TREATMENT TRIAL AND LONG-TERM FOLLOW-UP EVALUATION AMONG COMORBID YOUTH WITH MAJOR DEPRESSION AND A CANNABIS USE DISORDER

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Abstract

Objective—This study compared the acute phase (12-week) and the long-term (1 year) efficacy of fluoxetine versus placebo for the treatment of the depressive symptoms and the cannabis use of youth with comorbid major depressive disorder (MDD) and an cannabis use disorder (CUD) (cannabis dependence or cannabis abuse). We hypothesized that fluoxetine would demonstrate efficacy in the acute phase trial and at the 1-year follow-up evaluation. Data is also provided regarding the prevalence of risky sexual behaviors in our study sample.

Methods—We recently completed the first double-blind placebo-controlled study of fluoxetine in adolescents and young adults with comorbid MDD/CUD. A total of 70 persons participated in the acute phase trial, and 68 of those persons (97%) also participated in the 1-year follow-up evaluation. Results of the acute phase study have already been presented (Cornelius, Bukstein, et al., 2010), but the results of the 1 year follow-up assessment have not been published previously. All participants in both treatment groups also received manual-based cognitive behavioral therapy (CBT) and motivation enhancement therapy (MET) during the 12-week course of the study. The 1-year follow-up evaluation was conducted to assess whether the clinical improvements noted during the acute phase trial persisted long term.

Results—During the acute phase trial, subjects in both the fluoxetine group and the placebo group showed significant within-group improvement in depressive symptoms and in cannabis-related symptoms. However, no significant difference was noted between the floxetine group and the placebo group on any treatment outcome variable during the acute phase trial. End of study levels of depressive symptoms were low in both the fluoxetine group and the placebo group. Most of the clinical improvements in depressive symptoms and for cannabis-related symptoms persisted at the 1-year follow-up evaluation.

Conclusions—Fluoxetine did not demonstrate greater efficacy than placebo for treating either the depressive symptoms or the cannabis-related symptoms of our study sample during the acute phase study or at the 1-year follow-up assessment. The lack of a significant treatment effect for fluoxetine may at least in part reflect efficacy of the CBT/MET psychotherapy. A persistence of

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the efficacy of the acute phase treatment was noted at the 1-year follow-up evaluation, suggesting long-term effectiveness for the CBT/MET psychotherapy.

1. Introduction

Cannabis use disorders (CUD) (cannabis dependence and cannabis abuse) are the most common illicit substance use disorder in the United States (Agosti et al., 2002; Compton et al., 2004; Stinson et al., 2005). The prevalence of current cannabis dependence is much higher among adolescents (2.6%) and young adults (3.5%) than among adults 26 years old and older (0.4%) (Dennis et al., 2002; Compton et al., 2004), suggesting that CUD are primarily a disorder of youth. Depressive disorders such as major depressive disorder are commonly found among persons with CUD, and are found more commonly among persons with a CUD than would be expected by chance alone (Regier et al., 1990; Chen et al., 2002; Stinson et al., 2006). Nonetheless, despite the prevalence of cannabis use disorders, pharmacotherapy studies involving those disorders are scarce, and studies involving CUD in combination with comorbid major depressive disorder (MDD) or other psychiatric disorders are even less common. Pharmacotherapy studies among youthful comorbid populations are particularly rare.

Our own research group recently completed the first double-blind, placebo-controlled study of fluoxetine among youth with comorbid MDD and alcohol dependence. The results of the acute phase of that study were recently published (Cornelius, Bukstein, et al., 2010), though the results of the associated long-term (one-year) outcome assessment have not been previously published. That acute phase study compared the efficacy of fluoxetine 20 mg to that of placebo for treating the depressive symptoms and the cannabis-related symptoms of comorbid MDD/CUD youth. All participants in both treatment groups (the fluoxetine group as well as the placebo group) also received manual-based cognitive behavioral therapy (CBT) and motivation enhancement therapy (MET) during the 12-week abuse phase study. Fluoxetine was well tolerated in that acute phase study. No significant group-by-time interactions were noted for any depression-related or cannabis-related outcome variable over the 12-week study. Subjects in both the fluoxetine group and the placebo group showed significant within-group improvement in depressive symptoms and in number of DSM diagnostic criteria for a CUD. Large magnitude decreases in depressive symptoms were noted in both treatment groups, and end-of-study levels of depressive symptoms were low in both treatment groups. The investigators concluded that fluoxetine did not demonstrate greater efficacy than placebo for treating either the depressive symptoms or the cannabis-related symptoms of our youthful study population. The lack of a significant between-group difference in outcome symptoms was thought to result at least in part from the efficacy of the CBT/MET psychotherapy used in the acute phase trial.

In the current report, the primary focus is on the results of the 1-year follow-up assessment study, which had involved persons who had participated in the acute phase trial. The primary goal of the 1-year long-term follow-up assessment was to assess whether the clinical improvements noted during the acute phase trial persisted long-term. We hypothesized that the clinical improvements noted during the acute phase study would persist at the 1-year follow-up assessment. The current report also summarizes the results of

the acute phase study and provides descriptive data regarding risky sexual behaviors in the study population.

2. Method

2.1. Subjects

Before entry into this treatment protocol, the study was explained, and written informed consent was obtained from all subjects (minors provided written assent and a parent provided written consent) 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 NCT00149643). 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 14 and 25 years of age at the baseline of the acute phase study in order to be included in the study. At the baseline assessment, participants were evaluated for the DSM-IV diagnoses of a CUD and for MDD. The comorbid presence of both a current CUD 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 cannabis 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, et al., 1997; Puig-Antich, 1986). The DSM-IV diagnosis of a cannabis use disorder (cannabis abuse or dependence) was confirmed using the Substance Use Disorders Section of the Structured Clinical Interview for the DSM (SCID) (First et al., 1997), which is an instrument that has also been validated for use with adolescents as well as adults (Martin, et al., 2000). Current cannabis use (use within the prior 30 days) was also required to be included in the study. In addition, a minimum current level of depressive symptoms was also required for study inclusion, as 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. Subjects 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. Subjects who had received antipsychotic or antidepressant medication in the month prior to baseline assessment were excluded. Subjects with any substance abuse or dependence other than alcohol abuse or dependence, nicotine dependence, or cannabis abuse or dependence were excluded from the study. Subjects with any history of intravenous drug use were excluded from the study. Subjects 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 subjects 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

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 (Stout et al., 1994). 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 and colleagues (1991) and Jain and colleagues (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 another study physician (Dr. Douaihy) remained non-blinded in order to handle any problems which may have arisen. Study visits occurred at nine time points: upon initiation of protocol medication (week 0), at the end of each of the first four weeks of the treatment trial (weeks 1, 2, 3, and 4), and on an every-other week basis during the final eight weeks of the study (weeks 6, 8, 10, and 12). Ratings of symptom severity occurred at each of those study visits. The 1-year follow-up assessment was conducted one year following the baseline of the acute phase study, and utilized the same assessment instruments that were used in the acute phase study.

The therapeutic interventions utilized in this study were chosen in an effort to provide effective treatment for both the depressive symptoms and the cannabis use of our comorbid population. 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 cannabis use disorder, and Motivation Enhancement Therapy (MET) for treatment of the cannabis use disorder. That therapy had been adapted by the study investigators (particularly O.G.B.) to be age appropriate for the study population. Both CBT and MET have previously demonstrated efficacy for treating cannabis dependence, as demonstrated in a series of randomized controlled trials (Elkashef et al., 2008; Marijuana Treatment Project Research Group, 2004; Stephens et al., 2000; Stephens et al., 1994). The therapy was provided during each protocol visit during the treatment trial, so participants received psychotherapy on nine occasions (weeks 0, 1, 2, 3, 4, 6, 8, 10, and 12). Each of the 9 therapy sessions included therapy devoted to treatment of both the major depressive disorder and to the cannabis use disorder. The CBT 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, et al., 1997). This therapy was chosen because CBT has been reported to be more efficacious than alternative psychosocial interventions for the acute treatment of adolescents with MDD (Birmaher, et al., 2000). The CBT for treatment of CUD used in this study was modeled after the widely used techniques described in the CBT manual utilized in Project MATCH (Kadden, et al., 1994). The MET used in this study was adapted after the Motivation Enhancement Therapy used in Project MATCH (Miller, et al., 1992). All therapists in this study had obtained a master's degree in their field, had completed training courses in CBT and MET therapy, and had been providing therapy to comorbid adolescents and young adults for several years prior to their participation in this study. Thus, all therapists participating in this study were very experienced in their field, with particular expertise in conducting CBT and MET therapy with comorbid adolescents and young adults. At baseline, all study subjects were also offered informational brochures regarding the prevention of sexually transmitted diseases and avoiding risky sexual behaviors.

2.3 Assessment

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. To ensure a high level of participation for these evaluations, a $20.00 payment was made to patients completing each assessment (Festinger, et al., 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, et al., 1982), and was validated by 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, et al., 1961). Cannabis use behaviors and other substance use behaviors were assessed using the timeline follow-back method (TLFB) (Sobell LC, 1988). This instrument provided a daily tabulation of substance use behavior, thus providing detailed information on the quantity and frequency of this behavior. The primary cannabis use outcome variable was number of days of cannabis use. In addition, alcohol use outcome variables were assessed, including 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). The Side Effects Questionnaire for Children and Adolescents was use to monitor side effects during each assessment throughout the course of the clinical trial (Klein and Slomkowski, 1993). The Sexual Events Questionnaire (SEQ) was used to characterize sexual behaviors and their association with substance use (Bailey et al, 1998, Bailey et al., 2006).

2.3 Statistical Analysis

Descriptive statistics were calculated for all variables. Groups' continuous baseline measures were compared by independent, 2-tailed *t* tests for continuous variables. Groups' categorical baseline measures were compared by chi-square analysis, corrected for continuity. Statistical analyses were completed on an intent-to-treat study group basis. Outcome measures for depression and for cannabis use and alcohol use across treatment groups were compared by repeated measures analysis of variance. Repeated measure analysis ANOVA was chosen because of the low percentage of missing data in the study. The Last Observation Carried Forward (LOCF) method was used for handling missing data in the data analyses. 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 70 persons met all the inclusion criteria to participate in the Acute Phase Treatment Study, and all 70 of those persons entered and ultimately completed the acute phase study. No serious adverse events occurred during the course of the study. A total of 68 of those 70 subjects (97%) subsequently completed the 1-year follow-up assessment. Those subjects included 43 men and 25 women, including 38 Caucasians, 25 African-Americans, and 5 with mixed race, with an average age of 21.2 +/− 2.4 years. Most of these participants who entered the treatment trial (64/68, 94%) met DSM diagnostic criteria for cannabis dependence at baseline, and the other four subjects met diagnostic criteria for cannabis abuse. At baseline, the study subjects had been using cannabis an average of 76% of the days in the prior 30 days, meaning that frequent use of cannabis was the norm among the subjects entering our study sample. There were no significant differences between treatment groups on any baseline demographic or symptom severity variables.

During the acute phase study, a reduction of self-reported and observer-reported depressive symptoms of greater than 50% was noted in both the fluoxetine group and the placebo group. The majority of that improvement occurred during the first half of the clinical trial. Reductions in number of days of cannabis use were more modest, however, and that reduction was not statistically significant in either treatment group. In repeated measure analysis of variance, no significant time by treatment group interactions were noted for any depressive outcome variables or any cannabis or other substance-related outcome variables. However, a significant within-group improvement was noted for self-reported depressive symptoms (BDI), observer-rated depressive symptoms (HAM-D 27), number of DSM

cannabis dependence criteria, and number of DSM cannabis use disorder criteria (cannabis dependence criteria plus cannabis abuse criteria).

Males drank more heavily than females throughout the course of the acute phase study, as shown by a significant main effect of gender in the number of days of alcohol use in the past month, the average number of drinks per drinking occasion in the past month, and the number of days of binging on alcohol (drinking more than or equal to 5 drinks per occasion), though no other significant main effects of gender were noted on other depression-related or substance-use related variables. A significant time by gender effect was noted on total BDI score and on DSM cannabis abuse criteria count, with females showing a greater improvement with time on those two variables than males. However, no significant effect was noted between treatment assignment (flouxetine vs. placebo) and any demographic or symptom severity variable, so no variable served as a significant predictor of medication response. Also, path analyses were performed to determine whether the presence or absence of the S allele of the serotonin transporter gene (LS or SS genotype, versus LL genotype) affected treatment outcome. No significant effect of genotype was noted in those treatment outcome analyses.

From baseline of the acute phase study until the 1-year follow-up assessment, a significant decrease in self-reported depressive symptoms (BDI) and observer-rated depressive symptoms (HAM-D) was noted (p<0.001) across the entire study sample, and a significant decrease in days of marijuana use was also noted (p<0.001). However, that significant decrease in depressive symptoms and in cannabis use occurred during the acute phase study, while no further decrease occurred from the end of the acute phase study until the 1-year follow-up assessment. Indeed, small increases were noted in depressive symptoms, though those increases were not statistically significant, and the final mean BDI score (10.2 +/− 9.9) continued to be only half their baseline levels. Also, a modest increase in number of days of cannabis use was noted from the end of the acute phase study until the 1-year follow-up evaluation, though the level of use of cannabis was still 15% less at the 1-year follow-up evaluation (3.7 +/− 2.8 days/week) than it had been at the baseline of the acute phase study. No significant difference between the fluoxetine group and the placebo group was noted for any of the outcome variables at any time point.

The diagnostic assessments were repeated at the 1-year follow-up assessment, so the diagnostic profile of the study sample at that time point could be compared to that which had been noted at baseline. At the 1-year follow-up assessment, most of the subjects no longer met diagnostic criteria for either major depressive disorder of for a cannabis use disorder. Specifically, at the 1-year follow-up assessment, only 31% of subjects met diagnostic criteria for a current major depressive disorder, and only 43% of subjects met diagnostic criteria for a cannabis use disorder.

Patterns of sexual behavior of study subjects were assessed at the 1-year follow-up assessment, and those patterns were compared to those noted at baseline. At baseline, all but one of the study subjects (69 of 70, 99%) reported being sexually active. Of those study subjects, 9% reported having had lifetime 1 or 2 sexual partners, 29% reported having had 3 to 5 sexual partners, 32% reported having had 6 to 10 sexual partners, and 30% reported

having had more than 10 sexual partners. The most common forms of sexual behavior were vaginal sex (67 of 70, 97%) and oral sex (67 of 70, 97%), and 35 subjects reported having had anal sex (50%). Approximately 94% of study subjects reported having sex in conjunction with drug or alcohol use. In the study sample, 85% reported having sex at least occasionally while drunk, and 97% reported having had sex at least occasionally while high on cannabis. In that sample, 69% reported using condoms "always" or "almost always", while 26% reported using condoms about half the time, and 4% reported almost never or never using condoms. About 14% of subjects reported having tested positive for some sexually transmitted disease during their lifetime, while 48% reported having tested negative and 37% reported never having been tested for a sexually transmitted disease. None reported having tested positive for HIV/AIDS.

At the one-year follow-up assessment, a strong majority (95%) of study subjects reported having engaged in sexual behavior at some time in the previous year since study baseline. The most common form of sexual behavior was vaginal sex (95%), followed by oral sex (50%) and anal sex (28%). In that sample, 27% reported having only one sexual partner in the previous year, while 27% reported having two sexual partners in the previous year, 38% reported 3 to 5 partners in the previous year, and 8% reported having 6 to 8 partners in the previous year. 87% of subjects reported having had sex in the previous year in conjunction with drug or alcohol use. Approximately 83% reported having had sex at least occasionally while high on cannabis, and 81% reported having had sex at least occasionally while drunk. 66% reported always or almost always using condoms during sex, 19% reported using condoms about half of the time, and 15% reported never or almost never using a condom. 3% of the participants reported testing positive for a sexually transmitted disease during the previous year, 36% of the participants reported testing negative for a sexually transmitted disease during the previous year, while 60% reported not having been tested for a sexually transmitted disease in the last year.

4. Discussion

Fluoxetine did not demonstrate greater efficacy than placebo for treating either the depressive symptoms or the cannabis-related symptoms of our study sample at any point during the acute phase study or at the 1-year follow-up assessment. The lack of a significant treatment effect for fluoxetine may at least in part reflect efficacy of the CBT/MET psychotherapy. A persistence of the efficacy of the acute phase treatment was noted at the 1-year follow-up evaluation. For example, the level of depressive symptoms continued to be much lower than was observed at the baseline of the acute phase study, and levels of drug and alcohol use were somewhat lower than the levels noted at the study baseline. These findings suggest long-term effectiveness for the CBT/MET psychotherapy, particularly for the treatment of depressive symptoms. It is possible that a significant advantage for fluoxetine over placebo may have been detected with a more severely or more chronically depressed treatment sample or with a larger sample size. However, it is noteworthy that there was not even a trend for a significant difference between groups was noted on any depressive measure or substance use variable, suggesting that having a larger sample size would probably not have changed the findings of the study.

The finding of efficacy for CBT/MET therapy in the comorbid treatment population with major depression in combination with a CUD in the current study is consistent with findings from other studies involving youthful comorbid populations, such as studies demonstrating the effectiveness of CBT therapy among adolescents with comorbid major depressive disorder and an alcohol use disorder (Riggs et al., 2007; Cornelius, Bukstein, et al., 2009; Cornelius, Douaihy, et al., 2011; Cornelius, Douaihy et al., In Press). Thus, CBT therapy has now demonstrated efficacy in multiple studies involving multiple populations of youth with major depression in combination with a substance use disorder. The consistency of the findings suggests that CBT therapy is currently the standard of care for treating youth with major depressive disorder in combination with a cannabis use disorder and/or an alcohol use disorder. CBT therapy should probably be considered first-line treatment for that youthful comorbid population. The role of antidepressant medication in that population is unclear, and warrants further study.

The results of the current study also demonstrate that comorbid youth demonstrate high rates of risky sexual behaviors, and often use drugs and alcohol in association with sexual behavior. That population also was shown to have relatively low levels of testing for sexually transmitted diseases. Those finding suggest that comorbid youth should be a priority group for the evaluation and treatment of sexually transmitted disorders.

The results of this study should be interpreted in light of some limitations. First, 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 acute phase and long-term efficacy of SSRI medications in comorbid MDD/CUD adolescents and young adults. Second, the sample in this study was limited to outpatient comorbid MDD/CUD adolescents and young adults. Consequently, it is unclear to what extent the results of this study generalize to the treatment of comorbid MDD/CUD adults or to comorbid adolescents and young adults in more intensive treatment settings, such as inpatient settings or partial hospital settings, where profound depressive symptoms are more common. Because of the limited efficacy of SSRI medications among comorbid populations to date, pharmacotherapy trials involving non-SSRI medications are also warranted among comorbid populations of adolescents and adults. For example, a recent open label study involving the non-SSRI antidepressant medication mirtazapine has suggested efficacy for that mediation for treating persons with comorbid major depression in combination with an alcohol use disorder or a cannabis use disorder (Cornelius, Douaihy, & Clark, In Press). Double-blind placebo-controlled studies of mirtazapine and other non-SSRI medications appear to be warranted to clarify their potential efficacy in adolescent and adult comorbid populations. Studies are also warranted to clarify the subpopulations which respond best to various psychotherapies and various pharmacotherapies, and to clarify the optimal combinations of medication and psychotherapy for treating persons with comorbid disorders.

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