Available online at www.sciencedirect.com
SCIENCE DIRECT
Pharmacology, Biochemistry and Behavior 83 (2006) 370–379
PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR
www.elsevier.com/locate/pharmbiochembeh

Effect of bupropion on physiological measures of stress in smokers during nicotine withdrawal☆

Michael Kotlyar [a,b,*], Lisa H. Brauer [b], Mustafa al'Absi [c], David E. Adson [b], William Robiner [d], Paul Thuras [e], Jennifer Harris [f], Mary E. Finocchi [g], Carrie A. Bronars [f], Suzanne Candell [b], Dorothy K. Hatsukami [f]

[a] *Department of Experimental and Clinical Pharmacology, University of Minnesota College of Pharmacy, Minneapolis, MN, United States*
[b] *Department of Psychiatry, University of Minnesota, Twin Cities, Minneapolis, MN, United States*
[c] *Departments of Behavioral Sciences, Family Medicine, and Physiology, University of Minnesota Medical School, Duluth, MN, United States*
[d] *Department of Medicine, University of Minnesota, Twin Cities, Minneapolis, MN, United States*
[e] *Department of Psychiatry, VA Medical Center and University of Minnesota, Minneapolis, MN, United States*
[f] *Transdisciplinary Tobacco Use Research Center, University of Minnesota, Twin Cities, Minneapolis, MN, United States*
[g] *University of Minnesota College of Pharmacy, Minneapolis, MN, United States*

Received 16 August 2005; received in revised form 11 January 2006; accepted 18 February 2006
Available online 6 March 2006

Abstract

Studies suggest that among cigarette smokers trying to quit, stress undermines abstinence. Little research has assessed if therapies that increase smoking cessation rates impact physiological measures of stress response. Forty-three subjects completed this repeated-measures study in which a laboratory assessment was completed at baseline and after 17 days of treatment with either placebo ($n=15$), bupropion sustained release (150 mg twice daily) ($n=14$) or bupropion with stress reduction counseling ($n=14$). All subjects quit smoking 3 days prior to the second laboratory assessment. At each laboratory assessment physiological measures of stress (i.e. blood pressure, heart rate, plasma epinephrine, norepinephrine and cortisol concentrations) were measured during rest periods and in response to a speech, a math and a cold pressor task. Among subjects taking placebo, physiological measures of stress were generally lower at rest and during the stressors after smoking cessation. In those taking bupropion these measures were equivalent at the two assessments. Additionally, compared to placebo, those on bupropion had a greater diastolic blood pressure response to the speech stressor and greater systolic blood pressure response to the math stressor during the second laboratory session. This study suggests that bupropion may be maintaining physiological measures of stress during the nicotine withdrawal period.

Keywords: Bupropion; Mental stress; Smoking cessation; Nicotine addiction; Blood pressure; Heart rate; Catecholamines; Cortisol

1. Introduction

Laboratory and naturalistic studies suggest that among cigarette smokers trying to quit, stress undermines abstinence. There is little research however assessing if modifying the stress response during the acute nicotine withdrawal period can increase smoking cessation rates. Retrospective studies evaluating the relationship between smoking and stress have found that many smokers attempting to quit report that relapse occurred while experiencing some form of stress or tension (Borland, 1990; Brandon et al., 1990; Cummings et al., 1985; Shiffman, 1982; Shiffman and Waters, 2004; Swan et al., 1988). Additionally, several laboratory studies have demonstrated that

☆ Supported by University of Minnesota Academic Health Center Faculty Research Development Grant #01-01, Grant #M01-RR00400 from the General Clinical Research Centers program of the National Center for Research Resources and Grant #K23DA017307 from the National Institute on Drug Abuse.

* Corresponding author. Department of Experimental and Clinical Pharmacology, University of Minnesota, College of Pharmacy, 7-170 Weaver Densford Hall, 308 Harvard St SE, Minneapolis, MN 55455, United States. Tel.: +1 612 625 1160; fax: +1 612 625 3927.
E-mail address: kotly001@umn.edu (M. Kotlyar).

0091-3057/$ - see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.pbb.2006.02.017

during stressful situations (e.g., public speaking, unpleasant noise), smoking intensity or amount smoked increases as does self-reported desire to smoke (Cherek, 1985; Perkins and Grobe, 1992; Pomerleau and Pomerleau, 1987; Rose et al., 1983).

There is little data regarding the effect of smoking cessation pharmacotherapy on stress response during nicotine abstinence. Bupropion, having been shown to be more effective than placebo in achieving smoking abstinence, is currently the only non-nicotine pharmacotherapy approved for marketing in the United States as an aid to smoking cessation (Hurt et al., 1997; Jorenby et al., 1999). The mechanism by which it exerts this therapeutic effect however is unclear. Pharmacologically, bupropion (and/or its metabolites) inhibits norepinephrine and dopamine reuptake and exerts non-competitive antagonist activity at nicotinic acetylcholine receptors (Ascher et al., 1995; Fryer and Lukas, 1999; Slemmer et al., 2000). At this time, it is unclear which of these action(s) account for bupropion's efficacy at increasing smoking cessation rates although its effects on dopamine and norepinephrine are thought to be important (Richmond and Zwar, 2003). Behaviorally, bupropion has been shown to decrease smoking withdrawal symptoms and to attenuate cue-induced cigarette craving (Brody et al., 2004; Jorenby et al., 1999). There is little data however regarding the effect of bupropion on stress-related physiological measures particularly when used in smokers. Limited data suggest that bupropion may decrease response to stress. However these data was reported in a cross-sectional study comparing depressed patients treated with bupropion with unmedicated, non-depressed controls (Straneva-Meuse et al., 2004). Since depression may independently affect stress response (Light et al., 1998; Sheffield et al., 1998), it is difficult to ascertain the true effect of bupropion. Therefore, it is not known whether this data can be extrapolated to those trying to quit smoking. Given bupropion's known effects on mood and on smoking and its potential effect on stress, it is possible that modifying stress reactivity is one of the mechanisms associated with bupropion's efficacy in treating smokers.

It is also unknown if counseling sessions in which stress reduction techniques are taught and practiced would result in alterations in physiological parameters of stress. Studies assessing whether physiological measures of stress are reduced following stress reduction counseling have reported inconsistent results (English and Baker, 1983; Gaab et al., 2003; Seraganian et al., 1987; Vocks et al., 2004). The combination of pharmacotherapy with behavioral therapy has been found to be more effective than either individually in treating several psychiatric disorders (e.g. depression) (Reynolds et al., 1999) and it is possible that combination therapy would similarly have the greatest effect on physiological stress parameters.

Short-term laboratory paradigms have been used to examine stress induced physiological changes in smokers and should be useful in determining the effects of interventions that increase smoking cessation rates on stress response (al'Absi et al., 2003; Girdler et al., 1997; Kirschbaum et al., 1993b; Perkins et al., 1992; Roy et al., 1994; Straneva et al., 2000; Tersman et al., 1991; Tsuda et al., 1996). Physiological responses to mental stress in laboratory settings may correlate with individuals' physiological responses during stressful situations that commonly occur in life and that may lead to smoking relapse (Blumenthal et al., 1995; Stone et al., 1999). Commonly used laboratory mental stress tasks include asking subjects to speak in public or solve timed math problems while being observed (Strike and Steptoe, 2003). Such tasks have been shown to cause stress-related physiological responses, including increased efferent sympathetic tone and activation of the hypothalamic-pituitary-adrenocorticoid (HPA) system. Increased sympathetic tone can be measured by increases in blood pressure, heart rate and plasma catecholamine concentrations (Schoder et al., 2000; Yoshida et al., 1999). Activation of the HPA axis results in increased corticotrophin-releasing hormone (CRH) production, leading to the release of adrenocorticotropic hormone (ACTH) and ultimately to an increase in cortisol (Herman et al., 2003).

Better understanding bupropion's effects during the nicotine withdrawal period would provide additional information regarding the mechanism by which bupropion increases smoking cessation rates. The purpose of this study was to determine the effect of bupropion, with and without stress reduction counseling, on stress-related physiological measures in a controlled laboratory study examining smokers' response to stressors when undergoing nicotine withdrawal.

2. Methods

2.1. Design

In this repeated measures study, response to two mental stress tasks and a cold pressor task were assessed in smokers at two time-points: prior to quitting smoking and on the third day after quitting smoking (i.e. approximately 60 h after smoking cessation). The third day was chosen for the second laboratory assessment since withdrawal symptoms generally peak two to three days after smoking cessation (Hatsukami et al., 1984). All laboratory sessions occurred at approximately the same time of day (i.e. each session starting between 8 and 10 AM). After the first assessment subjects were randomized to one of three treatment groups: bupropion, matching placebo, or bupropion with behavioral counseling. Subjects were blinded regarding drug assignment and investigators were blinded regarding treatment assignment in those not receiving counseling. As recommended by the manufacturer, bupropion was administered for 14 days prior to subjects' quit date (GlaxoSmithKline, 2005). A dose of 150 mg was given once daily for 3 days followed by 150 mg given twice daily for an additional 14 days. A total of 17 days of medications was therefore taken with the start day timed such that the second laboratory assessment occurred approximately 4 weeks after the first. Subjects assigned to counseling received 4 individual counseling sessions occurring between the two laboratory assessment visits. Three days prior to the second laboratory assessment, subjects were asked to quit smoking. Smoking status was ascertained by subject report and verified by CO concentrations of <10 parts per million (ppm). Subjects who were unable to quit smoking for three days were dropped from the study and did not undergo a

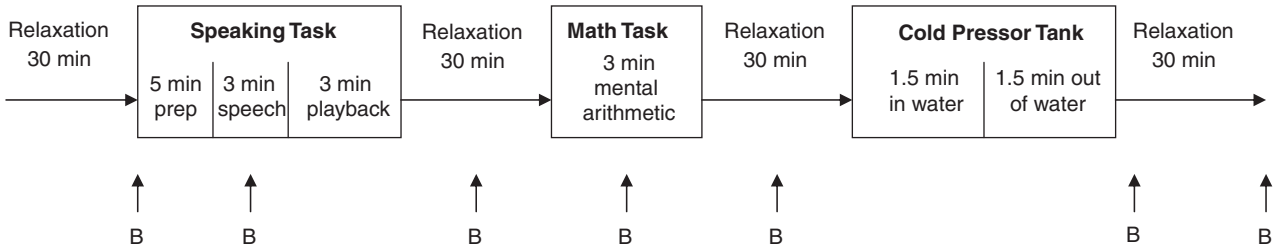

Fig. 1. Outline of each visit at which mental stress testing was performed. B = blood draw.

second laboratory assessment. Individuals who did not complete both laboratory sessions were replaced in the randomization schedule to assure that an approximately equal number of participants completed each treatment condition.

2.2. Subjects

Participants were recruited from the University of Minnesota and surrounding communities through flyers and newspaper advertisements. To be eligible, potential subjects had to be between the ages of 18 and 65, have smoked at least 15 cigarettes per day, and have an expired carbon monoxide (CO) concentration ≥ 10 ppm at the time of screening. Subjects with a current psychiatric illness, contraindication to bupropion administration (e.g. history of seizure or eating disorders), serious unstable medical condition, substance abuse within one year of starting the study, or on medication likely to interact with bupropion or interfere with study measures were excluded. The study was approved by the University of Minnesota Institutional Review Board and written informed consent was obtained from all subjects.

2.3. Laboratory assessment

Upon arrival for each laboratory visit at the General Clinical Research Center (GCRC), an indwelling catheter was inserted to facilitate blood draws and an automated sphygmomanometer was placed to obtain repeated blood pressure measurements. During the laboratory assessment subjects performed two mental stress tasks (public speaking and mental arithmetic) and a cold pressor task. A modified Trier Social Stress Test was utilized for the public speaking task (Kirschbaum et al., 1993a). In this task, subjects were presented with a hypothetical stressful scenario involving an interpersonal conflict. They were given 5 min to think about how they would handle such a conflict and then gave a 3-min speech on the topic in front of 2 people. Their speech was taped and replayed to them shortly after they finished speaking. A previously described protocol was used for the mental arithmetic task in which subjects performed a series of additions over a 3-min period (al'Absi et al., 1994). For the cold pressor task, subjects were asked to submerge their hand in an ice water slurry for a 90-s period.

Thirty-minute relaxation periods occurred prior to the speech task, between each task and after the cold pressor task (see Fig. 1). Blood pressure and heart rate were measured throughout the laboratory session; at 3-min intervals during the relaxation periods and at 1-min intervals during the speech and mental arithmetic task. During the cold pressor task, blood pressure and heart rate were measured once while the subject's hand was submerged in ice water and again 90 s after the hand was removed from the ice water. A total of seven blood draws occurred during the laboratory session from which plasma concentrations of epinephrine, norepinephrine and cortisol were determined. Blood draws occurred at the conclusion of the first relaxation period, 1 1/2 min into the speech, 15 min after the speech task, 1 1/2 min into the math task, 15 min after the math task and at 5 and 30 min after subjects removed their hand from ice water for the cold pressor task (Fig. 1). To assess subjective measures of stress the Audience Anxiousness Scale as modified by Abrams et al was administered prior to and after the speech task (Abrams et al., 2001; Leary, 1983). This scale was designed to assess anxiety symptoms when speaking or performing before an audience by asking 10 questions regarding worries or thoughts that occur in relation to a public speaking task. The questionnaire administered prior to the speech task evaluated anticipatory anxiety by asking the intensity of these symptoms that subjects expected they would experience during the speech whereas the questionnaire administered following the speech asked the intensity of these symptoms that occurred during the speech.

The plasma catecholamine assay procedure used was a modification of the procedure reported by Wang et al. (1999) using extraction kits acquired through ESA Inc. (Chelmsford, MA). It involves extraction of catecholamines from 1.0 ml of plasma with activated alumina, injection of the acid extract onto a reverse phase C-18 column and separation with a mobile phase consisting of 8.0% acetonitrile, 16% methanol and 100 mM phosphate buffer pH to 3.0 pumped at 1 mL/min. The amines are detected on an ESA II coulochem electrochemical detector. The lower limit of quantitation is 10 pg/ml in plasma. For samples with epinephrine concentrations lower than the lower limit of quantitation (10 pg/ml), a value of 5 pg/ml was used for purposes of analysis. Cortisol plasma concentrations were determined from 25 µl of plasma using an enzyme immunoassay (EIA) kit acquired from Diagnostic Systems Laboratories (Webster, TX) (DSL-10-2000 Active® Cortisol kit), the lower limit of quantitation for which is 0.5 µg/dl.

2.4. Counseling sessions

A 4-session multi-component counseling intervention was designed by two licensed psychologists (WR and SC) and was

conducted by one (SC). It incorporated general stress management approaches that have been widely reported in the literature for stress reduction (Everly and Lating, 2002) and that have been used in smoking cessation interventions (Fiore et al., 2000; Niaura and Abrams, 2002). The objectives of the counseling intervention included: educating participants about stress and psychophysiological stress response (session one); teaching basic stress management skills (i.e., diaphragmatic breathing, progressive relaxation, and positive visualization techniques; sessions 2 and 3); promoting skill generalization (session 4); and providing emotional support for the smoking cessation. Subjects' individual concerns related to coping with smoking cessation informed session content as targets for problem-solving. A progressive relaxation exercise was conducted and audiotaped for each participant during session one. Participants were given written summaries of the relaxation skills taught after each of the first three sessions as a guide for daily practice. Subjects were asked to practice relaxing for 10 min (with or without the tape) twice per day. As a check on the counseling intervention, subjects were requested to record their use of the techniques and their pre- and post-practice stress ratings on logs. The ratings on a 10-point subjective stress scale revealed that self-rated stress decreased (87.1%) or stayed the same (8.9%) for most home-practice sessions.

2.5. Statistical analyses

The primary objective of this study was to determine if bupropion (with or without counseling) affects stress response during two mental stress and a physical stressor tasks. Secondary objectives included assessing if bupropion alters resting levels of physiological parameters of stress during the nicotine withdrawal period and assessing if nicotine withdrawal alters physiological stress parameters.

To determine the magnitude of stress response for systolic blood pressure, diastolic blood pressure and heart rate, the average blood pressure attained during each stress period (i.e. during speaking, during math) were compared to the average values obtained during the relaxation period preceding the stressor. For plasma epinephrine and norepinephrine concentrations, the measure obtained during each stressor was compared to the measure obtained during the preceding relaxation period. Since changes in cortisol are expected to occur more slowly than changes in the other physiological measures assessed, change in cortisol (resting to during stressor) was not computed. Instead, cortisol concentrations were compared using blood draw as a continuous time measure. Mixed regression models (SAS PROC MIXED) were used to assess the change in measurements during each stressor. Time period, laboratory, and treatment group were treated as fixed effects. Individual intercept and slope were considered random effects in the models. Initial analysis results indicated that gender was a significant factor so it was added as an additional fixed effect. Significant differences were not observed between the two bupropion conditions with effect sizes for differences between the two bupropion conditions ranging from $r=0.04$ to $r=0.22$ for epinephrine, norepineprine and cortisol and from $r=0.04$ to $r=0.38$ for measures of heart rate and blood pressure. The two bupropion conditions were combined and compared to the placebo condition in the final analyses reported below. To assess differences in Audience Anxiousness Scale (AAS) scores analyses of covariance were used to compare treatment groups on pre and post speech AAS measures during laboratory 2 with the corresponding laboratory 1 scores as covariates.

3. Results

A total of 43 subjects completed this study and were included in the analysis. An additional 22 subject completed the first laboratory session but not the second and were therefore excluded from the analysis. Physiological response to stress was compared in completers and non-completers in the first laboratory session and no statistically significant differences were found. An examination of the effect sizes for group (completers vs. non-completers) by time interactions found nothing larger than $r=0.16$. Of those who completed the study, 14 were randomized to bupropion, 15 to placebo and 14 to bupropion with stress reduction counseling. Subjects' baseline demographics are listed in Table 1. No significant differences were found between groups. A significant gender effect was observed in most measures assessed and thus gender was added as a factor to all analytic models. Men generally had higher blood pressure and lower heart rate measurements than women with many of the differences reaching statistical significance. These gender differences are consistent with previous reports (Divison et al., 2004; Reckelhoff, 2001). Epinephrine was also higher in male participants than in females. There were no gender differences in norepinephrine. There were no significant laboratory × treatment × gender interactions, suggesting that differences observed between laboratory sessions in those receiving placebo compared with those receiving bupropion were not influenced by gender.

All stressors (i.e. speech, math, cold pressor) were effective in eliciting a physiological response. A significant period effect (all p values <0.05) emerged during all three stress tasks for all of the acutely reactive physiological measures assessed (i.e. blood pressure, heart rate, plasma catecholamine concentrations) with

Table 1
Baseline characteristics of subjects

Characteristics	Bupropion ($n=14$)	Placebo ($n=15$)	Bupropion+ Counseling ($n=14$)
	Number (%) or mean±SD		
Age	40.3±13.3	36.7±12.1	42.9±12.9
Women	6 (43)	4 (27)	9 (64)
Caucasian	12 (86)	11 (73)	13 (93)
Number of cigarettes per day	20.0±5.0	20.1±5.9	20.6±4.7
Exhaled carbon monoxide concentrations (parts per million)	21.9±10.4	19.3±6.9	20.7±8.0
Age subject started smoking daily	19.3±4.9	18.5±4.9	16.5±2.4
Fagerström Test for Nicotine Dependence	4.23±2.1	4.2±1.4	4.9±1.8
BMI	27.3±5.3	28.2±3.5	26.1±3.4

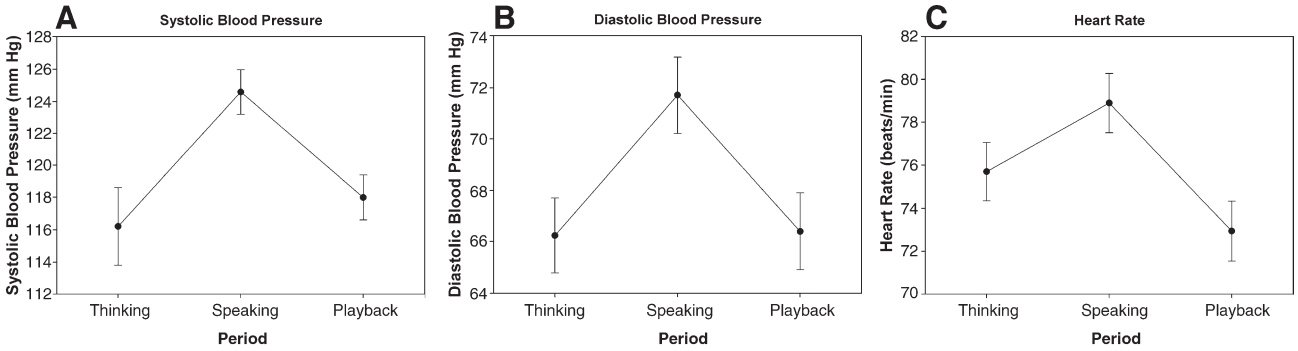

Fig. 2. Systolic blood pressure (panel A), diastolic blood pressure (panel B) and heart rate (panel C) response to the three components of the speech stress task (thinking, speaking, playback).

the exception of norepinephrine concentrations during the math stressor. During the speech task, speech delivery elicited a greater response than speech preparation or replay (Fig. 2) and corresponded to the timing of the blood draw. The speech delivery period was therefore used in reporting all results. No significant differences were observed in measures of Audience Anxiousness Scale (AAS). During the second laboratory period, pre-speech AAS scores were 24.8 and 26.8 in those taking placebo and bupropion, respectively. Post-speech AAS scores during the second laboratory period were 24.7 and 26.1, respectively.

3.1. Effect of treatment on blood pressure, heart rate and catecholamine concentrations

Overall, physiological parameters of stress were lower during the second laboratory session in subjects assigned to

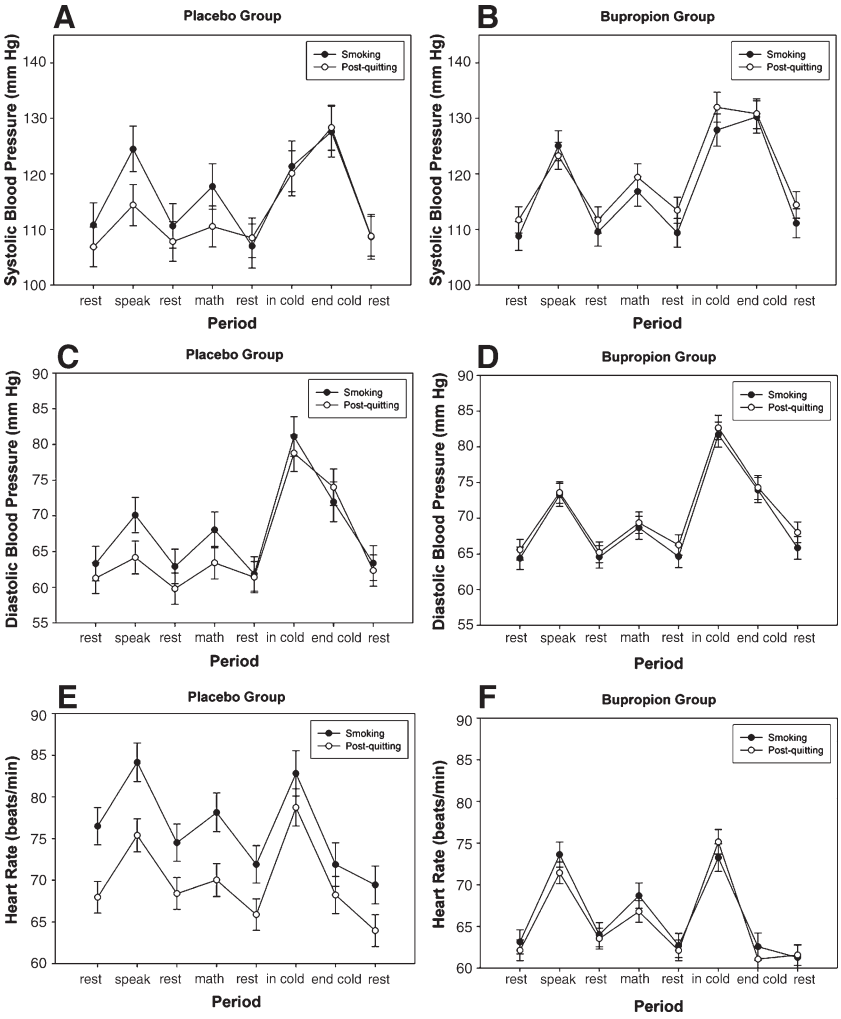

Fig. 3. Systolic blood pressure, diastolic blood pressure and heart rate (mean ± SE) in subjects receiving placebo (panels A, C, E) or bupropion (panels B, D, F) during laboratory sessions conducted prior to and 3 days after subjects quit smoking.

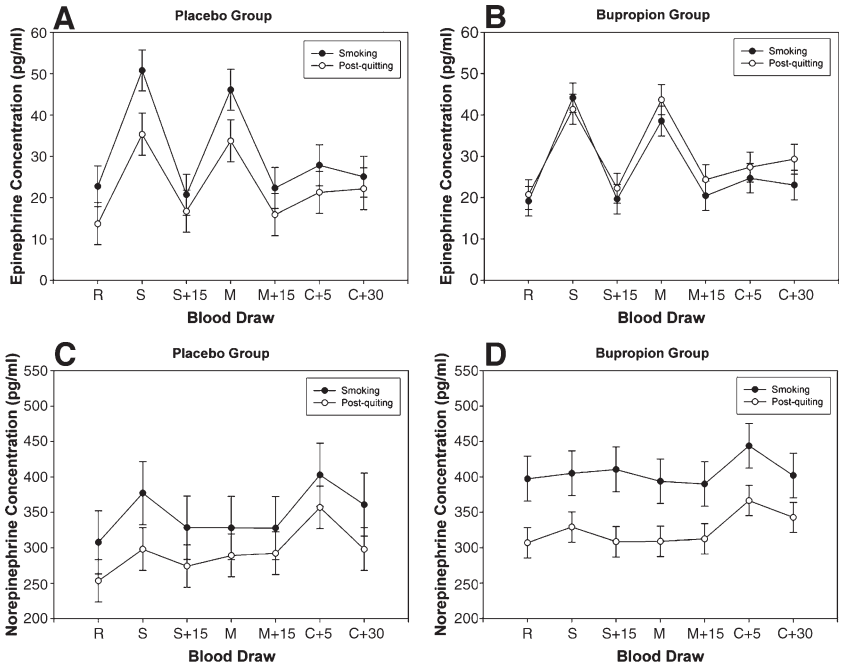

Fig. 4. Plasma epinephrine and norepinephrine concentrations (mean±SE) in subjects receiving placebo (panels A, C) or bupropion (panels B, D) during laboratory sessions conducted prior to and 3 days after subjects quit smoking. R=resting; S=during speech, S+15=15 min after speech task, M=math, M+15=15 min after math task, C+5=5 min after cold pressor task; C+30=30 min after cold pressor test.

placebo, whereas no differences between laboratory sessions were found in those assigned to bupropion. Similar results were also found for several measures of stress response.

For most of the parameters assessed, physiological measures during the second laboratory session were generally lower at all time-points than during the first (Figs. 3 and 4). A significant laboratory effect was seen for all of the measures during the speech task (all p values <0.05), for heart rate [$F(1,39)=11.38$, $p=0.0017$] and norepinephrine concentrations [$F(1,37)=13.53$, $p=0.0007$] during the math task and for epinephrine [$F(1,39)=8.21$, $p=0.0067$] and norepinephrine concentrations [$F(1,37)=11.60$, $p=0.00160$] during the cold pressor task. The decreases in physiological measures during the second laboratory session however were largely true only for subjects receiving placebo with much smaller differences observed in those receiving bupropion. Significant laboratory × treatment effects were seen for all measures except norepinephrine concentrations during the speech and math task and for heart rate during the cold pressor task (all p values <0.05). Physiological response to stress, as measured by the difference between measures obtained during the stress task and those obtained during the preceding relaxation period, for the mental stressors are summarized in Table 2. A significant laboratory × period × treatment effect was found for diastolic blood pressure during the speech task [$F(1,37)=4.21$, $p=0.0472$] and for systolic blood pressure during the math task [$F(1,37)=9.63$, $p=0.0037$] with a trend found for diastolic blood pressure during the math task [$F(1,37)=3.43$, $p=0.0720$]. This was also due largely to a smaller response observed during the second laboratory session in those taking placebo, with no such difference observed in those taking bupropion. No significant laboratory × period × treatment effects were found for the cold pressor task.

3.2. Effect of stress and treatment on plasma cortisol concentrations

Plasma cortisol concentrations increased during each laboratory session (Fig. 5) and a significant blood draw (time) × laboratory effect was found demonstrating that the increase over time was significantly greater during the second

Table 2
Change (mean±SE) between physiological measures obtained immediately preceding stress task (speech or math) and measures obtained during stress task

	Speech				Math			
	Laboratory 1		Laboratory 2		Laboratory 1		Laboratory 2	
	PBO	Bup	PBO	Bup	PBO	Bup	PBO	Bup
Systolic BP (mm Hg)	13.7±1.4	16.3±0.9	7.5±1.3	11.5±0.9	7.1±1.4	7.2±0.9	2.7±1.4	7.7±0.9
Diastolic BP (mm Hg)	6.8±0.8	8.9±0.6	2.9±0.9	8.0±0.6	5.1±0.9	4.1±0.6	3.6±0.9	4.2±0.6
Heart Rate (beats/min)	7.7±0.8	10.5±0.6	7.4±0.8	9.3±0.5	3.6±0.9	4.7±0.6	1.6±0.8	3.3±0.5
Epinephrine (pg/mL)	28.0±5.0	25.0±3.6	21.7±4.4	20.6±3.3	25.4±5.0	18.9±3.6	17.0±4.4	21.4±3.3
Norepinephrine (pg/mL)	69.3±26.0	7.72±19.0	44.7±19.3	22.2±14.1	−0.35±26.0	−16.8±19.0	15.1±19.3	0.5±14.1

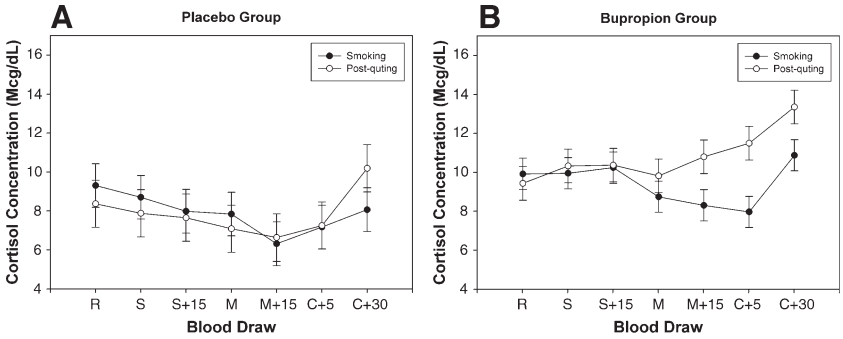

Fig. 5. Plasma cortisol concentrations (mean ± SE) in subjects receiving placebo (panel A) or bupropion (panel B) during laboratory sessions conducted prior to and 3 days after subjects quit smoking. R = resting; S = during speech, S + 15 = 15 min after speech task, M = math, M + 15 = 15 min after math task, C + 5 = 5 min after cold pressor task; C + 30 = 30 min after cold pressor test.

laboratory than during the first laboratory session [$F(1,550) = 25.53$, $p < 0.0001$], increasing by 0.23 over the course of the first laboratory but by 3.23 over the course of the second laboratory. In those receiving placebo, cortisol concentrations were similar during both laboratory sessions. In those receiving bupropion, however, a separation occurs after the fifth blood draw (the blood draw that occurs 15 min after the math stressor). At this blood draw there was no difference in average cortisol concentrations between laboratory sessions in those taking placebo (6.64 vs. 6.34 μg/dl), however in those taking bupropion, cortisol concentrations were significantly higher during the second laboratory session (10.80 vs. 8.30 μg/dl; $p < 0.007$). Similar results were found for the last 2 blood draws (Fig. 5).

4. Discussion

This study demonstrated that approximately three days after smoking cessation, physiological measures of stress response are attenuated in untreated smokers but unchanged in smokers receiving bupropion. Similarly, response to stress was lower in some measures among those receiving placebo and not changed in those taking bupropion.

There are conflicting data regarding the effect of high stress reactivity or increased HPA axis activity on smoking abstinence. Some investigations have found that smokers with exaggerated responses to stressors are more likely to relapse after a cessation attempt (Abrams et al., 1987, 1988; Brown et al., 2002; Emmons et al., 1989; Niaura et al., 1989; Swan et al., 1993) whereas others have found the opposite to be true (al'Absi et al., 2004, 2005). These conflicting results could potentially be explained by the time-frame (relative to smoking cessation) during which stress reactivity was assessed. Studies assessing reactivity during the pre-cessation period have generally shown that lower responses are associated with lower relapse rates, whereas the study assessing stress response during the acute withdrawal period suggested that lower responses were associated with higher relapse rates. Further research is needed to determine if relapse is associated with greater changes in stress response (i.e., indicating greater physiological perturbations following smoking cessation) rather than the absolute level of the stress response at one time-point. If this were found to be true, it would be consistent with our findings that bupropion maintains physiological measures at pre-cessation levels and its known effects in increasing quit rates although this is speculative at this time and requires further study.

The stress reduction counseling in this study did not confer additional effects on the physiological measures assessed beyond those seen with bupropion alone. Other studies have found differential physiological effects between counseling and antidepressant pharmacotherapy. A study of patients with coronary artery disease found that although SSRI antidepressants seemed to improve cardiac outcomes, no improvements were observed in patients treated with cognitive behavioral therapy. This was despite the effectiveness of the counseling in reducing symptoms of depression and enhancing perceived social support (Berkman et al., 2003; Taylor et al., 2005). This suggests that subjective measures of depression or stress may not correlate well with physiological changes. However more research is needed to clarify this relationship. Nonetheless, the benefit of smoking cessation counseling in increasing quit rates has been clearly established (Fiore et al., 2000). It should be emphasized that this study was not designed to assess the effects of stress reduction counseling on smoking cessation, rather the effects of stress reduction on physiological measures. It is possible that the intensity of brief counseling or the amount of time spent practicing the skills learned was not sufficient to effect physiological changes. Changes to the counseling protocol (i.e., content, number or duration of sessions) may have yielded different results. These are all areas for future investigation.

Our finding that physiological measures of stress response are attenuated after smoking cessation both at rest and during stress (in those not taking bupropion) adds to existing literature regarding the effects of abstinence on these measures. Although it is possible that the attenuation observed is due to habituation, our data suggesting lower resting values of stress markers is largely consistent with previously reported data. Data regarding magnitude of stress response after smoking cessation has been inconsistent. Tsuda et al. found that after an overnight abstinence, smokers had reduced resting diastolic blood pressure and heart rate, but had an enhanced diastolic blood pressure reactivity compared with those who smoked 30 min

prior to the assessment (Tsuda et al., 1996). Al'absi in a series of studies found that 12–18 h of abstinence decreased resting heart rate, did not alter resting blood pressure, but resulted in a greater systolic blood pressure response to stress compared to ad lib smoking (al'Absi et al., 2002, 2003). Ward et al. found that after 2 days of abstinence, resting heart rate decreased but there were no changes in blood pressure or in measures of cardiovascular reactivity in response to laboratory challenges (Ward et al., 1994). Elgerot found that 4 days of abstinence resulted in decreased concentrations of urinary catecholamine concentrations (Elgerot, 1978). Studies assessing longer-term abstinence (i.e., 6 weeks to 6 months) have found significant decreases in epinephrine and cortisol concentrations with no change in blood pressure or cardiovascular reactivity in response to stressors (Emmons et al., 1989; Puddey et al., 1984). Our results are consistent with previous studies demonstrating decreases (at rest and during stressors) in some physiological measures associated with stress. It is possible that the largest decreases do not occur until after the first 48 h of smoking cessation (the time period during which most previous studies have been conducted). This could potentially explain why our study revealed more consistent decreases across measures than previous investigations. Further research is necessary to better characterize the time course for these changes.

There has been little data to date regarding the effect of antidepressants in general or bupropion specifically on the physiologic response to mental stress. Two small studies conducted in patients with coronary artery disease suggest that 4 weeks of paroxetine (a selective serotonin reuprake inhibitor) attenuated blood pressure, heart rate and catecholamine response (Golding et al., 2002, 2005). A study comparing stress response in depressed patients being treated with paroxetine or bupropion to non-depressed, non-medicated controls found that those taking either antidepressant generally had lower response to stress than the controls. However, differences were observed between agents with bupropion appearing to have less of an attenuating effect compared to paroxetine (Straneva-Meuse et al., 2004). Since depression may alter stress response, interpretation of this finding is difficult (Light et al., 1998; Sheffield et al., 1998). In the present study, bupropion (relative to placebo) increased resting and stress-induced levels of physiological parameters associated with stress during the nicotine withdrawal period. Additionally, bupropion resulted in a significantly greater diastolic blood pressure response during the speech stressor and a significantly greater systolic blood pressure response and a trend toward a greater diastolic blood pressure response during the math task. Bupropion has been reported to be a weak central nervous system stimulant and to share a similar discriminative stimulus effect with nicotine (Rush et al., 1998; Young and Glennon, 2002). Bupropion may therefore have been substituting for some of nicotine's pharmacological effects, thereby resulting in a similar pattern of stress response after nicotine discontinuation. This study however does not directly address whether the effects observed are direct effects of bupropion or if these effects were secondary to bupropion's effect on some other aspect of the nicotine withdrawal syndrome (e.g. decreasing withdrawal symptoms or cue-induced craving may have independent effects on physiological measures of stress). Future studies using non-depressed, non-smokers would help resolve this issue. An additional future area for study is determining if these stimulatory effects of bupropion occur only during the nicotine withdrawal period or are maintained beyond this timeframe.

In this study both mental stressors resulted in a physiological response, however between the two mental stressors (i.e. speech and math), a larger response was generally elicited during the speech task relative to the math task. Since the order of tasks was maintained among all subjects, it is not clear whether this difference is a result of the speech being a more stressful task or whether the results were due to an order effect. Consistent with previous reports, epinephrine response was more robust to the mental stressors whereas norepinephrine response was stronger to the physical stressor (Dimsdale and Moss, 1980). Bupropion's differential effect on epinephrine and norepinephrine concentrations observed in this study is consistent with a study in which epinephrine concentrations were increased and norepinephrine decreased subsequent to the administration of desipramine administration, also an antidepressant that blocks the reuptake of norepinephrine (Eisenhofer et al., 1995). The mechanism for this is not clear.

There are several limitations to this study that must be considered when evaluating the data. The lack of a non-smoking control makes it difficult to determine weather the decreases in physiological measures seen in the placebo group were a result of nicotine withdrawal or habituation to the stressor. Nonetheless, the bupropion group did not demonstrate such a decrease suggesting that relative to placebo, bupropion caused an increase in measures of these physiological parameters. The lack of a same day control makes it difficult to separate daily variations in physiological effects from the effect of medication, however all subjects were tested during the same time of day to minimize any circadian variations. Since a counseling alone group was not included in this study, it is possible that stress reduction counseling has some independent effects on physiological markers of stress but that they are small relative to bupropion or that a ceiling effect is observed after bupropion administration such that no additional changes are observed after the addition of counseling. Nonetheless, this study suggests that adding brief stress reduction counseling to bupropion does not result in significant additional changes in physiological markers of stress.

In conclusion, this study demonstrates that laboratory methods are useful in determining medication induced changes in physiological measures of stress response. During the acute nicotine withdrawal period, we found that physiological measures of stress are attenuated in untreated smokers but remain largely the same in smokers treated with bupropion. These findings suggest that bupropion may be substituting for some of nicotine's physiological effects during the withdrawal period thus maintaining these physiological measures during this timeframe. It is unknown if maintenance of these measures account (at least in part) for bupropion's efficacy as an aid to smoking cessation.

Acknowledgments

We thank Karen Borup for her technical assistance and the nursing staff of the General Clinical Research Center.

References

Abrams DB, Monti PM, Pinto RP, Elder JP, Brown RA, Jacobus SI. Psychosocial stress and coping in smokers who relapse or quit. Health Psychol 1987;6:289–303.

Abrams DB, Monti PM, Carey KB, Pinto RP, Jacobus SI. Reactivity to smoking cues and relapse: two studies of discriminant validity. Behav Res Ther 1988;26:225–33.

Abrams K, Kushner M, Medina KL, Voight A. The pharmacologic and expectancy effects of alcohol on social anxiety in individuals with social phobia. Drug Alcohol Depend 2001;64:219–31.

al'Absi M, Lovallo WR, McKey BS, Pincomb GA. Borderline hypertensives produce exaggerated adrenocortical responses to mental stress. Psychosom Med 1994;56:245–50.

al'Absi M, Amunrud T, Wittmers LE. Psychophysiological effects of nicotine abstinence and behavioral challenges in habitual smokers. Pharmacol Biochem Behav 2002;72:707–16.

al'Absi M, Wittmers LE, Erickson J, Hatsukami D, Crouse B. Attenuated adrenocortical and blood pressure responses to psychological stress in ad libitum and abstinent smokers. Pharmacol Biochem Behav 2003;74:401–10.

al'Absi M, Hatsukami D, Davis GL, Wittmers LE. Prospective examination of effects of smoking abstinence on cortisol and withdrawal symptoms as predictors of early smoking relapse. Drug Alcohol Depend 2004;73:267–78.

al'Absi M, Hatsukami D, Davis GL. Attenuated adrenocorticotropic responses to psychological stress are associated with early smoking relapse. Psychopharmacology 2005;181:107–17.

Ascher JA, Cole JO, Colin JN, Feighner JP, Ferris RM, Fibiger HC, et al. Bupropion: a review of its mechanism of antidepressant activity. J Clin Psychiatry 1995;56:395–401.

Berkman LF, Blumenthal J, Burg M, Carney RM, Catellier D, Cowan MJ, et al. Effects of treating depression and low perceived social support on clinical events after myocardial infarction: the Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) Randomized Trial. JAMA 2003;289:3106–16.

Blumenthal JA, Jiang W, Waugh RA, Frid DJ, Morris JJ, Coleman RE, et al. Mental stress-induced ischemia in the laboratory and ambulatory ischemia during daily life. Association and hemodynamic features. Circulation 1995;92:2102–8.

Borland R. Slip-ups and relapse in attempts to quit smoking. Addict Behav 1990;15:235–45.

Brandon TH, Tiffany ST, Obremski KM, Baker TB. Postcessation cigarette use: the process of relapse. Addict Behav 1990;15:105–14.

Brody AL, Mandelkern MA, Lee G, Smith E, Sadeghi M, Saxena S, et al. Attenuation of cue-induced cigarette craving and anterior cingulate cortex activation in bupropion-treated smokers: a preliminary study. Psychiatry Res 2004;130:269–81.

Brown RA, Lejuez CW, Kahler CW, Strong DR. Distress tolerance and duration of past smoking cessation attempts. J Abnorm Psychol 2002;111:180–5.

Cherek DR. Effects of acute exposure to increased levels of background industrial noise on cigarette smoking behavior. Int Arch Occup Environ Health 1985;56:23–30.

Cummings KM, Jaen CR, Giovino G. Circumstances surrounding relapse in a group of recent exsmokers. Prev Med 1985;14:195–202.

Dimsdale JE, Moss J. Plasma catecholamines in stress and exercise. JAMA 1980;243:340–2.

Divison JA, Sanchis C, Artigao LM, Carbayo JA, Carrion-Valero L, Lopez de Coca E, et al. Home-based self-measurement of blood pressure: a proposal using new reference values (the PURAS study). Blood Press Monit 2004;9:211–8.

Eisenhofer G, Friberg P, Goldstein DS, Esler M. Differential actions of desipramine on sympathoadrenal release of noradrenaline and adrenaline. Br J Clin Pharmacol 1995;40:263–5.

Elgerot A. Psychological and physiological changes during tobacco-abstinence in habitual smokers. J Clin Psychol 1978;34:759–64.

Emmons KM, Weidner G, Collins RL. Smoking cessation and cardiovascular reactivity to stress. J Behav Med 1989;12:587–98.

English EH, Baker TB. Relaxation training and cardiovascular response to experimental stressors. Health Psychol 1983;2:238–59.

Everly GS, Lating JM. A clinical guide to the treatment of the human stress response. 2nd ed. New York: Kluwer Academic/Plenum Publishers; 2002.

Fiore M, Bailey WC, Cohen SJ, Dorfman SF, Goldstein MG, Gritz ER, et al. Treating tobacco use and dependence clinical practice guideline. Washington (DC): U.S. Dept. of Health and Human Services Public Health Service; 2000.

Fryer JD, Lukas RJ. Noncompetitive functional inhibition at diverse, human nicotinic acetylcholine receptor subtypes by bupropion, phencyclidine, and ibogaine. J Pharmacol Exp Ther 1999;288:88–92.

Gaab J, Blattler N, Menzi T, Pabst B, Stoyer S, Ehlert U. Randomized controlled evaluation of the effects of cognitive-behavioral stress management on cortisol responses to acute stress in healthy subjects. Psychoneuroendocrinology 2003;28:767–79.

Girdler SS, Jamner LD, Jarvik M, Soles JR, Shapiro D. Smoking status and nicotine administration differentially modify hemodynamic stress reactivity in men and women. Psychosom Med 1997;59:294–306.

GlaxoSmithKline. Zyban (bupropion hydrochloride) Sustained-Release Tablets package insert; 2005. Research Triangle Park (NC).

Golding M, Kotlyar M, Garbutt JC, Guzzo J, Sontz E, Hinderliter A, et al. Paroxetine modulates psychological and sympathetic responses during public speaking. J Clin Psychopharmacol 2002;22:98–9.

Golding M, Kotlyar M, Carson SW, Hoyler S, Lazarus C, Davidson C, et al. Effects of paroxetine on cardiovascular response to mental stress in subjects with a history of coronary artery disease and no psychiatric diagnoses. Psychopharmacology 2005;182:321–6.

Hatsukami DK, Hughes JR, Pickens RW, Svikis D. Tobacco withdrawal symptoms: an experimental analysis. Psychopharmacology 1984;84:231–6.

Herman JP, Figueiredo H, Mueller NK, Ulrich-Lai Y, Ostrander MM, Choi DC, et al. Central mechanisms of stress integration: hierarchical circuitry controlling hypothalamo-pituitary-adrenocortical responsiveness. Front Neuroendocrinol 2003;24:151–80.

Hurt RD, Sachs DP, Glover ED, Offord KP, Johnston JA, Dale LC, et al. A comparison of sustained-release bupropion and placebo for smoking cessation. N Engl J Med 1997;337:1195–202.

Jorenby DE, Leischow SJ, Nides MA, Rennard SI, Johnston JA, Hughes AR, et al. A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. N Engl J Med 1999;340:685–91.

Kirschbaum C, Pirke KM, Hellhammer DH. The 'Trier Social Stress Test'—a tool for investigating psychobiological stress responses in a laboratory setting. Neuropsychobiology 1993a;28:76–81.

Kirschbaum C, Strasburger CJ, Langkrar J. Attenuated cortisol response to psychological stress but not to CRH or ergometry in young habitual smokers. Pharmacol Biochem Behav 1993b;44:527–31.

Leary MR. Social anxiousness: the construct and its measurement. J Pers Assess 1983;47:66–75.

Light KC, Kothandapani RV, Allen MT. Enhanced cardiovascular and catecholamine responses in women with depressive symptoms. Int J Psychophysiol 1998;28:157–66.

Niaura R, Abrams DB. Smoking cessation: progress, priorities, and prospectus. J Consult Clin Psychol 2002;70:494–509.

Niaura R, Abrams DB, Monti PM, Pedraza M. Reactivity to high risk situations and smoking cessation outcome. J Subst Abuse 1989;1:393–405.

Perkins KA, Grobe JE. Increased desire to smoke during acute stress. Br J Addict 1992;87:1037–40.

Perkins KA, Grobe JE, Fonte C, Breus M. "Paradoxical" effects of smoking on subjective stress versus cardiovascular arousal in males and females. Pharmacol Biochem Behav 1992;42:301–11.

Pomerleau CS, Pomerleau OF. The effects of a psychological stressor on cigarette smoking and subsequent behavioral and physiological responses. Psychophysiology 1987;24:278–85.

Puddey IB, Vandongen R, Beilin LJ, English D. Haemodynamic and neuroendocrine consequences of stopping smoking—a controlled study. Clin Exp Pharmacol Physiol 1984;11:423–6.

Reckelhoff JF. Gender differences in the regulation of blood pressure. Hypertension 2001;37:1199–208.

Reynolds III CF, Frank E, Perel JM, Imber SD, Cornes C, Miller MD, et al. Nortriptyline and interpersonal psychotherapy as maintenance therapies for recurrent major depression: a randomized controlled trial in patients older than 59 years. JAMA 1999;281:39–45.

Richmond R, Zwar N. Review of bupropion for smoking cessation. Drug Alcohol Rev 2003;22:203–20.

Rose JE, Ananda S, Jarvik ME. Cigarette smoking during anxiety-provoking and monotonous tasks. Addict Behav 1983;8:353–9.

Roy MP, Steptoe A, Kirschbaum C. Association between smoking status and cardiovascular and cortisol stress responsivity in healthy young men. Int J Behav Med 1994;1:264–83.

Rush CR, Kollins SH, Pazzaglia PJ. Discriminative-stimulus and participant-rated effects of methylphenidate, bupropion, and triazolam in d-amphetamine-trained humans. Exp Clin Psychopharmacol 1998;6:32–44.

Schoder H, Silverman DH, Campisi R, Karpman H, Phelps ME, Schelbert HR, et al. Effect of mental stress on myocardial blood flow and vasomotion in patients with coronary artery disease. J Nucl Med 2000;41:11–6.

Seraganian P, Roskies E, Hanley JA, Oseasohn R, Collu R. Failure to alter psychophysiological reactivity in Type A men with physical exercise or stress management programs. Psychol Health 1987;1:195–213.

Sheffield D, Krittayaphong R, Cascio WE, Light KC, Golden RN, Finkel JB, et al. Heart rate variability at rest and during mental stress in patients with coronary artery disease: differences in patients with high and low depression scores. Int J Behav Med 1998;5:31–47.

Shiffman S. Relapse following smoking cessation: a situational analysis. J Consult Clin Psychol 1982;50:71–86.

Shiffman S, Waters AJ. Negative affect and smoking lapses: a prospective analysis. J Consult Clin Psychol 2004;72:192–201.

Slemmer JE, Martin BR, Damaj MI. Bupropion is a nicotinic antagonist. J Pharmacol Exp Ther 2000;295:321–7.

Stone PH, Krantz DS, McMahon RP, Goldberg AD, Becker LC, Chaitman BR, et al. Relationship among mental stress-induced ischemia and ischemia during daily life and during exercise: the Psychophysiologic Investigations of Myocardial Ischemia (PIMI) study. J Am Coll Cardiol 1999;33:1476–84.

Straneva P, Hinderliter A, Wells E, Lenahan H, Girdler S. Smoking, oral contraceptives, and cardiovascular reactivity to stress. Obstet Gynecol 2000;95:78–83.

Straneva-Meuse PA, Light KC, Allen MT, Golding M, Girdler SS. Bupropion and paroxetine differentially influence cardiovascular and neuroendocrine responses to stress in depressed patients. J Affect Disord 2004;79:51–61.

Strike PC, Steptoe A. Systematic review of mental stress-induced myocardial ischaemia. Eur Heart J 2003;24:690–703.

Swan GE, Denk CE, Parker SD, Carmelli D, Furze CT, Rosenman RH. Risk factors for late relapse in male and female ex-smokers. Addict Behav 1988;13:253–66.

Swan GE, Ward MM, Jack LM, Javitz HS. Cardiovascular reactivity as a predictor of relapse in male and female smokers. Health Psychol 1993;12:451–8.

Taylor CB, Youngblood ME, Catellier D, Veith RC, Carney RM, Burg MM, et al. Effects of antidepressant medication on morbidity and mortality in depressed patients after myocardial infarction. Arch Gen Psychiatry 2005;62:792–8.

Tersman Z, Collins A, Eneroth P. Cardiovascular responses to psychological and physiological stressors during the menstrual cycle. Psychosom Med 1991;53:185–97.

Tsuda A, Steptoe A, West R, Fieldman G, Kirschbaum C. Cigarette smoking and psychophysiological stress responsiveness: effects of recent smoking and temporary abstinence. Psychopharmacology 1996;126:226–33.

Vocks S, Ockenfels M, Jurgensen R, Mussgay L, Ruddel H. Blood pressure reactivity can be reduced by a cognitive behavioral stress management program. Int J Behav Med 2004;11:63–70.

Wang Y, Fice DS, Yeung PK. A simple high-performance liquid chromatography assay for simultaneous determination of plasma norepinephrine, epinephrine, dopamine and 3,4-dihydroxyphenyl acetic acid. J Pharm Biomed Anal 1999;21:519–25.

Ward MM, Swan GE, Jack LM, Javitz HS. Effect of smoking cessation and relapse on cardiovascular levels and reactivity. Psychopharmacology 1994;114:147–54.

Yoshida K, Utsunomiya T, Morooka T, Yazawa M, Kido K, Ogawa T, et al. Mental stress test is an effective inducer of vasospastic angina pectoris: comparison with cold pressor, hyperventilation and master two-step exercise test. Int J Cardiol 1999;70:155–63.

Young R, Glennon RA. Nicotine and bupropion share a similar discriminative stimulus effect. Eur J Pharmacol 2002;443:113–8.