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Influence of Acute Bupropion Pretreatment on the Effects of Intranasal Cocaine

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Abstract

Aims—The aim of this experiment was to determine the influence of acute bupropion pretreatment on subject-rated effects and choice of intranasal cocaine versus money.

Design—A randomized, within-subject, placebo-controlled, double-blind experiment.

Setting—An outpatient research unit.

Participants—Eight cocaine-using adults.

Measurements—Subjects completed 9 experimental sessions in which they were pretreated with 0, 100 or 200 mg oral immediate release bupropion. Ninety min later they sampled an intranasal cocaine dose (4 [placebo], 15 or 45 mg) and made 6 choices between that dose and an alternative reinforcer (US \$0.25), available on independent, concurrent progressive ratio schedules. Subjects also completed a battery of subject-rated, performance and physiological measures following the sample doses of cocaine.

Findings—After 0 mg bupropion, the high dose of cocaine (45 mg) was chosen 5 of 6 times on average compared to 2.25 of 6 choices for placebo cocaine (4 mg) ($p < 0.05$). Active bupropion reduced choice of 45 mg cocaine to 3.13 (100 mg) or 4.00 (200 mg) out of 6 drug choices on average. Bupropion also consistently enhanced positive subject-rated effects of cocaine (e.g. Good Effects; Willing to Take Again) while having no effects of its own.

Conclusions—The atypical anti-depressant, bupropion, acutely appears to reduce preference for intranasal cocaine versus a small amount of money but to increase reported positive experiences of the drug.

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Introduction

Data from the National Survey on Drug Use and Health indicate that 1.6 million Americans reported current cocaine use in 2009, making cocaine the most commonly used illicit stimulant in the United States [1]. Recent data from the European Monitoring Centre for Drugs and Drug Addiction estimated that a similar number of Europeans report current cocaine use [2]. Therefore, cocaine use remains a public health concern despite efforts to develop behavioral and pharmacological interventions.

Behavioral treatments grounded in operant theory have been implemented to manage cocaine use disorders (see [3]). These treatments reduce cocaine use by presenting non-drug alternative reinforcers when patients provide objective evidence of abstinence. Some have theorized that combining a pharmacotherapy with a behavioral treatment like abstinence reinforcement would result in enhanced efficacy relative to either treatment alone [4]. The results of recent research support this notion [5, 6, 7]. In one study, methadone-maintained cocaine and opioid dependent individuals were randomized to one of four groups: 300 mg bupropion daily plus abstinence reinforcement, placebo daily plus abstinence reinforcement, 300 mg bupropion daily plus a non-contingent voucher control or placebo daily plus a non-contingent voucher control [6]. Individuals in the bupropion plus abstinence reinforcement group had more cocaine free urines than those in the other groups, indicating that combining behavioral and pharmacological therapies results in improved outcomes. These results are even more striking considering the limited efficacy of bupropion in studies that tested bupropion alone or with background therapies that did not include abstinence reinforcement procedures [6, 8, 9].

Human laboratory drug self-administration research has been used to model drug use and to identify potential treatments for cocaine use disorders. For example, cocaine versus alternative reinforcer choice procedures model abstinence reinforcement treatments by having subjects choose between taking cocaine or earning a non-drug alternative reinforcer (i.e., being abstinent from cocaine; [3]). Previous drug self-administration research has also tested the efficacy of putative pharmacotherapies to reduce cocaine use in humans [e.g., 10, 11, 12] and has good predictive validity for the clinical efficacy of putative pharmacotherapies [13, 14].

The present experiment was designed to use human laboratory methods, particularly a cocaine versus alternative choice procedure, to examine the mechanisms that contributed to the positive results in the clinical trial described above [6] that demonstrated the enhanced efficacy of combining abstinence reinforcement and bupropion for managing cocaine use disorders relative to bupropion alone [6, 8, 9]. In this study, cocaine choice, as well as the subject-rated, performance and physiological effects of a range of doses of intranasal cocaine (4[placebo], 15 and 45 mg) were determined following pretreatment with oral immediate release bupropion (0, 100 and 200 mg).

Methods

Subjects

Eight non-treatment seeking adult subjects (5 men, 3 women; 6 Black, 1 White, 1 Hispanic) with recent histories of cocaine use who met criteria for a cocaine use disorder as determined by a computerized version of the Structured Clinical Interview for the DSM-IV completed the protocol. Subjects were 39 (± 3) years of age and weighed 83 (± 6) kg on average ($\pm$ SEM). Seven subjects reported daily use of cigarettes (12 $\pm$ 3 cigarettes/day). Seven subjects also reported weekly alcohol use (15 $\pm$ 4 drinks/week). In addition to cocaine use prior to screening (4 $\pm$ 1 days of use totaling US\$203 $\pm$ \$69 spent on cocaine in the past

week), subjects reported recent recreational use of other drugs. All subjects reported marijuana use, four subjects reported opioid use and three subjects reported benzodiazepine use in the month prior to screening. The Medical IRB of the University of Kentucky approved this study and subjects provided written informed consent before participating. Subjects were paid for their participation.

Prior to participation, all potential subjects had to undergo and pass a comprehensive physical- and mental-health screening. To meet inclusion criteria, subjects had to: 1) report recent cocaine use, 2) provide a urine sample positive for cocaine or benzoylecgonine during the initial screening process, 3) fulfill diagnostic criteria for a cocaine use disorder and 4) not be actively seeking substance abuse treatment. All subjects were in good health with no contraindications to experimental medication administration.

General Procedures

Subjects enrolled as outpatients at the University of Kentucky Chandler Medical Center Clinical Research and Development Operations Center (CRDOC) for ten sessions. Subjects were informed that during their participation they would receive bupropion, cocaine and matched placebo, administered orally and intranasally. Other than receiving this general information, subjects were blind to the specific drugs to be administered in each session. Subjects were told that the purpose of the study was to determine: 1) how the drug effects feel and influence mood, 2) the effects of the drugs on task performance, 3) whether subjects like the intranasal drug and are willing to take it again and 4) the effects of the drugs on physiology.

Practice Session—Subjects completed one practice session to familiarize them with experimental measures including the Drug Choice Procedure. Experimental medications were not administered during this session.

Experimental Sessions—Nine experimental sessions were completed and were conducted only on weekdays, at least 24 h apart. Experimental sessions started at 0800 and lasted for 7 h. During each session, subjects first received an oral dose of immediate release bupropion (0, 100 or 200 mg). These doses were selected to minimize any side effects associated with acute bupropion dosing (i.e., when used clinically, patients often take a lower dose of bupropion for several days to acclimate to the effects before moving to a clinically recommended dose, which is usually 300 mg/day [15]). Ninety min later, subjects sampled the cocaine dose available for that day (4 [placebo], 15 or 45 mg), based on pharmacokinetic data indicating that the peak plasma levels of oral immediate release bupropion occur at this time [15]. Subjects then made their choices between the available cocaine dose and an alternative reinforcer (US \$0.25), as described below.

Urine and expired breath samples were collected prior to each session to confirm drug and alcohol abstinence, respectively. Subjects occasionally tested positive for cocaine and tetrahydrocannabinol prior to experimental sessions. To ensure that they were not acutely intoxicated, subjects had to pass a field sobriety test prior to each session and no cocaine was administered until at least 2 h after subjects arrived at the laboratory. Subjects had to test negative for all other drug and alcohol use prior to completing experimental sessions. The female subjects received urine pregnancy tests prior to each session, which were negative throughout their participation.

Drug Choice Procedure

After sampling the cocaine dose available in each session, subjects made six choices between the drug and the alternative reinforcer at 30-min intervals by selecting one of two

options presented to them on a computer screen (“Dose” or “Money”). After making a choice, subjects then completed a number of responses using the computer mouse to earn that choice. Cocaine and the alternative reinforcer (US \$0.25) were available on independent, concurrent progressive ratio schedules such that the number of presses for the next choice increased systematically with each successive choice [16]. The initial ratio for either choice was 400 responses. Response requirements increased by 200 following a choice such that the full progression for each alternative was 400, 600, 800, 1000, 1200 and 1400 responses. This arrangement required subjects to expend effort to earn each chosen option, ensuring subjects made deliberate choices. The primary outcome variable for this measure was the number of drug choices.

Subject-Rated Measures

Subject-rated questionnaires were administered on a computer in a fixed order. Subjects completed these measures prior to the initial cocaine dose administration and 15 min after each dose administration. The measures included a Visual Analog Drug-Effect Questionnaire (see [17] for the individual items) and a Likert-Type Adjective-Rating Scale (ARS; [18]).

Performance Measure

The Digit-Symbol-Substitution Test (DSST) was used to assess changes in psychomotor performance following drug administration [19]. The DSST was completed at the same time as the subject-rated measures. The dependent measure was the percentage of trials completed correctly.

Physiological Measures

Heart rate, blood pressure and oral temperature were recorded immediately prior to the bupropion dose administration and at 15-min intervals thereafter until the subject met criteria for discharge from the CRDOC. Cardiac rhythmicity was recorded continuously throughout experimental sessions. Specific physiological safety criteria were in place to terminate participation [16], but no subjects were excluded from participation for exceeding these parameters, nor were any doses withheld.

Drug Administration

All drugs were administered in a double-blind fashion. Immediate release bupropion doses (0, 100 or 200 mg; UDL, Rockford, IL) were prepared by over-encapsulating commercially available drug in opaque gelatin capsules. Cocaine doses (4 [placebo], 15 and 45 mg) were prepared by combining the appropriate amount of cocaine HCl (Mallinckrodt, St. Louis, MO) with lactose to equal a total of 60 mg powder. An active placebo, 4 mg cocaine, was used in an attempt to increase subject “blindness”. This dose produces nasal numbing, but no discernible blood levels and is routinely used as the placebo in human laboratory studies involving intranasal drug administration [e.g., 20, 21].

During cocaine dose administration, a nurse presented the subject with the powder, a mirror and a standard razor blade. The subject was instructed to divide the powder into two even “lines” and insufflate one line of powder through each nostril using a 65-mm plastic straw within 2 min.

Data Analysis

Effects were considered significant for $p < 0.05$. Data from the Progressive Ratio Procedure were analyzed as number of drug choices using a two-factor, two-tailed, repeated-measures ANOVA with Bupropion (0, 100 and 200 mg) and Cocaine (4 [placebo], 15 and 45 mg) as

the factors (StatView, Cary, NC). Because individual subjects varied in their number of cocaine choices, and these different doses would affect subsequent subject-rated, performance and physiological measures, only measures obtained 15 min after the sampling dose (for subject-rated and performance data) or the maximum value observed 15 or 30 min after the sampling dose (for physiological data) were analyzed statistically. These data were analyzed in a manner identical to that used for the choice data.

If a significant interaction of Bupropion and Cocaine was observed, means for active bupropion doses were compared to means for the placebo bupropion dose within each cocaine dose condition using the Tukey *Post Hoc* test [22]. Means for each active dose condition were also compared to placebo. References to placebo below pertain to the 0 mg bupropion/4 mg cocaine condition. If a significant main effect of Bupropion was observed, means for active bupropion doses were compared to means for the placebo bupropion dose within each cocaine dose condition. If a significant main effect of Cocaine was observed, means for each active dose condition were compared to placebo. For brevity, if a significant interaction was observed, significant main effects are not reported.

To more fully examine the influence of bupropion pretreatment on the cocaine dose response curves (i.e., 4 [placebo], 15 and 45 mg cocaine following 0, 100 and 200 mg bupropion), trend analyses were conducted on measures with statistically significant outcomes using orthogonal polynomials to partition the curves into linear and quadratic components [22; 23; 24]. For brevity, if a significant quadratic trend was observed, significant linear trends are not reported.

Results

Number of Drug Choices

A significant interaction of Bupropion and Cocaine ($F_{4,28} = 2.95$) was observed on number of drug choices (Fig. 1). Following pretreatment with 0 mg bupropion, the 45 mg cocaine was chosen to a greater degree than placebo (average 5 of 6 versus 2.25 of 6 choices, respectively, $p < 0.05$) and a linear dose-effect function was obtained ($F_{1,28} = 19.62$, $p < 0.05$). Active bupropion suppressed choice of high dose cocaine with 3.13 and 4.00 of 6 choices made on average after pretreatment with 100 and 200 mg bupropion, respectively. After pretreatment with bupropion, the number of choices for 45 mg cocaine was no longer significantly higher than choices for placebo cocaine. The cocaine choice dose-effect function remained linear after pretreatment with 200 mg bupropion but showed a significant quadratic trend following pretreatment with 100 mg bupropion ($F_{1,28} = 10.59$, $p < 0.05$). In both cases, number of choices for the lower (15 mg) cocaine dose was slightly but not significantly higher after pretreatment with active versus placebo bupropion.

Subject-Rated, Performance and Physiological Measures

As shown in Table 1, cocaine alone at 15 and 45 mg increased scores on all 12 subject-rated items and on the Stimulant subscale of the ARS, while bupropion doses alone were devoid of effects on all subjective report measures (significant main effect of Cocaine; $F_{2,14}$ values 3.97). However, significant linear trends were only found on two measures (Good Effects; ARS Stimulant subscale) when cocaine was administered in the absence of active bupropion and only scores on the ARS Stimulant subscale following 45 mg cocaine were significantly different from placebo cocaine. Pretreatment with active bupropion enhanced subject-rated cocaine effects. Significant linear or quadratic trends were seen for 7 subject-rated measures when cocaine was administered after pretreatment with 100 mg bupropion and for all subject-rated measures following pretreatment with 200 mg bupropion. Further, significant differences between active and placebo cocaine were seen on the Nervous/Anxious item

when cocaine was combined with the 100 mg bupropion and on 5 measures (Active/Alert/Energetic; Good Effects; High; Rush; ARS Stimulant subscale) when cocaine was combined with 200 mg of bupropion. Consistent with the quadratic trends observed, 4 items (Good Effects, High, Rush; Willing to Pay For) had higher subject ratings at the 15 mg than at the 45 mg dose of cocaine in the 200 mg bupropion condition. The bottom panel of Fig. 1 illustrates a representative pattern of subject-rated effects with the Willing To Take Drug Again item (significant main effects of Bupropion [$F_{2,14} = 4.14$] and Cocaine [$F_{2,14} = 7.35$]; significant quadratic trends for all bupropion doses).

The DSST showed a significant interaction of Bupropion and Cocaine ($F_{4,28} = 3.41$) and a significant linear trend for improved performance after pretreatment with the 200 mg dose of bupropion, while bupropion and cocaine doses alone did not produce any significant effects. Heart rate (significant main effect of Cocaine; $F_{2,14} = 4.19$) and diastolic blood pressure (significant main effect of Bupropion; $F_{2,14} = 3.85$) tended to be elevated by cocaine under all bupropion dosing conditions but a significant linear trend on heart rate was seen only under the 200 mg bupropion condition. There were no significant effects observed on these measures when bupropion or cocaine doses were administered alone.

Discussion

In this experiment, 45 mg of intranasal cocaine was chosen to a greater degree than placebo following acute administration of 0 mg bupropion, but choice of high dose cocaine was decreased after active bupropion pretreatment. Although the absolute reduction in number of cocaine choices following bupropion dosing was small (reduction of approximately 1 or 2 choices out of 6 possible), this finding is consistent with those of a previously published clinical trial indicating that chronic bupropion can reduce cocaine taking when combined with abstinence reinforcement [6]. Bupropion also increased ratings on a number of the questionnaire items indicative of enhanced positive subjective effects following cocaine administration. Trend analyses indicated that bupropion pretreatment changed the shape of the cocaine dose response curves. Specifically, bupropion pretreatment flattened dose response curves for cocaine choice, whereas it accentuated or steepened the dose response curves for the subject-rated, performance and physiological measures.

The discordance between these two types of outcomes (i.e., reduced behavioral choice with enhanced subject-rated effects) is not without precedent. Similar results were observed in a previous study in which pretreatment with another putative pharmacotherapy, buprenorphine, enhanced some positive-subject-rated effects of cocaine, but reduced cocaine self-administration [25; also see [26] for a discussion of the issue]. The reasons for the discordance are unknown. One possibility is that subjects titrate their intake of high dose cocaine downward in the presence of enhanced subject-rated effects, particularly if unpleasant effects are enhanced along with positive effects. Thus, in a previous study of the cocaine-bupropion interaction, ratings of dysphoria on the LSD scale of the Addiction Research Center Inventory were increased by bupropion [27] while in the present study, ratings of Nervous/Anxious were increased along with the positive subject-rated effects of cocaine.

When an effect of bupropion was detected on subject-rated measures, it was generally the case that bupropion enhanced items indicative of abuse potential (e.g., Good Effects and Willing to Take Again). These findings are different from those of a previous human laboratory study, in which bupropion maintenance generally did not alter the subject-rated effects of intranasal cocaine [27]. The reason for the discordance between these two study findings is unknown but could be due to differences in the bupropion dosing regimens (i.e., acute in the present study, subchronic in [27]).

It is of interest to speculate on the clinical implications of this study, particularly in light of the discordant findings for behavioral and subject-rated measures. It is possible that the discordance between behavioral and subjective effects produced by bupropion is consistent with the mixed clinical trial findings from studies that have investigated bupropion for managing cocaine use disorders [6, 8, 9]. Specifically, cocaine use was reduced in the one study that combined bupropion with abstinence reinforcement [6], but bupropion was generally ineffective in other studies that did not use abstinence reinforcement as a treatment platform or when it was tested alone [6, 8, 9]. Thus, the choice test used here might better model the combination of a pharmacotherapy and a behavioral therapy that incorporates abstinence-contingent reinforcement as opposed to the use of bupropion with other therapeutic platforms lacking an abstinence contingency component.

There are several limitations that should be acknowledged in the present study. First, this experiment used an acute bupropion-dosing regimen with doses lower than those shown to be clinically effective [6] to provide an initial assessment of bupropion and cocaine interactions on the outcome measures. Bupropion pretreatment with higher and more prolonged dosing would have more clinical relevance, so future research should examine how a chronic bupropion regimen impacts the reinforcing effects of cocaine. Second, this study enrolled a relatively small number of non-treatment seeking subjects, although the sample size is comparable to other studies using similar within-subject designs (e.g., [27]). Non-treatment seekers were enrolled due to ethical issues surrounding administration of cocaine to individuals trying to abstain. Thus, the present enrollment criteria might limit generalizability. It is also possible that because subjects were not motivated to stop using drug, any effect of bupropion on cocaine choice or subject ratings was different from what would have been observed in individuals seeking treatment.

Bupropion reduced cocaine choice but enhanced subject-rated effects indicative of abuse potential in the present study. Previous reviews of human laboratory research suggest that measuring the impact of a putative pharmacotherapy on drug self-administration has good predictive validity for clinical efficacy (reviewed in [13, 14]). More work is needed, however, to better understand how the discordance between different human laboratory measures observed with bupropion translates to clinical outcomes, particularly across different behavioral treatment platforms.

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Fig. 1.

Mean number of drug choices for 8 subjects (top panel). Mean subject ratings of Willing to Take Again from the Drug-Effect Questionnaire for 8 subjects (bottom panel). X-axis: cocaine dose. Lines represent bupropion pretreatment conditions: 0 mg (squares), 100 mg (circles) and 200 mg (triangles). Filled symbols indicate a significant difference from placebo. Error bars indicate one SEM.

Table 1

Mean (SEM) values as a function of bupropion and cocaine dose condition for subjective, performance and physiological measures on which a significant effect was observed in the ANOVA that are not represented graphically. The maximum value for subject-rated items from the Drug-Effect Questionnaire is 100. The maximum value for score on the Adjective-Rating Scale Stimulant Subscale is 64. DSST means are expressed as percentage of trials completed correctly. Blood pressure means are expressed as mmHg. Heart rate means are expressed as beats per minute.

	Bupropion (0 mg)				Bupropion (100 mg)				Bupropion (200 mg)			
	PLB	15 mg	45 mg	Trend	PLB	15 mg	45 mg	Trend	PLB	15 mg	45 mg	Trend
<i>Drug-Effect Questionnaire</i>												
Active/Alert/Energetic	11.25 (5.97)	23.13 (7.79)	19.13 (5.93)	NS	11.25 (6.52)	20.50 (6.20)	20.75 (8.57)	NS	13.63 (6.87)	23.50 (7.39)	28.38 (9.54)	L
Any Effect	8.75 (4.77)	20.13 (8.65)	17.88 (5.01)	NS	11.63 (6.33)	22.63 (8.02)	25.88 (9.30)	L	8.88 (6.17)	26.75 (8.18)	27.13 (8.65)	L
Good Effects	7.13 (3.65)	16.00 (5.84)	19.25 (3.89)	L	11.50 (6.39)	22.88 (8.66)	20.63 (7.47)	NS	12.00 (7.82)	28.50 (8.79)	25.13 (7.60)	Q
High	10.63 (5.76)	19.13 (7.16)	19.38 (4.61)	NS	9.00 (5.83)	24.00 (8.00)	23.25 (7.88)	L	9.75 (7.63)	32.63 (9.13)	25.13 (8.22)	Q
Like Drug	8.38 (3.77)	18.63 (8.08)	22.25 (5.80)	NS	10.25 (5.48)	30.13 (11.64)	20.00 (7.90)	Q	10.63 (7.19)	31.25 (8.41)	30.88 (9.11)	L
Nauseated/Queasy/Sick to Stomach	3.38 (1.77)	3.13 (1.71)	4.13 (1.83)	NS	2.75 (1.85)	3.63 (2.03)	6.63 (2.31)	L	1.50 (0.80)	3.88 (1.79)	4.88 (1.81)	L
Nervous/Anxious	3.00 (1.52)	3.25 (1.56)	3.63 (1.78)	NS	3.13 (1.47)	3.50 (1.93)	7.63 (2.43)	L	1.75 (0.98)	4.25 (1.93)	5.88 (2.18)	L
Performance Impaired	3.63 (1.78)	1.63 (0.73)	5.88 (2.07)	NS	2.50 (1.38)	5.88 (3.79)	5.63 (1.86)	NS	1.25 (0.65)	7.13 (2.96)	10.75 (6.99)	L
Rush	8.75 (4.85)	15.88 (8.18)	16.00 (6.18)	NS	8.88 (6.58)	13.13 (5.72)	25.88 (10.14)	L	8.88 (7.33)	27.38 (9.58)	22.13 (9.72)	Q
Stimulated	9.13 (4.85)	19.50 (8.06)	18.00 (6.32)	NS	10.38 (6.02)	20.13 (6.22)	19.63 (8.60)	NS	11.88 (7.88)	23.50 (7.39)	26.13 (10.56)	L
Talkative/Friendly	12.25 (6.20)	18.13 (7.67)	15.25 (6.52)	NS	11.63 (6.32)	16.25 (5.93)	14.00 (9.25)	NS	9.13 (6.80)	20.25 (10.10)	20.63 (8.68)	L
Willing to Pay For	10.38 (6.38)	29.63 (9.04)	25.00 (6.07)	NS	9.75 (6.81)	23.88 (11.85)	24.38 (10.70)	NS	10.25 (6.32)	36.88 (12.57)	30.75 (10.25)	Q
<i>Adjective-Rating Scale</i>												
Stimulant Subscale	6.63 (1.10)	7.88 (0.58)	9.00 (0.78)	L	6.13 (1.16)	7.63 (1.02)	8.88 (0.95)	L	6.00 (1.15)	8.25 (1.26)	9.38 (1.10)	L
<i>DSST</i>												
Percentage of Trials Completed Correctly	92.09 (6.97)	92.49 (5.31)	90.78 (5.61)	NS	92.20 (5.14)	93.88 (3.69)	91.8 (5.92)	NS	90.09 (6.07)	91.11 (4.67)	95.93 (3.22)	L
<i>Physiological Measures</i>												
Diastolic Blood Pressure	74.75 (2.24)	79.13 (2.00)	77.88 (1.82)	NS	74.00 (1.79)	74.50 (2.67)	76.88 (1.59)	NS	73.63 (2.63)	74.63 (2.14)	76.38 (1.59)	NS
Heart Rate	74.00 (3.37)	78.25 (4.71)	79.63 (2.93)	NS	73.13 (3.29)	76.00 (2.63)	79.25 (3.61)	NS	71.63 (3.52)	75.38 (3.08)	79.25 (3.74)	L

Bolded values indicate a significant difference from placebo. An "L" under the trend column for each bupropion dose condition indicates a significant linear trend was detected for that cocaine dose response curve. A "Q" under the trend column for each bupropion dose condition indicates a significant quadratic trend was detected for that cocaine dose response curve. An "NS" under the trend column for each bupropion dose condition indicates no significant trend was detected for that cocaine dose response curve.