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Preliminary Study of Buprenorphine and Bupropion for Opioid Dependent Smokers

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Abstract

In this double-blind, placebo-controlled trial, bupropion (BUPRO, 300 mg/day) was compared to placebo (PBO) for concurrent treatment of opioid and tobacco addiction in 40 opioid-dependent smokers stabilized on buprenorphine (BUPRE, 24 mg/day). Participants received contingent, monetary reinforcement for abstinence from smoking, illicit opioids, and cocaine. Significant differences in treatment retention were observed (BUPRE+BUPRO, 58%; BUPRE+PBO, 90%). BUPRO treatment was not more effective than placebo for abstinence from tobacco, opioids, or cocaine in BUPRE stabilized patients. These preliminary findings do not support the efficacy of BUPRO, in combination with BUPRE, for concurrent treatment of opioid and tobacco addiction.

Keywords

opioid dependence; smoking cessation; bupropion; buprenorphine

Despite declining rates of smoking in the general population, rates of cigarette smoking continue to be elevated among those dependent on opioids, with estimates ranging from 71% to 98%.^{1, 2} Converging lines of evidence support the complex interaction between nicotine and the endogenous opioid system³, with opioids increasing cigarette smoking^{4–8} and nicotine and tobacco increasing opioid use⁹, and levels of the endogenous opioid, β -endorphin.^{10–13} Given the synergistic relationship between nicotine and opioids, the disproportionate rate of smoking in opioid users is not surprising.

Only recently have researchers begun to evaluate smoking cessation treatments for opioid-dependent individuals.^{8, 14–17} Interventions have involved behavioral treatments (e.g., supportive counseling, motivational interviewing, and contingency management [CM]) or behavioral treatment in conjunction with pharmacotherapy (i.e., nicotine patch, nicotine gum, or bupropion [BUPRO]). In general, these trials have shown modest or null findings in terms of cessation rates in this challenging population of smokers.

No placebo controlled trials of smoking cessation pharmacotherapies have been conducted in opioid dependent patients, although behavioral interventions have been compared to each other.^{14, 16} Further, all smoking cessation trials in opioid dependent smokers have involved

concurrent methadone maintenance treatment (MMT). In recent years, a new treatment option for opioid dependent patients has emerged in the form of buprenorphine (BUPRE) maintenance treatment (BMT). Although similar in efficacy to methadone, buprenorphine (when combined with naloxone) has reduced potential for diversion.^{18, 19} To date, no smoking cessation trials in BMT patients have been reported in the literature. The widening use of BMT and its agonistic effects on smoking warrant careful study in the context of a clinical trial.⁴

The purpose of this preliminary study was to evaluate the safety, tolerability, and efficacy of bupropion in opioid and nicotine dependent participants maintained on buprenorphine, using a randomized, placebo-controlled design. We selected bupropion since it has been well tolerated in MMT patients, both as a smoking cessation intervention¹⁵, and as an intervention for cocaine and opioid dependence.^{20–23} We chose to provide contingent monetary reinforcement for abstinence from smoking, illicit opioids, and cocaine, as the robust nature of contingency management procedures are an essential therapeutic platform to show pharmacotherapy effects in opioid and cocaine using patients.^{16, 24}

METHODS

Sample and Recruitment

Forty treatment-seeking male and female opioid- and nicotine-dependent smokers were recruited to take part in an outpatient clinical trial at the Opiate Treatment Research Program, at the Veteran's Affairs (VA) Connecticut Healthcare System in West Haven, CT. Responding to advertisements in the VA facility, participants were informed that they would be stabilized on buprenorphine and would receive either bupropion or placebo. They were instructed that the goal was to abstain from illicit opioid, cocaine, and tobacco use, and that monetary reinforcement would be provided for abstinence.

Eligible participants: (a) were age 18–65; (b) were currently opiate and nicotine dependent²⁵; (c) had smoked ≥ 10 cigarettes/day for the past year; (d) were seeking treatment for opiate and tobacco use; (e) had stable physical and psychiatric health; (f) had no current diagnosis of alcohol and other drug dependence or abuse (other than opioids, nicotine, and cocaine); (g) were not using prescription psychoactive drugs; and (h) for women, were not pregnant, planning pregnancy, or lactating. Eligibility was determined by a research psychiatrist based on physical, psychiatric and laboratory examination. Baseline measures included urine toxicology, the Structured Clinical Interview for DSM-IV (SCID)²⁶, the Addiction Severity Index (ASI)²⁷, and the Fagerstrom Test of Nicotine Dependence (FTND).²⁸ All participants provided written informed consent to participate in the current study, which was approved by the Yale and VA Human Studies Committees.

Design and Procedure

The study was a randomized, double-blind, placebo-controlled trial conducted during from August 2004 to August 2005. Participants were randomized to either bupropion (BUPRE +BUPRO, $n = 20$ [19 analyzed]) and placebo (BUPRE+PBO, $n = 20$) treatment. An urn randomization procedure was used to ensure balanced distribution on race and sex.²⁹ One enrolled participant (BUPRE+BUPRO) quit smoking prior to starting the trial, and was not included in the analyses. The study involved a 1-week dose run-up of buprenorphine and bupropion (or placebo), followed by a 10-week treatment period. Each participant was given a quit date beginning approximately one week after the bupropion treatment was started. Participants received counseling (1 hour/week) that emphasized motivational enhancement and skills training for relapse prevention and contingency management to help them to quit tobacco, illicit opioids, and cocaine. Each participant received US\$5.00 for being abstinent from tobacco (CO result <10 ppm), illicit opiates (<200 ng/mL for opioids), and cocaine use

(<300 ng/mL for benzoylecognine) for a maximum of US\$15.00 per week (US\$150.00 total possible). Urine assays were completed by the West Haven VA toxicology laboratory using an Olympus AU 640 Emit system. Participants were only discharged from the study for missing 3 consecutive days of medication or 3 consecutive counseling sessions.

Medications

Buprenorphine—Buprenorphine was administered as a sublingual tablet containing buprenorphine and naloxone in a ratio of 4:1. On day one of the trial, each participant received 4 mg, with 8 mg increases each day until reaching 24 mg on day 4. All weekday doses were directly observed. Take-home doses were also given for self-administration twice-a-day on Saturdays and Sundays. All participants were stabilized on 24 mg/day. Depending on individual needs, at the end of the 10-week trial, participants received a 2–4 week buprenorphine detoxification.

Bupropion—Sustained-release bupropion tablets or placebo were administered twice daily: once while attending the clinic for buprenorphine administration, and one to take home. Take-home doses were also given for self-administration twice-a-day on Saturdays and Sundays. Bupropion pills were over-encapsulated to match placebo pills. Participants initially received 150 mg/day of bupropion for 3 days, after which the dose was increased to 150 mg twice daily for the duration of the trial. At the end of the 10-week clinical trial, all participants were tapered off bupropion (or placebo) over a seven-day period.

Outcome Variables

Safety and tolerability were assessed, respectively, according to adverse events and treatment retention (weeks in study). The primary outcome measure was combined abstinence from smoking, illicit opioids, and cocaine. Smoking abstinence was based on expired carbon monoxide (CO < 10 ppm), obtained three times weekly (Monday, Wednesday, Friday).³⁰ All abstinence data reflect point-prevalence estimates at each observation time. We also obtained urine samples when carbon monoxide samples were taken to establish illicit opioid and cocaine use. Nicotine withdrawal³¹ and opioid withdrawal were assessed.³²

Statistical Analysis

All analyses were conducted with the Statistical Analysis System Version 9.1.3.³³ The current sample size of 40 was based on available resources, and the need to first determine if the combination of buprenorphine and bupropion was safe and tolerable. An additional goal was to characterize treatment effect sizes to inform subsequent power analyses for a larger trial, if warranted. Unless otherwise stated, values of $p < .05$ were considered statistically significant, based on two-tailed tests. Treatment retention was evaluated using Kaplan-Meier survival analysis. Abstinence from each of the three target substances, tobacco, cocaine, and opioid, together and individually, was analyzed using repeated-measures logistic regression. Abstinence data were analyzed under an intention-to-treat policy where missing observations were coded as positive for substance use. Cigarettes/day, carbon monoxide levels, and withdrawal were evaluated with repeated measures ANCOVA. In each repeated measures model, the effects of medication, time, and their interaction were assessed. Substance use was summarized into 5, biweekly periods (i.e., biweeks) while all other continuous outcomes were evaluated at the visit or weekly level. The value of the dependent measure at the initial visit (when no medication had been administered) was used as covariate. Exceptions included cocaine and opiate use, in which self-reported use in the 30 days preceding treatment was employed as the covariate.²⁷ Type I error rate was controlled using a Tukey adjustment.

RESULTS

Demographic Characteristics

Means and frequencies are presented for the entire sample since comparisons by treatment group revealed no statistically significant differences. The sample ($N = 39$) was comprised primarily of men (85%), mean age 34.2 ($SD = 11.2$). The majority of participants were white (82%), while the balance was African-American (8%) or other (10%). Most participants had at least high school education (51%), and were employed (72%). Baseline smoking characteristics were as follows: mean smoking rate, 23.8 cigarettes/day ($SD = 10.7$); CO level 14.6 ppm ($SD = 8.3$), and FTND score, 5.2 ($SD = 2.6$). All participants met DSM-IV lifetime criteria for opioid dependence, with 18.1 days ($SD = 14.5$) use in the 30 days preceding treatment. A 25% minority of participants also met DSM-IV lifetime criteria for cocaine dependence, with 1.1 days ($SD = 2.0$) use in the 30 days preceding treatment.

Adverse Events

Fewer BUPRE+PBO participants were administratively discharged for 3 consecutive missed-medication appointments ($n = 2$) than BUPRE+BUPRO participants ($n = 5$). Of the 4 remaining non-completers in the BUPRE+BUPRO group, 1 moved during the study and 3 were related to adverse events. The 3 adverse events included pancreatitis ($n = 1$), agitation ($n = 1$) and “disliked medication” ($n = 1$).

Retention

Survival analysis indicated that those treated in the BUPRE+BUPRO condition were retained at a lower rate (58%) than those in the BUPRE+PBO (90%), during the 10-week treatment period, *Log Rank Statistic* = 5.09, *d.f.* = 1, $p = .0241$ (see Figure 1).

Substance Use Outcomes

Combined Abstinence—Combined abstinence rates for smoking, opioid use, and cocaine use during the 10-week treatment phase did not differ, by medication, $\chi^2(1) = 2.76$, $p = .10$, biweek, $\chi^2(4) = 7.14$, $p = .13$, or their interaction, $\chi^2(4) = 2.87$, $p = .58$ (see Figure 2, Panel B). Overall combined abstinence rates were BUPRE+PBO (23.5%) and BUPRE+BUPRO (10.1%).

Cigarette Smoking—Abstinence rates during the 10-week treatment phase did not differ, by medication, $\chi^2(1) = .28$, $p = .50$, biweek, $\chi^2(4) = 1.53$, $p = .82$, or their interaction, $\chi^2(4) = 3.31$, $p = .51$ (see Figure 2, Panel B). Overall smoking abstinence rates were BUPRE+PBO (11.4%) and BUPRE+BUPRO (13.7%). A sensitivity analysis was undertaken defining abstinence as CO less than 8 and 3 ppm, respectively.^{30, 34} Although the relative superiority of BUPRE+BUPRO to BUPRE+PBO persisted, no statistically reliable differences were detected.

Opioid Use—Although some evidence for a medication effect was observed, no effects were statistically significant, $\chi^2(1) = 0.70$, $p = .40$, biweek, $\chi^2(4) = 2.82$, $p = .59$ or their interaction were seen $\chi^2(4) = 6.91$, $p = .14$ (see Figure 2, Panel C). Overall illicit opioid abstinence rates were BUPRE+PBO (85.0%) and BUPRE+BUPRO (77.5%).

Cocaine Use—Cocaine use tended to decline in both groups over time, biweek, $\chi^2(4) = 25.0$, $p < .0001$ (see Figure 2, Panel D). However, the trends in reduction differed slightly by medication group, medication \times biweek, $\chi^2(4) = 11.1$, $p = .0259$. No main effect of medication was seen, $\chi^2(1) = .06$, $p = .8046$. Overall cocaine abstinence rates were BUPRE+PBO (85.0%) and BUPRE+BUPRO (86.3%).

Other Outcomes

CO Reduction—Carbon monoxide levels did not change as function of treatment, time, or their interaction. Overall, carbon monoxide levels were BUPRE+PBO ($M = 14.4$, $SE = .68$) and BUPRE+BUPRO ($M = 12.9$, $SE = .71$).

Smoking Reduction—Cigarettes per day tended to decline somewhat during the treatment period, week, $F(9,277) = 9.09$, $p < .0001$, but no effects of medication, or medication \times week. Daily smoking rates were BUPRE+PBO ($M = 14.2$, $SE = 1.4$) and BUPRE+BUPRO ($M = 15.6$, $SE = 1.5$).

Nicotine and Opioid Withdrawal—Nicotine withdrawal tended to increase in week 1 of treatment, before declining to pre-quit levels, week, $F(9,291) = 4.84$, $p < .0001$, but no effects of medication, or their interaction. Opioid withdrawal also tended to peak in week 1 of smoking cessation, after which it rapidly declined, week, $F(9,293) = 10.2$, $p < .0001$.

DISCUSSION

In this study, we conducted a 10-week, randomized, placebo-controlled trial of bupropion in combination with buprenorphine for concurrent treatment of tobacco, opioid, and cocaine addiction in opioid addicted cigarette smokers. Participants were provided monetary reinforcement contingent on providing biochemical samples negative for carbon monoxide, opioids, and cocaine. A key observation in this study was that those treated with bupropion were significantly less likely to complete treatment. In addition, bupropion was not more effective than placebo for abstinence from tobacco, opioids, or cocaine in buprenorphine stabilized patients.

We observed that those taking bupropion and buprenorphine were significantly less likely to complete the 10-week course of treatment (58%) vs. (90%). In non-opioid dependent samples of smokers, discontinuation rates in bupropion treated smokers have been between 6–12%.³⁵ Richter and coworkers¹⁵, evaluated bupropion as a smoking cessation treatment in methadone-maintained patients. Although no placebo control group was included, bupropion was well tolerated, with just 4% of their sample discontinuing treatment due side effects. Two placebo-controlled trials of bupropion in MMT opioid dependent patients, where treatment was targeted primarily at cocaine abstinence, found no significant differences between bupropion and placebo-treated participants in terms of treatment completion^{20, 22} While the nature of the adverse events that precipitated discontinuation were not clearly related to bupropion, this level of differential attrition would not be clinically acceptable.

Few randomized, controlled trials of smoking cessation interventions in opioid dependent smokers have been published^{8, 16, 36}, all in MMT patients. In the current study, overall abstinence rates fell between those seen in these earlier studies, BMT+PBO (11.4%) and BMT+BUP (13.7%). In the two studies using pharmacotherapy (i.e., nicotine patch with no placebo control), one found a significant effect of contingency management¹⁶, while a more recent study found no effect of a tailored intervention including a motivational intervention, skills counseling, and relapse prevention.³⁶ In the former trial, 7-day, CO-confirmed abstinence rates averaged nearly 25% in CM-treated participants in the 12-week treatment period, while overall abstinence rates in the second study did not exceed 7%. Effective smoking cessation treatments for opioid dependent smokers remain elusive.

Unlike these earlier reports, we targeted not only smoking for abstinence, but also illicit opioid and cocaine use. We elected to promote cessation of all three substances since cessation of tobacco alone might have been undermined by the use of opioids or cocaine. A recent study by Peirce et al.³⁷ demonstrated that contingent reinforcement of stimulant and alcohol

abstinence in MMT patients increased abstinence from these drugs of abuse as well as illicit opioids. The issue of timing of smoking cessation in dually addicted smokers remains open to consideration.³⁸ Attempting to quit smoking while still using drugs of abuse, that cause behavioral disinhibition or which kindle the desire for nicotine, is likely impractical. The benefits of simultaneously quitting tobacco and opioids (as well as other illicit drugs) versus delaying treatment for smoking cessation after opioid addiction is stabilized needs to be further examined

This preliminary study had several limitations. First, this preliminary study was designed to assess safety and tolerability, as well as effect sizes for design of future studies, if warranted, and thus had limited statistical power. Second, we only evaluated participants newly started and stabilized on buprenorphine, and thus the question of bupropion's efficacy remains unassessed in those receiving buprenorphine maintenance therapy. Third, only one dose of bupropion was used and it is possible that lower doses of bupropion may have had cessation efficacy with reduced side effects c.f.,³⁹. Forth, the CM intervention was relatively simple and use of escalating or intermittent schedules of reinforcement, with larger magnitudes, might have produced statistically and clinically significant effects. Finally, participants were not followed-up after treatment, and thus the durability of treatment effects, if any, was not assessed.

In summary, the current study was a preliminary effort to evaluate the safety, tolerability, and efficacy of bupropion, in combination with buprenorphine, for concurrent treatment of opioid and tobacco addiction. While the current findings do not support this treatment, only a larger trial with adequate statistical power could definitively exclude this combination therapy. However, safety and tolerability issues raised here do not support such a study. There continues to be lack of effective, evidence-based smoking cessation treatments in opioid dependent individuals.

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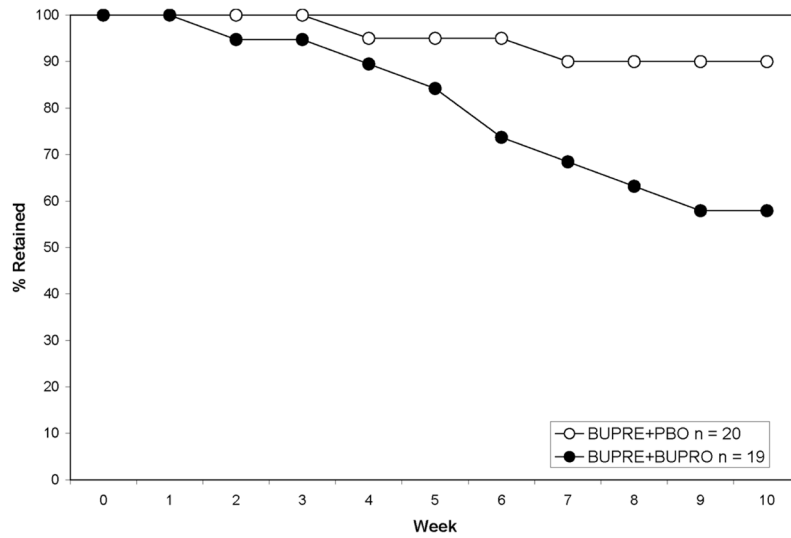


Figure 1. Retention rates by medication group in the 10-week treatment period. Fewer participants in the BUPRE+BUPRO condition were retained at a lower rate (58%) than those in the BUPRE+PBO (90%), $p = .0241$.

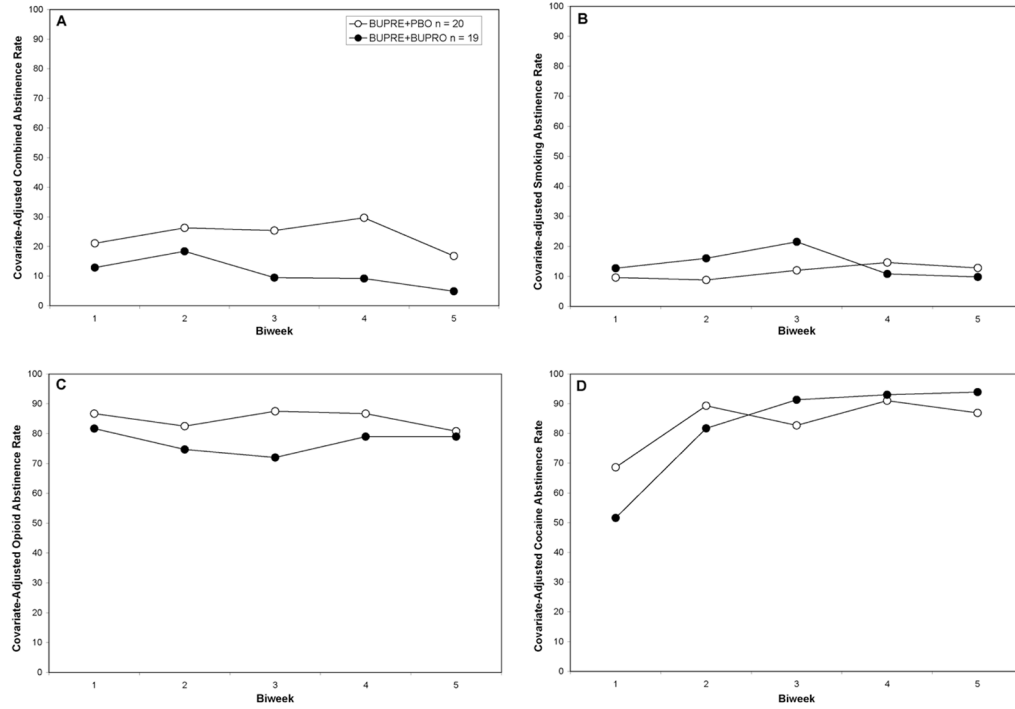


Figure 2.

Panel A. Combined abstinence rates in the 10-week treatment period, adjusted for baseline CO-level as well as days of illicit opioid and cocaine use in the 30-days preceding enrollment.

Panel B. Smoking abstinence rates in the 10-week treatment period, adjusted for baseline CO-level.

Panel C. Illicit opioid abstinence rates in the 10-week treatment period, adjusted for days of illicit opioid use in the 30-days preceding enrollment.

Panel D. Cocaine abstinence rates in the 10-week treatment period, adjusted for days of cocaine use in the 30-days preceding enrollment. Abstinence rates differed as function of biweek, $p < .001$ and medication \times biweek, $p = .0259$.