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RESEARCH REPORT

Bromocriptine reduces cigarette smoking

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Abstract

Aims. *Animal studies have shown that nicotine releases dopamine, a neurotransmitter implicated in drug reinforcement. We hypothesized that bromocriptine would decrease smoking behavior in humans.* **Design.** *The study was conducted double blind and subjects' order of dose exposure was randomized.* **Participants.** *The smoking behavior of 20 heavy smokers was recorded for 5 hours after ingesting placebo or one of two doses of bromocriptine (2.50 mg, 3.75 mg) over three sessions (one dose per session).* **Findings.** *There was a significant negative linear trend by dosage indicating shorter total puffing time with increasing bromocriptine dosages (*$p < 0.02$*). Other significant negative linear trends by increasing dosage include fewer number of puffs, fewer number of cigarettes smoked and mean latency to smoke after 3 hours (expected* C_{MAX} *on the drug (all ps* < 0.05*). There was a negative significant linear trend showing decreased plasma nicotine (*$p < 0.02$*) and cotinine (*$p < 0.005$*) with increasing dosages of bromocriptine. Shiffman/Jarvik Withdrawal Scale (SJWS) cigarette craving subscale scores decreased significantly across increasing dosages (linear trend* $p < 0.02$*). There was a significant negative linear trend (*$p < 0.05$*) on the Profile of Mood States (POMS) Vigor and Depression subscales, with subjects reporting decreased vigor and depression with increasing bromocriptine doses. No other mood effects were observed.* **Conclusion.** *These results support the hypothesis that dopaminergic mechanisms mediate cigarette smoking reinforcement.*

Introduction

Animal research (Clarke, 1990, 1992; Corrigall, 1991; Corrigall & Coen, 1991; Pontieri *et al.*, 1996; Rose & Corrigall, 1997) has pointed to the possibility that nicotine reinforcement may be, at least in part, controlled by dopaminergic mechanisms. Dopamine has been previously hypothesized to play a central role in mediating the reinforcing effects of other stimulant drugs, e.g. cocaine and amphetamines (Koob & Bloom, 1988; Wise & Rompre, 1989). In a repeated measures study, McEvoy *et al.* (1995) reported increased smoking in schizophrenics (evidenced by higher expired carbon monoxide and plasma nicotine levels) when they were given haloperidol, a dopamine antagonist, in comparison with their baseline levels when they were taking no antipsychotic medications. Recent studies exam-

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ining the effect of haloperidol on smoking in non-psychiatric subjects have shown that it increases a number of indices of smoking behavior. Dawe *et al.* (1995) reported significantly increased nicotine intake in postprandial smoking when subjects were pretreated with 5 mg haloperidol vs. placebo. Caskey *et al.* (1999) have reported increased rates of smoking in non-psychiatric subjects with acute administration of haloperidol vs. placebo (1.0 mg and 2.0 mg vs. placebo) and with higher vs. lower doses of haloperidol (1.0 and 0.5 mg).

Bromocriptine is an ergot alkaloid currently used for the treatment of amenorrhea, galactorrhea, prolactin secreting adenomas and Parkinson's disease. A single 2.5 mg dose of bromocriptine has been shown to suppress circulating prolaction levels by 47% to 96% (Thorner *et al.*, 1980); when given chronically, dosages range from 5.0 mg/day to over 100 mg/day depending on the indication (Vance, Evans & Thorner 1984). In tests with native D_1 (calf brain striatum/calf parathyroid) and D_2 receptors (pig anterior pituitary/canine brain striatum) and cloned D_1-like (D_1, D_5) and D_2-like (D_2, D_3, D_4) receptors, it appears that bromocriptine is equivalent to dopamine in affinity in binding to D_2 and D_3 receptors (Seeman, 1994). It thereby functions in much the same way that endogenous dopamine does, except that bromocriptine is more specific to certain types of receptors. It putatively exerts its therapeutic action through its potent agonism of post-synaptic D_2 receptors (Vance *et al.*, 1984). Stimulation of the postsynaptic D_2 receptor with bromocriptine causes a decrease in firing of the postsynaptic neuron.

Pilot data (Caskey *et al.*, 1999) indicated that acute administration of bromocriptine, a dopamine agonist, to a small sample of non-psychiatric subjects ($n = 5$) resulted in a significantly slower rate of smoking (2.5 mg vs. placebo). The current study was designed to replicate and extend the results of the bromocriptine pilot experiment (Caskey *et al.*, 1999) by increasing both the sample size and the dose range. It was hypothesized that there would be dose-dependent decrease in smoking behavior and nicotine intake with increasing doses of bromocriptine.

Methods

Subjects

Subjects were initially screened during a brief telephone interview. Subjects who reported any history of cardiac or respiratory/pulmonary illness or disease, endocrine or metabolic disorders, seizure disorders, treatment with any antipsychotic, anti-depressant or other psychotropic medication and/or taking any medication which could interact with bromocriptine were excluded. To be included in the study, subjects had to report that they had been smoking a minimum of 15 cigarettes per day for at least the past 2 years. Twenty heavy smokers (13 males, seven females) were recruited from the West Los Angeles Veterans Affairs Medical Center ($n = 11$) and general community ($n = 9$). Their mean age was 34.6 years (SD = 11.6; range = 18–58; one missing value). The mean level of education in years was 13.3 (SD = 1.8; range = 10–17). Subjects smoked a mean of 21.3 cigarettes per day (SD = 6.3; range = 12.5–35) and had smoked for a mean of 19.8 years (SD = 11.4; range = 4–42). Two subjects were included who smoked less than the required minimum of 15 cigarettes per day (12.5 and 14 cigarettes per day). These two subjects had reported smoking at least 15 cigarettes per day during the telephone interview, but subsequently reported smoking fewer cigarettes when they completed written questionnaires at the laboratory. Both subjects had CO levels greater than 25 p.p.m. when tested at 5:30 p.m. during the initial baseline visit.

Design and procedure

This study utilized a randomized, double-blind, repeated-measures design in which subjects served as their own controls. Subjects participated individually in one screening baseline visit and three experimental sessions spaced one week apart. Sessions were conducted at the West Los Angeles Veterans Administration Medical Center. Subjects were paid a total of $180 for participating in the baseline visit and three experimental sessions.

Baseline visit

A baseline visit was conducted with all subjects to provide an opportunity for more in-depth health screening and to familiarize potential subjects with experimental procedures. At the baseline visit subjects gave written informed consent, had a physical examination (including an ECG)

and completed background questionnaires. Health screening included a medical history and physical examination (including blood pressure, heart rate and weight). Smoking status was verified by carbon monoxide (CO $\geq$ 20 p.p.m.). Subjects smoked a cigarette through an experimental smoking apparatus to acquaint them with the experimental procedure. The apparatus (described below) was designed to measure smoking topography (e.g. puff duration). Subjects also completed both the Profile of Mood States (POMS) and the Modified Shiffman–Jarvik Withdrawal Scale (SJWS) to familiarize them with these questionnaires which were to be used repeatedly throughout experimental sessions.

Experimental sessions

Experimental sessions began at 8:30 a.m. (At the baseline session, subjects were instructed not to eat anything or drink any caffeinated beverages prior to coming to the experimental sessions in order to facilitate drug absorption. Subjects who reported having had food or caffeinated beverages after midnight were rescheduled.) Upon arrival each subject reported the time of completion of his or her most recent cigarette. Blood pressure was then measured. Subjects then completed a baseline questionnaire battery (including the Profile of Mood States [POMS] and Shiffman–Jarvik Withdrawal Scale [SJWS] (see below)). Next, subjects provided a baseline expired-air carbon monoxide sample. At this time subjects smoked a "loading cigarette" to start the experimental session. They were instructed to smoke as much or as little of one of their own cigarettes as they pleased. Blood was drawn exactly 2 minutes after completion of the loading cigarette. The drug (placebo, 2.5 mg or 3.75 mg) was administered after the blood draw. Another CO measurement, taken 20 minutes after the loading cigarette, was used as the baseline measurement for subsequent experimental analyses on CO changes. Breakfast was served 45 minutes after drug ingestion. Breakfast items included a 12-ounce bowl of cornflakes, 16 ounces of low-fat milk, 16 ounces of orange juice, 6 ounces of low-fat mixed fruit yogurt and three small cinnamon rolls.

Experimental sessions lasted a minimum of 5 to a maximum of 5.5 hours (see below). Subjects were instructed to smoke freely (*ad libitum*) using the smoking topography apparatus during the experimental sessions. Subjects smoked their own brand of cigarettes. Subjects watched videotaped movies for the remainder of the session by themselves. The movies were lighthearted comedies, which did not feature any scenes of actors smoking. The questionnaire battery (POMS, SJWS, additional measures of desire to smoke and two nausea measures) was given 30 minutes after completion of the loading cigarette. Before each successive cigarette, subjects were required to notify the experimenter via wireless intercom when they wanted to smoke another cigarette. Carbon monoxide and repeated questionnaire measures were taken before every cigarette. Time at which cigarette was lit, number of puffs, duration per puff, and time cigarette was extinguished were recorded. Immediately after each cigarette the subjects completed the two nausea scales. Carbon monoxide levels were measured again 20 minutes after each cigarette. Subjects completed the repeated questionnaire measures battery 30 minutes after each cigarette. In cases where subjects desired to smoke again prior to the repeated measures battery (i.e. less than 30 minutes) they first completed the battery, then were allowed to smoke. This procedure was repeated for each cigarette.

Blood was again drawn precisely 2 minutes after the first cigarette smoked after 3 hours post-drug ingestion (time of expected C_{max}) or 5 hours after drug ingestion if no cigarettes were smoked after the 3-hour mark. The session ended 5 hours after the drug was administered except to complete the CO and questionnaire assessments that followed cigarettes smoked during the half-hour immediately before the 5-hour mark. For example, if the subject requested to smoke at the 5-hour mark, they remained in the laboratory for another 30 minutes for CO testing at 5 hours 20 min and questionnaires at 5 hours 30 min. Subjects' blood pressure and heart rate were measured to ensure that they were within normal limits before subjects were released.

Apparati

A thermistor puff-detecting device was used to measure cigarette smoking topography (puff duration). This device consists of a thermistor (Victor Engineering) embedded in a commercially available cigarette holder (Aqua Filter). The thermistor is heated to 200°C by electrical cur-

rent. Cigarette smoke passing over the thermistor causes a drop in the thermistor's temperature causing a change in the thermistor's electrical resistance. Changes in the thermistor's resistance are converted into a voltage signal. Combining the thermistor apparatus with an electronic timing device enabled us to measure the time of onset and completion for each cigarette, puff duration, number of puffs per cigarette, etc. A Bedfont II Microsmokelyzer was used to measure expired air carbon monoxide. Blood pressure was measured manually using a sphygmomanometer.

Measures

Background measures. One-time-only background questionnaires included a measure of smoking history and demographic information (Smoker's Profile), the Fagerström Test for Nicotine Dependence (FTND; Heatherton *et al.*, 1991), the Smoking Motivation Questionnaire (SMQ; Russell *et al.*, 1974) and the Smoker's Beliefs Questionnaire (SBQ).

Smoking topography. Total number of cigarettes smoked and total number of puffs taken during the session were noted. Puff times were recorded by the puff detector, obtaining total puffing time and mean length of puffs over the session. The time in minutes to the first cigarette smoked after 3 hours on the drug was derived from the record of cigarette and drug onset times. If no cigarettes were smoked after the 3-hour mark, the time until the end of the session was substituted for the censored data point (e.g. 120 minutes).

Repeated subjective measures. Repeated-measure questionnaires included: (1) the Urge to Smoke questionnaire (UTS; Jarvik *et al.*, 2000), (2) Schuh & Stitzer's index, a four-item visual analog scale (SSI; Schuh & Stitzer, 1995), (3) a modified version of the Shiffman–Jarvik Withdrawal scale which contained only the non-craving related withdrawal items (SJWS-NC; Shiffman & Jarvik, 1976), (4) Profile of Mood States questionnaire (POMS), (5) a 100-mm Visual Analog nausea scale, (6) five-point Likert nausea scale, and (7) a single-item Strength of the Urge to Smoke (SUTS; Jarvik *et al.*, 2000).

Bioassays. Blood samples (10 ml) were assayed for nicotine and cotinine concentrations by gas chromatography. Breath samples were assessed for carbon monoxide content. Blood and breath samples were not taken from the first two participants entered into the study.

Data analysis

Repeated measures analysis of variance (*r*-ANOVA) was used to compare values different across the three sessions. Within each analysis, polynomial contrasts (linear and quadratic) examining the effect of dose in detail were tested (The dose–response was predicted to have a linear shape.) For the smoking topography indices (*total number of cigarettes*, *total puffing time*, *total number of puffs*, *mean length of puff* and *latency to smoke after 3 hours on drug*) which produced only a single measurement per session, a simple three-condition repeated measures analysis was conducted. For *plasma nicotine* and *plasma cotinine*, the values from the sample after the 3-hour mark were compared across sessions; the sample values from the pre-loading cigarette were used as within-session covariates to control for a differences in pre-drug values. The CO measures taken concurrently with the blood samples were also analyzed in this fashion. In addition, since other CO measures were also taken (contingent upon smoking), all available data were used to calculate mean CO values during three periods: within 1 hour of drug administration (including prior to drug administration), 1–3 hours after drug administration and 3–6 hours after drug administration (3×3 time $\times$ condition *r*-ANOVA). For each self-report measure (UTS, SUTS, SSI, SJWS subscales, POMS subscales, nausea), the mean value post-drug over all available data was calculated for each session. The *r*-ANOVA proceeded as with the topography measures.

The planned analyses specified above were tested with a directional hypothesis of greater effect with increasing dosages of bromocriptine (significance set at $\alpha = 0.05$ one-tailed). In addition to statistical significance, effect size values (partial-η^2; Cohen, 1988) were calculated to assess relative impact of the dose factor on the dependent variables. All statistical analyses were executed using SPSS for Windows.

Table 1. *Means and effect sizes for smoking topography for placebo and two doses of bromocriptine (standard deviations in parentheses)*

	Number of subjects	Mean for placebo	Mean for 2.5 mg	Mean for 3.75 mg	Effect size η^2	Linear trend
Total no. of cigarettes	20	3.0 (1.8)	2.6 (1.5)	2.3 (1.6)	0.20	$p = 0.044$
Total puffing time	20	72.3 (57.8)	55.4 (38.8)	50.6 (51.0)	0.29	$p = 0.011$
Total number of puffs	20	32.9 (22.3)	26.8 (14.4)	23.8 (17.0)	0.23	$p = 0.028$
Mean length of puffs	20	2.2 (1.1)	2.1 (0.8)	2.0 (1.0)	0.17	$p = 0.060$
Minutes to smoke after 3 hours on drug	20	50.7 (41.4)	71.3 (40.8)	73.5 (38.8)	0.23	$p = 0.028$

Results

Some data were lost due to events that occurred during the study. Blood was not drawn if the participant had recently vomited (four samples). Fourteen blood samples were lost when they were accidentally destroyed during preparation for shipping. Overall, seven of the lost samples were for the initial blood draw and 11 were for the draw after the 3-hour point. With the exception of the four samples not drawn for subject safety, the missing samples occurred basically at random. Some of the lost samples were within the same subject; the total number of subjects with a complete set of blood samples was nine.

Smoking topography

Several significant negative linear trends by increasing bromocriptine dose (placebo, 2.5 mg, 3.75 mg) were observed (see Table 1). The number of cigarettes subjects smoked decreased significantly with increasing levels of bromocriptine ($F[1,19] = 4.63$; $p < 0.05$). Subjects' total puffing time (summed over all puffs) decreased significantly with increasing bromocriptine levels ($F[1,19] = 7.88$; $p < 0.02$) and total number of puffs also decreased significantly with increasing levels of bromocriptine ($F[1,19] = 5.69$; $p < 0.05$). As total puffing time is partly a function of the total number of puffs, mean length of puff (total puffing time/total number of puffs) was examined. Mean puff duration also decreased significantly with increasing levels of bromocriptine ($F[1,19] = 4.01$; $p < 0.05$). The mean latency to smoke after the time of expected C_{max} for bromocriptine (3 hours) increased significantly with increasing bromocriptine ($F[1,19] = 5.66$; $p < 0.05$).

Biochemical assessments

Levels of plasma nicotine and cotinine were compared at the second blood draw across placebo and the two bromocriptine doses, covarying on the levels of nicotine and continine at the baseline blood draw at the beginning of the experimental sessions. Figures 1 and 2 show a significant negative linear trends for both nicotine and cotinine ($F[1,7] = 8.25$; $p < 0.05$ and $F[1,7] = 27.39$; $p < 0.001$, respectively) indicating that subjects took in less nicotine with increasing levels of bromocriptine (see Table 2).

Unlike the results for plasma nicotine and cotinine, the results using the CO measures taken 20 minutes after the blood draws failed to show any effect by drug condition ($F[1,19] = 0.64$; $p > 0.20$). On the other hand, the analysis of the within session trends did indicate an apparent effect of the drug. This trend over time in carbon monoxide values is presented in Fig. 3. There was a significant time by dose effect ($F[1,17] = 12.65$; $p < 0.005$). It can be seen in the figure that CO increased through the session for the placebo group but decreased in the two active drug conditions. Although the baseline values for the three groups appear to be different, this was not significant ($p > 0.20$).

Table 2. *Means and effect sizes for biological assessments for placebo and two doses of bromocriptine (standard deviations in parentheses)*

	Number of subjects	Mean for placebo	Mean for 2.5 mg	Mean for 3.75 mg	Effect size η^2	Linear trend
Plasma nicotine levels	9	23.9 (14.9)	22.6 (17.2)	18.3 (17.5)	0.54	$p = 0.012$
Plasma cotinine levels	9	229 (54.9)	214 (83.0)	192 (42.9)	0.80	$p = 0.000$
Expired carbon monoxide levels	20	25.0 (4.9)	25.2 (4.7)	23.9 (4.9)	0.01	$p = 0.495$

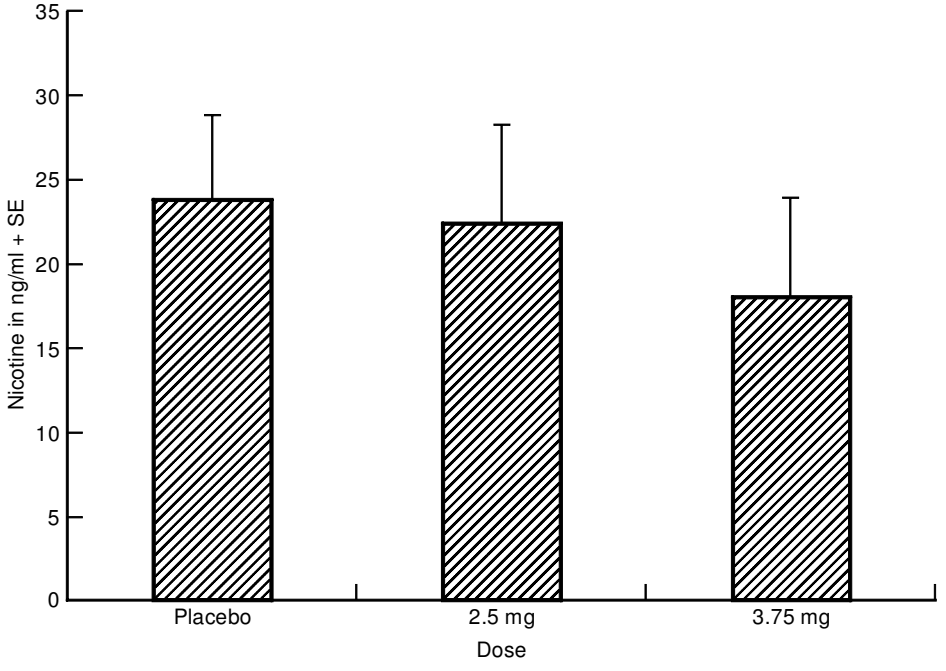

Figure 1. *Plasma nicotine levels by dose (adjusted means),* n = *9,* p < *0.05.*

Self-report measures

Table 3 presents the results for the self-report measures. There was a significant linear trend ($F[1,19] = 7.50$; $p < 0.02$) for desire to smoke to decrease with increasing bromocriptine as measured by the craving subscale of the SJWS. Despite the high intercorrelation of all the different measures of craving used in this study, this was the only significant effect observed. Only one of the subscales of the POMS showed a strong bromocriptine effect. There was a significant ($F[1,19] = 8.11$; $p < 0.02$) negative linear trend for the Vigor subscale such that subjects reported reduced vigor with increasing levels of bromocriptine. There was also an apparent effect of the drug on the Depression subscale of the POMS ($F[1,19] = 4.43$; $p < 0.05$) however the clinical significance of this effect was rather small, accounting for a change of less than 5-hundredths of a point on a four-point scale.

Nausea and vomiting

There was a near significant positive linear trend ($F[1, 9] = 3.17$; $p < 0.06$) for increasing nausea (measured with the Likert scale immediately after completion of cigarettes) with increasing bromocriptine levels. Five subjects vomited during the course of the experiment. All five vomited with the 3.75 mg dose and one of those five also vomited with the 2.5 mg dose. No subjects vom-

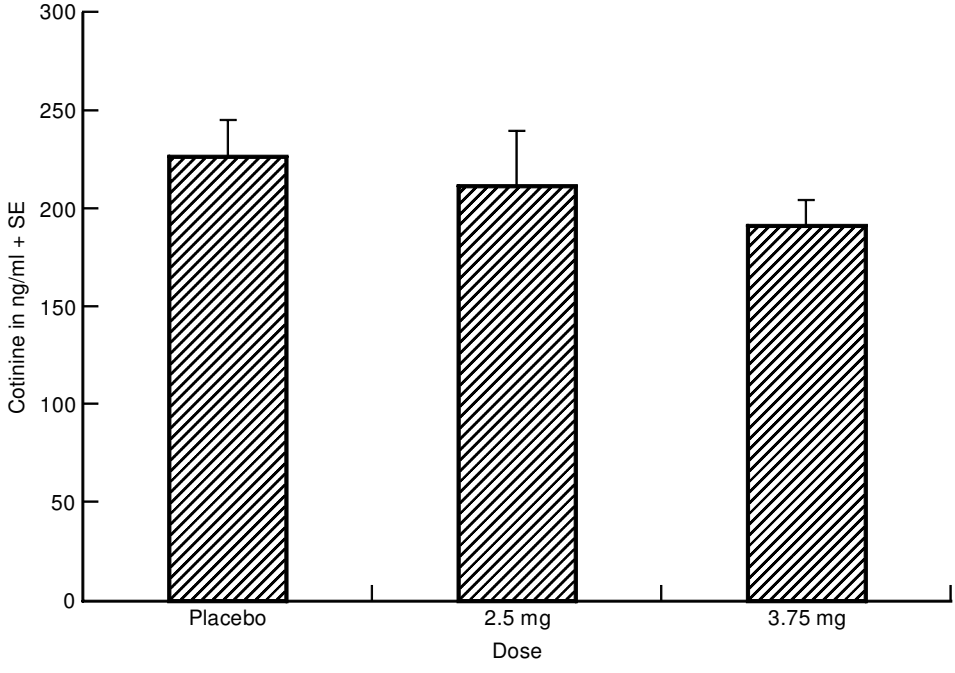

Figure 2. *Plasma cotinine levels by dose (adjusted means),* n = 9, p < 0.001.

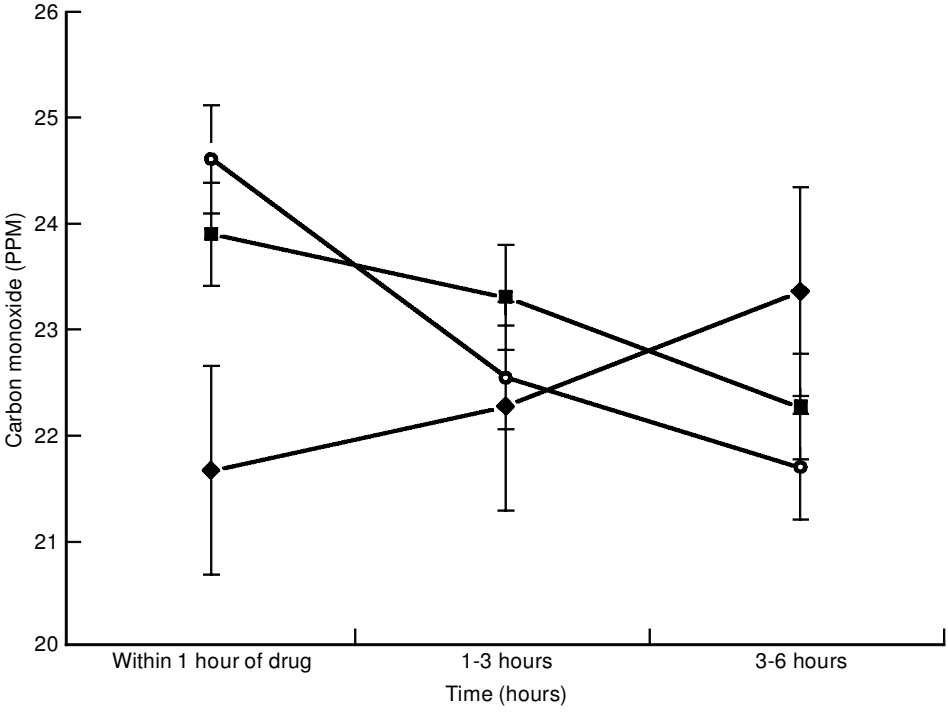

Figure 3. *Mean expired air carbon monoxide comparisons (◆ placebo, ■ low dose, ○ high dose).*

Table 3. *Means and effect sizes for self-report measures (craving, withdrawal, and mood) for placebo and two doses of bromocriptine (standard deviations in parentheses)*

	Number of subjects	Mean for placebo	Mean for 2.5 mg	Mean for 3.75 mg	Effect size η^2	Linear trend
UTS (1–7)[a]	18	3.91 (1.26)	3.61 (1.24)	3.71 (1.30)	0.03	$p = 0.462$
SUTS (1–7)[a]	18	3.41 (1.28)	2.72 (1.43)	3.03 (1.74)	0.05	$p = 0.354$
SSI (0–100)	20	39.9 (18.6)	35.9 (21.3)	37.3 (22.9)	0.01	$p = 0.639$
S-J craving (1–7)	20	4.46 (0.99)	3.63 (1.12)	3.72 (1.25)	0.28	$p = 0.013$
S-J psychological distress (1–7)	20	2.79 (0.70)	2.90 (0.74)	2.96 (0.83)	0.05	$p = 0.357$
S-J physical symptoms (1–7)	20	1.69 (0.77)	1.92 (0.92)	1.94 (1.27)	0.05	$p = 0.327$
S-J appetite (1–7)	20	3.56 (0.77)	3.56 (0.80)	3.29 (1.08)	0.05	$p = 0.356$
S-J stimulation/sedation (1–7)	20	2.55 (1.19)	3.40 (1.48)	3.12 (1.23)	0.15	$p = 0.085$
POMS vigor (1–5)	20	2.91 (0.86)	2.50 (0.93)	2.45 (0.98)	0.30	$p = 0.010$
POMS confusion (1–5)	20	1.59 (0.46)	1.62 (0.39)	1.62 (0.55)	0.00	$p = 0.791$
POMS fatigue (1–5)	20	1.40 (0.50)	1.52 (0.60)	1.51 (0.47)	0.06	$p = 0.286$
POMS anger/hostility (1–5)	20	1.12 (0.20)	1.07 (0.16)	1.10 (0.18)	0.05	$p = 0.320$
POMS depression (1–5)	20	1.16 (0.25)	1.13 (0.24)	1.14 (0.25)	0.19	$p = 0.049$
POMS tension (1–5)	20	1.44 (0.40)	1.56 (0.48)	1.60 (0.72)	0.07	$p = 0.241$

[a]UTS and SUTS were not given to first two participants in study.

ited with the placebo. No subjects had to be discontinued from the study, and subjects who did vomit typically reported that they felt better after vomiting. Besides the five subjects who actually vomited, three additional subjects experienced nausea. One subject experienced nausea with both the low and high dose, one subject had nausea only with the high dose and one had nausea only with the low dose.

Because of the possible effects of nausea on urge to smoke and smoking behavior, the variables which showed significant finding were reanalyzed with nausea ratings as a covariate. Unfortunately, nausea was only measured contingent on smoking so that ratings were not available if the subject stopped smoking during the session (possibly due to nausea). Hence the mean value of nausea over the session likely underestimates the degree of nausea experienced by the participants. A correction was implemented such that instead of mean nausea ratings, the slope of the available nausea ratings was calculated and utilized as the covariate in the modified analyses. Thus, if nausea were low but increasing prior to the discontinuation of smoking, this would be captured in the slope measure.

Table 4 presents the changes in significance and effect size with and without the nausea slope covariate. Introducing nausea as an explanatory variable reduced the significance levels of the linear trends for most of the topography measures and the effect sizes were reduced by approximately 50%. Two effects, total puffing time and latency to smoke, remained significant. The linear trend for nicotine levels was no longer significant after covarying for nausea, but the negative linear trend for cotinine levels remained highly significant, despite the covarying for nausea levels. The η^2 values associated with the self-report, i.e. non-behavioral, measures, showed reduced effects accounted for by the drug much like the topography measures. Despite the decrease in significance values, the effect size index, η^2 (Cohen, 1988), still indicates

Table 4. *Effects of covarying nausea on positive findings*

	Before covarying		After covarying	
	Effect size η^2	Linear trend	Effect size η^2	Linear trend
Smoking topography				
Total no. of cigarettes	0.20	$p = 0.044$	0.08	$p = 0.079$
Total puffing time	0.29	$p = 0.011$	0.12	$p = 0.034$
Total number of puffs	0.23	$p = 0.028$	0.10	$p = 0.051$
Mean length of puffs	0.17	$p = 0.060$	0.08	$p = 0.080$
Minutes to smoke after 3 hours	0.23	$p = 0.028$	0.12	$p = 0.031$
Biological assessments				
Plasma nicotine	0.54	$p = 0.012$	0.38	$p = 0.053$
Plasma cotinine	0.80	$p = 0.000$	0.66	$p = 0.007$
Mood measures				
S-J craving	0.28	$p = 0.013$	0.13	$p = 0.022$
S-J stimulation/sedation	0.15	$p = 0.085$	0.06	$p = 0.124$
POMS vigor	0.30	$p = 0.010$	0.15	$p = 0.017$
POMS depression	0.19	$p = 0.049$	0.02	$p = 0.358$

moderate to large effects for bromocriptine on these variables overall (range = 0.08 to 0.66).

Instances of vomiting were also examined as a binary covariate in re-analyses of total puffing time, plasma cotinine and POMS Vigor. In all cases, the linear contrast continued to be statistically significant when controlling for instances of vomiting ($F[1, 37] = 4.92$; $p < 0.04$ for total puffing time; $F[1, 37] = 44.94$; $p < 0.001$ for plasma cotinine; $F[1,37] = 10.74$; $p < 0.005$ for POMS Vigor). Total puffing time and POMS Vigor did not appear to be affected by vomiting ($p < 0.20$).

Caffeine dependence

Since the protocol required participants to be abstinent from caffeine, the effect of caffeine dependence, as measured by the self-reported number of caffeinated beverages consumed daily, was used as a covariate in a re-analysis of the total puffing time measure to ascertain if there might be a moderating effect. While those who consumed more caffeinated beverages did tend to smoke more during the experimental sessions ($r = 0.38$, ($p < 0.10$), there was no apparent effect of moderation in that the effect of bromocriptine remained unchanged ($F[1, 37] = 8.10$; $p < 0.01$; $\eta^2 = 0.18$) with caffeine intake as a covariate.

Discussion

The results from this study are consistent with the hypothesis that bromocriptine would decrease smoking and nicotine intake. Given the dopaminergic specificity of bromocriptine, the current results also lend support to hypothesized dopaminergic modulation of nicotine reinforcement. That is, the current data suggest that smoking decreases with increasing dopamine agonism.

These results do not appear to be attributable to withdrawal effects for several reasons. First, subjects were allowed to smoke *ad libitum* such that they were in control over their level of nicotine deprivation and withdrawal. In general, subjects smoked *more* in the placebo condition than in the bromocriptine conditions (total puffing time, total number of puffs, mean puff duration, smoking rate), yet they simultaneously were reporting more urges to smoke in the placebo condition.

Increased levels of nausea also appear to have been related to the decreased levels of smoking with higher levels of bromocriptine. The increase in nausea and vomiting episodes were not unexpected as nausea and vomiting are common side effects of bromocriptine. Vomiting is dopaminergically mediated. Thus cigarette smoking (and presumably desire/urge to smoke) and vomiting are both influenced by dopaminergic activity. The attenuation of the findings by using nausea

(rate of change) as a covariate raises the question as to whether the observed effects are the result of dopamine agonism, subjective nausea or a combination of both. The fact that the η^2 values remained relatively large (Cohen, 1988) after using nausea as a covariate suggest that bromocriptine also has effects on smoking behavior beyond those of inducing nausea and that, with a larger sample size, the significant effects on smoking behavior that were observed before covarying on nausea levels would still have been obtained after covarying for nausea.

None the less, a simple effect of nausea cannot be entirely ruled out due to limitations within the study. The two measures of nausea, the four-point scale and the visual analogue scale, while directly worded ("nausea") were formed *ad hoc* and thus their reliability and validity are unknown. A thorough review of the literature revealed no validated self-report measure of nausea to exist. Vomiting provides a more direct behavioral measure of nausea but the overall incidence of vomiting was relatively low so its use, *per se*, as a meaningful explanatory variable is limited (it had no effect on selected key analyses). A greater limitation was the fact that nausea ratings (like most of the self-report measures) were linked to cigarettes smoked; when participants stopped smoking, nausea scores were not collected. The use of estimated rate of change in nausea as a covariate was utilized as the best possible solution to this problem, but it is certainly an abstraction of limited data. While it is clear that bromocriptine affected smoking, the relative contributions of dopaminergic activity that is nausea-related versus nausea-unrelated remains to be properly tabulated. It can be said that there was no clear evidence of supremacy of one mode of action over the other.

From a practical point of view, these results suggest that bromocriptine may have some value as a smoking cessation treatment. The current data do indicate the possible problems with nausea induction. Bromocriptine prescriptions are typically gradually titrated up to therapeutic dose levels such that tolerance may develop, thereby reducing likelihood of nausea and vomiting. However, it is also possible that tolerance to the "anti-smoking" effect observed here acutely would also occur with long-term use. It is possible that a dose lower than 2.5 mg might produce less nausea and still reduce smoking.

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