Nicotine & Tobacco Research, Volume 15, Number 2 (February 2013) 567–571

Brief Report

Perceived Treatment Assignment and Smoking Cessation in a Clinical Trial of Bupropion Versus Placebo

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Received November 17, 2011; accepted May 8, 2012

Abstract

Introduction: Psychoactive effects of smoking cessation medications such as bupropion may allow participants in smoking cessation clinical trials to correctly guess their treatment assignment at rates greater than chance. Previous research has found an association between perceived treatment assignment and smoking cessation rates among moderate to heavy smokers (≥10 cigarettes per day [cpd]) in two bupropion clinical trials.

Methods: The aim of this study was to determine the impact of perceived treatment assignment on end-of-treatment cotinine-verified smoking abstinence at Week 7 and Week 26 among African American light smokers (≤10 cpd) enrolled in a double-blind, placebo-controlled study of bupropion. Participants (n = 390) included in this study reported their perceived treatment assignment on the end-of-treatment (Week 7) survey.

Results: Participants were predominantly female (63.1%), 48.1 years of age (SD = 11.2), and smoked an average of 8 cpd (SD = 2.5). Participants given bupropion were more likely to correctly guess their treatment assignment (69%; 140/203) than those assigned to placebo (51.3%; 96/187) (p < .0001). After adjusting for treatment condition, participants who perceived assignment to bupropion versus placebo were not more likely to be abstinent than those who perceived assignment to placebo at Week 7 or at Week 26. The interaction between treatment and perceived treatment assignment was also nonsignificant.

Conclusions: Consistent with two previous studies testing bupropion, participants assigned to bupropion were more likely to correctly guess their treatment assignment than those assigned to placebo. However, in contrast to previous studies with heavier smokers, perceived treatment assignment did not significantly impact cotinine-verified abstinence in light smokers.

Introduction

Smoking cessation agents aimed at addressing symptoms of nicotine withdrawal and cravings are psychotropic medications. As such, they may provide cues (e.g., symptom reduction, side effects) to participants that they indeed are receiving the active drug (Hughes & Krahn, 1985). The felt effects of the active drug may be apparent and create greater expectancy for the therapeutic effects of the drug. Consequently, smoking cessation pharmacological clinical trials may be vulnerable to differential outcomes resulting from expectation bias. The properties of psychotropic drugs may limit researchers' ability to control for participant expectations, introducing a potential confound that could impact the validity of the results. Conversely, a lack of expectation for the drug, as would occur if participants believed they were assigned to placebo, may serve to reduce the positive effect of expectancy on treatment outcome (Oken, 2008). As such, clinical trials are advised to assess perceptions of treatment assignment (Price, Finniss, & Benedetti, 2008) and whether these perceptions impact study outcomes (Hughes & Krahn, 1985).

Several nicotine replacement therapy (NRT) trials have reported participants' perceived group assignment and examined the association between perceived assignment and smoking abstinence (Mooney, White, & Hatsukami, 2004). However, only two studies investigated the impact of perceived treatment assignment on smoking abstinence in double-blind, randomized, clinical trials of bupropion (Schnoll et al., 2008; Thomas et al., 2008). Both trials included smokers who consumed at least 10 cigarettes per day (cpd). Thomas et al.'s sample was exclusively African American, whereas Schnoll et al.'s

doi:10.1093/ntr/nts143
Advance Access publication September 4, 2012

sample was predominantly White. In contrast to studies finding no relationship between perceived treatment assignment and smoking abstinence in NRT trials (Mooney et al., 2004), both bupropion studies found that perceiving bupropion assignment was positively associated with biochemically verified smoking abstinence at end-of-treatment and long-term follow-up even after controlling for actual treatment assignment. Their findings may indicate that participants' expectations of receiving the active drug enhanced the treatment effect of bupropion.

Previous studies examining the association between perceived treatment assignment and smoking abstinence focused on heavy smokers (>10 cpd). Light smokers (≤10 cpd) report greater motivation and readiness to quit than heavy smokers (Okuyemi et al., 2004), however, they experience difficulty quitting even with the aid of smoking cessation pharmacology such as nicotine gum (Ahluwalia et al., 2006). In order to better understand the effects of pharmacotherapy on light smokers' cessation rates, research is needed to assess the relationship between perceived treatment assignment and quit rates among these smokers. The present study investigated the impact of perceived treatment assignment on smoking abstinence rates for African American light smokers (≤10 cpd) in a clinical trial of bupropion (active versus placebo) combined with health education counseling (HE) at end-of-treatment (Week 7) and 6-month follow-up. We hypothesized that participants in the treatment group would be more likely to report that they were given the active treatment (buproprion) in comparison to participants assigned to the placebo condition and that perceived assignment to bupropion would be related to greater success in cessation.

Methods

Study Design

Data were obtained from a placebo-controlled, randomized, clinical trial of bupropion combined with HE for smoking cessation among African American light smokers. Participants were randomized to bupropion (150 mg bid) or placebo for seven weeks. Study staff reviewed all procedures with eligible participants, including that the study participants would be randomly assigned to either bupropion or placebo, and obtained written informed consent. At baseline, each participant received a culturally tailored smoking cessation guide designed for African American light smokers. All participants received six sessions of HE more than 16 weeks, and were followed up through study Week 26. The clinical trial was conducted at an urban, community-based health clinic that serves predominantly low-income, African American patients. See Cox et al. (2011) for a more detailed description of the clinical trial. All procedures were approved and monitored by the University of Kansas Medical Center Human Subjects Committee.

Study Participants

Eligible participants self-identified as African American, were 18 years or older, interested in quitting smoking, smoked 10 cpd or less for at least 2 years, smoked at least 25 days in the past month, and smoked for at least 3 years. Participants were excluded if they were currently using other tobacco products, smoking cessation medications, pregnant (or consider becoming pregnant) or breast feeding, or had medical conditions that impacted their eligibility (e.g., insulin-dependent diabetes).

Measures

Perceived group assignment

Perceived group assignment was assessed at Week 7 (end of treatment) using a single question, "Do you think you were given Zyban or placebo when you were in the study?" Participants had two response options: (1) Zyban and (2) placebo.

Smoking abstinence

Smoking abstinence was assessed using biochemically verified self-report at Week 7 and Week 26. If participants reported that they had not smoked "any cigarettes at all" in the past seven days, 7-day point prevalence smoking abstinence was confirmed using tests for salivary cotinine (<15ng/ml).

Baseline measures

Participants provided demographic, psychosocial, tobacco-specific, and health information at baseline. Standardized demographic questionnaires were used to document age, gender, relationship status, income, employment, and education. Participants reported cpd, whether they smoked menthol or non-menthol cigarettes, and number of quit attempts in the past year. Nicotine dependence was assessed using the Fagerström Test for Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerström, 1991). The FTND consists of six items including time to first cigarette after waking and cpd; scores range from 0–10 with higher scoring indicating greater dependence. Smoking within 30 mins of waking is indicative of significant nicotine dependence. Additionally, participants' salivary cotinine levels were assessed. Symptoms of depression were assessed using the 10-item Center for Epidemiological Studies Depression Scale (CESD-10; Cole, Rabin, Smith, & Kaufman, 2004).

Analyses

Statistical analyses were conducted using SPSS version 18. Participant characteristics and smoking history are summarized in Table 1. Two sample *t* tests and chi-square analyses were conducted to determine if there were significant demographic, psychosocial, and tobacco-specific differences between participants who perceived their treatment group assignment to be bupropion and those who perceived their assignment to be placebo. A chi-square test was conducted to determine whether there were significant differences between the bupropion assigned group and the placebo assigned group on their perceptions of treatment assignment. The association between perceived treatment assignment (assessed at Week 7) and smoking abstinence at Week 7 and Week 26 was investigated using multiple logistic regression. Initially actual treatment assignment was regressed on verified smoking abstinence, followed by adding perceived group assignment, then adding the interaction between perceived group assignment and actual treatment assignment.

Results

Participants

Of the 540 participants enrolled in the clinical trial and randomized to the treatment and placebo groups, 393 participants returned for the end-of-treatment (Week 7) survey, with 390 reporting their perceived treatment assignment. The sample was predominantly female (63.1%), 48.1 years of age (*SD* = 11.2), and smoked 8 cpd (*SD* = 2.5). Further, 70.3% smoked within 30 mins of

Table 1. Participant Baseline Characteristics

	Total (n = 390)	Perceived bupropion assignment (n = 231)	Perceived placebo assignment (n = 159)
Demographic variables			
Age in years, mean (*SD*)	48.1 (11.2)	48.6 (11.0)	47.5 (11.42)
Female, *n* (%)	246 (63.1%)	144 (62.3%)	102 (64.2%)
Married/living with partner, *n* (%)	113 (29%)	64 (27.7%)	49 (30.8%)
Monthly income <$1800, *n* (%)	241 (61.8%)	145 (62.8%)	96 (60.4%)
< High school graduate, *n* (%)	326 (83.6%)	190 (82.3%)	136 (85.5%)
Tobacco-related variables			
Cigarettes per day, mean (*SD*)	8 (2.5)	7.9 (2.6)	8.1 (2.5)
Smoke menthol cigarettes, *n* (%)	317 (81.3%)	184 (79.7%)	133 (83.6%)
Smoke within 30 mins of waking, *n* (%)	274 (70.3%)	161 (69.7%)	113 (71.1%)
FTND, mean (*SD*)	3.1 (1.7)	3.1 (1.7)	3.1 (1.6)
Serum cotinine in ng/ml, mean (*SD*)	265.9 (155.1)	255.7 (159.2)	280.8 (148.1)
24 hr quit attempts in last year, mean (*SD*)	3.3 (5.9)	3.7 (6.7)	2.8 (4.3)

Note. FTND = Fagerström Test for Nicotine Dependence. No statistically significant differences were found between those who perceived bupropion and those who perceived placebo on any baseline characteristics.

waking, and 81.3% smoked mentholated cigarettes. Participants who returned for the Week 7 follow-up and reported their perceived treatment assignment (n = 390) were more likely to be male, be older, smoke non-menthol cigarettes, report less nicotine dependence, and have lower baseline salivary cotinine levels than those not returning for the Week 7 evaluation (n = 150). Eleven of the 390 enrolled participants were lost to follow-up at Week 26 and were treated as smokers for the analyses.

Perceived Treatment Assignment

Of the 390 total participants, 230 (59%) perceived their assignment to be bupropion. There were no significant differences on the demographic, psychosocial, and smoking variables between participants who perceived bupropion and those who perceived placebo.

Blindness Integrity

Of the 187 participants assigned to placebo, 96 (51.3%) perceived their treatment assignment to be placebo, and 91 (48.7%) perceived bupropion. One hundred and forty of the 203 (69%) participants assigned to bupropion perceived their treatment assignment to be bupropion, and 63 (31%) perceived placebo. Participants assigned to bupropion (69%) were significantly more likely to correctly guess their treatment assignment than those assigned to placebo (51.3%) ($p < .0001$).

Association Between Perceived Treatment Assignment and Smoking Abstinence

Separate logistic regression analyses were performed with Week 7 and Week 26 smoking abstinence as the criterion variable (abstinence rates are presented in Table 2). The analyses included treatment assignment, perceived treatment assignment, and treatment assignment versus perceived treatment assignment. Participants assigned to bupropion were more likely to be abstinent at Week 7 than those assigned to placebo (OR = 2.78, 95% CI 1.42–5.42, p = .003). When added to the model with treatment assignment, perceived treatment assignment was not a significant predictor of abstinence at Week 7 (p = .57) and the interaction term was not statistically significant (p = .89). We found no treatment effect on smoking abstinence at Week 26 (p = .36), perceived treatment assignment did not predict Week 26 smoking abstinence (p = .31), and there was no significant interaction (p = .43).

Discussion

Consistent with our hypotheses, participants in the bupropion condition were more likely to correctly guess their treatment assignment than participants assigned to placebo. However, contrary to our hypotheses, we found no significant relationship between perceived treatment assignment and smoking abstinence when controlling for actual treatment assignment at Week 7 and Week 26. Following Hughes and Krahn's (1985) recommendation, we tested for bias to determine whether differences in perceived treatment assignment between participants assigned to treatment and those assigned to placebo impacted the validity of study results. We did not find any differences in smoking abstinence between those who correctly identified bupropion assignment and those who incorrectly perceived placebo assignment at either Week 7 or Week 26, indicating no bias in the findings. Our results suggest that

Table 2. Cotinine-Verified 7-Day Point Prevalence Abstinence

	Bupropion assignment, *n* (%)			Placebo assignment, *n* (%)		
Smoking abstinence	Perceived bupropion	Perceived placebo	Total (n = 203)	Perceived bupropion	Perceived placebo	Total (n = 187)
Quit at Week 7	47 (33.6 %)	17 (27.0 %)	64 (31.5%)	14 (15.4 %)	12 (12.5 %)	26 (13.9%)
Quit at Week 26	11 (17.5 %)	24 (17.1 %)	35 (17.2%)	14 (15.4 %)	10 (10.4 %)	24 (12.8 %)

perceived treatment assignment does not impact the relationship between treatment assignment and smoking abstinence.

The nonsignificant associations between perceived treatment assignment and smoking abstinence at Week 7 and Week 26 are in contrast to previous studies (Schnoll et al., 2008; Thomas et al., 2008). These studies found an association between perceived treatment assignment and smoking abstinence at each timepoint assessed. One difference in study design between the current study and the earlier studies is the number of response options for the item assessing perceived treatment assignment. The present study offered only two response options ("bupropion" and "placebo"), whereas, both Thomas et al. and Schnoll et al. provided participants with three response options when assessing perceived treatment assignment: "bupropion," "placebo," and "unsure" or "don't know." Thomas et al. also included a category for "some Zyban and some placebo", which was later collapsed with the "don't know' category for analysis. In both the studies, "unsure" or "don't know" was included as a third category in the analyses. However, in the earlier studies only a small proportion of the participants (18%) chose any one of the additional options, but we cannot determine the extent to which this difference impacted our results. A second difference between this study and the earlier studies is that both Thomas et al. and Schnoll et al. included only moderate to heavier smokers (≥10 cpd), whereas this clinical trial focused on light smokers (≤10 cpd). Third, the clinical trial examined by Schnoll et al. provided 10 weeks of bupropion treatment (Lerman et al., 2002), whereas the trial by Thomas et al. and the current trial provided seven weeks of treatment.

In this clinical trial, retention rates at Week 7 (when perceived treatment assignment was assessed) was 76% for those assigned to bupropion and 70% for those assigned to placebo (Cox et al., 2011).We observed some demographic differences between participants retained in the study and those lost to follow-up. Participants included in this study (i.e., attended the Week 7 study session) had lower nicotine dependence and lower baseline cotinine levels—characteristics that we would expect to yield higher abstinence rates. However, quit rates for the clinical trial were modest at Week 7 and nonsignificant at Week 26 (Cox et al., 2012). Therefore, given the small numbers of participants that were abstinent at Week 7 and the end of the study, our findings may be better explained by the overall low quit rates for light smokers treated with bupropion in this study. Several possibilities exist including that bupropion may be less effective for light smokers than for heavy smokers or light smokers may place less importance on pharmacotherapy in their smoking cessation efforts. In fact, 46% of all participants in the clinical trial and almost 40% of those assigned to bupropion reported that the study medication was not helpful in assisting them to quit (Nollen et al., 2012).

No prior studies have examined the relationship between perceived treatment assignment and smoking cessation among light smokers. Light smokers have generally been excluded from smoking cessation pharmacotherapy clinical trials and few studies have focused on this population of smokers (Fagan & Rigotti, 2009). Only three randomized control trials have examined the efficacy of NRTs versus placebo for light smokers (Ahluwalia et al., 2006; Cox et al, 2011; Shiffman, 2005). An additional study investigated the relative efficacy of two types of counseling combined with bupropion or NRT but did not include a placebo control group (Gariti et al., 2009). Findings from the placebo-controlled trials were mixed with one of the three studies supporting the efficacy of pharmacotherapy for smoking cessation with light smokers.

In conclusion, smoking is maintained by psychological and physiological factors. Smoking cessation medications target the physiological aspects of nicotine dependence; however, the psychological mediators for the effect of bupriopion that promote cessation among light smokers are not clearly understood (McCarthy et al., 2008). Expectancy has been shown to influence treatment outcome for several health-related conditions (Oken, 2008) and may be a mediatior for smoking cessation treatment. Future research should examine the role of expectancy related to pharmacotherapy for smoking cessation in light smokers. Evaluating light smokers' beliefs about the efficacy of pharmacological treatment for smoking cessation should also be considered in future studies.

Funding

The clinical trial was supported by the National Cancer Institute at the National Institutes of Health (NCI/NIH grant CA 091912 to L. S. C.). J. S. A. is supported in part by grant 1P60MD003422 from the National Institute for Minority Health Disparities at the NIH. The authors are solely responsible for the study design, data collection, analysis and interpretation of the data, writing the manuscript, and decision to submit the manuscript for publication.

Declaration of Interests

None declared.

Acknowledgments

We would like to express our appreciation to Swope Health Central, the recruitment site for the clinical trial, and the volunteers who participated in this research.

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