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Effects of Varenicline and Bupropion on Cognitive Processes Among Nicotine-Deprived Smokers

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Abstract

Nicotine deprivation is associated with craving, negative affect, and difficulty concentrating, which may contribute to subsequent relapse. Bupropion and varenicline are both effective treatments for smoking cessation, and evidence from clinical trials suggests that these treatments increase abstinence rates. However, the mechanism by which these medications reduce relapse remains unclear. Recent research has focused on cognitive processes, such as attention and working memory, which may predict relapse. In addition, there may also be sex differences in cognitive-related deficits during nicotine deprivation. The current sample consisted of 58 (22 females) daily smokers (at least 10 cigarettes per day) randomized to receive bupropion (300 mg/day), varenicline (2 mg/day), or placebo. After a 1-week run-up phase, participants completed a 9.5-hr laboratory session after overnight abstinence (CO verified). Participants completed measures of attention (Conners' Continuous Performance Task [CPT]), working memory (digits backward), and delay discounting. Measures of craving, withdrawal, and mood were also collected. Between-subjects ANCOVA models revealed that varenicline speeded reaction time, but reduced accuracy on the CPT compared with placebo. Sex moderated the effect of bupropion compared with placebo on working memory and delay discounting. Bupropion enhanced working memory for females but not males, and this pattern was reversed for delay discounting. The current data highlight the complex processes associated with nicotine deprivation and the need for future research to examine whether cognitive-related deficits are related to relapse. Identifying these mechanisms may help in the development of new pharmacological treatments.

Keywords

smoking abstinence; cognition; attention; varenicline; bupropion

There have been many advances in the development of medication treatment for smoking cessation. Evidence from clinical trials suggests that the two most common and effective medications, bupropion and varenicline, promote abstinence and reduce craving, negative affect, and reinforcement from smoking (Foulds, Steinberg, Williams, & Ziedonis, 2006; Gonzales et al., 2006; Jorenby et al., 2006; Lerman et al., 2002). Despite these advances, approximately 60% of smokers will relapse within six months (Fiore et al., 2008), and even fewer successfully quit on a yearly basis (Center for Disease Control, 2004). To better understand the mechanism by which these medications are effective, it is necessary to characterize the affective, cognitive, and behavioral effects of these treatments.

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Although bupropion and varenicline increase abstinence rates, they may exert their clinical effects via different mechanisms. Bupropion is a weak reuptake inhibitor of norepinephrine and dopamine and may produce mild stimulant-like effects (Cryan, Bruijnzeel, Skjei, & Markou, 2003). It also acts as a nicotine receptor (nAChR) antagonist, blocking the antinociceptive, motor, hypothermic, and convulsive effects of nicotine at the α4β2, α3β2, and α7 nAChRs (Slemmer, Martin, & Damaj, 2000). In contrast, varenicline is a partial agonist at the α4β2 nicotinic acetylcholine (nAChR) receptor and a full agonist at the α7 nAChR (Mihalak, Carroll, & Luetje, 2006). Animal studies have demonstrated that varenicline reduces nicotine self-administration and reduces the amount of dopamine released by nicotine (Coe et al., 2005; Rollema et al., 2007). Despite these differences, several studies have demonstrated that both bupropion and varenicline may play a role in cognitive processes such as attention and working memory (Chan, Tsun-Hon Wong, & Sheu, 2007; Wilens et al., 2005).

During nicotine deprivation, many smokers report withdrawal symptoms such as difficulty concentrating, impatience, feeling easily distracted, and restlessness (Hughes, 2007). Thus, recent research has focused on cognitive processes as putative factors associated with relapse (Acheson & de Wit, 2008; Patterson et al., 2009; Sofuoglu, Herman, Mooney, & Waters, 2009). Several studies have demonstrated abstinence-related deficits in inhibitory control, attention, and response time (Ashare & Hawk, in press; Harrison, Coppola, & McKee, 2009; Myers, Taylor, Moolchan, & Heishman, 2008). Furthermore, there is evidence that bupropion and varenicline may alleviate some of these deficits (Acheson & de Wit, 2008; Patterson et al., 2009; Sofuoglu et al., 2009). For example, Acheson & de Wit (2008) found that bupropion decreased lapses in attention after overnight abstinence but had no effect on inhibitory control. Although varenicline generally speeds reaction time during abstinence, its effects on attention and working memory are less consistent (Patterson et al., 2010; Patterson et al., 2009; Sofuoglu et al., 2009). Whereas some have found that varenicline enhanced sustained attention and working memory after three days of abstinence (Patterson et al., 2009), others have found no effects of varenicline on these processes (Sofuoglu et al., 2009). These mixed findings suggest that it may be important to examine potential moderators, such as sex.

Although few studies have focused specifically on sex effects, some evidence suggests that males and females may experience differences in cognitive-related deficits during nicotine deprivation. Among adolescent smokers, males tend to exhibit greater cognitive-related deficits, whereas females tend to report greater subjective symptoms of craving and withdrawal during abstinence (Jacobsen et al., 2005). Other studies have found that both males and females demonstrate abstinence-related cognitive deficits, but they differ in the type of cognitive process affected by abstinence. For instance, when treated with transdermal nicotine during abstinence both males and females exhibited faster reaction times, but only females responded more accurately on a vigilance task (Trimmel & Wittberger, 2004). In a recent study, males had more difficulty inhibiting responses, whereas females had more difficulty screening out distracting stimuli after overnight abstinence (Ashare & Hawk, in press).

The purpose of the present study was to compare the two most effective pharmacological treatments for smoking cessation (i.e., bupropion and varenicline) to a placebo control among nicotine-deprived smokers. To our knowledge this is the first laboratory study to simultaneously examine the effect of both medications across a variety of cognitive processes, including attention, working memory, impulsivity, and reaction time. Secondarily, we sought to examine whether sex moderates medication effects on these processes. In a between-subjects design, we predicted that compared with placebo, bupropion and varenicline would speed reaction time, reduce attention deficits, enhance

working memory, and reduce impulsive choices on a delay discounting task. Based on the mixed findings regarding sex differences in medication effects, we had no a priori hypotheses regarding these relationships.

Method

Overview of Study Design

This study used a between-subjects, double-blind, placebo-controlled design to examine the effects of varenicline and bupropion compared with placebo. Participants were randomized to receive bupropion, varenicline, or placebo and completed an intake session, a physical exam, a 1-week medication run-up period, and one laboratory session. Participants could earn up to $345 for completing all study procedures. All participants were nicotine deprived for 18 hours at the time of cognitive testing. The current analyses focus on cognitive measures assessed during the laboratory session.

Participants

Participants were recruited through advertisements in local newspapers and postings in community locations (bars, coffee shops, grocery stores). Eligible participants were adult smokers (18–60 years of age) who reported smoking at least 10 cigarettes per day for the past year, had baseline carbon monoxide (CO) levels greater than 10 ppm, and had urine cotinine levels greater than 150 ng/ml. Exclusion criteria included meeting criteria for a current (past 6 months) Axis I disorder (excluding nicotine dependence and alcohol abuse), illicit drug use (except occasional cannabis use), currently seeking treatment for smoking cessation, use of psychoactive drugs in the past month, women who were pregnant or nursing, or medical conditions contraindicating smoking behavior or use of bupropion or varenicline. The sample for the current study consisted of 62 participants, although four did not complete the cognitive tasks leaving 58 participants (22 females, 36 males) with cognitive task data. The average age was 35.9 (SD = 10.1). Participants were primarily Caucasian (67.2%) or African American (25.9%), and were primarily either high school or college educated (51.7% and 50%, respectively). Participants smoked on average 18.7 (SD = 8.0) cigarettes per day, had baseline CO readings of 29.9 ppm (SD = 14.5), and average Fagerstrom Nicotine Dependence Scores (FTND; Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991) of 5.6 (SD = 2.2; range 1–10 for measure). Table 1 depicts demographic and smoking characteristics by medication group.

Procedure

Intake session—All participants provided written informed consent at the start of the intake session, and all procedures were approved by the Yale University Human Investigation Committee. Participants were then screened for inclusion/exclusion criteria and completed a physical exam, which included basic blood work, urine toxicology, and a pregnancy test. Participants provided demographic and smoking history information including a 30-day Timeline Followback (TLFB) assessment of smoking behavior (Sobell & Sobell, 1992). Breath CO levels were assessed with a CO monitor (MCO2 Monitor, MicroDirect, Auburn, ME), and breath alcohol levels were assessed (Alco-Sensor III, Intoximeter, St. Louis, MO).

Medication pretreatment period—Eligible participants were randomized to one of three treatment conditions (bupropion, varenicline, or placebo) stratified by sex and were on the assigned medication for one week before the laboratory session. One week of pretreatment for both bupropion and varenicline is the typical pretreatment period used in smoking cessation trials (before the quit day), as steady state levels are achieved within this timeframe (Jorenby et al., 2006; Jorenby et al., 1999). Varenicline was titrated to steady-

state levels over 7 days (.5 mg daily for Days 1–2, .5 mg twice daily for Days 3–5, and 1.0 mg twice daily on Days 6 and 7). Bupropion was titrated to steady-state levels over 7 days (150 mg daily for Days 1–3, 300 mg daily on Days 4–7). At each administration, participants consumed two capsules (consisting of active and/or placebo capsules dependent on medication condition and titration schedule). Side effects were monitored throughout the study, and all medications were well tolerated. No participants discontinued because of adverse side effects, and none of the side effects ratings exceeded a threshold of minimal or mild. Medication compliance (which was 100%) was monitored with pill counts and riboflavin markers (Del Boca, Kranzler, Brown, & Korner, 1996) on Days 1 and 4. During each visit throughout the run-up week, TLFB data for smoking and CO breath samples were collected and medication administration was witnessed by study staff.

Laboratory session—On Day 8, participants completed one 9.5-hr laboratory session at the Yale Center for Clinical Investigation. Participants were instructed to abstain from alcohol for 24 hours before the laboratory session and to smoke a final cigarette at 10:00 p.m. the night before the laboratory session. Eighteen-hour abstinence was confirmed with a CO level less than 50% of baseline and later confirmed with plasma nicotine less than 4 ng/ml. Laboratory sessions began at 9:00 a.m., and baseline assessments of breath alcohol, plasma cotinine and nicotine levels, blood hormone levels (i.e., estrogen and progesterone), urine drug screen (except for cannabis; $n = 5$), and urine pregnancy screen were obtained. The final dose of medication was provided at 10:00 a.m. Cognitive testing began at 3:00 p.m. and took approximately 45 minutes. Before that, participants completed measures of craving, withdrawal, and mood every two hours and relaxed in a comfortable room with TV, movies, and reading materials. Participants did not have access to cigarettes.

Measures: Craving, Withdrawal, and Mood

The 10-item Questionnaire of Smoking Urges - Brief (QSU-B; Cox, Tiffany, & Christen, 2001) was used to assess subjective craving and rated on a visual analog scale (VAS) ranging from 1 (“strongly disagree) to 100 (“strongly agree”). The eight-item Minnesota Withdrawal Scale (MNWS; Hughes & Hatsukami, 1986) assessed the degree to which smokers experienced withdrawal symptoms and was rated on a 0–32 scale (none, slight, mild, moderate, severe). Mood ratings were assessed on an 11-point scale with nine items representing the two dimensions (valence and arousal), which comprise the circumplex model of affective space (Russell, 1980). These dimensions create four quadrants: positive-high arousal items (active, peppy); positive-low arousal (quiet, relaxed); negative-high arousal (nervous, angry); and negative-low arousal (bored, sad). In the current study, high and low arousal items were combined to create positive and negative mood scales.

Measures: Cognitive Tasks

Conners’ Continuous Performance Test (CPT-II)—The CPT-II is a computerized assessment tool originally designed to aid in the identification of attention problems (Conners & Staff, 2000). The CPT-II has been used to measure the effects of cigarette smoking and nicotine deprivation (e.g., Harrison et al., 2009). During the 14-min-long task, participants viewed a series of letters on a computer monitor. They were instructed to respond as quickly as possible to target stimuli (all letters but “X”) and to refrain from responding to a more rarely occurring nontarget stimulus (“X”). The CPT-II provides several outcome measures including signal detection measures such as detectability (d'; calculated as the difference between hit rate and false alarm rate) and response style (β; a measure of an individual’s response tendency where lower values reflect a style in which individuals respond more freely to ensure they respond to most or all targets and are less concerned about mistakenly responding to a nontarget), hit reaction time (RT; reaction time in milliseconds to target), and standard error of hit RT (a measure of response variability).

Digit Span—Digit Span is a subtest of the Wechsler intelligence and memory batteries (Wechsler, 1997) and consists of two parts: forward and backward. In the current study, only the backward portion of the subtest was administered. Participants are read a series of numbers and are required to repeat the digit sequence back to the research assistant in reversed order. This task requires storage of information for mental manipulation of the digits and is considered a measure of working memory (Baddeley, 1992).

Delay discounting—Delay discounting was measured with the 27-item Kirby (Kirby & Marakovic, 1996) and was assessed during the intake and the laboratory session. For each item, participants choose between two hypothetical monetary amounts associated with different delays (e.g., "Would you prefer $33 today or $80 in 14 days?"). The data are fitted to a hyperbolic function described by the following equation (Mazur, 1987): $V = A/(1 + kD)$. Here, V represents the present value of the delayed reward A at delay D. The discounting rate is described by a constant, k, with larger k-values indicating preferences for smaller, immediate amounts over larger, delayed ones. Thus, larger k-values reflect higher levels of impulsiveness. Participants were assigned k-values for the small, medium, and large delayed rewards based on procedures described in previous work (Kirby, Petry, & Bickel, 1999). The average of the three k-values was used as the dependent variable.

Statistical Analysis

Dependent measures from the CPT-II were detectability (d'), response style (β), hit RT, and RT variability (standard error of hit RT). The dependent measure from backward Digit Span was the total number of correct trials. The dependent measure from the delay discounting measure was the natural log of the average k-value. For each dependent variable, an analysis of covariance (ANCOVA) was used with medication group (placebo, bupropion, and varenicline) and sex as between-subjects factors and baseline cigarettes smoked per day was a covariate. We examined whether there were baseline differences across groups in delay discounting, and this value was used as an additional covariate in an ANCOVA. A repeated measures ANCOVA was also conducted to assess change from the baseline to the laboratory session to evaluate potential differences attributable to withdrawal. Craving, withdrawal, and mood were assessed before cognitive testing and were examined in separate ANCOVAs controlling for baseline scores on each measure. Significant medication effects were followed up with planned contrasts comparing bupropion versus placebo and varenicline versus placebo because we had no a priori hypotheses regarding differences between bupropion and varenicline. When there were significant medication by sex interactions, follow-up tests were conducted to examine sex differences within each medication group. Because gonadal hormone levels may influence the effects of nicotine on females (Benowitz, 1996), we included estrogen and progesterone levels as covariates in preliminary models. There were no differences in estrogen or progesterone levels across medication groups, nor did including these variables as covariates substantially alter results. Therefore, hormone levels were removed from subsequent models.

Results

Participant Characteristics

Table 1 depicts demographic and smoking characteristics for the sample by medication group and sex. The medication groups did not differ on any variable, ps > .18. Women were less likely to be employed full-time, $\chi^2(1) = 4.2$, $p < .05$, but tended to be better educated, $\chi^2(2) = 3.0$, $p = .08$. Women smoked fewer cigarettes ($M = 15.7$, $SD = 8.0$) than men ($M = 20.2$, $SD = 7.6$), $F(1, 57) = 5.0$, $p < .05$. Overall, there were no significant changes across time in smoking behavior during the run-up week; $F(1, 57) = 1.0$, $p = .32$, nor did sex or medication group moderate this effect, Fs < 1. Furthermore, there were no significant

changes from baseline (Day 1) to Day 4 in CO breath levels; all Fs < 1.4, ps > 0.27. Change scores for cigarettes per day and CO during the run-up week are reported in Table 1.

Medication Effects on Craving, Withdrawal, and Mood

Craving—There was an overall effect of medication on craving, $F(2, 57) = 3.2$, $p = .05$. Separate contrasts suggested that varenicline ($M = 34.4$, $SE = 4.1$) significantly reduced craving compared with placebo ($M = 49.1$, $SE = 3.9$), $F(1, 37) = 4.5$, $p < .05$, $d = 0.83$, whereas bupropion ($M = 42.7$, $SE = 3.7$) did not, $F(1, 39) = 1.7$, $p = .20$, $d = 0.38$. There were no significant effects of sex or sex × medication interactions on craving, ps > .12.

Withdrawal—Sex significantly moderated the effect of medication on nicotine deprivation, sex × medication interaction, $F(2, 57) = 3.4$, $p < .05$. Follow-up tests revealed that for the placebo group there were no differences between males and females, mean difference = .543; $F < 1$. There were marginal sex effects for both bupropion and varenicline, $F(1, 20) = 3.1$, $p = .08$, $d = 0.84$ and $F(1, 17) = 3.7$, $p = .06$, $d = 0.98$, respectively. Males taking bupropion ($M = 2.86$, $SE = 0.78$) tended to report less withdrawal than females taking bupropion ($M = 4.48$, $SE = 0.73$). In contrast, females taking varenicline ($M = 2.80$, $SE = 0.78$) tended to report less withdrawal than males ($M = 4.69$, $SE = 0.62$).

Mood—There was a marginal medication × sex interaction on negative mood, $F(2, 57) = 2.8$, $p = .07$. Follow-up tests revealed that among those taking placebo, females ($M = 29.7$, $SE = 4.1$) reported significantly greater negative mood than males ($M = 18.47$, $SE = 3.38$), $F(1, 18) = 4.1$, $p < .05$, $d = 1.03$. In contrast, there were no sex differences among those taking bupropion; $F < 1$ or varenicline, $F(1, 18) = 1.5$, $p = .22$. There were no significant sex or medication effects on positive mood, all ps > .35.

Medication Effects on Cognitive Tasks

Continuous Performance Test (CPT-II)—The overall medication effect on detectability was not significant, $F(2, 57) = 2.4$, $p = .1$. However, during acute deprivation the varenicline group tended to perform worse than the placebo group, $F(1, 37) = 4.1$, $p = .05$, $d = .60$, bupropion versus placebo, $F < 1$ (Figure 1a). There were no significant effects of medication on response style, all ps > .26. There was an overall effect of medication on hit RT, $F(2, 57) = 4.8$, $p < .02$, and follow-up tests revealed that compared with placebo, the varenicline group responded faster, $F(1, 37) = 5.8$, $p < .03$, $d = .82$, whereas there was no effect of bupropion compared with placebo, $F < 1$ (Figure 1b). Similar to detectability, the overall medication effect on hit RT variability was not significant, $F(2, 57) = 1.8$, $p = .17$, but the varenicline group demonstrated less variability in response time compared with placebo, $F(1, 37) = 5.5$, $p < .03$, $d = .81$, bupropion versus placebo, $F < 1$. There were no significant main effects of sex or interactions with medication for any CPT-II measure, ps > .16.

Digit Span—For working memory, there was a significant sex × medication interaction, $F(2, 57) = 4.4$, $p < .03$, sex $F < 1$, medication $F(2, 57) = 3.8$, $p < .05$. Follow-up tests revealed that among the placebo group males ($M = 7.12$, $SE = 0.55$) tended to perform better than females ($M = 5.61$, $SE = 0.67$), though this effect was not statistically significant, $F(1, 17) = 2.8$, $p = .10$, $d = .86$. In contrast, among those taking bupropion, females ($M = 6.82$, $SE = 0.62$) tended to have more total correct responses than males ($M = 5.26$, $SE = 0.49$); $F(1, 20) = 3.9$, $p = .05$, $d = .94$. There were no differences between males ($M = 5.37$, $SE = 0.54$) and females ($M = 4.17$, $SE = 0.67$) in the varenicline group, $F(1, 17) = 2.0$, $p = .16$, $d = .72$ (see Figure 2).

Delay discounting—There were no significant medication group or sex differences in delay discounting at baseline, Fs < 1.9, ps > .18. For the ANCOVA including baseline delay discounting as a covariate, there was a significant sex × medication interaction, $F(2, 55) = 4.1$, $p < .03$, sex $F(1, 55) = 2.1$, $p = .15$, medication $F < 1$. Follow-up tests revealed that for the placebo group, males ($M = -3.40$, $SE = .35$) made more impulsive choices compared with females ($M = -4.71$, $SE = .44$), $F(1, 18) = 5.2$, $p < .03$, $d = 1.2$. In contrast, there were no significant sex differences for either the bupropion or varenicline groups, $F(1, 20) = 2.1$, $p = .16$, $d = 0.74$, and $F(1, 17) = 1.9$, $p = .17$, $d = 0.69$, respectively (see Figure 3). For the repeated measures ANCOVA for delay discounting, there were no significant changes across time from baseline to the nicotine deprivation session, all Fs < 2, ps > .18.

Discussion

Based on evidence that smokers may experience deficits in cognitive processes during abstinence (Heishman, Kleykamp, & Singleton, 2010), we tested whether the two most common pharmacological treatments for smoking cessation, bupropion and varenicline, reduce abstinence-related decrements in cognitive performance among nicotine-deprived smokers. The current results suggest that treatments for smoking cessation may influence specific cognitive deficits purported to be related to abstinence. In the present sample of adult smokers, individuals taking varenicline responded faster during a sustained attention task (e.g., CPT-II) compared with those taking placebo. Although we found limited effects on attention, the current data suggest that bupropion and varenicline may influence cognition differently for males and females. There were significant sex differences in medication effects on working memory and delay discounting. Each of these findings and the implications for future research are discussed.

In the current study, nicotine-deprived smokers responded more slowly on an attention task when taking placebo compared with those taking varenicline. In contrast, there were no differences in response time between the bupropion and placebo groups. This finding is consistent with previous research (e.g., Patterson et al., 2009; Sofuoglu et al., 2009) suggesting that varenicline may enhance cognition by speeding the processing of stimuli. Human and animal studies have demonstrated that nicotine speeds reaction time across a variety of tasks (for reviews, see Heishman et al., 2010; Levin, McClernon, & Rezvani, 2006). Given that varenicline may mimic the effects of nicotine by increasing dopaminergic neurotransmission in the mesolimbic pathway through its partial agonist properties, this may partially explain its effects on reaction time (Wouda et al., 2011). Importantly, slower reaction time is associated with faster time to smoking resumption (Patterson et al., 2010). Patterson and colleagues (2010) demonstrated that among smokers who received placebo, those who exhibited the slowest reaction times relapsed more quickly. In contrast, there was no relationship between reaction time and relapse among those who received varenicline. Although the current study did not directly assess relapse, these findings suggest one possible mechanism by which varenicline exerts its clinical effects.

For the working memory and delay discounting tasks, the current data suggest that bupropion may have sex-specific effects during nicotine deprivation. For example, males in the placebo group performed slightly better than females in the placebo group, although this difference was not statistically significant. Among those taking bupropion, females had more correct responses than males, but there were no sex differences among those taking varenicline. The current conclusions are limited by the fact that we do not have a baseline level of performance. However, other studies have demonstrated that varenicline did not improve working memory accuracy (Patterson et al., 2009). These data are consistent with the equivocal findings regarding the acute effects of nicotine, nicotine-deprivation, and pharmacological treatments on working memory (Heishman et al., 2010; Kleykamp,

Jennings, & Eissenberg, 2011; Kleykamp, Jennings, Sams, Weaver, & Eissenberg, 2008). These discrepancies may be attributable in part to methodological differences, such as the sample being studied (e.g., schizophrenic patients vs. healthy controls; Sacco, Bannon, & George, 2004) or the types of memory processes that may be important during abstinence (e.g., working memory vs. episodic memory; Heishman et al., 2010). Importantly, some evidence suggests that deficits in working memory are associated with treatment failure among smokers with schizophrenia (Moss et al., 2009), suggesting that individual differences in baseline functioning may be an important indicator.

In contrast to the effects on working memory, males in the placebo group made more impulsive choices compared with females in the placebo group. There were no sex differences in either the bupropion or varenicline group. Because baseline values of delay discounting were controlled for, the current findings suggest that pharmacological treatments for smoking cessation may decrease the discounting of delayed rewards, at least among males. This may be important in light of evidence that higher levels of impulsivity are associated with increased relapse rates (Krishnan-Sarin et al., 2007). This is partially consistent with previous work, which found that effects of bupropion enhanced attention but had no effect on impulsivity (Acheson & de Wit, 2008). Although more research is needed to replicate the current findings, it suggests that reducing impulsivity may represent an important treatment target, and among men bupropion may help increase the value of delayed rewards.

Contrary to our hypotheses, the current study did not find an effect of medication on our measure of sustained attention (e.g., d' from the CPT-II). In fact, post hoc tests suggested that the varenicline group tended to perform worse than either those taking placebo or bupropion. There may be several explanations for this finding. The effect size may be modest, making it difficult to detect an effect with a relatively small sample size. Although this finding should be replicated in a larger sample, the current findings are consistent with previous research. Whereas some studies report attentional enhancement with varenicline, others report no effect. A recent meta-analysis of the effects of nicotine on cognition suggests that nicotine's positive effects may not generalize to all attention tasks (Heishman et al., 2010). For example, Heishman and colleagues (2010) found positive effects of nicotine on "alerting attention" but not "orienting attention." Thus, it may be important to specifically test various types of attention in future studies of the effects of bupropion and varenicline on cognition.

Given the mixed findings for the effects of varenicline and bupropion on cognition during nicotine deprivation, the current study highlights the importance of understanding whether these effects are specific among particular groups of smokers. We found evidence of sex differences in the effect of medication on two of our three cognitive tasks. Women taking bupropion appeared to perform better on a working memory task compared with men taking bupropion. Furthermore, men taking placebo made more impulsive choices than women, but these sex differences were not evident for either the bupropion or varenicline group. The data from clinical trials indicate that there are few sex differences in abstinence rates for either bupropion or varenicline (Schnoll, Patterson, & Lerman, 2007). Given our relatively small sample size we must be cautious in our interpretation of these findings. However, the current study suggests potential sex differences in the mechanisms by which these pharmacological treatments may increase abstinence.

The current study also found that bupropion and varenicline, relative to placebo, attenuated increases in craving, withdrawal and negative affect associated with nicotine deprivation. These findings extend work from both clinical trials (West, Baker, Cappelleri, & Bushmakin, 2008) and laboratory studies (Acheson & de Wit, 2008; Patterson et al., 2009).

Although medication effects on craving did not vary by sex, the effects of medication on withdrawal were moderated by sex. Specifically, males taking bupropion reported less withdrawal than females, but the pattern was reversed for the varenicline group. Furthermore, the females in the placebo group reported greater negative mood compared with males in the placebo group. The pattern of means suggested that both bupropion and varenicline attenuated sex differences in negative mood. Many smokers report that increases in craving, withdrawal, and/or negative affect precipitated a lapse during a quit attempt, but this relationship is complex (Piasecki, 2006). In addition to sex, other individual difference factors may play an important role in moderating this relationship. Thus, it remains to be seen what role these constructs play in relapse and should be a focus of future research.

There are several limitations of the current study that warrant mention. First, individual difference factors, such as baseline performance, may play an important role in the effects of medication on cognition during nicotine deprivation. In the current study, we used a between-subjects design and, except for delay discounting, we did not have a measure of baseline performance. Therefore, it may be difficult to determine whether our findings represent medication effects of nicotine deprivation or direct effects of medication. However, this was a placebo-controlled design and the placebo group provides a control for estimating the effects of medication during nicotine deprivation. Thus, the question regarding whether these medication effects interact with deprivation effects remains. In addition, the between-subjects design may also represent a strength in that the medication effects cannot be attributed to carryover effects. As noted above, we did not directly assess relapse in the current study. Therefore, we can only speculate about the role of cognitive processes in relapse. However, human laboratory models of smoking relapse (for a review, see McKee, 2009) can provide insight into the role of withdrawal-related cognitive deficits in the ability to resist smoking.

In summary, we found that two of the most common pharmacological treatments for smoking cessation, bupropion and varenicline, may influence specific aspects of cognitive deficits among nicotine deprived smokers. We found that those taking varenicline responded faster during a sustained attention task compared with those taking placebo, but there was no difference in accuracy. This is consistent with previous findings (e.g., Sofuoglu et al., 2009), and the effect on response time is consistent with varenicline's partial agonist properties at various nicotinic receptors (Wouda et al., 2011). Furthermore, we found that females taking bupropion performed better on a working memory task compared with males. Males in the placebo group exhibited preferences for smaller, more immediate rewards compared with females in the placebo group. The fact that there were no sex differences for either bupropion or varenicline suggests that these medications may attenuate impulsive choices, specifically among males. The current data highlight the complex processes associated with nicotine deprivation and the need for future research to examine whether deficits in these processes are related to relapse. Elucidating the underlying mechanisms leading to vulnerability to relapse may help identify important targets for new pharmacological treatments.

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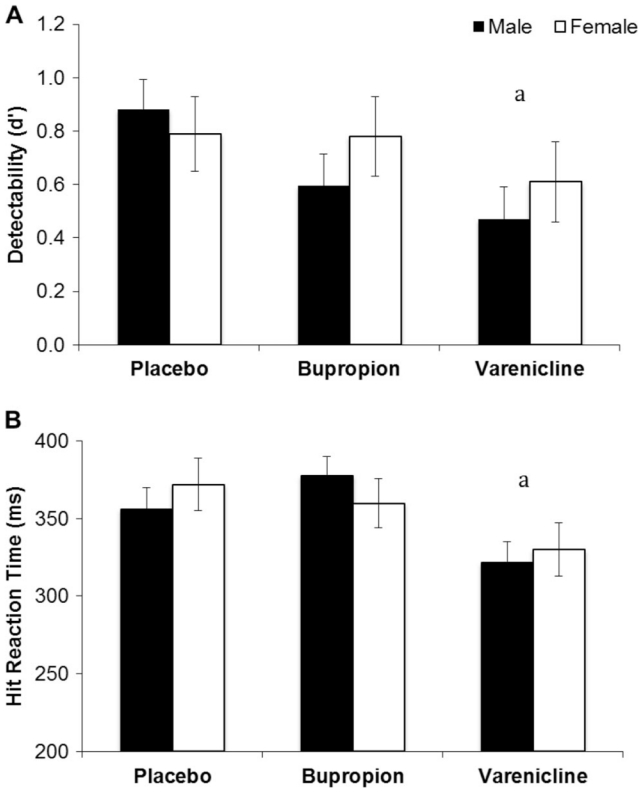

Figure 1.
Mean (*SE*) for detectability (A) and Hit reaction time (B) on CPT-II by medication group and sex. [a] varenicline group < placebo group, $p < .05$.

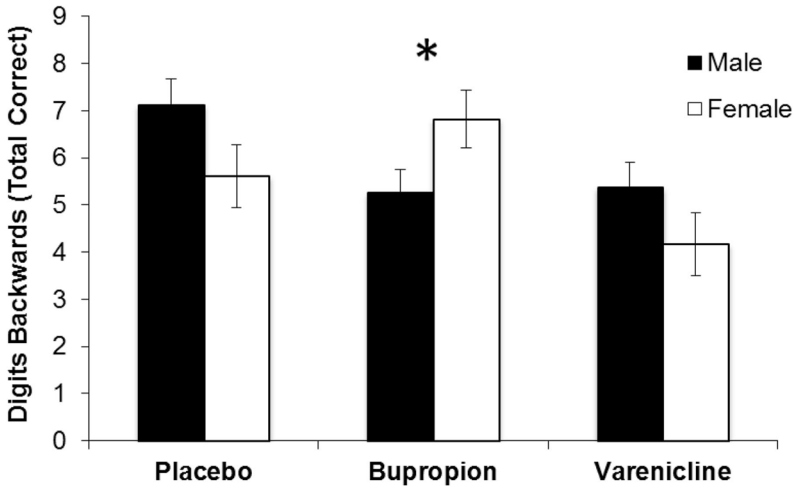

Figure 2.
Mean (*SE*) for Digit Span by medication group and sex. * $p < .05$.

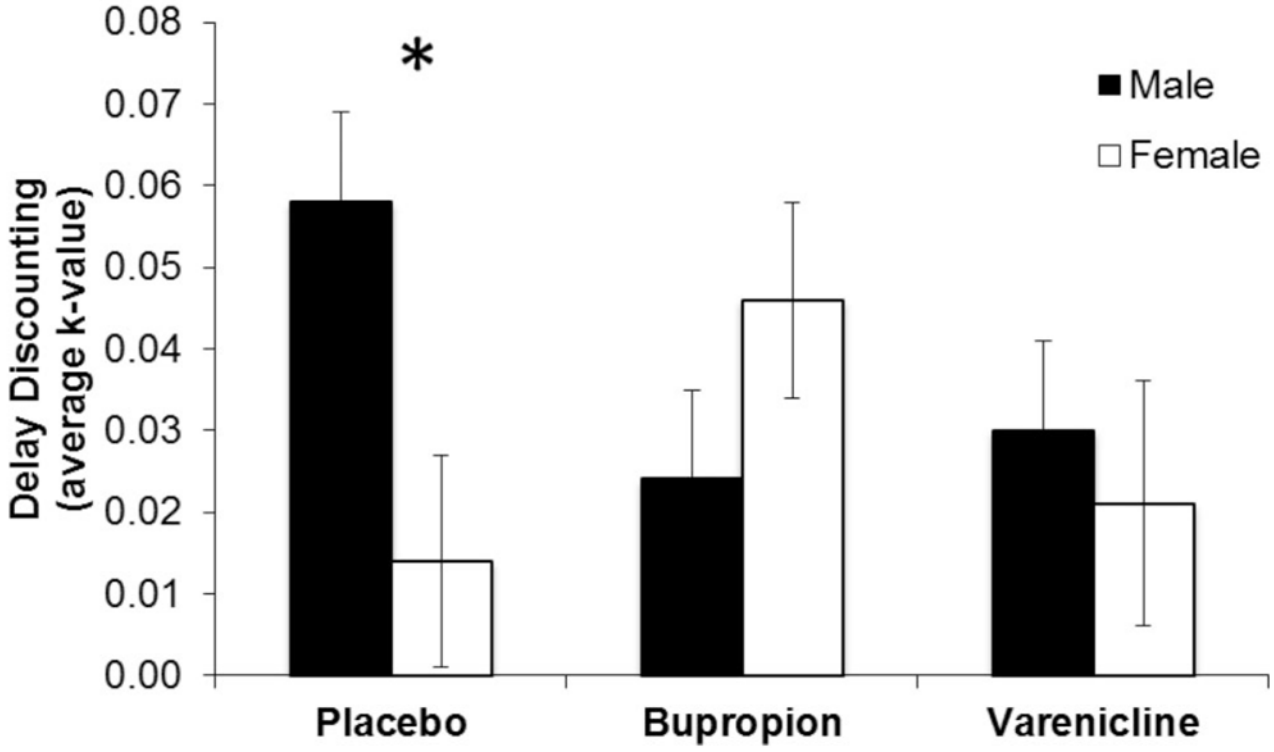

Figure 3.
Mean (*SE*) for delay discounting by medication group and sex. Values displayed are raw *k*-values. Natural log *k*-values were used in all analyses. * $p < .05$.

Table 1

Demographics and Smoking Characteristics by Medication Group and Sex (Total n = 58)

	Medication group					
	Placebo		Bupropion		Varenicline	
	Female (*n* = 7)	Male (*n* = 12)	Female (*n* = 8)	Male (*n* = 13)	Female (*n* = 7)	Male (*n* = 11)
Age	38 (9)	36 (11)	32 (9)	37 (10)	32 (12)	39 (11)
Ethnicity (% minority)	42.8%	33.3%	37.5%	23.1%	42.8%	45.5%
Education (% high school or less)	42.8%	58.3%	25%	46.2%	42.8%	72.7%
Employment (% full-time) *	14.2%	25%	0%	15.4%	0%	36.4%
DSM-IV alcohol abuse (n)	3	3	0	0	1	3
Alcohol use						
Number of drinks/week	6.5 (8)	14.5 (26)	7.5 (15)	6.2 (13)	6 (8)	9 (18)
Frequency of drinks/week (days)	1.6 (1.7)	2.2 (2.8)	1.5 (2.4)	1.0 (1.6)	1.5 (1.6)	1.5 (1.9)
Urine screen THC + (n)	0	3	1	1	0	0
FTND	4.4 (2.2)	6.6 (2.8)	5.8 (2.5)	5.7 (2.2)	5.3 (1.7)	5.3 (1.6)
CPD *	15.1 (8.2)	25.6 (7.8)	19.2 (8)	19.4 (7.2)	14.9 (9.2)	15.9 (4.9)
Baseline CO (ppm)	30 (9)	36 (19)	30 (14)	26 (11)	21 (13)	35 (15)
CPD change during run-up week	7.5%	13%	7%	21%	28%	14%
CO change during run-up week (ppm)	−13%	5%	−34%	−5%	3%	−27%

Note. Values are mean (*SD*), except where noted. Positive values for change scores represent a reduction in smoking/CO during the run-up week; Negative values indicate an increase.

CPD = cigarettes per day; FTND = Fagerstrom Test for Nicotine Dependence.

* sex difference, $p < .05$.