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ORIGINAL INVESTIGATION

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Acute doses of *d*-amphetamine and bupropion increase cigarette smoking

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Abstract *Rationale:* Bupropion is used clinically as a treatment for smoking cessation, but the processes by which it reduces smoking are poorly understood. Bupropion shares some neurochemical actions and behavioral effects with the psychostimulant amphetamine, and it has been shown that amphetamine increases smoking when administered acutely. The effects of single doses of bupropion on smoking have not been studied but, based on its similarities to amphetamine, we postulated that acute bupropion would also increase smoking. *Objective:* To measure the effects of single doses of amphetamine and bupropion on smoking and craving for cigarettes in smokers. *Methods:* Cigarette smokers who were not trying to quit participated in a three-session study in which they received placebo and a single dose of either *d*-amphetamine sulfate (10 and 20 mg; *n*=10) or bupropion hydrochloride (150 and 300 mg; *n*=12) after overnight abstinence. The three outcome measures were: i) subjective and behavioral effects of amphetamine and bupropion after a period of acute abstinence, ii) effects of amphetamine and bupropion on subjective responses to a single, smoked cigarette, and iii) effects of the drugs on number of cigarettes smoked during an ad libitum smoking period. *Results:* After the acute abstinence and before smoking, both amphetamine and bupropion increased self-reported mood and euphoria, but did not change ratings of craving or withdrawal. After subjects smoked a single smoked cigarette, they reported that bupropion reduced ratings of "buzzed" and "intensity". During the period of ad libitum smoking both amphetamine and bupropion increased the number of cigarettes smoked. *Conclusion:* Acute doses of both bupropion and amphetamine increase smoking in non-treatment-seeking smokers without altering ratings of craving or withdrawal. Bupropion reduced some of the sensory responses to the smoked cigarette. It remains to be determined why bupropion increases smoking when administered acutely under controlled conditions, while it helps to reduce smoking in patients trying to quit.

Keywords Stimulant · Craving · Withdrawal · Human · Smoking · Amphetamine · Bupropion

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Introduction

The primary subjective and physiological effects of smoking, including its addictive properties, are known to result from the central actions of nicotine. However, other neurotransmitter systems, including dopamine and noradrenaline, clearly play a role in the development and maintenance of smoking behavior and nicotine self-administration in rats (e.g., Shoaib et al. 1994; Stolerman and Jarvis 1995; Pontieri et al. 1996; Pich et al. 1997). In cigarette smoke, nicotine is rapidly absorbed into the brain where it activates nicotinic cholinergic receptors and, indirectly, other neurotransmitter systems including dopamine and norepinephrine. The dopamine system, in particular, is thought to be important for the reinforcing effects of nicotine (Stolerman and Jarvis 1995; Clark 1998; Pontieri et al. 1998; Shoaib 1998). However, most of our knowledge regarding the role of dopamine in the reinforcing effects of nicotine comes from studies with laboratory animals, and it is important to determine whether the same neurochemical processes mediate smoking behavior in humans.

One way to study the mechanisms involved in smoking in humans is to examine how drugs that change dopamine and norepinephrine neurotransmission affect smoking. In the present study, we examined the effects of two drugs, amphetamine and bupropion, both of which elevate synaptic dopamine and norepinephrine levels. Both drugs have been shown to affect smoking behavior, but the direction of their effects may depend on whether the drugs are administered acutely or chronically. Several stimulant drugs, including cocaine, caf-

feine, and amphetamine, have been shown to increase cigarette smoking when administered acutely (Schuster et al. 1979; Henningfield and Griffiths 1981; Chait and Griffiths 1983; Kelly et al. 1991; Roll et al. 1997). After acute amphetamine administration smokers report more satisfaction from cigarettes, and they report that cigarettes "taste better" and that smoking is "really enjoyable". In contrast, there are at least two reports that chronic administration of amphetamine decreases smoking and helps smokers who are trying to quit smoking. In an early study, Miller (1941) administered daily doses of *d*,*l*-amphetamine (*n*=24) or placebo (*n*=3) to smokers who wanted to quit, for 3–6 months. Ninety percent of patients treated with amphetamine stopped smoking for the treatment period, while placebo had no effect. Amphetamine reduced withdrawal symptoms, and the patients who continued to smoke reported that they lost their taste for tobacco, stating that it was no longer pleasurable or that they even found it distasteful. More recently, Low et al. (1984) reported similar results when *d*-amphetamine or placebo was administered for 1 week to smokers who did not want to quit. Amphetamine reduced the number of cigarettes smoked, self-reported smoking enjoyment and feeling of addiction. These findings suggest that amphetamine has opposite effects on smoking, depending on whether it is administered chronically or acutely. Bupropion is an atypical antidepressant which shares some neurochemical actions with amphetamine (Ferris et al. 1982; Trulson 1985; Nomikos et al. 1990) and which has recently been approved as a treatment for smoking cessation. Bupropion reduces smoking among patients who wish to quit, and these patients report that it reduces withdrawal symptoms (Ferry and Burchette 1994; Hurt et al. 1997; Ferry 1999; Hayford et al. 1999; Jorenby et al. 1999; Holm and Spencer 2000). However, there are no reports of the effects of bupropion on smoking after acute administration. Given the commonalities in the neurochemical and behavioral profiles of amphetamine and bupropion, we postulated that bupropion would, like amphetamine, increase smoking when administered acutely.

In the present study, non-treatment seeking smokers received single doses of *d*-amphetamine (10 and 20 mg) or bupropion (150 and 300 mg) after overnight abstinence. The study utilized a procedure that assessed the drugs' effects on ratings of craving and withdrawal after overnight abstinence, on responses to a single smoked cigarette, and on amount smoked during an ad libitum smoking period (King and Meyer 2000). Regular smokers who abstain from smoking overnight experience the onset of withdrawal symptoms, including increased craving for cigarettes (Hurt et al. 1998). One goal of the study was to assess the effects of amphetamine and bupropion on these early symptoms of withdrawal. A second goal was to determine whether amphetamine or bupropion increased or decreased the physiological and subjective responses to the first cigarette of the day. The third goal was to determine whether amphetamine and bupropion changed the number of cigarettes subjects smoked during a 3-h free-smoking period. Whereas a number of previous studies have investigated the effects of drug pretreatments on a single aspect of smoking behavior (e.g., withdrawal, responses to acute nicotine, or number of cigarettes smoked), few studies have examined all of these effects in a single procedure. The overall goal was to determine whether, and how, acute doses of amphetamine and bupropion increased cigarette smoking.

Materials and methods

Design

Two studies were conducted to examine the subjective, physiological, and behavioral effects of bupropion (study 1; *n*=12) and amphetamine (study 2; *n*=10) in regular smokers. Each study consisted of three sessions, in which subjects received placebo and one of two doses of active drug: *d*-amphetamine (10 and 20 mg) in one study or bupropion (150 and 300 mg) in the other study. Subjects abstained from smoking 12 h before each session. During the sessions subjects completed self-report questionnaires concerning their mood and cigarette cravings, and several physiological and behavioral measures were obtained. The amphetamine and bupropion studies were similar with some minor procedural differences, noted below.

Subjects

Seventeen male and female cigarette smokers not currently seeking treatment, aged 19–54 years, participated (Table 1). The bu-

Table 1 Summary of demographics and drug use for subjects in the bupropion (study 1) and amphetamine (study 2) studies

	Bupropion	Amphetamine
Age (years; mean±SD)	31±13	32±4
BMI (mean±SD)	25±4	25±1
Sex (*n*; female/male)	5/7	4/6
Race		
White/African-American/Asian	7/2/3	5/2/3
Marital status (*n*; not married)	11	10
Education (n)		
Partial college or college degree	11	10
Full-time student (*n*)	4	4
Cigarette use (per day; mean ±SD)	21±4	19±1
FTND (mean±SD)	6±2	5±0
Years smoked (mean±SD)	12±12	13±4
Current drug use		
Alcohol (mean±SD; drinks/week)	9±8	7±2
Caffeine (mean±SD; drinks/week)	2±3	2±0
Marijuana (*n*; >1 occasions/week)	1	3
Lifetime drug use		
Stimulants (*n*; ever used)	5	4
Opiates (*n*; ever used)	4	3
Tranquilizers (*n*; ever used)	3	1
Hallucinogens (*n*; ever used)	3	3
Marijuana		
Never used (*n*)	1	3
Used >50 times (n)	5	5
Inhalants (*n*; ever used)	5	0

propion study was initiated after the first four subjects had completed the amphetamine study. After this, new subjects were randomly assigned to either the amphetamine or bupropion study. Five subjects participated in both studies, four of them in the amphetamine study first and one in the bupropion study first. Volunteers were recruited from the community via posters, newspaper advertisements and word-of-mouth referrals. Initial eligibility was ascertained in a telephone interview. Subjects who smoked 15–32 cigarettes/day for at least 2 years, had a minimum of high school education, were fluent in English, and had a body mass index between 19 and 30 were scheduled for a face-to-face interview. At the interview, candidates completed the Fagerström Test for Nicotine Dependence (FTND; Heatherton et al. 1991), the Beck Depression Inventory (BDI; Beck et al. 1961), Quantity-Frequency Alcohol Inventory, and the Michigan Alcoholism Screening Test (MAST; Selzer 1971). Candidates who scored more than 9 on the BDI or more than 5 on the MAST and who reported drinking more than four drinks a day were excluded. Candidates completed a health questionnaire with a detailed section on current and lifetime recreational drug use, and a menstrual cycle history for women. A clinical psychologist interviewed candidates using the Structured Clinical Interview for DSM-IV Non-Patient Edition (SCID-NP; First et al. 1995). Candidates received a brief physical examination by the study physician and received an electrocardiogram. Candidates were excluded if they had serious medical conditions (i.e., history of cardiac, pulmonary, or liver problems); hypertension; abnormal electrocardiogram; current or past Major Axis I psychiatric disorder, including substance use disorders except Nicotine Dependence (APA 1994); positive urine toxicology during screening; any current prescription medication use; use of antidepressants, anticholinergics, beta-receptor blockers or bupropion within the past year; use of nasal decongestants, or "herbal medicines", within the past 2 weeks; history of stroke, brain tumor, personal or family history of a seizure disorder; currently trying to quit smoking; in women, pregnancy, lactation, or plans for pregnancy; unstable residence or working a night-shift; history of adverse reactions to drugs used in study.

Subjects provided written informed consent. The consent form stated that the experiment was designed to investigate the effects of drugs on mood and behavior and that subjects would receive any of a number of drugs (stimulant, antidepressant, sedative, drug used to treat Parkinson's disease, nicotine, or placebo). The consent form listed potential side effects of the drugs. Subjects were instructed to refrain from use of drugs other than nicotine and caffeine for 12 h before and 6 h after the sessions. A urine drug screen was performed during randomly selected sessions to detect the use of barbiturates, PCP, marijuana, stimulants, and opioids (none was positive). Women were tested for pregnancy before every session. The research protocol was approved by The University of Chicago's Institutional Review Board.

Procedure

Before the first session, subjects participated in a 30-min orientation session to familiarize them with the laboratory environment and the dependent measures. The environment was a comfortably furnished room with couches and upholstered chairs, casual tables and incandescent lighting. Subjects had access to magazines and board games, televisions and VCRs with a choice of movies, but they were not allowed to work or study during the sessions. During the orientation session a breath carbon monoxide (CO) test was administered, vital signs were measured and subjects practiced the self-report questionnaires.

For each of the three sessions, subjects arrived at the hospital at 7:00 p.m. on the night before the session. They spent the night before each session in the Clinical Research Center (CRC) to ensure that they had a standard amount of sleep and food before the sessions, and that they did not smoke or use other drugs in the 12 h before the session. Upon arrival at the CRC, subjects' vital signs were measured and women were tested for pregnancy. Dinner was provided and subjects completed self-report mood questionnaires (see below) at 9:00 p.m. They were free to relax for the remainder of the evening, but they were not allowed to smoke cigarettes. The next morning at 7:00 a.m., subjects were provided with a light breakfast, and at 7:30 a.m. they completed baseline mood, cigarette craving and withdrawal questionnaires, and vital signs were recorded.

The first phase of the procedure, the pre-cigarette phase, began at 8:15 a.m. when the subjects, under supervision of the nurses, swallowed the capsules containing one of the two doses of drug or placebo. The order of drug conditions was counterbalanced. Shortly after ingesting the capsule, subjects were escorted from the CRC to the Human Behavioral Pharmacology Laboratory. At 8:55 a.m. (bupropion study only) and at 9:30 a.m. (both studies) subjects completed subjective effects questionnaires and performance measures, and vital sign measurements were recorded. These measures provided an index of the direct subjective, behavioral and physiological effects of the drugs. At 10:15 a.m. subjects were instructed to smoke one cigarette of their usual brand, at their normal rate. This began the post-cigarette phase of the procedure. Immediately after smoking the cigarette, subjects rated their levels of craving and their desire for another cigarette, and subjects in the bupropion group also rated their sensory responses to the cigarette (e.g., taste, intensity) and the satisfaction they derived from it. Vital signs and CO levels were measured. At 11:05 a.m., 40 min after smoking the single cigarette, subjects again rated their level of craving and desire for a cigarette and vital signs and CO levels were measured. From 11:30 a.m. to 2:30 p.m., during the ad libitum smoking phase, subjects were allowed to smoke as much as desired of their preferred brand. They were instructed that they could smoke as much or as little as they desired. Popcorn was provided as a snack. The ad libitum smoking phase was videotaped. At 2:30 p.m., or after their last cigarette, vital signs and CO levels were measured, subjects completed a final set of questionnaires, and left the laboratory.

After completing all three sessions, subjects were debriefed by the investigator and received payment (US$270). They also received advice to quit smoking by the study psychologist.

Dependent variables

The subjective effects scales, behavioral and physiological measures are listed below. The primary dependent measures were subjective ratings of craving and desire for cigarettes during the pre- and post-cigarette phases, and number of cigarettes smoked and expired CO during the ad libitum smoking phase. Secondary dependent measures were subjective ratings of mood states, and physiological measures (i.e., heart rate and blood pressure).

Subjective or mood effects

Brief Questionnaire on Smoking Urges (BQSU; Cox et al. 1998)

This ten-item questionnaire is a shortened version of the QSU (Tiffany and Drobes 1991), and is designed to measure the primary intention and desire to smoke, anticipation of pleasure from smoking, and anticipation of relief from negative affect and nicotine withdrawal. The BQSU consists of two factors relating to the positive and negative reinforcing properties of smoking (Tiffany and Drobes 1991; Willner et al. 1995). Factor 1 indicates "primarily intention and desire to smoke, and anticipation of pleasure from smoking". Factor 2 reflects "anticipation of relief from negative affect and nicotine withdrawal, and urgent and overwhelming desire to smoke".

Minnesota Nicotine Withdrawal Scale (Hughes and Hatsukami 1986)

This brief, seven-item scale is a self-report instrument based on DSM-IV symptoms of nicotine withdrawal (i.e., depression, in-

somnia, irritability/frustration/anger, anxiety, difficulty concentrating, increased appetite, and restlessness; Hughes and Hatsukami 1998). Items are based on a 5-point Likert scale, and include subjects' ratings of perceived difficulty during smoking abstinence. The items are summed across symptoms for each subject's session and averaged between subjects. In a previous study, scores on this measure increased after short-term abstinence, indicating that it is sensitive to acute changes in smoking (King and Meyer 2000).

Visual Analog Scales (VAS)

Subjects rated subjective effects using a series of visual analog scales (VAS): a Mood VAS, a Drug Effects Questionnaire (DEQ) VAS, and a Cigarette Effects VAS. The Mood VAS consisted of a series of adjectives describing subjects' current state (e.g., "jittery", "light-headed", "relaxed", "head rush", and also included items for "pleasure" from cigarette, "feeling stimulated", and "desire to smoke"). These items have been shown to be sensitive to the acute effects of smoking after short-term abstinence (Perkins et al. 1993; Meliska and Gilbert 1997; King and Meyer 2000). The DEQ VAS contained four questions: "Do you feel any drug effects?" (rated from "none at all" to "a lot"), "Do you like the effects you are feeling now?" (rated from "dislike" to "like very much"), "Are you high?" (rated from "not at all" to "very"), and "Would you like more of what you consumed, right now?" (rated from "not at all" to "very much"). On the Cigarette Effects VAS, subjects rated the extent to which they felt dizzy and buzzed from the single cigarette, from "not at all" (0) to "extremely" (100). Subjects also rated the single cigarette on taste, satisfaction, smell, harshness and intensity.

Profile of Mood States (McNair et al. 1971; Schacham 1983)

The POMS is a 72-item questionnaire that consists of adjectives commonly used to describe momentary mood states. Subjects rated the adjectives from 0 (not at all) to 5 (extremely) according to how they felt at that moment. The items on the POMS have been factor analyzed to yield eight mood state scales: Anger, Anxiety, Confusion, Depression, Elation, Fatigue, Friendliness, and Vigor, and there are two intuitively derived scales: Arousal [(Anxiety+Vigor)-(Fatigue+Confusion)] and Positive Mood (Elation-Depression). These scales are sensitive to the mood-altering effects of several classes of drugs including nicotine, sedatives, and stimulants (de Wit and Griffiths 1991; Foltin and Fischman 1991; Levin et al. 1998). In this study the POMS provided a measure of baseline mood, the mood-altering effects of the amphetamine and bupropion, and the mood effects of the single cigarette.

Addiction Research Center Inventory (ARCI; Martin et al. 1971)

The ARCI contains 49 true or false statements sensitive to the effects of several drug classes. This version has five empirically derived scales: the Amphetamine (A) and Benzedrine group (BG) scales which measure stimulant-like effects, the Morphine-Benzedrine group (MBG) scale which measures euphoria, the Pentobarbital-Chlorpromazine-Alcohol Group (PCAG) scale which measures sedation, and the Lysergide (LSD) scale which measures dysphoric and somatic symptoms.

Performance measure

Psychomotor performance was determined with the Digit Symbol Substitution Test (DSST) of the Wechsler Adult Intelligence Test. The DSST is a paper and pencil test for which subjects are required to transpose a series of symbols for numbers as quickly and accurately as possible. The data from this test consist of the number of correct symbol transpositions during a 90-s trial.

Behavioral measure

The ad libitum smoking phase provided a direct measure of the subjects' desire to smoke. The number of cigarettes smoked during the 3-h period was recorded.

Physiological measures

Heart rate and blood pressure were measured with a Dynamap automated blood pressure monitor. Carbon monoxide was measured using a Bedfont Instruments Micro Smokerlizer.

Drugs

d-Amphetamine sulfate (5 mg tablet; Dexedrine, SmithKline Beecham, USA) and bupropion hydrochloride (100 mg tablet, immediate release; Wellbutrin, GlaxoWellcome, USA) were administered in opaque brown gelatin capsules (size 00) with dextrose as a filler. *d*-Amphetamine and its placebo were administered in two capsules and bupropion and its placebo were administered in five capsules. Placebo capsules contained only dextrose.

The doses of amphetamine and bupropion were chosen based on the lowest doses that reliably produce stimulant-like subjective effects. Acute doses of bupropion (up to 600 mg) have been safely tested in laboratory settings and these doses reportedly produce some stimulant-like subjective and physiological effects (Findlay et al. 1981; Fabre et al. 1983; Zung et al. 1983; Rush et al. 1998). Acute doses of *d*-amphetamine (5–20 mg) safely and reliably produce dose-related increases in subjective ratings of euphoria and elation (Henningfield and Griffiths 1981; Brauer and de Wit 1996; Rush et al. 1998).

Sample size determinations

The number of subjects needed was estimated by power analysis based upon self-reported ratings of craving for cigarettes obtained during a preliminary study (King and Meyer 2000). Power calculations indicated that 12 subjects would be sufficient to provide power of 0.80 or greater with a modest effect size of 25–30% and with alpha set at 0.05.

Data analysis

All data were expressed as a change from baseline (except DEQ, Cigarette Effects VAS and Expired CO) and presented as mean±SEM. Although there was some variability on certain baseline measures there was no systematic change in baseline scores across sessions.

Baseline levels of craving for nicotine were defined using the BQSU. A *t*-test was used to compare BQSU scores at 9:00 p.m. the evening before the session to BQSU scores the following morning (7:30 a.m.).

The amphetamine and bupropion studies were analyzed separately. Analyses were conducted using data from each of the three phases of the procedure. During the pre-cigarette phase, the primary dependent measure was craving for nicotine (BQSU) and secondary measures were the physiological and other subjective effects of the drugs. Measures were examined with two-way repeated measures analysis of variance using Statistica (ANOVA; drug:placebo, low, moderate dose×time: 40 and 85 min post-drug; StatSoft Inc., Tulsa, Okla., USA). During the post-cigarette phase the primary measures were craving and the Cigarette Effects VAS and secondary dependent measures were other subjective and physiological measures. These measures were analyzed by a two-way repeated measures ANOVA [drug:placebo, low, moderate dose×time: 125 and 170 min postdrug (i.e., 5 and 45 min post-cigarette)]. The Cigarette Effects VAS, which was only administered once, after the single cigarette in the bupropion study, was ana-

lyzed by a one-way ANOVA (drug:placebo, low, moderate dose). During the ad libitum smoking phase, the primary dependent measures were the number of cigarettes smoked and the levels of expired CO. These measures were analyzed by a one-way ANOVA (drug:placebo, low, moderate dose). The secondary dependent measures were not analyzed at this timepoint although they are displayed graphically for completeness. Post hoc comparisons were conducted with Fisher's least significant differences test. To protect against type I error, the number of pairwise comparisons was limited to two (*df*–1; Keppel 1991). The alpha for all analyses was set at <0.05 and trends were defined as $P<0.10$.

In exploratory analyses the drugs' effects on the baseline and primary dependent measures were compared in men and women. The study was not designed to compare responses in men and women because there were no strong reasons to expect sex differences in the drugs' effects. For increased power, these exploratory analyses were performed using combined data from the amphetamine and bupropion studies.

Results

Study 1:bupropion

The overall BQSU craving scores were significantly higher in the morning (before any capsules or cigarettes) than at 9:00 p.m. the previous evening [night: 3.8±0.4; morning: 4.6±0.4; $t(35)=4.1$, $P<0.05$]. The effect of overnight abstinence was apparent on both subscales of the BQSU, factor 1 [night: 4.8±0.4, morning: 5.6±0.4; $t(35)=3.6$, $P<0.05$] and factor 2 [night: 2.9±0.4, morning: 3.7±0.4; $t(35)=4.0$, $P<0.05$]. Mean scores on the Minnesota Nicotine Withdrawal Scale in the morning were 4.4±1.4. There were no differences in BQSU scores at baseline before sessions on which subjects received bupropion or placebo.

Table 2 Summary of *F* values (ANOVA) for effects of bupropion after overnight abstinence (change from before capsule to 40 and 85 min after capsule)

Dependent measure	Bupropion	Time	Bupropion×Time
Heart rate	1.4	1.7	<1
Systolic BP	<1	9.4*	<1
Diastolic BP	<1	<1	3.8*
DSST	1.6	1.4	2.6
DEQ			
Feel	<1	<1	3.9*
Like	<1	<1	1.3
ARCI			
A	6.6*	<1	<1
BG	1.0	<1	2.1
MBG	4.3*	<1	1.5
POMS			
Anxiety	1.6	<1	3.6*
Arousal	<1	<1	4.4*
Elation	1.1	<1	2.4
Friendliness	<1	<1	1.4
Positive Mood	<1	<1	<1
VAS			
Hungry	1.2	2.8	0.8
Stimulated	3.8*	<1	2.7
BQSU			
Factor 1	2.6	3.8	<1
Factor 2	<1	1.4	<1
Combined	<1	3.8	<1
Expired CO	<1	NA	NA

*$P<0.05$ NA, not applicable

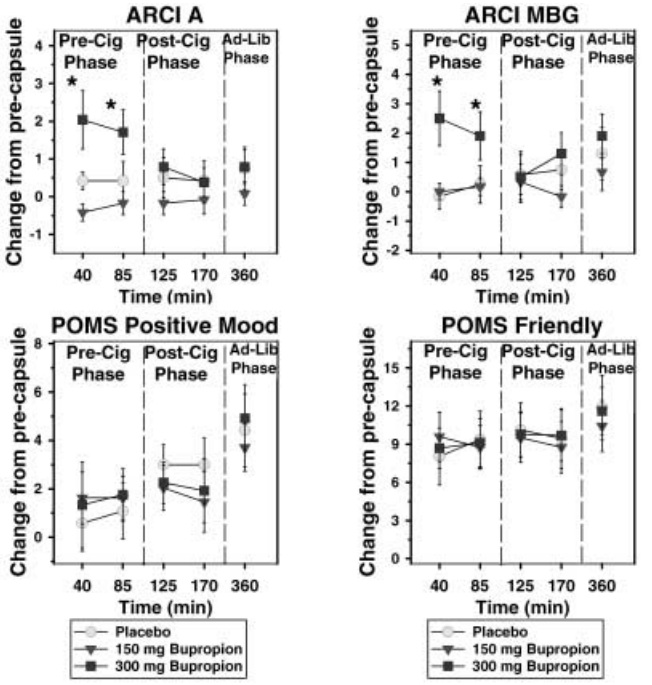

Fig. 1 Effects of bupropion on measures of stimulant-like effects (ARCI A scale) and euphoria (ARCI MBG scale; *top panels*), and Positive Mood and Friendliness scales of the POMS (*bottom panels*). Data represent change from pre-drug baseline. *Denotes significantly different from placebo ($P<0.05$)

Pre-cigarette phase

The significant effects from the ANOVA for each dependent measure during this phase are presented in Table 2. Bupropion (300 mg) increased diastolic pressure relative to placebo at the 85-min timepoint, but it did not affect DSST performance, craving for nicotine, withdrawal ratings, heart rate, or systolic blood pressure. Bupropion produced stimulant-like effects on the self-report measures. On the DEQ, bupropion (150 mg) increased ratings of "feel drug" at 40 min at 150 mg, compared to placebo. On the ARCI, bupropion (300 mg) increased scores on the A scale and the MBG scale (Fig. 1). On the POMS, bupropion (150 and 300 mg) increased ratings of "Arousal" at 85 and 40 min, respectively, for the two doses. It also increased ratings of "Anxiety" at both doses, at 85 min. On the VAS scales, bupropion (300 mg) increased self-reported "stimulation". There was a trend ($P=0.09$) for bupropion to reduce BQSU factor 1 scores.

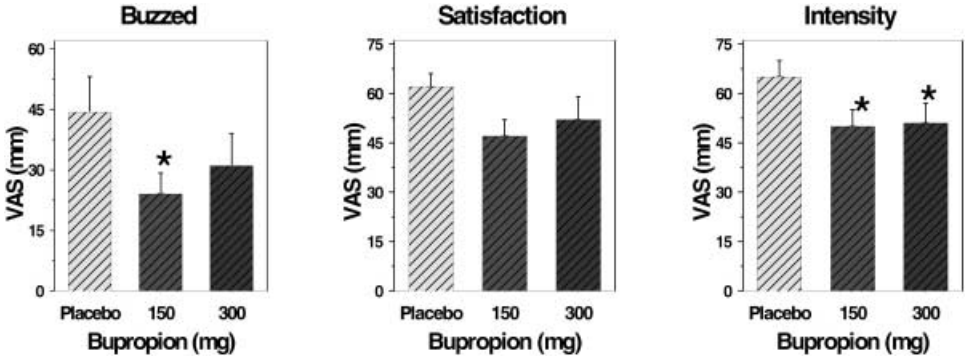

Fig. 2 Effects of bupropion on ratings of "Buzzed", "Satisfaction", and "Intensity" (Cigarette Effects VAS; maximum score 100) after smoking a single cigarette. *Denotes significantly different from placebo (P<0.05)

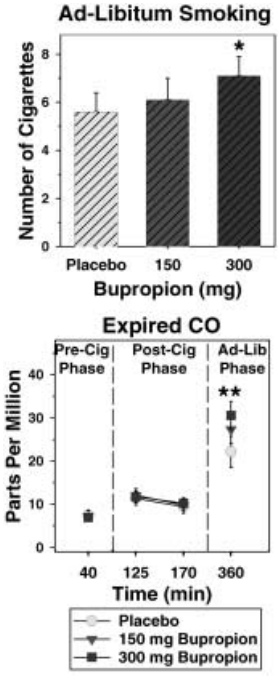

Fig. 3 Effect of bupropion on the number of cigarettes smoked during the 3-h ad libitum smoking phase (*top panel*) and on expired CO at the end of the session (*bottom panel*). *Denotes significantly different from placebo (P<0.05). **Indicates both doses significantly different from placebo (P<0.05)

Table 3 Summary of F values (ANOVA) for effects of bupropion after a single cigarette (5 and 45 min after the cigarette)

Dependent measure	Bupropion	Time	Bupropion×Time
Heart rate	1.4	23.6*	1.0
Systolic BP	<1	10.2*	<1
Diastolic BP	<1	7.1*	<1
DSST	2.6	<1	3.3
DEQ			
Feel	1.5	10.1*	<1
Like	1.3	<1	1.3
ARCI			
A	1.0	<1	1.1
MBG	1.0	<1	1.1
POMS			
Friendliness	<1	1.2	<1
VAS			
Hungry	<1	16.6*	<1
Stimulated	2.2	<1	<1
BQSU			
Factor 1	1.0	7.2*	<1
Factor 2	<1	3.4	<1
Combined	<1	8.2*	<1
Expired CO	1.6	45.7*	1.1

*P<0.05

Post-cigarette phase

Regardless of drug treatment, the single cigarette decreased craving for nicotine, and increased ratings of "feel drug" (DEQ), heart rate, blood pressure and expired CO. Bupropion (150 and 300 mg) reduced ratings of "intensity of cigarette" [Table 3, Fig. 2; F(2,22)=3.9, P<0.05], and the 150 mg dose also significantly reduced ratings of "buzzed" [F(2,22)=4.2, P<0.05; trend (P=0.08) at 300 mg]. There was also a trend for bupropion to reduce ratings of "satisfaction" [F(2,22)=3.2, P=0.06]. Bupropion did not affect any other measures of response to the single cigarette.

Ad libitum smoking phase

Bupropion (300 mg) increased the number of cigarettes subjects smoked, whereas the 150 mg dose had no significant effect [Fig. 3; F(2,22)=5.5, P<0.05]. Subjects smoked a mean of 0.3±0.3 cigarettes more after 150 mg bupropion than after placebo, and 1.5±0.6 cigarettes more after 300 mg bupropion. At the 150 mg dose, six subjects smoked more, three subjects smoked less, and three were unchanged, whereas at the 300 mg dose, eight subjects smoked more, two smoked less, and two were unchanged. Both doses of bupropion increased expired CO levels [Fig. 3; F(2,22)=7.7, P<0.05]. With 150 mg, the average change in levels of expired CO was +5.2±2.3 ppm, and with 300 mg this change was +8.4±2.4 ppm. At both doses, expired CO increased in ten subjects, decreased in one, and remained unchanged in one subject.

Study 2: amphetamine

BQSU craving scores were significantly higher in the morning (prior to capsule and cigarettes) than at 9:00 p.m. the previous evening [night: 3.8±0.3, morning: 4.3±0.3; $t(29)=3.3$, $P<0.05$]. Craving scores increased significantly from the night before to the following morning on factor 1 [night: 4.9±0.3, morning: 5.7±0.4; $t(29)=3.6$, $P<0.05$] and a trend for an increase in factor 2 [night: 2.7±0.4, morning: 3.0±0.4; $t(29)=1.8$, $P=0.08$]. Scores on the Minnesota Nicotine Withdrawal Scale in the morning were 2.4±1.1. Morning scores were not different on sessions when subjects received amphetamine or placebo.

Pre-cigarette phase

The main effects (amphetamine and time) and interactions from the ANOVA for each dependent measure during this phase are presented in Table 4. Amphetamine produced prototypic stimulant effects on the mood and drug effects scales. On the ARCI, 20 mg increased scores on the A scale compared to placebo (Fig. 4), and on the POMS, amphetamine increased ratings on the "Friendliness" scale (10 and 20 mg), "Elation" (10 mg) and "Positive Mood" (10 mg; Fig. 4). There was a trend for amphetamine to increase "Vigor" scores ($P=0.07$) and decrease "Anxiety" scores ($P=0.08$) on the POMS. Diastolic blood pressure was higher at 45 min than 85 min (main effect of time) but amphetamine did not change blood pressure. Amphetamine did not change the DSST scores, craving for nicotine, withdrawal, or physiological measures.

Post-cigarette phase

The single cigarette decreased self-reported ratings of craving on the BQSU, and increased ratings of "feel drug" and "like drug" (DEQ), expired CO, heart rate, and blood pressure. Amphetamine (10 mg) increased heart rate relative to placebo. The 20 mg dose increased systolic blood pressure and there was a trend ($P=0.06$) for amphetamine to increase diastolic blood pressure. Amphetamine did not affect the mood, craving, withdrawal scales, DSST performance, or levels of expired CO during this phase. The *F*-values for these variables are shown in Table 5.

Ad libitum smoking phase

Both the 10 and 20 mg doses of amphetamine increased the number of cigarettes the subjects smoked during the session [Fig. 5; $F(2,18)=4.3$, $P<0.05$]. After 10 mg, subjects smoked a mean of 1.4±0.7 more cigarettes than during the placebo session, and after 20 mg they smoked a mean of 1.8±0.8 more cigarettes. After 10 mg, seven

Table 4 Summary of *F* values (ANOVA) for effects of *d*-amphetamine after overnight abstinence (before and 40 and 85 min after capsule). The ARCI and POMS were only administered at 40 min

Dependent measure	Amphetamine	Time	Amphetamine×Time
Heart rate	<1	<1	1.4
Systolic BP	<1	<1	1.0
Diastolic BP	1.2	5.7*	<1
DSST	<1	17.5*	<1
ARCI			
A	4.0*	NA	NA
BG	1.7	NA	NA
MBG	<1	NA	NA
POMS			
Anxiety	3.0	NA	NA
Arousal	1.2	NA	NA
Elation	4.7*	NA	NA
Friendliness	6.3*	NA	NA
Positive Mood	4.8*	NA	NA
VAS			
Hungry	3.2	<1	<1
BQSU			
Factor 1	1.8	1.7	0.7
Factor 2	<1	2.8	<1
Combined	<1	2.4	<1
Expired CO	<1	NA	NA

*$P<0.05$ NA, not applicable

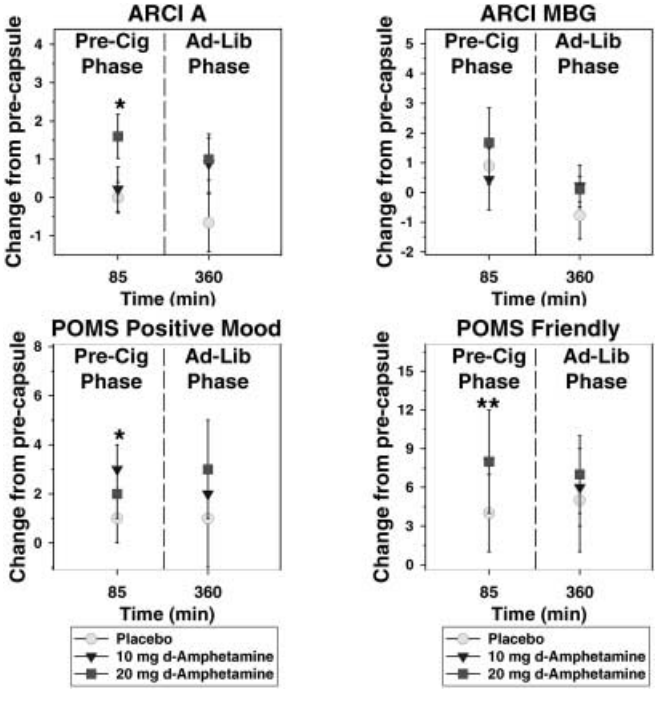

Fig. 4 Effects of amphetamine on ARCI A scale and ARCI MBG scale (*top panels*), and on POMS Positive Mood and Friendliness scales (*bottom panels*). Data represent change from baseline. *Denotes significantly different from placebo ($P<0.05$). **Indicates both doses significantly different from placebo ($P<0.05$)

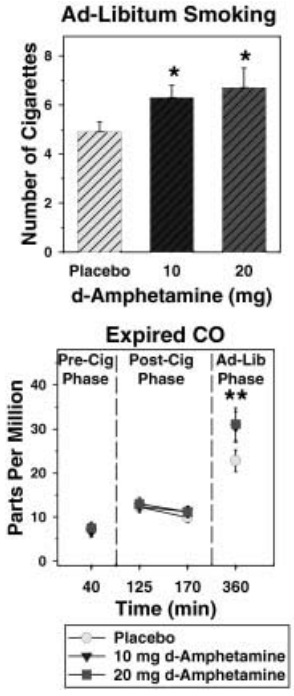

Fig. 5 Effect of amphetamine on the number of cigarettes smoked during the 3-h ad libitum smoking phase *(top panel)*, and levels of expired CO after the ad libitum smoking phase (*bottom panel*). *Denotes significantly different from placebo ($P<0.05$). **Indicates both doses significantly different from placebo ($P<0.05$)

Table 5 Summary of *F* values (ANOVA) for effects of *d*-amphetamine after a single cigarette (5 and 45 min after the cigarette). The ARCI, POMS and Cigarette Effects VAS were not administered during this phase

Dependent measure	Amphetamine	Time	Amphetamine×Time
Heart rate	4.0*	31.5*	1.2
Systolic BP	3.5*	6.6*	<1
Diastolic BP	3.3	7.4*	<1
DSST	1.0	<1	<1
DEQ			
Feel	<1	8.1*	2.1
Like	1.3	5.2*	<1
VAS			
Hungry	1.5	2.5	1.6
Stimulated	1.1	4.5	<1
BQSU			
Factor 1	1.5	17.7*	<1
Factor 2	1.3	7.1*	1.8
Combined	1.4	14.7*	<1
Expired CO	<1	19.5*	2.4

*$P<0.05$ NA, not applicable

subjects smoked more, one smoked less, and two remained unchanged. After 20 mg, six subjects smoked more, two subjects smoked less, and two subjects did not change. Both doses of amphetamine increased expired CO levels [Fig. 5; $F(2,18)=4.5$, $P<0.05$]. Compared to the placebo condition, the mean expired CO was 7.7±3.7 ppm higher after amphetamine (10 mg), and 8.3±3 ppm higher after amphetamine (20 mg).

Sex differences

Men and women did not differ on any measure.

Discussion

The present studies demonstrate that acute administration of both amphetamine and bupropion significantly increased smoking, compared to placebo. The 300 mg dose of bupropion, and both doses of amphetamine (10 and 20 mg), increased the number of cigarettes subjects smoked during a 3-h period of smoking, and expired CO levels were increased accordingly. The results with amphetamine are consistent with previous findings (Schuster et al. 1979; Henningfield and Griffiths 1981; Chait and Griffiths 1983), but the finding that acute doses of bupropion increase smoking is new.

Bupropion was recently approved as a pharmacological adjunct in the treatment of smoking cessation, and clinical studies have shown it is effective in helping smokers quit (Ferry and Burchette 1994; Hurt et al. 1997; Hayford et al. 1999; Jorenby et al. 1999). In light of its capacity to reduce smoking when administered chronically in a treatment setting, it is surprising that bupropion increases smoking when administered acutely. However, the apparently opposite effects of bupropion on smoking after acute and chronic administration parallel findings with amphetamine, a drug that shares both neurochemical actions and behavioral effects with bupropion. Amphetamine also increases smoking when administered acutely, while at least two studies have reported that chronic administration of amphetamine decreases smoking (Miller 1941; Low et al. 1984). These findings suggest that amphetamine and bupropion may have differential effects on nicotine self-administration when administered acutely or chronically.

Other results in these studies may provide clues as to how acute doses of amphetamine and bupropion increase smoking. One way that drugs may affect smoking is through their effects on mood or subjective effects. Both amphetamine and bupropion increase self-reported states of arousal, euphoria, and mood (Chait and Griffiths 1983; de Wit et al. 1986; Kelly et al. 1991; Brauer and de Wit 1996; Rush et al. 1998). Accordingly, in the present study both drugs increased scores on the ARCI Amphetamine (A) and Morphine-Benzedrine Group (MBG) scales and POMS Elation, Friendliness, and Positive Mood scales. It is possible that positive affective states increase the likelihood of smoking. Positive mood states are thought to contribute to relapse in abstinent smokers and alcoholics, and may facilitate drug-taking in general (Shiffman 1982; Doty and de Wit 1995; Miller et al. 1996). Another reason that amphetamine and bupropion

may increase smoking is because of their similarities to nicotine. Nicotine produces many of the same neurochemical and subjective effects typically seen with stimulant drugs, and thus amphetamine and bupropion may increase smoking through a priming effect (de Wit 1996). Pretreatment with nicotine itself has been reported to increase the probability of smoking in abstinent smokers (Henningfield et al. 1985; Chornock et al. 1992). Another mechanism by which amphetamine and bupropion may increase smoking is through their effects on motor activity, i.e., they may increase the rate of any ongoing behavior. There is no simple way to evaluate this possibility. However, the drugs did not increase other behaviors (e.g., the number of symbols completed on a digit-symbol substitution task), suggesting that the increase in behavior is to some extent specific, perhaps to motivationally significant conditioned stimuli or behaviors. In future studies it may be of interest to determine the specificity of the increased smoking behavior by examining other behaviors, including purely motor behaviors such as finger tapping, tracking, or reaction time tasks (e.g., Peck et al. 1979; Hamilton et al. 1983; Peck and Hamilton 1983) as well as conditioned behaviors such as responses to drug-related stimuli.

Another mechanism that might account for the increased smoking rate involves drug-induced changes in the sensory responses to cigarettes. Either increases or decreases in the subjective or sensory effects of a single cigarette could alter the amount smoked. In the present study, subjects reported blunted sensations of “intensity” and “buzzed” from the cigarette after bupropion. It is possible that subjects smoked more during the ad libitum phase to compensate for these diminished sensations. Unfortunately, we did not obtain these measures in the amphetamine-treated subjects. However, Henningfield and Griffiths (1981) reported a very different finding with amphetamine, i.e., that amphetamine increased ratings of “cigarette satisfaction” and subjects stated that their cigarettes “tasted better”. Procedural differences between the studies make it difficult to determine if these reflect true differences between bupropion and amphetamine.

Another process by which amphetamine and bupropion could increase smoking is by altering levels of nicotine craving. However, the present study provides little support for this idea. We obtained ratings of cigarette craving after overnight abstinence and after a single cigarette. Although craving ratings were moderately high after 12 h of abstinence, and declined immediately after the subjects smoked the single cigarette, neither amphetamine nor bupropion altered the ratings of craving. This is consistent with a previous report that bupropion did not decrease craving in abstinent smokers (Shiffman et al. 2000).

One factor that may influence the direction of effects of amphetamine and bupropion is the subjects’ motivation to quit smoking. In the present study and in the other studies in which acute amphetamine administration increased smoking, the subjects were not seeking to quit smoking (Schuster et al. 1979; Henningfield and Griffiths 1981; Chait and Griffiths 1983). In contrast, most of the studies reporting that either drug reduced smoking were conducted using smokers who were trying to quit (Miller 1941; Hurt et al, 1997). The motivation of the smokers could influence the direction of effects of the drugs on smoking. For example, smokers who want to quit might find blunted sensations of a cigarette helpful and desirable in their effort to reduce cigarette consumption, whereas smokers not trying to quit may increase their cigarette consumption to overcome the blunted effects of individual cigarettes. However, the motivation to quit cannot account entirely for the differences. In the Low et al. (1984) study, daily administration of amphetamine reduced smoking and reduced the pleasure and enjoyment of smoking in subjects who were not trying to quit. In addition, Ferry and Buchette (1994) reported that bupropion spontaneously decreased smoking in depressed smokers who were not trying to stop. Together, these data suggest that the motivation to quit might not account for the differential behavioral effects of acute and chronic amphetamine and bupropion on smoking.

The exact neurochemical mechanisms by which amphetamine and bupropion affect smoking are still not known. It is believed that their actions on dopaminergic systems are of key importance (Shoaib 1998). However, these drugs also have actions on other transmitter systems. Indeed, there is evidence that bupropion can also act as a nicotine receptor antagonist (Fryer and Lucas 1999; Slemmer et al. 2000). This could lead to a compensatory increase in smoking after acute administration and a reduction in smoking due extinction after chronic administration (Rose et al. 1989; Rose and Levin 1991).

Regardless of the mechanisms that may underlie the drugs’ effects in the present study, the observation that smoking increases after acute bupropion treatment might be of clinical significance during the early portion of smoking cessation treatment programs. Although it is clear that bupropion is helpful in reducing smoking when administered chronically, the present findings suggest that it may produce a transient increase in smoking. If the increase in smoking reported here also occurs outside the laboratory in clinical settings, it may interfere with patients’ early efforts to reduce or quit smoking and it may be advisable for physicians to caution their patients about this possibility (Kreuter et al. 2000).

The present data leave at least two questions unanswered. One question concerns the importance of the subject population, and in particular, the role of the subject’s desire to quit. It will be important to determine whether the effects of acute doses of amphetamine or bupropion also occur in individuals who want to quit. A second question concerns the mechanisms that account for the apparently opposite effects of acute and chronic amphetamine or bupropion. Further studies are needed to determine the time course of the change in the direction of effect, and whether either tolerance or sensitization can account for the apparent change in effects over time.

These experiments demonstrate the usefulness of this multicomponent experimental procedure. The design provides, within a single laboratory procedure, a measure of the drugs' effects on craving and mood after overnight abstinence, on subjective responses to a single, smoked cigarette, and on the number of cigarettes smoked. This provides a comprehensive picture of the drugs' subjective and physiological effects, and provides clues as to how the drugs influence ad libitum smoking. For example, in this study the procedure suggested one reason why subjects smoked more after bupropion (i.e., blunted sensations of a single cigarette).

Despite the advantages to studying different phases of the smoking process in a single procedure, there are also disadvantages. One disadvantage is that the phases may interact with one another, making it difficult to differentiate the effects of the drugs on different phases. Another disadvantage is that the combined procedure limits the duration that measures in any one phase can be measured. For example, because of the scheduling of the second and third phases of the procedure in this study it was difficult to determine the complete time course of the direct effects of bupropion and amphetamine. Although previous studies suggest that the subjective effects of amphetamine (10–20 mg) persist for at least 5-6 h (e.g., Hamilton et al. 1983; Chait et al. 1985; Wachtel and de Wit 1999), within the duration of our laboratory session, the time course of subjective and behavioral effects of an acute dose of bupropion has not been well documented. However, the half-life of bupropion is 8 h, suggesting that its effects should be sustained throughout the session (Posner et al. 1985). Nevertheless, these points need to be verified empirically.

In summary, these data show that amphetamine and bupropion, administered acutely, increased cigarette smoking without affecting subjective reports of craving for cigarettes. The mechanism by which the drugs increase smoking are not known, but might be related to enhancements in positive mood, priming or psychomotor stimulation. Bupropion may also increase smoking by dampening the sensory properties of cigarettes.

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