Influence of acute bupropion pre-treatment 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 pre-treatment on subject-rated effects and choice of intranasal cocaine versus money. Design A randomized, within-subject, placebo-controlled, double-blind experiment. Setting An out-patient research unit. Participants Eight cocaine-using adults. Measurements Subjects completed nine experimental sessions in which they were pre-treated with 0, 100 or 200 mg oral immediate release bupropion. Ninety minutes later they sampled an intranasal cocaine dose [4 (placebo), 15 or 45 mg] and made six 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 five of six times on average compared to 2.25 of six 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 six 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 antidepressant, bupropion, acutely appears to reduce preference for intranasal cocaine versus a small amount of money but to increase reported positive experiences of the drug.

Keywords Bupropion, cocaine, humans, performance effects, physiological effects, self-administration, subject-rated effects.

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 such as abstinence reinforcement would result in enhanced efficacy relative to either treatment alone [4]. The results of recent research support this notion [5–7]. 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. [10–12]) 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 pre-treatment with oral immediate release bupropion (0, 100 and 200 mg).

METHODS

Subjects

Eight non-treatment-seeking adult subjects (five men, three women; six black, one white, one 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 (±standard error of the mean [SEM]). Seven subjects reported daily use of cigarettes (12 ± three cigarettes/day). Seven subjects also reported weekly alcohol use (15 ± four drinks/week). In addition to cocaine use prior to screening (4 ± 1 days of use totaling US$203 ± $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 institutional review board (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: (i) report recent cocaine use, (ii) provide a urine sample positive for cocaine or benzoylecgonine during the initial screening process, (iii) fulfill diagnostic criteria for a cocaine use disorder and (iv) 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 out-patients at the University of Kentucky Chandler Medical Center Clinical Research and Development Operations Center (CRDOC) for 10 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: (i) how the drug effects feel and influence mood, (ii) the effects of the drugs on task performance, (iii) whether subjects like the intranasal drug and are willing to take it again and (iv) 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 hours apart. Experimental sessions started at 08.00 hours and lasted for 7 hours. 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 minutes later, subjects sampled the cocaine dose available for that day (4 [placebo], 15 and 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 hours 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-minute 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 that 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 minutes 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 administra-
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 examine more fully the influence of bupropion pre-treatment 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 [22–24]. 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 pre-treatment with 0 mg bupropion, the 45 mg cocaine was chosen to a greater degree than placebo (average five of six versus 2.25 of six 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 six choices made on average after pre-treatment with 100 and 200 mg bupropion, respectively. After pre-treatment 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 pre-treatment with 200 mg bupropion but showed a significant quadratic trend following pre-treatment 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 pre-treatment 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 $\geq 3.97$). 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. Pre-treatment with active bupropion enhanced subject-rated cocaine effects. Significant linear or quadratic trends were seen for seven subject-rated measures when cocaine was administered after pre-treatment with 100 mg bupropion and for all subject-rated measures following pre-treatment 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 five 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, four 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

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<table>
<thead>
<tr>
<th>Drug-effect questionnaire</th>
<th>Bupropion (0 mg)</th>
<th>Bupropion (100 mg)</th>
<th>Bupropion (200 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active/alert/energetic</td>
<td>11.25 (5.97)</td>
<td>23.13 (7.79)</td>
<td>19.13 (5.93)</td>
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<tr>
<td>Any effect</td>
<td>8.75 (4.77)</td>
<td>20.13 (8.65)</td>
<td>17.88 (5.01)</td>
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<td>Good effects</td>
<td>7.13 (3.65)</td>
<td>16.00 (5.84)</td>
<td>19.25 (3.89)</td>
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<tr>
<td>High</td>
<td>10.63 (5.76)</td>
<td>19.13 (7.16)</td>
<td>19.38 (4.61)</td>
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<tr>
<td>Like drug</td>
<td>8.38 (3.77)</td>
<td>18.63 (8.08)</td>
<td>22.25 (5.80)</td>
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<tr>
<td>Stressed/sick to stomach</td>
<td>3.38 (1.77)</td>
<td>3.13 (1.71)</td>
<td>4.13 (1.83)</td>
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<tr>
<td>Nervous/anxious</td>
<td>3.00 (1.52)</td>
<td>3.25 (1.56)</td>
<td>3.63 (1.78)</td>
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<td>Performance impaired</td>
<td>3.63 (1.78)</td>
<td>1.63 (0.73)</td>
<td>5.88 (2.07)</td>
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<tr>
<td>Rush</td>
<td>8.75 (4.85)</td>
<td>15.88 (8.18)</td>
<td>16.00 (6.18)</td>
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<td>Stimulated</td>
<td>9.13 (4.85)</td>
<td>19.50 (8.06)</td>
<td>18.00 (6.32)</td>
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<td>Talkative/friendly</td>
<td>12.25 (6.20)</td>
<td>18.13 (7.67)</td>
<td>15.25 (6.52)</td>
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<td>Willing to pay for</td>
<td>10.38 (6.38)</td>
<td>29.63 (9.04)</td>
<td>25.00 (6.07)</td>
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<td>Adjective-rating scale</td>
<td>6.63 (1.10)</td>
<td>7.88 (0.58)</td>
<td>9.00 (0.78)</td>
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<td>Stimulant subscale</td>
<td>392.09 (6.97)</td>
<td>92.49 (5.31)</td>
<td>90.78 (5.61)</td>
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<td>Percentage of trials completed correctly</td>
<td>92.20 (5.14)</td>
<td>93.88 (3.69)</td>
<td>91.8 (5.92)</td>
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<td>74.75 (2.24)</td>
<td>79.13 (2.00)</td>
<td>77.88 (1.82)</td>
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<td>Diastolic blood pressure</td>
<td>74.00 (3.37)</td>
<td>78.25 (4.71)</td>
<td>79.63 (2.93)</td>
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<td>Heart rate</td>
<td>73.13 (3.29)</td>
<td>76.00 (2.63)</td>
<td>79.25 (3.61)</td>
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</tbody>
</table>

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. Digit symbol substitution test (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. Bold-type values indicate a significant difference from placebo. ‘L’ under the trend column for each bupropion dose condition indicates that a significant linear trend was detected for that cocaine dose–response curve. ‘Q’ under the trend column for each bupropion dose condition indicates a significant quadratic trend was detected for that cocaine dose–response curve. ‘NS’ (not significant) under the trend column for each bupropion dose condition indicates that no significant trend was detected for that cocaine dose–response curve. PLB: placebo.
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 pre-treatment 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 pre-treatment. Although the absolute reduction in number of cocaine choices following bupropion dosing was small (reduction of approximately one or two choices out of six 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 pre-treatment changed the shape of the cocaine dose–response curves. Specifically, bupropion pre-treatment 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 pre-treatment 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 downwards 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 lysergic acid diethylamide (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 model more effectively 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 pre-treatment 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. Secondly, 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 understand more clearly how the discordance between different human laboratory measures observed with bupropion translates to clinical outcomes, particularly across different behavioral treatment platforms.

Declarations of interest
The authors declare no conflicts of interest relevant to this research.

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