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Subthreshold Substance Use and the Treatment of Resistant Depression in Adolescents

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Abstract

Objective—Despite the known association between substance use disorders (SUD) and major depressive disorder (MDD) among adolescents, little is known regarding substance use among adolescents with MDD.

Method—Youth with MDD who had not improved after an adequate SSRI trial (N = 334) were enrolled in the Treatment of SSRI-Resistant Depression in Adolescents (TORDIA) trial. Analyses examined substance use (via the Drug Use Severity Index) and changes therein in relation to treatment and depressive symptoms. Adolescents meeting SUD criteria via the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version at baseline were excluded.

Results—Substance use was common: 28.1% reported repeated experimentation at baseline. Substance-related impairment was associated with baseline depression severity, older age, physical/sexual abuse, family conflict, hopelessness, and comorbid oppositional defiant disorder/conduct disorder. There was significant improvement in substance-related impairment among adolescents who responded to MDD treatment. Baseline suicidal ideation was higher among subjects who progressed to high substance-related impairment (≥ 75 th percentile) versus those whose substance-related impairment remained low (< 75 th percentile), and parental depressive symptoms predicted persistence of high substance-related impairment during the study. MDD response was best among adolescents with low 12-week substance-related impairment scores regardless of whether they had high or low baseline substance-related impairment. There were no significant differential effects of specific treatments, pharmacological or CBT, on substance use.

Conclusions—Substance use is common among adolescents with treatment-resistant MDD. Subjects who had persistently low substance-related impairment or who demonstrated reduced substance-related impairment had better MDD treatment response, although the direction of this association is uncertain.

Keywords

substance use; depression; adolescents; treatment

Introduction

Substance use is twice as common among adolescents with depression (29.2%) compared to those who without depression (14.5%)¹. Depression has been associated with not only a higher rate but also an earlier onset of substance use^{2, 3} and a doubling of the risk of initiating alcohol use in adolescence⁴. A significant body of literature indicates that depression negatively affects substance use treatment outcomes of adolescents with SUD⁵⁻¹⁰, and findings from adult samples suggest that even occasional substance use and/or moderate alcohol use may be associated with poorer response to treatment of depressive symptoms^{11, 12}. Previous studies have not, however, examined the association of substance use and treatment response in treatment-resistant MDD among youth without SUD via the KSADS.

Findings from adult samples also suggest that anti-depressant treatment attenuates substance use. A meta-analysis of studies of anti-depressants (mostly selective serotonin reuptake inhibitors [SSRIs]) for the treatment of adults with comorbid MDD and SUD yielded a modest pooled effect size (0.25) on self-reported quantity of substance use.¹³ Moreover, studies that reported finding greater effects on depression symptoms were also associated

with favorable effects in reducing substance use.¹³ Few clinical trials for adolescents with MDD-SUD comorbidity have been conducted. Two small trials of sertraline (N=10; placebo-controlled)¹⁴ and fluoxetine (N=13; open-label)¹⁵ reported mixed findings. A third double-blind placebo controlled study of fluoxetine 10mg/day for adolescents with MDD-SUD was stopped prematurely, following enrollment of 34 subjects, due to lack of efficacy.¹⁶ In the largest study of this topic to date, Riggs and colleagues randomized 126 adolescents with MDD, conduct disorder, and SUD to 16 weeks of either fluoxetine 20mg/day or placebo, in addition to SUD-focused CBT.¹⁷ Self-reported substance use decreased in both groups; however between-group differences were not significant. There was a greater proportion of negative urine screens and greater reduction in self-reported days of drug use independent of treatment group, among subjects whose depression remitted.

We set out to examine the demographic and clinical correlates of substance use as well as its prevalence among 334 adolescents enrolled in the multi-site, National Institute of Mental Health (NIMH)-funded Treatment of SSRI-Resistant Depression in Adolescents (TORDIA) trial. Based on the extant literature, we expected that substance use would be significantly associated with greater depression severity and duration, oppositional defiant disorder or conduct disorder (ODD/CD), anxiety, and history of physical or sexual abuse.¹⁸⁻²¹ In addition, the current article addresses three central questions that have received little attention to date. First, does the severity of substance-related impairment at baseline predict outcome of treatment for depression? Second, are changes in depressive symptoms associated with changes in severity of substance use? Third, is treatment of MDD associated with changes in substance-related impairment, and does this association depend on the specific type of MDD treatment?

Method

A detailed description of the study design, inclusion and exclusion criteria, and 12-week outcome are presented elsewhere²².

Participants

Participants were adolescents aged 12 to 18 years enrolled in the TORDIA study. All participants had a DSM-IV MDD diagnosis via the KSADS-PL, with clinically significant depression, defined as a total score ≥ 40 on the Child Depression Rating Scale-Revised (CDRS-R)²³ and a score ≥ 4 on Clinical Global Impression- Severity (CGI-S)²⁴, despite an adequate treatment with an SSRI for at least 6 weeks (defined as a dosage of the equivalent of 20 mg. of fluoxetine) and a final 2 weeks at a dosage equivalent to 40 mg of fluoxetine, unless this dose could not be tolerated.

Exclusion criteria were: a diagnosis of alcohol or drug abuse or dependence, as assessed by the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version [KSADS])²⁵ or diagnoses of bipolar I or II, psychosis, autism, or eating disorder on the KSADS; completing ≥ 2 adequate SSRI trials; history of non-response to an adequate trial of venlafaxine; prior trial of CBT, with ≥ 7 sessions; on medications with psychoactive properties, excluding some study-allowed medications at stable doses (≥ 6 weeks duration); hypertension (diastolic BP ≥ 90); and females who were pregnant, breast-feeding, or not reliably using contraception.

The study was approved by each site's local IRB; all participants gave written informed assent (and consent after they turned age 18), and parents gave informed consent in accordance with local IRB regulations.

Randomization and treatment

Participants were randomly assigned to one of four treatments: a change to second SSRI; a change to venlafaxine; a change to a second SSRI combined with MDD-focused CBT (i.e. no systematic focus on substance use); or a change to venlafaxine combined with CBT. Randomization was balanced both within and across sites on: incoming treatment medication, comorbid anxiety, chronic depression (duration ≥ 24 months), and suicidal ideation (BDI item 9 ≥ 2).

Measures

Age, sex, race, parental education and income were assessed by parent and youth report. In addition, the following measures were administered: 1) Children's Depression Rating Scale-Revised (CDRS-R) a 17-item interview (range from 17-113); 2) Clinical Global Impressions-Improvement Subscale (CGI-I), range 1 (very much improved) to 7 (very much worse); 3) Beck Depression Inventory (BDI)26, a 21-item self-report measure with scores ranging from 0-63; 4) Beck Hopelessness Scale (BHS)27, a 20 item self-report questionnaire with scores ranging from 0 (no hopelessness) to 20; 5) Suicide Ideation Questionnaire – Junior (SIQ-Jr)28, a 15-item self-report measure, was completed to assess suicide risk, with a total score of 31 or above indicating an elevated suicidal risk; 6) Conflict Behavior Questionnaire – Adolescent version (CBQ-A)29, a 20 item questionnaire that measure conflict and negative communication perceived by each family member; and 7) Drug Use Screening Instrument (DUSI)30; youth were asked about frequency of use of 11 illicit drugs, and 15 additional items evaluated drug-related impairment. The impairment items assessed attitudes and behaviors regarding alcohol and drugs such as: craving or strong desire to use them, using them for the needed effect, feeling unable to control self, feeling hooked on them, missing activities, breaking rules/law or missing curfew, mood swings related to drug use, having a car accident, accidentally hurting oneself or others, being engaged in serious arguments or fights, having trouble in getting along with friends, experiencing withdrawal symptoms, problems remembering, drinking in large quantities, and trouble resisting their use. The total DUSI impairment score (which was used in this paper) has a range of 0-100, calculated by multiplying the fraction of items endorsed by 100 (e.g. a subject endorsing 3 items will have a score of $3/15 \times 100 = 20$). Impairment items on the DUSI comment the past 12 months, whereas frequency items comment the past month.

Urine drug screens were requested at baseline. However, because only 43.4% of the sample provided a urine drug screens, and because some drug screens were obtained at baseline whereas others were obtained during the study, data or analyses regarding the urine drug screens are not presented.

Outcomes

The primary MDD outcome, “adequate clinical response” at week 12, was defined as a 50% reduction in CDRS score and a CGI-I score of 2 or less. Response was rated by an independent evaluator. For analyses, subjects were divided into two groups based on whether their DUSI scores were below the 75th percentile at baseline (“low use”) or above the 75th percentile at baseline (“high use”). This percentile-based definition of low and high use was employed because it allows for comparisons within the TORDIA sample and because the 75th percentile of DUSI impairment scores coincided with the prevalence of recurrent substance experimentation by 25% of the sample, and the high correlation between these groups. A cut-off score of 30 for the DUSI impairment score was found to be sensitive and specific in a sample of adolescents without psychiatric illness. 30 However, the present study excluded subjects with SUD at intake and therefore this cutoff was not appropriate for the current study. The primary substance use outcome was DUSI group status at 12 weeks, classified as remaining low (<75th percentile at baseline and 12 weeks), worsening (<75th

percentile at baseline, $\geq 75^{\text{th}}$ percentile at 12 weeks), remaining high ($\geq 75^{\text{th}}$ percentile at baseline and 12 weeks), or improving ($\geq 75^{\text{th}}$ percentile at baseline, $< 75^{\text{th}}$ percentile at 12 weeks). Pair wise comparison was conducted to examine the baseline differences between the “remaining low” and the “worsening” group on one hand, and between the “remaining high” and “improving” group on the other hand. It should be noted that despite the terms “high” and “low” with respect to substance use, all of the substance use described at intake falls below KSADS diagnostic threshold for SUD. Five subjects had SUD at week 12, all of whom were in the “remaining high” category.

Statistical analysis

Intention to treat analysis was computed with respect to assignment to MDD treatment while completer analysis was computed for change in DUSI scores. The Statistical Package for Social Sciences (SPSS 14.0) and STATA were used to conduct statistical analyses. Independent sample t-test and Pearson and Spearman correlation coefficients were conducted to test for association between the baseline DUSI impairment score and, respectively, the other baseline binary, nominal, and continuous variables. Pearson chi-square and t-tests were used to examine the baseline predictors of change in impairment scores (categorized as described above). Mixed regression models were used to examine whether change in DUSI impairment scores (used as a continuous variable) was associated with response to treatment. The model included a fixed response effect, a fixed time effect, and an interaction term which respectively estimated the group effect, the rate of change over time, and the specific rate for each group (responders vs. non responders). Similar models were conducted to examine the effect of medication and CBT on DUSI impairment. P-values less than 0.05 were considered to be statistically significant.

At week 12, the DUSI was missing for 60 patients (18.0%). The missingness was due to dropout (N=44) and due to participant's refusal to answer or clerical error (N=16). Patients with complete and missing data were compared with respect to baseline variables and response. Compared to patients with no missing data, those with missing data had lower response rate (26.7% vs. 52.2%, $p < 0.01$), higher rates of history of sexual abuse (26.8% vs. 14.9%, $p = 0.03$) and suicide attempts ($p = 0.04$), lower CGAS scores ($p = 0.05$) and higher baseline DUSI impairment scores ($p = 0.05$).

Results

Prevalence and Correlates of Substance Use

The total analyzable sample consisted of 334 patients. At intake, 179 patients (54.6%) had used one or more substances at least once, and 90 patients (28.1%) had used at least one substance 3-9 times or more in the previous month. The most commonly used substance was alcohol (36.1%), followed by painkillers (24.2%) and marijuana (22.7%) (See Table 1). The mean DUSI impairment score at intake was 11.0 ± 18.8 . DUSI impairment at intake was associated with older age ($r = 0.18$, $p < 0.01$), earlier age of onset of current MDD ($r = 0.21$, $p < 0.01$), history of sexual abuse ($r = 0.15$, $p = 0.01$), ODD/CD ($r = 0.16$, $p = 0.01$), and higher baseline BDI ($r = 0.17$, $p < 0.01$), CDRS ($r = 0.11$, $p < 0.05$), hopelessness ($r = 0.13$, $p < 0.05$), and CBQ-A ($r = 0.18$, $p < 0.05$) scores (See Table 2). DUSI impairment was significantly correlated with frequency of substance use ($r = 0.40$, $p < 0.01$). Moreover, impairment was significantly associated with frequency of use of alcohol ($r = 0.43$, $p < 0.01$) and marijuana ($r = 0.42$, $p < 0.01$) specifically. On the other hand, DUSI impairment score was not significantly associated with CGAS ($r = -0.06$, $p = 0.32$).

Association between Baseline Substance Use and MDD Treatment Response

There was no significant difference in baseline DUSI impairment score and response at week 12 between non-responders (12.8 ± 20.4) and responders (9.0 ± 16.8 , $t=1.8$, $p=0.07$). Similarly, there was no significant association between *frequency* of substance use at intake and response at week 12: response rate for subjects with zero use = 47.0% vs. 49.2% for those with any frequency of substance use, $p=0.69$). Response rate for subjects who had used any substance ≥ 3 times was 42.2% versus 50.4% for those who had not used any substance ≥ 3 times ($p=0.19$). In order to ensure that these findings were not a result of our selected 75th percentile cutoff, the analysis was re-run using a mixed model with DUSI as a continuous variable, with similar results.

Association between Change in DUSI impairment scores and Change in Depressive Symptoms

In the mixed regression models, there was a significant interaction between response and time ($p<0.01$) indicating that responders showed significant improvement in their DUSI impairment scores while non-responders did not show significant improvement. In TORDIA, less severe depression, less family conflict, and absence of nonsuicidal self injurious behavior were independent predictors of response to treatment. 31 Even after controlling for these variables in the mixed model, the association between response and improvement in DUSI impairment persisted.

The 25th, 50th, and 75th percentile DUSI impairment scores were 0, 0, and 13.3, respectively. The 75th percentile score was used to categorize the change in the DUSI impairment scores. Impairment scores remained low (<13.3) for 66.0%, worsened for 6.9%, remained high (≥ 13.3) for 17.9%, and improved for 9.1%. Among those with low baseline impairment, 90.5% remained low while 9.5% worsened. On the other hand, among those with high baseline impairment (≥ 13.3), 66.2% remained high while 33.8% improved.

For subjects with DUSI impairment scores available both from baseline and 12-weeks, response rates were significantly higher among subjects with low DUSI scores (<13.3) at 12-weeks, compared to subjects with high DUSI scores (≥ 13.3) at 12-weeks ($p=0.003$), regardless of whether they had high or low DUSI scores at intake. In fact, the response rate was highest among subjects who had high DUSI scores at intake but low DUSI scores at 12-weeks (68.0% responders), which was numerically but not significantly ($p=0.25$) higher than among subjects who had low DUSI scores at both time-points (55.8% responders), and significantly higher than among subjects who remained (36.8%) or ended (36.7%) in the high DUSI group ($p=0.01$ & 0.04 respectively).

The baseline predictors of change in DUSI impairment scores were examined (Table 3). Of particular note, among subjects with low DUSI impairment scores at baseline, suicidal ideation (SIQ) was significantly higher within the subgroup that had high DUSI impairment scores at 12 weeks. There a significant association between change in DUSI impairment scores and change in SIQ over time ($b=-0.08$, $p=0.001$). In addition, among subjects with high baseline DUSI scores, higher parental BDI at baseline was associated with persistence of high DUSI scores at 12 weeks (See Table 4).

Changes in Substance Use during Treatment for MDD

At week 12, 41.7% had used one or more substances at least once, while 15.6% had used at least one substance 3-9 times or more. The frequency of alcohol use did not change for 173 patients (63.8%), decreased for 63 patients (23.2%), and increased for 35 patients (12.9%). Overall, there was a significant decrease in frequency of alcohol use over time ($b=-0.46$,

$p=0.02$). Changes in frequency of alcohol use over time were not associated with MDD response ($p=0.89$).

The frequency of cannabis use did not change for 209 patients (93.3% of which were not using cannabis), decreased for 36 patients (72.2% of which stopped), and increased for 23 patient (73.9 % of which initiated). Similar to alcohol, there was an overall decrease in the frequency of marijuana use ($b=-0.04$, $p=0.02$); however, this was not associated with MDD response ($p=0.14$).

The trajectory of change in overall substance use was not influenced by whether or not treatment included CBT ($p=0.64$) or whether the patients were switched to venlafaxine or SSRI ($p=0.80$). Changes in frequency of alcohol use over time were not associated with receipt of CBT ($p=0.99$), or type of medication ($p=0.81$). Similarly, changes in frequency of cannabis use over time were not associated with receipt of CBT ($p=0.99$), or type of medication ($p=0.81$). Finally, changes in DUSI impairment scores over time were not associated with receipt of CBT ($p=0.64$), or type of medication ($p=0.83$).

Discussion

This study examined substance use among youth with treatment-resistant MDD who did not meet criteria for a substance use disorder. More than half of the sample had used a substance at least once, and approximately one-quarter reported repeated experimentation with substances (≥ 3 times) at baseline. Baseline substance-related impairment was associated with objective (CDRS) and subjective (BDI) ratings of depression. Substance-related impairment was also associated with older age, history of physical or sexual abuse, greater family conflict, hopelessness, and comorbid ODD/CD. There was a trend toward greater substance-related impairment, but not frequency of substance use among non-responders to the MDD treatment protocol. Controlling for potential confounds, there was a significant improvement in substance-related impairment among MDD responders to the MDD treatment protocol. However, MDD response was not associated with changes in the frequency of substance use. Baseline suicidal ideation was higher among subjects who progressed to high substance-related impairment compared to those whose substance-related impairment remained low. In contrast, baseline parental BDI scores were higher among subjects whose substance-related impairment remained high compared to those who decreased from high to low substance-related impairment during the study. MDD response was greatest among subjects with low 12-week substance-related impairment regardless of whether they had high (68.0%) or low (55.8%) baseline substance-related impairment. MDD response was significantly lower among subjects with high 12-week substance-related impairment, regardless of whether they had high (36.7%) or low (36.8%) substance-related impairment at baseline. Finally, there were no significant differential effects of specific treatments, pharmacological or CBT, on substance use impairment or frequency.

These findings must be interpreted in the context of methodological limitations of this study. First, despite the longitudinal methodology, with only 2 assessments this study does not allow for determination of the direction of the observed associations. It is equally possible that decreasing substance use leads to improvement in mood, or that improvement in mood results in decreased substance use. Second, the DUSI category of "painkillers" does not explicitly distinguish between medications such as acetaminophen, opiates, or barbiturates, such that this category combines medications with lesser and greater propensity for misuse. Third, the DUSI is a self-report instrument. Several adolescents reported recurrent substance use along with endorsing an impairment item on the DUSI, despite not meeting SUD criteria via the KSADS. Some adolescents may be more likely to disclose substance use in a self-report instrument than in an interview.³² Although the KSADS includes information from

adolescents as well as from parents, it is possible that adolescents with undetected SUD were included in TORDIA. Reasons that substance-using adolescents did not receive a DSM-IV SUD diagnosis via the KSADS are that they may not have met the severity threshold of clinical significance, or problems related to substance use may not have been recurrent. Relatedly, this study did not include urine toxicology. Fourth, DUSI data were not available for all subjects at 12-weeks, and subjects with missing data differed in some ways from those with both baseline and 12-week DUSI data. This may influence the reported findings; however it is not possible to determine in which direction the data may have been skewed. The finding that subjects who did not provide data at 12-weeks had greater baseline substance use than those with complete data is consistent with previous findings that a history of substance use predicts drop-out among adolescents in treatment for depression³³. Finally, despite the large TORDIA sample, the examination of substance use comprises a secondary analysis that is not sufficiently powered to take into account multiple potential covariates or confounds, and therefore a limited number of variables could be included in multivariable models.

A cut-off score of 30 for the DUSI impairment score was found to be sensitive and specific in a sample of adolescents without psychiatric illness.³⁰ Given the exclusion of adolescents with SUD from TORDIA, it is not surprising that the mean DUSI impairment score in the present study was 11.0 ± 18.8 . Nonetheless, findings suggest that even substance use that falls short of a diagnosis of SUD via the KSADS is associated with similar clinical correlates as SUD and that subjects with DUSI impairment scores of at least 13.3 at 12-weeks showed poorer response to MDD treatment. These findings underscore the importance of characterizing substance-related impairment even among adolescents with MDD who do not suffer from SUD. Indeed, previous studies have found that substance use is associated with suicidality, legal problems, high-risk sexual behavior, injuries, and functional impairment.³⁴⁻⁴⁰ The presence of these indicators should increase the clinician's index of suspicion of substance use and vice versa.

Consistent with previous studies, substance-related impairment was associated with depressive severity, history of physical or sexual abuse, and comorbid ODD/CD. In contrast, comorbid anxiety was not associated with substance use at baseline. Previous studies found that anxiety is associated with SUD among youth⁴¹, and predicts SUD among youth with MDD.¹⁹ Because the present study examines sub-threshold substance use, as opposed to SUD, this finding is not directly comparable to previous studies and replication is warranted. The association between substance use and family conflict could have been anticipated on the basis of prior research.⁴²⁻⁴³

This study examined whether baseline substance-related impairment predicts outcome of treatment for depression. For the overall sample, there was a trend toward greater baseline substance-related impairment, but not substance use frequency, among MDD treatment non-responders. For subjects with available DUSI scores at both time points, substance-related impairment at 12-weeks was associated with MDD treatment response at 12-weeks. High baseline substance-related impairment was associated with lower MDD treatment response only if it remained high. Similarly, low baseline substance-related impairment was only associated with higher MDD treatment response if there was also low substance-related impairment at 12-weeks. Controlling for other variables that were associated with MDD treatment response in TORDIA, MDD treatment responders had significantly greater reduction in substance-related impairment compared to non-responders. We are not aware of any studies regarding the association of substance use with treatment response among adolescents with MDD. However, a study of 94 adults with MDD openly treated with fluoxetine indicated that even when consumed in moderation, alcohol is associated with decreased treatment response among adults with MDD. These findings converge with those

of a recent study of 126 adolescents with comorbid MDD and SUD in which subjects whose depression remitted had a greater proportion of negative urine drug screens and greater reduction in past-month self-reported days of drug use¹⁷. In that study, substance use did not decrease significantly among non-remitters. An earlier pilot study also noted an association between changes in depressive symptoms and frequency of substance use.¹⁴ A meta-analysis of pharmacological treatment of adults with MDD and comorbid SUD found that studies with larger effect sizes for depression were more likely to have a favorable impact on quantity of substance use¹³. Nonetheless, as acknowledged above, present findings do not inform our understanding regarding the direction of these associations. Future studies with multiple time-points are required to test for mediation.

Finally, this study examined whether treatment of MDD is associated with changes in substance use, and whether this association depends on the specific type of MDD treatment. The majority of subjects, 84% (230/274), did not demonstrate changes in substance-related impairment. For the overall sample, 9% decreased from high to low DUSI impairment, and 7% increased from low to high DUSI impairment. Within the 200 subjects with low baseline DUSI impairment, 19 (10%) demonstrated high DUSI impairment at 12 weeks. Within the 74 subjects with high baseline DUSI impairment, 25 (34%) demonstrated low DUSI impairment at 12 weeks. No between-treatment differences in changes in substance use or impairment were observed. The study by Riggs and colleagues indicated that treatment with fluoxetine demonstrated superiority over placebo in terms of proportion of negative urine drug screens, whereas no significant between-group difference in self-reported substance use was detected.¹⁷ Previous smaller placebo-controlled trials had failed to demonstrate superiority of active treatment with sertraline or fluoxetine over placebo with respect to the reduction of substance use.¹⁴⁻¹⁶

This is the first study to our knowledge that specifically examines the association of substance use with treatment of treatment-resistant MDD among adolescents. Present findings suggest that even adolescents without SUD experience substance-related impairment and that substance-related impairment is potentially more strongly associated with predicting MDD treatment response than is the frequency of substance use. Since higher substance-related impairment at 12 weeks is associated with decreased probability of MDD treatment response, it is important to recognize that suicidal ideation and parental depressive symptoms are associated with initiation and persistence, respectively, of substance-related impairment. Although present findings do not allow for definitive conclusions, they suggest that substance use is clinically noteworthy even if symptoms of SUD are denied during interviews with the adolescent or his/her parents. Clinicians treating adolescents with MDD should be aware of the potential effects of even relatively low substance use and impairment on depression treatment. When substance use is detected, psychoeducation should be emphasized throughout MDD treatment and specific strategies to address substance use, such as motivational interviewing and refusal skills, should be employed as needed.

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References

1. SAMHSA. The NSDUH Report: Depression and the initiation of alcohol and other drug use among youths aged 12 to 17. Rockville, MD: Substance Abuse and Mental Health Services Administration, Office of Applied Studies; 2007.

2. Costello EJ, Erkanli A, Federman E, Angold A, Costello EJ, Erkanli A, Federman E, Angold A. Development of psychiatric comorbidity with substance abuse in adolescents: effects of timing and sex. *Journal of Clinical Child Psychology*. 1999; 28(3):298–311. [PubMed: 10446679]
3. Kelder SH, Murray NG, Orpinas P, Prokhorov A, McReynolds L, Zhang Q, Roberts R. Depression and substance use in minority middle-school students. *American Journal of Public Health*. 2001; 91(5):761–766. [PubMed: 11344884]
4. Kaplow JB, Curran PJ, Angold A, Costello EJ, Kaplow JB, Curran PJ, Angold A, Costello EJ. The prospective relation between dimensions of anxiety and the initiation of adolescent alcohol use. *Journal of Clinical Child Psychology*. 2001; 30(3):316–326. [PubMed: 11501249]
5. Cornelius JR, Maisto SA, Martin CS, Bukstein OG, Salloum IM, Daley DC, Wood DS, Clark DB. Major depression associated with earlier alcohol relapse in treated teens with AUD. *Addictive Behaviors*. 2004; 29(5):1035–1038. [PubMed: 15219354]
6. Bukstein OG, Glancy LJ, Kaminer Y. Patterns of affective comorbidity in a clinical population of dually diagnosed adolescent substance abusers. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1992; 31(6):1041–1045. [PubMed: 1429402]
7. Subramaniam G, Stitzer M, Clemmey P, Kolodner K, Fishman M. Baseline depressive symptoms predict poor substance use outcome following adolescent residential treatment. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2007; 46(8):1062–1069. [PubMed: 17667484]
8. Riggs PD, Baker S, Mikulich SK, Young SE, Crowley TJ, Riggs PD, Baker S, Mikulich SK, Young SE, Crowley TJ. Depression in substance-dependent delinquents. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1995; 34(6):764–771. [PubMed: 7608050]
9. Lubman DI, Allen NB, Rogers N, Cementon E, Bonomo Y. The impact of co-occurring mood and anxiety disorders among substance-abusing youth. *Journal of Affective Disorders*. 2007; 103(1-3): 105–112. [PubMed: 17291589]
10. Deykin EY, Buka SL, Zeena TH, Deykin EY, Buka SL, Zeena TH. Depressive illness among chemically dependent adolescents. *American Journal of Psychiatry*. 1992; 149(10):1341–1347. [PubMed: 1530070]
11. Bricker JB, Russo J, Stein MB, Sherbourne C, Craske M, Schraufnagel TJ, Roy-Byrne P. Does occasional cannabis use impact anxiety and depression treatment outcomes?: results from a randomized effectiveness trial. *Depression and Anxiety*. 2007; 24(6):392–398. [PubMed: 17096386]
12. Worthington J, Fava M, Agustin C, Alpert J, Nierenberg AA, Pava JA, Rosenbaum JF. Consumption of alcohol, nicotine, and caffeine among depressed outpatients. Relationship with response to treatment. *Psychosomatics*. 1996; 37(6):518–522. [PubMed: 8942202]
13. Nunes EV, Levin FR. Treatment of Depression in Patients With Alcohol or Other Drug Dependence: A Meta-analysis. *JAMA*. 2004; 291(15):1887–1896. [PubMed: 15100209]
14. Deas D, Randall CL, Roberts JS, Anton RF. A double-blind, placebo-controlled trial of sertraline in depressed adolescent alcoholics: a pilot study. *Human Psychopharmacology: Clinical and Experimental*. 2000; 15(6):461–469. [PubMed: 12404308]
15. Cornelius JR, Bukstein OG, Birmaher B, Salloum IM, Lynch K, Pollock NK, Gershon S, Clark D. Fluoxetine in adolescents with major depression and an alcohol use disorder: an open-label trial. *Addictive Behaviors*. 2001; 26(5):735–739. [PubMed: 11676382]
16. Findling, RL.; McNamara, NK.; Stansbrey, RJ.; Demeter, CA.; Lingler, J.; Faber, J.; Pagano, M. Fluoxetine versus placebo treatment of depression and co-morbid substance use. Paper presented at: Annual meeting of the American Academy of Child and Adolescent Psychiatry; Boston. 2007.
17. Riggs PD, Mikulich-Gilbertson SK, Davies RD, Lohman M, Klein C, Stover SK. A Randomized Controlled Trial of Fluoxetine and Cognitive Behavioral Therapy in Adolescents With Major Depression, Behavior Problems, and Substance Use Disorders. *Arch of Pediatrics and Adolescent Medicine*. 2007; 161(11):1026–1034.
18. King C, Ghaziuddin N, McGovern L, Brand E, Hill E, Naylor M. Predictors of Comorbid Alcohol and Substance Abuse in Depressed Adolescents. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1996; 35(6):743–751. [PubMed: 8682755]

19. Rao U, Ryan N, Dahl R, Birmaher B, Rao R, Williamson D, Perel J. Factors Associated With the Development of Substance Use Disorder in Depressed Adolescents. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1999; 38(9):1109–1117. [PubMed: 10504809]
20. King CA, Naylor MW, Hill EM, Shain BN, Greden JF, King CA, Naylor MW, Hill EM, Shain BN, Greden JF. Dysthymia characteristic of heavy alcohol use in depressed adolescents. *Biological Psychiatry*. 1993; 33(3):210–212. [PubMed: 8448270]
21. Clark DB, De Bellis MD, Lynch KG, Cornelius JR, Martin CS. Physical and sexual abuse, depression and alcohol use disorders in adolescents: onsets and outcomes. *Drug & Alcohol Dependence*. 2003; 69(1):51–60. [PubMed: 12536066]
22. Brent D, Emslie G, Clarke G, Wagner KD, Asarnow JR, Keller M, Vitiello B, Ritz L, Iyengar S, Abebe K, Birmaher B, Ryan N, Kennard B, Hughes C, DeBar L, McCracken J, Strober M, Suddath R, Spirito A, Leonard H, Melhem N, Porta G, Onorato M, Zelazny J. Switching to Another SSRI or to Venlafaxine With or Without Cognitive Behavioral Therapy for Adolescents With SSRI-Resistant Depression: The TORDIA Randomized Controlled Trial. *JAMA*. 2008; 299(8):901–913. [PubMed: 18314433]
23. Poznanski E, Freeman L, Mokros H. Children's Depression Rating Scale-Revised. *Psychopharmacology Bulletin*. 1984; 21:979–989.
24. Guy, W. Publication ADM. 2nd. Washington, DC: US Government Printing Office; 1976. ECDEU Assessment Manual for Psychopharmacology; p. 76-338.
25. Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, Williamson D, Ryan N. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): Initial Reliability and Validity Data. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1997; 36(7):980–988. [PubMed: 9204677]
26. Beck A, Steer R, Garbin M. Psychometric properties of the Beck Depression Inventory: Twenty-five years of evaluation. *Clinical Psychology Reviews*. 1988; 8:77–100.
27. Beck, A.; Steer, R. Manual for the Beck Hopelessness Scale. San Antonio, TX: Psychological Corporation; 1988.
28. Reynolds W, Mazza J. Assessment of suicidal ideation in inner-city children and young adolescents. *School Psychology Reviews*. 1999; 28:17–30.
29. Robin, A.; Foster, S. Negotiating parent adolescent conflict. New York: Guilford; 1989.
30. Kirisci L, Mezzich A, Tarter R. Norms and sensitivity of the adolescent version of the drug use screening inventory. *Addictive Behaviors*. 1995; 20(2):149–157. [PubMed: 7484309]
31. Asarnow JR, Emslie G, Clarke G, Wagner KD, Spirito A, Vitiello B, Iyengar S, Shamseddeen W, Ritz LM, Birmaher B, Ryan N, Kennard B, Mayes T, Debar L, McCracken J, Strober M, Suddath R, Leonard H, Porta G, Keller M, Brent D. Treatment of Selective Serotonin Reuptake Inhibitor-Resistant Depression in Adolescents: Predictors and Moderators of Treatment Response. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2009; 48(3):330–339. [PubMed: 19182688]
32. Fendrich M, Yun Soo Kim J. Multiwave analysis of retest artifact in the National Longitudinal Survey of Youth drug use. *Drug and Alcohol Dependence*. 2001; 62(3):239–253. [PubMed: 11295329]
33. Gilbert M, Fine S, Haley G, Gilbert M, Fine S, Haley G. Factors associated with dropout from group psychotherapy with depressed adolescents. *Canadian Journal of Psychiatry*. 1994; 39(6): 358–359.
34. Spirito A, Jelalian E, Rasile D, Rohrbeck C, Vinnick L, Spirito A, Jelalian E, Rasile D, Rohrbeck C, Vinnick L. Adolescent risk taking and self-reported injuries associated with substance use. *American Journal of Drug & Alcohol Abuse*. 2000; 26(1):113–123. [PubMed: 10718167]
35. Fergusson DM, Horwood JL, Swain-Campbell N. Cannabis use and psychosocial adjustment in adolescence and young adulthood. *Psychological Medicine*. 2002; 32(6):1123–1135.
36. Poulin C, Graham L. The association between substance use, unplanned sexual intercourse and other sexual behaviours among adolescent students. *Addiction*. 2001; 96(4):607–621. [PubMed: 11300964]

37. Shrier LA, Harris SK, Sternberg M, Beardslee WR. Associations of depression, self-esteem, and substance use with sexual risk among adolescents. *Preventive Medicine*. 2001; 33(3):179–189. [PubMed: 11522159]
38. Wu P, Hoven CW, Liu X, Cohen P, Fuller CJ, Shaffer D. Substance use, suicidal ideation and attempts in children and adolescents. *Suicide & Life-Threatening Behavior*. 2004; 34(4):408–420. [PubMed: 15585462]
39. Esposito-Smythers C, Spirito A, Esposito-Smythers C, Spirito A. Adolescent substance use and suicidal behavior: a review with implications for treatment research. *Alcoholism: Clinical & Experimental Research*. 2004; 28(5 Suppl):77S–88S.
40. Lynskey MT, Glowinski AL, Todorov AA, Bucholz KK, Madden PAF, Nelson EC, Statham DJ, Martin NG, Heath AC. Major Depressive Disorder, Suicidal Ideation, and Suicide Attempt in Twins Discordant for Cannabis Dependence and Early-Onset Cannabis Use. *Arch Gen Psychiatry*. 2004; 61(10):1026–1032. [PubMed: 15466676]
41. Goodwin RD, Fergusson DM, Horwood LJ, Goodwin RD, Fergusson DM, Horwood LJ. Association between anxiety disorders and substance use disorders among young persons: results of a 21-year longitudinal study. *Journal of Psychiatric Research*. 2004; 38(3):295–304. [PubMed: 15003435]
42. Godley MD, Kahn JH, Dennis ML, Godley SH, Funk RR, Godley MD, Kahn JH, Dennis ML, Godley SH, Funk RR. The stability and impact of environmental factors on substance use and problems after adolescent outpatient treatment for cannabis abuse or dependence. *Psychology of Addictive Behaviors*. 2005; 19(1):62–70. [PubMed: 15783279]
43. Guo J, Hill KG, Hawkins JD, Catalano RF, Abbott RD, Guo J, Hill KG, Hawkins JD, Catalano RF, Abbott RD. A developmental analysis of sociodemographic, family, and peer effects on adolescent illicit drug initiation. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2002; 41(7):838–845. [PubMed: 12108809]

Table 1

Number of times each drug used

	Number	Percent
Alcohol		
No use	210	63.8
Any use	119	36.2
1-2 times	76	23.1
3-9 times	32	9.7
10-20 times	5	1.5
>20 times	6	1.8
Cocaine/Crack		
No use	314	96.3
Any use	12	3.7
1-2 times	8	2.5
3-9 times	4	1.2
Marijuana		
No use	252	77.3
Any use	74	22.7
1-2 times	40	12.3
3-9 times	20	6.1
10-20 times	6	1.8
>20 times	8	2.5
Stimulants/Uppers		
No use	308	95.4
Any use	15	4.6
1-2 times	8	2.5
3-9 times	5	1.5
>20 times	2	0.6
LSD¹/Mescaline		
No use	322	99.4
Any use	2	0.6
1-2 times	1	0.3
>20 times	1	0.3
Tranquilizer		
No use	320	98.8
Any use	4	1.2
1-2 times	3	0.9
3-9 times	1	0.3
Painkillers		
No use	247	75.8
Any use	79	24.2
1-2 times	42	12.9

	Number	Percent
3-9 times	21	6.4
10-20 times	9	2.8
>20 times	7	2.1
Heroin/Opiates		
No use	323	99.4
Any use	2	0.6
1-2 times	1	0.3
10-20 times	1	0.3
PCP²		
No use	323	99.7
Any use	1	0.3
1-2 times	1	0.3
Gases or Fumes		
No use	318	97.8
Any use	7	2.2
1-2 times	5	1.5
3-9 times	2	0.6
Other		
No use	301	94.4
Any use	18	5.6
1-2 times	7	2.2
3-9 times	3	0.9
10-20 times	1	0.3
>20 times	7	2.2
Any Substance		
No use	151	45.8
Any use	179	54.6
1-2 times	89	26.6
3-9 times	52	15.6
10-20 times	15	4.5
>20 times	23	6.9

Note:

¹LSD: Lysergic acid diethylamide.

²PCP: Phenylcyclohexylpiperidine

Table 2
Drug Use Screening Instrument (DUSI) Impairment Scores by Baseline Demographic and Clinical Variables

	Impairment	
	Mean $\pm$ SD	p-value
Gender		
M	9.8 $\pm$ 16.6	0.47
F	11.5 $\pm$ 19.7	
Caucasian		
No	11.6 $\pm$ 19.2	0.79
Yes	10.9 $\pm$ 18.8	
College graduate (Parent)		
No	10.5 $\pm$ 18.3	0.83
Yes	10.9 $\pm$ 18.7	
Physical Abuse		
No	10.3 $\pm$ 18.3	0.18
Yes	14.4 $\pm$ 21.3	
Sexual Abuse		
No	9.6 $\pm$ 17.1	0.03
Yes	17.3 $\pm$ 24.7	
Physical or Sexual abuse		
No	9.4 $\pm$ 16.9	0.01
Yes	15.4 $\pm$ 23.1	
PTSD¹		
No	10.7 $\pm$ 18.7	0.28
Yes	15.1 $\pm$ 21.3	
Anxiety		
No	10.9 $\pm$ 17.8	0.76
Yes	11.6 $\pm$ 21.1	
ADHD²		
No	11.0 $\pm$ 18.8	0.76
Yes	10.1 $\pm$ 17.9	
Oppositional/Conduct		
No	9.9 $\pm$ 17.6	0.03
Yes	19.8 $\pm$ 24.8	
Stimulant Medication		
No	11.3 $\pm$ 19.2	0.42
Yes	8.8 $\pm$ 16.0	
Sleep Medications		
No	10.3 $\pm$ 17.8	0.23
Yes	14.1 $\pm$ 22.8	
Anxiolytics		

Impairment		
	Mean $\pm$ SD	p-value
No	11.0 $\pm$ 18.6	0.92
Yes	11.5 $\pm$ 25.7	
Response at week 12		
No	12.8 $\pm$ 20.4	0.07
Yes	9.0 $\pm$ 16.8	

Note:

¹ PTSD: Post-traumatic stress disorder.

² ADHD: Attention-deficit hyperactivity disorder.

Table 3
Demographic and Clinical Variables at Baseline By Change in Drug Use Screening Instrument (DUSI) Scores from Baseline to 12-Week Outcomes

	Low & remained Low	Low & worsened	P
No. of Subjects	181	19	
Demographic Characteristics			
Age	15.7 ± 1.6	15.6 ± 1.4	0.82
Sex (% Female)	121 (66.9)	15 (78.9)	0.28
Race/Ethnicity (% White)	150 (82.9)	17 (89.5)	0.74
Education (% ≥ College Graduate)	85 (49.4)	10 (52.6)	0.81
Clinical Characteristics			
Children's Depression Rating Scale	57.9 ± 10.7	62.3 ± 11.9	0.09
Children's Global Assessment Scale	51.2 ± 7.2	49.3 ± 7.9	0.28
Clinical Global Impressions Severity	4.4 ± 0.7	4.4 ± 0.6	0.99
Beck Depression Inventory	19.2 ± 12.3	23.1 ± 15	0.21
Beck Hopelessness Scale	9.9 ± 5.8	11.2 ± 5.4	0.36
Comorbidity			
Anxiety (Including PTSD ¹)	66 (37.5)	6 (31.6)	0.80
Post Traumatic Stress Disorder	11 (6.1)	2 (10.5)	0.36
ADHD ²	32 (17.7)	3 (16.7)	1.00
Oppositional/Conduct	12 (6.7)	2 (10.5)	0.63
Dysthymia	50 (28.1)	3 (15.8)	0.41
First Episode	43 (24.4)	7 (36.8)	0.27
Duration Current MDD ³ Episode	23.0 ± 19.4	27.3 ± 29.7	0.39
Age Onset Current MDD Episode	14.8 ± 2.3	14.4 ± 3.6	0.46
History of Physical Abuse	17 (9.6)	4 (21.1)	0.13
History of Sexual Abuse	22 (12.4)	1 (5.3)	0.70
Borderline Features			
History of Suicide Attempts	25 (14.0)	0 (0.0)	0.14
History of Self-injurious Behavior	56 (31.5)	6 (33.3)	1.00
History of Impulsive Aggression	24 (13.5)	4 (22.2)	0.30
History of Maltreatment	22 (12.4)	4 (22.2)	0.27
Suicidality			
History of Suicide Attempts	35 (19.4)	3 (15.8)	1.00
SIQ ⁴	39.4 ± 21.7	54.5 ± 26.4	0.005
Any History of Suicidality	131 (73.2)	15 (78.9)	0.78
Parental Psychopathology			
Beck Depression Inventory	9.5 ± 9.2	8.5 ± 7.4	0.66
Beck Anxiety Inventory	8.4 ± 9.0	8.5 ± 5.4	0.98
Family Environment			
Conflict Behavior (Adolescent)	8.1 ± 6.0	9.9 ± 6.3	0.26
Conflict Behavior (Parent)	9.2 ± 5.8	8.9 ± 5.8	0.84

	Low & remained Low	Low & worsened	P
Med Assignment			
SSRI ⁵	89 (49.2)	9 (47.4)	0.36
Venlafaxine	92 (50.8)	10 (52.6)	
CBT⁶ Assignment	85 (47.0)	11 (57.9)	
Response	101 (55.8)	7 (36.8)	0.12

Note:

¹ PTSD: Post-traumatic stress disorder.

² ADHD: Attention-deficit hyperactivity disorder.

³ MDD: Major depressive disorder.

⁴ SIQ: Suicide ideation questionnaire.

⁵ SSRI: Selective serotonin reuptake inhibitors.

⁶ CBT: Cognitive behavioral therapy.

Table 4
Demographic and Clinical Variables at Baseline By Change in Drug Use Screening Instrument (DUSI) Scores from Baseline to 12-Week Outcomes

	High but improved	High & remained high	P
No. of Subjects	25	49	
Demographic Characteristics			
Age	16.5 ± 1.5	16.1 ± 1.4	0.80
Sex (% Female)	17 (68.0)	35 (71.4)	0.79
Race/Ethnicity (% White)	16 (64.0)	42 (85.7)	0.03
Education (% ≥ College Graduate)	15 (68.2)	21 (44.7)	0.07
Clinical Characteristics			
Children's Depression Rating Scale	59.5 ± 7.1	58.8 ± 9.4	0.74
Children's Global Assessment Scale	50.7 ± 8.6	50.9 ± 8.0	0.94
Clinical Global Impressions Severity	4.6 ± 0.7	4.5 ± 0.6	0.42
Beck Depression Inventory	21.4 ± 8.8	21.9 ± 11.3	0.83
Beck Hopelessness Scale	12.1 ± 4.3	11.8 ± 5.2	0.84
Comorbidity			
Anxiety (Including PTSD ¹)	8 (33.3)	14 (28.6)	0.68
Post Traumatic Stress Disorder	1 (4.0)	3 (6.1)	1.00
ADHD ²	5 (20.0)	5 (10.2)	0.29
Oppositional/Conduct	3 (12.0)	8 (16.3)	0.74
Dysthymia	8 (32.0)	15 (30.6)	0.90
First Episode	8 (33.3)	11 (22.9)	0.40
Duration Current MDD ³ Episode	14.6 ± 13.3	21.5 ± 15.6	0.07
Age Onset Current MDD Episode	16.6 ± 2.2	15.6 ± 2.0	0.05
History of Physical Abuse	3 (12.0)	8 (16.7)	0.74
History of Sexual Abuse	6 (24.0)	11 (22.9)	0.92
Borderline Features			
History of Suicide Attempts	7 (28.0)	10 (20.4)	0.46
History of Self-injurious Behavior	9 (36.0)	27 (55.1)	0.12
History of Impulsive Aggression	5 (20.0)	11 (22.4)	0.81
History of Maltreatment	5 (20.0)	13 (26.5)	0.54
Suicidality			
History of Suicide Attempts	8 (32.0)	13 (26.5)	0.62
SIQ ⁴	40.0 ± 19.3	41.3 ± 21.8	
Any History of Suicidality	22 (88.0)	42 (87.5)	1.00
Parental Psychopathology			
Beck Depression Inventory	6.5 ± 5.3	10.5 ± 11.1	0.04
Beck Anxiety Inventory	7.4 ± 6.2	10.2 ± 10	0.23
Family Environment			
Conflict Behavior (Adolescent)	9.6 ± 6.6	9.7 ± 5.9	0.99
Conflict Behavior (Parent)	9.0 ± 6.1	10.1 ± 5.9	0.50

	High but improved	High & remained high	P
Med Assignment			
SSRI ⁵	13 (52.0)	24 (49.0)	0.81
Venlafaxine	12 (48.0)	25 (51.0)	
CBT⁶ Assignment	14 (56.0)	24 (49.0)	0.57
Response	17 (68.0)	18 (36.7)	0.01

Note:

¹ PTSD: Post-traumatic stress disorder.

² ADHD: Attention-deficit hyperactivity disorder.

³ MDD: Major depressive disorder.

⁴ SIQ: Suicide ideation questionnaire.

⁵ SSRI: Selective serotonin reuptake inhibitors.

⁶ CBT: Cognitive behavioral therapy.