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Double-Blind Placebo-Controlled Trial of Methylphenidate in the Treatment of Adult ADHD Patients With Comorbid Cocaine Dependence

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In this 12-week double-blind placebo-controlled trial of methylphenidate (MTP) versus placebo in 48 cocaine-dependent attention-deficit/hyperactivity disorder (ADHD) adults, the authors sought to determine whether MTP would be safe, control ADHD symptoms, and affect cocaine use. Efficacy indexes revealed significantly greater ADHD symptom relief in the MTP group. There were no group differences in self-reported cocaine use, urinalysis results, or cocaine craving. Because of the relatively small sample size, the results are preliminary. However, we found that MTP improved subjective reports of ADHD symptoms and did not worsen cocaine use while participants were in treatment.

Attention-deficit/hyperactivity disorder (ADHD) has been shown to persist into adulthood in 11% to 80% of children who are diagnosed with this syndrome (Barkley, 1990; Faraone, Biederman, Spencer, Wilens, Seidman, Mick, & Doyle, 2000; Mannuzza, Klein Bessler, Malloy, & LaPadula, 1993; G. Weiss & Hechtman, 1993). Although controversial, several lines of data, including epidemiological, familial/genetic, and neuroimaging studies, support the validity of this diagnosis in adults (Faraone & Biederman, 1999; Faraone et al, 2000; Murphy & Barkley, 1996; Spencer, Biederman, Wilens, & Faraone, 1994).

Adults with ADHD have been shown to be at higher than average risk for a variety of comorbid conditions, such as affective disorders, anxiety disorders, academic underachievement, and occupational difficulties (Biederman et al., 1993; Borland & Heckman, 1976; Mannuzza et al., 1993). Furthermore, the persistence of ADHD into adulthood is associated with a host of complications, including marital dissolution, intellectual and neuropsychological deficits, impulsivity, and criminality (Biederman et al., 1993; Downey, Pomerleau, & Pomerleau, 1996; Downey, Stelson, Pomerleau, & Giordani, 1997; Mannuzza, Klein, Konig, & Giampino, 1989).

Studies have found that ADHD is overrepresented in adults undergoing treatment for cocaine, alcohol, and other drug dependence (Carroll & Rounsaville, 1993; Clure et al., 1999; Levin, Evans, & Kleber, 1998; Schubiner et al., 2000; Wilens, Spencer, & Biederman, 1995). Furthermore, evidence suggests that ADHD may adversely affect the outcome of substance abuse treatment (Biederman, Wilens, Mick, Faraone, & Spencer, 1998; Carroll & Rounsaville, 1993; Whitmore et al., 1997). The possibility of attempts at self-medication of ADHD symptomatology by using various substances, particularly cocaine, has also been proposed (Carroll & Rounsaville, 1993; Khantzian, 1997).

ADHD's underlying pathophysiology is believed to be due to an inherited abnormality in catecholamine function, particularly dopamine, in the frontosubcortical structures. It is hypothesized that individuals with ADHD have an inherited deficiency of dopamine in certain areas of the frontal lobe and limbic systems (Barkley, 1990; Comings et al., 1991; Faraone & Biederman, 1999). Pemoline and methylphenidate (MTP) act to increase dopamine as well as norepinephrine activity in the brain by inhibiting reuptake of these neurotransmitters into the presynaptic neuron (McMillen, 1983; Molina & Orsingher, 1981). Cocaine produces increases in dopamine in the mesolimbic, mesocortical "reward pathway," and a large body of evidence indicates that it is this action that mediates the dependence-producing properties of cocaine (Fischman & Johanson, 1996; Johanson & Schuster, 1995; Kuhar, Ritz, & Boja, 1991). Therefore, it appears that ADHD and cocaine dependence may be linked by a neural "need" for dopamine stimulation. This link may explain, in part, the observed association between these two conditions. That is, the use of cocaine may serve the purpose of increasing dopamine activity for individuals with ADHD (i.e., the "self-medication hypothesis"; Khantzian, 1985). However, King, Brooner, Kidoff, Stoller, and

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Mirsky (1999) found a significant prevalence (16.7%) of adult ADHD among a population of opioid abusers, suggesting that alternate mechanisms may also be involved.

Agonist therapy (e.g., methadone, nicotine gum and patch) is based on the premise that medications with actions similar to the abused drugs reduce the reinforcing effect of the drugs and reduce craving. Although there are relatively few controlled studies, pharmacotherapy for ADHD in adults has been shown to be effective (Spencer, Biederman, & Wilens, 2000). The first-line agents for treatment of ADHD in both children and adults are the psychomotor stimulants. These agents have revealed response rates of up to 70% to 80% when used at medium to high doses (Wilens & Spencer, 2000). However, albeit in the absence of empirical evidence, this class of medications is often considered to be contraindicated for use by substance abusers because of concerns regarding increased risk for relapse, perhaps by means of pharmacological priming or discriminative stimulus mechanisms that might trigger stimulant abuse (Post & Kopanda, 1976; S. R. Weiss & Post, 1998).

Despite these concerns, however, reports have suggested the efficacy of stimulant medications in patients with active substance use disorders (Castaneda, Levy, Hardy, & Trujillo, 2000; Levin, Evans, McDowell, & Kleber, 1998; Riggs, Thompson, Mikulich, Whitmore, & Crowley, 1996; Schubiner et al., 1995; Turnquist, Frances, Rosenfeld, & Mobarak, 1983). These uncontrolled trials suggest that psychomotor stimulants may be both safe and effective for individuals with the dual diagnoses of ADHD and substance abuse both with respect to alcohol and stimulant abuse/dependence. To date, no controlled trials have been conducted on the efficacy of stimulant medications among cocaine-abusing ADHD adults. This randomized, double-blind, placebo-controlled trial was designed to test the efficacy of MTP in treatment-seeking adults with current ADHD and cocaine dependence. Specifically, we wished to determine whether the use of MTP in this population (a) was safe (i.e., no significant increase in rates of adverse events and dropping out), (b) controlled ADHD symptoms, and (c) led to reduced cocaine craving and use.

Method

Participants

Participants were recruited by advertisements in local newspapers and radio broadcasts. Those who responded to the advertisements were screened over the telephone for basic enrollment criteria: (a) current cocaine use, (b) some evidence of ADHD symptoms (i.e., the probable presence of four or more current ADHD symptoms, as evidenced by answers to telephone screening questions), and (c) willingness to enter a treatment program. Once this initial screen was completed, candidates were asked to attend a screening visit.

Participants were required to be between the ages of 18 and 55 years, meet *Diagnostic and Statistical Manual of Mental Disorders* (4th ed. [*DSM–IV*]; American Psychiatric Association, 1994) criteria for current cocaine dependence, provide a urine specimen with a positive urine toxicology result for cocaine metabolite, meet criteria for the diagnosis of ADHD as a child and as an adult (described later), and be willing to enter an intensive outpatient treatment program. Candidates who scored less than an estimated IQ of 75 on the Shipley Institute of Living scale (Shipley, 1967) were excluded because of concerns that they may not be capable of providing informed consent, complying with the study requirements, and providing reliable and valid data.

All participants underwent a detailed medical, psychiatric, and substance abuse screening visit to ensure that they had no medical/psychiatric contraindications to research participation and met inclusion criteria. Medical screening included a complete history and physical examination with standard laboratory tests (including mandatory tuberculin screening and voluntary HIV testing) and electrocardiogram. Psychiatric and substance abuse screening included the Structured Clinical Interview (SCID) for *DSM–IV* (First, Spitzer, Gibbon, & Williams, 1995) and the Addiction Severity Index (ASI; McLellan et al., 1985). Schizophrenia, bipolar disorder, dementia, and delirium were exclusionary criteria. Candidates with other Axis I and Axis II psychopathology were allowed to participate providing they were capable of giving informed consent, were not in need of emergency psychiatric treatment, and were able to comply with study requirements. Candidates were excluded if they had any clinically significant medical condition or clinically significant abnormality in routine laboratory testing (including liver function tests and electrocardiogram), were pregnant, or were unable to comprehend and respond to the measures used in the study. All participants provided informed consent before both screening procedures as well as entry into the controlled trial. The Institutional Review Board of the Wayne State University School of Medicine approved the study.

Study Procedures

This study was a double-blind, placebo-controlled, randomized trial comparing MTP with placebo. It was initially structured to have three arms, including one with pemoline. However, the pemoline arm was dropped after the first year because of recruitment difficulties. In addition, preliminary analysis showed no differences between the effects of pemoline and MTP. The duration of the trial was 13 weeks, including 1 week of baseline testing and 12 weeks of treatment.

On provision of informed consent to enter the trial, each participant was randomly assigned to receive either MTP or placebo. The sample was stratified by gender so that each arm (MTP vs. placebo) would have equal numbers of women and men. Men were further stratified on the basis of antisocial personality disorder and women on the basis of borderline personality disorder to ensure balance of these potentially important prognostic factors.

To maintain anonymous conditions, an independent pharmacist compounded study medications. The doses of MTP were titrated from an initial dosage for the first 2 or 3 days (10 mg of MTP three times a day) to a second-level dosage (20 mg three times a day) for the next 4 to 5 days and finally to the target dosage of 30 mg three times a day by Day 8. Participants were seen weekly by a physician or nurse practitioner to assess response to medications and the development of any adverse effects. Although double-blind conditions were not broken during the course of the study, the treating physician (Howard Schubiner) was able to request a lower dose of medication if warranted by the emergence of perceived side effects.

All participants received twice-weekly cognitive–behavioral group therapy (CBT) for cocaine dependence. A manual was developed to specify the format and content of the 24 group therapy sessions. The development of this manual was guided by the principles and strategies outlined in the Project MATCH CBT manual (Kadden et al., 1992) and a cognitive–behavioral cocaine treatment manual (Carroll, 1998). An experienced, certified sub-

stance abuse counselor led the group therapy sessions. Each group, composed of 2 to 6 participants, included only individuals from this research study.

Weekly individual CBT sessions were held to help participants cope with ADHD symptoms in general and as they relate to substance abuse. An individual CBT manual for ADHD was developed for this study. During Session 1, the therapist addressed the topic of understanding, accepting, and coping with the ADHD diagnosis. Handout materials were provided from several popular books on coping with ADHD in adulthood (Hallowell & Ratey, 1994; Murphy, 1995a, 1995b; Nadeau, 1996). For subsequent sessions, the therapist used materials from the *ADHD Therapy Resource Book* as appropriate. Topic areas and suggested materials were listed, and copies of all handouts/exercises for each problem area were included in the *ADHD Therapy Resource Book*. Issues such as problems with impulse control, poor interpersonal skills, ineffective coping strategies, and deficient anger-management skills, which may pose obstacles to the ADHD person's success in achieving and maintaining cocaine abstinence, were assessed. Cognitive–behavioral strategies such as role-playing, challenging irrational beliefs and expectations, stress management, and skills training were used. These sessions were conducted by a senior psychologist (Karen K. Saules) and four predoctoral, master's-level psychologists. A weekly meeting was held to ensure quality and control for therapist drift.

Participants attended the clinic three times per week, typically on a Monday-Wednesday-Friday schedule. Throughout the trial, at each visit, participants were expected to provide a urine specimen and complete forms for that particular visit. Medication was provided for the time period between the current visit and the next scheduled visit. Urine specimen collection and medication administration were conducted under direct observation by research staff. At each visit, the participant completed the assessment measures as specified next, most of which were adapted for computer administration.

Measures

To determine cocaine dependence and obtain information on psychiatric comorbidity, the SCID for *DSM–IV* was conducted on all participants during the screening interview. To determine ADHD diagnosis, participants also underwent a structured clinical interview to assess ADHD symptoms in childhood and adulthood. The diagnostic reliability of this interview has been established in a previous study of 201 participants with current substance abuse disorders, resulting in Cohen kappas for interrater reliability of 0.72 to 0.88, comparable with those found for other SCID diagnoses (Schubiner et al., 2000). Ratings were made based on expression of the nine inattentive and nine hyperactive/impulsive symptoms in childhood and adulthood. Interviewers were trained to probe for specific examples of behavior to support the presence of each symptom. The interviewers (master's-level, predoctoral trainees) received didactic training on how to conduct the semi-structured ADHD interview and then served as a corater for two interviews before being allowed to conduct them independently. Reliability checks consisted of comparing symptom ratings on the corated interviews with both interviewers and providing supervisory feedback to resolve discrepant ratings. All interviews were reviewed by the senior psychologist (Karen K. Saules) to verify that differential diagnoses (e.g., substance-induced attentional problems) had been ruled out and that ADHD criteria were met. For the purposes of this study, to be diagnosed with ADHD, the participant must have (a) met full *DSM–IV* criteria for ADHD (i.e., have at least six of the nine inattentive or hyperactive-impulsive symptoms to a clinically significant degree) as an adult, (b) met full *DSM–IV* criteria for ADHD as a child (in retrospect), and (c) had no other psychiatric disorder that would better explain the ADHD symptomatology (e.g., drug-induced symptoms, bipolar disorder).

Measures assessing safety included a weekly side effects checklist based on Barkley's (1990) version with the addition of cardiac symptoms. Medication compliance was assessed at every visit by participants completing a computerized questionnaire on the number of pills taken each day since the previous visit. Dosage adjustments were made based on input from the patient when the medication compliance and side effects forms were reviewed in weekly consults with medical staff. Routine laboratory tests and electrocardiograms were repeated monthly and at the end of the study. Because depression is commonly associated with ADHD (Biederman et al., 1993), the Beck Depression Inventory (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) was administered at baseline and at each study week.

ADHD outcome measures included the physician-rated and self-rated efficacy indexes and the ADHD Symptom Checklist, similar to prior trials in adults with ADHD (Wilens et al., 1999). At the end of each month of the trial (Weeks 5, 9, and 13), both physician and study participants were asked to rate the degree to which the ADHD symptoms had changed since admission and the degree to which they had improved or worsened using the Global Improvement Scale, which ranged from 1 (*very much improved*) to 7 (*very much worse*). The participants also completed a form at those visits indicating their belief regarding their assigned treatment condition. The ADHD Symptom Checklist was completed at baseline and at the beginning of each study week to track changes in ADHD symptoms across time. Participants rated recent (past week) severity of each of the 18 *DSM–IV* ADHD symptoms on a 4-point Likert-type scale (0 = *not at all*; 1 = *just a little*; 2 = *pretty much*; 3 = *most of the time*).

Substance use outcomes include urinalysis, ASI, Tiffany Cocaine Craving Scale (Tiffany, Singleton, Haertzen, & Henningfield, 1993), and self-report. An observed urine sample was collected at every visit (three times per week). Toxicology assays were conducted with the Abbott TDx urine drug testing immunoassay system (Abbott, N. Chicago, IL), a fluorescent polarization immunoassay procedure (*TDx Operators Guide*). In addition to testing for the presence of cocaine metabolite, all samples were tested for opiates, barbiturates, phencyclidine, and amphetamine.

The ASI is a structured interview designed to assess problem severity in seven areas of functioning (medical condition, employment, drug use, alcohol use, illegal activity, family relations, and psychiatric status) that are commonly affected by substance abuse. In each area, questions are asked that determine the number, extent, and duration of problems over the person's lifetime and within the past 30 days. The ASI provides subjective severity ratings and an objective composite score for each area of life functioning assessed. In the present study, the ASI was repeated monthly, including at termination.

The Tiffany Cocaine Craving Scale was completed at baseline and at the beginning of each study week to track changes in craving dimensions across time. This 45-item questionnaire asks about current craving for cocaine. The questionnaire was administered weekly throughout the study. It includes five factor-analytically derived subscales: Desire to Use Cocaine, Intention and Planning to Use Cocaine, Anticipation of Positive Outcomes From Cocaine Use, Anticipation of Relief From Withdrawal or Dysphoria, and Lack of Control Over Cocaine Use. At each visit (three times per week), participants were asked to complete a form indicating (a) how many days they used various drugs (e.g., nicotine, alcohol, cocaine, opiates, marijuana, benzodiazepines,

barbiturates, amphetamine, hallucinogens), (b) how much of each drug they used, and (c) how much out-of-pocket expense was associated with each drug class since the previous visit.

Data Analysis

Demographic and clinical baseline comparisons between the MTP and placebo groups used *t* tests and chi-square analysis for continuous and categorical variables, respectively. The *t* tests were also used to test for compliance differences by group. Retention between groups was assessed using Kaplan–Meier curves and tested using the log-rank statistic. Group differences in the occurrence of side effects and number of people with reduced dosages or discontinued medication because of side effects were tested using chi-square analysis or Fisher's exact test. Mann–Whitney tests were used to test for group differences in severity of symptoms, and McNemar's tests were used to test for changes in occurrence of side effects over time.

To test the efficacy of MTP on ADHD symptom control outcomes, the ADHD Symptom Checklist, assessing the number of symptoms and symptom severity, was used in mixed-effects regression models. The models, with participants as random effects and group assignment as a fixed effect, are efficient and powerful in the presence of missing data (Murray, 1998). As secondary analysis, data from the visit with the lowest reported symptoms for each participant were examined using *t* tests. Because of the highly skewed responses on the 7-point physician efficacy index, group differences were tested using the chi-square statistic on the participant's last visit. The self-rated efficacy index had more dispersion and was tested using *t* tests. To test reduced cocaine cravings and use, the five subscales of the Tiffany Cocaine Cravings Scale were examined separately in mixed-effects regression models. Group differences to time of first confirmed cocaine-negative urine specimen were assessed using Kaplan–Meier curves, and percentage of confirmed cocaine-negative urine specimens or amount spent on cocaine by group was assessed with *t* tests and Mann–Whitney tests. There was no difference in the mean number of urine specimens collected by group (placebo $M = 22.0$ and MTP $M = 18.7$).

For all statistical analyses, the groups were defined by randomization assignment and entry to the trial. The planned sample size of 30 participants per treatment arm had a power of 80% to detect one standard deviation difference in means between the MTP and placebo at an alpha level of .05. The final sample size of 24 per group had a reduced but still adequate power (80%) to detect 0.83 standard deviation in means between the MTP and placebo.

Results

A total of 932 people responded to advertisements about the research study. Of these, 338 were eligible for the study based on the telephone screening procedures. We evaluated 106 people in person for the study, 79 of whom met all eligibility criteria. Overall, 59 people were randomized and enrolled into the study, but 11 participants were assigned to the pemoline group, which was dropped from the analysis.

Demographic and clinical characteristics for the 48 individuals randomized to the placebo and MTP groups are shown in Table 1. No significant baseline differences were detected between groups; however, the MTP group had higher mean ASI psychiatric composite scores than the placebo group, $t(43) = 2.10$, $p = .042$.

Table 1
Participants' Baseline Data by Treatment Group

Variable	Placebo ($n = 24$)	MTP ($n = 24$)
Age (years)		
M	35.8	38.3
SD	6.8	6.3
Male (%)	92 ($n = 22$)	88 ($n = 21$)
White (%)	79 ($n = 19$)	63 ($n = 15$)
No. days using cocaine in last 30 days		
M	13.75	13.29
SD	8.50	9.86
No. hyperactive symptoms		
M	6.25	5.42
SD	2.79	2.80
No. inattentive symptoms		
M	4.79	4.92
SD	2.84	2.99
Mean BDI scores		
M	20.2	24.7
SD	7.76	9.50
ASI		
Drug use		
M	.2392	.2093
SD	.0584	.0750
Alcohol use		
M	.1316	.1895
SD	.1690	.2123
Illegal activity		
M	.1190	.1155
SD	.1824	.1735
Medical condition		
M	.0982	.1179
SD	.1540	.2617
Family relations		
M	.3016	.3079
SD	.2492	.2946
Psychiatric status[a]		
M	.2738	.3910
SD	.1742	.1987
Employment		
M	.4000	.5007
SD	.2276	.2176
Any Axis I comorbidity (%)	50.0	62.5
Affective disorders (%)	50.0	58.3
Anxiety disorders (%)	12.5	12.5
Other Axis I disorders (%)	—	8.3

Note. MTP = methylphenidate; BDI = Beck Depression Inventory; ASI = Addiction Severity Index.
[a] $t(43) = 2.10$, $p = .042$.

Safety

Retention in the study did not differ by group; 58% of the placebo group and 45% of the MTP group completed the study. The mean number of visits attended did not differ by groups (placebo $M = 28.4$, MTP $M = 24.1$). However, 8% of the placebo group dropped out before Visit 12 (4 weeks) compared with 29% of the MTP group. Of the possible visits before dropout or completion, only 17% were missed by the placebo group and 12% by the MTP group. Compliance with medication was high in both groups; on aver-

age, 88.5% of the pills dispensed were reported to be taken as indicated. The mean dose for the MTP group was 26.25 mg ($SD = 6.47$).

Side effects were common before receiving medication (e.g., 83% of the placebo group and 67% of the MTP group complained of being anxious) and remained so for the duration of the study (Table 2). Severity of insomnia ($Z = 2.45$, $p = .014$) and sadness ($Z = 2.08$, $p = .038$) were higher in the MTP group at baseline. Occurrence of insomnia or trouble sleeping was also higher in the MTP group during the course of the study, $\chi^2(1, N = 48) = 4.09$, $p = .043$. Study medication was discontinued in 1 participant because of side effects; this individual was later determined to have been assigned to the placebo group. Overall 25% of the MTP group had their dose decreased versus 8% for the placebo group (Fisher's exact test, $p = ns$).

Adverse events were reported in 2 participants assigned to the MTP group. A 51-year-old man had an elevated blood pressure of 178/112 on one occasion, and a 55-year-old man had an episode of disorientation, insomnia, and anxiety lasting several hours. These clinical events resolved with a reduction of MTP dose.

There were no group differences in the proportion of participants guessing their study medication correctly by group at any time. The percentage guessing correctly out of three choices at the end of the 1st month was 44% (44% for placebo and 43% for MTP) and only increased slightly to 55% at the end of the 3rd month.

ADHD Symptoms Outcomes

There were no baseline group differences in the number of inattentive or hyperactive symptoms or their severity from the ADHD Symptom Checklist (Table 3). Using mixed-effects models that incorporate all follow-up information, there was no group effect for the inattentive symptoms; however, the MTP group had a marginal lower number of hyperactive symptoms, $F(1, 535) = 2.57$, $p = .1098$.

The physician-rated and self-rated efficacy indexes showed that improvements ranged from 1 (*very much improved*) to 4 (*no change*) on the 7-point scale (see Table 3). No one was rated or rated themselves as having their symptoms deteriorate during the study. The physician rated 21% of the placebo group as having moderate improvement versus 77% of the MTP group, $\chi^2(1, N = 48) = 8.32$, $p = .0039$. The MTP group rated themselves as significantly better than the placebo group ($M = 2.68$ vs. 1.93), $t(23) = 2.46$, $p = .02$.

Substance Use Outcomes

Cocaine use in the past month and mean ASI drug composite scores did not differ by group at baseline (see Table 3). During the study, there were no group differences in the proportion of days that participants reported using cocaine or in the amount of money they reported spending on cocaine. Overall, the placebo group spent a total $23,583 on cocaine during the course of the trial and the MTP group spent $15,520. Although the median number of days to the

Table 2
Percentage of Participants Reporting Side Effects at Baseline and During Study

Side effects	Baseline		Worst occurrence during study	
	Placebo ($n = 24$)	MTP ($n = 24$)	Placebo ($n = 24$)	MTP ($n = 24$)
Chest pain	—	8	8	—
Palpitations	—	13	4	—
Dizzy	8	17	4	8
Stomachaches	13	13	13	13
Nightmares	17	21	13	21
Headaches	21	33	25	25
Nausea or upset stomach	25	21	21	33
Euphoric, unusually happy	29	17	29	42
Drowsiness	33	46	42	25
Tics or nervous movements	33	29	21	17
Decreased appetite	38	50	25	50
Insomnia or trouble sleeping[a]	42	63	33	63
Irritability	42	63	54	58
Sadness[a]	54	75	38	63
Talk less with others	54	46	50	46
Stare a lot or daydream	63	71	71	50
Anxious	83	67	63	79

Note. Severity of side effects was recorded on a 4-point Likert-type scale ranging from 0 (*not at all*) to 3 (*very much*). A side effect was counted as occurring if the participant indicated "pretty much" or "very much." The maximum severity of each side effect after randomization was used to assess worst occurrence during study. MTP = methylphenidate.
[a]Severity of insomnia ($Z = 2.45$, $p = .014$) and sadness ($Z = 2.08$, $p = .038$) were higher in the MTP group at baseline. Occurrence of insomnia or trouble sleeping was higher in the MTP group during the course of the study, $\chi^2(1, N = 48) = 4.09$, $p = .043$.

Table 3
ADHD Symptom and Cocaine Use Outcomes by Treatment Group

Variable	Placebo (n = 24)	MTP (n = 24)
No. inattentive symptoms		
M	2.83	2.13
SD	2.96	2.85
No. hyperactive symptoms		
M	4.78	3.42
SD	3.18	2.67
No. days using cocaine in past 30 days		
M	14.58	15.42
SD	2.91	3.29
Amount spent on cocaine in past 30 days		
M	$97.19	$62.54
SD	$124.88	$48.53
Longest continuous abstinence (days)		
M	5.17	5.17
SD	5.53	6.22
Urine samples tested negative for cocaine (%)		
M	0.42	0.50
SD	0.32	0.50
Physician efficacy ratings showing moderate improvement (1 or 2 on 7-point scale)*	21%	77%
Physician efficacy ratings at 4 weeks	44% (n = 18)	77% (n = 13)
Physician efficacy ratings at 8 weeks	36% (n = 12)	60% (n = 12)
Physician efficacy ratings at 12 weeks	56% (n = 11)	50% (n = 8)
Participant efficacy ratings showing moderate improvement (1 or 2 on 7-point scale) at last visit*	42%	73%
Participant efficacy ratings at last visit*		
M	2.68	1.88
SD	0.95	0.80
Participant efficacy ratings at 4 weeks[a]		
M	3.00	2.57
SD	0.88	0.85
Participant efficacy ratings at 8 weeks[b]*		
M	3.08	2.08
SD	0.90	0.79
Participant efficacy ratings at 12 weeks[c]		
M	2.64	1.75
SD	0.92	0.89

Note. MTP = methylphenidate.
[a] Placebo group n = 19; MTP group n = 14.
[b] Placebo group n = 12; MTP group n = 12.
[c] Placebo group n = 11; MTP group n = 8.
* $p < .05$.

first cocaine-negative urine sample was less in the MTP group (6 for the MTP group vs. 8 for the placebo group), the difference was not statistically significant. The percentage of cocaine-negative urine samples did not differ by group (42% for the placebo group vs. 50% for the MTP group), and the mean longest continuous abstinence from cocaine was identical for the two groups (5.17 days). The five subscale means of the Tiffany Cocaine Craving measure were similar at baseline by groups and showed no evidence of changing differentially by group over the trial.

Discussion

Consistent with results of uncontrolled trials of stimulant medications with adult ADHD substance abusers (Castaneda et al., 2000; Levin et al., 1998; Riggs et al., 1996; Schubiner et al., 1995; Turnquist et al., 1983), results of this study suggest that MTP may be safely administered to adults with comorbid ADHD and cocaine dependence. No participants required discontinuation of MTP because of adverse side effects. Requests for dose reductions were common and typically deemed to be clinically indicated, a scenario that is common in the treatment of ADHD among non-cocaine-dependent patients. However, the frequency of dose reduction requests is particularly interesting given the known propensity of study participants to abuse stimulants such as cocaine. These results are also consistent with the findings of Grabowski et al. (Grabowski et al., 1997, 2001; Roache, Grabowski, Schmitz, Creson, & Rhoades, 2000), who did not find serious adverse effects in three studies using stimulants in cocaine-dependent adults who did not have ADHD.

Regarding the efficacy of MTP to alleviate ADHD symptomatology among cocaine-dependent adults, patients' weekly checklist of symptom ratings did not reveal a significant effect, although there was a trend toward symptom reduction in the hyperactive-impulsive domain. The relatively small sample size limited our power to detect significant changes using the count of symptoms. However, on the global improvement efficacy indexes, a more subjective ratings scale, physician and participants ratings showed greater improvement for those on active medication but not at all points during the study. It is not surprising that ADHD symptomatology was attenuated in both groups, because all participants were exposed to an intensive outpatient therapy regimen that included twice-weekly group therapy and once-weekly individual therapy; the latter was designed specifically to help participants develop skills for better management of ADHD-related deficits. Others have reported considerable benefit from cognitive–behavioral approaches, particularly in combination with pharmacotherapy, for the treatment of ADHD (Johnston & Leung, 2001; Murphy, 1995a; Searight, Burke, & Rottnek, 2000).

The question of adequate study anonymity is important. Although research staff and participants were unaware of medication group status, effects of stimulant medications may appear to be obvious at times. We did not find significant differences in participants' perceptions of which medication they were taking, nor were there differences in the frequency of requests for dose adjustments. However, it is possible that the physician was able to guess treatment assignment. We recommend that future trials incorporate physician's perception of drug assignment.

With respect to cocaine use, results indicate no difference in self-reported cocaine use, amount of money spent on cocaine, or frequency of cocaine-negative urine specimens between the two groups. Although there has been concern that MTP might cause an increase in cocaine use, our data do not substantiate that hypothesis. This suggests that cocaine dependence and ADHD may not be tightly linked pathophysiologically. We found no evidence of differentially decreased craving, suggesting that MTP may not act to alter receptors involved in cocaine use and craving. It may be that chronic cocaine usage alters brain function to such a degree that MTP's efficacy is compromised relative to that found for ADHD patients who are not cocaine dependent (Bartzokis, Beckson, et al., 1999; Bartzokis, Goldstein, et al., 1999).

Our results do not support the interpretation of "kindling" of cocaine use by MTP (i.e., cocaine use did not increase among those taking MTP). This is consistent with the work of Grabowski et al., who did not find evidence of increased craving among cocaine-dependent adults treated with MTP (Grabowski et al., 1997; Roache et al., 2000). This is interesting given the results of a 2001 study by Rush and Baker demonstrating that MTP produces similar effects on measures of abuse potential to cocaine. Our clinical experience suggests that few patients with ADHD and substance abuse experience an increase in drug use once treated with stimulant medications, whereas many appear to benefit from treatment of ADHD.

This study is limited by its small sample size and large number of statistical tests. Because of recruitment difficulties, target numbers were not achieved. It is interesting to reflect on this in light of the apparent prevalence of ADHD among cocaine abusers. Our telephone screening techniques identified 338 of 932 (36%) as candidates (i.e., likely having cocaine dependence and ADHD). However, we were only able to interview 106 individuals, usually because of the social and psychological difficulties created by cocaine dependence.

A substantial proportion of participants dropped out of the study, including 55% of the MTP group. Although this is comparable to similar studies (Grabowski et al., 1997), caution is warranted in the interpretation of our findings. We were not able to monitor participants after the study concluded, and it is possible that some participants in the MTP group had exacerbations of cocaine use or MTP-related side effects that were not captured in our data. Therefore, our findings regarding the safety of MTP and lack of evidence for priming should be seen as preliminary.

We assessed adherence to the study medications by self-report rather than biological markers or electronic devices. This may have caused an overestimation of adherence or an underestimation of MTP abuse. However, participants were monitored very closely during the study and were not given more than a 3-day supply of MTP at any time.

This study used immediate-release MTP as the active agent. There are now longer acting stimulant medications available (e.g., MTP delivery systems such as Concerta and amphetamine/dextroamphetamine [Adderall-XR]) that appear to have advantages over immediate-release MTP in the treatment of adult ADHD. It is, therefore, possible that use of these medications may have better results in this population.

We found additional comorbidity in our population, such as high rates of affective disorders, which is likely to complicate treatment. Schmitz et al. (2000) demonstrated that, compared with their nondepressed counterparts, depressed, cocaine-abusing patients had more overall distress, poorer psychiatric functioning, higher rates of anti-social personality disorder, higher cocaine cravings, and lower self-efficacy to refrain from cocaine use. This study was not designed for treatment of depression, and future studies should consider treatment for affective disorders in addition to ADHD in this population.

Although we did not demonstrate a reduction in cocaine use, neither was there evidence of an increase in cocaine use (i.e., kindling) nor a large number of MTP-related side effects (i.e., sensitization). It has been shown that ADHD can adversely affect substance abuse treatment outcome (Biederman et al., 1998; Carroll & Rounsaville, 1993; Whitmore et al., 1997), and it appears clear that such dually diagnosed patients provide a challenge to effective substance abuse treatment. Although medical therapy for ADHD in this population resulted in subjective symptom improvement while participants were in treatment, it is not a panacea for cocaine dependence. Physicians are wise to remain cognizant of abuse potential; however, our results suggest that MTP may be safely and effectively used to treat ADHD in a population of cocaine-dependent adults. Because of the sizable prevalence of ADHD among those with drug dependence and the importance of developing active medications for treatment of cocaine abuse, we believe that future studies of agonist therapies can proceed based on the results of this trial. In addition to the newer stimulants, nonstimulant medications, such as atomoxetine (Spencer et al., 1998) and bupropion (Wilens et al., 2001), have been shown to be effective in the treatment of ADHD. Evaluation of some of these agents as well as larger trials with stimulants should be conducted for adults with cocaine dependence and ADHD.

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