Psychopharmacology (2000) 148:33–40

ORIGINAL INVESTIGATION

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The effect of bupropion on nicotine craving and withdrawal

Received: 24 February 1999 / Final version: 15 August 1999

Abstract *Rationale and objectives:* Bupropion has demonstrated efficacy for smoking cessation. Given the importance of nicotine craving and withdrawal in the smoking cessation process, the current study examined the effects of bupropion on these parameters during smoking abstinence. *Methods:* During a 2-day Baseline phase with ad lib smoking, 91 non-depressed smokers (who were not trying to quit permanently) were administered measures of nicotine craving, withdrawal symptoms, and timed measures of cognitive performance five times daily. Participants were then assigned randomly to a 14-day treatment regimen with bupropion 300 mg/day, bupropion 150 mg/day, or placebo. Thereafter, the above measures were re-administered during 3 days of abstinence on a closed research ward. *Results:* Relative to placebo, 300 mg bupropion significantly reduced abstinence-associated increases in rated depression, difficulty concentrating, and irritability, and attenuated a decrease in positive affect. The results also suggested that bupropion might have a positive effect on performance measures during the withdrawal period. No effects were observed on craving, anxiety, restlessness, or hunger. The lack of findings on craving measures may be explained by a floor effect; except on the first day of abstinence, neither drug nor placebo groups showed much craving elevation during abstinence. *Conclusions:* Study results indicate that bupropion ameliorates some nicotine withdrawal symptoms.

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Key words Nicotine · Smoking cessation · Craving · Withdrawal · Bupropion

Introduction

Tobacco use is the leading cause of premature death in the United States (National Cancer Institute 1997). As the vast majority of smokers (70%) report wanting to quit smoking (US Centers for Disease Control and Prevention 1994), finding effective methods of smoking cessation challenges health care professionals to explore innovative approaches to treating nicotine addiction.

Pharmacologic aids have become central in smoking cessation treatment, as indicated by the recent guidelines issued by the Agency for Health Care Policy and Research (US Department of Health and Human Services 1996). The efficacy of nicotine replacement therapy (NRT), the major form of pharmacologic therapy for smoking cessation, has been well established (Fiore et al. 1994; Silagy et al. 1994; Tang et al. 1994). The mechanism most often cited to explain NRT's efficacy is relief of craving and withdrawal (Benowitz 1993; Hughes and Glaser 1993). Both nicotine polacrilex gum and transdermal nicotine have been shown to reduce the intensity of craving and nicotine withdrawal symptoms associated with smoking cessation (Transdermal Nicotine Study Group 1991; Sachs et al. 1993). Nicotine craving and disturbed affect, central elements of nicotine withdrawal (American Psychiatric Association 1994), are particularly important clinical symptoms, as they are often thought to be responsible for smoking relapse (Brandon et al. 1987, 1990; Killen et al. 1991; Glassman 1993; Shiffman et al. 1996).

A drug recently approved by the FDA as an aid to smoking cessation is a sustained-release form of bupropion (BP) (Zyban, Glaxo Wellcome, Inc.), an aminoketone marketed since 1989 for use as an antidepressant. BP is primarily a noradrenergic agonist, but also has some dopaminergic activity (Ferris and Cooper 1993; Settle 1993). The drug's primary mechanism of action in

smoking cessation is unknown, and may be different from that of NRT.

Initial interest in BP as an aid to smoking cessation arose from anecdotal reports of successful quit attempts by smokers prescribed the drug for its antidepressant properties. Subsequently, four placebo-controlled, double-blind studies have demonstrated BP to be efficacious as an aid to smoking cessation (Ferry et al. 1992; Ferry and Burchette 1994; Hurt et al. 1997; Jorenby et al. 1999). Although the FDA-approved labeling notes some effect against craving and withdrawal, published data have yet to establish the efficacy of BP against craving. The two published studies addressing this question (Hurt et al. 1997; Jorenby et al. 1999) report conflicting results of a treatment effect on composite withdrawal scores that included craving. These data question whether the mechanism of action of BP on cessation may, at least, in part, be separate from relief of craving and withdrawal and craving symptoms.

Clinical studies may not accurately reflect effects on craving and withdrawal, as those with the most intense symptoms may relapse, complicating analysis. Also, craving and withdrawal tend to diminish with sustained abstinence. Thus, clinical trials may confound abstinence and symptoms. The purpose of the current study was to assess the effect of BP on craving and nicotine withdrawal during smoking abstinence in a clinical laboratory setting. In addition to assessing subjective craving and withdrawal symptoms, we also objectively assessed cognitive performance, which has also been shown to degrade when smokers are nicotine deprived (Snyder and Henningfield 1989; Snyder et al. 1989).

It has been proposed that BP might deter smoking by blocking reinforcement from smoking (especially when treatment is started before the patient quits smoking), which might account for anecdotal reports of loss of desire to smoke. Accordingly, we also assessed the effect of BP on smokers' evaluative responses to the first cigarette smoked after the 72-h abstinence.

Materials and methods

Overview

This was a parallel, randomized, double-blind study comparing the efficacy of treatment with BP 150 mg/day, BP 300 mg/day (titrated from 150 mg/day on the first 3 treatment days followed by 300 mg/day for the remainder of the study), and placebo on nicotine craving and withdrawal.

Participants were non-depressed, highly nicotine-dependent smokers who were not trying to quit smoking. Measures included self-reports of craving and nicotine withdrawal, as well as performance on math, logic and reaction-time tasks. Figure 1 represents the study timeline. Baseline craving and withdrawal were assessed five times daily for 2 days during ad lib smoking (Baseline phase). This was followed by 14 days of treatment with the assigned study drug, while smoking ad lib (Treatment phase). After this, craving and withdrawal were re-assessed (again, five times daily) during 3 days of smoking abstinence, with continued treatment with the assigned study drug (Abstinence phase). Finally, treatment was terminated; participants resumed smoking, and rated their satisfaction with their first cigarette after abstinence (Resumption phase).

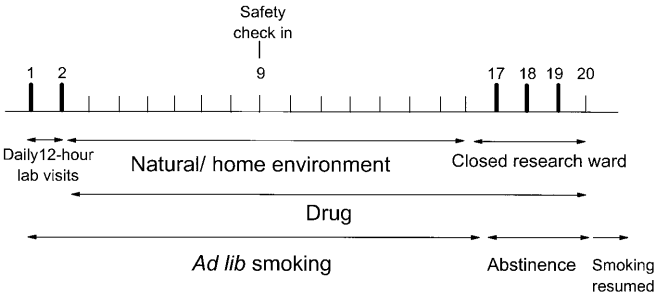

Fig. 1 Study timeline. *Numbers* denote study day; *thick vertical lines* denote assessment days. During the Baseline phase (study days 1 and 2), participants smoked ad libitum during daily 12-h visits to the study site. The Treatment phase consisted of study days 3–16. Participants self-administered study drug in the home environment while continuing ad libitum smoking. During the Abstinence phase (days 17–19), participants were housed in the closed research site while abstaining from smoking. On day 20, participants resumed ad libitum smoking (Resumption phase)

The Institutional Review Board of the University of Pittsburgh approved study procedures.

Participants

Participants were 109 chronic, heavy cigarette smokers. They were recruited through newspaper advertisements and were paid $850.00 for their participation. To qualify, participants had to have been aged 20–55 years, have smoked an average of ≥25 cigarettes a day for the past 5 years, have baseline serum cotinine concentrations >200 ng/ml and expired air carbon monoxide level >10 ppm, Fagerstrom Tolerance Questionnaire scores >7, and have had difficulty abstaining from smoking in the past (>2 on a relevant question). To perform cognitive tests, participants had to demonstrate basic math and logical reasoning skills. Participants were required to be in good health (verified by physical examination, 12-lead electrocardiogram, clinical labs and chest X-ray). Exclusion criteria included factors related to susceptibility to seizure, such as the presence or family history of a seizure disorder, a history of head trauma, predisposition to seizures (such as a history of stroke or brain tumor), or current use of medications or treatment regimens that lower seizure threshold. Other exclusionary criteria were current episode of major depression, history or current diagnosis of anorexia nervosa, bulimia, schizophrenia, bipolar disorder, panic disorder, obsessive-compulsive disorder, history of dependence on alcohol or a non-nicotine substance within the past year, current illicit drug use (verified by urine drug screen), use of psychoactive or investigational drug within 4 weeks of the study treatment phase, clinically significant history of cardiovascular, respiratory, endocrine, hepatic (including a history of hepatitis), genitourinary or gastrointestinal disease or a disease or disorder that would have interfered with the absorption, distribution, metabolism, or excretion of drugs, history of adverse reactions to any drug, medical dressings or tape, history of abnormal bleeding tendencies, prior treatment with BP, concurrent treatment for smoking cessation, or use of tobacco products other than cigarettes. Pregnant or lactating women were excluded, as were women of childbearing potential who were not using an effective contraceptive method.

Twelve of the 109 participants enrolled in the study did not complete the Baseline phase (consent withdrawn, n=5; failure to meet inclusion/exclusion criteria, n=7) and were never randomized to treatment. Of the 97 participants randomized, five were discontinued prematurely: two for protocol violation (both BP300, both positive urine drug screen for cocaine on study day 16), two (both PBO) voluntarily withdrew consent on days 17–18, and one (PBO) for an adverse experience (hives) on day 18. In addition,

one participant (PBO) violated the protocol by smuggling cigarettes into the study site and smoking (confirmed by plasma nicotine content) during the Abstinence phase. Data from these six participants were excluded from statistical analyses.

Most of the 91 participants who contributed data to the analyses were male (59%), and Caucasian (81%). Their average age was 34.5 (SD=9.02) years, and they had been smoking for 19.2 (SD=8.67) years. At enrollment, these participants reported averaging 35.5 (SD=9.32) cigarettes per day and 1.8 (SD=3.43) previous quit attempts. The mean Fagerstrom Tolerance score for this sample was 9.3 (SD=1.17). Nine participants (10%) (four BP150, three BP300, and two PBO) had a prior history of major depression, one of whom (BP300) met diagnostic criteria for current dysthymia. There were no significant differences between the three treatment groups on any of these characteristics.

Procedure

Data were collected on a residential research unit using a palmtop computer, which was referred to as the Electronic Diary (ED). The study was divided into five phases: Training, Baseline, Treatment, Abstinence, and Resumption.

Training

Participants were trained in the use of the ED (through instruction and practice with feedback) in a group session on the day preceding study day 1. Each of the self-reported symptom descriptors was defined, and participants completed three practice trials of the assessment of nicotine craving and withdrawal over the course of training. Participants practiced two trials of the Reaction Time task. To develop a stable baseline for the Math and Logic tasks, participants practiced extensively until they had completed 11 trials or until their performance had clearly improved and then reached a plateau (as indicated by trend analyses of their scores).

Baseline phase (study days 1–2)

During this phase, participants smoked ad libitum during two 12-h days at the study site. (Participants were tested at the study site but released for the evening.) Beginning at 8:00 a.m. and at 3-h intervals thereafter (each day at 8 a.m., 11 a.m., 2 p.m., 5 p.m., and 8 p.m.), participants completed the nicotine craving and withdrawal assessment and performance assessments, and vital signs were tested. Expired air carbon monoxide (CO) measures were taken at 11:00 a.m. and 8:00 p.m.; sleep disturbance was assessed at 8:00 a.m., soon after participants arrived.

Treatment phase (study days 3–16)

During this phase, participants self-administered study medication in their home environment. Participants were instructed to maintain their typical smoking rate and intake of coffee, tea, or other xanthine-containing beverages or food, and to abstain from alcohol and illicit drugs during their participation in the study. On study day 9, participants visited the laboratory for safety assessment; vital signs, blood sample for serum cotinine and a CO sample were collected, and concomitant medications were reviewed.

Abstinence phase (study days 17–19)

On the afternoon of day 16, participants returned to the study site, where they were housed for the following 4 days and nights. During their stay, participants engaged in unstructured leisure activities, were served three meals and an evening snack daily, and had access to a variety of snacks and non-alcoholic beverages of their choosing. Research personnel dispensed study medication. On day 16, participants were instructed to continue smoking normally. Assessment procedures were reviewed, and participants completed one assessment to refamiliarize them with the procedure. Smoking abstinence began at 8 a.m. on day 17. Participants were directed to smoke a cigarette immediately prior to the 8:00 a.m. assessment. During this phase, the assessments were administered five times daily, following the schedule used in the Baseline phase, above. Vital signs were checked and a blood sample for tests of serum cotinine and/or plasma concentrations of BP and its major metabolites was collected after each administration of the assessments. CO measurements were conducted after the second and fifth assessment each day. The final treatment dose was administered on day 19.

Resumption phase (study day 20)

On the morning of day 20, 72 h after the start of the Abstinence phase, participants completed a final nicotine craving and withdrawal assessment, vital signs were checked, and a CO sample was collected. Immediately following, participants were instructed to smoke a single cigarette. Five minutes after this cigarette, a CO sample was collected, and the participants completed a smoking satisfaction questionnaire. Ad libitum smoking was resumed, and participants were released.

Instrumentation

Participants completed assessments of craving and nicotine withdrawal symptoms and several performance tasks on the ED, a palm-top computer that administered assessments and stored the data for later analyses. ED is described in Shiffman et al. (1996) and has been used in other studies (Shiffman et al. 1995; Paty 1997). Entry of self-report data on ED precludes missing data (i.e., skipped items) and entry of out-of-range values. ED can also administer cognitive tasks requiring precise timing of stimulus presentation and response latency.

Assessments

Nicotine craving and withdrawal self report

To assess nicotine craving and withdrawal symptoms, participants were serially presented with 30 symptom descriptors (see Data reduction and screening for a list of symptom descriptors), rating each on a 4-point intensity scale (NO!!, no??, yes??, YES!!). Symptom descriptors were designed to represent symptoms of nicotine withdrawal from the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV; American Psychiatric Association 1994) as well as assessing symptoms of nicotine craving.

Performance assessment

At each assessment, following the symptom assessment, participants were presented with the following timed performance tasks (see Shiffman et al. 1995), in random order: (1) *Simple Reaction Time*: participants responded as quickly as possible to the appearance of an obvious on-screen stimulus by pressing any key; (2) *Mental Arithmetic (Math)*: participants were to add or multiply two serially presented numbers and select the correct response from displayed options by pressing the corresponding key; (3) *Logic*: participants assessed the truth of statements about the spatial relationship between two on-screen symbols. Response latency and accuracy were recorded for each task. We scored the percentage of correct problem solutions and median response latency on correct responses (the median minimizes the influence of outlying data points; analysis of correct responses makes response latency somewhat independent of correct task solution). Percent correct data were arcsine transformed prior to analysis.

Sleep Disturbance Questionnaire

In order to assess BP's effect on insomnia, an additional DSM-IV criterion for nicotine withdrawal, participants completed the Sleep Disturbance Questionnaire. At the 8 a.m. assessment on each assessment day, participants rated their prior night's sleep, reporting difficulty falling asleep, the degree to which they felt well rested (NO!!, no??, yes??, YES!!), and the number of times they awoke through the night.

Day 20 smoking satisfaction

Participants reported their response to the first cigarette they smoked after the 72-h Abstinence period by completing a 13-item Smoking Satisfaction Questionnaire derived from the Cigarette Evaluation Scale (CES; Westman et al. 1992). Items on the questionnaire were designed to measure subjective satisfaction with smoking. Domains assessed included: taste/strength of cigarette, satisfaction with cigarette (was it satisfying?, did you like it?), and cognitive/physiological effects of smoking (help you concentrate?, less irritable?, reduce craving?). Data from the 13-item questionnaire were factor analyzed; three factors, accounting for 69% of the item variance, were retained: smoking satisfaction, reduced craving and irritability, and strength of cigarette. Factor scores were computed (expressed as T-scores) for each assessment and used in analysis.

Safety assessments

Safety assessments during the study included vital signs (sitting blood pressure and pulse) and monitoring for spontaneously reported adverse experiences during the Baseline, Treatment and Resumption phases.

Data reduction and screening

Nicotine craving and withdrawal symptom self report

Nicotine craving and withdrawal items were grouped conceptually according to DSM-IV criteria for nicotine withdrawal, with an additional group to assess craving. This yielded seven summary scores, which assessed craving (Need a cigarette?, Smoking now would be a relief?, Urge to smoke?, Smoking now would be satisfying?, Want to smoke?, Crave a cigarette?), depression (Depressed?, Sad?, Blue?, Miserable?, Happy?, Enthusiastic?), irritability (Contented?, At Ease?, Irritable?, Frustrated/Angry?), anxiety (Tense?, Anxious?, Calm?), hunger (Hungry?, Desire sweets?), difficulty concentrating (Spacey?, Hard to concentrate?, Mentally sharp?, Alert?), and restlessness (Restless?). Four additional items (Energetic?, High Energy?, Sleepy?, Tired?) were presented in the assessment, but were not used in the analyses. For each assessment, mean scores were calculated for each DSM-IV category.

Math and Logic tasks

To be included in analysis, participants needed to demonstrate task mastery, operationalized as correctly responding at a better than chance rate across assessments on study day 2. This criterion was met by all participants for the Math task, and by 80 participants for the Logic task. Learning effects on study day 1 were also assessed (by repeated-measures ANOVA on trends) to ensure a stable baseline measurement. Because the analysis showed continued improvement over day 1 on both the Math and Logic tasks, only day 2 data were used as the baseline measure. For the Math task, correctly answering fewer than 25% was considered to be chance responding (based on a binomial distribution; the task required selecting from among six responses). On the Logic task, which was a True-False task, less than 60% accuracy was considered to be chance responding.

Data analysis

Group differences in dependent variable changes from Baseline phase to Abstinence phase were of central interest in this study. We first assessed phase-related changes in the placebo group, in order to evaluate the measures' ability to detect withdrawal effects. Treatment effects in changes from Baseline to Abstinence were assessed with 3×2 (treatment group×phase) mixed-model ANOVAs. Significant group×phase interactions indicated an effect of BP treatment. Because the 150 mg and 300 mg doses of BP frequently yielded different effects, we report the results for each dose, rather than reporting the overall contrast of BP versus placebo. The Abstinence phase was defined to include only days 18–19, because participants smoked at the beginning of day 17. Conversely, the data from day 17 provided an opportunity to observe the acute emergence of craving and withdrawal during the first 12 h of abstinence. Such detailed assessments may reveal effects that are hard to detect in larger time blocks. Because abstinence began immediately after participants smoked at the beginning of day 17, we expected craving and withdrawal to increase over the day, reflecting the onset of withdrawal. Analyses examined the trend over assessments within the day (i.e., with progressively longer abstinence), while controlling for within-day trends during Baseline.

Results

Treatment compliance

Participants were highly compliant with the medication regimen. Percent compliance (total mg taken/total mg prescribed) was calculated beginning on study day 3 (first day of the treatment phase). The average compliance rate across groups was 99% (BP150=98.3%, BP300=98.9%, and PBO=99.1%), and all participants reported at least 88% compliance.

Abstinence phase (days 18–19)

We first evaluated the changes from Baseline to Abstinence observed in the PBO group, which reflect our assessment of nicotine withdrawal. In the PBO group, depression, irritability, anxiety, and difficulty concentrating increased significantly during the Abstinence period, $ts(27)>4.30$, all $Ps<0.0005$, while hunger decreased significantly during the Abstinence period, $t(27)=-2.13$, $P<0.05$. There was no effect of abstinence on craving in the PBO group.

Relative to PBO, BP300 treatment significantly attenuated abstinence-related increases in depression, irritability, and difficulty concentrating, $F(1,88)>9.15$, $Ps<0.01$. BP150 also significantly attenuated increases in irritability, $F(1,88)=7.34$, $P<0.01$ (Fig. 2), but not in depression or difficulty concentrating. Neither dose of BP affected the observed changes in anxiety and hunger. No significant BP effect was noted for craving.

Performance tasks

In the PBO group, median response latency for correct responses on Math and Logic decreased from Baseline to

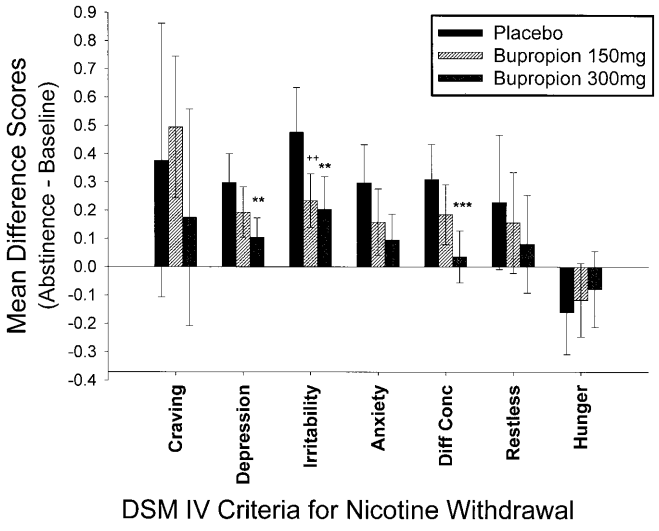

Fig. 2 Changes in nicotine withdrawal symptoms from baseline to abstinence for each treatment group. Means were calculated using all scores from all assessments completed on days 1 and 2 (Baseline) and days 18 and 19 (Abstinence). *Error bars* indicate SEM. BP300 vs PBO: **P*<0.05; ***P*<0.01; ****P*<0.001. BP150 vs PBO: +*P*<0.05; ++*P*<0.01; +++*P*<0.001

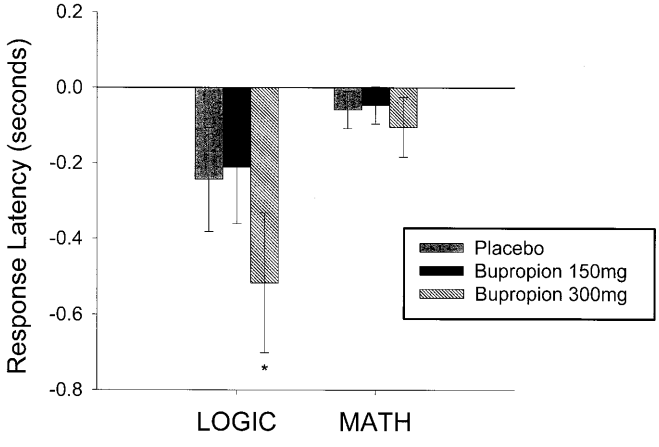

Fig. 3 Changes in math and logic response latency and accuracy from baseline to abstinence for each treatment group. *Error bars* indicate SEM. BP300 vs PBO: **P*<0.05; ***P*<0.01; ****P*<0.001. BP150 vs PBO: +*P*<0.05; ++*P*<0.01; +++*P*<0.001

Abstinence, and evidence of performance improvements from day 18 to day 19, suggesting continued improvement due to a practice effect. However, it is still possible to assess the effect of treatment, as abstinence-related decrements and training-related improvements in performance can coexist in the data, and contrasts between BP-treated and PBO-treated subjects can still illuminate the effects of BP. In the Logic task, participants treated with BP300 showed shorter response latencies than those on placebo, $F(1,71)=5.88$, $P<0.05$ (Fig. 3). BP treatment also seemed to improve response accuracy. Although neither BP dose individually met criteria for significance, there was an overall effect of BP treatment, $F(2,71)=3.83$, $P<0.05$. The data suggest that the effect was driven by the 300 mg dose, $F(1,71)=3.68$, $P<0.06$; BP150 had no effect. BP treatment had no significant effect on changes in Math response latency or accuracy from Baseline to Abstinence. There was neither an effect for abstinence nor BP treatment, on the Reaction Time task.

Sleep disturbance

The three items from the sleep disturbance questionnaire were factor analyzed to calculate a single score (from a one-factor solution) for each assessment; factor scores were expressed as T-scores (M=50, SD=10). No abstinence-induced changes in sleep were observed in the PBO group, and no effects of BP were detected.

Day 17: acute abstinence effects

Data from day 17, when participants first began to abstain, were analyzed separately to assess the effect of BP treatment on acute withdrawal effects associated with the onset and initial progression of nicotine abstinence. The analysis examined trends in response over the course of the five assessments on day 17, which represented progressively longer nicotine deprivation. Specifically, assessment number (1–5) was included as an additional within-subject factor in the ANOVAs. The three-way interactions in the resulting 3×2×5 [treatment group×phase (Baseline versus day 17)×assessment number] ANOVAs tested whether BP treatment moderated changes over the course of day 17, while controlling for Baseline trends.

As before, we first tested the trends in the PBO group, to establish the effects of withdrawal, then examined BP treatment effects. In the PBO group, craving increased significantly as abstinence proceeded over the course of day 17, relative to Baseline, $F(4,24)=3.28$, $P<0.05$ (see Fig. 4). Thus, in contrast to the test of craving effects on days 18 and 19, the trend over day 17 assessments was sensitive to abstinence effects. BP treatment had no effect on this trend. Hunger was observed to decrease over day 17, $F(4,24)=4.58$, $P<0.01$; BP had no effect. No other time effects or treatment effects were observed.

Performance tasks

No significant phase×assessment interactions were observed in the PBO group for any performance task variable on day 17. However, a significant group×phase×assessment interaction was observed in the Reaction Time Task, $F(8,170)=2.60$, $P<0.05$, due to decreases in response accuracy over time in the BP150 group.

Smoking satisfaction questionnaire

Eighteen participants (eight BP150, five BP300, five PBO) declined to smoke a cigarette on study day 20

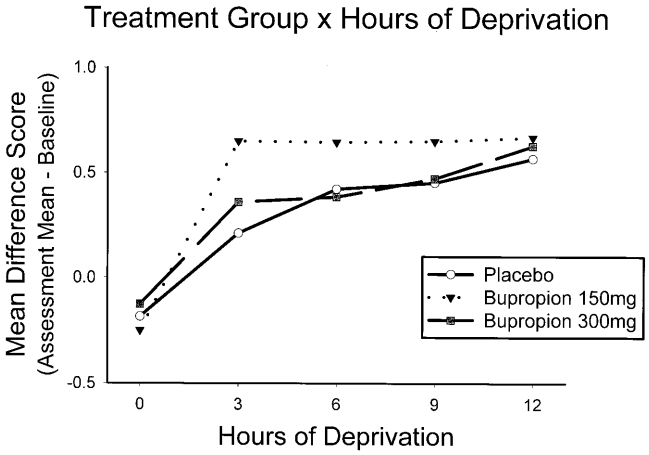

Fig. 4 Baseline-adjusted craving over day 17 for each treatment group

when instructed to do so. These participants did not complete the smoking satisfaction questionnaire, leaving 73 completed assessments. There were no BP effects on any of the three factors: smoking satisfaction (PBO, M=52.98, SD=9.88; BP150, M=48.59, SD=11.052; BP300, M=48.73, SD=8.89), reduced craving and irritability (PBO, M=52.56, SD=11.53; BP150, M=49.01, SD=10.05; BP300, M=48.77, SD=8.43) and strength of cigarette (PBO, M=51.71, SD=10.43; BP150, M=50.78, SD=8.77; BP300, M=47.86, SD=10.66).

Adverse events

Twenty percent of participants reported at least one adverse event, but all event types were equally common among PBO and BP groups.

Discussion

Prior research has shown that bupropion is an effective treatment for smoking cessation. The present results demonstrate that a 300 mg/day dose of BP has some efficacy against withdrawal symptoms. On days 2 and 3 of abstinence, BP attenuated abstinence-associated increases in several DSM-IV symptoms of nicotine withdrawal: depression, irritability, and difficulty concentrating. However, no BP effects were observed for other symptoms such as anxiety, restlessness, and hunger. Other analyses suggested that BP's effects might be concentrated in the domain of affective symptoms. We also performed analyses based on empirically derived scores based on factor analysis. The analysis yielded seven factors accounting for 68% of the item variance: Craving, Positive affect, Fatigue, Tension, Difficulty concentrating, Hunger, and Depression. (Despite the similar labels, item composition differed from that of the DSM-IV scoring.) Besides Craving, the "positive affect" factor was significantly affected by BP treatment: BP300 treatment significantly decreased abstinence-related decreases in factor-scored positive affect, $F(1,88)=8.55$, $P<0.01$. This effect on withdrawal-induced affective disturbance may be partially responsible for BP's efficacy in smoking cessation.

In this study, there was no evidence of a BP effect on nicotine craving. On day 17, the first day of abstinence, craving increased over the course of the day as deprivation increased. BP treatment did not blunt this abstinence-induced increase. Craving did not increase in the placebo group during days 2 and 3 of smoking abstinence, making the effects of BP on craving on those days difficult to evaluate. Other literature suggests that craving may show only transient increases during abstinence (e.g., Shiffman et al. 1997). The day 17 assessments may have tapped these initial increases, while reduction in craving – due to both the passage of time and to acclimatization to an environment with few smoking stimuli – may have impeded assessment of craving on days 18 and 19. Inconsistent results in the current literature further complicate the understanding of BP's effect on craving. The only other published studies on symptom relief (Hurt et al. 1997; Jorenby et al. 1999) have reported conflicting results regarding BP's effect on a symptom composite that included craving. However, the FDA-mandated labeling for Zyban suggests that it may have some inconsistent or intermittent effect on craving. More complex analyses by Grasela et al. (1998), taking into account symptom trends over time, did demonstrate some craving relief of craving.

The lack of clear effects on craving suggests that craving relief may not be central to BP's effect on abstinence: BP promotes abstinence in the absence of a measurable effect on craving. NRT has more consistently been demonstrated to relieve withdrawal-induced affective disturbance and craving, which may serve as its primary mechanism of action (Abelin et al. 1989; Rose et al. 1990; Tonnesen et al. 1991; Transdermal Nicotine Study Group 1991; Sachs et al. 1993).

BP showed a modest influence on cognitive performance. Henningfield and colleagues (Snyder and Henningfield 1989; Snyder et al. 1989) have documented that nicotine withdrawal decreases both logic and math performance, and that these decrements are reversible through administration of nicotine (via nicotine medications). In this study, performance testing indicated that 300 mg/day of BP may help moderate some of the performance decrement observed in nicotine withdrawal. The fact that even smokers on PBO showed improved, rather than impaired, performance, suggests that subjects were still learning the task, and complicates interpretation of these data. No withdrawal-induced performance impairments could be detected in this study. However, BP-treated smokers showed more improvement than PBO during abstinence, suggesting a positive effect on performance in withdrawal. That no effects were seen for performance on simple Reaction Time or on the Math task suggests that this is not a very robust or general effect.

What is the mechanism by which BP promotes smoking cessation? The fact the BP seemed primarily to blunt

mood affective changes might lead to speculation that the therapeutic effect of BP was due to its antidepressant effects. That is unlikely, as participants with current major depression were excluded from the study, and only about 10% of those included had a lifetime history of depression.

It has been speculated that BP might impact smoking and cessation in part by reducing the satisfaction and reinforcement smokers derive from cigarettes. This speculation is fueled by the fact that BP treatment is often started prior to smoking cessation (to allow BP levels to reach steady state), thus exposing smokers to smoking while on BP and hypothetically providing an opportunity to extinguish the reinforcing effects of smoking. However, we found no effect of BP treatment on smoking satisfaction. Our assessment was limited to a single cigarette, smoked after 3 days of abstinence. It is possible that an effect on smoking satisfaction would be seen under repeated, normal smoking under BP maintenance. For now, this mechanism remains to be proven.

The mechanism by which BP affects smoking cessation and withdrawal is unknown. BP has noradrenergic activity and, to a lesser extent, dopaminergic activity that may result in activation and mood elevation, or may partially mimic nicotine effects. It is unlikely that BP promotes abstinence from smoking by blunting craving and withdrawal, as its effects on abstinence seem more robust than those on craving or withdrawal.

Design considerations and limitations

Several limitations in the study's design and results limit our conclusions. Although the study did produce increases in craving very early in abstinence, no sustained increase in craving was observed during days 2 and 3 of abstinence, perhaps because of the sterile environment of a research ward. Hughes et al. (1984) have also noted that lack of environmental cues related to smoking can suppress craving. The inpatient setting during abstinence may also have accounted for the paradoxical decrease in hunger during that 72-h period because of the unlimited access to snacks (see Gilbert and Pope 1982; Perkins et al. 1995).

As the sample of participants in the current study were chronic, heavy smokers, highly dependent on nicotine, one must be cautious in generalizing the results to the smoking population at large. Interpretation of current results is limited further by the study design. The sequence of conditions (Baseline followed by Abstinence) was fixed: therefore, sequential effects (e.g., fatigue, learning of tasks) were not controlled in the design. However, BP's effects should be isolated by the PBO group comparisons. Because all participants abstained during the second assessment phase, we cannot separate the effects of treatment from those of smoking abstinence on the dependent measures. Study design also limited assessment of BP's effects, as the analysis was restricted to very short-term withdrawal effects due to the short abstinence period. An analysis of a longer course of withdrawal might have revealed additional treatment effects.

Finally, the design did not specifically assess the effects of BP during continued smoking. Participants were observed while smoking prior to BP administration, and in abstinence after BP treatment. Thus, the design cannot distinguish BP effects specific to nicotine withdrawal from more general BP effects that might be evident even during smoking. We had administered a single assessment, for practice, on day 16, while subjects were still smoking. This assessment showed no BP effects on any measure, but a single practice assessment was not considered a reliable or adequate measure of this effect. This remains a task for future research.

The study benefited from intensive, real-time measurement of symptoms, which is likely to be more reliable than summary reports in clinical trials. The controlled setting also eliminated variability due to participants' individual environments, and allowed for almost continuous verification of smoking abstinence.

In summary, the results of the current study indicate that BP may alleviate some symptoms of nicotine withdrawal and may improve some measures of performance during smoking cessation. Data suggest that BP 300 mg/day acts primarily to improve affect during withdrawal. Significant effects of BP were limited largely to the 300 mg/day dose, which is the dose recently approved as an aid to smoking cessation by the FDA. BP150/day typically produced effects intermediate to 300 and PBO, but were not significantly different from PBO. The study suggests that BP's effects on craving and withdrawal are more modest than its effects on abstinence (refraining from smoking), suggesting that other mechanisms are also involved.

Acknowledgements This study was funded by Glaxo-Wellcome.

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