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Naltrexone-bupropion combinations do not affect cocaine self-administration in humans

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Abstract

The FDA has not yet approved a pharmacotherapy for cocaine use disorder despite nearly four decades of research. This study determined the initial efficacy, safety, and tolerability of naltrexone-bupropion combinations as a putative pharmacotherapy for cocaine use disorder. Thirty-one (31) non-treatment seeking participants with cocaine use disorder completed a mixed-design human laboratory study. Participants were randomly assigned to the naltrexone conditions (i.e., 0, 50 mg/day; between-subject factor) and maintained on escalating doses of bupropion (i.e., 0, 100, 200, 400 mg/day; within-subject factor) for at least four days prior to the conduct of experimental sessions. Cocaine self-administration (IN, 0, 40, 80 mg) was then determined using a modified progressive ratio and relapse procedure. Subjective and cardiovascular effects were also measured. Cocaine produced prototypical dose-related increases in self-administration, subjective outcomes (e.g., “Like Drug”), and cardiovascular indices (e.g., heart rate, blood pressure) during placebo maintenance. Naltrexone and bupropion alone, or in combination, did not significantly decrease self-administration on either procedure. Low doses of bupropion (i.e., 100 mg) blunted the effects of the cocaine on subjective measures of “Like Drug” and “Stimulated”. No unexpected adverse effects were observed with naltrexone and bupropion, alone and combined, in conjunction with cocaine. Together, these results do not support the use of these bupropion-naltrexone combinations for the treatment of cocaine use disorder. Future research should determine if novel drug combinations may decrease cocaine self-administration.

Keywords

Cocaine; self-administration; naltrexone; bupropion

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Introduction

Approximately 2 million Americans over the age of 12 years old reported current cocaine use, making cocaine the most widely used stimulant in the United States (Substance Abuse and Mental Health Services Administration [SAMHSA], 2021). Cocaine overdoses increased 26.5% from June 2019 to May 2020 (CDC, 2020). One in every five drug overdose deaths involves cocaine (Hedegaard et al., 2020). In addition to increased mortality, chronic cocaine use is related to several health concerns including cardiovascular toxicity, increased emergency room admission rates, and low birth weight (Chen et al., 1996; Miller et al., 1995; Sanvisens et al., 2021; Schwartz et al., 2010). Cocaine use also increases risks for other health concerns including cigarette smoking, co-morbid psychological disorders, and contracting and spreading sexually transmitted infections (Rounsaville et al., 1991; Sanvisens et al., 2021; Van Tieu & Koblin, 2009).

Cocaine use disorder is a chronic condition (McLellan, 2000), warranting long-term pharmacological treatments to supplement current evidence-based practices (e.g., contingency management, cognitive behavioral therapy; De Crescenzo et al., 2018; Schierenberg et al., 2012). However, there has yet to be an FDA-approved pharmacotherapy for cocaine use disorder (Czoty et al., 2016) despite it being a research priority for nearly four decades (Schuster & Snyder, 1989).

One promising approach is the combination of pharmacotherapies to treat cocaine use disorder (Stoops & Rush, 2014). There are several putative benefits to combining medications: (1) combining two medications at lower doses may reduce stimulant use while minimizing the risk of side effects (Goeders & Guerin, 2008); (2) combining two medications with some efficacy as monotherapies may result in additive or synergistic reductions in stimulant use (see Rush et al., 2021); and (3) cocaine produces its direct effects by inhibiting the function of transporters for the monoamine neurotransmitters dopamine, serotonin, and norepinephrine (Czoty et al., 2016; Fleckenstein et al., 2000; Rothman & Glowa, 1995). Using multiple pharmacotherapies with diverse pharmacological effects could target these systems better than currently available medications that are more pharmacologically selective.

Bupropion (i.e., Wellbutrin®, Zyban ®) is a dopamine and norepinephrine reuptake inhibitor and nicotinic acetylcholine receptor antagonist approved for depression, seasonal affective disorder, and smoking cessation. Its effects on cocaine self-administration have been studied using preclinical and human laboratory models and have been evaluated in clinical trials as a standalone and adjunct treatment for cocaine use disorder. In one study, intravenous bupropion (1.8 mg/kg/hr) increased responding maintained by cocaine (0.0032 mg/kg) in rhesus monkeys (n=4) following a 7–10-day maintenance period (de Moura et al., 2020). In a human laboratory study, acute bupropion (100 and 200 mg p.o.; immediate release) decreased choice for intranasal cocaine (45 mg) relative to placebo pretreatment (Stoops et al., 2012). Bupropion has also been evaluated in several clinical trials for cocaine use disorder with mixed results. In one 25-week, randomized, controlled trial, methadone-maintained participants who received 300 mg oral bupropion (p.o.) plus contingency

management had fewer cocaine-positive urine samples compared to controls (Poling et al., 2006). These results contrast with other clinical trials that did not report any bupropion-related (300 mg) decreases in cocaine use (Margolin et al., 1995; Shoptaw et al., 2008).

Naltrexone is a synthetic opioid antagonist approved for the treatment of alcohol and opioid use disorders. Previous preclinical work investigating the impact of naltrexone on cocaine self-administration has been mixed. Carroll and colleagues (1986) reported acute injections of naltrexone (0.5, 1 or 2 mg/kg) increased cocaine self-administration in food-satiated rats. Subsequent preclinical studies reported decreases in cocaine self-administration following naltrexone dosing. Mello et al. (1990) reported decreased cocaine self-administration in rhesus monkeys following naltrexone maintenance (0.32–3.20 mg/kg/day). Additionally, Ramsey et al. (1999) found intracranial administration of 1.0 μg naltrexone into the ventral tegmental area decreased cocaine self-administration in rats. No human laboratory studies have determined the effect of naltrexone on cocaine self-administration. However, naltrexone has been reported to decrease some of the positive subjective effects of cocaine in humans (Comer et al., 2013; Sofuoglu et al., 2003). Two clinical trials determined the impact of naltrexone on cocaine use in individuals with co-morbid alcohol and cocaine use disorders. In a small preliminary trial (N = 7) conducted by Oslin et al. (1999) naltrexone decreased the number of days participants reported using cocaine, although this trial did not include a control group. In a larger randomized, placebo-controlled trial, participants with a DSM-IV diagnosis of cocaine and alcohol dependence who received naltrexone alone and in combination with disulfiram did not differ in the rates of cocaine abstinence compared to controls (Pettinati et al., 2008).

Despite the limited evidence supporting the use of bupropion and naltrexone to treat cocaine dependence, these drugs in combination are approved as a pharmacotherapy for obesity (Tek, 2016), a significant public health concern that affects 42% of Americans (Hales et al., 2020). Although obesity and cocaine dependence are typically considered distinct clinical entities, both diseases involve perturbation of central biogenic amine systems (i.e., comparable reductions in striatal D_2 dopamine receptors in obese and drug-addicted individuals; Wang et al., 2004) and can be defined behaviorally as increased saliency of food or drug over other reinforcers. Given the common neurobiological and behavioral factors involved in obesity and cocaine use disorders, advances made in the treatment of one disorder may inform the pharmacological management of the other. Previous studies have demonstrated bupropion and naltrexone modestly reduced body weight when tested as monotherapies (Gadde et al., 2001; Lee & Fujikoka, 2009). However, their combination significantly reduced body weight (Tek, 2016). As noted above, bupropion and naltrexone have limited effectiveness when tested as monotherapies for cocaine dependence. Whether bupropion-naltrexone combinations may be more effective for cocaine dependence than the individual drugs alone is unknown.

Given the lack of research on the impact of drug combinations on cocaine use, the purpose of this study was to assess the individual and combined effects of naltrexone and bupropion on cocaine self-administration in humans. In the present study, a mixed model design was used to measure the effects of oral naltrexone (between-subject) and sustained-release bupropion (within-subject) maintenance on cocaine (within-subject) self-administration in

participants with cocaine use disorder. Participants were randomly assigned to receive naltrexone (0 or 50 mg) and received all possible bupropion doses (0, 100, 200, 400 mg). The reinforcing effects of intranasal cocaine (0, 40, and 80 mg) were assessed using a progressive ratio and relapse procedure. Progressive ratio schedules yield information about the relative reinforcing strength of different stimuli (e.g., cocaine; Comer et al., 2008; Stafford et al., 1998), whereas relapse procedures provide an opportunity to ethically assess a return to substance use under high-cost conditions (i.e., large response requirements; Haney et al., 2008). Both procedures predict the efficacy of putative pharmacotherapies for stimulant use disorder (Haney & Spealman, 2008).

Methods

The Institutional Review Board of the University of Kentucky Medical Center approved the conduct of the study. All participants gave their sober, written, informed consent prior to being enrolled in the study.

Participants

Thirty-one (N=31) non-treatment seeking participants completed this study. Inclusion criteria included: (1) the ability to speak and read English; (2) being between 18–55 years old; (3) having a body-mass index (BMI) of 19–29; (4) self-reporting current cocaine use, verified by benzoylecgonine-positive urine sample; and (5) meeting diagnostic criteria for cocaine abuse or dependence as determined by a Structured Clinical Interview for DSM-IV. During the screening process participants completed a medical history questionnaire, laboratory chemistries (e.g., blood chemistry screen, complete blood count and urinalysis), electrocardiogram, and a brief psychiatric examination. Participants were excluded from the study if: (1) medical screening results were deemed abnormal by a study physician (e.g., electrocardiogram beyond normal limits, abnormal chemistry values deemed clinically significant); (2) they had a history of a serious physical disease (i.e., impaired cardiovascular functioning, chronic obstructive pulmonary disease, seizures) or psychiatric disorder that would interfere with study participation; or (3) they had current or past histories of substance abuse or dependence that would interfere with study participation. Decisions to exclude participants on these criteria were based on the review of screening materials and/or history and physical examination conducted by a study physician.

Enrolled participants were also discharged from the study if at any time during the experimental sessions cocaine increased their heart rate above 130 bpm, systolic pressure above 180 mmHg, or diastolic pressure above 120 mmHg, or if clinically significant and/or prolonged ECG abnormalities were noted. No participants were discharged for any of these reasons. Three participants voluntarily ended their participation: two for personal reasons and one due to self-reported muscle spasms. Their data were not included in the final analyses.

Drugs and Dosing Procedures

Participants were maintained on a combination of bupropion (0, 100, 200, and 400 mg/day; terminal half-life of 7 to 46 hours; Masters et al., 2016) and naltrexone (0 or 50 mg/day;

terminal half-life of 1.1 to 10.3 hours; Gonzalez & Brogden, 1988) maintenance doses for at least four days to reach steady state levels before beginning experimental sessions. All participants received bupropion doses in an ascending order. Participants were maintained on the same dose of naltrexone based on their group assignment (between-subject; 0 or 50 mg) throughout the duration of their participation.

All drugs were administered in a double-blind fashion. Only lead investigators and Investigational Drug Service pharmacy staff had access to dose orders to maintain blinding. These individuals did not interact with participants during experimental sessions, nor did they collect experimental data.

Sustained-release bupropion (0, 100, 200, 400 mg/day, administered in two divided doses) and naltrexone (0 or 50 mg/day, administered in two divided doses) were prepared by over-encapsulating commercially available doses in size 0 capsules. Naltrexone and bupropion doses were selected based on the results of previous research, which indicate they can be safely administered in combination with cocaine to individuals who regularly use cocaine (Levin et al., 2002; Oliveto et al., 2001). Placebo capsules contained only cornstarch and were otherwise identical to the capsules that contained active drug. Cocaine doses (0, 40, 80 mg) were prepared by combining the appropriate amount of powdered cocaine for each dose with lactose monohydrate powder for a total of 120 mg of powder. Placebo was prepared in an identical fashion, but only contained lactose monohydrate powder. Intranasal cocaine administration was modeled after prior cocaine self-administration research (see Rush et al., 2021).

Randomization

Participants were urn randomized to one of two oral naltrexone maintenance conditions: 0 and 50 mg/day. Urn randomization is a statistical procedure used to randomly assign participants to groups while balancing groups on certain participant characteristics (Wei & Lachin, 1988), in this case sex and years of cocaine use (>15 or <15 years). Within each naltrexone condition all bupropion doses were administered in an ascending order. The order of cocaine self-administration sessions (i.e., progressive ratio and relapse procedures) was held constant within subjects but counterbalanced between subjects (see Table 1 and Experimental Sessions section below). Cocaine dose order was randomized for each participant.

General Procedures

Participants were enrolled as inpatients at the University of Kentucky Clinical Research Unit (CRU) for up to 32 days and were acclimated to the CRU (day 1), completed one drug-free practice session (day 2), one medical safety session, and twelve (12) experimental sessions (one naltrexone dose by four bupropion doses by three cocaine doses) during enrollment (See Table 1 for an overview of experimental procedures). During inpatient admission, participants were maintained on a caffeine-free diet and provided urine samples daily and expired breath samples at the beginning of each session to confirm abstinence from illicit drug and alcohol use, respectively. Urine pregnancy tests were conducted daily for female

participants and were negative throughout the study. Participants were permitted to smoke cigarettes outside of experimental sessions while accompanied by a staff member.

Medical Safety Session (Day 3)

Prior to beginning naltrexone maintenance, participants completed a medical safety session in which they received intranasal cocaine doses that approximated the maximum daily dose available during experimental sessions (i.e., 240 mg). Medical safety sessions were also completed to permit comparison of subjective responses to cocaine between naltrexone groups. During this session, intranasal cocaine doses (i.e., 0, 10, 20, 40, 60 and 80 mg) were administered in ascending order at 45-minute intervals unless cardiovascular indices (heart rate, blood pressure) exceeded the established safety thresholds. This did not occur in any participants. Subjective-effects measures were completed 30 minutes before placebo cocaine administration (i.e., 0 mg), immediately after dose administration, and at 15-minute intervals following each dose.

Naltrexone and Bupropion Maintenance (Days 4-31)

Participants received maintenance medication(s) twice daily following the medical safety session at 0700 and 1900 hours. Maintenance medications were withheld if a subject's heart rate was ≥100 bpm or systolic or diastolic pressure were ≥150 or 100 mmHg, respectively. In addition, the UKU side effects scale (Lingjaerde et al., 1987) was completed daily to monitor for the emergence of side effects.

A block of three experimental sessions began following the fourth day of maintenance under each naltrexone-bupropion dose condition. Upon the completion of the first block, participants were maintained on the second bupropion dose (i.e., 100 mg/day) for four days prior to beginning the second block of three experimental sessions. This cycle continued for four total bupropion doses (0, 100, 200, 400 mg/day). Participants were subsequently discharged following the twelfth experimental session.

Experimental Sessions (Days 8–10; 15–17; 22–24; 29–31)

There were 12 total experimental sessions in this study. Each session involved a sampling phase, a progressive ratio self-administration procedure, and a relapse self-administration procedure. The sampling phase was always first whereas the order of the progressive ratio and relapse procedures were counterbalanced across participants and fixed within-subjects. As a result of counterbalancing, the times discussed in the *Modified Progressive Ratio Procedure* and *Relapse Procedure* sections below depended on the order in which they were completed by the participant. The description below describes a scenario in which the progressive ratio procedure occurred first.

Sampling Phase.—Participants completed a sampling phase in each experimental session to acquaint them with the effects of the cocaine dose that was available during that session. Baseline subjective-effects and physiological measures were completed at approximately 0900 hours. The intranasal cocaine dose (0, 40, or 80 mg) available during that session was administered at 0930 hours. Subjective and physiological measures were completed

immediately after dosing and at 15-minute intervals until 1015 hours, when the sampling phase ended.

Modified Progressive Ratio Procedure.—The first self-administration phase began 45 minutes following the completion of the sampling phase, at approximately 1100 hours. The reinforcing effects of intranasal cocaine were assessed during maintenance on bupropion-naltrexone combinations using a progressive ratio procedure. During this phase, participants were given up to 10 opportunities to earn $1/10^{th}$ of the cocaine dose that was insufflated during the Sampling Phase. Prior to the beginning of this phase, participants were instructed that the total amount of drug earned would be administered after the completion of the entire progressive ratio procedure. Participants earned portions of the total cocaine dose by responding (i.e., clicking) on a computer mouse. The initial ratio to obtain the first $1/10^{th}$ of the dose of intranasal cocaine available was 400 clicks. The response requirement for each subsequent ratio increased by 100 clicks (i.e., 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300). Progressive ratio schedules have been used extensively to measure changes in the reinforcing effects of cocaine following pretreatment and maintenance medications (Stoops, 2008). The primary dependent measure was the number of ratios completed. After completion of the procedure, the total earned dose was presented to the participant for self-administration at approximately 1200 hours. Participants then insufflated the chosen dose and completed subjective and physiological measures at 15-minute intervals for 45 minutes. The session ended at approximately 1245 hours.

Relapse Procedure.—The second self-administration phase began at 1330, 45 minutes following the end of the first session. In addition to the progressive ratio procedure, a relapse procedure modeled after Haney et al. (2008) was used to measure the reinforcing effects of cocaine. Relapse procedures are effective at modeling motivation to return to substance use. In these procedures, the initial cost to access cocaine is high, modeling the large financial and social cost of relapse (Haney et al., 2008). Rather than using a financial cost (e.g., Haney et al.), the initial response requirement to obtain cocaine doses was large in the present study. Participants were given up to 10 opportunities to earn $1/10^{th}$ of the cocaine dose insufflated during the Sampling Phase. Before this phase, participants were instructed that the total amount of drug earned would be administered after completing the entire relapse procedure. Like the progressive ratio procedure, participants were able to earn portions of the cocaine dose by responding on a computer mouse. However, the initial ratio to obtain a dose of intranasal cocaine was 2000 clicks. Participants were informed that this response requirement would remain in place if they chose not to respond for drug. After a participant made their first choice for drug and completed 2000 clicks to earn that dose, the response requirement was reduced to 200 clicks for each remaining response ratio. The primary dependent measure for this procedure was the number of response requirements completed. After completion of the procedure, the dose earned was administered at approximately 1430 hours. Participants then insufflated the chosen dose and completed subjective and physiological measures at 15-minute intervals for 45 minutes. The session ended at approximately 1515 hours.

Subjective Effects Measures

Subjective-effects measures included an investigator-developed Visual Analog Scale and the Adjective Rating Scale which are sensitive to the effects of stimulants (Rush et al., 2003; Rush et al., 2009; Oliveto et al., 1992).

Cardiovascular Measures

Heart rate, blood pressure, and heart rhythmicity (*via* 3-lead ECG telemetry) were recorded using a Dinamap digital monitor (Critikon, Pro 1000, Tampa, FL). Telemetry-certified nurses interpreted the ECG results with instructions to contact a study physician regarding abnormalities.

Participant Payments

Participants were compensated $40 for each day that they resided in the inpatient unit and received a $40 completion allowance for each of these days if they completed the entire study.

Data Analysis

Demographics.—Continuous scale demographic data (e.g., alcohol, cigarette, and cocaine use) from participants in each naltrexone cohort (i.e., 0 or 50 mg/day) were compared using independent samples t-tests with a Bonferroni Correction. Counts of nominal scale demographic data (i.e., sex, race) were analyzed using a chi-square test of independence.

Medical Safety Session.—Physiological and subjective effects data obtained during the medical safety sessions were analyzed as peak effect (i.e., maximal response observed after dosing) using a 3 × 2 mixed model ANOVA with a Greenhouse-Geisser correction for sphericity with cocaine (within-subject factor; 0, 40 and 80 mg) and naltrexone (between-subject factor; 0 and 50 mg/day) as the factors.

Self-Administration.—Progressive ratio and relapse procedure data (i.e., number of ratios completed) were analyzed using a 3 × 4 × 2 mixed-model ANOVA with the addition of bupropion (within-subject factor; 0, 100, 200 and 400 mg/day) as a factor. Planned comparisons were conducted following any statistically significant three-way interaction (cocaine x bupropion x naltrexone) identified from the omnibus ANOVA. These analyses compared the dose effect of cocaine alone (i.e., during maintenance on 0 mg bupropion and 0 mg naltrexone, henceforth referred to as placebo maintenance) with the cocaine dose effect curves during maintenance on each of the seven bupropion-naltrexone maintenance conditions using two-way ANOVAs. Differences were inferred from these analyses if the main effect of Maintenance Condition or the interaction of Maintenance Condition and Cocaine attained statistical significance.

Subjective Responses.—Physiological and subjective effects data obtained during the sampling phases were analyzed as peak effect in a similar fashion as the progressive ratio and relapse procedures. Physiological and subjective effects data from the self-administration phases were not analyzed statistically because participants ingested varying amounts of the available dose of cocaine.

Results

Demographics

Table 2 shows the demographics of the participants in each naltrexone group. Participants in each naltrexone group did not differ significantly from one another on any demographic variable ($p > .05$). No significant relationships between naltrexone dose and gender (X^2 (1, N = 31) = 0.011, p = 0.92) or naltrexone dose and race (X^2 (3, N = 31) = 2.40, p = 0.50) were observed.

Medical Safety Session

Subjective Effects Questionnaires.—Cocaine dose-relatedly increased ratings on 18 items of the Visual Analog Scale (Active Alert Energetic; Any Effect; Bad Effect; Euphoric; Good Effect; High; Irregular Heartbeat; Like Drug; Nauseated; Nervous/Anxious; Performance Impaired; Performance Improved; Rush; Shaky/Jittery; Stimulated; Talkative/Friendly; Willing to Pay For; Willing to Take Again; $F_{5,25}$ = 3.78 – 20.34; $\eta 2$ = 0.12 – 0.41; $p < 0.05$) and both subscales of the Adjective Rating Scale (Sedative, Stimulant; $F_{5,25}$ = 5.61, 11.03; $\eta 2$ = 0.16, 0.28; $p < 0.05$, respectively). No statistically significant differences were observed on Visual Analog Scale or Adjective Rating Scale measures between naltrexone groups ($F_{5,25}$ = 0 – 2.53; $\eta 2$ = 0 – 0.08; $p > 0.05$). Additionally, no group and cocaine interactions were observed ($F_{5,25}$ = 0.195 – 1.867; $\eta 2$ = 0.01 – 0.06; $p > 0.05$)

Cardiovascular Measures.—Cocaine dose-dependently increased heart rate and systolic and diastolic blood pressure (i.e., main effect: $F_{5,25}$ = 10.30 – 26.34; $\eta 2$ = 0.26 – 0.48; $p < 0.05$). No statistically significant naltrexone group differences were observed on any cardiovascular measures ($F_{5,25}$ = 0.0 – 1.73; $\eta 2$ = 0.0 – 0.06; $p > 0.05$) and no significant group and cocaine interactions were detected ($F_{5,25}$ = 0.461 – 0.998; $\eta 2$ = 0.02 – 0.03; $p > 0.05$).

Experimental Sessions

Progressive Ratio.—Figure 1 (top panel) shows the results from the progressive ratio procedure. Cocaine significantly increased the number of ratios completed across maintenance conditions (i.e., main effect: F = 32.63; $\eta 2$ = 0.70; $p < 0.001$) in the omnibus ANOVA. Neither naltrexone ($F_{1,28}$ = 3.36; $\eta 2$ = 0.104; p = 0.08) nor bupropion (F = 0.74; $\eta 2$ = 0.03; p = 0.52) had a statistically significant effect on the number of ratios completed. No two- or three-way interactions between cocaine, naltrexone, or bupropion ($\eta 2$ = 0.02 – 0.07; p = 0.87 – 0.14) were observed on the progressive ratio procedure.

Relapse Procedure.—Figure 1 (bottom panel) shows the results on the relapse procedure. As with the progressive ratio procedure, cocaine significantly increased the number of ratios completed across the maintenance conditions (i.e., main effect: F = 69.76; $\eta 2$ = 0.71; $p < 0.001$). Neither naltrexone ($F_{1,29}$ = 4.02; $\eta 2$ = 0.12; p = 0.06) nor bupropion (F = 0.15; $\eta 2$ = 0.01; p = 0.92) had a statistically significant effect on the number of ratios completed on the relapse procedure and no two- or three-way interactions ($\eta 2$ = 0.01 – 0.09; p = 0.80 – 0.10) were observed.

Subjective Effects Questionnaires.—Table 3 summarizes the results of the subjective effects questionnaires during the experimental sessions. Cocaine dose-dependently increased ratings on all items from the Visual Analog Scale (except "Sluggish"; i.e., main effect: $F_{5,25}$ = 6.53 – 43.48; $\eta 2$ = 0.18 – 0.6; $p \leq 0.005$) and the *Stimulant* subscale of the Adjective Rating Scale (i.e., main effect: $F_{5,25}$ = 39.15; $\eta 2$ = 0.57; $p < 0.001$). The omnibus ANOVA revealed a cocaine x naltrexone x bupropion interaction for seven items on the Visual Analog Scale (See Table 3; Active Alert Energetic; Good Effect; Like Drug; Performance Impaired; Stimulated; Willing to Pay For; Willing to Take Again; $F_{5,25}$ = 2.55 – 3.94; $\eta 2$ = 0.08 – 0.12; $p \leq 0.05$). Planned comparisons of the cocaine dose effect during maintenance on placebo (circles; left panels) versus 100 mg bupropion alone (squares, left panels) revealed a statistically significant interaction of cocaine and maintenance condition on measures of "Like Drug" ($F_{5,28}$ = 6.48; p = 0.01) and "Stimulated" ($F_{5,28}$ = 3.53; p = 0.04; Figure 2). Bupropion blunted the effects of cocaine on these measures. No significant effects of maintenance were revealed by the planned comparisons on the other five items.

The omnibus ANOVA also revealed a statistically significant main effect of bupropion (F_5 = 3.15 – 3.16; p = 0.03 – 0.05) for ratings of "Any Effect" and "High". Bupropion increased the ratings of both measures compared to placebo maintenance. Naltrexone had no effect on ratings from the Visual Analog Scale or Adjective Rating Scale ($F_{5,25}$ = 0.01 – 3.50; $\eta 2$ = 0.0 – 0.11; $p > 0.05$).

Cardiovascular Measures.—The omnibus ANOVA revealed a main effect of cocaine on systolic blood pressure, diastolic blood pressure, and heart rate ($F_{5,25}$ = 35.50 – 42.82; $\eta 2$ = 0.55 – 0.60; $p \leq 0.001$). Bupropion significantly increased the effects of cocaine on systolic blood pressure ($F_{5,25}$ = 3.84; $\eta 2$ = 0.12; p = 0.01), diastolic blood pressure ($F_{5,25}$ = 5.07; $\eta 2$ = 0.15; p = 0.004), and heart rate ($F_{5,25}$ = 25.02; $\eta 2$ = 0.46; $p \leq 0.001$). Naltrexone had no effect on any cardiovascular measures. No cocaine x naltrexone x bupropion interactions were observed. Figure 3 shows these effects for heart rate.

Discussion

This study evaluated the effects of naltrexone (0, 50 mg/day) and bupropion (0, 100, 200, 400 mg/day) maintenance on the reinforcing, subjective, and physiological effects of intranasal cocaine (0, 40, 80 mg/day) in non-treatment seeking participants with cocaine use disorder. Below we discuss the results of this study in the context of the existing literature.

Cocaine Alone

The dose-dependent increases in cocaine self-administration align with decades of human laboratory research demonstrating the robust reinforcing effects of cocaine in humans (see Regnier et al., 2022 for a review). During the medical safety session, cocaine was well tolerated and produced prototypic increases in subjective and cardiovascular effects. In experimental sessions, cocaine engendered dose-related increases in subjective ratings during placebo maintenance. Although cocaine also significantly increased heart rate and blood pressure, these effects were not clinically concerning for an acute drug response, and cocaine was well tolerated across all maintenance conditions.

Bupropion Alone

Bupropion produced modest effects on cardiovascular and subjective measures but no effects on self-administration when tested alone. Cardiovascular effects were limited to a slight increase in blood pressure and heart rate, indicating that bupropion was safe and well tolerated.

The lack of effects of bupropion on self-administration in this study contrasts with the results of a Stoops et al. (2012) study, in which acute bupropion decreased choices for 45 mg intranasal cocaine. However, participants in the current study were maintained on bupropion during a four-day maintenance period, whereas Stoops et al. (2012) administered oral bupropion acutely, 90 minutes prior to completing drug choice procedures. It is unclear why acute dosing had a significant effect on cocaine choice whereas chronic dosing did not. A rigorous preclinical comparison of the effects of acute and repeated d-amphetamine treatment on cocaine self-administration found that acute treatment increased cocaine choice, while chronic treatment decreased cocaine choice (Thomsen et al., 2013).

No prior human laboratory studies have directly compared acute and maintenance treatment conditions, and only one drug, buprenorphine, has previously been tested across separate studies using acute and maintenance dosing procedures. In those studies, buprenorphine decreased human cocaine self-administration under both conditions (Foltin & Fischman, 1994, 1996). However, increases in several subjective measures were observed (e.g., “speedball”-like effects, feelings of sedation, cocaine cravings) following only acute pretreatment suggesting acute and maintenance pharmacotherapies can differentially impact the effects of cocaine. Similarly, in Stoops et al. (2012) acute bupropion increased the effects of cocaine on ratings on several positive subjective effects measures following cocaine administration, whereas in the present study bupropion maintenance slightly blunted the effects of cocaine on similar measures. Bupropion alone had no impact on the reinforcing effects of cocaine. The contrasting results between Stoops et al. and the current study illustrate the potential differential effects of acute and chronic bupropion dosing on the subjective and reinforcing effects of cocaine.

In addition to the dosing regimen differences between the present study and Stoops et al. (2012), each study used different bupropion and cocaine doses. In Stoops et al. participants were pretreated with 0, 100, or 200 mg immediate release bupropion, whereas 0, 50, 100, and 200 mg BID sustained release bupropion was provided in the present study. Stoops et al. used 4 (placebo), 15, and 45 mg cocaine doses compared to 0, 40 and 80 mg in the present study. Stoops et al. found that 100 and 200 mg acute bupropion doses significantly decreased 45 mg cocaine choice, whereas no effects of bupropion maintenance were found in the present study. Despite the variance in dose, the differences in the results of these studies may be partially explained by the dosing regimen. This is evidenced by the similar bupropion doses included in the present study having no effect on cocaine choice for doses used by Stoops et al. (i.e., 45 mg). Bupropion maintenance may become slightly less effective after several days of maintenance. This would warrant the investigation of larger bupropion maintenance doses (i.e., 400 mg) on the reinforcing effects of smaller cocaine doses (i.e., 15 mg).

Naltrexone Alone

Naltrexone produced no effects on subjective and cardiovascular measures and a small, but statistically non-significant decrease on cocaine self-administration. The absence of a difference in subjective and cardiovascular responses to cocaine between the naltrexone maintenance groups indicates naltrexone was safe and well tolerated. The lack of a statistically significant decrease in cocaine self-administration between naltrexone conditions revealed from the omnibus ANOVA is consistent with Moerke et al. (2017) who found that naltrexone had no effects on cocaine choice in adult rhesus monkeys when provided alone. However, these results are inconsistent with the decreased cocaine self-administration following treatment with naltrexone reported in rhesus monkeys by Mello et al. (1990), suggesting the effects of naltrexone on cocaine choice in a laboratory setting are mixed. The present study is the first to measure the effects of naltrexone on cocaine use in a human laboratory setting, preventing direct comparison across studies. However, the results of this study align with the lack of effect of naltrexone on cocaine abstinence found by Pettinati et al. (2008) in a randomized, placebo-controlled trial in participants with a DSM-IV diagnosis of cocaine and alcohol dependence. Additionally, participants in that study received 100 mg/day naltrexone maintenance, double the dose tested in the present study.

Bupropion-Naltrexone Combination

Combining bupropion and naltrexone did not alter the reinforcing effects of cocaine. The absence of an effect of bupropion and naltrexone combinations is consistent with a human laboratory study conducted by Stoops et al. (2015), wherein neither bupropion (300 mg) nor naltrexone (50 mg), alone or combined, altered the reinforcing effects of intranasal methamphetamine (10 and 30 mg) in participants who reported recent illicit stimulant use. The results of the current study are inconsistent with a randomized, controlled trial, in which participants who received a depot injection of 380 mg naltrexone every three weeks and 450 mg bupropion daily exhibited small but statistically significant decreases in methamphetamine positive urine samples (Trivedi et al., 2021). The results of this study and of prior bupropion-naltrexone combination research do not support the use of this combination as a treatment for cocaine use disorder. Any effects generated in a laboratory setting may lack the robustness required to produce clinically significant effects in a treatment setting. However, the slight decrease in self-administration produced by naltrexone, combined with prior preclinical data, suggest further studying of naltrexone as an adjunct pharmacotherapy for cocaine use disorder may be warranted. Future research required may include naltrexone combined with a maintenance medication other than bupropion.

The absence of an effect of naltrexone-bupropion maintenance on cocaine self-administration is also consistent with other studies that have shown cocaine-taking in the human laboratory is difficult to alter with pharmacological interventions (Regnier et al., 2022). However, this may be attributable to the methods used. For example, in the present study, participants responded on a computer mouse to obtain doses of cocaine, with no other choice available. However, in several studies in our laboratory (e.g., Stoops et al., 2012; Rush et al., 2021, Rush et al., 2010, Lile et al., 2020) participants chose between varying

doses of cocaine and money. This alternative reinforcer availability may decrease the probability participants choose cocaine, making the progressive ratio procedure used in the present study a less sensitive test of the reinforcing effects of cocaine. Further, the studies above found a statistically significant decrease in the reinforcing effects of cocaine following acute bupropion, topiramate/phentermine, and d-amphetamine dosing, respectively. This provides evidence the best way to measure self-administration of cocaine and the eventual effects of a medication on cocaine taking behavior is with a choice procedure in which alternative, monetary reinforcers are available. Previous human laboratory studies outside of our laboratory have also demonstrated decreases in cocaine self-administration following d-amphetamine (Greenwald et al., 2010; Rush et al., 2010; Lile et al., 2020) and higher modafinil doses (i.e., 300 and 400 mg; Foltin et al., 2016; Hart et al., 2008) using similar procedures.

Assessing Multiple Self-Administration Procedures

The results obtained from the progressive ratio and relapse procedures were similar. While the progressive ratio procedure has remained generally consistent over time, the relapse procedure used in the present study is one of several human laboratory variations developed over the past thirty years. In an early model of cigarette smoking relapse, following three days of abstinence, participants were randomly assigned to either remain abstinent during a several hour exposure phase on the fourth day, or smoke five cigarettes. During a subsequent five-day post-exposure phase, in which participants were encouraged to remain abstinent from cigarettes, participants who smoked in the exposure phase were more likely to relapse during the post-exposure phase (Chornock et al., 1992. More modern relapse procedures are integrated into a self-administration paradigm. In these procedures participants choose between cocaine and decreasing amounts of money following a period of abstinence (Walsh et al.,2001; Donny et al., 2004). In a variation of Donny et al. and Walsh et al., Haney et al. (2008) had participants respond on an initially lean schedule of reinforcement to obtain marijuana, following a period of abstinence. In that study, participants were required to pay $10 to obtain marijuana following three days of abstinence. However, subsequent schedule requirements following drug choice were fixed at a reduced amount (i.e., $3) rather than descending. It is difficult to determine the extent that these are value models of relapse and provide information beyond that of the progressive ratio. These models inform the conditions under which participants will return to drug use following a period of abstinence. However, there has yet to be a demonstration of a relapse procedure with results different than the inverse of a progressive ratio.

One significant difference between Haney et al., Donny et al., and the present study is that relapse procedures occurred following a period of abstinence in Haney et al. and Donny et al. This procedure may provide a more accurate model of relapse than the procedures used in the present study. In the present study, the results obtained from the progressive ratio and relapse procedures were nearly identical. This suggests that the results of the relapse procedure did not provide any novel information about the participants' drug choice.

Limitations

There are several study limitations that should be acknowledged. First, a fully within-subjects design was not used, but doing so would have doubled the length of participation for participants, which was not feasible. Second, despite potential limitations to external validity, participants were only enrolled if they were not treatment-seeking. This was done to avoid ethical issues regarding providing cocaine to individuals that were attempting to quit or reduce their use. Third, cocaine was administered intranasally to participants who primarily reported smoking as their main route of cocaine administration. This might have produced atypical cocaine choices during experimental sessions and could limit the generalizability of the results to only individuals who use cocaine intranasally. However, facility restrictions prevented the manufacture and administration of smoked cocaine. Additionally, the use of intranasal cocaine has been considered acceptable in prior studies due to the shared pharmacodynamic effects of smoked and intranasal cocaine.

The self-administration procedures included in the current study were limited to a single cocaine administration at the end of the session, which differs from some other human laboratory self-administration procedures in which the drug is administered immediately following completion of individual response requirements (Stoops et al., 2010; Haney et al., 2011; Foltin et al., 2016). For example, in Bolin et al. (2016) participants were provided six opportunities to respond for a sampled cocaine dose or an alternative reinforcer, with each choice immediately reinforced. The design used in the present study creates a delay between the completion of a response requirement and the administration of cocaine. This delay between a response and the stimulus it produces is an essential determinant of reinforcing value (Mazur, 1987) and might have influenced the reinforcing effects of cocaine under these conditions and/or the sensitivity of this outcome to the study interventions.

Conclusion

The results of this study further demonstrate the safety and tolerability of bupropion and naltrexone maintenance with intranasal cocaine. However, maintenance on either drug, alone or in combination, did not affect cocaine self-administration, suggesting these bupropion-naltrexone combinations would not be effective for treating cocaine use disorder. Future research should examine the effects of novel drug combinations on cocaine self-administration.

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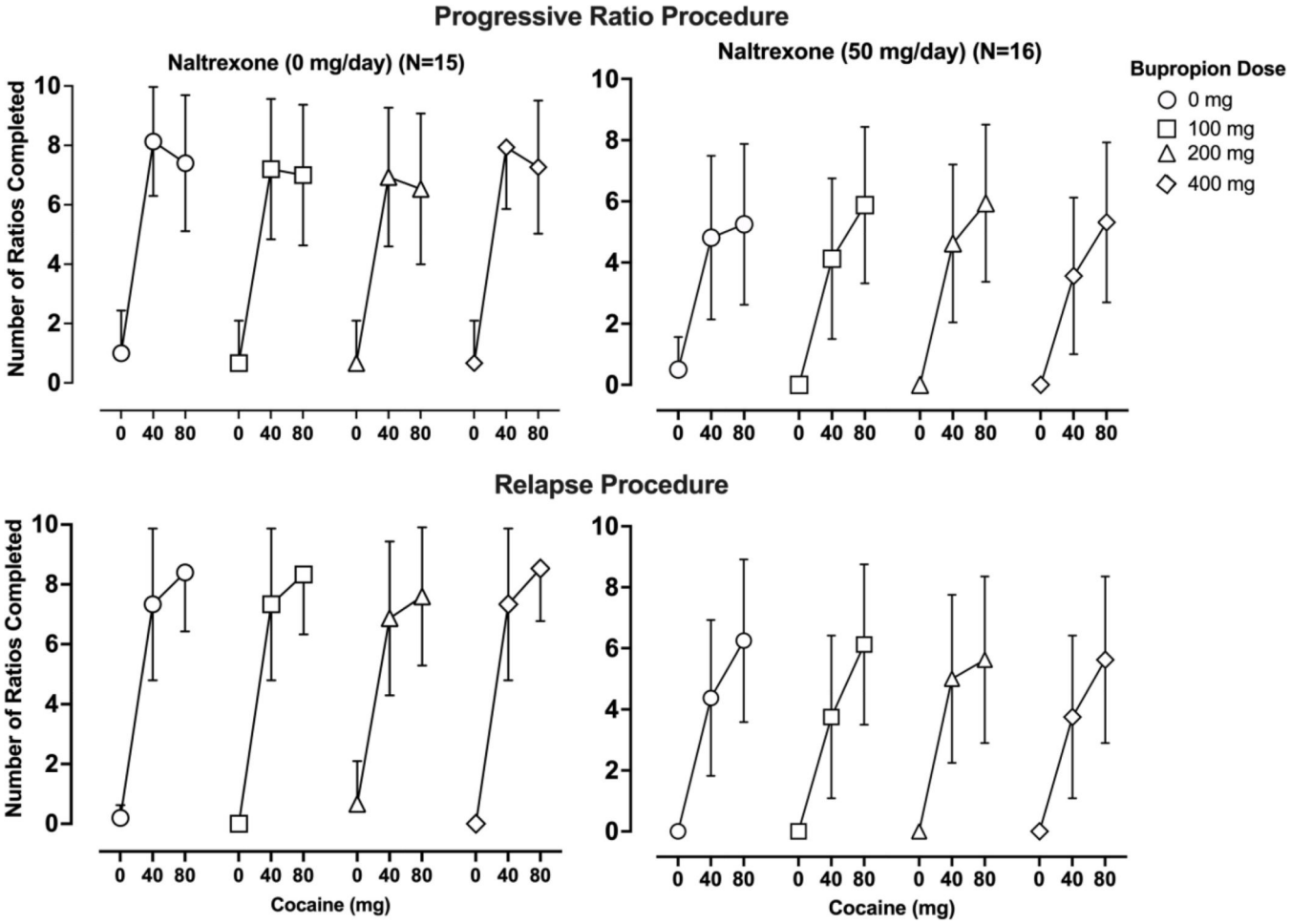

Figure 1.

Mean number of Progressive Ratio (top row) and Relapse Procedure (bottom row) ratios completed across all participants. Statistically significant dose-related increases in ratios completed were observed between cocaine doses across all bupropion and naltrexone maintenance conditions for both the progressive ratio and relapse procedures. Error bars (95% confidence interval) were removed in either direction if the bar surpassed the possible number of ratios completed (i.e., > 10 or < 0).

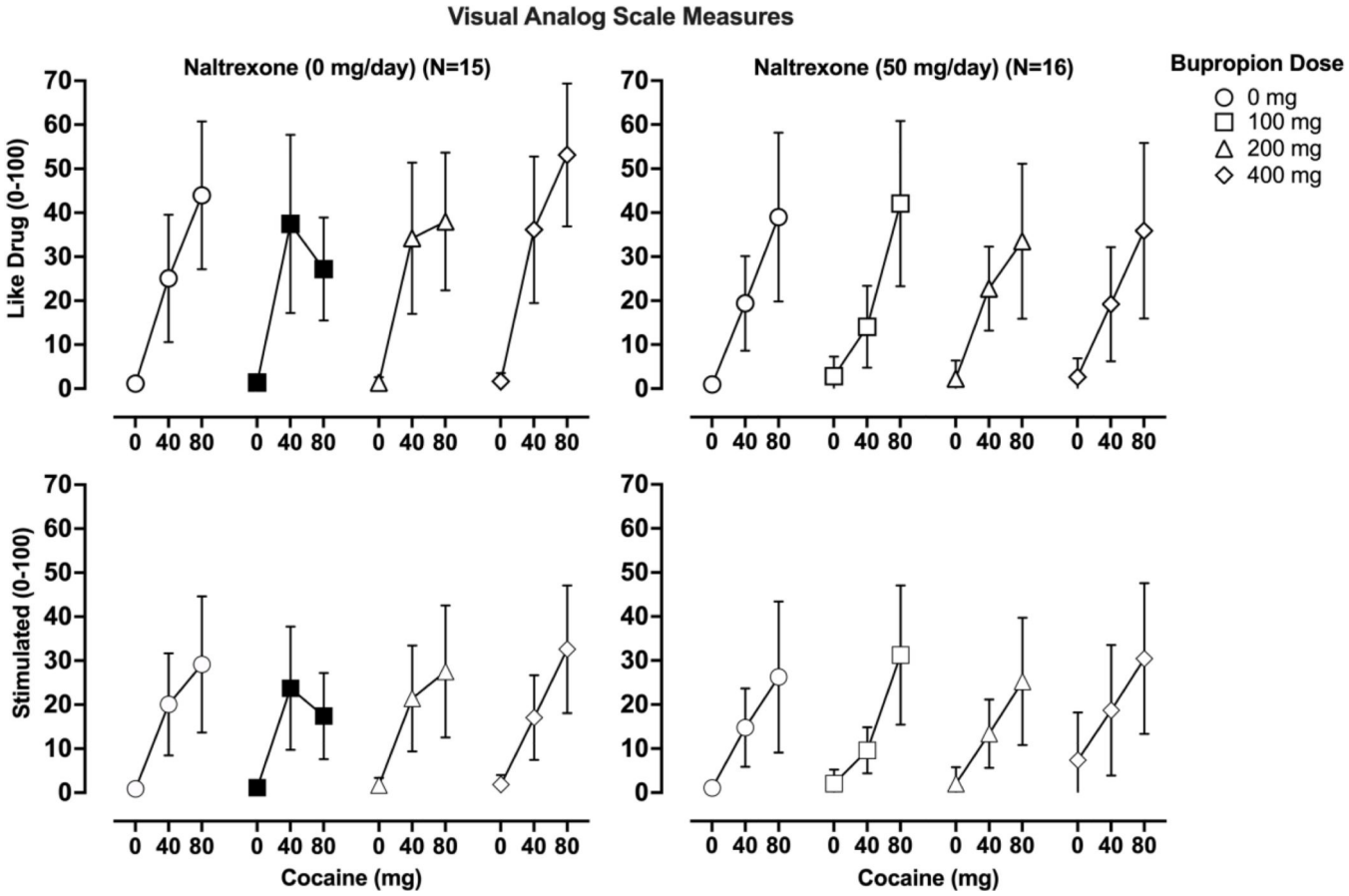

Figure 2.

Visual Analog Scale (VAS) measures of "Like Drug" (top row) and "Stimulated" (bottom row) across all cocaine and bupropion doses for participants in the 0 mg naltrexone group (left column) and the 50 mg naltrexone group (right column). Filled symbols indicate the cocaine dose effect under maintenance condition differed significantly from the cocaine dose effect observed with maintenance on 0 mg/day naltrexone plus 0 mg/day bupropion (i.e., circles in the left panel).

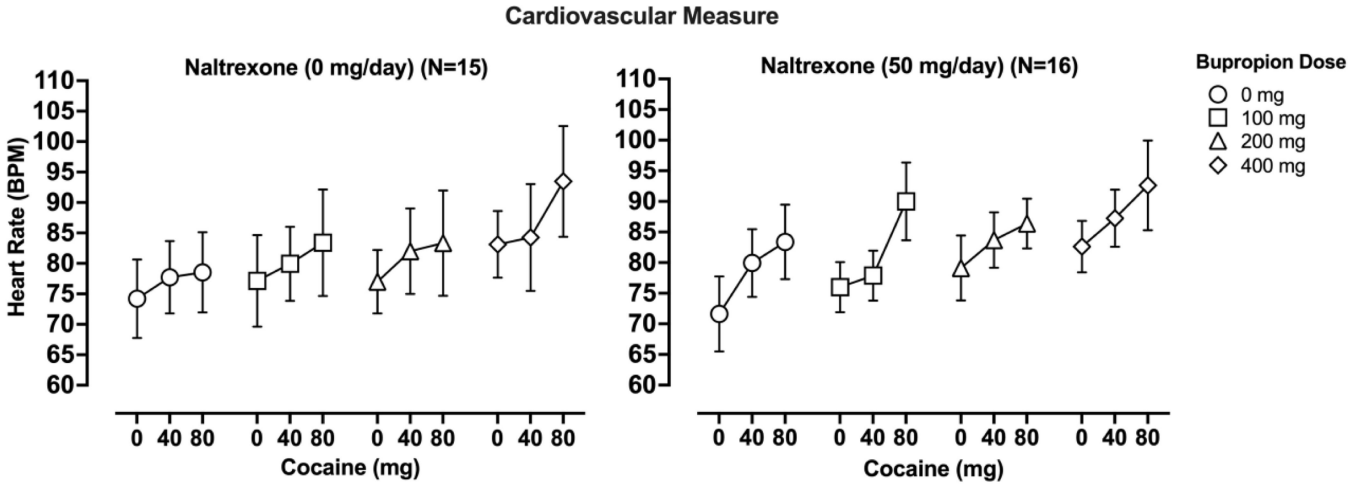

Figure 3.

Heart rate measures across all cocaine and bupropion doses for participants in the 0 mg naltrexone group (left column) and 50 mg naltrexone group (right column).

Table 1.

Overview of experimental sessions for each participant. The order of the Progressive Ratio and Relapse procedures were counterbalanced across all participants.

Day	Experimental Procedures
1	Admission and acclimation to the Clinical Research Unit
2	Practice Session
3	Medical Safety Session. Intranasal cocaine challenge (i.e., 0 [placebo], 10, 20, 40, 60 and 80 mg administered in fixed order). Placebo (i.e., 0 mg) administered at 0930. Subjective-effect measures completed 30 min before placebo administration (i.e., 0900), immediately following and at 15 and 30 minutes after each dose. Subsequent cocaine administrations separated by 45 min.
4–10	Bupropion (0 mg/day) and naltrexone (0 or 50 mg/day) maintenance. Bupropion-naltrexone administered in divided doses twice daily (0700 and 1900 hours).
8–10	Experimental Sessions. Reinforcing effects of intranasal cocaine (0 [placebo], 40 and 80 mg) determined using a relapse and progressive-ratio self-administration procedure. The order of these procedures was constant within subjects but counterbalanced across subjects.
11–17	Bupropion (100 mg/day) and naltrexone (0 or 50 mg/day) maintenance. Bupropion-naltrexone administered in divided doses twice daily (0700 and 1900 hours).
15–17	Experimental Sessions (Relapse & Progressive Ratio).
18–24	Bupropion (200 mg/day) and naltrexone (0 or 50 mg/day) maintenance. Bupropion-naltrexone administered in divided doses twice daily (0700 and 1900 hours).
22–24	Experimental Sessions (Relapse & Progressive Ratio).
25–31	Bupropion (400 mg/day) and naltrexone (0 or 50 mg/day) maintenance. Bupropion-naltrexone administered in divided doses twice daily (0700 and 1900 hours).
29–31	Experimental Sessions (Relapse & Progressive Ratio).
32	Discharge

Table 2.

Overview of participant demographics. DAST = Drug Abuse Screening Test; MAST = Michigan Alcohol Screening Test; AUDIT = Alcohol Use Disorders Identification Test.

	Naltrexone (0 mg) (N = 15)	Naltrexone (50 mg) (N = 16)
Demographics		
Age (mean, ±SD)	43.07 (*5.62*)	42.56 (*5.14*)
Female/Male (n)	4/11	4/12
Race (n)		
African American	9	12
Caucasian	4	4
Hispanic/Latino	1	
Biracial	1	
Education (Years; mean, ±SD)	12.27 (*1.33*)	12.72 (*1.03)*
Alcohol and Cigarette Use (mean, ±SD)		
DAST	8.47 (*4.56*)	9.50 (*4.50*)
MAST	7.80 (*7.39)*	7.94 (*8.17*)
AUDIT	6.60 (*3.89)*	5.44 (*3.74*)
Drinks/Week	12.23 *(11.29)*	9.88 (*8.76*)
Cigarettes/Day	10.67 (*7.90*)	10.40 (*6.25*)
Cocaine Use (mean, ±SD)		
Years Used	17.40 (*6.36*)	19.31 (*8.55*)
Days Used Past Week	3.27 (*1.71*)	3.06 (*2.02*)
Days Used Past Month	14.87 (*8.03*)	12.50 (*8.85*)
Money Spent Past Week ($)	175.67 (*183.45*)	120 (*83.03*)
Money Spent Past Month ($)	523.33 (*415.78)*	408.12 (*301.40*)
Past Month Drug Use (mean, ±SD)		
Days Used Opioids	2.07 (*2.99*)	0.69 (*2.02*)
Days Used Cannabis	10.07 (*13.12*)	6.81 (*2.02*)

Table 3.

Results of the omnibus ANOVA for all subjective, self-administration, and cardiovascular measures.

	Cocaine		Bupropion		Naltrexone		Cocaine + Bupropion		Cocaine + Naltrexone		Bupropion + Naltrexone		Cocaine + Naltrexone + Bupropion	
	p	η^2	p	η^2	p	η^2	p	η^2	p	η^2	p	η^2	p	η^2
VAS														
Active Alert Energetic	**<0.001**	**0.48**	0.12	0.07	0.69	0.01	0.24	0.05	0.26	0.05	0.25	0.05	**0.02**	**0.09**
Any Effect	**<0.001**	**0.59**	**0.05**	**0.10**	0.65	0.01	0.29	0.04	0.39	0.03	0.53	0.02	0.06	0.07
Bad Effect	**<0.001**	**0.27**	0.61	0.02	0.67	0.01	0.62	0.02	0.71	0.01	0.66	0.01	0.68	0.01
Euphoric	**<0.001**	**0.34**	0.32	0.04	0.07	0.11	0.71	0.02	0.06	0.11	0.32	0.04	0.55	0.02
Good Effect	**<0.001**	**0.55**	**0.02**	**0.11**	0.47	0.02	0.31	0.04	0.30	0.04	0.24	0.05	**0.05**	**0.08**
High	**<0.001**	**0.60**	**0.03**	**0.10**	0.53	0.01	0.15	0.06	0.30	0.04	0.57	0.02	0.11	0.06
Irregular Heartbeat	**<0.001**	**0.23**	0.13	0.07	0.90	0.001	0.22	0.05	0.73	0.01	0.89	0.003	0.75	0.02
Like Drug	**<0.001**	**0.57**	0.18	0.05	0.34	0.03	0.15	0.06	0.21	0.05	0.11	0.07	**0.01**	**0.12**
Nauseated	**0.01**	**0.18**	0.41	0.03	0.60	0.01	0.30	0.04	0.89	0.002	0.33	0.04	0.12	0.06
Nervous/Anxious	**<0.001**	**0.31**	0.23	0.05	0.45	0.02	0.45	0.03	0.39	0.03	0.65	0.01	0.48	0.03
Performance Impaired	**<0.001**	**0.29**	0.15	0.07	0.71	0.01	0.22	0.05	0.72	0.01	0.88	0.003	**0.04**	**0.09**
Performance Improved	**0.005**	**0.21**	0.19	0.05	0.79	0.003	0.30	0.04	0.64	0.01	0.47	0.03	0.08	0.08
Restless	**0.005**	**0.23**	0.19	0.05	0.79	0.003	0.30	0.04	0.64	0.01	0.47	0.03	0.47	0.03
Rush	**<0.001**	**0.57**	0.08	0.09	0.69	0.01	0.24	0.05	0.33	0.04	0.60	0.02	0.60	0.02
Shaky/Jittery	**<0.001**	**0.34**	0.14	0.07	0.23	0.04	0.56	0.02	0.89	0.001	0.75	0.01	0.26	0.05
Sluggish	0.14	0.07	0.22	0.05	0.86	0.001	0.46	0.03	0.33	0.04	0.64	0.01	0.38	0.04
Stimulated	**<0.001**	**0.49**	0.19	0.06	0.85	0.001	0.60	0.02	0.37	0.03	0.41	0.03	**0.01**	**0.12**
Talkative/Friendly	**<0.001**	**0.36**	0.51	0.02	0.92	0	0.66	0.02	0.43	0.03	0.84	0.01	0.19	0.05
Willing to Pay For	**<0.001**	**0.53**	0.06	0.10	0.40	0.03	0.24	0.05	0.20	0.05	0.17	0.06	**0.02**	**0.10**
Willing to Take Again	**<0.001**	**0.60**	0.13	0.07	0.53	0.01	0.42	0.03	0.31	0.04	0.15	0.06	**0.03**	**0.09**
Self-Administration														
Progressive Ratio	**<0.001**	**0.632**	0.516	0.025	0.077	0.104	0.867	0.011	0.141	0.068	0.324	0.039	0.698	0.019
Relapse	**<0.001**	**0.71**	0.924	0.005	0.055	0.122	0.770	0.014	0.095	0.085	0.797	0.011	0.700	0.018
Adjective Rating Scale														
Stimulated	**<0.001**	**0.574**	0.054	0.088	0.909	0.000	0.064	0.074	0.449	0.023	0.320	0.039	0.315	0.040
Sedated	<0.077	0.101	0.256	0.046	0.803	0.002	0.152	0.060	0.685	0.007	0.980	0.001	0.565	0.022

	Cocaine		Bupropion		Naltrexone		Cocaine + Bupropion		Cocaine + Naltrexone		Bupropion + Naltrexone		Cocaine + Naltrexone + Bupropion	
	p	η^2	p	η^2	p	η^2	p	η^2	p	η^2	p	η^2	p	η^2
Cardiovascular														
Systolic Blood Pressure	**<0.001**	**0.596**	**0.012**	**0.117**	0.832	0.002	0.576	0.025	0.678	0.012	0.217	0.050	0.378	0.035
Diastolic Blood Pressure	**<0.001**	**0.577**	**0.004**	**0.149**	0.902	0.001	0.372	0.036	0.795	0.008	0.486	0.027	0.938	0.008
Heart Rate	**<0.001**	**0.550**	**0.001**	**0.463**	0.689	0.006	0.071	0.067	0.187	0.058	0.875	0.007	0.127	0.057