or placebo administered in identical-looking opaque capsules. Active medication and matching placebo were prepared by the research pharmacy at the Western Psychiatric Institute and Clinic of the University of Pittsburgh Medical Center. Patient randomization was conducted by urn randomization, stratified by gender. All subjects were initially given 1 capsule (10 mg fluoxetine or placebo), which was increased after 2 weeks to 2 capsules (20 mg fluoxetine or placebo), which was the target dose of the study. The low dose of 10 mg as a starting dose was used in this study in order to maximize subject safety and to minimize the risk of medication side effects. Our dosage range was based on the findings of Riddle et al. (Riddle, King, Hardin, Scahill, Ort, Chappell, Rasmussen & Lechman, 1991) and Jain et al. (Jain, Birmaher, Garcia, Al-Shabbout & Ryan, 1992), as well as with our own experience in our open label pilot study with comorbid adolescents (Cornelius et al., 2001). Drs. Cornelius, Bukstein, and Clark prescribed all protocol medications for patients participating in this study. The study was conducted in a double-blind fashion, though one study physician remained non-blinded in order to handle any problems which may have arisen. Ratings of alcohol use and symptom severity were conducted weekly for the first month, and biweekly for the second and third month.

Intensive manual-based therapy was provided to all subjects in both treatment groups in this study. Therapy consisted of Cognitive Behavior Therapy (CBT) for treatment of major depressive disorder and for treatment of the alcohol use disorder, and Motivation Enhancement Therapy (MET) for treatment of the alcohol use disorder. The therapy was provided during each protocol visit during the treatment trial, so participants received psychotherapy on nine occasions: baseline, week 1, week 2, week 3, week 4, week 6, week 8, week 10, and week 12. The Cognitive Behavior Therapy for depression used in this study utilized the widely used techniques of cognitive therapy that have been adapted for treatment of adolescent depression, as described by Brent et al. (Brent, Holder, Kolko, Birmaher, Baugher, Roth, Iyengar & Johnson, 1997). This therapy was chosen because cognitive behavioral therapy has been reported to be more efficacious than alternative psychosocial interventions for the acute treatment of adolescents with major depressive disorder (Birmaher, Brent, Kolko, Baugher, Bridge, Holder, Iyengar & Ulloa, 2000). The cognitive behavior therapy for treatment of alcohol use disorder used in this study utilized the widely used techniques described in the CBT manual utilized in Project MATCH (Kadden, Carroll, Donovan, Cooney, Monti, Abrams, Litt & Hester, 1994). The Motivation Enhancement Therapy used in this proposed study was adapted after the Motivation Enhancement Therapy used in Project MATCH (Miller, Zweben, DiClemente & Rychtarik, 1992).

Assessments for this study were completed by a Master's level staff member with several years of experience conducting assessments with comorbid adolescents. All assessors also completed a comprehensive clinical assessors training program, lasting between 2 and 3 months. All raters participating in the proposed treatment study must have demonstrated adequate levels of inter-rater reliability prior to administering ratings. Experiential training included observation of experienced assessors with independent coding of instruments (at least 5 sessions). Agreement with the interviewing clinician must have exceeded 90% for advancement to administering assessments with an assisting supervisor present. Prior to performing solo interviews, the assessor must have completed a minimum of two assessments with a supervisor present but not assisting, and coding must have achieved 90% agreement with the observing supervisor. After the completion of formal training, monitoring continues through periodic joint interview

reliability evaluations with pairs of interviewers. Pill counts were used to ensure compliance with protocol medication. The validity of participant's self-reported drinking was assessed with breath alcohol levels. To ensure a high level of participation for these evaluations, a \$20.00 payment was made to patients completing each assessment (Festinger, Marlowe, Dugosh, Croft & Arabia, 2008).

Subjects' diagnoses were finalized after case presentations at diagnostic conferences, attended by two study faculty members and the assessors. This "best estimate" diagnostic procedure (which is utilized for the SCID and SCID II as well as for the K-SADS) is in accordance with the method described by Leckman et al. (Leckman, Sholomskas, Thompson, Belanger & Weissman, 1982), and was validated by Kosten & Rounsaville (Kosten & Rounsaville, 1992). Observer-rated depressive symptoms were assessed with the Hamilton Rating Scale for Depression (HAM-D-27) (Hamilton, 1960). Participant-rated depressive symptoms were assessed with the Beck Depression Inventory (BDI) (Beck, Ward, Mendelson, Mock & Erbaugh, 1961). Drinking behavior was evaluated using the timeline follow-back method (TLFB) (Sobell LC, Sobell MB, Leo, & Cancilla, 1988). This instrument provided a daily tabulation of drinking behavior, thus providing detailed information on the quantity and frequency of this behavior. The primary alcohol use outcome variables included number of drinks per drinking day, the number of drinking days, and the number of heavy drinking days (defined as greater than or equal to 4 drinks per day for women and 5 for men).

2.3 Statistical Analysis

Descriptive statistics were calculated for all variables. Continuous baseline measures were compared by independent, 2-tailed *t* tests for continuous variables. Categorical baseline measures were compared by chi-square analysis, corrected for continuity. Statistical analyses were completed on an intent-to-treat study group. Outcome measures for depression and for drinking across treatment groups were compared by repeated measures analysis of variance. Survival analysis was used to test time to remission of depressive symptoms by means of the Cox procedure. All tests of significance were 2-tailed. An alpha level of less than or equal to 0.05 was used in the study. All analyses were conducted using the Statistical Package for the Social Sciences, version 15.0 (Norusis, 1992).

3. Results

A total of 118 persons signed informed consent to participate in the acute phase study and completed the baseline assessment. Of those persons, 50 met all the inclusion criteria to participate in the Acute Phase Treatment Study, including 22 males and 28 females. These participants included 43 Caucasians, 4 African-Americans, and 3 with mixed race. The 68 persons who were excluded were typically excluded because of lack of current Major Depressive Disorder, though a milder depressive disorder was typically present.

All 50 of the persons who had signed consent for inclusion in the study completed the entire baseline assessment and were randomized to study medications, and all 50 were included in outcome analyses. There were no significant differences between treatment groups on demographic variables, though the fluoxetine group was somewhat less severely depressed at baseline (Table 1). None of the subjects discontinued participation in the study because of medication side effects. No serious adverse events occurred during the course of the study. Subjects in the study tolerated the study medication (fluoxetine) very well. Side effects were rare and mild. No subject in either treatment group exhibited suicide plan or intent at any time during the course of the treatment trial. No subjects in the study exhibited an increased level of suicidal ideations while receiving fluoxetine. No subject in the study made a suicide attempt.

All but three of the subjects completed the entire 12-week treatment trial. All 50 subjects completed the treatment trial through at least the midpoint of the treatment trial (week 6). The three subjects who discontinued participation in the treatment study during the second half of the treatment trial did so at the suggestion of the treatment team because of persistent severe depressive symptoms. All three of those persons who discontinued participation in the medication trial were in the placebo group. All three of those persons were immediately treated with open label fluoxetine outside the study protocol, and all three demonstrated decreases in their depressive and alcohol use symptoms during the next six weeks.

In repeated measure analysis of variance, no time by treatment group interactions were significant for any depressive outcome variables or on any drinking-related variables (Table 2). Males drank more drinks per day and more drinks per occasion than females throughout the course of the study, as shown by a gender main effect on repeated measures analysis of variance, though gender did not significantly interact with other variables. Within-group BDI depressive symptoms and HAM-D-27 depressive symptoms both decreased at a $p < 0.001$ significance level in both the fluoxetine group and the placebo group during the 12-week course of the acute phase study, as shown on paired t-tests. The number of DSM-IV alcohol use disorder symptoms also decreased at a $p < 0.001$ significance level in both treatment groups during the study, as shown on paired t-tests. It was also noted that the number of days of heavy alcohol use was significantly associated with lack of remission of BDI depression scores both at the midpoint of the study (week 6; $F = 6.8$, $df = 1$, $p = 0.013$) and at the end of the study (week 12; $F = 9.1$, $df = 1$, $p = 0.004$), where remission of BDI depression was defined as a score of less than 8 on the BDI.

4. Discussion

Fluoxetine was well tolerated in this study population. However, fluoxetine did not demonstrate efficacy for treating either the depressive symptoms or the alcohol-related symptoms of our study sample of comorbid adolescents. Specifically, no significant group-by-time interactions were noted for any depression-related or drinking-related outcome variable. However, in both treatment groups, significant within-group improvement was noted for both depressive symptoms and for level of drinking. End-of-study levels of depression and drinking were low in both treatment groups. The clinical improvement that was noted in both treatment groups may have resulted either from the CBT and MET therapy that the subjects received or may have reflected the natural course of their disorders. These findings are consistent with previous reports of a prominent “placebo” effect among adolescents (Klein, Mannuzza, Koplewicz, Tancer, Shah, Liang & Davies, 1998). The lack of a significant between-group difference in depressive symptoms and in drinking may reflect limited medication efficacy, or may result from limited sample size or from efficacy of the CBT/MET psychotherapy. It is possible that a significant advantage to fluoxetine may have been detected with a larger sample size. The published literature mainly consists of under-powered studies in this field. Large multi-site studies are warranted to further clarify the efficacy of SSRI medications in this adolescent MDD/AUD population. Until the time when more definitive studies can be performed, the results of the current study suggest that psychological intervention should be considered first-line treatment for this population, with pharmacotherapy offered to those who do not respond to this intervention alone.

The number of days of heavy alcohol use was significantly associated with lack of remission of BDI depression scores ($BDI < 8$) both at the midpoint of the study and at the end of the study. Those findings suggest a link between the depressive symptoms and the level of alcohol consumption of comorbid MDD/AUD adolescents. If depressive symptoms were to some extent substance-induced, this may partially account for the apparent lack of efficacy for

fluoxetine observed in the study. Further work is warranted to clarify the nature of the link between depressive symptoms and alcohol consumption among comorbid adolescents.

The results of this study should be interpreted in light of some limitations. First, the sample in this study was limited to outpatient comorbid MDD/AUD adolescents. Consequently, it is unclear to what extent the results of this study generalize to the treatment of comorbid MDD/AUD adults or to comorbid adolescents in more intensive treatment settings, such as inpatient settings or partial hospital settings. Second, the period of observation in our trial was short in terms of the natural history of major depression and of alcohol use disorders. Continuation studies and long-term follow-up studies would be necessary to determine the long-term results of the treatments. Third, the sample size in the present study was limited. Large multi-site trials of selective serotonergic medications would be needed to more definitively evaluate the clinical utility of SSRI medications in comorbid MDD/AUD adolescents.

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Table 1
Demographic Characteristics and Clinical Characteristics of Randomized Subjects

	Placebo (n=26)		Fluoxetine (n=24)		Total (n=50)		Ø	Sig
	%		%		%			
Sex (% female)	61.5%		50.0%		56.0%		0.674	0.412
Ethnic (% white)	88.5%		83.3%		86.0%		0.273	0.602
Baseline	Placebo (n=26)		Fluoxetine (n=24)		Total (n=50)		t	Sig
BDI Total	Mean	s.d.	Mean	s.d.	Mean	s.d.	2.10	0.041
HAM-D 27	22.12	7.50	17.25	8.87	19.78	8.47	2.65	0.011
Alcohol Count (DSM)	22.88	8.79	16.88	7.09	20.00	8.50	0.46	0.650
Alcohol Count (DSM)	5.38	2.32	5.08	2.34	5.24	2.31		
Current Major Depression								
Symptom Count (DSM)	7.38	1.24	7.08	1.32	7.24	1.27	0.84	0.408
Drinks per day	3.06	1.49	2.32	1.41	2.70	1.49	1.80	0.078
Drinks per occasion	6.91	2.49	5.58	2.84	6.27	2.72	1.77	0.084
Days of Alcohol Use per Week	3.19	1.35	3.01	1.75	3.10	1.54	0.41	0.686
Heavy Drinking Days per Week	2.28	1.01	1.70	1.07	2.00	1.07	1.99	0.053
12 Weeks (end of study)								
BDI Total	10.46	10.80	6.79	7.49	8.70	9.45	1.38	0.173
HAM-D 27	8.31	8.97	4.54	7.06	6.50	8.25	1.64	0.107
Alcohol Count	2.85	2.96	2.42	2.04	2.64	2.55	0.59	0.557
Current Major Depression								
Symptom Count	5.27	2.54	4.83	2.12	5.06	2.33	0.66	0.515
Drinks per day	1.73	1.61	1.56	1.44	1.65	1.52	0.39	0.702
Drinks per occasion	4.90	3.36	5.12	3.54	5.01	3.41	-0.22	0.824
Days of alcohol use per week	1.87	1.43	1.88	1.52	1.87	1.46	-0.02	0.982
Heavy Drinking Days per Week	1.35	1.21	1.04	1.15	1.20	1.18	0.91	0.367

Table 2

Between – Group Comparisons of Treatment Outcome

	time			time × sex			time × treatment		
	F	sig.		F	sig.		F	sig.	
BDI Total	4.322	0.019		0.322	0.726		0.686	0.509	
HAM-D 27	6.444	0.003		0.755	0.476		0.425	0.656	
Drinks per day	0.497	0.612		0.919	0.406		1.545	0.224	
Drinks per occasion	0.999	0.376		0.503	0.608		1.531	0.227	
Days of alcohol use per week	1.282	0.287		0.775	0.467		0.127	0.881	
Heavy Drinking Days per Week	0.629	0.538		0.891	0.417		1.617	0.210	
Alcohol Count (DSM symptoms)	7.954	0.007		0.68	0.414		0.062	0.804	
Current MDD Symptom Count (DSM)	3.694	0.061		0.138	0.712		0.03	0.864	
			sex			treatment			
	F	sig.		F	sig.				
BDI Total	2.473	0.123		6.859	0.012				
HAM-D 27	2.418	0.127		9.899	0.003				
Drinks per day	5.289	0.026		0.982	0.327				
Drinks per occasion	8.025	0.007		1.886	0.176				
Days of alcohol use per week	0.113	0.738		0.008	0.929				
Heavy Drinking Days per Week	2.497	0.121		1.779	0.189				
Alcohol Count	0.147	0.703		0.361	0.551				
Current Major Depression Symptom Count	0.018	0.894		0.713	0.403				