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Major Depression and Treatment Response in Adolescents with ADHD and Substance Use Disorder

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Abstract

Background—Major depressive disorder (MDD) frequently co-occurs in adolescents with substance use disorders (SUD) and attention deficit hyperactivity disorder (ADHD), but the impact of MDD on substance treatment and ADHD outcomes and implications for clinical practice are unclear.

Methods—Adolescents (n=303; ages 13-18) meeting DSM-IV criteria for ADHD and SUD were randomized to Osmotic Release Methylphenidate (OROS-MPH) or placebo and 16 weeks of cognitive behavioral therapy (CBT). Adolescents with (n=38) and without (n=265) MDD were compared on baseline demographic and clinical characteristics as well as non-nicotine substance use and ADHD treatment outcomes.

Results—Adolescents with MDD reported more non-nicotine substance use days at baseline and continued using more throughout treatment compared to those without MDD ($p<0.0001$ based on Timeline Followback; $p<0.001$ based on urine drug screens). There was no difference between adolescents with and without MDD in retention or CBT sessions attended. ADHD symptom severity (based on DSM-IV ADHD Rating Scale) followed a slightly different course of

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improvement although with no difference between groups in baseline or 16-week symptom severity or 16 week symptom reduction. There was no difference in days of substance use or ADHD symptom outcomes over time in adolescents with MDD or those without MDD treated with OROS-MPH or placebo. Depressed adolescents were more often female, older, and not court ordered.

Conclusions—These preliminary findings suggest that compared to non-depressed adolescents with ADHD and SUD, those with co-occurring MDD have more severe substance use at baseline and throughout treatment. Such youth may require interventions targeting depression.

Keywords

Major depressive disorder; substance use disorder; attention deficit hyperactivity disorder; adolescents; comorbid disorder; treatment outcomes

1.0 Introduction

Identifying efficacious treatments is a substantial concern in the treatment of adolescents with substance use disorders (SUD). The majority of adolescents with SUD have co-occurring psychiatric disorders (Rowe et al., 2004; Riggs et al., 2007). Psychiatric comorbid disorders have been associated with poorer treatment outcomes (Buckstein and Horner, 2010; Magura et al., 2008; Baker et al., 2007) although not consistently (Crowley et al., 1998; Rivers et al., 2001) and little is known about the impact of specific comorbid disorders on treatment outcomes. If SUD treatment outcomes differ based on the presence of specific co-occurring psychiatric disorders, comprehensive strategies can be developed to target SUD in the context of these disorders in order to maximize treatment outcomes.

Both externalizing disorders (e.g., attention deficit hyperactivity disorder [ADHD], conduct disorder) and internalizing disorders (e.g., major depressive disorder [MDD], anxiety) commonly co-exist in adolescents with SUD (Shane et al., 2003; Rowe et al., 2001). In pooled data from 4930 adolescents in multisite studies of SUD, 72-74% had conduct disorders, 61-64% had ADHD, 53% had depression, and 61% had both internalizing and externalizing disorders (Chan et al., 2008).

Depression has been associated with increased substance use severity. Adolescents with MDD or dysthymia and SUD had more substance dependence diagnoses (Riggs et al., 1995), and MDD severity was associated with more symptoms of substance dependence (Whitmore et al., 1997). In a community sample of high school students, increased lifetime occurrence of MDD or dysthymia was associated with increased lifetime alcohol use disorders (Rohde et al., 1996).

Findings have been mixed about the relationship between depressive symptoms and substance treatment outcomes in studies that do not include specific treatment for depression. Number of MDD symptoms at substance treatment initiation was not related to drug use at 2-year follow-up in delinquent adolescents with SUD (Crowley et al., 1998), although symptoms of depression at intake were associated with lack of improvement in drug use in adolescents in another study (Dobkin et al., 1998). Only two of the studies reporting associations between depression and substance use severity or treatment outcome, however, have used diagnostically driven measures of MDD such as the Diagnostic Interview Schedule for Children (Costello et al., 1982; Fisher et al., 1991) and reported outcomes specific to MDD (Whitmore et al., 1997; Crowley et al., 1998).

There are a few randomized controlled trials (RCTs) of MDD pharmacotherapy in adolescents with SUD. An RCT of fluoxetine versus placebo (n=126) in adolescents with

MDD and SUD receiving concurrent CBT for SUD showed greater reduction in symptoms of depression on one of two measures with fluoxetine. Although days of past month substance use decreased in both groups there was no difference between groups (Riggs et al., 2007). Another RCT of fluoxetine versus placebo (n=50) in adolescents with MDD receiving concurrent Motivation Enhancement Therapy (MET)/CBT for alcohol use disorder (AUD) showed reductions in depression and alcohol use but no difference between groups on either outcome (Cornelius et al., 2009). Similarly, in an RCT of fluoxetine versus placebo in adolescents and young adults (n=70) with MDD and cannabis use disorder (CUD), receiving MET and CBT for depression and CUD, reductions in depression did not differ between groups and amount of cannabis use did not improve significantly in either group (Cornelius et al., 2010). However, in these trials, CBT even when targeted to SUD, may have also contributed antidepressant effects and minimized SUD outcome differences between medication and placebo groups (Riggs et al., 2007; Nunes and Levin, 2004). Furthermore, none of these trials were adequately powered to detect the effect of treating depression on substance use outcomes. It therefore remains unclear whether pharmacological or other treatments targeted to co-occurring MDD impact SUD outcomes. However, adolescents whose depression remitted did have a significant reduction in drug use compared with those whose depression did not remit, regardless of whether taking fluoxetine or placebo (Riggs et al., 2007), which is consistent with findings in adults (Brown et al., 1997).

A recent RCT of psychostimulant medication (osmotic release methylphenidate, OROS-MPH) was conducted in adolescents (n=303) with ADHD concurrently receiving CBT for co-occurring SUD. There were reductions in adolescent-reported ADHD symptoms and substance use in both medication and placebo groups with no differences between groups, although participants treated with OROS-MPH had fewer parent-rated ADHD symptoms and more negative urine drug screens (Riggs et al., 2010). This trial provides a unique opportunity to compare substance treatment outcomes in adolescents who have both an internalizing disorder, MDD, and an externalizing disorder, ADHD. This report asks the following exploratory questions:

1. Is co-occurring MDD associated with any demographic or clinical characteristics at substance treatment entry?
2. Is co-occurring MDD associated with treatment response (non-nicotine substance use, ADHD symptoms)?
3. Is co-occurring MDD associated with adherence to substance use treatment visits or retention?

2.0 Methods

Data from the 16-week RCT of OROS-MPH or placebo in combination with weekly individual CBT targeting SUD were used to compare adolescents with MDD (n=38) and without MDD (n=265). The trial was conducted at 11 community treatment sites affiliated with the NIDA Clinical Trials Network.

2.1 Participants

Participants were 303 adolescents (ages 13-18) meeting DSM-IV criteria for ADHD and at least one non-nicotine SUD. Diagnoses of MDD, ADHD, and conduct disorder were determined by clinician-administered, semi-structured diagnostic interview (Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children-Epidemiological Version, 4th Edition (K-SADS-E) (Orvaschel and Puig-Antich, 1987; Geller et al., 2000). Scores of ≥ 22 on the DSM-IV ADHD Rating Scale (ADHD-RS;

DuPaul et al., 1998) were required for inclusion. Substance abuse and dependence diagnoses were determined from the Composite International Diagnostic Interview (CIDI) (Cottler et al., 1989; Robins, 1988; Crowley et al., 2001). Adolescents with a history of tic disorder, pregnancy, current or lifetime psychotic or bipolar disorder, serious medical illness, significant suicidal risk, or taking psychotropic medications were excluded from participation as were adolescents with abuse, dependence or past month use of methamphetamine, or current or past year opioid dependence.

Participants were recruited from existing outpatient substance treatment referral sources and community-outreach (e.g., media advertising, schools, primary care providers). The study was approved and overseen by the institutional review boards of the community treatment sites and academic centers affiliated with each site. Participants provided assent and their parent or guardian provided written consent if a non-emancipated minor. Participants 18 years or older provided written informed consent.

2.2 Measures

Substance use measures—The primary outcome measure for substance use was number of days of non-nicotine substance use, including drugs and alcohol, collected for the past 28 days at baseline and weekly throughout the 16-week trial using standardized Timeline Followback (TLFB) procedures (Sobell and Sobell, 1992; Miller and Del Boca, 1994). Urine drug screens were also collected at screening/baseline and weekly throughout the trial using a rapid system screening for amphetamine, barbiturates, benzodiazepines, cocaine, methamphetamine, opiates and THC. Results were analyzed based on the number of urine drug screens negative for drugs of abuse. This approach avoids imputation of "positive" urine toxicologies if an expected sample is missing (Ling et al., 1997).

ADHD measure—The primary outcome measure for ADHD was the DSM-IV ADHD-RS symptom checklist (DuPaul et al., 1998) administered by medical clinicians with the adolescent at baseline for the prior 28 days and weekly throughout the study. The scale is medication sensitive and correlated with ADHD in children and adolescents (Bostic et al., 2000; Prince et al., 2000).

2.3 Procedures

Participants were randomized to either OROS-MPH or matching placebo. Participants were titrated to a 72 mg daily dose or the highest dose tolerated. All participants received 16 weeks of individual, evidence-based CBT (Kadden et al., 1995; Monti et al., 1989; Waldron et al., 2001) as a manual-standardized outpatient substance treatment.

2.4 Data Analysis

Baseline demographic and clinical characteristics were compared in adolescents with and without MDD using t-tests for continuous variables and chi-square tests (or Fisher's exact test) for categorical variables.

Data plots were developed based on raw data, and longitudinal data analyses of the prospectively collected data were conducted using all data points to evaluate trajectories of change in non-nicotine substance use and ADHD symptoms. For the longitudinal analyses and data plots, past 28-day measures of non-nicotine substance use were converted to past 7-day use (by dividing by 4) to be consistent with the weekly time frame for administration of the ADHD-RS and collection of urine drug screens. All longitudinal analyses were adjusted for baseline differences between the groups in age, gender, and court-ordered status. Population-average linear mixed models with an AR(1) correlation structure, and MDD status, time (linear and potentially higher order terms), and MDD by time interaction(s) as

predictors were fitted. If the group by time interaction was not significant, it was deleted for the longitudinal model.

To further assess whether there was any interaction between treatment group (OROS-MPH or placebo) and the presence or absence of MDD, analyses were conducted to compare trajectories of substance use and ADHD symptoms over time between those receiving OROS-MPH and those receiving placebo within the MDD group (n=19 receiving OROS-MPH; n=19 receiving placebo) and within the group without MDD (n=133 receiving OROS-MPH; n=132 receiving placebo) in addition to exploring an interaction model involving treatment group, presence or absence of MDD, and time.

Study retention, CBT visit adherence, abstinence, and negative urine drug screens were compared in adolescents with and without MDD using t-tests and chi-square tests.

3.0 Results

3.1 Baseline characteristics in adolescents with and without MDD

Baseline demographic and clinical characteristics of adolescents with and without MDD are presented in Table 1. Adolescents with MDD were older (17.0 vs. 16.4 years old; p=0.01), more often female (42% vs. 18%; p=0.0007), less likely to be court mandated to substance treatment (11% vs. 26%; p=0.04), and had more days of past month non-nicotine substance use (18.8 vs. 14.1 days; p=0.005). There were no differences between the groups in ADHD symptom severity (ADHD-RS scores), presence of current conduct disorder, total number of substance abuse or dependence diagnoses, or any specific substance abuse or dependence diagnosis at baseline. Groups were balanced with regard to random assignment of participants with and without MDD to OROS-MPH or placebo.

3.2 Substance use and ADHD symptoms in adolescents with and without MDD

Figures 1 and 2 show the longitudinal raw data plots for adolescents with and without MDD for days of non-nicotine substance use and ADHD symptom severity over the 16-week trial. Raw data plots are shown because the use of multiple covariates in the longitudinal models makes clear visual presentation of these models difficult.

The trajectory for each of these outcomes followed a cubic model in time (weeks). In the longitudinal model, controlling for covariates, (estimated) mean days of non-nicotine substance use in the prior 7 days began 1.18 days higher at baseline in the adolescents with MDD (t_{298}=4.64, p ⟨0.0001) and this difference persisted throughout treatment with a mean reduction of 1.53 days of use per week by week 16 (95% CI=1.12 - 1.94). In the longitudinal model, controlling for covariates, there were no significant differences in ADHD symptom severity at baseline between the groups (mean 1.03 point higher for those with MDD; t_{300}=0.53, p=0.59). ADHD symptom severity did follow a slightly but significantly different course of improvement in the two groups (MDD by week effect, p=0.007; MDD by week^2 effect; p =0.02; MDD by week^3 effect; p= 0.048). Adolescents with MDD had a 19.91 point reduction (95% CI=14.36 -25.46) and those without MDD had a 22.03 point reduction in symptom severity by week 16 (95% CI=20.00 - 24.05), which did not differ significantly between groups (t_{3212}=0.70, p=0.48). There was no significant difference in ADHD symptom severity between groups at week 16 (mean 3.15 point higher for those with MDD; t_{3212}=1.29, p=0.20).

In interaction models, including medication treatment, there was no main or interaction effect of OROS-MPH for either days of non-nicotine substance use or ADHD symptom severity outcomes. In a subgroup longitudinal model for non-nicotine substance use in adolescents without MDD the group receiving OROS-MPH had 0.36 fewer days of

substance use at baseline (t_{261}=-2.14, p=0.03) but there was no significant interaction of OROS-MPH with time. However, in adolescents with MDD a significant time interaction with OROS-MPH was found for ADHD symptom severity, and cubic curves for OROS-MPH and placebo were compared. There were no significant differences in ADHD symptom severity at baseline between treatment groups (mean 3.68 point lower for OROS-MPH, t_{36}=-1.04, p=0.31). The OROS-MPH group had a 19.38 point reduction (95% CI=11.95 - 26.81) and the placebo group had a 20.29 point reduction in symptom severity by week 16 (95% CI=13.24 - 27.34), which did not differ significantly between treatment groups (t_{386}=0.17, p=0.86). There were also no significant differences in ADHD symptom severity between treatment groups at week 16 (mean 2.77 point lower for OROS-MPH; t_{386} =-0.63, p=0.53).

3.3 Retention and adherence in adolescents with and without MDD

There was no difference between those with and without MDD in study completion (71.1% vs. 75.5%, respectively, p=0.56) or CBT visit adherence (67.3 vs. 70.3 percent of sessions attended, respectively; p=0.52). However, adolescents with MDD had significantly fewer days of abstinence (47.1 vs. 67.3 days; p=0.001), a lower percent of days abstinent (47.2 vs. 68.8 percent of days; p< 0.0001) as well as fewer negative urine drug screens (1.6 vs. 3.6; p= 0.0007) (Table 2).

4.0 Discussion

In adolescents with ADHD and SUD, those with co-occurring MDD used drugs and/or alcohol on significantly more days prior to treatment entry, as well as throughout and at the end of treatment compared to those without MDD. Depressed adolescents also had fewer days of abstinence and fewer negative urine drug screens during treatment despite having similar rates of treatment completion and adherence and comparable reduction in ADHD symptom severity compared to non-depressed adolescents. There was no difference, however, in reduction in days of non-nicotine substance use in those with or without MDD during treatment for SUD.

These findings are consistent with most previous studies that reported depression was associated with more severe substance use problems in clinical and community samples (Rohde et al., 1996; Whitmore et al., 1997; Riggs et al., 1995). Our finding that adolescents who had co-occurring MDD but no reported therapy targeted to MDD had poorer SUD outcomes is consistent with findings in adolescents by Dobkin et al. (1998) but not Crowley et al. (1998). However, most prior studies have not reported the association between MDD and SUD treatment outcomes in well-characterized samples of adolescents with MDD such as this one.

The presence of MDD was not associated with ADHD treatment response in this sample. Adolescents with and without MDD began the trial with no difference in severity of ADHD symptoms. Although those without MDD had a larger decrease in symptom severity during the initial weeks, this difference between groups leveled out and does not appear to be clinically meaningful since there was no difference between the groups in symptom improvement or final symptom severity at the end of the trial. Similar to our finding that the presence of MDD was not meaningfully related to ADHD outcomes, the presence of symptoms of depression or anxiety did not appear to impede response to atomoxetine for ADHD in children and adolescents treated with atomoxetine alone or in combination with fluoxetine (Kratochvil at al., 2005).

Given the similarity in both ADHD symptom severity at treatment initiation and ADHD outcomes in both groups, it is also unlikely that ADHD symptoms or treatment response

were responsible for the differences in non-nicotine substance use outcomes in those with and without MDD. ADHD was similarly unrelated to SUD outcomes in the controlled trial of fluoxetine for MDD in adolescents also receiving CBT for SUD where adolescents with or without ADHD had similar substance treatment as well as depression outcomes (Riggs et al., 2009).

Depressed adolescents in this sample tended to be older, female, and fewer were court-mandated to substance treatment compared to those without MDD. Depression and mood disorders have been reported as more likely in substance using adolescent females than males (Grella et al., 2001; Buckstein et al., 1992; Deykin et al., 1992).

Co-occurring MDD did not appear to impact CBT treatment adherence or study completion. Some prior studies similarly found no association between comorbid disorders and treatment attendance (Rivers et al., 2001; Rowe et al., 2004), although an association between internalizing symptoms and better treatment completion was found in an earlier study (Kaminer et al., 1992). Since attendance at CBT visits and retention rates in the study did not differ in adolescents with and without MDD, adherence to the psychosocial intervention or retention also cannot account for the difference between non-nicotine substance use in the adolescents with and without MDD.

The current treatment literature does not provide a clear answer to whether providing targeted treatments for both MDD and SUD will improve SUD outcomes in adolescents (Riggs et al, 2007; Cornelius et al., 2009; Cornelius et al., 2010; Deas et al., 2000). However, given the finding from this study that MDD is associated with greater severity of SUD and continued higher use throughout and at the end of SUD treatment and preliminary evidence that depression remission is associated with improved SUD outcomes (Riggs et al., 2007), targeting both for treatment may be helpful. Studies in adults with MDD and SUD suggest that treating both may improve outcomes (Rao and Chen, 2008). Receiving psychiatric services in addition to SUD treatment was associated with improved outcome (Ray et al., 2005), and manualized behavioral therapies including CBT have been shown to decrease substance or alcohol use and/or depressive symptoms in adults (Carroll, 2004; Maude-Griffin et al., 1998; Brown et al., 1997).

There may be alternate factors impacting SUD outcomes for adolescents with MDD, SUD, and ADHD, such as the severity of the disorders, additional burden of other disorders, psychosocial functioning, or quality of life. For example, number of days of heavy alcohol use was associated with lack of remission of depression in adolescents (Cornelius et al., 2009). However, the association between SUD or MDD severity and outcomes was not evaluated in this sample.

Finally, we also evaluated whether the use of OROS-MPH or placebo might be associated with different outcomes in the adolescents with MDD or the adolescents without MDD. There was no difference in either days of non-nicotine substance use or ADHD symptom severity outcomes over time in either group when OROS-MPH and placebo were compared, consistent with the primary outcomes for the entire sample in the main study (Riggs et al., 2010). While there is some evidence for the efficacy of psychostimulants in reducing symptoms of depression (Candy et al., 2008), the finding that substance use outcomes do not differ with its use in the adolescents with MDD is consistent with the prior studies that found psychopharmacology for depression was not associated with improvement in substance use, at least in the presence of CBT (Riggs et al., 2007, Cornelius et al., 2009, Cornelius et al., 2010). Other possible benefits of treating ADHD with OROS-MPH, given the poor treatment completion and adherence and worse outcomes reported in adolescents

with ADHD and SUD (Grella et al., 2001, Rowe et al., 2004, Wise et al., 2001) were also not apparent.

Since pharmacological and psychosocial treatments specifically targeted to MDD were not allowed in this study, we could not evaluate the impact of combining treatments for MDD and SUD, although the effects of such combined treatment may have been masked by possible antidepressant effects of the SUD-focused CBT here as well. Since there was also no measure of depression symptom change during the trial, it is also not clear whether a difference in depression response or remission, even absent treatment targeted to depression, would have helped close the gap in drug use outcomes between those with and without MDD, as findings from a prior study suggest (Riggs et al., 2007). The age of onset and timing of onset of MDD in relation to the SUD and measures of other concurrent psychiatric disorders were not available. Finally, with 38 patients with MDD, options for questions and analyses were limited. For example, a subgroup analysis for adolescents with MDD or estimating the group by time interaction would have been more reliable with a larger sample. Further validation is needed to provide support for the generalizability of these findings.

Outcomes with SUD treatments in adolescents remain modest, and co-occurring conditions are the rule rather than the exception. Preliminary results from this study, which includes thorough diagnostic assessment of MDD with the K-SADS-E, extend previous research by suggesting that the presence of co-occurring MDD in the context of ADHD and SUD is associated with greater severity of SUD and continued higher use in the absence of treatment specifically targeted to MDD. It is also associated with specific clinical characteristics (older age, female gender, fewer court referrals). Adequately powered trials evaluating treatments focused on MDD in the context of SUD and other frequently present, co-occurring psychiatric disorders are needed. In the interim, mechanisms for assessing and treating these disorders are essential in SUD treatment settings since their presence appears to interfere with maximizing SUD outcomes.

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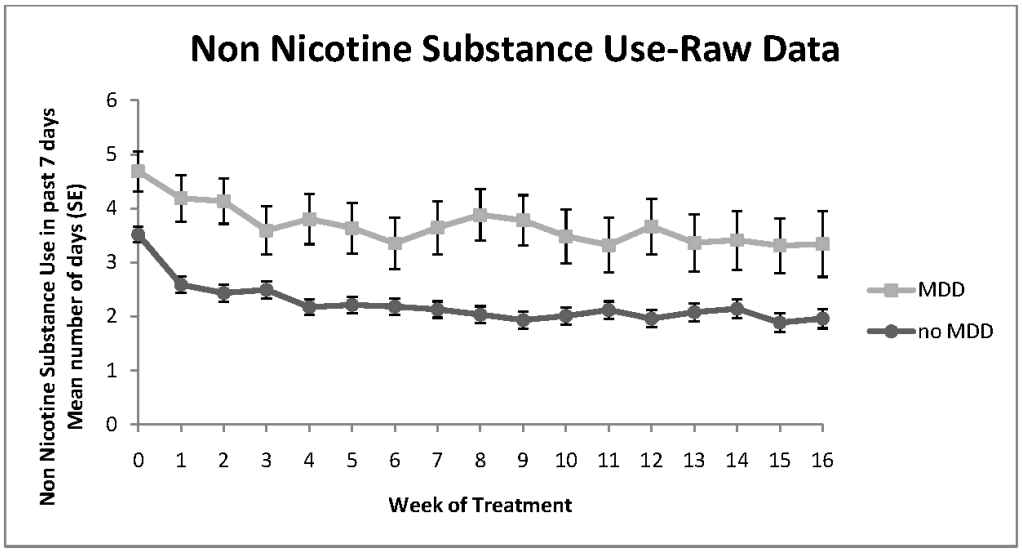
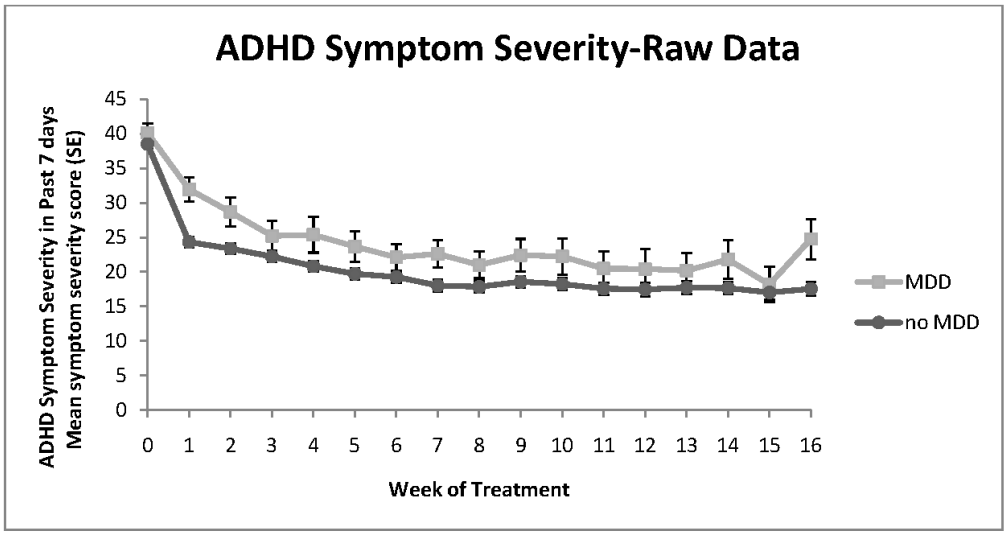


Based on the Timeline Followback. SE –Standard Error. MDD-Major Depressive Disorder.

Figure 1.
Non Nicotine Substance Use



Based on the Attention Deficit Hyperactivity Disorder Rating Scale. SE—Standard Error. MDD—Major Depressive Disorder

Figure 2.
ADHD Symptom Severity

Table 1

Baseline Demographic and Clinical Characteristics Associated with Major Depressive Disorder

Demographic	Major Depressive Disorder Present N=38	Major Depressive Disorder Absent N=265	p
	%	%	
Randomized to OROS –MPH	50.0	49.8	0.98
Female Sex	42.1	18.1	**0.0007**
Race[1]			0.23
Caucasian	69.4	60.7	
African-American	5.0	22.9	
Native American/Asian/Pacific Islander/Mixed Race/Other	5.6	16.4	
Hispanic Ethnicity	7.9	16.2	0.18
Abuse & Dependence Diagnoses			
Alcohol	55.3	56.2	0.91
Cannabis	92.1	92.1	0.99[5]
Cocaine	13.2	9.4	0.56[5]
Amphetamine	7.9	3.8	0.21[5]
Hallucinogen	10.5	12.8	0.99[5]
PCP	0.0	0.8	0.99[5]
Inhalant	2.6	1.9	0.56[5]
Opiate	21.1	11.3	0.11[5]
Sedative	10.5	9.8	0.78[5]
Other	0.0	1.1	0.99[5]
Conduct Disorder (current)	36.8	31.7	0.53
Court Mandated	10.5	26.0	**0.04**
	Mean(SD)	**Mean(SD)**	
Age (years)	17.0 (1.3)	16.4 (1.3)	**0.01**
ADHD symptom severity[2]	40.2 (8.1)	38.5 (9.0)	0.29
Number of days non-nicotine substance use-past 28 days[3]	18.8 (8.8)	14.1 (9.4)	**0.005**
Number of days non-nicotine substance use-past 7 days[3,4]	4.7 (2.2)	3.5 (2.4)	**0.005**
Number of days nicotine use-past 28 days[3]	19.4 (11.8)	15.8 (12.5)	0.10
Number of days nicotine use-past 7 days[3,4]	4.8 (2.9)	4.0 (3.1)	0.10
Number of non-nicotine abuse/dependence diagnoses	2.1 (1.2)	2.0 (1.3)	0.52

[1] Race was not available for 5 subjects (2 for MDD, 3 for no MDD).

[2] Based on the Attention Deficit Hyperactivity Disorder Rating Scale.

[3] Based on the Timeline Followback.

[4] Past 7-day use calculated by dividing 28 day measure by 4. T-tests for continuous variables and chi-square tests for categorical variables were used, except

[5] Fisher's exact test. P-values < 0.05 were bolded.

Table 2

Substance Use, Visit Adherence, and Retention Outcomes Associated with Major Depressive Disorder

Variable	Major Depressive Disorder		p
	Present N=38	**Absent N=265**	
	%	**%**	
Study completion-16 week[1]	71.1	75.5	**0.56**
	Mean(SD)	**Mean(SD)**	
Number of days abstinent during trial[2, 3]	47.1 (37.5)	67.3 (34.4)	**0.001**
Percent of days abstinent during trial[2,3]	47.2 (34.3)	68.8 (28.6)	**<.0001**
Percent CBT visit attendance	67.3 (24.7)	70.3 (26.7)	0.52
Number of negative urine drug screens[3]	1.6 (2.8)	3.6 (4.7)	**0.00074**

[1] Attendance at week-16 research visit.

[2] Based on the Timeline Followback.

[3] Timeline Followback and urine drug screens were not available for 6 subjects (1 for MDD, 5 for no MDD). T-tests for continuous variables and chi-square tests for categorical variables were used, except

[4] t-test for unequal variances. P-values < 0.05 were bolded.