Published in final edited form as:

Am J Drug Alcohol Abuse. 2011 November ; 37(6): 487–490. doi:10.3109/00952990.2011.598591.

Bupropion-SR for Smoking Cessation in Early Recovery from Alcohol Dependence: A Placebo-Controlled, Double-Blind Pilot Study

Maher Karam-Hage^{a,*}, Stephen Strobbe^b, Jason D. Robinson^a, and Kirk J. Brower^b

^aThe University of Texas M. D. Anderson Cancer Center

^bUniversity of Michigan Medical School

Abstract

We conducted a double-blind pilot study involving 11 alcohol and nicotine dependent patients randomized to receive either bupropion or placebo. Four of 6 patients on bupropion and 1 of 5 patients on placebo were abstinent from smoking at the end of medication phase. Those in the bupropion group reported significantly less craving ($p < 0.02$) and less exposure to cigarette smoke over time (expired CO; $p < 0.01$). There were no serious adverse events, and no main effects of medication group on either per subject or total number of adverse events. All those who completed treatment remained abstinent from alcohol.

Keywords

Bupropion; smoking cessation; alcohol dependence

INTRODUCTION

Cigarette smoking prevalence in the general population is currently estimated to be under 20% (1). However, among alcohol dependent (AD) patients, between 75% and 90% have been found to be smokers (2,3). AD patients are more likely to die from smoking-related illnesses than from alcoholism itself (4). Several pharmacotherapies have been used, in addition to behavioral therapies, as successful smoking cessation treatments in different subpopulations, but no smoking cessation regimen has been conclusively established in the subpopulation of those with both nicotine and alcohol dependence (AD). Nicotine replacement, in particular the patch, was reported to have less efficacy among patients with current drinking or history of AD compared with none (5). Varenicline is the most recent and most efficacious smoking cessation medication available, however reports of increased depressive symptoms and suicidal ideation among those with mental health disorders have restricted its use, especially among substance users and alcoholics, as both groups have a high incidence of comorbid psychiatric disorders. Bupropion, a well established smoking cessation treatment (6), seems to be effective for those with history of AD (5).

*Correspondence to: Maher Karam-Hage, Department of Behavioral Science, The University of Texas M. D. Anderson Cancer Center, 1155 Pressler St., Unit 1330, Houston, TX 77030, Tel: 713-792-7113 Fax: 713-745-4286, maherkaram@mdanderson.org.

However, it has yet to be conclusively established that bupropion is safe and effective in AD individuals who are in the early stages of recovery from alcohol dependence. Two reports, which were based on post hoc analysis, suggest that bupropion can be used safely and effectively to treat smoking cessation among the alcohol dependent in different stages of recovery (7,8). However, one prospective study found that adding bupropion to the nicotine patch did not improve smoking cessation outcome rates beyond those of the patch alone among alcoholic veterans in early recovery (9). Thus, it is unclear whether bupropion is effective for smoking cessation among AD individuals in early recovery, it seems to be safe, we hope that our study serves as a “proof of concept” that would stimulate further research in this area.

The aim of this pilot study was to evaluate the efficacy of bupropion to increase smoking cessation, decrease exposure to smoking, and reduce nicotine withdrawal symptoms, in alcoholics in early recovery, using a randomized, double-blind, placebo-controlled clinical trial. We hypothesized that bupropion would increase smoking abstinence, reduce nicotine withdrawal symptoms, and reduce smoking exposure among those who were unable to maintain smoking abstinence. Our secondary aim was to monitor the safety of bupropion in this sample of alcohol and nicotine dependent smokers.

METHODS

In a double-blind, placebo-controlled randomized design, our study participants were six female and five male nicotine-dependent (ND) and AD patients. Participants were in early recovery (more than 6 weeks but less than 6 months since their last drink) and had sought treatment for alcohol dependence at the University of Michigan outpatient addictions treatment program. The inclusion criteria included being 18 to 65 years old, smoking 10 or more cigarettes per day (CPD) continuously for at least 1 year and having nicotine dependence based on a Fagerström Test of Nicotine Dependence (FTND) (10) with a score of 3 or more, reporting interest in smoking cessation, and meeting DSM-IV alcohol dependence criteria, based on SCID administration (11). Exclusion criteria consisted of: having any current or past-year substance use disorder other than alcohol, having a personal or family history of a seizure disorder, having a predisposition to seizures (such as a history of brain tumor, severe head trauma, or stroke), or eating disorders, or having abnormally high liver function tests (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] levels greater than 3 times the maximum of normal). This protocol was approved by the University of Michigan Institutional Review Board (IRB), and written informed consent was obtained.

During a one year period, 224 patients admitted to the outpatient intensive treatment program were screened. Only 30 patients were eligible as dependent on alcohol and nicotine only, and 20 were interested in participating. Of those 20, six were not eligible based on other criteria after baseline screening visit and three chose to withdraw from the study prior to randomization for different reasons (e.g., changed their mind, logistical impediments) and therefore were not randomized. The remaining 11 were randomized to receive either bupropion-SR 150 mg (once per day for 7 days then twice per day for 7 weeks) or identically appearing placebo capsules. An eight-week course of medication was chosen for

comparability with other bupropion trials (12). All participants received the booklet “You Can Quit Smoking” (13) with minimal smoking cessation counseling (10 minutes per visit, consisting of going over the booklet). Laboratory measures of liver and kidney functioning and bupropion levels were collected at screening and at Weeks 4 and 8 of the study medication phase. In addition, self-reported smoking abstinence was corroborated with collateral information (as identified and approved to contact by patients with their written consent). The numbers of cigarettes smoked, and any alcohol drinking were recorded for each patient via the Time Line Follow Back (TLFB) method (14). Study clinicians, which included addiction psychiatry fellows, a nurse specialist (2nd author), or an addiction psychiatrist (1st author), provided the counseling. They also collected questionnaire data at every visit including the Wisconsin Smoking Withdrawal Scale (WSWS) (15), a measure of nicotine withdrawal symptoms, and the Brief Symptom Inventory (BSI) (16), a measure of psychological distress. To confirm self-reports of abstinence we collected expired carbon monoxide (CO) and an alcohol breathalyzer sample at every visit, and urine drug screens at four random visits. All participants were compensated up to \$100 in 4 installments.

Our primary analytic strategy used a multilevel modeling approach to examine the effects of medication group and time (in days post-randomization) on repeated measures of smoking exposure (CPD and expired CO levels) and smoking withdrawal symptoms (WSWS). The multilevel modeling approach provides a generalization to the classic linear regression model, using likelihood functions instead of least squares to estimate effects. We applied the Kenward-Roger correction to control for the possibly inflated Type I error rates that can occur with repeated-measures data taken from small samples (17). To test the effect of medication group upon smoking abstinence rates, we used Fisher’s Exact Test. The 11 participants who were randomized to active medication (6 participants) or placebo (5 participants) were our analyzed intention-to-treat population.

RESULTS

On average, participants smoked approximately one pack of cigarettes per day at baseline, and reported problem drinking in the last 18.8 years for those randomized to bupropion and 20.8 years for those who were on placebo (NS). The mean FTND score was at 5.2 for bupropion and 4.4 for placebo group (NS). Two participants discontinued medication prior to completing the treatment phase, one because of anxiety (placebo subject) and another because of insomnia (bupropion subject). In all, a total of 9 of 11 randomized participants completed the medication phase of the study. All of the participants received weekly group treatments for alcohol dependence, and all remained abstinent from alcohol (confirmed with breathalyzer and liver enzymes in addition to reports of collateral informants) and drugs (confirmed with urine drug screens).

Our main outcome measures were smoking exposure (CPD and expired CO) and withdrawal severity (WSWS score) at each time point, with abstinence at end of treatment (EOT) as a secondary outcome measure (given our small sample size). We analyzed levels of CPD, CO, and withdrawal symptoms by modeling medication group, time post-medication, and the interaction between the two terms as fixed effects, with medication group as a random effect. There were no significant effects of medication group or time on CPD or the BSI. For

smoking abstinence at EOT, 4 of 6 patients on bupropion and 1 of 5 patients on placebo were abstinent ($OR = 2.08$, 95% CI [0.50, 127.90]). As shown in Figure 1a significant medication $\times$ time interaction was found for expired CO, $F(1, 68.4) = 7.03$; $p < 0.01$, with the regression line slopes indicating that participants in the bupropion group produced less expired CO ($PE = -2.66$, $SE = 0.45$, $t(68.3) = -5.93$, $p < 0.0001$) than those in the placebo group ($PE = -0.87$, $SE = 0.51$, $t(68.6) = -1.72$, $p = 0.09$) over time. Figure 1b illustrates a significant medication $\times$ time interaction was found for the craving dimension on WSWS, $F(1, 68.6) = 5.72$, $p < 0.02$, with the regression line slopes indicating that participants on bupropion reported less craving over time ($PE = -0.48$, $SE = 0.13$, $t(68.4) = -3.61$, $p = 0.0006$) during treatment than those on placebo ($PE = 0.00$, $SE = 0.15$, $t(68.8) = 0.00$, $p = 0.99$).

In terms of adverse events following randomization, depressed mood ($n=5$), constipation ($n=3$), and fatigue ($n=3$) were the symptoms most frequently reported by patients. Eight other adverse events were reported by two patients in the study. There was no main effect of medication group on either individual or total number of adverse events. We found no significant main effects for the medication group compared with placebo on any of the laboratory values on baseline, or follow-up, or the interaction of treatment and time on follow-up values. Laboratory results included albumin, ALT, AST, bilirubin, gamma-glutamyl transferase (GGTP), and creatinine. As would be expected, a significant main effect of the medication group was found for bupropion exposure ($F(1,13) = 8.93$, $p < .02$), with patients in the bupropion group all having bupropion blood values indicative of taking the medication ($M = 42.8$ ng/ml, $SE = 10.25$, range = 28 to 102 ng/ml) compared to those taking placebo ($M = 0$).

DISCUSSION

We found a significant reduction in smoking exposure and withdrawal symptoms, as evidenced by significantly lower levels of expired CO and WSWS craving. In addition, more bupropion- vs. placebo-treated patients achieved abstinence in this study, although not to a statistically significant level due to the small sample size. Finally, all those who finished our study had remained abstinent from alcohol. Our finding of a significant reduction in smoking exposure is notable as smoking reduction has been shown to lead to cessation in nonalcoholic individuals (18).

We found that prescribing bupropion for recently abstinent AD patients (6 weeks to 6 months after their last drink) did not cause any undue risks compared to placebo, nor were any seizures reported. We hope this finding will encourage further studies and clinical use of bupropion among alcoholics in early recovery. Nevertheless, the small sample size and low incidence of seizures does not allow any firm conclusions to be made about the risk of seizures in this population. Our study has several limitations. The most important is its small sample size. In addition, it included a very select population of individuals who met criteria for only nicotine and alcohol dependence, as well as mostly white females. Despite these limitations, this study yields important preliminary data on the efficacy and safety of bupropion that are promising for smoking cessation among patients in recent recovery from

alcohol dependence. We hope our study serves as a proof of concept and stimulates larger controlled clinical trials in this difficult to treat sub-population.

Acknowledgments

We wish to thank the psychiatry residents and addiction fellows at the University of Michigan Medical School who helped collect the data (in particular, Chandan Nayak, MD), and The University of Michigan Medical School Advisory Council on Clinical Research and the University of Michigan's General Clinical Research Center (GCRC) Grant # MO1 RR00042 for their support.

Reference List

1. CDC. Cigarette use among high school students--United States, 1991–2009. *MMWR Morb Mortal Wkly Rep*. 2010; 59(26):797–801. [PubMed: 20613702]
2. Bobo JK. Nicotine dependence and alcoholism epidemiology and treatment. *J Psychoactive Drugs*. 1989 Jul; 21(3):323–329. [PubMed: 2681630]
3. Joseph AM. Nicotine treatment at the Drug Dependency Program of the Minneapolis VA Medical Center. A researcher's perspective. *J Subst Abuse Treat*. 1993 Mar; 10(2):147–152. [PubMed: 8389895]
4. Hurt RD, Offord KP, Croghan IT, et al. Mortality following inpatient addictions treatment. Role of tobacco use in a community-based cohort. *JAMA*. 1996 Apr 10; 275(14):1097–1103. [PubMed: 8601929]
5. Hays JT, Schroeder DR, Offord KP, et al. Response to nicotine dependence treatment in smokers with current and past alcohol problems. *Ann Behav Med*. 1999; 21(3):244–250. [PubMed: 10626032]
6. McAfee T, France E. Sustained-release bupropion for smoking cessation. *N Engl J Med*. 1998 Feb 26; 338(9):619–620. [PubMed: 9480438]
7. Leeman RF, McKee SA, Toll BA, et al. Risk factors for treatment failure in smokers: Relationship to alcohol use and to lifetime history of an alcohol use disorder. *Nicotine Tob Res*. 2008 Dec; 10(12):1793–1809. [PubMed: 19023831]
8. Hayford KE, Patten CA, Rummans TA, et al. Efficacy of bupropion for smoking cessation in smokers with a former history of major depression or alcoholism. *Br J Psychiatry*. 1999; 174:173–178. [PubMed: 10211174]
9. Grant KM, Kelley SS, Smith LM, Agrawal S, Meyer JR, Romberger DJ. Bupropion and nicotine patch as smoking cessation aids in alcoholics. *Alcohol*. 2007 Aug; 41(5):381–391. [PubMed: 17889314]
10. Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO. The Fagerström Test for Nicotine Dependence: A revision of the Fagerström Tolerance Questionnaire. *Br J Addiction*. 1991; 86(9):1119–1127.
11. First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JB. Structured Clinical Interview for Axis I DSM-IV Disorders, Patient Edition (SCID-II, version 2.0). New York: Biometrics Research Department, New York State Psychiatric Institute; 1994.
12. Hurt RD, Sachs DP, Glover ED, et al. A comparison of sustained-release bupropion and placebo for smoking cessation. *N Engl J Med*. 1997 Oct 23; 337(17):1195–1202. [PubMed: 9337378]
13. US Department of Health and Human Services. You can quit smoking. Consumer guide. 2006. Available at: URL: <http://www.ahrq.gov/consumer/tobacco/quits.pdf>.
14. Shiffman S. How many cigarettes did you smoke? Assessing cigarette consumption by global report, time-line follow-back, and ecological momentary assessment. *Health Psychol*. 2009; 28(5):519–526. [PubMed: 19751076]
15. Welsch SK, Smith SS, Wetter DW, Jorenby DE, Fiore MC, Baker TB. Development and validation of the Wisconsin Smoking Withdrawal Scale. *Exp Clin Psychopharmacol*. 1999; 7(4):354–361. [PubMed: 10609970]
16. Derogatis, LR.; Spencer, PM. The Brief Symptom Inventory (BSI): Administration, Scoring and Procedures Manual. Baltimore: Clinical Psychometric Research; 1982.

17. Kenward MG, Roger JH. Small sample inference for fixed effects from restricted maximum likelihood. *Biometrics*. 1997 Sep; 53(3):983–997. [PubMed: 9333350]
18. Hughes JR, Carpenter MJ. Does smoking reduction increase future cessation and decrease disease risk? A qualitative review. *Nicotine Tob Res*. 2006 Dec; 8(6):739–749. [PubMed: 17132521]

a

b

Figure 1.

a. Results for continuous measures of smoking confirmed by expired CO

b. Results of cigarette craving measures by progression of time in weeks