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Bupropion Sustained-Release for Pregnant Smokers: A Randomized, Placebo Controlled Trial

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Abstract

Background—Bupropion is used to treat depression during pregnancy. However, its usefulness as a smoking cessation aid for pregnant women is not fully known.

Objective—To evaluate the preliminary efficacy of bupropion sustained-release for smoking cessation during pregnancy.

Study design—We conducted a randomized, prospective, double-blind, placebo-controlled, pilot trial. Pregnant women who smoked daily received individualized behavior counseling and were randomly assigned to a 12-week, twice-a-day treatment with 150 mg bupropion sustained-release or placebo. The primary study objectives were to 1) determine whether bupropion sustained-release reduces nicotine withdrawal symptoms on the quit date and during treatment period compared to placebo; and 2) whether it increases 7-day point prevalence abstinence at the end of treatment period and at the end of pregnancy.

Results—Subjects in the bupropion (n = 30) and placebo (n = 35) groups were comparable in age, smoking history, number of daily smoked cigarettes, and nicotine dependence. After

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The study was conducted at: Department of Obstetrics & Gynecology, The University of Texas Medical Branch (UTMB) at Galveston, TX; UTMB Regional Maternal Child Health program (RMCHP) clinics at Pearland, TX, and Pasadena, TX.

Conflict of interest: The authors report no conflict of interest

Clinical trial registration: ClinicalTrials.gov, www.clinicltrials.gov, NCT01390246).

Condensation: Adjunctive use of bupropion sustained-release compared to placebo for smoking cessation during pregnancy reduced cravings and nicotine withdrawal symptoms and increased quit rates during treatment.

controlling for maternal age and race, bupropion sustained-release reduced cigarette cravings (1.5 ± 1.1 vs 2.1 ± 1.2, $P = 0.02$) and total nicotine withdrawal symptoms (3.8 ± 4.3 vs 5.4 ± 5.1, $P = 0.028$) during the treatment period. Administration of bupropion sustained-release reduced tobacco exposure, as determined by levels of carbon monoxide in exhaled air (7.4 ± 6.4 vs 9.1 ± 5.8, $P = 0.053$) and concentrations of cotinine in urine (348 ± 384 ng/mL vs 831 ± 727 ng/mL, $P = 0.007$), and increased overall abstinence rates during treatment (19% vs 2%, $P = 0.003$). However, there was no significant difference in 7-day point prevalence abstinence rates between the two groups at the end of medication treatment (17% vs 3%, $P = 0.087$) and at the end of pregnancy (10% vs 3%, $P = 0.328$).

Conclusion—Individual smoking cessation counseling along with the twice-daily use of 150 mg bupropion sustained-release increased smoking cessation rates and reduced cravings and total nicotine withdrawal symptoms during the treatment period. However, there was no significant difference in abstinence rates between groups at the end of medication treatment and at end of pregnancy, likely due to the small sample size. A larger study is needed to confirm these findings and to examine the potential benefit/ risk ratio of bupropion sustained-release for smoking cessation during pregnancy.

Keywords

bupropion sustained-release; pregnancy; smoking cessation

Introduction

Despite the well-known obstetrical, fetal, and developmental complications associated with cigarette smoking, 15.9% of all pregnant women continue to smoke throughout pregnancy.[1] Behavioral interventions are only modestly effective in helping pregnant women quit smoking.[2,3] Smoking cessation medications increase the chance of quitting smoking in men and non-pregnant women,[2] and they could also be used to reduce cigarette cravings and withdrawal and to enhance quit rates during pregnancy.

Bupropion sustained-release (SR), an antidepressant, is commonly used to promote smoking cessation in males and non-pregnant females.[4] The effectiveness of bupropion (Zyban ®, Wellbutrin ®) as a smoking cessation aid for pregnant women was suggested in a prospective observational study, in which pregnant smokers receiving bupropion 150 or 300 mg daily had higher quit rates than controls.[5]

Based on this information, we conducted a randomized, prospective, double-blind placebo-controlled, pilot trial of the preliminary efficacy of bupropion SR in combination with behavioral counseling for smoking cessation during pregnancy. The primary study objectives were to determine 1) whether bupropion SR reduces nicotine withdrawal symptoms on the quit date and during medication treatment; and 2) whether bupropion SR increases 7-day point prevalence abstinence at the end of medication treatment and at the end of pregnancy compared to placebo. Secondary objectives included assessment of bupropion SR on overall quit rates during treatment and on adverse effects during pregnancy when compared to placebo.

Materials and Methods

Prior to implementation, the study protocol was reviewed and approved by The University of Texas Medical Branch (UTMB) Institutional Review Board and was registered on Clinicaltrials.gov (ClinicalTrials.gov Identifier NCT01390246). An independent Data Safety and Monitoring Board (DSMB) reviewed ongoing trial data, including efficacy rates and serious adverse events (SAEs) through the study.

Recruitment

Pregnant smokers were recruited through the UTMB Ob/Gyn Department clinics and the UTMB Regional Maternal Child Health Program (RMCHP) clinics. Referrals from heath care providers were also accepted. In addition, the study was advertised through printed flyers, posters, and electronic media in RMCHP clinic waiting areas. Pregnant smokers who expressed interest in the research study were then screened for eligibility using inclusion and exclusion criteria.

Inclusion and Exclusion Criteria

Inclusion criteria were: women ≥ 18 years of age between 13 and 30 weeks' gestation, smoking ≥ 10 cigarettes per day (CPD) prior to pregnancy and 5 CPD for the preceding 7 days, English or Spanish speaking, and having the intent to carry to term.

Exclusion criteria were: current illicit drug or alcohol abuse or dependence; multiple gestation; treatment for psychiatric disorder within the last 6 months; unstable medical problems (pregnancy-induced hypertension [blood pressure (BP) > 140/90 mg Hg], preeclampsia, threatened abortion, hyperemesis gravidarum); known fetal congenital abnormality; seizure disorder; use of psychotropic medication; use of medication known to lower the seizure threshold; anorexia/bulimia; a personal history of closed head trauma with > 30 minutes of loss of consciousness or amnesia or resulting in skull fracture or subdural hematoma/ brain contusion; current use of any other smoking cessation treatment; and current use of methadone.

Consent and Randomization

Prior to participation in the study, all subjects agreed and signed the IRB-approved informed consent. To ensure comparability of subjects in the treatment groups, we employed the urn randomization method.[6] The groups were balanced for 2 variables: gestational age at study entry and number of CPD. Subjects, primary investigators, and research nurses were blinded to pharmacotherapy group assignment.

Study design

The study protocol consisted of 10 visits: first—enrollment, randomization, and study medication dispensation; second—the scheduled quit date; third to sixth— medication therapy progress assessment; seventh—the end of pregnancy (36–38 weeks' gestation); and eighth to tenth—1-, 3-, and 6-month postnatal assessments of abstinence (Figure 1). Participants received either bupropion SR or matched placebo orally once daily for three days followed by twice daily for a total medication treatment of 12 weeks.

The University of Iowa Pharmaceuticals was contracted for production, labeling, and bottling of the active drug and placebo tablets. To confirm patients' proper use of medication, participants were asked to keep a daily diary of the number of pills taken. Subjects then returned the study drug bottles at the next study visit to the research nurse who performed pill counts for compliance records. Compliance to study medication was also biochemically confirmed as described below in *Biochemical measures* section.

Both groups received behavioral interventions, which included 35-minute counseling sessions at each of the first 2 visits (enrollment and on the quit day) and 10 minutes of smoking cessation counseling at subsequent visits. Counseling sessions were delivered by a research nurse using a motivational interviewing approach,[7,8] which was previously shown to be effective in pregnant smokers.[9]

Measures

Prior to the smoking intervention, baseline standardized questionnaires assessed demographics, smoking history/status, as well as medical and obstetrical history. Additional questionnaires assessed confidence and motivation to quit, concerns about excessive weight gain, and confidence in bupropion as a smoking cessation aid. The questionnaires were based on the clinical trials published previously, [10,11] and each parameter was measured using a 5-point scale (1=least likely/mostly disagree, 5=highly likely/mostly agree). Nicotine dependence was assessed using the 6-item Fagerstrom Test of Nicotine Dependence (FTND).[12] The Minnesota Nicotine Withdrawal Scale (MNWS)[13] and the Prime Score[14] questionnaires were completed at every visit, including baseline.

At every visit, a research nurse monitored the smoking status of all subjects (i.e., CPD, exhaled carbon monoxide [CO]) and adverse events (AEs). Exhaled CO was measured using a Vitalograph carbon monoxide monitor (Lenexa, KS) according to the manufacturer's recommendations. A urine sample was collected at each visit and stored at −80°C. AEs, including SAEs, were assessed on all subjects during interviews by the research nurse at each study visit. We monitored for maternal AEs that could be related to bupropion, such as seizures, BP > 140/90 mm Hg, headache, insomnia, rhinitis, dry mouth, and anxiety. We defined *apriori* which AEs would be considered fetal and neonatal SAEs: intrauterine fetal demise, preterm delivery (< 34 weeks), clinically suspected fetal growth restriction, congenital malformations, cardiovascular anomalies, low birth weight (< 10%), Apgar scores < 7 at 5 minutes, and neonatal length of hospital stay > 3 days. Research nurses also abstracted data on pregnancy and neonatal outcomes from electronic medical records after delivery.

Biochemical measures

The accuracy of self-reported smoking abstinence during study visits was confirmed by an exhaled CO level of < 4 parts per million (ppm)[15,16] and by urinary cotinine level of < 50 ng/mL.[17,18] Cotinine in urine was quantified using the validated liquid chromatography-mass spectrometry (LC/MS) method;[19,20] sample extraction was based on the procedure described by Peterson et al.[21] Patients' compliance to study medication was confirmed by

concentrations of bupropion in urine and its metabolites (hydroxybupropion [OHBUP] and threohydrobupropion [TB]) using the method reported previously.[22,23]

Retention

Subjects received phone call reminders prior to each study visit. If a participant missed the appointment, the research staff called to reschedule. If research personnel were unable to reach a subject after multiple attempts, the reason for withdrawal was identified as “lost to follow-up”. These subjects were classified as smokers for the purpose of analysis. Subjects were reimbursed as follows: $35 for each of the visits 1-7, $50 for each of the visits 8-9 and $75 for visit 10. The participants received the compensation at the end of study visits 3, 6, 7, 8, 9, and 10.

Data analysis

The original sample was based on detecting a difference in MNWS symptoms (i.e., cigarette craving and total withdrawal scores) between bupropion and placebo groups as a measure of potential efficacy. The study was powered for three outcomes: cigarette cravings, total MNWS withdrawal scores, and quit rates. A previous study of smoking cessation in pregnant women reported a standardized difference of d = 1.0 for cravings and d = 0.6 for total MNWS.[24] In addition, a study of Hurt et al, 1997, reported a 45% quit rate among male and non-pregnant female smokers treated with bupropion SR for cessation, while 19% quit rate was observed among those receiving placebo.[25] The initial targeted enrollment of 50 women per group would yield a power of 0.85 with an alpha of 0.05 to detect differences in total MNWS scores, 0.99 power to detect differences in craving scores, and 0.80 power to detect differences in quit rates. However, two years after the trial had initiated, the sample size was re-estimated because the original calculations were overpowered for some measures and the enrollment into the study was more difficult than expected. Thus, 30 subjects per group was still sufficiently powered (0.80) for the craving score; however, the total MNWS score was powered to 0.65 and quit rate to 0.60.

Baseline characteristics between groups were compared using a 2-sample *t* test for continuous variables and Chi-square (or exact test) for categorical variables. Likewise, the *t* and Chi-square tests were used to test for differences between groups on birth outcomes. For continuous outcome variables measured at each visit (MNWS, most smoking outcomes), a linear mixed model with a random effect for subject and fixed effects for group, time point, and the interaction was run. For dichotomous outcomes measured at each visit (abstinence, AE), a general estimating equation with a binomial distribution and logit link function and effects for group, time point, and the interaction was evaluated.

Results

Five hundred and eleven pregnant women were approached by research nurses to determine their study eligibility. Of these subjects, 200 (39%) did not meet inclusion criteria, 246 subjects (48%) were not enrolled for various reasons (Figure 1), and 65 pregnant women (13%) were enrolled in the study. Of the recruited 65 subjects, 30 were randomized to the bupropion group and 35 to the placebo group.

Demographic and Baseline Characteristics

Table 1 presents demographic and baseline characteristics of study participants. The average gestational age at enrollment was 18.9 ± 4.5 weeks. Participants reported average smoking of 18 ± 8 CPD prior to pregnancy and 12 ± 8 CPD at enrollment. The distribution of demographic and baseline characteristics was similar in both groups except race/ ethnicity (49% white/ non-Hispanic in the placebo group vs 77% white/ non-Hispanic in the bupropion group, $P = 0.011$) and age (27.5 ± 6.5 years vs 24.5 ± 5.6 years, $P = 0.051$).

Fifty-seven percent of women enrolled had previously tried to quit smoking during their current pregnancy. The average total FTND and PRIME scores as well as the average scores for motivation and confidence to quit did not differ among study groups (Table 1). The average level of worries about excessive weight gain due to intervention was not very high (2.4 ± 1.6), and many participants believed that bupropion would be helpful (mean score 3.9 ± 0.8) to them for smoking cessation.

Smoking abstinence

Seven-day point prevalence abstinence was defined at each visit as no cigarettes (not even a puff) in the last 7 days, levels of CO in exhaled air < 4 ppm,[15,16] and concentrations of cotinine in urine < 50 ng/mL.[17,18] The point prevalence abstinence rates during the treatment assessment period (visits 2–6) between study groups were significant (2% in the placebo group vs 19% in the bupropion group, $P = 0.003$, Figure 2). There was no significant difference in abstinence rates between bupropion and placebo groups at the end of medication treatment, visit 6, (17% vs 3%, $P = 0.087$) and at the end of pregnancy, visit 7 (10% vs 3%, $P = 0.328$), and during the postpartum period (visits 8–10).

Compared to baseline levels of self-reported cigarette consumption, there was at least a 50% reduction in cigarettes smoked per day during treatment, at the end of pregnancy, and postpartum in both groups (Table 2). Although, this reduction in cigarette consumption was not statistically significant between the groups, exhaled CO and urinary cotinine concentrations during treatment (visits 2–6) were higher in the placebo group than the bupropion group ($P = 0.011$ and $P < 0.001$, respectively, Table 2).

There was no significant difference between the groups in total nicotine withdrawal symptoms ($P = 0.068$) and tobacco cravings ($P = 0.08$) in the unadjusted analysis; however, after controlling for maternal age and race, these measures were statistically significant between groups with the placebo groups having greater withdrawal symptoms and craving during treatment ($P = 0.028$ and $P = 0.02$, respectively, Table 2).

Birth and delivery outcomes

There were no significant differences between treatment groups in birth weight, infant length, head circumferences, Apgar score at 5 minutes, and pH values in arterial and venous cord blood (Table 3). The gestational age ($P = 0.058$) and Apgar score at 1 minute ($P = 0.064$), although not statistically significant, trended higher in the bupropion group.

SAEs occurred in five subjects in the placebo group and two in the bupropion group. In the placebo group, four involved an infant stay greater than three days (two cases of premature

delivery, one for respiratory distress, and one for hyperbilirubinemia). The other SAE in the placebo group was due to a maternal hospitalization for diabetes management. The two SAEs in the bupropion group involved a subject who developed superimposed preeclampsia requiring delivery at 32 weeks 2 days and an infant with a cord blood pH value of 7.01. Following clinical review, both events were considered unlikely related to the study medication.

Maternal outcomes

There were no differences between bupropion and placebo groups in body mass index (32.9 ± 9.4 vs 39.8 ± 9.6, $P = 0.52$) at the end of pregnancy, systolic BP (116 ± 8 mmHg vs 122 ± 14 mmHg, $P = 0.464$) and diastolic BP (70 ± 9 mmHg vs 75 ± 11 mmHg, $P = 0.396$), and pulse rate, (81 ± 12 beat per minute vs 82 ± 12 beat per minute, $P = 0.721$).

Subjects in both groups reported moderate or severe adverse effects that are known side effects of bupropion, including headache (29% vs 11%, $P= 0.157$), difficulty sleeping (25% vs 7%, $P= 0.123$), runny nose (17% vs 7%, $P= 0.397$), dry mouth (37.5% vs 14%, $P= 0.308$), and anxiety (33% vs 18%, $P= 0.22$). The percentage of subjects who experienced moderate or severe adverse effects was not statistically different between groups.

Compliance with study medication and retention

The proportion of adherence to the study medication in the bupropion group was 87.4%, compared to 82% in the placebo group ($P= 0.31$). While the majority of subjects in both groups were able to correctly guess which treatment they received ($P= 0.049$), 33% of subjects in the placebo group believed they received bupropion SR, and 29% of subjects in the bupropion group believed they received placebo.

There was a high rate of early withdrawal from the study; only 20% of all subjects completed the clinical trial (30% of subjects in the bupropion group vs 11% in the placebo group, $P= 0.12$). There were no differences in education level, number of adults and children in household, annual income, smoking and psychosocial variables in the subjects who withdrew from the study vs those who stayed in the study. Higher completion rates were observed among subjects who lived with a partner vs those who did not ($P = 0.013$). In addition, the slightly higher completion rate in the cohort was associated with Hispanic vs non-Hispanic ethnicity ($P = 0.07$) and part-time ($P= 0.080$) vs non- or full-time workers (whose completion rates were similar).

Comments

In this randomized placebo controlled pilot study of bupropion SR for smoking cessation during pregnancy, bupropion SR reduced nicotine cravings and withdrawal symptoms compared to placebo and increased overall cessation rates during medication treatment. Abstinence rates were not statistically significant between groups at the end of pregnancy and postpartum, likely due to the small sample size. The medication was relatively well tolerated, and the serious adverse event rate was similar between groups (although numerically lower in the bupropion SR compared to the placebo group). These findings

suggest that bupropion SR may be a promising adjunctive medication for smoking cessation during pregnancy.

It is noteworthy that we used a conservative estimate for cigarette abstinence, counting those who were lost to follow-up as smokers. It is possible that some of the individuals who quit smoking with bupropion or placebo and were lost to follow-up may have been tobacco free at the end of treatment and after pregnancy. During the treatment period, bupropion SR significantly reduced smoking as determined by levels of CO in exhaled air and concentrations of cotinine in the urine of pregnant women. The results of our study are in agreement with a previous observational study of bupropion SR effectiveness in pregnancy[5] as well as with the existing literature on non-pregnant smokers showing that compared to placebo, bupropion can approximately double the chance of smoking cessation success.[25]

A significant impact of bupropion SR compared to placebo on measures of cravings and nicotine withdrawal symptoms during treatment was observed. This finding is consistent with other studies showing that bupropion SR reduces cravings for tobacco and signs and symptoms of nicotine withdrawal.[25] It is noteworthy that many of the signs of nicotine withdrawal can also commonly occur during pregnancy (irritability, anxiety, difficulty concentrating, insomnia, restlessness, increased appetite, depressed mood, and drowsiness),[26] and use of medications that reduce nicotine withdrawal could be especially beneficial during pregnancy to improve smoking cessation rates. Since the bupropion SR compared to the placebo group had lower overall nicotine withdrawal symptoms (which include insomnia and anxiety), but higher reports of at least one episode of insomnia and anxiety during treatment, it seems likely that these two symptoms may have been in part due to the medication in the bupropion SR group.

One of the major goals of prenatal management in women who smoke during pregnancy is to decrease the preterm delivery and low birth weight in neonates. Although our study was not powered to detect differences in neonatal outcomes, the difference in gestational age and Apgar score at 1 minute was in favor of the bupropion group.

Previous studies have shown that bupropion results in modest weight loss in patients with depression[27] and hypertension.[28] Our study did not reveal any differences between the bupropion and placebo groups in body weight, systolic and diastolic BP, and pulse rate. SAEs were not significantly different between groups. One subject in the bupropion group at 32.0 weeks' gestation was diagnosed with superimposed preeclampsia. The association between preeclampsia and antidepressant use during pregnancy has been previously suggested.[29,30] However, a recent study of an exposure-outcome relation within a nationwide Medicaid cohort did not find an association between bupropion use during pregnancy and preeclampsia (RR: 1.06; 95% CI:0.91–1.25).[31]

There are some limitations to the present study. One of the factors that affected enrollment of eligible subjects to the pilot study is the social stigma associated with both prenatal smoking and prenatal use of medications. It appears that there is a general misperception of risks associated with prenatal smoking and the potential benefit-to-risk ratios of smoking cessation with bupropion SR. An integrated effort of medical providers who can directly

address these issues along with education of eligible women and family members provided via clinic media and printed material should overcome the challenges associated with recruitment in future studies. A high rate of early withdrawal from the clinical trial was another challenge encountered in this study. Implementation of home visits in future studies could help retain the recruited number of subjects through 10 visits, beginning in pregnancy and following through the postpartum period (up to 6 months after delivery).

The present study provides preliminary evidence that bupropion SR could be beneficial for smoking cessation during pregnancy. This result is encouraging because placebo controlled trials of nicotine replacement therapy for smoking cessation during pregnancy have not shown increased smoking cessation rates.[32] A large scale study is warranted to fully examine the efficacy and safety of bupropion SR for smoking cessation during pregnancy.

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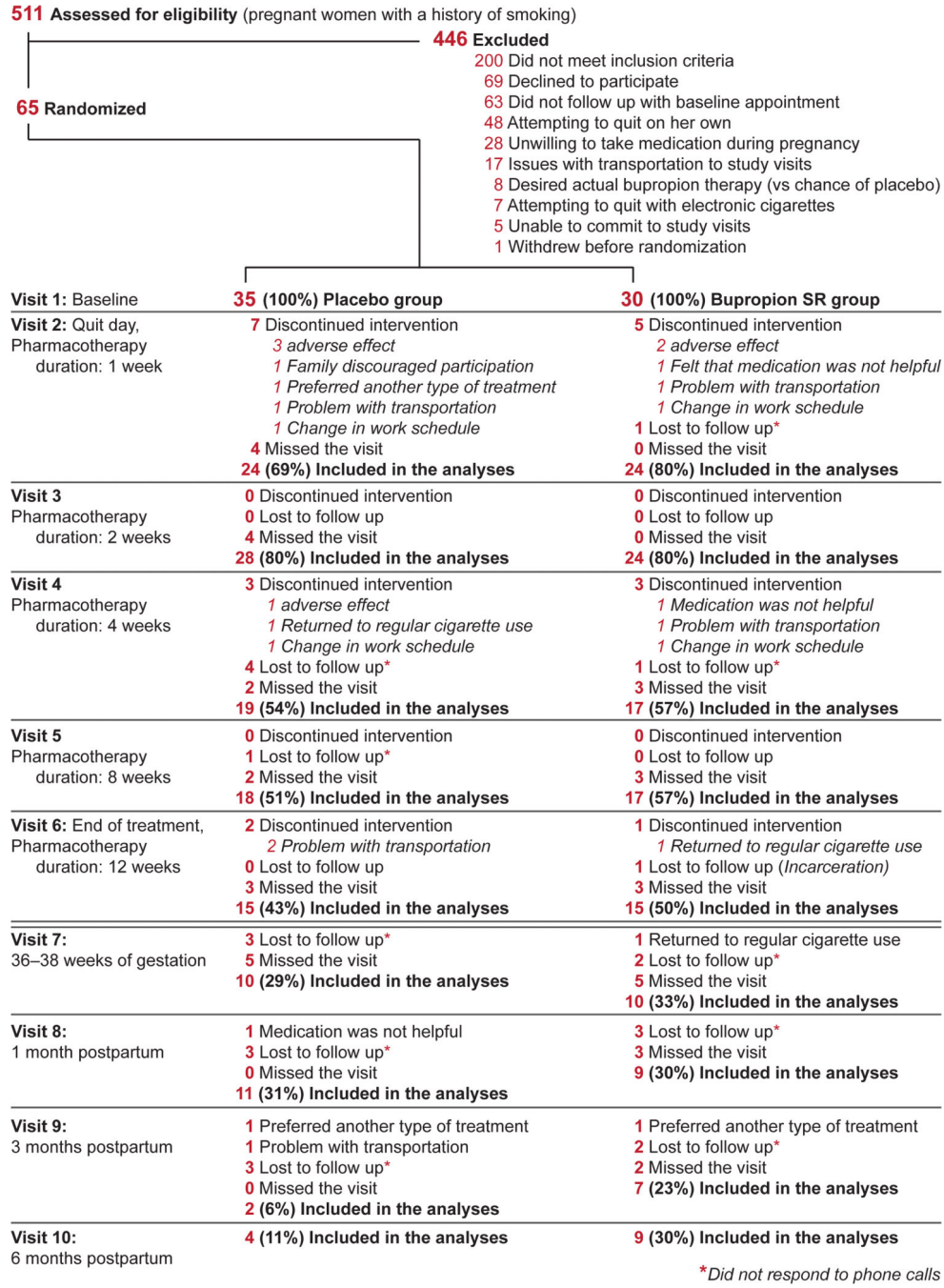

Figure 1.
Consort diagram.

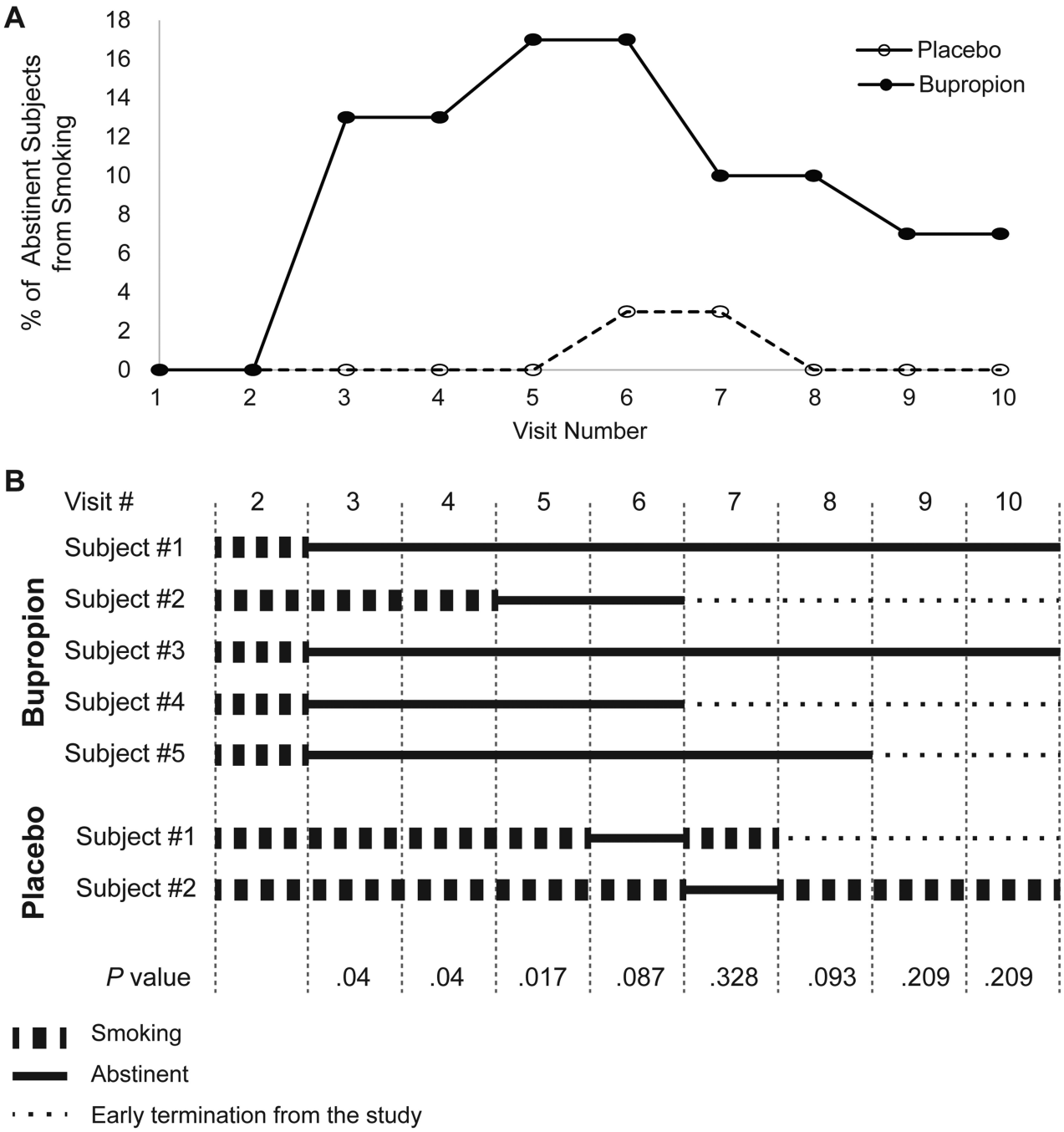

Figure 2.

Rates of confirmed abstinence from smoking (A) and assessment of smoking status in confirmed quitters (B) during treatment period (visits 2–6), at the end of pregnancy (visit 7), and in the postpartum period (visits 8–10).

Abstinence was defined as no cigarettes (even a puff) in the last 7 days, levels of carbon monoxide (CO) in exhaled air < 4 ppm, and concentration of cotinine in urine less than 50 ng/mL. Five subjects in the bupropion group achieved abstinence during the treatment period. Four out of 5 subjects achieved 7-day point prevalence abstinence one week after the

quit date (visit 3) and one subject 7 weeks after the quit date (visit 5). All 5 subjects in the bupropion group remained abstinent up to the last visit during the treatment period (visit 6). In the placebo group, one subject achieved 7-day point prevalence abstinence at visit 6, and another subject was abstinent at visit 7. Only 3/5 subjects who achieved abstinence during treatment in bupropion group, continued the study after visit 6 (end of treatment period) and remained abstinent at the end of pregnancy (visit 7).

If a subject missed a visit, she was counted as abstinent if she met the above criteria before and after this visit. All subjects are included at all time points. Missing data are recorded as smoking.

Table 1

Baseline characteristics[a]

Characteristics	Placebo (n = 35)	Bupropion (n = 30)	*P* value
Demographics			
Age, in years, mean (SD)	27.5 (6.52)	24.5 (5.56)	0.051
Race/ethnicity, n (%)			
White/ non-Hispanic	17 (49)	23 (77)	0.011
White/ Hispanic	5 (14)	3 (10)	
White/ none reported		1 (3)	
Black/ non-Hispanic	13 (37)	2 (7)	
Black/ Hispanic	0 (0)	1 (3)	
Marital status, n (%)			
Single	27 (77)	23 (77)	0.946
Married	8 (23)	7 (23)	
Educational status, n (%)			
≤ High school graduate	25 (71)	20 (67)	0.831
Some college	10 (29)	10 (33)	
Employment status, n (%)			
Unemployed	19 (54)	16 (53)	0.199
Employed part- or full-time	16 (46)	14 (47)	
Income estimate per year, n (%)			
< $10,000	18 (51)	14 (47)	0.679
$10,000–$30,000	11 (31)	11 (37)	
$30,000–$100,000	5 (14)	5 (17)	
Not reported	1 (3)		
Obstetrical			
Gestational age at randomization (weeks.days), mean (SD)	18.2 (1.2)	18.5 (1.4)	0.826
Smoking history			
Age when started smoking in years, mean (SD)	15.7 (5.4)	14.8 (2.8)	0.414
Number of cigarettes per day before pregnancy, mean (SD)	16.1 (6.2)	19.6 (10.1)	0.092
History of drug use, n (%)			
None	24 (68)	21 (70)	0.901
Marijuana	9 (26)	7 (23)	
Cocaine	1 (3)	1 (3)	
Street drugs	1 (3)	1 (3)	
Living with smoker, n (%)			
No	12 (34)	6 (20)	0.228
Yes	23 (66)	23 (77)	
Not reported		1 (3)	

Characteristics	Placebo (n = 35)	Bupropion (n = 30)	*P* value
Nicotine dependence			
FTND score, mean (SD)	4.6 (1.9)	3.9 (1.7)	0.147
Psychosocial status			
Total PRIME score, mean (SD)	4.3 (4.4)	3.6 (4.9)	0.127
Motivation and confidence to quit			
Motivation to quit smoking at this time, mean (SD)	4.3 (0.9)	4.0 (0.7)	0.182
Confidence to quit smoking at this time, mean (SD)	3.5 (1.1)	3.6 (0.8)	0.989

SD = standard deviation

[a]Values are numbers of participants unless stated otherwise

Table 2

Cigarette consumption, carbon monoxide and cotinine levels, tobacco cravings, and total score of withdrawal symptoms

	Placebo, mean (SD)	Bupropion, mean (SD)	*P* value	
			controlling for baseline	controlling for baseline, age & race
Cigarettes per day				
Baseline, Visit 1	10.7 (6.9)	13.4 (9.3)	0.202	
Quit date, Visit 2	5.8 (4.3)	7.2 (7.6)	0.959	0.93
Treatment assessment period, Visits 2–6	5.0 (4.8)	4.7 (6.3)	0.068	0.216
Weeks 36–38, Visit 7	1.6 (2.5)	4.6 (5.9)	0.665	0.441
Postpartum, Visits 8–10	4.3 (3.9)	4.1 (3.5)	0.55	0.749
Exhaled carbon monoxide (ppm)				
Baseline, Visit 1	10.2 (6.5)	13.4 (8.5)	0.117	
Quit date, Visit 2	8.7 (5.4)	9.2 (7.3)	0.509	0.988
Treatment assessment period, Visits 2–6	9.1 (5.8)	7.4 (6.4)	0.011	0.053
Weeks 36–38, Visit 7	5.5 (5.1)	7.2 (4.7)	0.514	0.662
Postpartum, Visits 8–10	8.6 (5.7)	10.5 (8.6)	0.613	0.745
Cotinine (ng/mL)				
Baseline, Visit 1	822.7 (685.9)	657.6 (479.4)	0.295	
Quit date, Visit 2	843.5 (692.4)	404.7 (402.9)	0.066	0.24
Treatment assessment period, Visits 2–6	830.5 (727.3)	347.8 (383.9)	<0.001	0.007
Weeks 36–38, Visit 7	542.6 (671.2)	484.1 (462.1)	0.96	0.666
Postpartum, Visits 8–10	997.1 (609.8)	755.5 (729.0)	0.365	0.749
Total score of withdrawal symptoms (no craving)				
Baseline, Visit 1	4.43 (5.77)	5.22 (6.05)	0.62	
Quit date, Visit 2	4.88 (4.61)	4.75 (4.87)	0.978	0.713
Treatment assessment period, Visits 2–6	5.35 (5.14)	3.77 (4.27)	0.068	0.028
Craving for tobacco				
Baseline, Visit 1	1.79 (1.64)	1.63 (1.55)	0.742	
Quit date, Visit 2	2.33 (1.31)	2.04 (1.08)	0.786	0.622
Treatment assessment period, Visits 2–6	2.07 (1.23)	1.50 (1.11)	0.08	0.02

SD =standard deviation

Table 3

Birth and delivery outcomes.

Outcome measures	Placebo/BUP, N° of subjects	Placebo, mean (SD)	Bupropion, mean (SD)	Placebo/BUP		*P* value
				Minimum	Maximum	
Birth weight, gr	30 / 27	3111 (543)	3223 (501)	1860 / 2087	4536 / 4055	0.299
Infant length at birth, cm	28 / 27	49 (2.5)	50 (2.3)	41 / 45	53 / 55	0.25
Head circumference, cm	26 / 26	33.5 (1.8)	34.1 (1.22)	30 / 32	37 / 37	0.265
Apgar score at 1 minute	29 / 27	7.8 (1.6)	8.3 (1.0)	2 / 5	9 / 9	0.064
Apgar score at 5 minute	29 / 27	8.8 (0.6)	9.0 (0.3)	7 / 8	10 / 10	0.201
Cord blood arterial pH	8 / 9	7.3 (0.04)	7.3 (0.06)	7.2 / 7.2	7.32 / 7.37	0.541
Cord blood venous pH	11 / 11	7.3 (0.05)	7.3 (0.12)	7.26 / 7.02	7.42 / 7.42	0.898
Infant length of hospital stay, days	28 / 27	2.8 (3.1)	2.4 (2.8)	1 / 1	14 / 16	0.612
Neonatal intensive care unit admission, number (%)	28 / 27	3 (11%)	1 (4%)	N/A	N/A	0.611
Gestational age, weeks.days	30 / 26	38.2 (1.4)	38.7 (1.6)	33.5 / 32.3	40 /40.3	0.058
Preterm birth < 34 weeks, number (%)	30 / 26	1 (3%)	1 (4%)	N/A	N/A	1.0

BUP =-bupropion; SD = standard deviation, N/A = non-applicable