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Abuse Potential of Oral Phendimetrazine in Cocaine-Dependent Individuals: Implications for Agonist-like Replacement Therapy

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Abstract

Objectives—Phendimetrazine is a prodrug for the monoamine releaser phenmetrazine, a drug with known abuse potential. Preclinical studies suggest that phendimetrazine has limited abuse potential and may have promise as an agonist-like replacement therapy for cocaine dependence. This study evaluated the abuse potential of phendimetrazine in humans.

Methods—Nine cocaine-dependent individuals (N = 9) were enrolled to investigate the abuse potential of phendimetrazine and d-amphetamine using a double blind, placebo-controlled, within-subject design. Subjective and cardiovascular effects of oral phendimetrazine (35, 70, and 105 mg), d-amphetamine (10, 20, and 30 mg), and placebo were assessed in quasi-random order across eight sessions lasting approximately eight hours each.

Results—d-Amphetamine (20 and 30 mg) significantly increased cardiovascular measures in a time- and dose-related manner but phendimetrazine did not systematically alter cardiovascular measures. Although d-amphetamine and phendimetrazine significantly increased ratings indicative of abuse potential (e.g., drug liking) and stimulant-like effects relative to placebo, these increases were generally small in magnitude, with phendimetrazine producing significant effects on fewer abuse-related measures and at fewer time points than d-amphetamine.

Conclusions—These preliminary findings suggest that oral phendimetrazine and d-amphetamine may have limited abuse potential in cocaine-dependent individuals. These findings

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collectively emphasize that the clinical utility of medications to treat cocaine-use disorders should be weighed carefully against their potential for abuse and diversion, with careful attention paid to evaluating abuse potential in a clinically relevant population of interest. Future studies are needed to further elucidate the potential utility of phendimetrazine as an agonist-like replacement therapy for cocaine dependence.

Keywords

phendimetrazine; subjective effects; abuse potential; cocaine dependence; agonist replacement therapy

Introduction

The identification of putative pharmacotherapies to manage cocaine-use disorders is a high priority (Montoya and Vocci, 2008; Kampman, 2008) but few promising medications have been identified and even the most promising candidates demonstrate limited efficacy (Elkashef et al., 2008; Herin et al., 2010; Karila et al., 2010; Brensilver et al., 2013). Cocaine enhances extracellular concentrations of dopamine, serotonin, and norepinephrine by inhibiting the reuptake of these neurotransmitters at their respective transporters. Cocaine may also cause a conformational change at the transporter that allows neurotransmitter to passively “leak” from the cell, further enhancing extracellular neurotransmitter concentrations via inverse agonism (Heal et al., 2014). Therefore, drugs that increase extracellular monoamine concentrations (i.e., monoamine agonists) may have utility in the treatment of cocaine-use disorders.

A uniform finding in the medications development literature at the preclinical, human laboratory, and clinical levels of analysis is that monoamine releasers reduce cocaine intake (Grabowski et al., 2004; Herin et al., 2010; Longo et al., 2010; Mooney et al., 2009; Stoops and Rush, 2013). Despite the efficacy of agonist replacement therapies for the management of opioid and nicotine dependence (Henningfield, 1995; Ling et al., 1994), many agonist medications are considered to have high abuse and diversion potential. Coupled with negative sociopolitical perceptions of agonist replacement and harm-reduction approaches (Matheson et al., 2013), support for this therapeutic strategy remains anemic.

Phendimetrazine (Bontril®), a DEA schedule III medication in the United States, is used to treat obesity. Phendimetrazine is a weak monoamine releaser but is metabolized into phenmetrazine, a more potent norepinephrine and dopamine releaser with known abuse potential (Rothman et al., 2002; Chait et al., 1987; Corwin et al., 1987). As phendimetrazine is a prodrug for phenmetrazine, it has a slower onset and likely has decreased abuse potential (Balster and Schuster, 1973; Schindler et al., 2009; Huttunen et al., 2011). Phendimetrazine shares discriminative stimulus effects with d-amphetamine and cocaine (Banks et al., 2013a; de la Garza and Johanson, 1987; Evans and Johanson, 1987) but is a less potent locomotor stimulant than d-amphetamine and methamphetamine (Jones and Holtzman, 1994). Phendimetrazine is a relatively weak reinforcer and maintains drug self-administration under limited conditions (Corwin et al., 1987; Griffiths et al., 1979). Phendimetrazine also reduces cocaine-choice behavior and attenuates cocaine self-administration in non-human primates

(Banks et al., 2013b, 2013c). These findings collectively suggest that phendimetrazine may have promise as a putative pharmacotherapy for cocaine-use disorders.

The abuse potential of phendimetrazine has yet to be systematically evaluated in humans, however, which limits a full understanding of the feasibility of its use to treat cocaine dependence. This study compared the abuse potential of oral phendimetrazine and d-amphetamine (positive control, with demonstrated abuse potential in stimulant users [Stoops et al., 2005]) to placebo in a sample of cocaine-dependent volunteers. These individuals were selected because they would be most likely to receive phendimetrazine therapeutically if it were adopted as a medication to reduce cocaine use. We hypothesized that d-amphetamine would significantly increase cardiovascular measures and ratings of positive, abuse-related subjective effects compared to placebo but phendimetrazine would not significantly increase ratings on these measures. Cardiovascular outcomes (i.e., heart rate and blood pressure) and ratings of positive subjective effects (e.g., Like Drug) and drug strength (e.g., Any Effect) were the primary dependent measures.

Methods

Subjects

Nine (N = 9) volunteers who met diagnostic criteria for Cocaine Dependence according to the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV; American Psychiatric Association, 2000) were enrolled in this study. One volunteer also met diagnostic criteria for alcohol dependence but was not physiologically dependent and was therefore not excluded from participation. Volunteers had experience with a variety of other substances but did not meet dependence criteria for any of these drugs. Sample characteristics are presented in Table 1. Briefly, volunteers were required to be between the ages of 18 and 55, have a recent history of cocaine use (verified by a benzoylecgonine positive urine drug screen), be without contraindications to d-amphetamine or phendimetrazine, meet diagnostic criteria for Cocaine Abuse or Dependence as determined by a computerized version of the Structured Clinical Interview for the DSM-IV, use a medically effective form of birth control (females only), and be otherwise healthy as judged by the study physician. Volunteers with current or past histories of significant physical disease, cardiovascular disease, chronic obstructive pulmonary disease, head trauma or central nervous system tumors, seizure disorder, and serious psychiatric disorders other than substance abuse or dependence were excluded from participation. The consent document and experimental procedures were approved by the Institutional Review Board at the University of Kentucky Medical Center and were conducted according to guidelines established in the Declaration of Helsinki.

Drugs

Drug doses were prepared by over-encapsulating commercially available immediate-release formulations of d-amphetamine (10 mg; Barr Labs, Pomona, NY, U.S.A.) and phendimetrazine (35 mg; Valeant Pharmaceuticals International Inc., Laval, Quebec, Canada) with cornstarch in opaque capsules. Placebo capsules contained only cornstarch. The doses of d-amphetamine were selected based on previous studies that have determined the behavioral effects of d-amphetamine in human subjects with a history of stimulant use

(e.g., Marks et al., 2014; Oliveto et al., 1998; Stoops et al., 2004, 2007). Phendimetrazine doses (35, 70, and 105 mg) were selected because these doses are commonly prescribed to treat obesity.

Study design

This within-subject, double blind, placebo-controlled study consisted of one practice and eight experimental sessions. One volunteer had to repeat a session due to technical difficulties. Volunteers were familiarized with the daily routine and experimental procedures during the practice session but no medications were administered. During each experimental session, volunteers received one of eight possible dose conditions (placebo [twice], 10, 20, or 30 mg d-amphetamine and 35, 70, or 105 mg phendimetrazine). All volunteers received placebo and each dose of d-amphetamine and phendimetrazine in random order except that they received a lower dose of each drug before receiving the highest dose. This strategy was employed to improve safety and reduce the likelihood of an adverse reaction to the highest dose of either drug. Placebo was administered twice and the data from these sessions were subsequently averaged to reduce the potential impact of expectancy effects on placebo responses (i.e., a placebo effect). Determination of responding following multiple exposures to a treatment condition is a common control procedure in behavioral pharmacology studies (e.g., Makris et al., 2007).

Procedures

Upon arrival, volunteers were fed a low-fat breakfast, completed a field sobriety test, and provided an expired-air sample that was tested for the presence of alcohol using a hand-held breathalyzer (Intoximeter Inc., St. Louis, MO, U.S.A.). Expired breath carbon monoxide levels (piCO⁺ Smokerlyzer, Bedfont Scientific Ltd., Kent, England) were also required to be 10 ppm to reduce the likelihood that volunteers had recently used cannabis. Volunteers also provided a urine specimen that was screened for the presence of amphetamines, benzodiazepines, barbiturates, cocaine, cannabis, and opioids. If an expired-air sample was positive for alcohol or if a urine sample was positive for illicit drugs other than cannabis, cocaine, or experimentally administered d-amphetamine, the session was rescheduled.

Urine drug screens were positive for Δ^9 -tetrahydrocannabinol (Δ^9 -THC; i.e., cannabis) before an average of 3.78 sessions (range 0–8). Three volunteers provided Δ^9 -THC-positive urine specimens before each session and three never tested positive for Δ^9 -THC. The remaining three presented urine specimens that were positive for Δ^9 -THC in 1–5 sessions. Benzoyllecgonine (i.e., cocaine) positive urine specimens were obtained prior to an average of 6.78 sessions (range 1–9). Eight volunteers provided benzoyllecgonine positive urine samples prior to six or more sessions. Urine drug screens were positive for d-amphetamine an average of 1.11 times (range 0–2) during the study. Eight volunteers were positive for d-amphetamine at least once and all positive urine drug screens were only obtained on sessions that immediately followed experimental administration of d-amphetamine. Urine pregnancy tests for female volunteers were negative throughout the study.

At the outset of each session, cardiovascular indices were recorded starting at approximately 90 min before dose administration and once every 30 min for the remainder of the session

using an automated digital vital-signs monitor (Dinamap Pro, GE Medical Systems, Milwaukee, WI, U.S.A.). Baseline subjective-effects measures were collected 30 min prior to dosing. Drug administration took place at approximately 1000 hours and then the subjective-effects battery was completed once per hour for the remainder of the session. Lunch was provided at approximately 1300 hours. Volunteers who reported daily cigarette smoking were allowed to smoke one cigarette approximately 1 hour prior to dose administration and 30 min after lunch. At the 6-hour time point, volunteers also completed the Street Value and End-of-Day Questionnaires. Volunteers were then discharged if their vital signs and sobriety were within acceptable limits. Experimental sessions were separated by at least 24 hours. This minimum interval between sessions was chosen on the basis of pharmacokinetic data that indicate that the half-life of d-amphetamine is 8–10 hours (Angrist et al., 1987) and the half-life of phendimetrazine is approximately 2 hours (8 hours for phenmetrazine; Dart, 2004), allowing at least two half-lives to elapse between sessions. The average length between sessions was 2.8 days.

Subjective-effects battery

The subjective-effects battery was administered on an Apple Macintosh computer (Apple, Cupertino, CA, U.S.A.) and included the short form of the Addiction Research Center Inventory (ARCI; Haertzen et al., 1963; Martin et al., 1971; Jasinski, 1977), the Adjective Rating Scale (Oliveto et al., 1992), and a 20-item investigator-developed Drug-Effect Questionnaire (Rush et al., 2003; Stoops et al., 2003). A Street Value Questionnaire asked volunteers what the drug dose they received would be worth on the street. The End-of-Day Questionnaire asked volunteers to rate the overall “Strength,” “Liking,” “Good Effects,” “Bad Effects,” and “Desire to Take Again” of the dose they received on a 100-unit visual-analog scale. Because planned comparisons did not reveal significant differences between active doses and placebo on any item from the End-of-Day or Street Value Questionnaires these measures are not discussed further.

Data analysis

The alpha level was set at $P < 0.05$ for planned comparisons based upon our hypotheses and was not adjusted for multiple comparisons. Dunnett’s test was used to compare the effects of active drug doses to averaged placebo responses at each time point tested for all outcomes. Planned comparisons were conducted in the context of two-way repeated-measures analyses of variance (ANOVAs) based upon a priori hypotheses. Omnibus F -tests revealed significant main effects of Time but there were no significant main effects of Dose or Dose $\times$ Time interactions. Because main effects of Time are not particularly informative and planned comparisons are not dependent upon the results of omnibus ANOVAs, we focus on the results of the comparisons of interest below (Ruxton and Beauchamp, 2008; Sokal and Rohlf, 1995). We did not control for any other variables in these analyses and the effects of dosing order were not evaluated in this study. We hypothesized that d-amphetamine would significantly increase heart rate and blood pressure, ratings of positive subjective effects such as Like Drug, and measures indicative of drug strength such as Any Effect compared to placebo. Phendimetrazine was not hypothesized to significantly alter cardiovascular function or increase ratings on these subjective-effects measures relative to placebo.

Results

Cardiovascular effects

Figure 1 shows time-course data for systolic and diastolic blood pressure and heart rate following acute administration of immediate release d-amphetamine (left) and phendimetrazine (right). The intermediate and high doses of d-amphetamine (20 and 30 mg) increased systolic blood pressure in a dose- and time-related manner compared to placebo. Peak increases in systolic blood pressure were observed approximately 2.5 to 3 hours following oral administration of d-amphetamine. The high dose of d-amphetamine also increased diastolic blood pressure at several time points but these effects were less systematic compared to its effects on systolic blood pressure. Phendimetrazine did not significantly affect systolic or diastolic blood pressure relative to placebo. d-Amphetamine and phendimetrazine produced similar increases in heart rate relative to placebo across the six-hour session but these increases were generally small in magnitude (i.e., less than 10 bpm) and somewhat less orderly than those observed on blood pressure.

Subjective effects

Addiction Research Center Inventory (ARCI)—Planned comparisons revealed significant increases in ratings on the A, LSD, and PCAG subscales of the ARCI at the pre-dosing time point for 10 mg of d-amphetamine but there were no significant differences from placebo on any subscale of the ARCI for any dose of d-amphetamine or phendimetrazine following drug administration (data not shown).

Adjective Rating Scale—The low and high dose of d-amphetamine and the high dose of phendimetrazine significantly increased ratings on the stimulant subscale of the Adjective Rating Scale (see Tables 2 and 3). Increased ratings on items in the stimulant subscale were evident within 1 hour at the lowest dose of d-amphetamine but dissipated rapidly. Similar statistically significant increases were observed for the highest dose of d-amphetamine at the 2- and 4-hour time points and at the 3-hour time point for the high dose of phendimetrazine. Neither drug significantly increased ratings of sedative-like effects.

Drug-Effect Questionnaire—Figure 2 shows time-course data for subject ratings on four representative measures from the Drug-Effect Questionnaire: “Any Effect” (top), “Stimulated” (second row), “Like Drug” (third row), and “Bad Effects” (bottom). Ratings of “Any Effect” were significantly elevated 2–5 hours following the intermediate dose (20 mg) of d-amphetamine and 2–3 hours after the high dose (30 mg) of d-amphetamine compared to placebo. Effect sizes (d_z) for peak increases on ratings of “Any Effect” following the 20 and 30 mg doses of d-amphetamine were 1.44 and 1.68, respectively. A similar dose- and time-related pattern of ratings for “Any Effect” was evident following oral phendimetrazine but these ratings were generally smaller in absolute magnitude relative to d-amphetamine and were not statistically different from placebo at any time point. Effect sizes for peak ratings of “Any Effect” following the low, intermediate, and high doses of oral phendimetrazine were 0.35, 0.40, and 0.84, respectively.

d-Amphetamine significantly increased ratings of positive, abuse-related effects (e.g., “Euphoric,” “Good Effects,” “High,” “Like Drug,” “Willing to Pay For,” and “Willing to Take Again”) and stimulant-like effects (e.g., “Restless,” “Stimulated,” and “Talkative-Friendly”). Figure 2 shows representative outcomes for “Like Drug” and “Stimulated.” At peak effect for ratings of “Like Drug” following oral d-amphetamine, effect sizes ranged from 0.56 to 1.04. Phendimetrazine increased ratings on a smaller number of positive items at fewer time points relative to d-amphetamine. For example, phendimetrazine significantly increased ratings of “Like Drug” at only the 3-hour time point for the 70 mg dose (effect sizes at peak ranged from 0.15 to 0.54; see Figure 2 and Table 2).

The highest doses of d-amphetamine (20 and 30 mg) also transiently increased some ratings of negative subjective effects such as “Anxious,” “Bad Effects,” (see Figure 2) and “Performance Impaired.” Similarly, the low dose of phendimetrazine (35 mg) increased ratings of “Bad Effects” at the 3-hour time point and the highest and lowest dose of phendimetrazine significantly increased ratings of “Nauseous” at the 2- or 3-hour time point, respectively. Peak increases in ratings on items from the Drug-Effect Questionnaire generally occurred 2–3 hours after administration of d-amphetamine and phendimetrazine. Although both drugs sporadically increased ratings of positive, negative, and stimulant-like effects these increases were lower in absolute magnitude and less persistent compared to ratings of global drug effects (i.e., “Any Effect”). The mean difference from averaged placebo on ratings of other subjective-effects measures that were significantly affected by d-amphetamine and phendimetrazine across the 6-hour session is shown in Table 2 and Table 3, respectively.

Discussion

This study compared the abuse potential of oral phendimetrazine and d-amphetamine to placebo in cocaine-dependent individuals. Phendimetrazine did not significantly increase blood pressure above placebo in a dose- or time-dependent fashion at any dose tested. In contrast, higher doses of d-amphetamine significantly increased systolic blood pressure as an orderly function of time and dose. The cardiovascular effects of d-amphetamine were similar in absolute magnitude to those reported previously (Marks et al., 2014; Rush et al., 2004; Stoops et al., 2007). d-Amphetamine significantly increased ratings on several measures from the subjective-effects battery that reflect increased abuse potential (e.g., “Euphoric,” “High,” “Like Drug,” “Willing to Take Again”). Phendimetrazine only significantly increased ratings of “Like Drug” at a single time point following oral administration of the 70 mg dose. Both drugs increased ratings on measures of stimulant-like effects (e.g., “Stimulated” and “Restless”). These findings collectively suggest that although the effects of d-amphetamine and phendimetrazine were detectable and increased ratings of positive and stimulant-like effects, orally administered phendimetrazine appears to have relatively low abuse potential in non-treatment-seeking, cocaine-dependent individuals. Increases in positive subjective drug effects were also relatively transient and small in absolute magnitude following oral d-amphetamine administration in the current study. This route of administration also produces slower onset of effects relative to other routes. So, although it is unlikely devoid of abuse potential because of the medium to large effect sizes obtained at

peak effect, oral d-amphetamine may also have relatively limited potential for abuse in cocaine-dependent individuals.

Few studies have investigated the abuse-related behavioral effects of phendimetrazine and this is the first study to assess the abuse potential of phendimetrazine in humans. Phendimetrazine increases drug-appropriate responding in animals trained to discriminate d-amphetamine (de la Garza and Johanson, 1987; Evans and Johanson, 1987) and cocaine (Banks et al., 2013a) suggesting that it may have some potential for abuse. Phendimetrazine maintained responding in only one of two existing self-administration studies (Corwin et al., 1987; Griffiths et al., 1979). This discrepancy may be attributed to differences in phendimetrazine doses between studies as doses lower than 0.5 mg/kg/infusion failed to function as reinforcers. The current findings extend the existing literature to suggest that acute oral phendimetrazine may have limited abuse potential in cocaine-dependent humans, but higher doses likely need to be tested.

Phendimetrazine may be a promising agonist-like replacement because it attenuated the reinforcing effects of cocaine in non-human primates (Banks et al., 2013b, 2013c). That phendimetrazine did not persistently increase ratings on measures indicative of abuse potential in the current study provides additional support for its use to treat cocaine dependence. Although subjective-effects measures are useful and reliable indicators of abuse potential, they do not always parallel patterns of naturalistic drug-taking behavior (Bolin et al., 2013). Drug self-administration procedures more effectively evaluate the reinforcing effects of drugs (Bolin et al., 2013; Comer et al., 2008; Jones and Comer, 2013) and future studies are needed to assess the reinforcing effects of phendimetrazine and its effect on cocaine self-administration in humans.

As indicated above, oral d-amphetamine may also have limited abuse potential in this population. Although d-amphetamine typically increases ratings of abuse-related subjective effects (e.g., Foltin and Fischman, 1991; Schuh et al., 2000; Rush et al., 2001; Stoops et al., 2004; Stoops et al., 2007; Sevak et al., 2010; Vansickel et al., 2010), a critical consideration is that recreational or subclinical populations of stimulant users were enrolled in many previous studies. Cocaine-dependent individuals who use cocaine regularly may be less sensitive to oral d-amphetamine. Comer and colleagues (2013) recently reported that smoked cocaine (12, 25, and 50 mg) significantly increased ratings of “Drug Liking,” “High,” and “Pay for the Drug” in heavy cocaine users but oral d-amphetamine (10 and 20 mg) did not. Reporting of subjective drug effects may also be influenced by other procedural factors. For example, oral d-amphetamine (15 and 30 mg) increased ratings of “Good Effects” and “High” in a recent study with a similar sample of cocaine users (Marks et al., 2014) and the absolute magnitude of these ratings were, in some cases, more than double those observed in the current study. In the study by Marks and colleagues (2014), volunteers were encouraged to attend to the effects of the drug because they could choose to take the drug in a later session. The lack of a self-administration component and/or different instruction set in the current study may account for the differences in the relative magnitude of the effects of d-amphetamine between these studies. In line with Comer and colleagues (2013), the current findings may suggest that, although it is likely not devoid of abuse

potential, oral d-amphetamine may have relatively limited abuse potential under certain conditions in cocaine-dependent individuals.

These findings collectively highlight two key factors that affect the abuse potential of candidate medications for cocaine dependence. Route of administration and rate of onset are critically important in determining abuse potential (Grabowski et al., 2004; Carter and Griffiths, 2009) as a slow rate of onset and lower magnitude drug effect likely contributes to the low abuse potential of orally administered medications (Kollins et al., 1998). The abuse-related behavioral effects of agonist medications may also vary as a function of drug use history. Studies with clinically relevant samples (i.e., active stimulant drug users) are most informative in this regard (Grabowski et al., 2004; Carter and Griffiths, 2009). When making clinical decisions regarding the use of agonist-like medications to treat cocaine-use disorders, the potential for diversion and abuse of a candidate medication should be weighed carefully against its therapeutic efficacy. Phendimetrazine may have a low risk of diversion because it must first be metabolized to phenmetrazine, which slows the rate of onset of its effects and prohibits diversion to use by other routes (e.g., intranasal insufflation).

Although the current study provides preliminary insight into the abuse-potential of phendimetrazine in humans, several limitations are apparent. First, the use of a chronic dosing regimen would more closely approximate the therapeutic use of phendimetrazine. Second, the effects of d-amphetamine and phendimetrazine were determined following a single exposure to each active dose. A more rigorous investigation of the behavioral effects of these drugs would involve multiple exposures to each active dose. However, we chose not to employ this strategy to minimize the number of drug exposures (i.e., to enhance safety) and reduce the burden on volunteers. Third, volunteers were not required to abstain from using cocaine outside of experimental sessions, which may have reduced their sensitivity to the effects of the study medications. Perhaps the behavioral effects of phendimetrazine and d-amphetamine would be more pronounced in individuals who are in remission from their cocaine use. Fourth, there is a possibility that the administration of medication in one session may have affected responding in subsequent sessions. Despite the use of a relatively short 24-hour washout period, we feel confident that carryover effects were unlikely to have occurred because at least 2 half-lives had passed between sessions and there were no systematic differences in responding on outcome measures at baseline or during sessions in which a d-amphetamine positive urine result was obtained. Lastly, a relatively small sample size ($N = 9$) was used in the current study. As a result, the present study was only adequately powered to detect very large effects on all measures with planned pair-wise comparisons (i.e., minimum detectable effect size of $d_z = 1.06$). Because of the potentially inflated Type II error rate, these results do not permit definitive conclusions regarding the abuse potential of these medications in cocaine users but can be used to inform the design of larger studies to evaluate their abuse potential with greater confidence. Sample sizes of 34 and 199 would be needed to detect medium ($d_z = 0.5$) and small ($d_z = 0.2$) effects, respectively, with 80% power for all measures reported above using planned pair-wise comparisons. Although statistical power is an important consideration from a scientific standpoint, a careful balance must be struck between scientific rigor and the efficient use of resources and ethical issues (e.g., risks to participants) in designing and conducting behavioral studies that involve the administration of medications to human subjects.

Conclusions

In sum, these findings should be considered preliminary and interpreted cautiously but suggest limited abuse potential for oral, immediate release phendimetrazine. These outcomes may support the viability of phendimetrazine as a putative pharmacotherapy for cocaine dependence. Although findings from studies that rely on subjective effects may be used to make some preliminary assertions about abuse potential, there is no standardized or accepted threshold that is considered to be indicative of enhanced abuse potential per se. Therefore, findings from other lines of research (e.g., drug self-administration, post-marketing studies, etc.) are needed for the most rigorous and informative assessment of abuse potential. Future studies are also needed to determine the influence of phendimetrazine maintenance on the abuse-related and reinforcing effects of cocaine. The current findings point to the importance of assessing the abuse potential of candidate medications for cocaine dependence in the most appropriate and clinically relevant population, cocaine-dependent individuals, as they may respond differently to these medications than recreational stimulant users. Although many monoamine agonist (e.g., d-amphetamine) and agonist-like (e.g., phendimetrazine) medications carry some inherent risk for abuse and diversion, their efficacy to reduce cocaine use in clinically relevant populations suggest that these risks should be carefully considered along with potential clinical benefits to guide decisions regarding the use of pharmacotherapeutic interventions in cocaine-dependent individuals.

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Figure 1.

Mean time-course data for systolic and diastolic blood pressure expressed as millimeters of mercury (mmHg) and heart rate expressed as beats per minute (bpm) following oral d-amphetamine (left panel) and phendimetrazine (right panel). Open circles represent averaged placebo. Open squares represent the respective low dose of d-amphetamine (10 mg) and phendimetrazine (35 mg), inverted triangles represent the intermediate doses (20 and 70 mg, respectively), and open diamonds represent the high doses (30 mg and 105 mg, respectively). The same averaged placebo data are shown in both panels for reference. Filled symbols indicate a significant difference from placebo at a given time point ($P < 0.05$). Error bars are omitted for clarity.

Figure 2.

Mean time-course data for subject ratings of Any Effect (top); Stimulated (second row); Like Drug (third row); and Bad Effects (bottom) from the Drug-Effect Questionnaire following oral d-amphetamine (left panels), phendimetrazine (right panels), and averaged placebo (both panels). The remaining details are the same as those for Figure 1.

TABLE 1

Sample characteristics (N = 9)
Sample demographic information.

Age (years)	39.33 (29–48)
Sex (n)	
Male:Female	5:4
Race (n)	
African-American	7
Caucasian	2
Weight (kg)	71.29 (54.8–82.1)
Past-month Cocaine Use	
Amount used (g)	7.9 (1–25)
Days used	10.5 (3–25)
Alcohol drinks/week	14.22 (< 1–30)
Daily Tobacco Use	
Cigarettes (n = 7)	9.5 (3–20)
Cigarillos (n = 1)	3

Note: Table values are presented as mean (range) unless otherwise noted

TABLE 2

d-Amphetamine Subjective Effects

Mean differences and standard deviation from averaged placebo on subjective-effects ratings for each dose of oral d-amphetamine across the 6-hour session.

	PRE	1	2	3	4	5	6
10 mg d-Amphetamine							
Adjective Rating Scale							
Stimulant	-0.28 (2.04)	1.94 (2.04)	1.39 (2.04)	0.61 (2.04)	0.56 (2.04)	0.72 (2.04)	1.11 (2.04)
Drug Effect Questionnaire							
Euphoric	2.39 (6.29)	3.17 (6.29)	5.83 (6.29)	3.56 (6.29)	4.94 (6.29)	4.00 (6.29)	1.94 (6.29)
Good Effects	2.28 (6.95)	4.72 (6.95)	0.83 (6.95)	6.50 (6.95)	1.72 (6.95)	3.17 (6.95)	1.07 (6.95)
Like Drug	2.22 (7.00)	7.28 (7.00)	2.39 (7.00)	6.56 (7.00)	1.94 (7.00)	-0.39 (7.00)	0.50 (7.00)
Rush	2.11 (5.59)	-1.06 (5.59)	5.61 (5.59)	6.22 (5.59)	1.61 (5.59)	0.89 (5.59)	1.56 (5.59)
Stimulated	2.11 (6.52)	3.94 (6.52)	0.28 (6.52)	6.56 (6.52)	1.39 (6.52)	2.17 (6.52)	-1.44 (6.52)
Willing to Pay For	2.17 (5.01)	4.33 (5.01)	4.00 (5.01)	-0.44 (5.01)	0.78 (5.01)	-4.11 (5.01)	-1.00 (5.01)
Willing to Take Again	2.11 (7.22)	7.11 (7.22)	4.39 (7.22)	4.67 (7.22)	-2.72 (7.22)	-4.28 (7.22)	0.56 (7.22)
20 mg d-Amphetamine							
Drug Effect Questionnaire							
Anxious	0.33 (4.49)	-1.61 (4.49)	2.06 (4.49)	-1.28 (4.49)	4.17 (4.49)	1.39 (4.49)	5.61 (4.49)
Any Effect	0.22 (8.98)	2.50 (8.98)	12.94 (8.98)	13.28 (8.98)	11.94 (8.98)	8.94 (8.98)	6.94 (8.98)
Bad Effects	0.06 (7.48)	0.11 (7.48)	2.39 (7.48)	6.22 (7.48)	8.33 (7.48)	5.67 (7.48)	1.50 (7.48)
Euphoric	0.06 (6.29)	4.06 (6.29)	6.94 (6.29)	6.00 (6.29)	2.17 (6.29)	3.33 (6.29)	3.72 (6.29)
High	0.11 (6.03)	2.06 (6.03)	6.33 (6.03)	3.44 (6.03)	2.39 (6.03)	5.11 (6.03)	3.67 (6.03)
Performance Impaired	0.0 (5.93)	0.05 (5.93)	6.22 (5.93)	3.61 (5.93)	3.94 (5.93)	0.89 (5.93)	0.89 (5.93)
Rush	-0.22 (5.59)	4.50 (5.59)	5.17 (5.59)	3.67 (5.59)	4.06 (5.59)	3.33 (5.59)	3.56 (5.59)
30 mg d-Amphetamine							
Adjective Rating Scale							
Stimulant	-0.06 (2.04)	1.28 (2.04)	2.06 (2.04)	1.72 (2.04)	2.22 (2.04)	1.50 (2.04)	0.89 (2.04)
Drug Effect Questionnaire							
Any Effect	0.11 (8.98)	5.94 (8.98)	12.28 (8.98)	15.17 (8.98)	6.72 (8.98)	7.61 (8.98)	6.50 (8.98)

	Time Point (Hours)						
	PRE	1	2	3	4	5	6
High	0.11 (6.03)	1.28 (6.03)	2.56 (6.03)	5.44 (6.03)	1.39 (6.03)	0.00 (6.03)	0.22 (6.03)
Restless	0.06 (4.37)	-2.17 (4.37)	4.39 (4.37)	3.06 (4.37)	1.17 (4.37)	1.94 (4.37)	1.89 (4.37)
Rush	0.11 (5.59)	3.17 (5.59)	5.83 (5.59)	6.33 (5.59)	3.39 (5.59)	1.33 (5.59)	0.56 (5.59)
Sluggish-Fatigued-Lazy	0.06 (9.67)	8.06 (9.67)	-2.50 (9.67)	1.17 (9.67)	0.56 (9.67)	8.50 (9.67)	7.50 (9.67)
Stimulated	-0.11 (6.52)	1.50 (6.52)	4.50 (6.52)	7.67 (6.52)	-0.17 (6.52)	0.50 (6.52)	1.11 (6.52)
Talkative-Friendly	0.06 (5.91)	1.78 (5.91)	4.00 (5.91)	-0.17 (5.91)	6.39 (5.91)	1.06 (5.91)	0.94 (5.91)

Note: Values are expressed as the Mean Difference (*SD*) from averaged placebo for subject ratings at each time point. Negative values represent a decrease relative to averaged placebo. Bolded values indicate a statistically significant difference from averaged placebo according to Dunnett's test, $P < 0.05$.

TABLE 3

Phendimetrazine Subjective Effects

Mean differences and standard deviation from averaged placebo on subjective-effects ratings for each dose of oral phendimetrazine across the 6-hour session.

	PRE	1	2	3	4	5	6
35 mg Phendimetrazine							
Drug Effect Questionnaire							
Active-Alert-Energetic	0.28 (10.42)	1.50 (10.42)	12.22 (10.42)	2.56 (10.42)	3.61 (10.42)	1.33 (10.42)	0.72 (10.42)
Bad Effects	0.17 (7.48)	2.00 (7.48)	1.83 (7.48)	6.89 (7.48)	1.67 (7.48)	0.11 (7.48)	-0.28 (7.48)
Nauseous	0.39 (5.62)	2.67 (5.62)	4.72 (5.62)	5.00 (5.62)	0.94 (5.62)	0.56 (5.62)	0.78 (5.62)
Sluggish-Fatigued-Lazy	0.61 (9.67)	9.06 (9.67)	-0.50 (9.67)	3.17 (9.67)	1.44 (9.67)	1.94 (9.67)	1.06 (9.67)
70 mg Phendimetrazine							
Drug Effect Questionnaire							
Like Drug	-0.11 (7.00)	0.17 (7.00)	3.83 (7.00)	6.44 (7.00)	2.50 (7.00)	2.39 (7.00)	0.39 (7.00)
Stimulated	0.33 (6.52)	2.61 (6.52)	2.83 (6.52)	5.67 (6.52)	2.50 (6.52)	2.72 (6.52)	1.78 (6.52)
Talkative-Friendly	0.06 (5.91)	0.89 (5.91)	3.89 (5.91)	2.06 (5.91)	5.17 (5.91)	3.17 (5.91)	3.39 (5.91)
105 mg Phendimetrazine							
Adjective Rating Scale							
Stimulant	-0.28 (2.04)	0.50 (2.04)	0.72 (2.04)	1.83 (2.04)	1.56 (2.04)	1.39 (2.04)	0.67 (2.04)
Drug Effect Questionnaire							
Nauseous	-0.06 (5.62)	2.56 (5.62)	4.94 (5.62)	4.00 (5.62)	2.61 (5.62)	2.56 (5.62)	1.00 (5.62)
Restless	-0.06 (4.37)	-0.50 (4.37)	4.17 (4.37)	0.83 (4.37)	1.72 (4.37)	1.28 (4.37)	1.22 (4.37)
Sluggish-Fatigued-Lazy	-0.06 (9.67)	5.17 (9.67)	1.17 (9.67)	4.39 (9.67)	3.11 (9.67)	9.50 (9.67)	2.28 (9.67)
Stimulated	0.11 (6.52)	4.72 (6.52)	5.83 (6.52)	4.78 (6.52)	2.83 (6.52)	1.50 (6.52)	1.33 (6.52)

Note: Values are expressed as the Mean Difference (*SD*) from averaged placebo for subject ratings at each time point. Negative values represent a decrease relative to averaged placebo. Bolded values indicate a statistically significant difference from averaged placebo according to Dunnett's test, $P < 0.05$.