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## Repeated Dosing with Oral Cocaine in Humans: Assessment of Direct Effects, Withdrawal and Pharmacokinetics

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### Abstract

Cocaine withdrawal symptoms are thought to play a role in relapse; studies characterizing the symptomatology have yielded mixed findings. This study sought to examine the pharmacodynamic/pharmacokinetic profile of repeated high dose exposure to oral cocaine and characterize acute and protracted withdrawal in cocaine abusers. This study employed a repeated-dosing, single-blind design in which subjects (n=9), resided for 40 days on a closed ward. They were maintained for two 4-day cocaine exposure periods (Days 1-4 & Days 9-12, cocaine 175 mg, p.o.; 5 hourly doses [875 mg/day]) separated by a 4-day matched placebo exposure period (Days 5-8). After these 12 days, an additional period of 28 days of placebo maintenance followed (Days 13-40). Test sessions were conducted during each phase; measures of mood, drug effects, sleep, pharmacokinetics, and prolactin were collected throughout the study. The dosing regimen produced cocaine plasma concentrations ( $C_{max}$  of 680 ng/mL) 2- to 3-fold higher than typically seen in acute dose studies. Prototypic psychostimulant effects, including subjective ratings of euphoric effects [liking, high, good effects] and significant cardiopressor effects, were sustained during the active dosing periods, corresponding to the rise and fall of plasma cocaine. Withdrawal-like symptoms (i.e., disruptions of sleep, increased ratings of anxiety, irritability, crashing) were observed within 24-hr after cessation of dosing. Cocaine reduced prolactin acutely, but no sustained alterations were observed for this measure or for other signs or symptoms during the 28-day abstinence period. These findings indicate that exposure to controlled high doses of cocaine produces modest symptoms consistent with cocaine withdrawal within hours of cessation of dosing but provide no evidence of symptoms persisting beyond 24 hours.

### Keywords

cocaine; withdrawal; pharmacokinetics; stimulants

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Cocaine dependence continues to be a significant public health concern. Data from the 2007 National Survey on Drug Use and Health indicate that the number of Americans who had used cocaine in the past month has remained relatively stable since 2002 (SAMHSA, 2008). Cessation of regular cocaine use is thought to result in withdrawal symptoms, such as dysphoric mood, changes in appetite, fatigue, vivid and/or unpleasant dreams and increased or decreased psychomotor activity and sleep (APA, 2000). Research efforts have been directed toward identifying, developing, and testing pharmacologic agents and behavioral strategies for the treatment of cocaine withdrawal because withdrawal symptoms, of varying severity and duration, are believed to occur within a few hours to several days following cessation of repeated cocaine use and may contribute to relapse to cocaine use (Kampman et al., 2002; Poling, Kosten, & Sofuoglu, 2007).

One early open report based upon interviews with individuals in treatment for cocaine use proposed a model of cocaine withdrawal consisting of three distinct temporal phases, which were described as “crash,” “withdrawal,” and “extinction” (Gawin & Kleber, 1985). The “crash” occurred within hours to a few days after cocaine use and was characterized by profound fatigue, lethargy, and depression. “Withdrawal” was characterized by milder symptoms and craving for cocaine 1 to 10 weeks after cessation of cocaine use; while “extinction” lasted indefinitely and was characterized primarily by recurrent desire or craving for cocaine. A subsequent study compared cocaine abusers to matched control subjects during a 28-day inpatient stay in a controlled setting (Weddington et al., 1990). In contrast to the earlier tri-phasic model, withdrawal symptoms were highest during the first few days of abstinence and declined linearly thereafter. Cocaine abusers reported significantly higher scores on indices of mood distress and had higher resting heart rate, but few other significant differences were observed. Subsequent studies of patients undergoing cocaine detoxification have reported a similar linear decline in symptomatology (Coffey, Dansky, Carrigan, & Brady, 2000; Gillin, Pulvirenti, Withers, Golshan, & Koob, 1994; Kowatch, Schnoll, Knisely, Green, & Elswick, 1992; Satel et al., 1991); although, this has not been observed in all studies (Flowers et al., 1993; S. D. Martin, Yeragani, Lodhi, & Galloway, 1989). Other signs and symptoms that have been reported include sleep disturbance and altered dopaminergic function (Gillin, Pulvirenti, Withers, Golshan, & Koob, 1994; Malison et al., 1998); but these, too, have not been consistently identified (Coffey, Dansky, Carrigan, & Brady, 2000; Weddington et al., 1990).

Some of the discrepancies across and within studies may be attributable to the variability of substance abuse patterns in patients entering treatment programs. The majority of clinical studies examining cocaine withdrawal and the neurobiological consequences of chronic cocaine use have been conducted primarily in cocaine abusers undergoing detoxification in either inpatient or outpatient settings. There are substantial individual differences in substance abuse patterns among cocaine users who present for treatment. Other studies have examined cocaine withdrawal after some regimen of controlled cocaine dosing, some as brief as a single dose (Foltin & Fischman, 1997; Johanson, Roehrs, Schuh, & Warbasse, 1999; McDougle et al., 1994; McDougle et al., 1992; Pace-Schott, Stickgold, Muzur, Wigren, Ward, Hart, Clark et al., 2005; Pace-Schott, Stickgold, Muzur, Wigren, Ward, Hart, Walker et al., 2005; Watson, Bakos, Compton, & Gawin, 1992). In one study (Foltin & Fischman, 1997), cocaine dependent subjects were allowed to self-administer up to twelve doses of 32 mg/70 kg intravenous cocaine per day over a two- or three-day “binge.” Modest cocaine withdrawal symptomatology (e.g., depression, irritability) was observed in the first 48 h following the three-day, but not the two-day, “binge” period. The results of these laboratory studies are consistent with previous clinical findings suggesting that cocaine withdrawal symptoms are most prevalent during early abstinence (Satel et al., 1991; Weddington et al., 1990).

Importantly, although initial clinical characterization of cocaine abstinence symptomatology indicated significant symptoms during long-term abstinence (i.e., 1 to 10 weeks; Gawin and Kleber, 1985), these previous controlled studies only examined approximately two weeks of abstinence. Moreover, in some studies, subjects regulated their own cocaine intake and took varied amounts of drug, which could have contributed between subject-variability to the findings. Therefore, the purpose of the present study was to characterize the direct effects of repeated oral dosing regimen designed to produce elevated and sustained pharmacological exposure to cocaine and to measure both acute and prolonged cocaine abstinence symptoms during blinded discontinuation of dosing in a controlled setting. An additional goal of this project was to assess the pharmacokinetic profile of oral cocaine and to use these data to assist in defining effects occurring when cocaine concentrations were ascending and descending and after complete elimination. Acute withdrawal was defined as the first 24 hours following cessation of cocaine administration, and protracted withdrawal was assessed for 28 days thereafter.

## Materials and Methods

### Subjects

Nine subjects (seven male; two female) with an average age of  $35.0 \pm 1.8$  years completed the study. They were recruited through local newspaper advertisements and word-of-mouth and were paid for their participation. The Institutional Review Board of the Johns Hopkins Bayview Medical Center approved the study; all volunteers provided informed consent. Exclusion criteria included any history of seizures, cardiovascular disorders, diabetes, any current medical condition requiring medication, or abnormal laboratory values judged clinically significant. All subjects were determined to be healthy by physical examination, electrocardiogram (ECG), laboratory tests, and structured psychiatric interview (Structured Clinical Interview; (First, Spitzer, & Gibbon, 1996). Female subjects were tested for pregnancy before admission and each week while residing on the research unit; all results were negative. Five other subjects were enrolled but did not complete the experiment. One subject was diagnosed with pericarditis before any cocaine was administered and was hospitalized for treatment, two left the experiment for personal reasons, and two were discontinued due to paranoia after dosing with cocaine on the first day, both of whom were female.

All subjects smoked cocaine and averaged  $22.9 \pm 2.0$  days of use in the preceding 30 days but were not seeking treatment for their drug abuse. Seven smoked cigarettes but were not physically dependent on other drugs of abuse. Subjects were within the normal weight range with a mean weight of  $146 \pm 6.04$  lb. Urine samples were collected daily from all subjects and were randomly analyzed for the presence of illicit drugs; no illicit drug use was detected in any volunteer during participation.

### Study Design

This inpatient study used a single-blind, within-subject, repeated-dosing (active drug, placebo, active drug, followed by a prolonged placebo wash-out) design. Subjects resided on an inpatient research unit for approximately 40 days and were maintained on a caffeine-free diet throughout the study. They habituated to the residential unit and practiced computer tasks for at least one day before starting the study. Thereafter, subjects received a single oral capsule five times daily (0800, 0900, 1000, 1100, and 1200) for 40 consecutive days. Eating was prohibited from 2 h before the first and 1 h after the last dose. During Phase 1, each capsule contained 175 mg cocaine (i.e., 875 mg total/day) for the first 4 days of dosing. Placebo capsules were administered for the next 4 days (Study Days 5-8). During Phase 2, cocaine (875 mg, p.o. total/day) was then again administered on the next 4 days (Study Days 9-12) followed by a 28-day, placebo-controlled washout. Thus, both Phase 1 and Phase 2 were designed to capture the direct

acute effects of cocaine compared to placebo and acute withdrawal effects (i.e., over a 4-day period of abstinence), while Phase 2 was also designed to capture any protracted withdrawal during abstinence. Experimental sessions (see below for details) were conducted on the first and last day of each of the first two maintenance phases (i.e., Study Days 1, 4, 5, and 8, respectively), on Day 9 (i.e., the first day of the second cocaine maintenance phase), and Days 22, 30 and 40 (i.e., the 10th, 18th, and 28th day of the placebo wash-out phase (see Table 1a for study schema). Other measures, described below, were completed daily during the experimental protocol.

### Rationale for Dose Selection

We conducted an earlier study in which a wide array of oral cocaine doses were examined using a repeated dosing regimen (Juffer, Walsh, & Cone, 1998) to determine doses for this study. The repeated 5-hourly doses were designed to produce sustained plasma concentrations of cocaine for a period of several hours to mimic the type of extended exposure that occurs during a natural cocaine use cycle or “binge.” In the earlier ascending tolerability study, five hourly doses of oral cocaine were examined ranging from 100 mg up to 400 mg (i.e., 500 to 2000 mg, p.o. total per day, respectively). The dose used in this study, 175 mg  $\times$  5 doses (875 mg, p.o. total) was chosen because 1) it was generally well tolerated by the majority of subjects in the first study, and 2) it produced peak plasma concentrations of cocaine similar to or higher than those produced by intravenous and smoked doses cocaine in prior human laboratory studies endorsed by participants as relevant to illicit use e.g., (Baker, Jatlow, Pade, Ramakrishnan, & McCance-Katz, 2007; Evans, Cone, & Henningfield, 1996).

### Drug

Cocaine hydrochloride (Mallinckrodt Specialty Chemical Company, St. Louis, Mo.) was weighed by individual dose using a Mettler Balance AE166. The weighed cocaine HCl was compressed into a size-0 opaque gelatin capsule (Elanco Products, Co., Indianapolis, Ind., a division of Eli Lilly and Company) and loose-filled with lactose (Amend Drug and Chemical Co., Inc., Irvington, N.J.). Each capsule was hand polished with a soft cloth to remove residual powder. The placebos were matched-capsules filled with lactose.

### Experimental Sessions

Experimental sessions were conducted from 0730 to 1500 in an isolated testing room designed to provide a consistent level of lighting, heat, sound, and visual stimuli equipped with a personal computer (Computer, Cupertino, Calif.), which recorded subjective and physiological responses. The research assistant/research nurse remained seated behind the computer, initiated the data collection, monitored the subjects, and provided observer ratings. Data collection proceeded from 30 min before the first capsule administration through 180 min after the last capsule for a total session duration of 7.5 h (see Table 1b for the schedule of events during sessions).

**Physiological Measurements**—Heart rate, systolic blood pressure, diastolic blood pressure, respiration, and skin temperature were measured continuously from 30 min before the first capsule administration until the end of the 7.5 hour session and recorded at 1-min intervals. These data were derived and collected in a manner similar to what we have previously reported (Walsh, Haberny, & Bigelow, 2000). Photographs of the eye were taken 30 min before the first capsule and at 15-min intervals thereafter for the duration of the session using a camera (Polaroid, Cambridge, MA) modified with a mounted brace to ensure a standard distance from the eye. Electroencephalographic and Doppler carotid blood flow data were also collected but are being reported elsewhere.

**Subject- and Observer-rated Measures**—Subject-rated measurements included visual analog scales, street value assessments, and adjective rating scales. These scales are identical to those that we have previously reported (Walsh, Haberny, & Bigelow, 2000). Subjects also completed the Addiction Research Center Inventory (ARCI) short form (W. R. Martin, Sloan, Sapira, & Jasinski, 1971) 30 minutes before drug administration and every hour following capsule administration until the end of the session. Observer ratings were collected an adjective rating scale previously described (Walsh, Haberny, & Bigelow, 2000).

### Daily Measures

Vital signs (heart rate, blood pressure, respiration, temperature) were recorded on the residential unit before each dose and throughout each study day to monitor safety. The St. Mary's Hospital Sleep Questionnaire (Ellis et al., 1981) was collected each morning at 7:00AM. A performance battery, the Digit Symbol Substitution Test (McLeod, Griffiths, Bigelow, & Yingling, 1982) and the Digit Enter and Recall Task were completed at 4:00 PM. The Profile of Mood States (POMS)(McNair, Lorr, & Droppleman, 1971), the Beck Depression Inventory (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), the State-Trait Anxiety Index (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1973), and a 6-item visual analog questionnaire (How much... are you craving cocaine right now?, do you desire cocaine right now? How... tired, depressed, irritable are you? Do you feel like you are crashing?) were completed at 6:00 PM each day. These tasks were presented on a personal computer in a quiet test room located within the residential unit.

### Safety Procedures

Instructions were given to withhold oral medication if systolic blood pressure was greater than 140 mmHg, diastolic blood pressure was greater than 90 mmHg, heart rate was greater than 120 bpm for over 4 min, or any other physical or mental status signs or symptoms that, in the clinical judgment of the investigator or physician, were of sufficient magnitude to present a danger to the subject. Nursing staff dispensed all capsules. A crash cart was always available, and a licensed physician was on call at all times.

### Prolactin Analysis

Blood samples (5 ml) were drawn via an indwelling intravenous catheter from the antecubital vein in order to conduct analyses on plasma prolactin levels during cocaine maintenance. Plasma prolactin analyses were conducted because prolactin is under the inhibitory control of dopamine systems (see discussion). Prolactin samples were drawn on cocaine sessions days (see Table 1b) 15 min before the first capsule administration and 5 h after the first capsule administration (i.e., Days 1 and 4 of dosing during both active cocaine phases [Days 1, 4, 9 & 12]). Prolactin samples were also drawn on days 13 -19, day 26, 33, and 40 and assayed by using a commercial radioimmunoassay (Immunanalysis, Pomona, CA).

### Definition of Cocaine Withdrawal

Cocaine withdrawal was divided into two stages based upon experimental findings described above (Coffey, Dansky, Carrigan, & Brady, 2000; Gillin, Pulvirenti, Withers, Golshan, & Koob, 1994; Kowatch, Schnoll, Knisely, Green, & Elswick, 1992; Satel et al., 1991). The first stage, acute withdrawal, was defined as the period shortly following the end of cocaine administration (sometimes referred to as “crashing”), when cocaine blood levels began to decrease (i.e., 5-24 hours after the first dose). The second stage, prolonged withdrawal, was defined as the time period 24 hours after the first dose when there were no appreciable cocaine levels in the blood (i.e., during placebo maintenance).



## Cocaine and Cocaine Metabolite Assay

Blood samples (5 ml) were drawn via indwelling intravenous catheters from the antecubital vein. Samples were collected on all session days (see Table 1b) 15 min before the first capsule administration, 30 min and 1, 2, 3, 4, 5, 6, 7, 8, 12, and 24 h after the first capsule administration. The samples were immediately centrifuged, the plasma drawn off and frozen at  $-70^{\circ}\text{C}$ . Concentrations of cocaine, benzoylecgonine (BE), ecgonine methyl ester (EME), and norcocaine were assayed using liquid chromatographic-atmospheric pressure chemical ionization-tandem mass spectrometry (LC-APCI-MSMS) from the first and fourth day of cocaine dosing during the first active dosing phase (detailed information on the adapted LC-MSMS method employed for these analyses is provided as online supplemental material).

## Statistical Analysis

Data were analyzed using parametric analysis of variance (ANOVA) for raw time course data and for transformed data (e.g., peak maximum scores) where appropriate. For all repeated measures analyses, significance levels were adjusted for violations of the assumption of sphericity using Huynh-Feldt corrections. Effects were considered significant when  $p \leq 0.05$ . For brevity, only significant effects of drug (cocaine vs. placebo) or interactions with drug are reported; effects for which only a significant main effect of time was observed are not reported.

Physiological data (collected on a minute-by-minute basis) were initially collapsed to yield averages over 30-minute periods to correspond with the data collection schedule for other pharmacodynamic outcomes. Physiological, subjective and observer-rated measures from the first four sessions were compared by three-factor ANOVA (Drug [Placebo vs. Cocaine], Session Day [1<sup>st</sup> vs. 4<sup>th</sup> day of dosing] and Time) for repeated-measures in order to compare the pharmacodynamic effects of cocaine and placebo maintenance. Pharmacokinetic values (except  $T_{\max}$ ) for the 1st and 4th day of cocaine dosing of the first active dosing phase were analyzed using Student's t-test.  $T_{\max}$  was analyzed using the nonparametric signed rank test.

Prolactin data collected within the cocaine dosing sessions were initially compared using a 3-factor repeated ANOVA (Phase [2 of active dosing]  $\times$  Day [1 vs. 4 of dosing]  $\times$  Time [pre & post dosing]). Average baseline prolactin values for one male volunteer (64.6 ng/mL) far exceeded the average for the group (11.1 ng/mL). The Grubb's test (also known as the Extreme Studentized Deviate) confirmed that this subject was a significant statistical outlier; thus, his data were excluded from analysis.

Acute abstinence was examined by comparing outcomes collected on the residential unit during either the late afternoon (i.e., 4:00 PM performance battery), evening (i.e., 6:00 PM questionnaire battery), or morning (i.e., 7:00 AM sleep questionnaire) after dosing for cocaine compared to placebo. Repeated ANOVA was employed with 3-factors (Drug [Placebo vs. Cocaine]  $\times$  Phase (1-2)  $\times$  Day of Phase [1 - 4]). The effects of potential prolonged cocaine abstinence were examined through 1-factor ANOVA repeated measures across days of wash-out including the last day of cocaine treatment (Day 12); the number of days varied as a function of the outcome measure as some were collected daily but others only intermittently (e.g., prolactin).

## Results

### Pharmacokinetic Analyses of Cocaine and Cocaine Metabolites

Figure 1 shows plasma concentrations (ng/mL) of cocaine, BE, EME, and norcocaine for the 1<sup>st</sup> and 4<sup>th</sup> day of cocaine dosing during the first 4-day dosing period. Analysis of time-to-maximum concentration ( $T_{\max}$ ) revealed no differences between the sessions for cocaine or its metabolites (Table 2). Plasma concentrations of cocaine and its metabolites reached  $T_{\max}$

(averaged across the two sessions) as follows: 4.5 hr for cocaine, 5.0 hr for norcocaine, 5.2 hr for EME, 6.0 hr for BE (calculated mean from time zero [time at which the first dose was given]. Analysis of the calculated  $C_{\max}$  concentrations of cocaine and norcocaine revealed no differences between the 1<sup>st</sup> and 4<sup>th</sup> day of dosing; cocaine  $C_{\max}$  concentrations reached above 500 ng/mL on average by 1 hr after the last dose. However, there were significant differences in BE concentrations whereby levels were higher on the 4<sup>th</sup> day, and for EME whereby levels were lower on the 4<sup>th</sup> day of dosing (Table 2;  $p < .05$ ); these differences are also apparent in the time-action curve (Figure 1). BE and EME were still detected in 100% of the samples at 24 hours after the first cocaine dose. Cocaine was still detectable in 12 of 18 samples, while norcocaine was detected in only 6 of 18 samples at the 24-hr time point. For most other pharmacokinetic parameters, no other differences between the first and fourth day of dosing were observed except for increased AUC and decreased clearance for norcocaine (Table 2).

### Direct Pharmacodynamic Response to Cocaine

The experimental sessions used to examine the direct effects of repeated dosing with cocaine compared to placebo (Sessions 1, 2, 3, and 4; corresponding to Days 1, 4, 5, and 8, respectively) were selected after separate statistical comparisons of all active maintenance sessions (1, 2, and 5; Days 1, 4, and 9) and all placebo maintenance sessions (3, 4, 6, 7, and 8; Days 5, 8, 22, 30, and 40) revealed few differences between the repeated tests across the broad array of measures collected.

**Physiological Measures**—Cocaine maintenance significantly increased heart rate, systolic and diastolic blood pressure (see Figure 2; statistics in legend) relative to placebo maintenance. Figure 2 illustrates the data for heart rate (derived from the inter-beat interval; IBI) and diastolic and systolic blood pressures. Repeated dosing with oral cocaine administration across both sessions increased heart rate by approximately 15 to 20 beats per minute from baseline levels. The greatest absolute increase was observed in the hour following the first dose, but heart rate rose steadily with repeated dosing and stabilized around the time of the final dose administration (i.e., 4 hr after the first dose) with no further increase noted. A time-dependent decrease in heart rate was observed during placebo sessions. Similar effects were observed for both systolic and diastolic blood pressure; however, blood pressure increased more gradually, peak effects were observed 3.5 h after the first dose, and maximum increases produced by oral cocaine were on the order of 10 to 15 mm Hg and 5 to 10 mm Hg for systolic and diastolic blood pressure, respectively. There were no significant differences between treatment days (i.e., the 1<sup>st</sup> versus the 4<sup>th</sup> day of cocaine or placebo) on these outcomes, with one exception: there was a significant dose by session interaction ( $F[1,8]=16.3$ ;  $p = .004$ ) that was attributed to a higher resting heart rate on day 4 of cocaine dosing compared to day 1 that was evident throughout much of the session and is shown in Figure 2. Cocaine increased pupil diameter ( $F[1, 8] = 162$ ;  $p < .0001$ ; data not shown) within 1 hr of the first dose; this effect (about 1 mm diameter increase) was sustained. There was no effect of cocaine on skin temperature.

**Subjective Measures**—Cocaine significantly increased subjective ratings on several visual analog scales, including ratings of “high,” “like the drug” (both shown in Figure 3), “any drug effect,” “good effects,” and “desire for cocaine” ( $F[1,8] > 5.0$ ;  $p < .05$ ). Oral cocaine increased ratings on these measures gradually, with an initial peak (i.e., an increase from baseline of 15 to 20 points) observed 1 h after the first dose, and the final peak (i.e., an increase from baseline of 40 to 50 mm) observed approximately 4.5 to 5 h after the first dose. Data collected during the test session revealed no significant effects of cocaine on visual analog ratings of “bad effects,” “tired,” “depressed,” “irritable” or “crashing.” There were no significant differences as a function of repeated dosing (i.e., no difference between day 1 and day 4 of dosing) for the visual analog measures.

Cocaine increased scores on the LSD scales of the ARCI as a function of time ( $F[7, 56] = 8.6$ ;  $p < .05$ ; data not shown). Scores on the LSD scale peaked at about 5 h after the first cocaine dose with a maximum increase of about 7 points. There was also a significant interaction of drug and time on the Benzedrine scale ( $F[7,56] = 2.6$ ;  $p < .05$ ). This was a function of an initial modest increase produced by cocaine followed by a modest decrease after the 4<sup>th</sup> dose, while the placebo function was flat throughout. There were no significant effects of drug on the PCAG, Amphetamine or MBG scales of the ARCI.

Data shown in the upper right panel of Figure 3 illustrate the mean scores for subject-rated cocaine adjective scale; the shape of this function is similar to those of the visual analog outcomes. However, there was a significant interaction effect for dose  $\times$  session ( $F[1,8]=10.2$ ;  $p < .001$ ) due to higher observed scores on the 4<sup>th</sup> day compared to the 1<sup>st</sup> day of active cocaine (similar interaction effects were found on subject-rated adjective scales of “stimulated,” “fidgety,” “jittery,” and “tremor”). Subject estimations of drug street value were significantly increased by cocaine (Figure 3) gradually throughout the experimental sessions peaking within 0.5 hour of the last dose at about \$10.00. Finally, cocaine produced significant increases on the POMS for the Tension-Anxiety, Confusion-Bewilderment and the Total Mood Disturbance scales in comparison to placebo ( $p < .05$ ).

**Observer Ratings**—Cocaine produced significant increases on observer ratings of “drug effect,” “difficulty concentrating,” “fidgety,” “jaw clenching,” “tremor/shaky” and “sweating,” ( $F[4, 112] > 2.7$ ;  $p < .05$ ) but no effects on “talkative,” “edgy,” “irritable mood,” or “stammering.” No differential effects were found based upon day of dosing (i.e., day 1 versus day 4).

**Prolactin**—The initial data analysis revealed no effect of test phase or day of phase within the active dosing periods. Thus, plasma prolactin concentrations reported here were collapsed across the four session days ( $n=32$  samples for both pre- and post-cocaine). Baseline mean prolactin concentrations ( $11.12 \text{ ng/ml} \pm 0.59$ ) were significantly higher than those collected 5 hr after the first dose ( $4.78 \text{ ng/ml} \pm 0.91$ ) (Pre- versus Post;  $F[1,31] = 45.44$ ;  $p < 0.01$ ).

### Effects of Acute Withdrawal From Cocaine

Acute withdrawal effects were examined through measures collected during the latter part of the experimental sessions (when cocaine plasma concentrations were declining) and those collected daily on the residential unit (i.e., measures collected once between 4 and 16 hr after the last daily dose of cocaine or placebo on Days 1 through 16; see Methods for specified times). Figure 4 illustrates the relationship between the withdrawal-related measure, self-reported “Crashing,” over the course of experimental session (data shown are from the session on the 4<sup>th</sup> day of dosing) as a function of cocaine plasma concentrations. As can be seen, ratings of “crashing” are at zero at the start of the session and begin to rise only as the last dose of cocaine is administered. The onset of subjective reports of crashing coincides with the time at which peak plasma concentrations of cocaine are achieved. Thereafter, ratings of crashing rise as plasma concentrations of cocaine begin to decline. These ratings remained elevated for several hours after session as shown in Figure 5 relative to days when placebo was administered ( $F[1,8]=5.6$ ;  $p < .05$ ); although this effect was significant, there were substantial inter-individual differences on this measure. However, by examining the data shown for Day 5 (the first day of placebo dosing after cocaine), it is evident that scores for crashing had returned to zero within 30-hrs after cessation of dosing. Scores on the Tension-Anxiety scale (Figure 5, middle panel) of the POMS ( $F[1,8]=11.6$ ;  $p=0.009$ ) were also significantly increased at 6-hr after the last cocaine dose but had declined after the first day of placebo dosing (i.e., at 30 hr after the last cocaine dose). Finally, data shown in the bottom of Figure 5 illustrate that cocaine significantly decreased total sleep time on the St. Mary's Sleep Questionnaire ( $F[1,8]=8.1$ ;  $p=$



022) relative to placebo maintenance. This finding, though, was largely due to decreased sleep time during the day (day and nighttime sleeping are queried as separate outcomes with the St. Mary's Questionnaire) (i.e., main effect of Drug,  $p < 0.05$ ), but there was a small and significant decrease in sleep time during the night (i.e., interaction of Drug, Phase, and Day,  $p < 0.05$ ). These findings correspond with increases in subjective reports of waking early during cocaine maintenance (i.e., main effect of Phase,  $p < 0.05$ ). There were no significant effects on other sleep outcomes, the Beck depression scale, the STAI, other visual analog scales (e.g., depressed, irritable, tired, desire or craving for cocaine) or the performance measures during cocaine maintenance relative to placebo maintenance.

### Effects of Prolonged Cocaine Abstinence

Data gathered outside of experimental sessions (i.e., sleep, performance and subjective ratings) across the 28-day placebo washout were analyzed to determine whether there were any effects of prolonged cocaine abstinence relative to the final day of cocaine dosing (see Table 1 Day 12). Statistical analysis revealed a significant effect of Day within the study on estimates of "Time to Wake Up" and "Time to Get Up" on the Saint Mary's Sleep Questionnaire ( $p$  values  $< 0.05$ ). On the last day of cocaine dosing, the average estimates were 11 and 11.22 minutes, respectively. During the placebo washout period, these estimates were generally increased modestly but significantly by up to 2 min. Statistical analysis also revealed a significant main effect of Day in the study on Total Correct on the DSST ( $p < 0.05$ ). This effect was due to a general improvement on this task throughout the protocol. There were no significant effects observed on any of the other daily measures. Lastly, plasma prolactin levels did not change significantly from those observed in the morning on the final day of oral cocaine administration throughout the remainder of placebo maintenance sessions with mean values of approximately 10-14 ng/mL. There were no significant effects on other daily measures (i.e., Beck, STAI, visual analog scales, digit enter and recall), observed during this period.

### Discussion

Repeated administration of oral cocaine produced significant elevations of cocaine in plasma, reaching concentrations higher than those typically seen after administration of acute or repeated experimental dosing (Baker, Jatlow, Pade, Ramakrishnan, & McCance-Katz, 2007; Evans, Cone, & Henningfield, 1996). The average peak concentrations observed here (i.e., 681 ng/mL) exceed by 2- to 3-fold those typically reported after acute administration of moderate doses by other routes, including smoking, intravenous, and intranasal (Donovan et al., 2005; Evans, Cone, & Henningfield, 1996; Jenkins, Keenan, Henningfield, & Cone, 2002; Wilkinson, Van Dyke, Jatlow, Barash, & Byck, 1980); however, concentrations in this range have been reported after high dose administration (Kolbrich et al., 2006) and sustained infusions (Ambre et al., 1988) and repeated dosing (Ambre et al., 1988; Jufer, Walsh, & Cone, 1998). The time action curves for cocaine and its metabolites, BE, EME and norcocaine, were similar to one another with all four virtually eliminated from plasma within 19 hr of the last dose. Norcocaine, a minor metabolite formed through direct N-demethylation (Hawks, Kopin, Colburn, & Thoa, 1974) and through secondary metabolism of N-oxide (Kloss, Rosen, & Rauckman, 1983), is not typically found in plasma after cocaine given by routes of administration other than oral (Jufer, Walsh, & Cone, 1998). Norcocaine was reliably detected in the present study at concentrations about 10-fold lower than the parent compound; because it is reported to have activity comparable to cocaine (Hawks, Kopin, Colburn, & Thoa, 1974), its potential contribution to the observed pharmacodynamic effects cannot be excluded. The analytic method developed herein is an advance over our prior method (Lin, Moody, Bigelow, & Foltz, 2001) in that simultaneous assay of cocaine, BE, EME and norcocaine were achieved with good reliability, sensitivity and chromatographic separation.

Consistent with previous human studies of acute doses of oral cocaine (Rush & Baker, 2001; Smith, Jones, & Griffiths, 2001; Van Dyke, Jatlow, Ungerer, Barash, & Byck, 1978), the full constellation of prototypic psychostimulant effects was observed after repeated oral dosing (875 mg/day given over 5 hr). Positive subject ratings of euphoric effects (e.g., “liking for the drug” and “high”) appeared within 0.5 hr of the first dose and continued rising linearly until 1 hr after the last dose; thus, the time-action curves for an array of subject-rated measures corresponded closely to the rise and fall of cocaine plasma concentrations. Similarly, heart rate and blood pressure showed sustained increases over the dosing period but remained significantly elevated 3 hr after the last dose. Thus, this dosing regimen produced clinically relevant levels of cocaine exposure with concomitant sustained pharmacodynamic responses typical of cocaine, mimicking more closely, than single dose studies, the “binge-like” exposure characteristic of illicit cocaine use.

Outcomes from studies of repeated cocaine administration in humans have been mixed with some reports of tolerance (Mendelson, Sholar, Mello, Teoh, & Sholar, 1998), sensitization (Kollins & Rush, 2002; Walsh, Haberny, & Bigelow, 2000), and no change in response (Rothman et al., 1994); this is not surprising given the variability in dosing regimens employed. While the present study provides no evidence to suggest that tolerance developed to the repeated dosing regimen; there was modest evidence of sensitization with regard to the effects on heart rate and response to cocaine, whereby heart rate and systolic blood pressure elevations were significantly greater on the 4<sup>th</sup> day of dosing compared to the 1<sup>st</sup> day. This enhanced cardiovascular response has been observed in two earlier studies after repeated dosing with oral cocaine, one in which the cardiovascular response to oral cocaine itself was enhanced (Kollins and Rush 2002) and one in which the response to intravenous cocaine was enhanced for up to one week after oral cocaine maintenance (Walsh, Haberny, & Bigelow, 2000). There was limited evidence for sensitization to the subject-rated effects of cocaine on mood; differences were seen only on a subset of adjective-rating scales, including jittery, fidgety, stimulated and tremor.

Despite the sustained exposure and response to cocaine over the 4-day dosing regimen (and the blinded placebo maintenance on days following active dosing), evidence for signs and symptoms of withdrawal was relatively modest and confined to the earliest time period after discontinuation of cocaine (within 24 hr). Cocaine withdrawal is typically characterized by disruptions of mood, sleep and appetite. In the present study, there was evidence that subjects reported feelings of “crashing;” the time course for which paralleled the decline in cocaine plasma concentrations. Moreover, by evening, subjects reported elevated ratings of anxiety-related symptoms (Tension-Anxiety scale of the POMS,) along with decreased ratings of “comfortable” and “relaxed.” However, these differences had dissipated by the morning after dosing as evidenced by data from the first day of the subsequent placebo phase. There was no evidence of acute depressive symptomatology during withdrawal from cocaine in contrast to prior reports using the same instrument (i.e., the Beck Depression Inventory; (Foltin & Fischman, 1997; Satel et al., 1991; Weddington et al., 1990); however, it is important to note, that even in these studies, scores tend to be fairly low throughout the observation period. It is unlikely that collecting withdrawal-related measures once daily limited our ability to detect relevant signs and symptoms as other studies reporting cocaine withdrawal phenomenology have used a similar approach (Foltin & Fischman, 1997; Weddington et al., 1990). In the present study, sleep was also significantly disrupted by the cocaine dose regimen to the extent that the total amount of sleep was less during the active cocaine phases compared to the placebo phases. Interestingly, this was accounted for, in large part, by decreased daytime sleeping in this closed residential setting. Unlike many typical illicit cocaine binges that may begin later in the day or evening, cocaine dosing occurred during the early morning and early afternoon hours in the present study, which likely accounts for the daytime sleep disruption.

Prolactin release from the pituitary gland is known to be under inhibitory control by dopamine; thus, prolactin has been examined as a marker for hypo- and hyper-dopaminergic responsivity after cocaine administration. Consistent with prior reports on acute exposure to cocaine (Farre et al., 1997; Heesch et al., 1996; Mendelson, Teoh, Mello, Ellingboe, & Rhoades, 1992), circulating levels of prolactin were significantly decreased by cocaine- in this case, by approximately 60% compared to baseline. However, there was no evidence to suggest that prolactin was suppressed or elevated during the withdrawal phase as values had returned to baseline concentrations within 24 hr (i.e., about 13.2 ng/mL) and remained stable through the 28-day placebo-controlled withdrawal phase. However, it is important to note that, as all of the subjects were using cocaine prior to entry, it is not possible to have a true baseline assessment that is verifiably unaffected by cocaine exposure. While others have reported no significant change in prolactin concentrations during withdrawal, consistent with the present findings, a few studies have suggested that prolactin levels may be persistently, but modestly (Satel et al., 1991), elevated in some, but not all patients (Kranzler & Wallington, 1992) undergoing cocaine detoxification. The present study supports the suggestion that the symptomatology resulting from abstinence following pharmacological exposure to high doses of cocaine may be of modest severity and fairly short-lived. This study examined emergence of withdrawal-like signs and symptoms in a closed environment under placebo-controlled, single-blinded conditions. Acute withdrawal symptoms were observed, consistent with those included in the diagnostic criteria for cocaine withdrawal (including dysphoric mood symptoms and disruptions of sleep); however, these were limited to the first 24 hr after cessation of dosing when cocaine plasma levels were still detectable but declining. This study provided no evidence of protracted mood or biological disruptions during the longer 28-day observation period. In the natural environment of a cocaine-dependent individual, other factors, that may stem from behavior during binge-use of cocaine rather than as a direct pharmacological consequence of cocaine exposure, including failure to sleep and eat during an extended period of drug use, likely contribute to the magnitude of symptoms and, perhaps, their duration during detoxification from cocaine.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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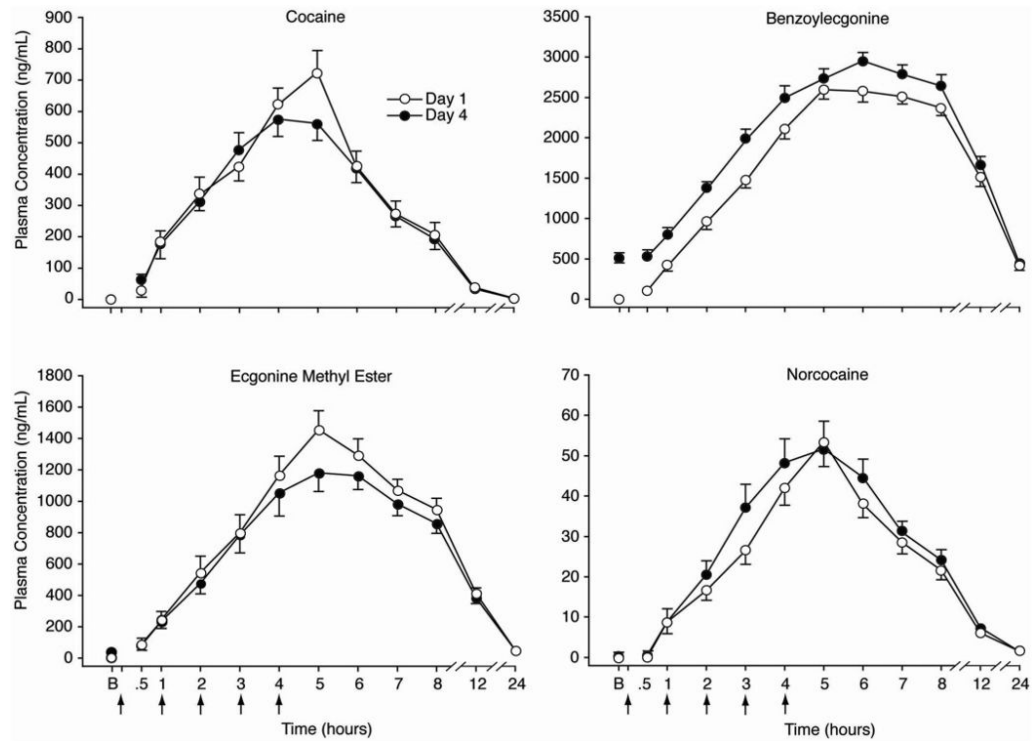
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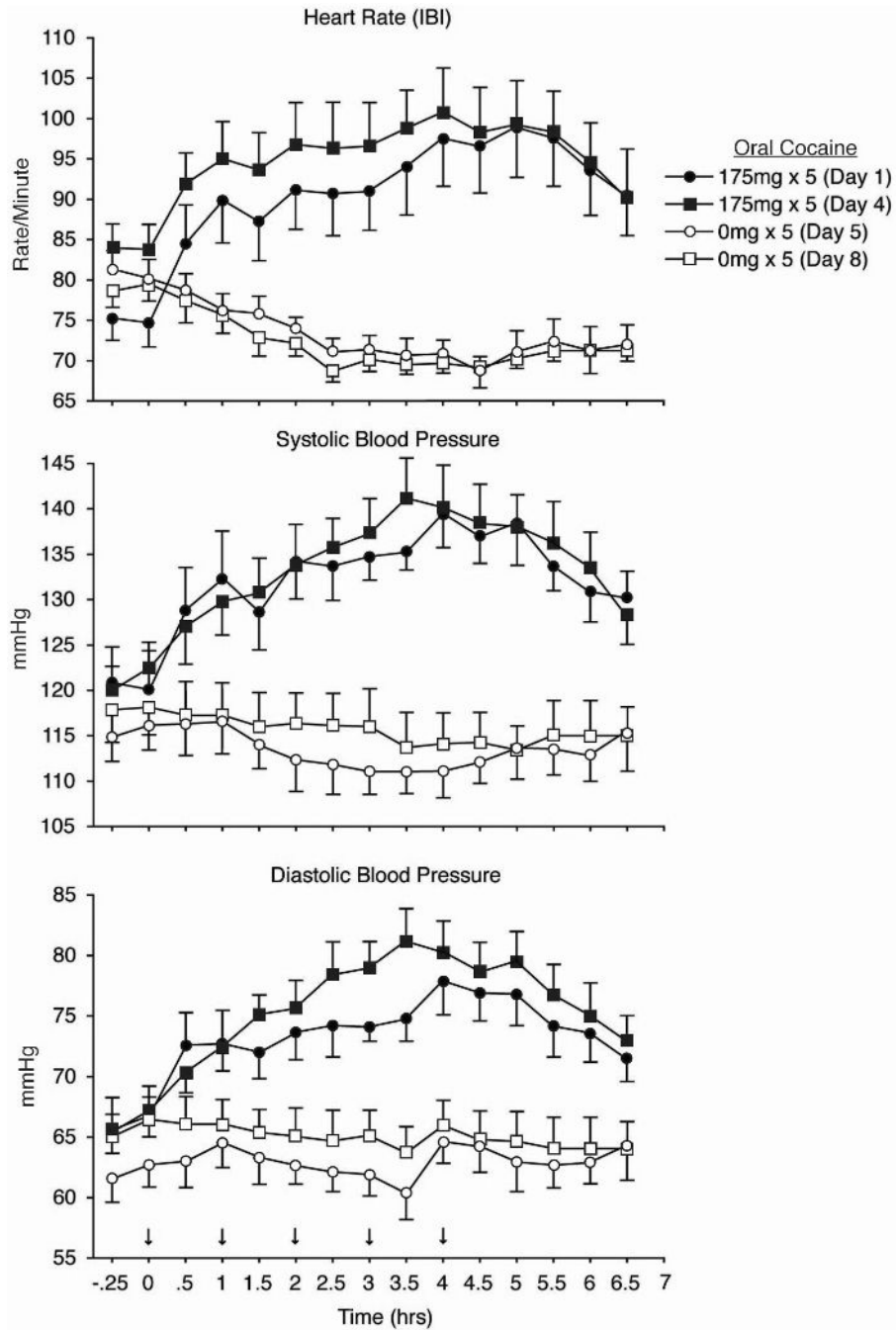


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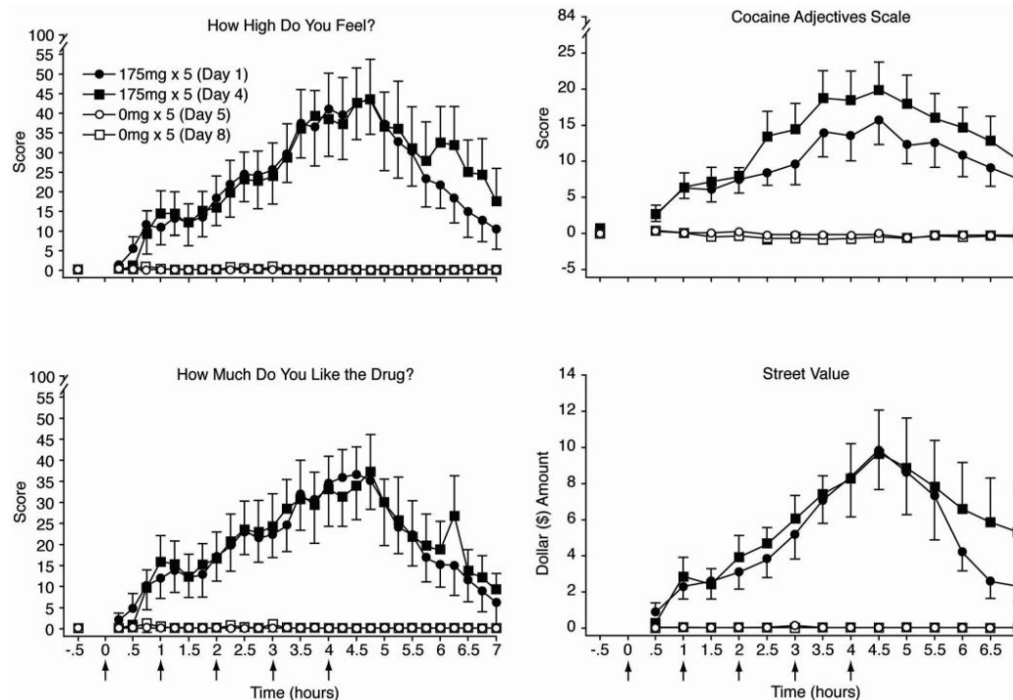


**Figure 1.**

Mean plasma concentrations (ng/mL) of cocaine, benzoyllecgonine, ecgonine methyl ester, and norcocaine are shown ( $n=9 \pm 1$  SEM). Along the abscissa, time (hr) is shown relative to the first cocaine dose, B is baseline (0.5 hr before dosing), and arrows designate administration of each of the five 175 mg oral cocaine doses. Open circles indicate values for Session 1 (day 1 of dosing), and filled circles represent values for Session 2 (day 4 of dosing).

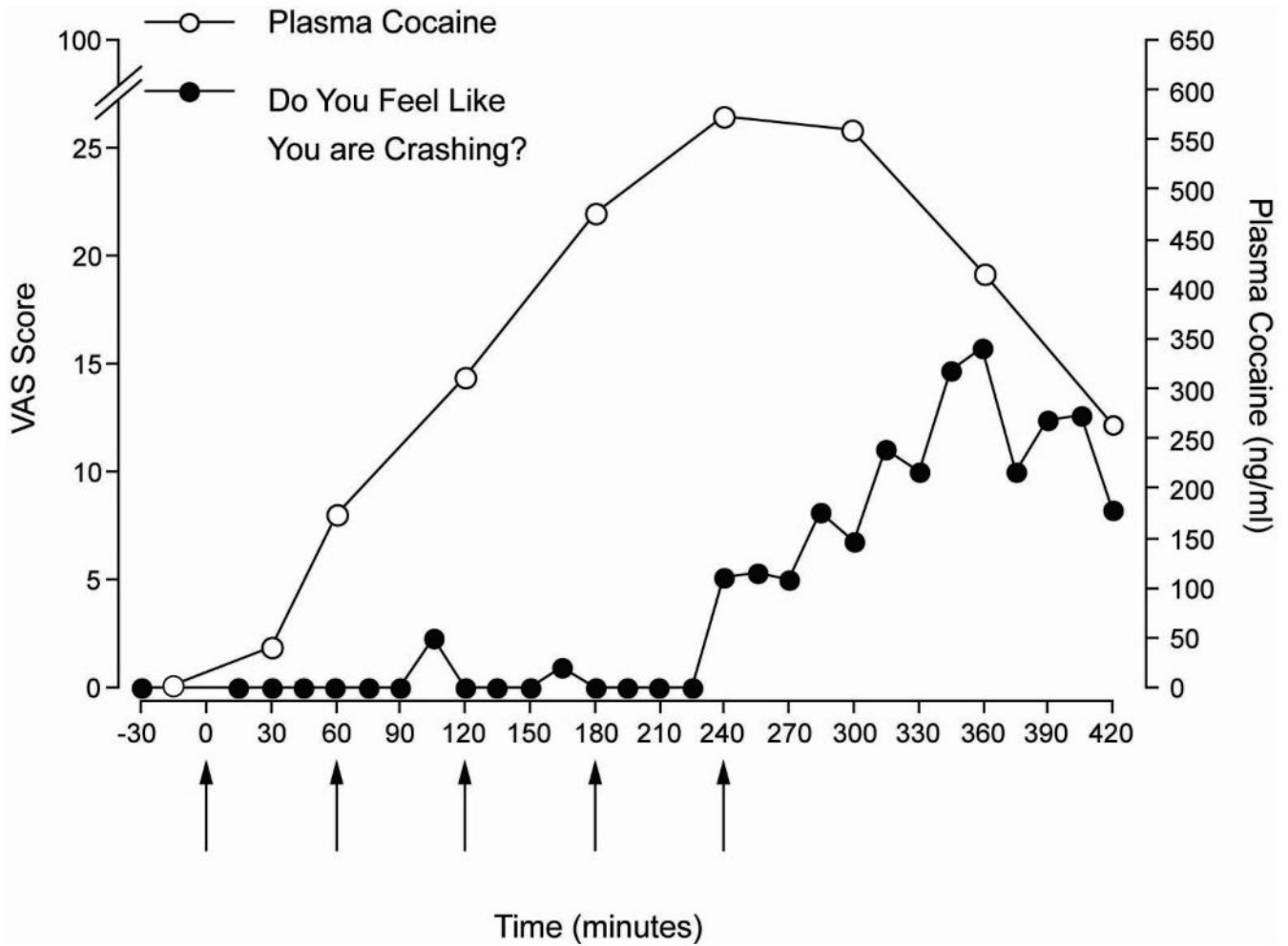
**Figure 2.**

Panels illustrate the time action curve for heart rate (upper panel), systolic blood pressure (middle panel) and diastolic blood pressure (lower panel) following administration of the 1<sup>st</sup> and 4<sup>th</sup> days of consecutive dosing with cocaine and placebo, respectively. Statistically significant effects of cocaine were observed for the three outcomes ( $df = [1, 8]$  heart rate  $f = 30.3$ ; systolic pressure  $f = 81.4$ ; diastolic pressure  $f = 161$ ;  $p \leq .001$ ). Data shown are mean values ( $n = 9$ ;  $\pm 1$  SEM) Closed circles and squares represent data from active cocaine sessions (days 1 and 4; sessions 1 & 2); open circles and squares represent data from placebo sessions (days 5 and 8; sessions 3 & 4). Arrows designate the five time points at which oral cocaine or placebo capsules were administered.



**Figure 3.**

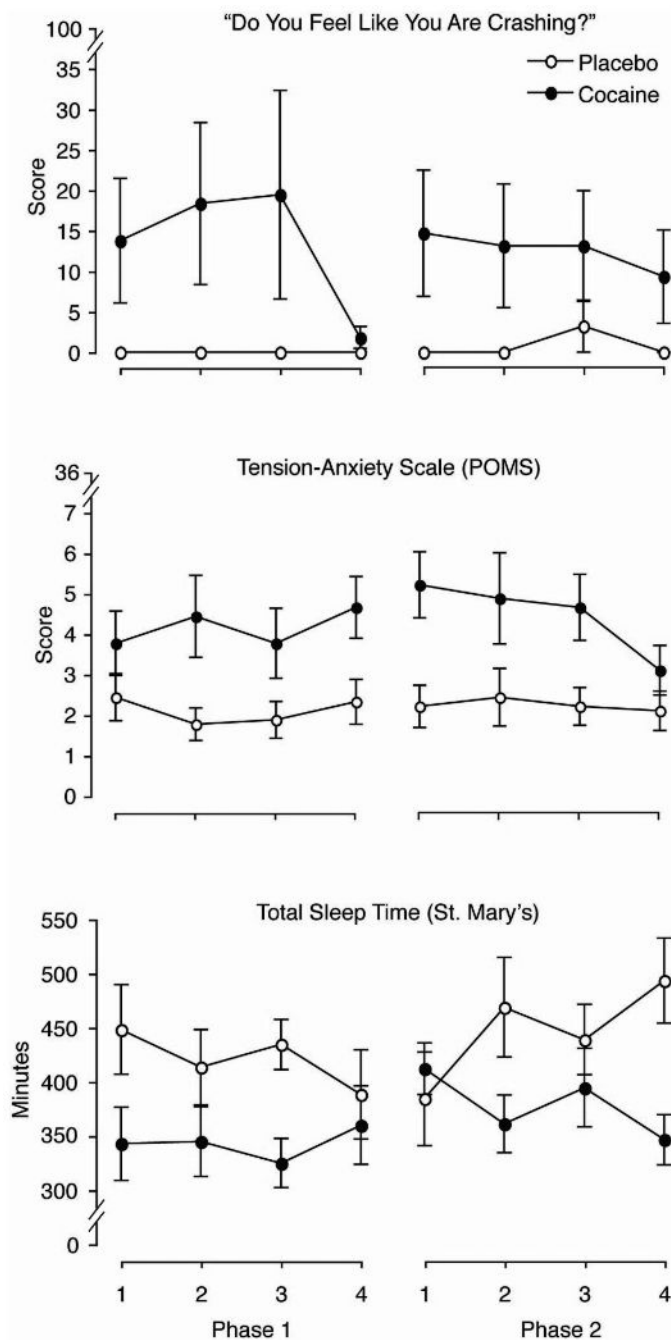
Time course functions for subject-rated visual analog measures of high (upper left panel) and “liking” for the drug (lower left panel), the summary score for subject-rated cocaine adjective rating scale (upper right panel) and subject estimates of the street value for the study drug (\$) are shown. Closed circles and squares represent data from active cocaine sessions, and open circles and squares represent data from placebo sessions. Data shown are mean values (n=9) and vertical bars represent the 1 S.E.M. Arrows designate the five time points at which oral cocaine or placebo capsules were administered.



**Figure 4.**

Mean data (n=9) are shown from Session 2 (Day 4 of cocaine dosing; Phase 1) for visual analog ratings of “Do You Feel Like You Are Crashing?” (left y-axis) and mean plasma cocaine concentrations (ng/mL; right y-axis) as a function of time in session. Arrows designate the five time points at which oral cocaine was administered.



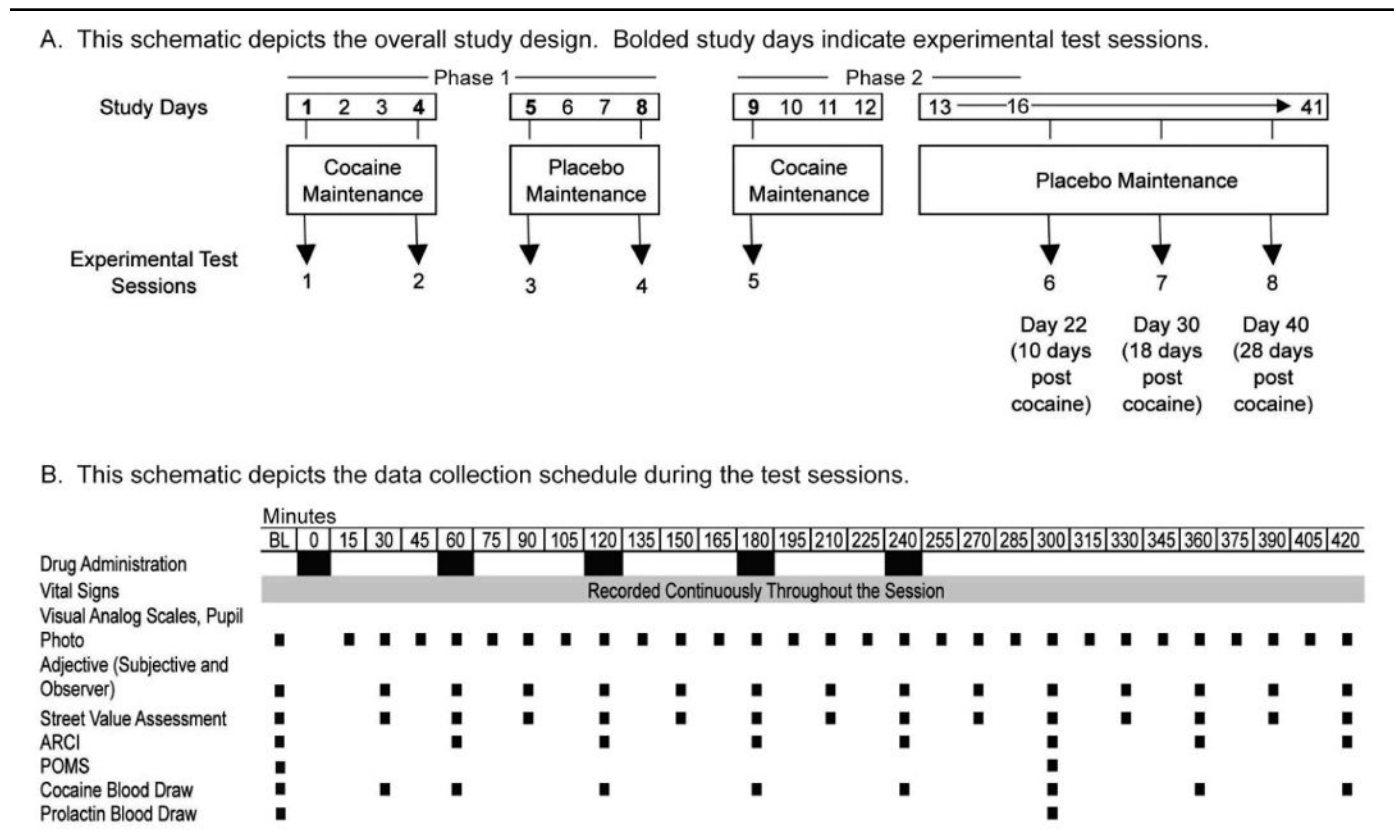


**Figure 5.**

Data are shown across the study phases as a function of day of dosing (Phase 1(Days 1-4 cocaine)-placebo (Days 5-8), Phase 2 cocaine (Days 9-12)-placebo (Days 13-16) for the visual analog scale "Do You Feel Like You Are Crashing?"(upper panel), the Tension-Anxiety summary scale score (POMS and total sleep time (hr) from the St. Mary's Questionnaire. Active dosing days are represented by closed circles and placebo dosing by open circles. Data are mean values ( $n=9; \pm 1$  SEM).

Table 1

Overview of the repeated dosing study design (A) and the data collection flow for sessions (B).



**Table 2**

Pharmacokinetic parameters of cocaine and its metabolites from the first versus fourth day of consecutive oral dosing (175 mg × 5 hourly doses, total of 875 mg/day)

Analyte /Parameter	Day 1 (Session 1)	Day 4 (Session 2)	p
Cocaine			
C <sub>max</sub> (ng/mL)	738 ± 201	625 ± 121	0.129
T <sub>max</sub> (h)	4.67 ± 1.00	4.22 ± 0.97	NS
AUC (µg/mL)(h)	3.77 ± 0.97	3.50 ± 0.64	0.286
Cl (L/h)	251 ± 83	259 ± 53	0.624
t <sub>1/2</sub> (h)	2.47 ± 0.55	2.15 ± 0.62	0.254
BE			
C <sub>max</sub> (ng/mL)	2751 ± 290	3063 ± 284	<u>0.0461</u>
T <sub>max</sub> (h)	5.89 ± 0.78	6.00 ± 1.12	NS
AUC (µg/mL)(h)	34.3 ± 2.7	37.9 ± 4.5	0.0653
Cl/f (L/h)	25.8 ± 2.6	23.4 ± 3.0	0.0856
t <sub>1/2</sub> (h)	6.29 ± 1.09	6.35 ± 1.11	0.799
EME			
C <sub>max</sub> (ng/mL)	1464 ± 361	1281 ± 308	<u>0.0236</u>
T <sub>max</sub> (h)	5.11 ± 0.33	5.33 ± 1.12	NS
AUC (µg/mL)(h)	12.6 ± 2.3	11.4 ± 2.3	0.0597
Cl/f (L/h)	72.3 ± 16.7	80.6 ± 22.2	0.0565
t <sub>1/2</sub> (h)	3.84 ± 0.52	3.89 ± 0.52	0.0846
Norcocaine			
C <sub>max</sub> (ng/mL)	53.5 ± 15.2	57.4 ± 13.4	0.377
T <sub>max</sub> (h)	5.00 ± 0.0	5.00 ± 0.87	NS
AUC (ng/mL)(h)	324 ± 50	368 ± 44	<u>0.0494</u>
Cl/f (L/h)	2766 ± 479	2408 ± 281	<u>0.0485</u>
t <sub>1/2</sub> (h)	2.33 ± 0.60	2.49 ± 0.72	0.291