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Bupropion-SR for Smoking Reduction and Cessation in Alcohol-Dependent Outpatients: A Naturalistic, Open-Label Study

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Abstract

Background—We sought to determine whether sustained-release bupropion (bupropion-SR) reduces smoking and promotes smoking cessation among alcohol-dependent (AD) smokers while they are in early recovery from alcohol.

Methods—We conducted an open-label, naturalistic study among AD smokers enrolled in an outpatient treatment program. The treatment group (n=58) was offered bupropion-SR and brief smoking cessation counseling. A control group (n=57) was matched to the treatment group by age, sex, ethnicity, cigarette use, and years of alcohol dependence. The controls received no smoking cessation intervention. We collected tobacco and alcohol abstinence data for 6 months after enrollment.

Results—Participants in the treatment group were more likely to abstain from smoking than controls, at any of the follow-up time point. The treatment group smoked less cigarettes per day (CPD) at baseline, 30 days and 180 days post-baseline, compared to controls. These findings persisted after adjusting for possible covariates.

Conclusion—Bupropion-SR may be helpful to quit or reduce smoking for recently abstinent AD individuals.

Keywords

alcohol dependence; bupropion; nicotine; treatment; smoking; cessation

INTRODUCTION

An estimated 80% of alcohol-dependent (AD) individuals are reported to be smokers [1;2], and approximately 70% of these AD smokers are nicotine dependent [2-4]. Although many adverse health consequences are attributed to the use of either alcohol or cigarettes alone, when used together, they give rise to multiplicative and even exponential health risks [5-8].

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Smoking cessation is rarely a component of treatment programs for alcohol and other drug dependence [9], despite tobacco use being the leading cause of death among current or former patients in alcohol or substance dependence treatment programs [10]. Evidence suggests that many AD patients are interested in quitting smoking either during or right after treatment for alcohol dependence [9]. Furthermore, studies have found that adding a tobacco cessation component to alcohol dependence treatment programs does not impact recovery from alcohol dependence and may even improve patients' chances of maintaining abstinence from alcohol [11;12]. Unfortunately, while one of the most safe and effective treatments is nicotine replacement therapy (NRT) [13], it has been found to be less efficacious among alcohol dependent smokers than among smokers in the general population [14]. One potential alternative is sustained-release bupropion (bupropion-SR), which has been shown to be an effective smoking cessation aid in the general population as a monotherapy [15] and in combination with nicotine replacement therapy (NRT) [16-18]. Bupropion-SR has been found to be effective in patients with a history of alcohol dependence who have been abstinent for over 12 months [19;20]. However, its safety and effectiveness during early recovery (between 1 to 12 months of alcohol abstinence) in AD individuals has not yet been conclusively established [21]. In one prospective study during early recovery from alcohol, adding bupropion-SR to the nicotine patch was well tolerated but it did not improve smoking cessation outcomes among AD military veterans in alcohol treatment [22]. Additionally, two retrospective studies showed that bupropion-SR increased smoking cessation rates in AD outpatients who had been abstinent for more than 12 months but not among those who were currently drinking. [19;20]. Thus, it is unclear whether bupropion-SR by itself is a safe and effective smoking cessation treatment for AD patients during early recovery.

One major advantage of bupropion-SR over the newer non-nicotine-based smoking cessation medication varenicline, when used among AD smokers, may be its antidepressant effect. AD patients in treatment have been shown to have high rates of psychiatric comorbidities [23], such as depression, anxiety, and insomnia [24;25], and these comorbidities may put AD patients' at higher risk of developing varenicline-associated neuropsychiatric symptoms, according to the black box warning recently mandated by the U.S. Food and Drug Administration [26].

We conducted an open-label naturalistic study among AD smokers enrolled in an outpatient alcohol treatment program and matched them to controls who received no smoking cessation treatment. Our goal was to determine whether bupropion-SR reduced smoking and promoted smoking cessation among AD smokers while they were in early recovery from alcohol. We also sought to evaluate any emergence of adverse events to help determine the safety of prescribing bupropion-SR for this population.

METHODS

Participants

Study participants were actively enrolled in an outpatient program for alcohol dependence treatment at the University of Michigan and another affiliated community hospital. To be included in the study, patients had to be AD, as classified in the fourth edition of the

Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), and be in *early* full remission (i.e., 1-12 months of abstinence). In addition, they had to be DSM-IV nicotine dependent and have smoked 10 or more cigarettes daily over the previous year. Patients were excluded from the study if they had been abstinent from alcohol for more than a year, were actively undergoing smoking cessation treatment, were older than 65 years, or had a history of seizure, severe head trauma, an eating disorder, bipolar disorder, or schizophrenia. The smokers in the control group were not necessarily motivated to quit and they did not receive any smoking cessation counseling or medication while they were enrolled in the alcohol treatment program. The study and data collection were approved by the Institutional Review Board at the University of Michigan.

The treatment group started with 351 patients who were screened between July 2000 to July 2002. All potential participants with psychiatric comorbidities (i.e., depression, anxiety, or insomnia) were evaluated by an addiction psychiatrist (first author) and were treated and stabilized for at least one month before starting bupropion-SR treatment. About half the sample (179) met the study inclusion criteria. Of those 179 patients, only 58 were interested in quitting smoking within the next 6 months and in taking the study medication for that purpose. Participants consented to take bupropion-SR either to try quitting in the following 4 weeks or to prepare themselves to quit (if they were not ready to quit within 4 weeks). To provide controls for the smoking cessation intervention (medication and brief counseling), we used previously collected data from a similar group of patients who did not receive any smoking cessation intervention. These data were collected in the same treatment center among alcoholic-dependent smokers who received treatment for alcohol dependence but did not receive any assistance for smoking cessation (methodology published elsewhere [27]). We selected 57 controls from this control database of 389 patients as best matches. All controls had completed questionnaires upon enrolling in the alcohol treatment program and had 3-and 6-month follow-up data available.

Cases and controls were matched using case-control sampling (PROC SURVEYSELECT; SAS Version 9.2, SAS Institute Inc, Cary, NC) that was stratified on the basis of age, sex, race/ethnicity, number of cigarettes per day (CPD) at baseline, and years of AD. Case-control sampling was conducted because of the large discrepancy between the numbers of smokers who met the inclusion criteria from the controls database (n=218) and treatment group participants (n=58), and because of the potential for confounding represented by the stratified factors. Even though the number of study-eligible smokers in each group was nearly identical, it is unknown how many smokers in the control group would have accepted bupropion-SR if treatment had been offered. Further, the unaided smoking cessation abstinence rate for the entire control group sample was around 10%, as we previously published [27].

Procedures

Information about patient characteristics, motivation to quit smoking, CPD, drinks per day, years of smoking and drinking, and alcohol treatment participation was collected at baseline for both groups. At post-baseline follow-up time points, we collected data about CPD and alcohol use (reported as the number of drinks per drinking day), in addition to eliciting

information about side effects from the medication. The vast majority of patients in both treatment and control group received outpatient group therapy for alcohol dependence at least one session per week for 3 to 6 months, while some received an additional one-on-one individual session per week. The follow-up time points for treatment group were as follows: the first visit occurred between 1- and 4-week after patients started bupropion-SR, the second visit occurred between 5-12 weeks, and the third visit around 6 months ($\pm$ one month). Patients began 8 weeks of Bupropion-SR pharmacotherapy while still using tobacco, with instruction to quit two weeks after initiating medication. Control group patients had a slightly different schedule of follow-ups, at 4 weeks ($\pm$ one week) and at 6 months ($\pm$ one month) for data collection (Fig. 1). At each outpatient visit, we collected data about related potential covariates, including the number of drinks per drinking day during the previous week and the number of Alcohol Anonymous (AA) sessions attended per week during the previous period (as this could affect the amount of smoking or drinking). CPD was collected as an ordinal variable coded as '0' for none, '1' for 1-10 CPD, '2' for 11-20 CPD, '3' for 21-30 CPD, and '4' for $\geq$ 31 CPD. Abstinence from smoking during the previous week was determined from the CPD and was calculated using the intent-to-treat (ITT) approach, a conservative approach that treats subject drop-outs and missing data points as "relapses" in order to minimize Type I error. We also analyzed the models using only the available data (i.e., efficacy subset analysis), but the results were similar to those of the ITT approach, so we decided to report the ITT results only. In the treatment group, self-reports of smoking abstinence were corroborated in a subgroup ($n=34$) by measuring expired carbon monoxide (CO). Self-reported abstinence correlated above $r=0.8$ with expired CO, using the recommended cut-off of ≥ 8 ppm [28].

Statistical Approach

We used a multilevel modeling approach (a hierarchical linear model) to examine the effects of treatment and time (in days since baseline) on repeated measures of 7-day point prevalence of reported CPD (with ordinal categories). To analyze the CPD and abstinence models, we used generalized linear mixed model (GLMM; SAS PROC GLIMMIX version 9.2, SAS Institute Inc, Cary, NC), a special case of the linear mixed model (LMM) designed for nonparametric data. LMM is designed to analyze nested data (i.e., time nested within person) and allows for estimation of variance and covariance components at each level of the data structure. For CPD, we used a cumulative logit model to analyze CPD as an ordinal variable, calculating the odds ratios using '4' (≥ 31 CPD) as the reference category (meaning that odds ratios greater than 1 indicate decreased CPD). For the models involving abstinence from smoking we used a binary logit model to analyze CPD as a binary variable (smoking any number of cigarettes vs. not smoking during the previous week). For both CPD and abstinence analyses, we modeled treatment, time (days since starting medication at baseline), and the interaction between the two terms as fixed effects, with patients as a random effect. To determine differences in baseline dependence and demographics between the treatment and control groups, we used chi-square and t-test analyses to evaluate the categorical and continuous data, respectively, with an alpha of 0.05.

RESULTS

Treatment and Side Effects

Baseline dependence level and demographic information are shown in Table 1. Because we used matched case-control sampling, the baseline measures did not differ between the treatment and control groups. Slightly more than half of the patients in the treatment group (56.0%) started bupropion-SR at 150 mg/day. The remainder of the treatment group was started on 100 mg/day because of an existing predisposition in this population for anxiety or insomnia, which happens to also be among the most common side effects of bupropion, requiring precaution and warranting a lower dosage where indicated. On the eighth day, all patients were instructed to increase their dose to twice a day. However, patients were allowed to reduce intake to once a day if they were not tolerating the increase. At the first follow-up, 65% reported taking 300 mg/day of bupropion-SR and the remaining 35% were taking 150-200 mg/day. While these doses were lower than intended, they are still within the bupropion-SR range (150-300 mg) found to be effective for smoking cessation [29]. Our flexible dosing procedure was intended to minimize side effects, as a result the rate of side effects was indeed comparable to those reported in the Physicians' Desk Reference (PDR) [30] for bupropion-SR, specifically under the label Zyban®.

The side effects most commonly reported in this study were insomnia (24% vs. 40% in the PDR), anxiety (15% vs. 8% in the PDR), and dry mouth (12% vs. 10% in the PDR). Two patients discontinued bupropion-SR before their first follow-up visit, one because of insomnia and the other because he decided he was not ready to quit smoking. Two other patients never started bupropion-SR, although it was prescribed. Three patients were lost to follow-up after the baseline visit and were assumed to have relapsed to both drinking and smoking. In all, seven patients (13.7%) stopped taking bupropion-SR by the first follow-up but were included in the analysis as intent to treat model. To our knowledge, no other patient stopped taking the medication after the first follow-up visit.

Abstinence Outcomes

Treatment was found to have a significant main effect, with patients receiving bupropion-SR more likely to abstain from smoking at any given time point than controls (odds ratio [OR] = 6.16; 95% confidence interval [CI]: 2.04-18.61; $p < 0.002$). Time was found to have a significant main effect, with abstinence increasing over time (OR=1.01; 95% CI: 1.01-1.1; $p < 0.0001$). However, the interaction between treatment and time was non-significant ($p < 0.13$). The main effects of treatment and time remained significant even after co-varying for sex, race/ethnicity, number of drinking days during the previous week, and number of AA sessions attended during the previous week. (Table 1)

Reduction in CPD Outcomes

Treatment was found to have a significant main effect on number of cigarettes smoked, thereby indicating that patients receiving bupropion-SR smoked fewer CPD (i.e., reported fewer CPD on the ordinal scale) at any given time point than controls (OR=4.19; 95% CI: 2.11, 8.31; $p < 0.0001$). The significance of this main effect was not diminished by the inclusion of the covariates sex, race/ethnicity, number of drinking days during the previous

week, and number of AA sessions attended during the previous week. However, increases in CPD were associated with increases in the number of drinking days during the previous week (OR=0.62; 95% CI: 0.44, 0.88; $p<0.02$) and increases in the number of AA sessions attended during the previous week (OR=0.73; 95% CI: 0.58, 0.93; $p<0.02$).

Additionally, a significant interaction between treatment and time was found in the CPD data ($p<0.02$; Fig.# 2). To decompose the interaction, we calculated ORs by comparing treatment and control groups at three time points: Baseline, 30 days (1-month) post-baseline, and 180 days (6-month) post-baseline. The ORs at baseline (OR=2.90; 95% CI: 1.34, 6.26; $p<0.007$), 30 days post-baseline (OR=3.51; 95% CI: 1.69, 7.27; $p<0.008$), and 180 days post-baseline (OR=9.08; 95% CI: 3.53, 23.32; $p<0.0001$) indicate that the treatment group smoked fewer CPD at all three time points, compared to the control group. This interaction effect of treatment and time remained significant even after co-varying for sex, race/ethnicity, number of drinking days during the previous week, and number of AA sessions attended during the previous week. (Fig. 2)

DISCUSSION

Recent studies have shown that bupropion-SR may help non-motivated smokers to quit altogether by first facilitating a reduction in their smoking, but to our knowledge, this effect has not been studied in recently alcohol abstinent AD individuals. Our findings suggest that bupropion-SR can help recently abstinent AD individuals quit smoking or significantly reduce their CPD, consistent with Hatsukami's findings that non-AD smokers reduced their CPD while taking bupropion-SR, which seemed to help some patients increase their motivation and readiness to eventually quit smoking [31]. In addition to medication, our treatment group received 5-10 minutes "brief counseling" for smoking cessation. As per the clinical practice guidelines, this "minimal" or "brief counseling" has an established effect on the subjects' likelihood of quitting cigarette smoking in the general population [32]. Unfortunately, because our control group did not receive any smoking cessation treatment (counseling or medications), we cannot determine based on our data whether the subjects in the treatment group were more likely to stop smoking due to bupropion therapy, counseling, or both. However, our findings suggest that bupropion-SR should be further evaluated using controlled studies in this understudied population.

As an added advantage, recovering AD smokers who reduce or quit smoking may be more successful in maintaining alcohol sobriety. This is because smoking and drinking alcohol does induce neurochemical and behavioral interactions; for instance, smoking is often identified by patients as a cue to drinking and vice versa [33]. In fact, quitting smoking during the first year of alcohol abstinence has been correlated with better rates of long-term alcohol abstinence (up to 9 years of follow-up) [34]. In our study, the number of drinking days in the previous week predicted CPD in the previous week. We did not present the data on alcohol consumption during the period of our study, as it was self-reported and it is not a main outcome or focus of this study.

Further, in our sample, the reported side effects of bupropion-SR were comparable with those reported in the PDR, this may be due to adopting of a slower titration schedule and

employing a flexible dosing regimen. While the non-standardized dose is not an ideal for comparison purposes; here again, the value of this strategy is replicating “real practice conditions” and still achieve statistical significance. This favorable side effects profile is encouraging and supports the notion of safety as for prescribing bupropion-SR in this population, particularly important since patients receiving bupropion-SR were more likely to abstain from smoking at any given time point than controls and were more likely to remain abstinent over time.

Interestingly, in our sample, increased attendance at AA meetings was associated with an increase in CPD. To note, it is known by sponsors and others at AA meetings as the “traditional wisdom” is to recommend against making major life decisions or changes (including quitting smoking) during the first year of recovery from alcohol. This stems out of fear those changes (including smoking cessation) would provoke a relapse to alcohol or drugs [35-38]. This culture may have a direct impact on patients’ thinking about reducing smoking or their ability to quit smoking. Alternatively, this increase in CPD might also reflect an individual's attempt to socialize or relate to others during or after attending an AA meeting. This influence from the AA culture may have impacted our results; however, having matching controls for our treatment group, who received the same alcohol treatment program and philosophy including AA attendance, provides additional rigor and validity to our findings [27].

Our study had several limitations. First, it was an open-label, naturalistic study, and did not include a placebo/non-intervention control group. In addition to self-selection bias, as patients who agreed to take bupropion may have been more motivated to reduce or quit smoking than those who declined bupropion treatment. Similarly limiting is the non-standardized follow-up intervals between the groups. Nonetheless, this type of naturalistic design allowed us to examine the impact of such intervention in real treatment setting and study the behavior of patients accordingly, in contrast to the alternative method of recruiting volunteer participants from the community. Second, we did not quantify nicotine dependence using a clinically validated measure other than CPD and the DSM-IV diagnosis of nicotine dependence. Third, the demographic profile of our overall sample (both groups) was likely not representative of all AD smokers who seek treatment, given the large proportion of whites and women in our study. Fourth, drinking and smoking outcomes were based on self-report, as only partial biochemical corroboration was provided for smoking outcomes (i.e., expired carbon monoxide in a subsample). Nonetheless, we would not expect a difference in the self-reporting of smoking between the treatment and control groups; according to previous reports, 80%-90% of self-reported data in smoking cessation studies in treatment settings correlates to the biological confirmation [39]. Finally, we did not collect demographic or substance use data for analysis on patients who met the inclusion criteria but were not interested in quitting smoking by starting treatment with bupropion-SR.

Despite these limitations, our data suggest an important role for bupropion-SR in AD smokers as a viable pharmacological alternative to NRT or varenicline. This is particularly important in light of recent FDA warnings, that varenicline must be used with caution in patients with a history of psychiatric comorbidities [26]. In addition, NRT alone has been reported to have very limited efficacy if any in AD smokers [12].

We hope that our work will stimulate further research on bupropion-SR in this population of smokers, as large-scale randomized controlled trials of bupropion-SR, alone and in combination with NRTs, would be needed in this particular group of alcohol dependent smokers during early recovery from alcohol.

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Fig. (1).
Schema of Study and follow-up visits

Fig. (2). Forest plot of the significant effect of the treatment-time interaction on CPD, depicted at three time points. *In the general logit model, '4'(<31 CPD) is the reference category, meaning that OR's greater than 1 indicate decreased CPD

Table 1**Baseline Demographic and Smoking Characteristics**

Categorical Measures	Control (N=57) % (N)	Treatment (N=58) % (N)	Total (N=115) % (N)
Sex			
Female	43.9 (25)	55.2 (32)	49.6 (57)
Race/ethnicity			
African American, non-Hispanic	14.0 (8)	8.6 (5)	11.3 (13)
White, non-Hispanic	82.5 (47)	86.2 (50)	84.5 (97)
Other, including Hispanic	3.5 (2)	5.2 (3)	4.4 (5)
Baseline cigarettes/day			
10 or fewer	22.8 (13)	22.4 (13)	22.6 (26)
11-20	49.1 (28)	48.3 (28)	48.7 (56)
21-30	14.0 (8)	13.8 (8)	13.9 (16)
31 or more	14.0 (8)	15.5 (9)	14.8 (17)

Continuous Measures	Mean (SD)	Mean (SD)	Mean (SD)
Age, years	36.93 (10.8)	39.26 (10.3)	38.10 (10.6)
Expired CO, ppm	N/A	21.13 (11.6)	21.13 (11.6)
Years smoking	19.05 (10.9)	20.7 (10.5)	19.89 (10.7)
Years drinking	18.13 (9.6)	17.8 (10.7)	17.95 (10.1)
AA visits during the previous week	1.18 (0.7)	1.09 (0.6)	1.13 (1.7)
Drinking days during the previous week	5.77 (6.7)	5.29 (7.3)	5.53 (7.0)

All frequencies are calculated within group (column). There were no significant differences between the groups for any of the comparisons. CO=carbon monoxide. AA= Alcoholics Anonymous. SD=standard deviation. N/A=not applicable.