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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.