Bupropion and Naltrexone for Smoking Cessation: A Double-Blind Randomized Placebo-Controlled Clinical Trial

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Combination of non-nicotine pharmacotherapies has been underexamined for cigarette smoking cessation. A randomized, double-blind, parallel-group double-dummy study evaluated two medications, bupropion (BUP) and naltrexone (NTX), in treatment-seeking cigarette smokers ($N = 121$) over a 7-week treatment intervention with 6-month follow-up. Smokers were randomized to either BUP (300 mg/day) + placebo (PBO) or BUP (300 mg/day) + NTX (50 mg/day). The primary outcome was biochemically verified (saliva cotinine, carbon monoxide) 7-day, point-prevalence abstinence. BUP + NTX was associated with significantly higher point-prevalence abstinence rates after 7-weeks of treatment (BUP + NTX, 54.1%; BUP + PBO, 33.3%), $P = 0.0210$, but not at 6-month follow-up (BUP + NTX, 27.9%; BUP + PBO, 15.0%), $P = 0.09$. Continuous abstinence rates did not differ, $P = 0.0740$ (BUP + NTX, 26.2%; BUP + PBO, 13.3%). Those receiving BUP + NTX reported reduced nicotine withdrawal, $P = 0.0364$. The BUP + NTX combination was associated with elevated rates of some side effects, but with no significant difference in retention between the groups.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ The potential for improving cigarette smoking abstinence rates through the combination of NNPs, with different mechanisms of action, has been underexamined. Two medications, BUP and NTX have been evaluated as a smoking cessation combination pharmacotherapy in two small trials with equivocal results.
WHAT QUESTION DID THIS STUDY ADDRESS?
☑ Whether BUP + NTX compared to BUP + PBO was superior at promoting smoking cessation rates.

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE
☑ BUP + NTX is a potentially effective smoking cessation treatment.
HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE
☑ Our findings may lead to increased clinical pharmacological research into NNPs for smoking cessation.

Recent efforts to achieve higher smoking cessation rates have turned to combination pharmacotherapies (CPs) for nicotine dependence.[1–3] Initial efforts at developing CPs focused on existing nicotine replacement therapies (NRTs), most commonly coupling the nicotine patch and an ad libitum system (i.e., nicotine gum, lozenge, inhaler, or nasal spray). NRT + NRT combinations held the potential for higher delivery of nicotine and provision of both stable and acute dosing for craving and withdrawal symptom relief; however, reported effects have been clinically modest.[4] With the advent of non-nicotine pharmacotherapies (NNPs), such as bupropion and varenicline, CP research expanded to include NRT + NNP treatments.[5] Multiple trials have combined bupropion (BUP) and the nicotine patch. The benefits of adding NRT to BUP seem to be limited.[6] More recently, research has examined the combination of NRT with varenicline.[7–10] Of the three controlled clinical trials, two reported no benefit of adding the nicotine patch to varenicline

for long-term abstinence,[8,10] whereas one substantially larger study did find evidence favoring the CP.[9]

The potential for improving abstinence rates through non-nicotine CPs with different mechanisms of action is plausible but not well studied.[11–13] Two studies compared the combination of BUP and varenicline to varenicline alone, with encouraging findings for the CP, specifically among heavy smokers.[12,13] The combination of BUP and naltrexone (NTX) was initially proposed for smoking cessation in weight-concerned[14] and overweight or obese smokers,[15] based on the weight-suppressant effects of NTX. Although preliminary studies yielded equivocal results, recent US Food and Drug Administration approval of this CP for the treatment of obesity provides a basis for further investigation of its therapeutic potential for smoking cessation.[16]

An alternative pharmacologic rationale for BUP + NTX as a CP for smoking cessation is based on the different and possibly

complementary mechanisms of action. BUP is posited to act through inhibiting reuptake of noradrenaline and dopamine,[17] and may antagonize nicotine by occupying some cholinergic receptors.[18] NTX is a mu-opioid antagonist that may inhibit some mesolimbic dopamine activity[19] and alter cholinergic receptors' function and expression in the brain.[20] Therefore, these two drugs may act through both the same and different transmitter systems.

BUP effectively improves several nicotine withdrawal symptoms, including decreases in positive affect, increases in negative affect, irritability, concentration impairment, and craving.[21–23] NTX may work to abate craving and urges to smoke.[24,25] BUP seems to dampen the rewarding effects of smoking slips[22] and NTX may also block the reinforcing effects of smoking, thus serving as relapse-prevention agents.[24] NTX may be particularly helpful in attenuating the rewarding effects of slips that occur in high stress situations,[26] as well as attenuating reactivity to smoking stimuli.[19] Thus, BUP may palliate most withdrawal complaints and craving, with NTX offering further improvement in craving as well as protection from slips to smoking.

Combining BUP and NTX may offset side effects associated with each medication, thus enhancing medication compliance; one of the proposed benefits of the CP. BUP most frequently produces the side effects of insomnia and dry mouth. The side effect profile of NTX may include headache, sedation, distractibility, and dysphoria marked by irritability and negative affect. Although some of these effects are consistent with nicotine withdrawal, studies of NTX in nondependent adults[27] have reported dysphoric effects marked by heightened negative affect, irritability, and distractibility. An obvious approach to counteract dysphoric effects in NTX therapy is to use adjunctive antidepressant therapy. Combination of an antidepressant (fluoxetine and paroxetine, respectively) with NTX has led to improved retention in treatment of opioid-dependent individuals.[28] Finally, BUP as a component of the CP provides antidepressant effects that may enhance efficacy, whereas the agonist-like and antagonist effects of BUP + NTX may counter the side effects of each.

The current controlled clinical trial evaluated the additive effects of combining two NNPs using a randomized, double-blind, double-dummy design in a sample of 121 treatment-seeking cigarette smokers diagnosed with nicotine dependence. Two medication treatment groups were assessed over a 7-week treatment phase: BUP (300 mg/day) + placebo (PBO) vs. BUP (300 mg/day) + NTX (50 mg/day). The goal was to obtain preliminary data on the predicted benefits of BUP + NTX compared to BUP + PBO on smoking cessation efficacy, retention, and treatment tolerability. The primary outcome measure was 7-day, biochemically confirmed, point-prevalence abstinence analyzed under an intention-to-treat policy where missing values were coded to indicate relapse to smoking.

RESULTS
Sample description
The demographic and smoking history characteristics of participants at randomization are presented in **Table 1**. No significant differences were observed between medication groups.

Table 1 Baseline characteristics of participants by treatment group

Characteristics	BUP + PBO $n = 60$	BUP + NTX $n = 61$
Age, y[a]	39.5 (11.2)	40.2 (11.3)
Gender, % female	50.2	50.4
Race, % white	93.3	85.3
Marital status, % married	44.1	42.0
Employed, %[b]	61.0	67.0
Cigarettes/day	18 (6.0)	19.3 (5.4)
Years smoked	17.0 (11.7)	16.9 (11.9)
FTND	5.8 (1.2)	5.7 (1.2)
Quit attempts[c]	5.3 (5.6)	4.7 (6.7)
Motivation level, 0–10	9.1 (1.1)	9.1 (1.0)
Total saliva cotinine, ng/mL[c]	330.4 (170.5)	310.4 (167.7)
CO	23.8 (12.8)	28.2 (13.3)

BUP, bupropion; CO, carbon monoxide; FTND, Fagerström Test of Nicotine Dependence; NTX, naltrexone; PBO, placebo.
Note. Continuous measures were analyzed using t tests. Categorical measures analyzed with χ^2 tests. No significant differences were observed.
[a]Continuous variables reported as means and SDs. [b]Employed indicates % of subjects who reported full- or part-time employment. [c]Quit attempts and baseline cotinine were positively skewed and were transformed as follows prior to analysis: $\log_{10}$ (quit attempts + 1) and $\log_{10}$ (total urine cotinine). Mean reported quit attempts and total urine cotinine were transformed back into original scale for ease of interpretation.

Retention
Survival analysis indicated no difference in dropout rates between medication groups (see **Figure 1**), log-rank statistic, $\chi^2(1) = 0.2676$; $P = 0.6049$, with 51.3% of participants completing 7 weeks of treatment. The two medication groups did not differ in the number of weeks of treatment completed (M = 3.9; SD = 2.2).

Side effects
The "ever" occurrence of 24 side effects was compared between treatment groups. Higher rates of side effects were reported in the BUP + NTX relative to BUP + PBO for lightheadedness, $\chi^2(1) = 3.70, P = 0.0543$ (9.8% vs. 1.7%); nausea, $\chi^2(1) = 3.82, P = 0.0507$ (13.1% vs. 3.3%); stomach aches $\chi^2(1) = 7.94, P = 0.0048$ (16.4% vs. 1.7%); shakiness $\chi^2(1) = 4.46, P = 0.0347$ (11.7% vs. 6.7%); and muscle aches $\chi^2(1) = 4.71, P = 0.0299$ (11.5% vs. 1.7%). In the intention-to-treat sample of 121 subjects, the following health conditions were noted: hypertension ($n = 6$), diabetes ($n = 1$), asthma ($n = 3$), gastroesophageal reflux disease ($n = 7$), and high cholesterol ($n = 9$). By category of prescribed medication, results were as follows: antihypertensive ($n = 8$), anti-acid reflux ($n = 7$), asthma inhaler ($n = 3$), anti-cholesterol ($n = 8$), and hormone birth control ($n = 7$).

Relatively few subjects discontinued participation in this trial due to medication adverse events (BUP + PBO = 4; BUP + NTX = 3). At total of six subjects had their dosage of bupropion reduced to 150 mg per day due to side effects, whereas two subjects (one from each condition) discontinued NTX. Only one
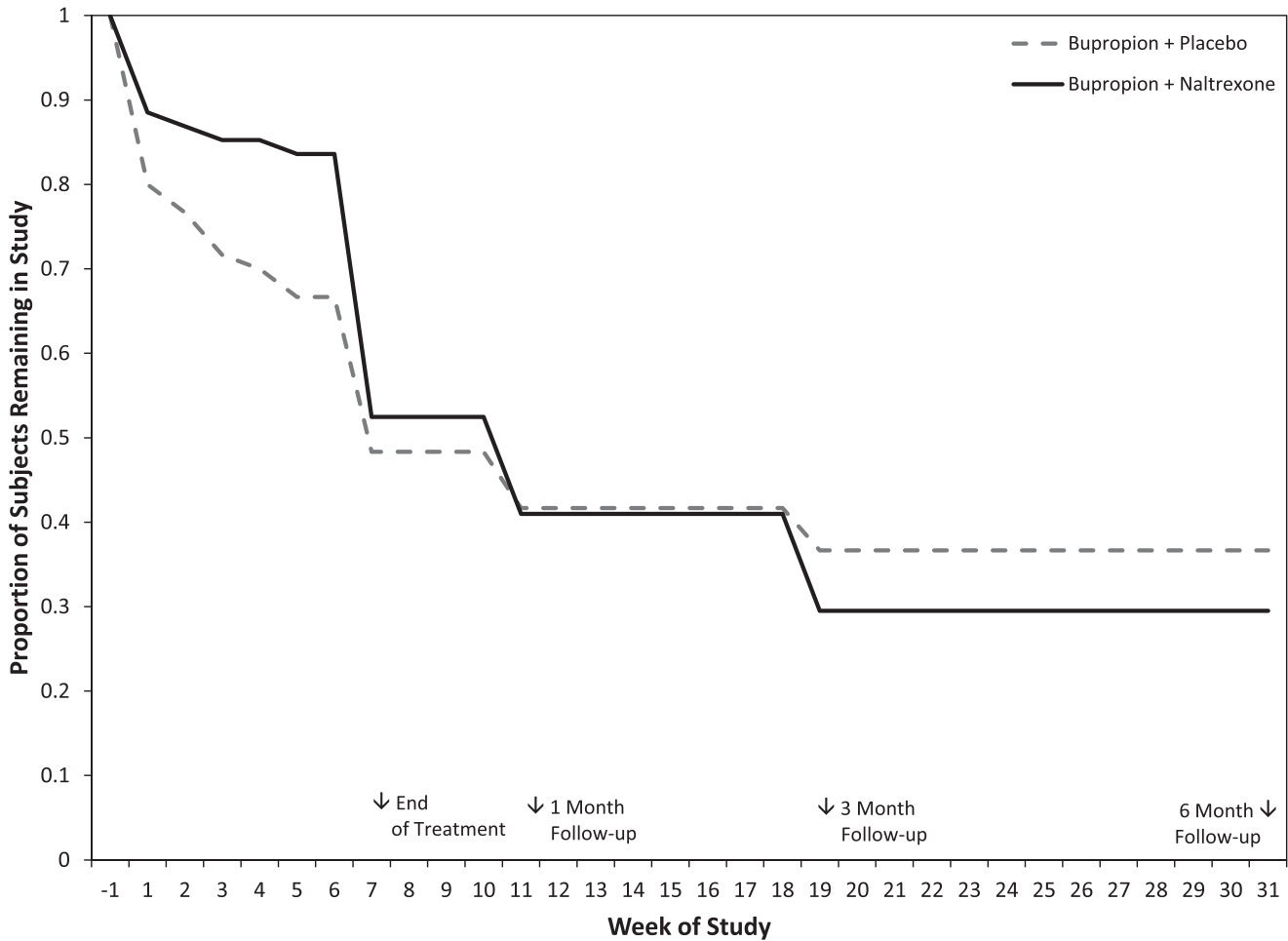
Figure 1 Participant retention figure. Proportion of subject retained in the study over treatment and follow-up periods.

serious adverse event occurred in this trial. A subject receiving BUP + PBO developed hematospermia.[29] He discontinued medication and continued in the trial, during which time his hematospermia completely remitted.

Vital signs
Weight, diastolic blood pressure, systolic blood pressure, and heart rate were evaluated weekly during the treatment periods. Baseline values were included as covariates.

Body weight
No effects of medication, time, or their interaction were observed.

Heart rate
Heart rate tended to decline slightly during the treatment phase, $F(6, 333) = 2.42$, $P = 0.0264$.

Systolic blood pressure
Over the treatment phase, average systolic blood pressure for those in the BUP + NTX condition (M = 126.29; SE = 0.98) was higher than for those in the BUP + PBO condition (M = 123.34; SE = 1.10), $F(1, 108) = 4.00$, $P = 0.0480$.

Diastolic blood pressure
No effects of medication, time, or their interaction were observed.

Abstinence rates
The primary outcome of this study was the point-prevalence abstinence rate (based on saliva cotinine tests and no reported smoking in the 7 days prior to the visit with a carbon monoxide (CO) ≤ 8 parts-per-million). In this intention-to-treat analysis, missing values were imputed to indicate smoking relapse. **Figure 2** presents the results of this analysis starting at treatment week 5 and running through the 6-month follow-up phase. It shows both observed abstinence rates (shown in parentheses) and those estimated (derived the logistic statistical model) from the repeated-measures logistic regression.

Across the study period, point-prevalence abstinence rates for each treatment group at each assessment time point are displayed in **Figure 4**, and were higher in the combination BUP + NTX group compared to the BUP + PBO group. Medication, $\chi^2(1) = 4.41$, $P = 0.0357$, and time effects, $\chi^2(4) = 26.52$, $P < 0.0001$, were observed with abstinence rates declining over the course of the study. Differences between medication groups at each time point were evaluated, revealing a significant difference in
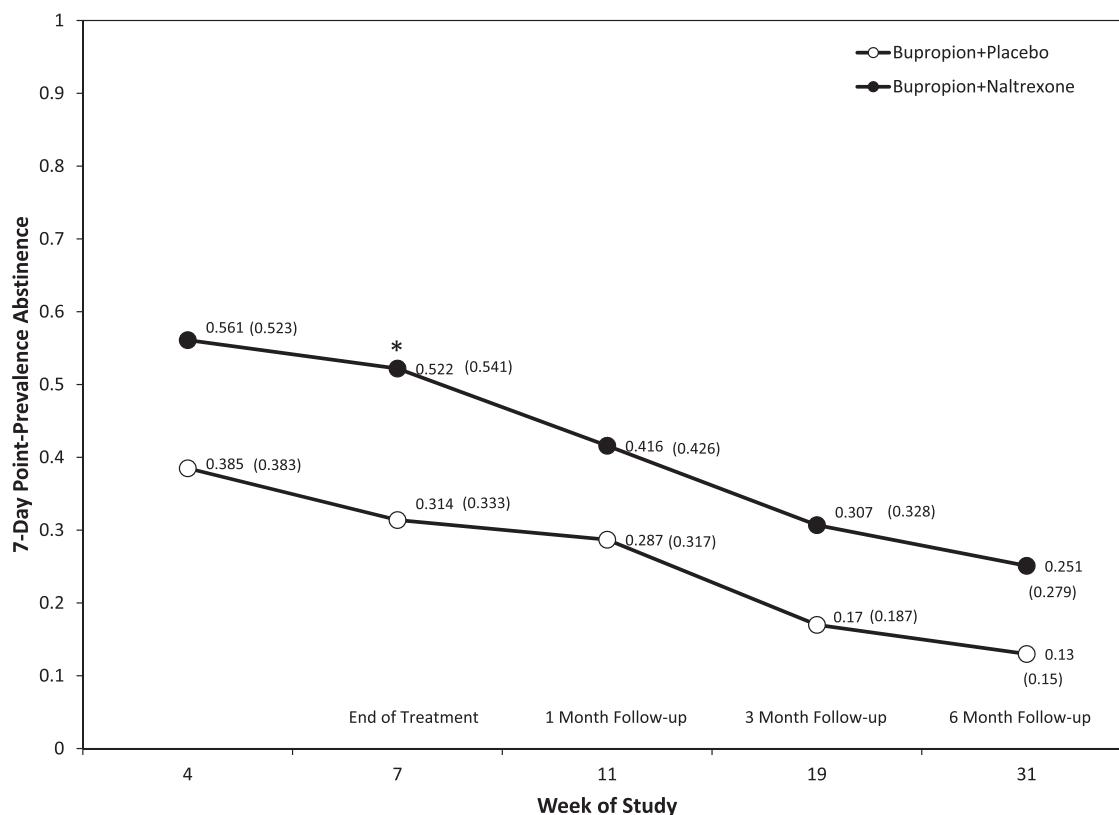
Figure 2 Biochemically confirmed (saliva cotinine), 7-day, point-prevalence abstinence rates significantly differed between medication groups with bupropion + naltrexone subjects. Estimated (derived the logistic statistical model) and observed abstinence rates (presented in parentheses) are displayed at each time point.

abstinence rates favoring the CP treatment condition at the end of treatment (week 7), $z(476) = 2.31$, $P = 0.0210$ (see **Figure 4**). Survival analysis indicated continuous abstinence rates did not significantly differ, BUP + NTX (26.2%) compared to BUP + PBO (13.3%), log-rank statistic, $\chi^2(1) = 3.1911$, $P = 0.0740$.

SUBJECTIVE MEASURES
Minnesota Nicotine Withdrawal Scale
Total nicotine withdrawal scores (Minnesota Nicotine Withdrawal Scale) showed an effect of medication, $F(1, 118) = 4.48$, $P = 0.0364$, time, $F(6, 457) = 7.59$, $P < 0.0001$, and their interaction, $F(6, 457) = 2.64$, $P = 0.0159$ (see **Figure 3**). Minnesota Nicotine Withdrawal Scale scores differed at week 2 (1-week post-quit), $t(268) = -2.97$, $P = 0.0032$.

Questionnaire of smoking urges
Anticipated pleasure from smoking, $F(6, 472) = 29.16$, $P < .0001$, and anticipated withdrawal relief, $F(6, 437) = 19.17$, $P < 0.0001$ declined across the treatment phase in both groups. No medication or medication by time effects were observed.

Positive and negative affect scales
No effects were observed for positive affect. Negative affect declined across the treatment phase, $F(6, 434) = 4.28$, $P = 0.0003$. No medication or medication by time effects were observed.

Integrity of study blind
Subjects receiving BUP + NTX were significantly more likely to accurately judge their medication assignment than BUP + PBO subjects at week 1, $\chi^2(1) = 10.15$, $P = 0.0014$, and week 7, $\chi^2(1) = 11.08$, $P = 0.0009$. The BUP + PBO judged their medication assignment at chance levels of accuracy (week 1 = 53.6%; week 7 = 53.6%), whereas those in the BUP + NTX condition ascertained their medication assignment accurately far above chance (week 1 = 84.6%; week 7 = 85.7%). At week 7, the most common reasons given for medication judgments in the BUP + NTX treated subjects were presence of side effects (38.7%) and ease of not smoking (40.8%).

Adherence
Those receiving BUP + PBO (M = 7:52 a.m.; SE = 17 minutes), reported taking their morning doses earlier (BUP + PBO, M = 8:30 a.m., SE = 22 minutes), $t(102) = 2.43$, $P = 0.0167$. No differences were observed for the evening doses (BUP + PBO, M = 7:34 p.m., SE = 22 minutes; BUP + NTX, M = 7:05 p.m., SE = 23 minutes). No differences in the mean interval between doses was observed for medication assignment (BUP + PBO, M = 11.08 hours, SE = 13 minutes; BUP + NTX, M = 11.3, SE = 11 minutes). No differences were found in the average number of doses reported taken for morning doses out of a possible 49 (BUP + PBO, M = 29.4, SE = 2.2; BUP
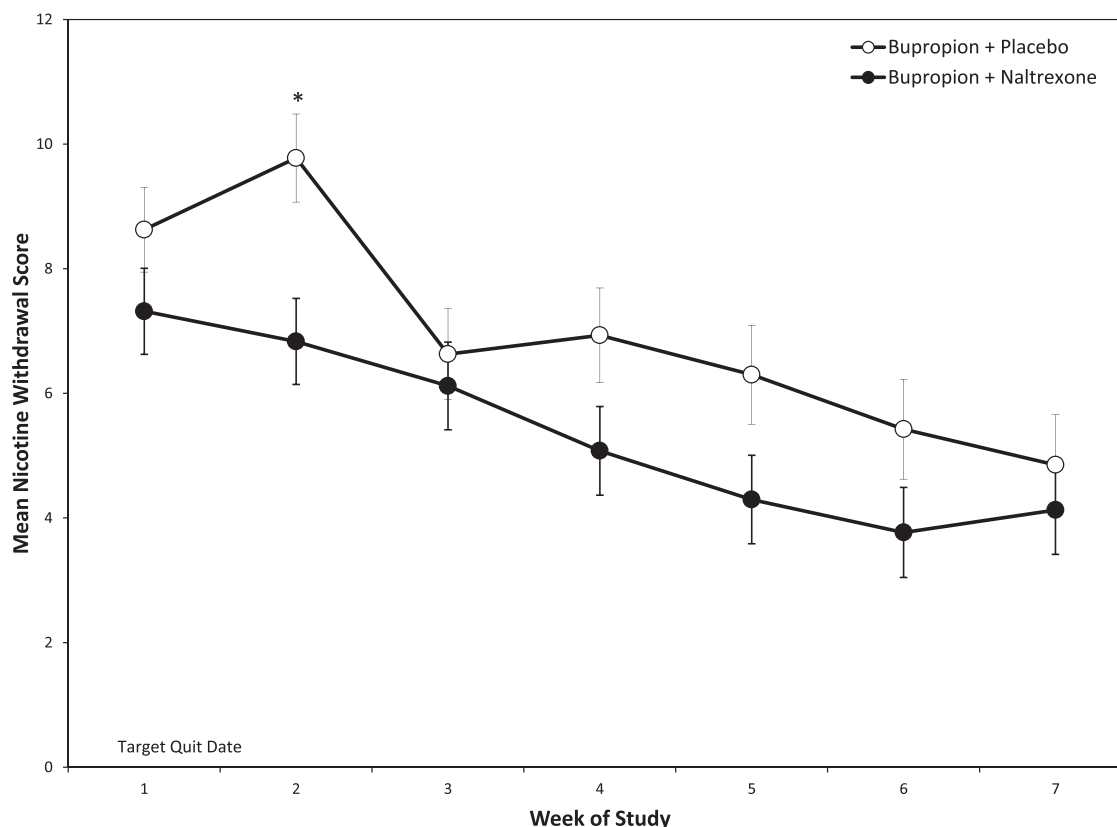
Figure 3 Nicotine withdrawal symptoms as measured by the Minnesota Nicotine Withdrawal Scale, varied significantly as a function of medication, time, and their interaction.

+ NTX, M = 30.1, SE = 2.6), or evening doses out of a possible 46 (BUP + PBO, M = 27.9, SE = 2.1; BUP + NTX, M = 28.7, SE = 2.5). Adherence rates for the total 95 doses did not differ by medication assignment, $\chi^2(1)$ = 0.66, P = 0.4167 (BUP + PBO, 64.7%; BUP + NTX, 69.6%). The rate of subjects taking 80% or more of the 95 total possible dosages did not differ by medication, $\chi^2(1)$ = 2.0538, P = 0.15 (BUP + PBO, 45.1%; BUP + NTX, 59.6%).

DISCUSSION
Key observations
In this first randomized, controlled double-dummy parallel groups study, we found that treatment-seeking smokers receiving the combination of BUP + NTX were more likely to be abstinent from tobacco during treatment than those receiving BUP + PBO. The combination of BUP + NTX was tolerated as well as BUP + PBO as indexed by retention rates and medication adherence levels; however, subjects receiving BUP + NTX treatment reported more side effects. BUP + NTX was superior to BUP + PBO at reducing nicotine withdrawal during the critical 1 week following the target quit date.

Smoking cessation
At the end of the 7-week treatment period, those receiving BUP + NTX achieved a point-prevalence abstinence rate of 54.1% compared to 33.3% for those treated with BUP + PBO.

The BUP + NTX treated subjects exhibited numerically greater rates of continuous abstinence compared to BUP + PBO, 26.2% vs. 13.3%, respectively, although the effect was not statistically significant. Our results differ from the two previous studies of BUP + NTX that showed equivocal findings.[15,30] This study involved a sample four to six times larger than the earlier studies, and used a dosage of NTX one-half to one-third higher.

Safety and tolerability
Rates of subject attrition did not differ between treatment conditions, although some side effects occurred more frequently in the BUP + NTX group, in particular, reports of lightheadedness and nausea. Elevated rates of nausea have been reported in the two smoking cessation studies of BUP + NTX,[15,30] as well as in studies of Contrave (BUP + NTX) for weight loss.[16] Nausea is a common side effect in those treated with NTX alone or with NRT in quitting smokers.[31,32] Lightheadedness or dizziness have been documented in a prior treatment study of NTX alone[31] and in Contrave trials.[16]

Nicotine withdrawal
Nicotine withdrawal plays a critical role in relapse to cigarette smoking.[33] Nicotine withdrawal is generally worse in the initial weeks following cessation, after which most symptoms return to baseline levels.[34] In this study, BUP + NTX was superior to BUP + PBO in suppressing the nicotine withdrawal syndrome after 1 week of

abstinence. Bupropion is known to effectively decrease several nicotine withdrawal symptoms, including increased negative affect, decreased positive affect, irritability, concentration impairment, and cravings.[21–23] NTX is posited to facilitate smoking cessation by reduction in craving for tobacco. It is unclear why the addition of NTX to BUP led to the pattern of withdrawal symptom relief seen in this trial, as previous trials have not generally observed this.

Tobacco craving

NTX or NTX plus the nicotine patch have been shown to decrease tobacco craving compared to PBO or the nicotine patch alone, respectively.[24,25,31,32] Specifically, previous studies have found effects on both of the Questionnaire of Smoking Urges subscales. In this study, a pattern favoring BUP + NTX was observed for factor 2 (i.e., anticipated withdrawal relief), but was not significant. It may be that the dose of NTX used in this study was insufficient to provide maximal craving relief. In fact, O'Malley et al.[32] found that in subjects treated with NRT, and a dose of 25, 50, or 100 mg of NTX, that NTX subjects receiving the highest dose of NTX showed the greatest reductions in craving.

Weight

Two studies found some evidence that BUP + NTX suppressed post-cessation weight gain.[15,30] In one trial, overweight or obese smokers were specifically evaluated.[15] In the present study, weight gain was low in the total sample, with no differences between groups. One factor that might have accounted for limited weight gain and no differences between groups is that BUP has a weight suppressant effect following smoking cessation.[23]

Limitations

This study has some limitations. Study sample size was relatively small, but had sufficient power to examine whether or not the combination medication should be further investigated. Nevertheless, attrition rates in this study were unusually high compared to the published literature. Ideally, medication taking would be measured directly (i.e., direct observation) or through a strong indirect method (e.g., adulterating medication with a tracer, such as riboflavin). Instead, diary card records were used, an indirect subjective approach to the measurement of medication taking vulnerable to error and bias. We failed to identify the psychological mechanism of the observed treatment effects; more frequent assessment or use of ecological momentary assessment of withdrawal, craving, and affect would likely have improved this study. The study sample was 89.3% white, limiting race-based comparisons with other reports with greater racial diversity. An essential bulwark against experimental bias is the study blind because it minimizes the effects of investigator and subject expectations. In our study, those receiving BUP + NTX judged their medication assignment substantially above chance, whereas subjects receiving BUP + PBO judged their assignment at chance levels.

CONCLUSIONS AND FUTURE DIRECTIONS

This study is clinically significant in that it demonstrates the efficacy of combining BUP and NTX on the primary outcomes of smoking cessation and nicotine withdrawal. Strengths include being a rigorous randomized, controlled trial with adequate sample size and resultant statistical power. Results are strengthened by evidence of good self-reported adherence to the study medication regimens. Our assessment of blindness integrity is rare in medication trials, yet aids in evaluating results and informing future designs.

New treatments to assist the growing population of smokers refractory to current interventions are needed. Proceeding to examine mechanisms of action of combined BUP and NTX will inform the optimal dosing strategy for this combination pharmacotherapy. To the extent that these initial findings are confirmed in a larger trial, future studies might consider the newer sustained-release formulation of BUP and NTX in a single combination pill (e.g., Contrave), which offers advantages in terms of medication compliance and convenience. Additional evaluation of different ratios of BUP and NTX should be explored (e.g., Contrave uses a ratio of 90 mg of BUP to 8 mg of NTX). Additionally, future studies might consider whether specific populations of smokers are more likely to benefit from this combination approach.

METHODS
Participants

The study protocol and all related materials were reviewed and approved by the University of Minnesota Committee for the Protection of Human Subjects (Study Number: 0603M83886) and registered with ClinicalTrials.gov (NCT00419731). Participants were recruited through advertisements in local media, and underwent a telephone interview to establish initial eligibility from April 2007 to April 2010. Male and female subjects meeting the following eligibility criteria were randomized: (a) age between 18 and 65 years; (b) smoked at least 10 cigarettes daily for at least 1 year; (c) English speaking; (d) women of childbearing potential using effective contraception and provided a urine sample for a pregnancy screen; (e) willingness to reduce alcohol consumption during study to two or fewer standard drinks/day; (f) no contraindications to use of BUP (i.e., monoamine oxidase inhibitors, seizure disorders, or other clinical history predisposing one to seizures); (g) no contraindications of NTX (i.e., opioid use in the past 30 days; hepatocellular injury); (h) good physical health as established by a review of a health history form by our study nurse practitioner; and (i) no active, untreated major mental illness.

Procedures

The research was conducted at the Tobacco Research Programs, a component of the Department of Psychiatry at the University of Minnesota. The study occurred over the course of 33 weeks and involved three consecutive phases: (1) baseline; (2) treatment; and (3) follow-up (see **Figure 4**).

Baseline

Callers meeting initial telephone screen criteria received an appointment for an orientation meeting, consent process, and a pretreatment evaluation, which included a medical history and physical examination. Assessment involved laboratory evaluation of the liver, kidneys, and thyroid function, heart rate and blood pressures, and weight. In addition, tests were conducted for pregnancy (urine). The Fagerström Test of Nicotine Dependence was used as a measure of nicotine dependence.[35] Study eligibility was determined after two visits, after which subjects were randomized to treatment and given study medications.

Treatment

At day 8, after 7 days of medication induction, participants had their target quit date. At this and the following 6 weekly visits that bracketed the treatment phase, subjects provided CO samples, completed subjective
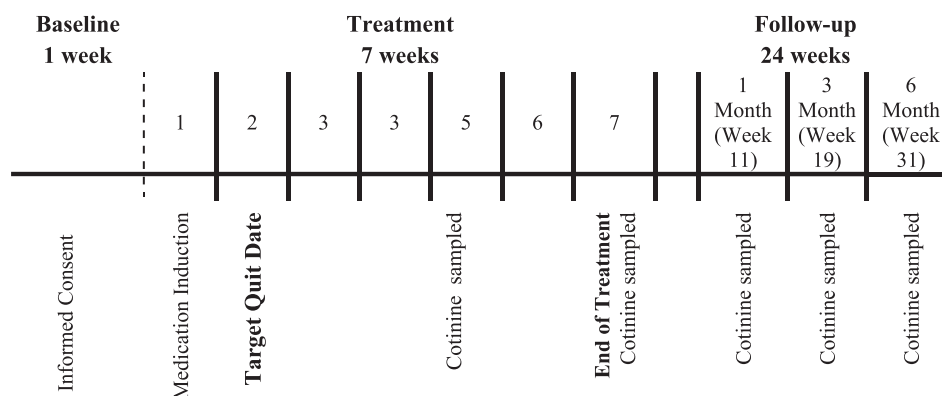
Figure 4 Study design showing the three phases of the trial: baseline, treatment, and follow-up. The targeted quit date occurred during week 1 of treatment, following a 7-day medication induction phase. At weeks 5 and 7 (end of treatment), 1-month follow-up, 3-month follow-up, and 6-month follow-up, saliva cotinine samples were collected from those reporting abstinence from tobacco in the preceding week and having a carbon monoxide ≤8 parts-per-million. Participants discontinued medication at the end of the treatment phase (week 7). The initial counseling session prior to target quit date lasted 20 minutes. All subsequent sessions included counseling lasting ~10 minutes.

measures, underwent assessment of vital signs, returned daily diary cards of smoking and medication taking, and received a 1-week supply of study medication. At weeks 5 and 7, abstinent subjects provided a saliva sample for assessment of cotinine levels.

Follow-up

Participants returned to the clinic for evaluation 1, 3, and 6 months post-treatment. Assessment procedures were the same as in the treatment phase except that saliva samples were collected at each visit from eligible subjects.

Interventions

Pharmacotherapy. The study medications were dispensed in a placebo-controlled, double-dummy design. Two different medications were used (i.e., BUP sustained release (SR) of 150 mg, twice each day, and PBO or NTX of 25 mg, twice each day). NTX pills were jacketed to look identical to the PBO pills. The dose of 300 mg of BUP was based on the US Food and Drug Administration guidelines,[36] whereas the dose of NTX was chosen as being intermediary in the range of doses used in the literature.[24,31,37,38] BUP SR treatment began 7 days prior to target quit date to achieve functional plasma levels. In order to maintain blindness of the study, NTX therapy began at the same time, even though NTX did not require a 7-day induction phase. Participants were instructed to take two pills by mouth each morning and one pill each night for 3 days. For these first 3 days, subjects took 150 mg of BUP SR in the morning and a second pill that was either PBO or NTX (25 mg); each evening, they took a pill that was either PBO or NTX (25 mg). Beginning at day 4 of the induction phase and throughout the remainder of the treatment phase, each participant took two pills in the a.m. (i.e., one BUP SR pill (150 mg) and one pill containing either NTX (25 mg or PBO)) and two pills in the p.m. (i.e., one BUP SR pill (150 mg) and one pill containing either NTX (25 mg) or PBO), 8 to 12 hours after the a.m. pills.

Behavioral counseling

Brief behavioral counseling was provided to all subjects. It involved a structured presentation on the benefits of quitting, a review of coping skills to deal with craving and withdrawal, and support and encouragement.[39] The initial counseling session prior to target quit date lasted 20 minutes. All subsequent sessions included counseling lasting ~10 minutes.

Measures

Primary outcome measures. Smoking was recorded on daily diaries that captured information about the time at which each cigarette was smoked. The primary outcome variable was 7-day, biochemically verified, point-

prevalence abstinence across the treatment and follow-up phases.[40] At each clinic visit, subjects provided expired CO samples in parts-per-million; samples were considered positive if CO levels exceeded 8 parts-per-million.[41] At weeks 5 and 7 during treatment and at every follow-up visit, those reporting abstinence from smoking in the preceding 7 days and who provided a CO ≤8 parts-per-million were also asked to provide a saliva sample for analysis of cotinine concentrations. Saliva samples were analyzed by Salimetrics (State College, PA, USA), and were considered positive for tobacco use if cotinine levels exceeded 15 ng/mL.[41]

An adverse events form was used to assess the duration, severity, and frequency of the most common side effects reported in clinical trials of BUP and NTX.[31,42] The adverse events form included a section to evaluate the extent to which the event was judged to be related to the study drugs (i.e., unrelated, unlikely, possible, or probable).

Secondary outcome measures

The Minnesota Nicotine Withdrawal Scale was used to assess symptoms of nicotine withdrawal from the *Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition*.[43,44] Urges and cravings to smoke were assessed via the brief version of the Questionnaire of Smoking Urges.[45,46] The Questionnaire of Smoking Urges consists of two scales derived from factor analysis: factor 1 (smoking for positive reinforcement, anticipated pleasure from smoking), and factor 2 (smoking for negative reinforcement, anticipated withdrawal relief). The Positive and Negative Affect Scale[47] yielded two subscale scores measuring positive affect (e.g., alertness, enthusiasm) and negative affect (e.g., sadness, distress). The integrity of the study blind was assessed at treatment weeks 1 and 7 by having participants judge their medication assignment and provide reasons for those judgments.

Statistical analysis

Sample size. The primary outcome was 7-day, biochemically confirmed, point-prevalence smoking abstinence. This analysis was conducted under an intention-to-treat policy: missing values were coded to indicate relapse to smoking. Continuous abstinence indicated negative tests of point-prevalence abstinence at each of five time points (weeks 5 and 7 of treatment, and months 1, 3, and 6 of follow-up). Sample size calculations were made using a specialized macro for repeated measures designs.[48] In order to estimate treatment effects, point-prevalence abstinence rates were pooled from six placebo-controlled trials of BUP.[21,49–53] Total available sample sizes at each time point in the study are displayed in **Figure 5**.

Assumptions

All analyses were conducted using the Statistical Analysis System version 9.4.[54] Unless otherwise stated, values of $P < 0.05$ were considered
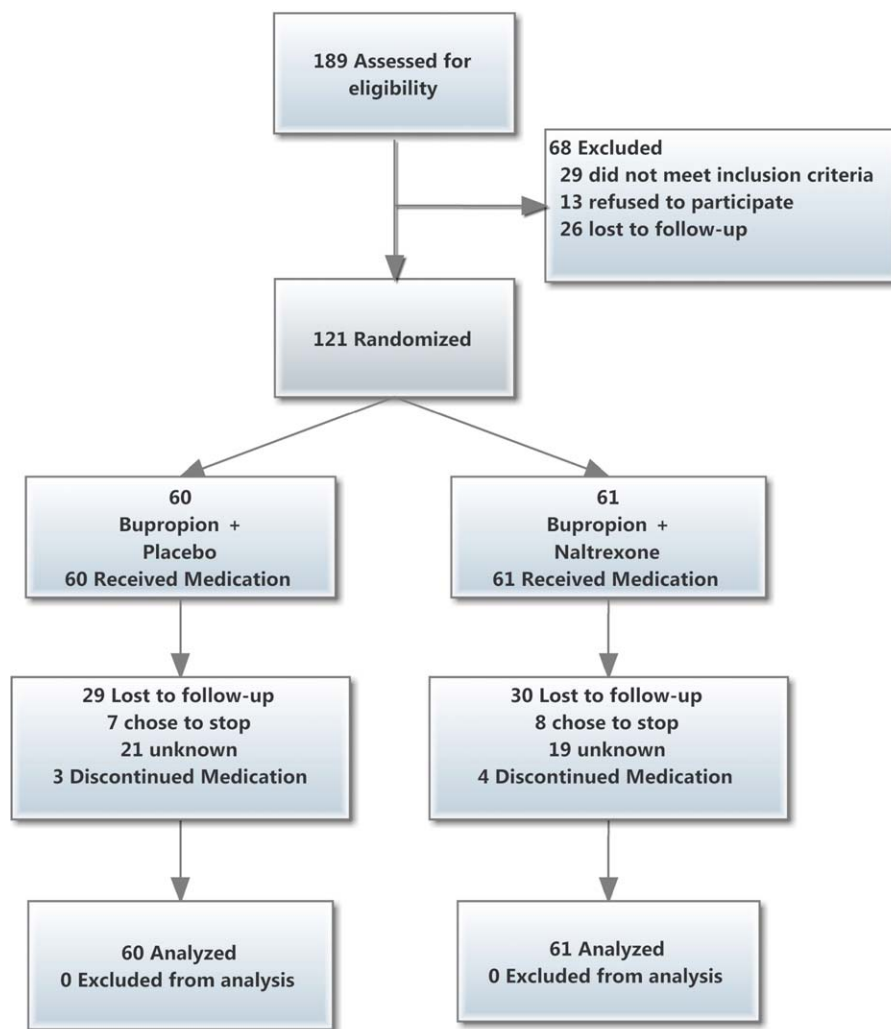
Figure 5 Study participant flow diagram (CONSORT). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

statistically significant, based on two-tailed tests. Due to participant attrition and occasional missing data, the number of subjects or data points available for statistical analysis varied, except for the primary outcome in which missing values were imputed to indicate smoking (see **Figure 2**). All confidence intervals are constructed with $\alpha = 0.05$.

Repeated measures

Repeated measures analyses were conducted in the framework of generalized linear mixed models[55] with the MIXED procedure for linear outcomes and GENMOD procedure for nonlinear outcomes of daily smoking abstinence, with specification of appropriate error distributions (i.e., binomial) and link functions (i.e., logistic). In all analyses, the effects of medication (i.e., BUP + PBO or BUP + NTX), time (i.e., week), and their interaction were tested. Average baseline scores for all measures (except for abstinence status) were included in treatment phase analyses as covariates.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

AUTHOR CONTRIBUTIONS

M.M., J.S., S.A., J.G., P.P., A.O., and D.H. wrote the manuscript. M.M., J.S., S.A., J.G., P.P., and D.H. designed the research. M.M. and A.O. performed the research. M.M. analyzed the data.

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