Published in final edited form as:

J Am Acad Child Adolesc Psychiatry. 2011 September ; 50(9): 903–914. doi:10.1016/j.jaac.2011.06.010.

Randomized Controlled Trial of Osmotic-Release Methylphenidate with CBT in Adolescents with ADHD and Substance Use Disorders

Paula D. Riggs, MD, Theresa Winhusen, PhD, Robert D. Davies, MD, Jeffrey D. Leimberger, PhD, Susan Mikulich-Gilbertson, PhD, Constance Klein, LCSW, Marilyn Macdonald, BA, Michelle Lohman, RN, Genie L. Bailey, MD, Louise Haynes, MSW, William B. Jaffee, PhD, Candace Hodgkins, PhD, Elizabeth Whitmore, PhD, Kathlene Trello-Rishel, MD, Leanne Tamm, PhD, Michelle C. Acosta, PhD, Charlotte Royer-Malvestuto, MEd, Geetha Subramaniam, MD, Marc Fishman, MD, Beverly W. Holmes, MSW, Mary Elyse Kaye, BSN, Mark A. Vargo, PhD, George E. Woody, MD, Edward V. Nunes, MD, and David Liu, MD

Drs. Riggs, Davies, Mikulich-Gilbertson, and Whitmore, and Ms. Klein, Ms. Macdonald, and Ms. Lohman are with the University of Colorado Denver. Dr. Winhusen is with the University of Cincinnati. Dr. Leimberger is with the Duke Clinical Research Institute. Dr. Bailey is with Brown University, and Stanley Street Treatment and Resources, Inc. Ms. Haynes is with the Medical University of South Carolina. Dr. Jaffee is with Harvard University. Dr. Hodgkins is with Gateway Community Services. Drs. Trello-Rishel and Tamm are with the University of Texas. Dr. Acosta is with the Center for Technology and Health and National Development and Research Institutes, Inc. Dr. Woody and Ms. Royer-Malvestuto are with the University of Pennsylvania. Drs. Subramaniam and Fishman are with Johns Hopkins University. Dr. Subramaniam is also with the Division of Clinical Neuroscience and Behavioral Research, National Institute on Drug Abuse (NIDA), National Institutes of Health (NIH). Dr. Fishman is also with the Mountain Manor Treatment Center. Ms. Holmes is with the Lexington/Richland Alcohol and Drug Abuse Council. Ms. Kaye is with the University of Pittsburgh. Dr. Vargo is with Operation PAR, Inc. Dr. Nunes is with Columbia University and the New York State Psychiatric Institute. Dr. Liu is with the Center for Clinical Trials Network, NIDA, NIH.

Abstract

Objective—To evaluate the efficacy and safety of osmotic-release methylphenidate (OROS-MPH) compared to placebo for attention deficit hyperactivity disorder (ADHD) and impact on

© 2011 American Academy of Child & Adolescent Psychiatry. Published by Elsevier Inc. All rights reserved.

Correspondence to: Paula D. Riggs University of Colorado Denver Mail Stop F478 12469 E. 17th Place, Room 235 Aurora, CO 80045 (303) 724-2235 (phone) (303) 724-2274 (fax) paula.riggs@ucdenver.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

The contents of this manuscript are solely the responsibility of the authors and do not necessarily represent the official views of the National Institute on Drug Abuse.

Disclosure: Dr. Bailey has received research support from the National Institute of Drug Abuse (NIDA), Titan Pharmaceuticals, Inc., and Alkermes, Inc. Dr. Trello-Rishel has served on the speakers' bureau for Shire. Dr. Woody is a member of the RADARS System post-marketing study external advisory group, which is administered by Denver Health, and supported by pharmaceutical companies. He has served as a consultant for Alkermes. Drs. Riggs, Winhusen, Davies, Leimberger, Mikulich-Gilbertson, Jaffee, Hodgkins, Whitmore, Tamm, Acosta, Royer-Malvestuto, Subramaniam, Fishman, Vargo, Nunes, and Liu, and Ms. Klein, Ms. Macdonald, Ms. Lohman, Ms. Haynes, Ms. Holmes, and Ms. Kaye report no biomedical financial interests or potential conflicts of interest.

Clinical Trial Registration Information -- Attention Deficit Hyperactivity Disorder (ADHD) in Adolescents with Substance Use Disorders (SUD); clinicaltrials.gov; NCT00264797,

substance treatment outcomes in adolescents concurrently receiving cognitive behavioral therapy (CBT) for substance use disorders (SUD).

Method—16-week randomized controlled multi-site trial of OROS-MPH + CBT versus placebo + CBT in 303 adolescents (aged 13-18), meeting DSM-IV diagnostic criteria for ADHD and SUD. Primary outcomes: (1) ADHD- clinician-administered ADHD Rating Scale (ADHD-RS), adolescent informant; (2) Substance- adolescent reported days of use in the past 28 days. Secondary outcome measures included parent ADHD-RS and weekly urine drug screens (UDS).

Results—There were no group differences on reduction in ADHD-RS scores (OROS-MPH: -19.2, 95% confidence interval [CI], -17.1 to -21.2; placebo, -21.2, 95% CI, -19.1 to -23.2) or reduction in days of substance use (OROS-MPH: -5.7 days, 95% CI, 4.0-7.4; placebo: -5.2 days, 95% CI, 3.5-7.0). Some secondary outcomes favored OROS-MPH including lower parent ADHD-RS scores at 8 (mean difference [md]=4.4, 95% CI, 0.8-7.9) and 16 weeks (md=6.9; 95% CI, 2.9-10.9) and more negative UDS in OROS-MPH (mean=3.8) compared to placebo (mean=2.8; $P=0.04$).

Conclusions—OROS-MPH did not show greater efficacy than placebo for ADHD or on reduction in substance use in adolescents concurrently receiving individual CBT for co-occurring SUD. However, OROS-MPH was relatively well tolerated and was associated with modestly greater clinical improvement on some secondary ADHD and substance outcome measures.

Keywords

osmotic-release methylphenidate; randomized controlled trial; ADHD; substance use disorders; adolescents

INTRODUCTION

Individuals with attention deficit hyperactivity disorder (ADHD) have at least twice the lifetime risk for substance use disorders (SUD) compared to non-ADHD controls.¹⁻³ As many as 30-50% of adolescents referred to substance treatment have co-occurring ADHD.^{4,5} Despite high rates of co-occurrence, ADHD often goes untreated in community-based substance treatment programs and is associated with poorer substance treatment outcomes.⁵⁻⁷ Clinicians may be reluctant to prescribe psychostimulants for ADHD in adolescents with SUD due to lack of research on their efficacy and safety in substance abusing youth or concerns about medication abuse and diversion.^{1,3,8}

Only one previous controlled psychostimulant medication (pemoline) trial has been conducted on adolescents with co-occurring ADHD and SUD, showing pemoline to have greater efficacy than placebo for ADHD, but no impact on substance use in the absence of behavioral treatment for SUD.⁹ Additional research is needed to evaluate whether psychostimulant medications are safe and effective for ADHD in adolescents with SUD and improve substance treatment outcomes. The current study addresses the need for additional research addressing whether psychostimulant medication is safe and effective for ADHD in adolescents with SUD and improves substance treatment outcomes. We hypothesized that participants treated with OROS-MPH + CBT would have greater reduction in ADHD symptoms (ADHD-RS scores, adolescent informant) and in days of past-28-day non-tobacco substance use compared to those treated with placebo + CBT.

OROS-MPH was selected as the study medication because once-daily dosing would enhance medication compliance and it is considered to have lower abuse and diversion liability compared to shorter-acting psychostimulant medications.¹⁰ Substance treatment, consisting of weekly individual CBT, was provided to all participants in order to comply with ethical

and human subjects' protection requirements to provide standard of care treatment for SUD and was manual-standardized across 11 participating sites to reduce variability and potential site effects.

METHOD

PARTICIPANTS

Participants were 303 adolescents (ages 13-18 years) recruited from existing referral sources (e.g. juvenile justice, social services agencies), primary care and mental health clinics, schools, and media advertising at 11 community-based substance treatment programs in the National Institute on Drug Abuse (NIDA) Clinical Trials Network (CTN). Institutional Review Boards approved the protocol prior to participant enrollment, which occurred between March 2006 and September 2008. Written informed consent was obtained from all participants (and parent/guardian for minors) before baseline assessment. Criteria for study participation included meeting Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition)¹¹ (DSM-IV) diagnostic criteria for current ADHD and at least one non-tobacco SUD. Exclusion criteria were current or past psychotic disorder, bipolar disorder, suicide risk, opiate dependence, methamphetamine abuse or dependence, cardiac illness or serious medical illness, pregnancy, past month use of psychotropic medications or participation in other substance or mental health treatment.

RANDOMIZATION AND BLINDING

The Alza Corporation prepared OROS-MPH and matching placebo, which was supplied to the CTN contract pharmacy (EMINENT Services Corporation) by McNeil Consumer and Specialty Pharmaceuticals (distributor for *Concerta*). Randomization blocks were stratified by site. Sites were provided blinded medication bottles for each randomized participant.

INTERVENTIONS

Medication—Participants were started on a 18 mg dose of OROS-MPH/matching placebo and titrated to a single fixed morning dose of 72mg (or highest dose tolerated) during the first two study weeks, post-randomization.

Cognitive Behavioral Therapy (CBT)—Participants in both medication groups received manual-standardized, individual CBT using motivational enhancement approaches throughout the 16 week medication trial.¹² The efficacy and feasibility of training and implementation of the manual-driven CBT used in this study has been demonstrated in previous studies and cognitive behavioral principles have been widely adopted and are used in most existing community-based substance treatment programs.^{13,14} Master's level CBT therapists were trained and certified by the study's national trainer (Ms. Klein), who was herself trained and certified as both therapist and trainer by the developer of the manual.^{13,14} All CBT sessions were audio-taped and approximately 5% were selected and independently rated for fidelity and adherence by Ms. Klein. Of 147 sessions rated, 138 (94%) were rated as adherent.

DIAGNOSTIC AND OUTCOME MEASURES

K-SADS-E—The Schedule for Affective Disorders and Schizophrenia for School-Age Children-Epidemiologic Version (K-SADS-E)¹⁵ was administered by study physicians or masters' level clinicians and used to determine current DSM-IV diagnosis of ADHD. Study physicians and masters' level clinicians were trained to administer the K-SADS-E by the PI (Riggs) and Co-Investigator (Davies) at a 3-day national protocol training (face-to-face) meeting prior to protocol implementation. Ongoing clinical supervision related to the

administration of the K-SADS-E were addressed by the PI/lead team on weekly national protocol teleconference calls.

Comprehensive International Diagnostic Interview (CIDI)—The CIDI is a computer-assisted structured diagnostic assessment, administered by research staff, to establish DSM-IV diagnoses of abuse or dependence in 11 drug categories: tobacco, alcohol, cannabis, cocaine, hallucinogens, inhalants, opiates, sedatives, phencyclidine, amphetamines, and club drugs.¹⁶ The reliability and psychometric validity of DSM-IV substance diagnoses generated by the CIDI in adolescents is well-established.¹⁶

ADHD Outcome Measures—Because there is no clear “gold standard” outcome measure for ADHD in adolescents, three senior ADHD clinical researchers (Timothy Wilens, MD, James Swanson, PhD, and Len Adler, MD) consulted to the NIDA CTN and PI/protocol development team on selection of ADHD outcome measures. The clinician-administered DSM-IV ADHD Rating Scale¹⁷ (ADHD-RS; adolescent informant) was selected by consensus as the most valid, reliable, and feasible primary ADHD outcome measure for this study.¹⁷⁻²¹ Medical clinicians were trained to administer the ADHD-RS by completing CD-ROM training (developed by Timothy Wilens, M.D.) and required to pass a post-training proficiency test and complete booster training and proficiency testing approximately every 6 months throughout the trial. The severity of ADHD symptoms was rated by clinicians who administered the ADHD-RS weekly to adolescent informants using specific behavioral examples to illustrate the range of symptom severity for each of 18 ADHD symptoms, anchored to ADHD-RS rating scale (0=never/rarely; 1=sometimes; 2=often; 3=very often).

Secondary ADHD outcome measures: (1) ADHD-RS (parent informant) was administered by medical clinicians to parents at study weeks 8 and 16; (2) Clinical Global Impression-Improvement (CGI-I) was assessed monthly by medical clinicians who were blind to participants’ medication status, but who may have administered ADHD, substance, and adverse effects assessment measures. Medical clinicians were trained in the administration of the CGI-I by the PI/lead investigative team. ADHD treatment response was defined a priori as a final CGI-I score of 1 (very much improved) or 2 (much improved) with respect to the participant’s baseline ADHD severity (with scores >2 considered CGI-I non-responders); (3) Adolescent Relapse Coping Questionnaire (ARCO)²² contained two items which asked participants about change in their “problem-solving ability” and acquisition of “focused coping skills” for managing temptations to use drugs/alcohol at treatment completion. These questions were selected to assess differences between OROS-MPH and placebo treatment groups in participants’ acquisition of skills specifically targeted in CBT/substance treatment; (4) Massachusetts General Hospital (MGH) Liking Scale: one question taken from the MGH Liking Scale - “Do you think the medication has been effective in treating your ADD/ADHD symptoms?” - was administered at week 16 week as a secondary ADHD outcome measure.

Substance Outcome Measures—The primary substance outcome measure is the number of days of past-28-day non-tobacco drug/alcohol use, assessed using standardized timeline follow-back (TLFB) procedures.²³ The validity of adolescent self-reported drug use has been established in a number of previous studies, when confidentiality is assured as it was in the current trial.²⁴ The mean number of negative urine drug screens (UDS) was a secondary substance outcome measure. Using negative, as opposed to positive, UDS avoids the problem of imputing a positive UDS result for any missed weekly sample collections.²⁵

Safety and Treatment Compliance Measures—Safety measures included a baseline physical examination, electrocardiogram, and a detailed medical and cardiovascular history.

Laboratory assessments ascertained at baseline and 16 weeks included liver function tests, complete blood count with differential, and urinalysis. Pregnancy tests were performed at baseline and monthly in female subjects. Adverse events (AEs) and serious adverse events (SAEs) were systematically assessed by medical clinicians during weekly research visits. Medication compliance was assessed by pill counts in conjunction with weekly review of subjects' medication diaries and self-reported medication compliance. Discrepancies between pill counts (expected number of returned pills) and adolescents' self-reported medication compliance diaries were resolved using the most conservative estimate of medication compliance (e.g. assuming lost or unreturned pills/bottles not taken). The MGH Diversion Questionnaire, developed by Wilens and colleagues, is a self-administered assessment of the medication misuse/diversion (e.g., selling the medication, taking more than prescribed, etc.) was completed monthly.

STATISTICAL METHODS

Statistical Power and Sample Size—The number of participants targeted for randomization nationally, across all participating sites, was 300 participants (150 per treatment arm). The effect size of OROS-MPH for ADHD has consistently been shown to be 0.8 or greater in non-substance abusing youth. Thus, a sample size of 300 participants was assumed to have >0.8 power to detect a difference in ADHD-RS scores between OROS-MPH and placebo (primary aim). Since the impact of psychostimulant treatment for ADHD (compared to placebo) on substance treatment outcomes is not known, the study was powered to detect an effect size of 0.4 (low to medium effect size) or greater on days of past 28 day non-tobacco substance use at treatment termination. Power was calculated using a procedure and computer program described in Hedecker, Gibbons & Waternaux²⁶ and assuming as much as 10% attrition per month.

Primary analyses were intent-to-treat (ITT), including all randomized study participants, and were conducted using SAS statistical software. The primary outcome variables for ADHD and SUD used likelihood based methods (i.e. mixed [random coefficient] models within SAS Proc Mixed version 8.2).²⁷ Since past 28-day drug use differed moderately from normality, results were confirmed with more general methods not assuming normality within SAS Proc GLIMMIX.²⁸

Each outcome was assessed with the same mixed model design, including a fixed treatment group effect, a fixed time effect, and a treatment by time interaction, estimating the average group specific intercepts, rates of change over time, and group specific differences in those rates, respectively. Linear, quadratic, and cubic relationships with time in the fixed and random effects were evaluated and non-significant higher order terms dropped to determine the best modeling of time. Fixed site effects were also examined (as a main effect and interaction with time and treatment) and dropped if not significant to simplify model interpretation. Specified random effects that allowed the intercept and curve (e.g. slope) of the lines to vary by subject and serially-correlated residual errors (i.e. spatial power approach) were considered in determining model fit with likelihood-based procedures.²⁹ For ADHD, "time" consisted of baseline and weekly assessments measured as days from randomization. For SUD, time and corresponding past 28-day use was calculated "backwards" for each subject from his/her final observation in increments of 28 days because of varied study end times due to the trial design and visit windows. This method was advantageous in standardizing final 28-day assessment periods. Results from these analyses were similar to results computing past 28-day substance use "forwards" from baseline.

Treatment responses (defined as a CGI-I score of 1 or 2) over time (weeks 4, 8, 12, and 16) between groups were compared using a general linear mixed model approach expedited by

SAS Proc GLIMMIX,²⁸ specifying a binary outcome and logit link. Logistic models evaluating different relationships with time in the fixed and random effects were fit and fixed site effects were evaluated for inclusion as a main effect and interaction with time and treatment. Minimum values for the Akaike information criterion determined the best model.²⁹ Responder rates at the end of treatment (i.e., 16 weeks) were compared between groups with and without using multiple imputed values from the general linear mixed model approach for the missing data.³⁰ These methods all allow for estimates of changes in repeated measures in the presence of missing data, assuming those data were missing at random.^{30,31} The pattern of missing data was evaluated with chi square tests comparing groups at each time point. Secondly, treatment response using the last available assessment was compared between groups with a chi square test.

All comparisons utilized a two-tailed, .05 significance level. The approach of Hochberg³² was used to account for multiple endpoints for the two primary hypotheses. Pearson Chi-square tests were used to compare treatment differences for categorical variables and the t-test or the non-parametric Kruskal-Wallis test was used for continuous outcomes.

RESULTS

PATIENT DISPOSITION

As shown in Figure 1, 1334 adolescents were pre-screened, 450 were consented and screened, and 303 were randomized to OROS-MPH or placebo and included in ITT analyses. There were no statistically significant differences between groups in study completion, compliance with weekly research visits or CBT session attendance, or medication compliance. The most conservative measure of medication compliance, determined by weekly pill counts of the number returned divided by number of pills prescribed and assuming that non-returned pills/bottles were not taken, was 79%. Medication compliance, based on adolescent self-reports, was 82.3% overall.

DEMOGRAPHIC AND BASELINE CHARACTERISTICS

There were no statistically significant differences between groups at baseline on demographics, primary outcomes or other relevant clinical characteristics (Table 1). The mean (standard deviation [SD]) age was 16.5 (1.3) years; and 78.9% were male. Race and ethnicity were self-classified. Race: Caucasian, 61.7%; African American, 23.2%; other, 15.1%. Ethnicity: Hispanic, 15.2%. At baseline, participants had moderately severe ADHD (mean ADHD-RS=38.7 (8.9)) and reported using non-tobacco substances about half of the days in the past month (mean=14.6/28 days).

EFFICACY OUTCOMES

Prior to conducting longitudinal analyses, we confirmed that there were no statistically significant differences between groups with regard to the pattern the percentage of primary outcome data that was missing (ADHD-RS: OROS-MPH=21.2%; placebo=24.5%, $P>0.05$; days of substance use assessed: OROS-MPH=11.9%; placebo=16.5%, $P>0.05$). Additionally, completers (N=227) were not different from non-completers (N=76) on baseline demographic or clinical characteristics (ADHD-RS scores; days of past-28 day substance use; number of substance use disorders- all $P>0.05$) and the proportion of completers did not differ by treatment assignment ($P>0.05$).

ADHD

Primary ADHD Outcome: Figure 2 illustrates the longitudinal course of DSM-IV ADHD-RS scores over time by treatment group. There was a clinically and statistically significant decrease in ADHD score in both treatment groups but no between-group difference:

estimated decrease from baseline to study end for the OROS-MPH + CBT group was -19.2 (95% CI, -17.1 to -21.2 ; $P<0.001$) and for the placebo + CBT group was -21.2 (95% CI, -19.1 to -23.2 , $P<0.001$). Likelihood-based criterion determined that the longitudinal course of adolescent DSM-IV ADHD-RS score in the ITT sample followed a cubic curve with random subject and linear time effects and serially correlated residual errors.

Secondary ADHD Outcomes

ADHD-RS Parent Informant: Parent ADHD-RS scores were significantly lower in participants treated with OROS-MPH + CBT compared to placebo + CBT at 8 weeks (OROS-MPH, $N=85$, mean score= 26.0 (10.5); placebo, $N=79$, mean score= 30.4 (12.5); mean difference between groups= 4.4 ; 95% CI, 0.8 - 7.9 ; $P=0.0163$ t-test) and at 16 weeks (OROS-MPH, $N=84$, mean score= 24.0 (11.8); placebo, $N=68$, mean score= 30.9 (13.0); mean difference between groups= 6.7 ; 95% CI, 2.9 - 10.9 ; $P<0.001$ t-test).

CGI-I: When the logit model with a linear time effect and random intercept that adjusted for a significant site effect was implemented via the general linear mixed model, the proportion of ADHD treatment responders (CGI-I score of 1 or 2) was surprisingly low in OROS-MPH + CBT (25.5%) and not significantly different ($P=0.715$) from placebo + CBT (23.2%). Rates of treatment response were even lower with multiple imputation for missing data and not significantly different ($P=0.418$) between OROS-MPH + CBT (23.4%) and placebo + CBT (19.1%). Similarly, there was not a statistically significant difference ($P=0.64$) in treatment responders based on participants' last CGI-I rating (OROS-MPH + CBT= 23.6% , $N=144$; placebo + CBT= 21.3% , $N=141$). Of completers, 26.1% were treatment responders in the OROS-MPH + CBT group ($N=119$) and 22.2% were treatment responders in the placebo + CBT group ($N=108$) which was also not statistically different between groups ($P=0.50$). As a validity check of the CGI-I measure, CGI-I responders were compared to non-responders with regard to change in ADHD-RS scores in completers. Responders (CGI-I=1, 2) had significantly greater decline in ADHD-RS scores (mean= -26.4 [11.6 SD]) compared to non-responders (CGI-I >2 ; mean= -18.8 [11.7], $P<0.001$; mean difference= -7.6 , 95% CI, -11.2 to -4.0 ; Cohen's $d=0.66$).

ARCQ Change in "Problem-Solving Ability" and "Focused Coping Skills": Compared to placebo, adolescents treated with OROS-MPH + CBT reported significantly greater improvement in their "problem solving ability" (median difference between groups= 7 , favoring OROS-MPH; 95% CI, 3 - 8 ; $P=0.002$, Cohen's $d=0.35$) and acquisition of "focused coping skills" (median difference between groups= 4 , favoring OROS-MPH; 95% CI, 1 - 7 ; $P=0.02$, Cohen's $d=0.25$).

MGH Liking Scale: In response to the MGH Liking Scale question "Do you feel that your medication has been effective in treating your ADD/ADHD symptoms?", the median affirmative response was significantly greater in participants treated with OROS-MPH (median= 6 , (5,8) 25th, 5th percentile, $N=144$) than in those treated with placebo (median= 5 (2,6), $N=141$; $P<0.001$, Cohen's $d=0.56$).

Substance Use

Primary Substance Outcome: Figure 3 shows the longitudinal course of days of past 28-day nontobacco drug use (TLFB) over time by treatment group, indicating that there was a clinically and statistically significant decrease in both the OROS-MPH + CBT (-5.7 days, 95% CI, -7.4 to -4.0 ; $P<0.001$) and placebo + CBT groups (-5.2 days; 95% CI, -7.0 to -3.5 ; $P<0.001$) but no between-group difference (Chi-square= 3.5 , 3df, $P=0.321$). Likelihood-based criteria determined that the longitudinal course of adolescent-reported days of non-tobacco drug use in the past 28 days in the ITT sample followed a quadratic

curve with random subject and linear time effects. Table 2 shows the response of the primary ADHD and substance outcome variables based on estimates from the longitudinal models (also see Figures 2 and 3).

Secondary Substance Outcomes: Adolescents treated with OROS-MPH + CBT had significantly more negative UDS (3.8, 95% CI, 3.0-4.6) compared to participants treated with placebo + CBT (2.8, 95% CI, 2.1-3.5; $P=0.05$, Cohen's $d=0.22$) and there was no difference between groups in the number of UDS collected (11.7, 11.3, respectively).

MEDICATION TOLERABILITY, SAFETY, ADVERSE EVENTS

Ninety-six percent of participants treated with OROS-MPH achieved the maximum daily dose of 72mg, and 86.6% sustained this dose throughout the trial. Participants treated with OROS-MPH had more treatment-emergent study-related AEs per subject (mean=2.4, 95% CI, 1.9-2.9) compared to placebo (mean=1.6, 95% CI, 1.3-1.9; $P=0.02$). More participants treated with OROS-MPH had permanent reductions in their medication dose compared to placebo (10.7% vs. 6.8%, respectively). Specific AEs treated with placebo (panic/anxiety (1); auditory hallucinations/vomiting (1); nausea/upper abdominal pain (2); influenza (1); rash (1); nervousness (1); depressed mood (1); mass (1)). Eleven SAEs occurred throughout the trial. Four SAEs occurred in participants treated with OROS-MPH, only one of which was judged as study-related, in which a participant was briefly hospitalized for evaluation of psychosis after attending a "rave" at which he ingested unknown substances. Seven SAEs occurred in participants treated with placebo, four of which were judged as possibly study-related and resulted in brief hospitalizations for syncope, drug toxicity, asthma, and increased aggression, respectively.

Seventy percent of participants (OROS-MPH, 68%; placebo, 72%) reported using drugs or alcohol on days they took study medication, but only 4 (2.8%) taking OROS-MPH and 3 (2.1%) taking placebo, reported possible adverse interactions between medication and drugs/alcohol taken on the same day.

Medication Abuse and Diversion—There were no statistically significant differences between OROS-MPH and placebo, respectively, on self-reported medication abuse ("taking more medication than prescribed", 4.8% vs. 2.8%, $P>0.05$) or diversion ("selling medication to others", 2.1% vs. 1.4%, respectively, $P>0.05$; "letting others take your medication", 3.5% vs. 1.4%, respectively, $P>0.05$) as assessed by the MGH Abuse and Diversion Questionnaire.

Assessment of Study Blind—At study exit, adolescents and clinicians were asked to guess whether the adolescent had been on active medication or placebo during the trial. Of participants taking OROS-MPH, 59.8% guessed correctly; clinician guesses were 59.7% correct. Of participants taking placebo, 66.7% guessed correctly; clinician guesses were 67.3% correct. The percent of correct guesses was significantly greater than chance based on chi-square tests of association ($p<0.001$) for both the adolescents and clinicians. However, given that there were no significant group differences on measures relying on adolescent or clinician ratings, it is unlikely that the correct guesses biased the trial toward finding a medication effect.

DISCUSSION

The main study finding from this multi-site trial is that OROS-MPH failed to show greater efficacy than placebo for ADHD in adolescents concurrently receiving CBT as outpatient substance treatment based on the primary outcome measure (ADHD-RS, adolescent

informant) and medical clinician ratings (CGI-I) of ADHD treatment responders (secondary outcome measure). Moreover, compared to placebo, participants treated with OROS-MPH did not have greater reduction in days of past-month drug use beyond that achieved in substance treatment with CBT. Despite non-abstinence in most participants, OROS-MPH demonstrated a fairly good overall safety profile and was relatively well tolerated. However, it is important to point out that the study was not powered to address safety and there were some safety concerns, including more treatment emergent adverse events with OROS-MPH compared to placebo.

The primary study outcome suggests that clinicians should refer adolescents with co-occurring ADHD and SUD to substance treatment without initiating OROS-MPH, or perhaps any medication, for ADHD before or during substance treatment. However, our confidence in this clinical implication is somewhat diminished in consideration of secondary outcomes favoring OROS-MPH including: (1) lower ADHD-RS scores, based on parent informants at 8 and 16 weeks; (2) more adolescents treated with OROS-MPH reported that medication was helpful in treating their ADHD; (3) greater improvement in problem-solving ability and coping skills for managing temptations to use drugs/alcohol (targeted in CBT); (4) more negative urine drug screens.

Although these secondary outcomes suggested some “added benefit” of OROS-MPH compared to placebo treatment, further consideration of potential reasons for failed efficacy on the primary outcome measure is warranted in the context of study limitations, including:

1. Reliability of the ADHD-RS, adolescent informant. The validity of the clinician-administered ADHD-RS based on patients as self-informants is well established in adults with ADHD.¹⁸⁻²¹ Due to the paucity of studies in adolescents, there is no current consensus regarding the most valid outcome measures for ADHD in adolescents with or without SUD. However, several studies support the reliability of clinician-assessed ADHD symptom severity based on adolescent informants.^{4,9,13,14,22-24} In the current study, several steps were taken to enhance the reliability of the ADHD-RS including clinicians’ careful attention to educating adolescent participants about ADHD symptoms which included specific examples to illustrate the range of ADHD-RS symptom severity ratings. Due to the limitations of study design and methodology we cannot further evaluate the validity of the ADHD-RS based on adolescent informants or rule out the possibility of a Hawthorne effect, whereby symptoms may improve in response to experimental study.
2. Was medication compliance sufficient to support trial validity? Medication compliance was at least 80% (even by the most conservative measure). In addition, participants treated with OROS-MPH reported more psychostimulant-related adverse events. Taken together, this suggests that medication compliance was at least adequate to support trial validity.
3. Was OROS-MPH efficacy compromised by non-abstinence, given that most participants reported using drugs/alcohol on days they took medication? The results of two previous controlled medication trials suggest that the failure of OROS-MPH to separate from placebo in the current trial is not likely to be explained by participants’ non-abstinence. The first was a randomized controlled trial of pemoline (a schedule III psychostimulant) for ADHD in 69 non-abstinent adolescents with co-occurring SUD in which pemoline showed superior efficacy than placebo for ADHD (effect size=0.5) but there was no reduction in substance use in either group in the absence of concurrent substance treatment.⁹ Similarly, a controlled trial of atomoxetine in 147 adults with ADHD and alcohol use disorders

reported greater efficacy for atomoxetine compared to placebo despite non-abstinence (effect size=0.48; 43% vs. 21% symptom reduction, respectively), but no group differences in alcohol use in the absence of substance treatment.³³ The efficacy of active medication for ADHD in non-abstinent participants not receiving concurrent substance treatment suggests that the failure of OROS-MPH to separate from placebo in the current trial is not likely to be explained by participants' substance use, but does raise the question of whether CBT may have contributed to the more than 50% reduction in ADHD symptoms in both groups.

4. Did CBT contribute to ADHD treatment response and failed efficacy? Three controlled psychostimulant (methylphenidate) medication trials in non-abstinent adults with co-occurring ADHD and SUD have reported significant reductions in ADHD symptoms but no difference between medication and placebo when participants concurrently received weekly CBT for SUD.³⁴⁻³⁶ The potential contribution of CBT to failed efficacy was not highlighted or seriously considered in these adult studies published between 2002 and 2007. However, when we obtained similar results in a 12-week controlled trial of atomoxetine + CBT (for SUD) in 70 adolescents with ADHD and SUD conducted concurrently with this study and published in 2010³⁷, we did raise the question of whether CBT contributed to the failure of atomoxetine to separate from placebo, given emerging research suggesting the efficacy of CBT for ADHD in adults.^{38,39} Limitations of study design prevent further determination of the potential contribution of CBT to OROS-MPH's failed efficacy for ADHD in the current trial. However, results of this study add to a growing suspicion that CBT (for SUD) may contribute to ADHD treatment response and warrants further investigation.

In summary, the primary outcome of this study does not support the efficacy of OROS-MPH for ADHD in adolescents who are concurrently receiving individual CBT as outpatient substance treatment. However this result should be interpreted with caution and considered in the context of study limitations and secondary outcomes favoring OROS-MPH, consistent with the consideration given to multiple informants and measures in many pediatric medication trials. Additional studies are needed that are specifically designed to address whether CBT (for SUD) contributes to ADHD and perhaps other co-occurring psychiatric symptom reduction. Finally, additional research is needed to determine the most reliable and valid ADHD outcome measures and optimal frequency of assessment in adolescents with co-occurring disorders in order to move the field forward in ways that will increase scientific knowledge and which may improve treatment outcomes for the large subgroup of our nation's youth.

Acknowledgments

The project described was supported by the following grants from the National Institute on Drug Abuse (NIDA): U10 DA13716 (PDR, RDD, SMG, CK, MM, ML, EW); U10 DA13732 (PDR, TW, RDD, SMG, CK, MM, ML, EW); U10 DA15831 (GLB, WBJ); U10 DA13727 (LH, BWH); U10 DA13720 (CH, MAV); U10 DA20024 (KTR, LT); U10 DA13035 (EVN, MCA); K24 DA022412 (EVN); U10 DA13043 (CRM, GEW); U10 DA13034 (GS, MF); K12 DA000357 (GS); U10 DA20036 (MEK). Drug and matching placebo were provided by Ortho McNeil Janssen Scientific Affairs, LLC.

Timothy Wilens, MD (Harvard University) provided technical assistance for K-SADS-E training, and with Len Adler, MD (New York University) and James Swanson, PhD (University of California, Los Angeles) served as external consultants to the National Institute of Drug Abuse (NIDA) and the primary investigator (PI)/lead team on the selection of study outcome measures. Jeffery Leimberger, PhD (Duke Clinical Research Institute) and Susan Mikulich-Gilbertson, PhD (University of Colorado Denver) provided biostatistical expertise. Ashley Kayser, MAS (University of Colorado Denver) provided expert editorial assistance in preparing the manuscript. Suzell Klein, MA (University of Colorado Denver) and Frankie Kropp, MS (University of Cincinnati) provided administrative and training support for implementation. The following people provided site medical support: Georgia Welnick, RN (Lexington/Richland Alcohol and Drug Abuse Council); Himanshu Upadhyaya, MD (Medical University of South

Carolina); Jill Ridley, RN (Synergy Outpatient Services, University of Colorado Denver); Eileen Duggan, MD (Crittendon Children's Center); Steven Cuffe, MD (Lexington/Richland Alcohol and Drug Abuse Council); Charles Maddix, RN (Gateway Community Services); Roberto Dominguez, MD (University of Miami); Betsy Macaraig, RN (Stanley Street Treatment and Resources, Inc.); John Thomas, MD (Rehab After Work); Michael Sheehan, MD (Operation PAR, Inc.). The following individuals collected data at participating sites: Ashley Myracle, MA (Synergy Outpatient Services, University of Colorado Denver); Michelle Rapoza (Stanley Street Treatment and Resources, Inc.); Kim Pressley, MA (Lexington/Richland Alcohol and Drug Abuse Council); John Bensinger, MA (Addiction Medicine Services, Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center); Christine Neuenfeldt, PhD (Gateway Community Services); Randi Adelman, NP (St. Luke's-Roosevelt Hospital Center); and Julia Hemphill (Operation PAR, Inc.).

REFERENCES

1. Wilens TE, Gignac M, Swezey A, Monuteaux MC, Biederman J. Characteristics of adolescents and young adults with ADHD who divert or misuse their prescribed medications. *J Am Acad Child Adolesc Psychiatry.* Apr; 2006 45(4):408–414. [PubMed: 16601645]
2. Kessler RC, Adler L, Ames M, et al. The prevalence and effects of adult attention deficit/hyperactivity disorder on work performance in a nationally representative sample of workers. *J Occup Environ Med.* Jun; 2005 47(6):565–572. [PubMed: 15951716]
3. Katusic SK, Barbaresi WJ, Colligan RC, Weaver AL, Leibson CL, Jacobsen SJ. Psychostimulant treatment and risk for substance abuse among young adults with a history of attention-deficit/hyperactivity disorder: a population-based, birth cohort study. *J Child Adolesc Psychopharmacol.* Oct; 2005 15(5):764–776. [PubMed: 16262593]
4. Whitmore, EA.; Riggs, PD. Developmentally informed diagnostic and treatment considerations in comorbid conditions. In: Liddle, HA.; Rowe, CL., editors. *Adolescent Substance Abuse: Research and Clinical Advances.* Cambridge University Press; Cambridge, U.K.: 2006. p. 264-283.
5. Rowe CL, Liddle HA, Greenbaum PE, Henderson CE. Impact of psychiatric comorbidity on treatment of adolescent drug abusers. *J Subst Abuse Treat.* Mar; 2004 26(2):129–140. [PubMed: 15050090]
6. Wise BK, Cuffe SP, Fischer T. Dual diagnosis and successful participation of adolescents in substance abuse treatment. *J Subst Abuse Treat.* 2001; 21(3):161–165. [PubMed: 11728790]
7. Grella CE, Hser YI, Joshi V, Rounds-Bryant J. Drug treatment outcomes for adolescents with comorbid mental and substance use disorders. *J Nerv Ment Dis.* 2001; 189(6):384–392. [PubMed: 11434639]
8. Sussman S, Pentz MA, Spruijt-Metz D, Miller T. Misuse of “study drugs:” prevalence, consequences, and implications for policy. *Subst Abuse Treat Prev Policy.* 2006; 1:15. [PubMed: 16764722]
9. Riggs PD, Hall SK, Mikulich-Gilbertson SK, Lohman M, Kayser A. A randomized controlled trial of pemoline for attention deficit hyperactivity disorder in substance abusing adolescents. *J Am Acad Child Adolesc Psychiatry.* 2004; 43(4):420–429. [PubMed: 15187802]
10. McBurnett K, Starr HL. OROS methylphenidate hydrochloride for adult patients with attention deficit/hyperactivity disorder. *Expert Opin Pharmacother.* 2011; 12(2):315–324. [PubMed: 21226641]
11. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 4th ed. American Psychiatric Association; Washington, DC: 1994.
12. Nunes EV, Ball S, Booth R, et al. Multisite effectiveness trials of treatments for substance abuse and co-occurring problems: Have we chosen the best designs? *J Subst Abuse Treat.* Jun; 2010 38(Suppl 1):S97–S112. [PubMed: 20307801]
13. Waldron HB, Kaminer Y. On the learning curve: the emerging evidence supporting cognitive-behavioral therapies for adolescent substance abuse. *Addiction.* Nov; 2004 99(Suppl 2):93–105. [PubMed: 15488108]
14. Waldron HB, Turner CW. Evidence-based psychosocial treatments for adolescent substance abuse. *J Clin Child Adolesc Psychol.* 2008; 37(1):238–261. [PubMed: 18444060]
15. Orvaschel, H. *Schedule for Affective Disorder and Schizophrenia for School-Age Children Epidemiologic Version.* Nova Southeastern University, Center for Psychological Studies; Ft. Lauderdale, FL: 1994.

16. Cottler LB, Robins LN, Helzer JE. The reliability of the CIDI-SAM: a comprehensive substance abuse interview. *Br J Addict.* 1989; 84(7):801–814. [PubMed: 2758153]
17. DuPaul, GJ.; Power, TJ.; Anastopoulos, AD.; Reid, R. *ADHD Rating Scale-IV: Checklists, Norms, and Clinical Interpretation.* Guilford Press; New York, NY: 1998.
18. Adler LA, Faraone SV, Spencer TJ, et al. The reliability and validity of self- and investigator ratings of ADHD in adults. *J Atten Disord.* May; 2008 11(6):711–719. [PubMed: 18025250]
19. Adler LA, Shaw D, Stein MA, et al. Updates in attention-deficit/hyperactivity disorder: current concepts and future developments. *J ADHD Relat Disord.* 2009; 1(1):63–83.
20. Zhang S, Faries DE, Vowles M, Michelson D. ADHD Rating Scale IV: psychometric properties from a multinational study as a clinician-administered instrument. *Int J Methods Psychiatr Res.* 2005; 14(4):186–201. [PubMed: 16395872]
21. Szomlajski N, Dyrborg J, Rasmussen H, Schumann T, Koch SV, Bilenberg N. Validity and clinical feasibility of the ADHD rating scale (ADHD-RS) A Danish Nationwide Multicenter Study. *Acta Paediatr.* Feb; 2009 98(2):397–402. [PubMed: 18775056]
22. Myers MG, Brown SA. The Adolescent Relapse Coping Questionnaire: psychometric validation. *J Stud Alcohol.* 1996; 57(1):40–46. [PubMed: 8747500]
23. Sobell, LC.; Sobell, MB. Timeline Follow-back: a technique for assessing self-reported alcohol consumption. In: Litten, RZ.; Allen, JP., editors. *Measuring Alcohol Consumption: Psychosocial and Biochemical Methods.* Humana Press; Totowa, NJ: 1992. p. 41-72.
24. Winters, KC. Clinical perspectives on the assessment of adolescent drug abuse. In: Liddle, HA.; Rowe, CL., editors. *Adolescent Substance Abuse: Research and Clinical Advances.* Cambridge University Press; Cambridge, U.K.: 2006. p. 223-240.
25. Ling W, Shoptaw S, Wesson D, Rawson RA, Compton M, Klett CJ. Treatment effectiveness score as an outcome measure in clinical trials. *NIDA Research Monograph* 98-4125. 1997; 175:208–220.
26. Hedeker D, Gibbons RD, Waternaux C. Sample size estimation for longitudinal designs with attrition: Comparing time-related contrasts between two groups. *J Educ Behav Stat.* 1999; 24:70–93.
27. SAS Institute Inc.. *SAS/STAT User's Guide.* Version 8. SAS Institute Inc.; Cary, NC: 1999. The MIXED Procedure; p. 2083-2226.
28. Schabenberger, O. Introducing the GLIMMIX Procedure for Generalized Linear Models. *SUGI 30.* SAS Institute; Cary, NC: 2007.
29. Jones, RH. *Longitudinal Data with Serial Correlation: A State-Space Approach.* Chapman and Hall; New York, NY: 1993.
30. McCulloch, CE.; Searle, SR. *Generalized, Linear, and Mixed Models.* John Wiley & Sons; New York, NY: 2001. Generalized linear mixed models (GLMMs); p. 220-246.
31. Brown, H.; Prescott, R. *Applied Mixed Models in Medicine.* John Wiley & Sons; New York, NY: 1999.
32. Hochberg Y. A sharper bonferroni procedure for multiple tests of significance. *Biometrika.* 1988; 75:800–802.
33. Wilens TE, Adler LA, Weiss MD, et al. Atomoxetine treatment of adults with ADHD and comorbid alcohol use disorders. *Drug Alcohol Depend.* 2008; 96(1-2):145–154. [PubMed: 18403134]
34. Levin FR, Evans SM, Brooks DJ, Garawi F. Treatment of cocaine dependent treatment seekers with adult ADHD: double-blind comparison of methylphenidate and placebo. *Drug Alcohol Depend.* 2007; 87(1):20–29. [PubMed: 16930863]
35. Levin FR, Evans SM, Brooks DJ, Kalbag AS, Garawi F, Nunes EV. Treatment of methadone-maintained patients with adult ADHD: double-blind comparison of methylphenidate, bupropion, and placebo. *Drug Alcohol Depend.* 2006; 81(2):137–148. [PubMed: 16102908]
36. Schubiner H, Saules KK, Arfken CL, et al. Double-blind placebo-controlled trial of methylphenidate in the treatment of adult ADHD patients with comorbid cocaine dependence. *Exp Clin Psychopharmacol.* 2002; 10(3):286–294. [PubMed: 12233989]

37. Thurstone C, Riggs PD, Salomonsen-Sautel S, Mikulich-Gilbertson SK. Randomized, controlled trial of atomoxetine for attention-deficit/hyperactivity disorder in adolescents with substance use disorder. *J Am Acad Child Adolesc Psychiatry*. 2010; 49(6):573–582. [PubMed: 20494267]
38. Safren SA, Sprich S, Mimiaga MJ, et al. Cognitive behavioral therapy vs relaxation with educational support for medication-treated adults with ADHD and persistent symptoms: a randomized controlled trial. *JAMA*. 2010; 304(8):875–880. [PubMed: 20736471]
39. Solanto MV, Marks DJ, Wasserstein J, et al. Efficacy of meta-cognitive therapy for adult ADHD. *Am J Psychiatry*. 2010; 167(8):958–968. [PubMed: 20231319]

Figure 1. Study Flow Diagram

Note: CBT = cognitive behavioral therapy; OROS = osmotic-release methylphenidate

Figure 2. Change in DSM-IV Attention-Deficit/Hyperactivity Disorder Rating Scale (ADHD-RS) Scores by Treatment Group

Note: Estimates are derived from the cubic longitudinal model with random subject and linear time effects and serially-correlated residual errors. OROS = osmotic-release methylphenidate.

Figure 3. Change in Past 28 Day Non-Tobacco Drug Use by Treatment Group

Note: Past 28-day drug use trajectories were modeled based on the assumption of normal distribution for the response variable (Intent-to-treat sample; here, N=302, 1 subject did not have valid data for this variable). Estimates were derived from the selected quadratic longitudinal model with random subject and linear time effects. OROS = osmotic-release methylphenidate.

Table 1

Baseline Clinical Characteristics by Treatment Group

Variable	OROS-MPH + CBT (N=151)	Placebo + CBT (N=152)	All (N=303)
ADHD Severity			
ADHD Rating Scale score, mean (SD)	38.1 (9.0)	39.3 (8.8)	38.7 (8.9)
ADHD Diagnostic Subtype, No. (%) ^a			
Combined	104 (68.9)	104 (68.4)	208 (68.6)
Inattentive	43 (28.5)	42 (27.6)	85 (28.1)
Hyperactive-Impulsive	4 (2.6)	4 (2.6)	8 (2.6)
Not otherwise specified	0 (0)	2 (1.3)	2 (0.7)
Substance Severity			
Days non-tobacco substance use, No./28 (SD)	14 (9.6)	15.1 (9.4)	14.6 (9.5)
Non-tobacco abuse/dependence diagnoses, No. (SD)	2.1 (1.2)	1.9 (1.3)	2.0 (1.2)
Dependence Diagnoses, No. (%) ^b			
Cannabis dependence	95 (62.9)	107 (70.4)	202 (66.7)
Alcohol dependence	48 (31.8)	42 (27.6)	90 (29.7)
Cocaine dependence	11 (7.3)	11 (7.2)	22 (7.3)
Hallucinogen dependence	11 (7.3)	4 (2.6)	15 (5.0)
Sedative dependence	5 (3.3)	3 (2.0)	8 (2.6)
Amphetamine dependence	3 (2.0)	1 (0.7)	4 (1.3)
PCP dependence	0 (0)	1 (0.7)	1 (0.3)
Inhalant dependence	1 (0.7)	0 (0)	1 (0.3)
Opiate dependence ^d	0 (0)	1 (0.7)	1 (0.3)
Other dependence	1 (0.7)	0 (0)	1 (0.3)
Abuse Diagnoses, No. (%) ^b			
Alcohol abuse	40 (26.5)	40 (26.3)	80 (26.4)
Cannabis abuse	43 (28.5)	34 (22.4)	77 (25.4)
Opiate abuse	20 (13.2)	17 (11.2)	37 (12.2)
Hallucinogen abuse	10 (6.6)	13 (8.6)	23 (7.6)
Sedative abuse	14 (9.3)	8 (5.3)	22 (7.3)
Amphetamine abuse ^c	6 (4.0)	3 (2.0)	9 (3.0)
Cocaine abuse	3 (2.0)	5 (3.3)	8 (2.6)
Inhalant abuse	1 (0.7)	4 (2.6)	5 (1.7)
Other abuse	1 (0.7)	1 (0.7)	2 (0.7)
PCP abuse	1 (0.7)	0 (0)	1 (0.3)
Major Depressive Disorder, No. (%)	19 (12.6)	19 (12.5)	38 (12.5)
Conduct Disorder, No. (%)	48 (32)	50 (33)	98 (32.3)

Note: CBT = cognitive behavioral therapy; OROS-MPH = osmotic-release methylphenidate; PCP = phencyclidine.

^a One subject did not meet diagnostic criteria for attention-deficit/hyperactivity disorder (ADHD) and one subject did not have an Attention-Deficit/Hyperactivity Disorder Rating Scale (ADHD-RS) score of 22 or greater but both were included in analyses.

^b Two subjects did not meet diagnostic criteria for a non-tobacco substance use disorder but were included in analyses.

^c Excluding methamphetamine.

^d Current opiate dependence was an exclusion criterion; one subject with opiate dependence >1 year prior to study entry was enrolled/randomized.

TABLE 2

Estimated Measures of Attention-Deficit/Hyperactivity Disorder (ADHD) and Substance Use Disorder (SUD) by Treatment Group in the Intent-To-Treat Sample (N=303)

	ADHD-RS		SUD (Days of past 28 day non-tobacco drug use)	
Treatment Group	OROS-MPH + CBT (N=151)	Placebo + CBT (N=152)	OROS-MPH + CBT (N=151)	Placebo + CBT(N=152)
Study Week, mean ^a (95% Confidence Intervals)				
Week 0	36.2 (34.6-37.7)	37.6 (36.1-39.1)	14.0 (12.5-15.4)	15.2 (13.8-16.7)
Week 4	20.6 (19.1-22.1)	21.4 (19.9-22.9)	11.0 (9.7-12.4)	11.7 (10.3-13.0)
Week 8	18.2 (16.6-19.9)	18.2 (16.5-19.8)	9.1 (7.7-10.5)	9.6 (8.2-11.1)
Week 12	20.0 (18.1-21.9)	19.4 (17.5-21.3)	8.2 (6.8-9.6)	9.1 (7.6-10.5)
Week 16	17.0 (14.7-19.3)	16.4 (14.1-18.8)	8.3 (6.7-9.9)	10.0 (8.3-11.7)

Note: ADHD-RS = Attention-Deficit/Hyperactivity Disorder Rating Scale; CBT = cognitive behavioral therapy; OROS-MPH = osmotic-release methylphenidate.

^aEstimated ADHD score and number of days of substance use in previous 28 days. Means are used for predicted individual scores, adjusted for fixed and random effects derived from the polynomial random coefficient model selected for each variable from likelihood-based criteria.