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Naltrexone plus bupropion reduces cigarette smoking in individuals with methamphetamine use disorder: A secondary analysis from the CTN ADAPT-2 trial

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Abstract

Introduction: Methamphetamine (MA) use is marked by high rates of comorbid tobacco smoking, which is associated with more severe drug use and worse clinical outcomes compared to single use of either drug. Research has shown the combination of naltrexone plus oral bupropion (NTX-BUP) improves smoking cessation outcomes in non-MA-using populations. In the Accelerated Development of Additive Pharmacotherapy Treatment (ADAPT-2) study, NTX-BUP successfully reduced MA use. Our aim in this secondary data analysis was to examine changes in cigarette smoking among the subgroup of participants reporting comorbid tobacco use in the ADAPT-2 trial.

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CRediT authorship contribution statement

Joy Schmitz, Angela Stotts: Conceptualization, Methodology, Supervision, Writing - Original Draft. **Jin Yoon: Writing – Original Draft; Visualization. Thomas Northrup, Yolanda Villarreal, Luba Yammine, Michael Weaver**: Writing – Review and Editing. **Thomas Carmody**: Formal analysis. **Steven Shoptaw, Madhukar Trivedi**: Project administration, Funding Acquisition.

Dr. Madhukar Trivedi:

Within the past 12 months, Dr. Trivedi has provided consulting services to Axsome Therapeutics, Biogen MA Inc., Cerebral Inc., Circular Genomics Inc, Compass Pathfinder Limited, Daiichi Sankyo Inc, GH Research Limited, Heading Health Inc, Janssen, Legion Health Inc, Merck Sharp & Dohme Corp., Mind Medicine (MindMed) Inc, Merck Sharp & Dhome LLC, Naki Health, Ltd., Neurocrine Biosciences Inc, Otsuka American Pharmaceutical Inc, Otsuka Pharmaceutical Development & Commercialization Inc, Praxis Precision Medicines Inc, Relmada Therapeutics, Inc, SAGE Therapeutics, Signant Health, Sparian Biosciences Inc, Takeda Pharmaceutical Company Ltd, and WebMD. He sits on the Scientific Advisory Board of Alto Neuroscience Inc, Cerebral Inc., Compass Pathfinder Limited, Heading Health, GreenLight VitalSign6 Inc, Legion Health Inc, and Merck Sharp & Dohme Corp. He holds stock in Alto Neuroscience Inc, Cerebral Inc, Circular Genomics Inc, GreenLight VitalSign6 Inc, Legion Health Inc. Additionally, he has received editorial compensation from American Psychiatric Association, and Oxford University Press.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Methods: The multi-site ADAPT-2 study used a randomized, double blind, sequential parallel comparison design to evaluate treatment with extended-release injectable NTX (380 mg every 3 weeks) combined with once-daily oral extended-release BUP (450 mg/day) vs matching injectable and oral placebo in outpatients with moderate or severe MA use disorder. The study assessed smoking outcomes, based on self-reported timeline followback (**TLFB**) data, twice/week for 13 weeks.

Results: Of the 403 participants in the ADAPT-2 trial, 290 reported being current cigarette smokers (71.9 %). The study found significant differences (p's < 0.0001) for each smoking outcome indicating greater change in the proportion of nonsmoking days, number of cigarettes smoked per week, and consecutive nonsmoking days, all favoring the group receiving NTX-BUP versus placebo.

Conclusions: NTX-BUP was associated with significant reductions in self-reported cigarette smoking in the context of concurrent treatment for MA use disorder. These off-target medication effects warrant prospective investigation using biochemically confirmed measures of smoking abstinence. The development of NTX-BUP as a co- addiction treatment strategy has a potential for high public health impact.

Keywords

Methamphetamine; Tobacco use; Naltrexone; Bupropion; ADAPT-2 trial; Co-occurring substances; Combination pharmacotherapy

1. Introduction

Cigarette smoking is the leading preventable cause of death and morbidity in the US, annually costing more than $300 billion from medical expenses and lost productivity (National Center for Chronic Disease et al., 2014; Xu et al., 2015). Smoking prevalence has steadily decreased over the last 50 years in the general population but remains disproportionately higher among individuals with mental health and substance use disorders (Han et al., 2022; Smith et al., 2020). Indeed, approximately half the cigarettes sold in the US are consumed by these individuals (Grant et al., 2004; Hayhurst et al., 2021). Co-morbid smoking is especially high among populations that use psychomotor stimulants, with as many as 87–92 % of individuals with methamphetamine (MA) use disorder reporting current cigarette use (Weinberger & Sofuoglu, 2009; Yoon et al., 2021). Compared to their non-smoking counterparts, stimulant users who smoke cigarettes exhibit more severe addiction-related problems and poorer treatment outcomes (Weinberger & Sofuoglu, 2009).

Treatment providers have historically been hesitant to offer smoking cessation support to individuals with substance use disorders (**SUDs**), despite surveys showing that 44 % to 80 % of individuals in drug treatment programs are interested in quitting their tobacco use (Gentry et al., 2017; Kelly et al., 2019; Prochaska et al., 2004). Alarmingly, only 12 % of those receiving stimulant use disorder treatment receive concurrent smoking-cessation treatment (Kelly et al., 2019; Weinberger & Sofuoglu, 2009). The longstanding belief that targeting cigarette smoking during treatment for a SUD might negatively impact an individual's primary drug use has not been borne out in systematic reviews of published studies

(McKelvey et al., 2017). In general, quitting smoking or concurrent smoking cessation treatment does not result in worsening of SUD outcomes, with several studies demonstrating improved outcomes on both primary substance of abuse and tobacco (Apollonio et al., 2016; Prochaska et al., 2004; Thurgood et al., 2016). Moreover, smoking cessation has numerous health benefits for reducing the risk of tobacco-related morbidity and mortality among persons with SUD (Bandiera et al., 2015). In a 20-year follow-up study of gay and bisexual men who participated in a behavioral trial for MA dependence, cigarette smoking more than tripled standardized mortality rates (Passaro et al., 2019).

Bupropion is an FDA-approved pharmacotherapy for smoking cessation that has been examined in the context of MA use disorder treatment (Anderson et al., 2015; Elkashef et al., 2008; Heinzerling et al., 2013; Heinzerling et al., 2014; Shoptaw et al., 2008; Winhusen, Brigham, et al., 2014). Two of these studies evaluated bupropion for MA use disorder, but also reported off-target effects of bupropion on cigarette smoking. Elkashef et al. (2008) found no effect for bupropion 150 mg administered twice/day (**BID**) (N = 79) on MA use, but reported a difference in number of reported days of cigarette smoking that favored bupropion compared to placebo. The groups did not differ on the rate of decrease in reported smoking days across the trial, however. Similarly, a subsequent trial comparing bupropion 150 mg/bid to placebo for reducing MA use (N = 73) observed no effects of bupropion on MA use, however, post hoc findings found differences in cigarette smoking with participants receiving bupropion showing significantly greater reductions in the number of cigarettes smoked per day during the trial compared to participants receiving placebo ($p = 0.002$) (Shoptaw et al., 2008). In the NIDA Clinical Trials Network (CTN) S-CAST trial (Winhusen et al., 2012; Winhusen, Brigham, et al., 2014), bupropion (300 mg/d) was included as part of a multicomponent smoking cessation treatment that was offered in the context of outpatient SUD treatment for cocaine and MA use disorder. At the end of 10 weeks, the group receiving concurrent smoking cessation treatment had significantly higher smoking point-prevalence abstinence rates compared to the control group receiving SUD treatment only (25.5 % vs 2.2 %). No group differences on stimulant (MA, cocaine) abstinence outcomes occurred. Thus, bupropion as a monotherapy has shown positive but mixed evidence of benefit in reducing cigarette smoking in adults with MA use disorder.

One strategy for improving the efficacy of bupropion has been to add a second agent that may confer synergistic effects on selected outcomes (Stoops & Rush, 2014). Bupropion plus naltrexone has been tested as a combination pharmacotherapy for smoking cessation and, recently, for the treatment of MA use disorder. In a study of treatment-seeking cigarette smokers *without* MA or other comorbid SUDs (N = 121), the combination of bupropion and naltrexone improved smoking outcomes significantly, with higher 7-day point-prevalence abstinence following 7-weeks of treatment with the active medication combination (54.1 %) vs. bupropion alone (33.3 %) (Mooney, Schmitz, et al., 2016). The combination of bupropion and naltrexone has also demonstrated efficacy in treating MA use disorder. Positive findings from an open-label pilot study (Mooney, Hillhouse, et al., 2016) were recently confirmed in the NIDA CTN ADAPT-2 clinical trial of 403 adults with moderate or severe MA use disorder where those receiving oral bupropion plus injectable naltrexone

produced significantly higher rates of MA-negative urine drug screens compared to placebo (Trivedi et al., 2021).

Whereas the synergistic effect of bupropion plus naltrexone is not fully understood, both agents act upon the dopaminergic system via distinct mechanisms, considered crucial for the rewarding effects of stimulants like methamphetamine and nicotine. Bupropion, by inhibiting reuptake of noradrenaline and dopamine, enhances dopamine neurotransmission, producing stimulant-like effects that may ameliorate withdrawal symptoms such as negative affect and craving during acute abstinence. Naltrexone is a mu-opioid antagonist that may work by inhibiting some mesolimbic dopamine activity and alter cholinergic receptors' function and expression in the brain (Almeida et al., 2000; Hutchison et al., 1999). Thus, a pharmacologic rationale exists for hypothesizing that this medication combination may increase smoking abstinence in individuals with MA use disorder.

The aim of this secondary data analysis was to evaluate the efficacy of oral extended-release bupropion (450 mg per day) in combination with extended-release injectable naltrexone (380 mg every 3 weeks) on cigarette smoking outcomes in a large sub-sample of current smokers in the ADAPT-2 trial for the treatment of MA use disorder (Trivedi et al., 2021). We hypothesized that relative to placebo, the active medication combination would be associated with greater increases in the number of self-reported nonsmoking days and duration of consecutive nonsmoking days, along with decreases in the number of cigarettes smoked per week.

2. Methods

2.1. Study design and procedures

The ADAPT-2 trial (NCT03078075); previously described in Trivedi et al. (2021) was a multi-site, randomized, double-blind trial that used a sequential-parallel comparison design to evaluate extended-release injectable naltrexone (380 mg every 3 weeks) combined with once- daily oral extended-release bupropion (450 mg per day) (NTX-BUP) compared with matching injectable and oral placebo in adult outpatients with moderate or severe MA use disorder. The National Institute on Drug Abuse (NIDA), Clinical Trials Network central institutional review board and institutional review boards at the participating sites (as needed) approved the study protocol.

In the first 6-week stage of the trial, the study randomized participants in an approximate 1:3 ratio to receive either the active combination (NTX-BUP) or placebo. In the second 6-week stage of the trial, participants in the placebo group who did not have a response, defined as at least three MA-negative urine tests out of a possible four obtained during week 5 through 6, underwent randomization again in a 1:1 ratio in week 7 to either NTX-BUP or placebo.

Throughout the study, participants attended twice-weekly clinic visits for urine drug screening, safety monitoring, and assessments. The study administered naltrexone or placebo every 3 weeks. Bupropion or placebo was provided weekly in matching blister cards and included a 3-day dose run up/down regimen at the start and end of the trial, week 1 and 13, respectively.

2.2. Participants

The study recruited adults (18–65 years old) seeking treatment to quit or reduce MA use from communities near the 8 participating trial sites using print, radio, Web, and television advertising. Eligible participants met DSM-5 criteria for moderate or severe stimulant (MA type) use disorder; reported MA use on at least 18 of the 30 days before consent; had 2 or more MA-positive urine samples obtained at least 2 days apart within 10 days prior to randomization; and were opioid-free at the time of randomization. The study excluded participants if they were undergoing concurrent treatment for another SUD, had an expected need for opioid-containing medications (e.g., planned surgery) during the trial, or did not meet additional criteria that would ensure that participation would be safe (e.g., having conditions that increased the risk of seizure or taking medications that were contraindicated). Having a diagnosis of a specific medical or psychiatric disorder was not routinely exclusionary, but evaluated on a case-by-case basis by the study physician.

The study used the Tobacco Use History (TUH) questionnaire to identify a subsample of participants as being current cigarette smokers if they reported smoking cigarettes every day (non-zero response to the TUH item: “On average, about how many cigarettes do you now smoke each day?”) or some days (non-zero response to TUH item: “On how many of the past 30 days did you smoke cigarettes?”). Of the initial 403 participants enrolled in the parent study, 290 (71.9 %) reported current cigarette smoking.

2.3. Assessments and outcomes

At intake, the study staff administered the TUH to assess smoking status, including mean number of cigarettes smoked each day, age when first started smoking, and how soon after waking is first cigarette smoked. Self-reported substance use, including cigarette smoking, was measured using the Timeline Followback (TLFB) (Sobell & Sobell, 1992) completed by research staff at each clinic visit. Smoking outcomes based on TLFB included: 1) number (proportion) of non-smoking days each week; 2) longest duration of consecutive non-smoking days; and 3) number of cigarettes per day. The primary MA treatment response, as originally defined in the main trial, was at least 3 MA-negative urine tests out of a possible 4 at the end of Stage 1 (weeks 5–6) and at the end of Stage 2 (weeks 11–12).

2.4. Statistical analysis

The study analyzed the proportion of nonsmoking days per week and number of cigarettes smoked per week using a repeated measures mixed-effects model appropriate for sequential parallel comparison design (SPCD) trials (Doros et al., 2013). Models contained a weekly time effect and were covariate-adjusted for baseline MA use days, tobacco use days, age, and sex. Models used all available data, with missing values assumed to be missing at random within each stage. Outcomes were reported as the estimated change from baseline (the period 30 days prior to randomization) to week 6 (for Stage 1) and from week 7 to week 12 (for Stage 2). The overall treatment effect statistic (h) was a weighted mean of the treatment effect in Stage 1 and Stage 2. Longest duration of consecutive non-smoking days was assessed for each stage. Change from baseline to Stage 1 and change from Stage 1 to Stage 2 were also analyzed using the method developed by Doros and colleagues (Doros et

al., 2013) but without a repeated time effect. An additional exploratory analysis compared smoking outcomes between MA responders and MA non-responders, and across the four MA response by treatment groups (NTX-BUP, placebo) using the Wilcoxon two-sample test and the Kruskal-Wallis one-way ANOVA nonparametric test, respectively, for non-normally distributed data.

3. Results

3.1. Sample description

Table 1 shows baseline characteristics of current smokers according to medication group assignment in Stage 1 and Stage 2. The study randomized a total of 290 participants in Stage 1. Participants were 65 % male; mostly white (71 %); with an average age of 40.0 (SD = 9.8) years; and smoking, on average, 11.5 (SD = 6.3) cigarettes per day. Of the 207 participants in the placebo group, a total of 155 were classified as MA non-responders in Stage 1 and underwent second randomization to either receive NTX-BUP or placebo in Stage 2.

The amount of missing TLFB data was small and balanced across groups. Overall, the percentage of missing smoking data from the TLFB was 3.2 %. In Stage 1, 6.1 % and 5.1 % of participants in the NTX-BUP and placebo groups, respectively, had missing days on the TLFB. In Stage 2, percent missing days was 4.2 % and 1.1 % for NTX-BUP and placebo, respectively.

3.2. Smoking outcomes

Proportion of nonsmoking days per week.—Fig. 1 (panel A) shows the proportion of nonsmoking days per week by medication group across stages of the trial. The model estimated mean (*SE*) change in the proportion of non-smoking days from baseline to week 6 (Stage 1) was 0.099 (0.02) for placebo and 0.187 (0.04) for NTX-BUP. The mean change in the proportion of nonsmoking days per week from week 6 to week 12 (Stage 2) was 0.080 (0.02) for placebo and 0.206 (0.04) for NTX-BUP. The overall effect ($h = 0.110$; $SE = 0.03$) was statistically significant, indicating a greater increase in nonsmoking days for individuals receiving NTX-BUP, $Z = 3.93$, $p < 0.0001$.

Number of cigarettes per week.—Fig. 1 (panel B) shows cigarettes smoked per week by medication group across stages of the trial. The model estimated mean (*SE*) change in number of cigarettes per week was − 15.90 (1.91) for placebo and − 28.23 (4.86) for NTX-BUP in Stage 1 and − 16.11 (2.46) for placebo and − 28.02 (4.22) for NTX-BUP in stage 2, yielding an overall significant effect, $h = -12.06$ (2.86), $Z = -4.21$, $p < 0.0001$.

Consecutive nonsmoking days.—The model estimated mean (*SE*) change in number of consecutive nonsmoking days from baseline to Stage 1 was 2.48 (0.56) for placebo and 4.82 (1.00) for NTX-BUP, and the mean change from Stage 1 to Stage 2 was 1.76 (0.54) for placebo and 5.54 (1.08) for NTX-BUP; yielding an overall significantly greater increase in duration of consecutive non-smoking days for individuals receiving the active medication combination, $h = 3.16$ (0.78), $Z = 4.06$, $p < 0.0001$. Fig. 2 shows the mean duration of consecutive nonsmoking days by medication group across stages of the trial.

3.3. Smoking outcomes by MA response status

Table 2 shows the median (25th, 75th percentile) values for each smoking outcome by MA response status and medication group for Stage 1 and Stage 2. Differences (not significant) were in the direction favoring MA responders treated with NTX-BUP.

4. Discussion

We conducted a secondary analysis of associations of naltrexone plus bupropion combination on smoking outcomes using data from the largest randomized trial conducted to date evaluating the efficacy of NTX-BUP for the treatment of MA use disorder (Trivedi et al., 2021). In the main analysis, the active medication combination produced significant reductions in MA-positive urine drug screens compared to placebo. The results of the current analyses mirror the findings of the main trial in showing efficacy for NTX-BUP, in this case by improving self-reported measures of cigarette consumption among participants with MA use disorder who were concurrent cigarettes smokers. The potential of NTX-BUP is noteworthy and encouraging, given the high comorbidity rates of cigarette smoking and stimulant use in this difficult-to-treat population.

We found a consistent pattern of results for each of 3 smoking outcomes of interest. Compared to placebo and across both stages of the trial, participants who received NTX-BUP reported a significant increase in the number of non-smoking days and the duration of consecutive non- smoking days, along with a decrease in the number of cigarettes smoked per week. By design, the 2-stage adaptive trial provided replication of the Stage 1 medication effect on smoking in Stage 2. Notably, Stage 1 placebo-treated nonresponders who were subsequently randomized to receive NTX-BUP in Stage 2 also demonstrated improved smoking outcomes, similar to those observed in the NTX-BUP group during Stage 1.

Bupropion is an FDA-approved, first-line treatment for smoking cessation. The strategy of combining effective medications to boost or enhance treatment effects is not new and has shown support when combining nicotine replacement therapies with each other (Lindson et al., 2019) and with non-nicotine medications (Fiore et al., 2008). The research question in the current study was based in part on the findings of a previous trial (Mooney et al., 2016), which showed that in a sample of 121 treatment-seeking cigarette smokers, bupropion (300 mg/day) and naltrexone (oral, 50 mg/day) combination was associated with significantly higher biochemically confirmed 7-day, point-prevalence abstinence after 7 weeks of treatment compared to bupropion alone (54.1 % vs. 33.3 %). Unlike the sample in the previous trial, participants of the current study were MA users who were not seeking treatment for smoking cessation. In addition, the parent trial did not offer behavioral counseling to support quit attempts. Taken together, these findings isolate a medication “signal” for the combination therapy and support the need for future confirmatory studies of this combination pharmacotherapy approach in persons with MA use and perhaps other substance use disorders who are motivated to stop smoking.

Whereas the mechanisms linking smoking and methamphetamine use are not fully understood, synergies between the dopaminergic and nicotinic cholinergic reward systems

provide neurobiological evidence of why the two drugs are used together (Gatch et al., 2008). Behaviorally, co-use of mutually reinforcing substances, whereby changes in consumption of one substance lead to corresponding changes in consumption of the other substance, has been referred to as the “cascade model” hypothesis (Dodge et al., 2009; McPherson et al., 2018). In the McPherson study, contingency management targeting MA use was effective in increasing both MA and (off-target) smoking abstinence simultaneously during treatment of MA use disorder, providing evidence of a cascading down effect. Winhusen and colleagues reported a significant association between decreased cocaine (but not methamphetamine) use and smoking abstinence in stimulant users receiving smoking cessation treatment (Winhusen, Kropp, et al., 2014). Results from our exploratory subgroup analyses did not show a significant association between achieving MA abstinence and reduced smoking, however the directionality of the effects favored the MA responder group. It is likely that the small and unbalanced number of MA responders coupled with high variability in the data limited the ability to detect reliable differences. At the same time, the lack of subgroup effects may imply that the efficacy of NTX-BUP in reducing smoking is independent of reductions in MA use. Future studies should use fine-grained assessment methods to accurately describe the association between reduction in MA use and smoking.

This study has several strengths and limitations. The main strength is that we obtained these findings from data originally collected in the context of a prospective randomized controlled trial consisting of a large and diverse population of outpatients seeking treatment for MA use disorder (Trivedi et al., 2021). The sociodemographic characteristics of the subgroup of cigarette smokers included in the current analyses were representative of the full sample. The parent trial reported high rates of treatment completion (78 %) and medication adherence (>75 %), thereby reducing the impact of missing data on potential bias and statistical power. At the same time, limitations associated with post hoc analyses apply, along with general limitations of the parent trial (e.g., low representation of women; lack of direct confirmation of medication adherence). In addition, the main limitation of this study was reliance on participant-reported smoking at each visit using the TLFB; although, this potential response bias is reduced by the use of randomization as well as a lack of expectation for participants to quit smoking, i.e., smoking cessation was not the primary aim of the study. As mentioned, that we observed replication of Stage 1 treatment effects in Stage 2 provides additional confidence in the validity of these results. Future studies of NTX-BUP for smoking cessation should include biochemical verification of tobacco use and abstinence.

In conclusion, NTX-BUP was effective in reducing cigarette smoking in the context of treatment for MA use disorder. Whereas full cessation of smoking was not the goal or expectation, it is noteworthy that the mean duration of consecutive nonsmoking days for Stage 1 and Stage 2 (5.36 and 6.36, respectively) in the NTX-BUP treated groups approached 7-day point prevalence abstinence. These off-target medication effects warrant prospective investigation using biochemically confirmed measures of smoking abstinence. National survey data show that smoking rates declined by 10.9 % from 2006 to 2019 among adults with SUDs, an encouraging trend that has prompted the call for continued efforts to integrate smoking cessation therapies into existing SUD treatments (Han et al., 2022). The combination of naltrexone plus bupropion, when offered in the context of evidence-based

smoking cessation treatment, represents a promising co-addiction treatment strategy for treating two of the deadliest drug addictions.

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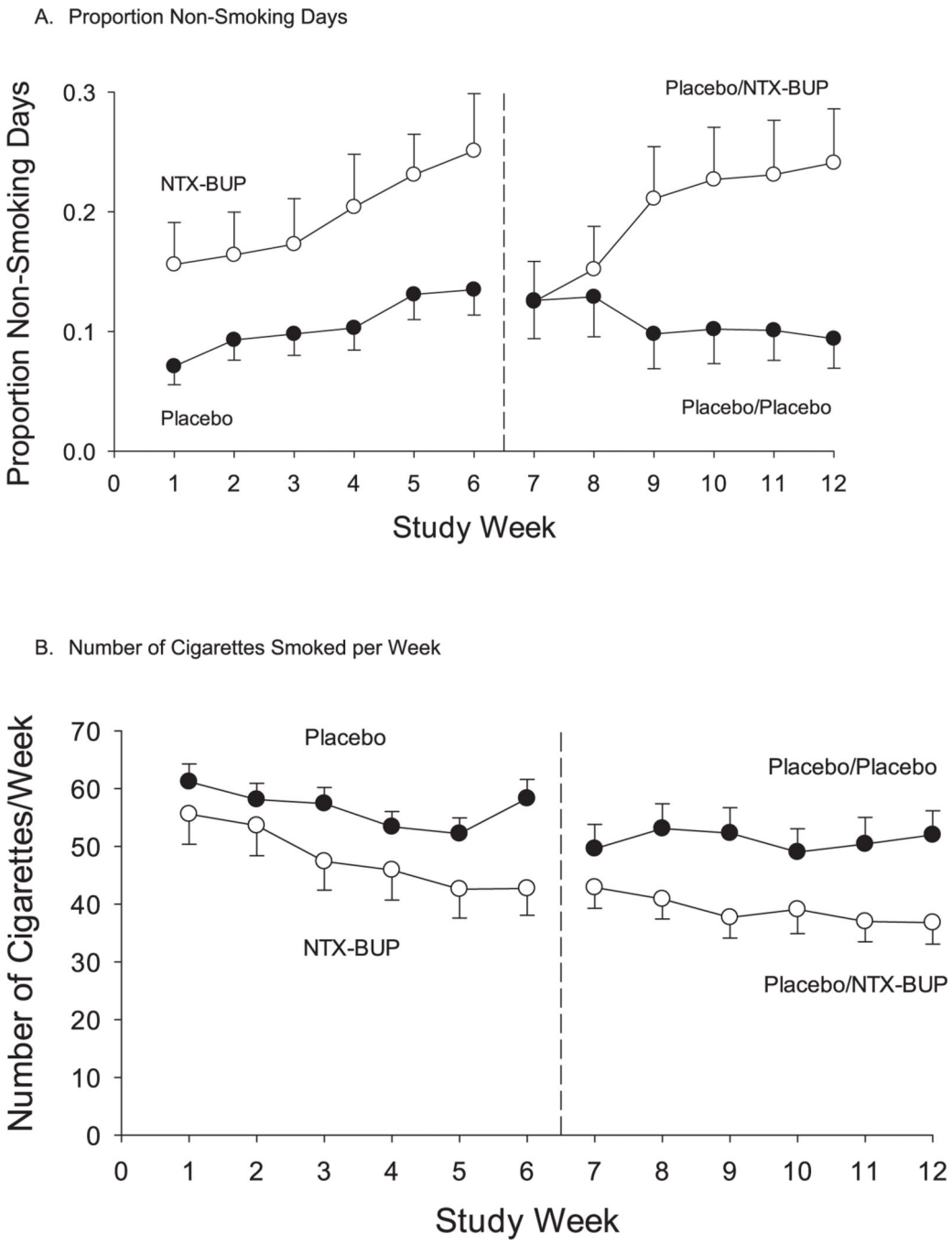

Fig. 1.

Panel A shows the proportion of non-smoking days per week by medication group by Stage 1 (weeks 1 through 6) and Stage 2 (weeks 7 through 12). NTX-BUP refers to the combination of naltrexone and bupropion. In Stage 2, placebo/NTX-BUP refers to participants in the placebo group who did not have a response in Stage 1, defined as at least three methamphetamine-negative urine samples, and were assigned to the NTX-BUP group in Stage 2. Placebo/placebo refers to participants in the placebo group who did not have a response in Stage 1 and were assigned to placebo in Stage 2. Panel B shows

cigarettes smoked per week by medication group across stages of the trial. For both smoking outcomes, the effect of medication group was significant in each stage and overall, $p < 0.05$.

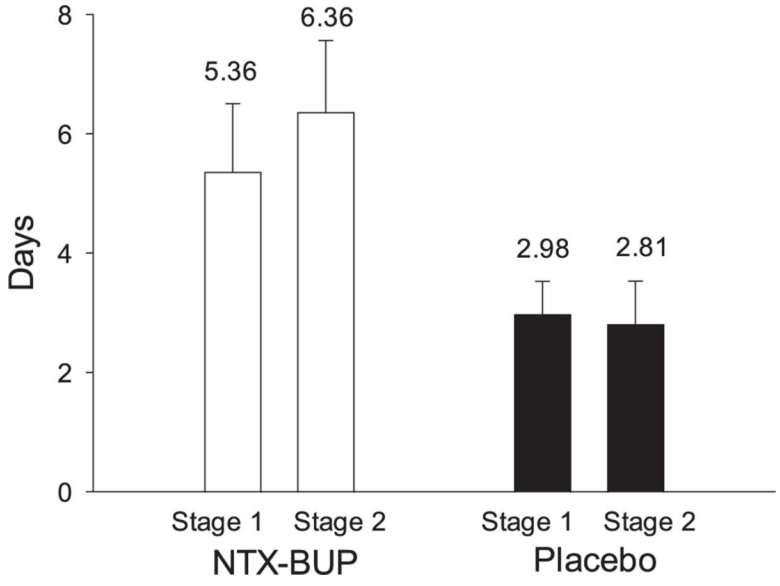

Fig. 2.

Consecutive non-smoking days by medication group for Stage 1 (weeks 1 through 6) and Stage 2 (weeks 7 through 12).

Table 1

Baseline characteristics of the participants.

Characteristic	All participants	Stage 1		Stage 2[a]	
	Total (N = 290)	NTX-BUP (N = 83)	Placebo (N = 207)	Placebo/ NTX-BUP (N = 80)	Placebo/ Placebo (N = 75)
Demographic, N (%)					
Male	190 (65.5)	58 (69.9)	132 (63.8)	49 (61.2)	53 (70.7)
Race					
Black	35 (12.1)	6 (7.2)	29 (14.0)	6 (7.5)	17 (22.7)
White	206 (71.0)	61 (73.5)	145 (70.0)	61 (76.2)	43 (57.3)
Other	49 (16.9)	16 (19.3)	33 (15.9)	13 (16.2)	15 (20.0)
Hispanic	35 (12.1)	8 (9.6)	27 (13.0)	14 (17.5)	11 (14.7)
Age, mean (SD)	40.0 (9.8)	40.9 (10.7)	39.6 (9.3)	40.0 (9.9)	40.1 (9.0)
Education					
Less than high school	30 (10.3)	7 (8.4)	23 (11.1)	7 (8.8)	8 (10.7)
High school	82 (28.3)	23 (27.7)	59 (28.5)	24 (30.0)	15 (20.0)
More than high school	178 (61.4)	53 (63.9)	125 (60.4)	49 (61.2)	52 (69.3)
Marital Status					
Married	64 (22.1)	18 (21.7)	46 (22.2)	18 (22.5)	15 (20.0)
Never married	144 (50.0)	35 (42.2)	109 (52.7)	40 (50.0)	43 (57.3)
Other	80 (27.6)	29 (34.9)	51 (24.6)	21 (26.2)	17 (22.7)
Employment status					
Employed	109 (37.6)	33 (39.8)	76 (36.7)	28 (35.0)	31 (41.3)
Unemployed	122 (42.1)	32 (38.6)	90 (43.5)	32 (40.0)	30 (40.0)
Other	59 (20.3)	18 (21.7)	41 (19.8)	20 (25.0)	14 (18.7)
Smoking and MA use, mean (SD)					
Average cigarettes smoked per day	11.5 (6.3)	12.1 (7.8)	11.2 (5.6)	10.2 (5.8)	10.6 (4.9)
Days of cigarette smoking in past 30	27.86 (6.0)	27.72 (6.2)	27.92 (6.0)	28.24 (5.6)	27.39 (6.5)
Days of MA use in past 30	26.8 (4.0)	27.3 (3.6)	26.6 (4.2)	26.8 (4.1)	26.2 (4.3)

[a]In Stage 2, placebo/NTX-BUP refers to participants in the placebo group who did not have a response in Stage 1, defined as at least three methamphetamine-negative urine samples, and were assigned to the NTX-BUP group in Stage 2. Placebo/placebo refers to participants in the placebo group who did not have a response in Stage 1 and were assigned to placebo in Stage 2.

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Table 2

Median (interquartile range 25th and 75th percentile) and statistical results corresponding to comparison between MA responders and non-responders by treatment group on smoking outcomes.

Smoking outcome	MA responders[a]		MA non-responders		p value (Wilcoxon, Kruskal-Wallis)	
	Naltrexone-Bupropion	Placebo	Naltrexone-Bupropion	Placebo	2 groups[b]	4 groups
Stage 1	**N = 15**	**N = 7**	**N = 61**	**N = 196**		
Proportion of non-smoking days per week	0.10 (0, 0.67)	0.02 (0, 0.10)	0 (0, 0.26)	0 (0, 0.09)	0.106	0.131
Number of cigarettes smoked per week	195 (52, 316)	456 (159, 520)	246 (128, 395)	273 (175, 430)	0.599	0.228
Longest consecutive non-smoking days	2 (0, 21)	1 (0, 2)	0 (0, 4)	0 (0, 2)	0.099	0.257
Smoking outcome	**MA responders[a]**		**MA non-responders**		**p value (Wilcoxon, Kruskal-Wallis)**	
	Naltrexone-Bupropion	**Placebo**	**Naltrexone-Bupropion**	**Placebo**	**2 groups[b]**	**4 groups**
Stage 2	**N = 8**	**N = 1**	**N = 72**	**N = 74**		
Proportion of non-smoking days per week	0.02 (0, 0.07)	0.01 (0.01, 0.01)	0.02 (0, 0.22)	0.02 (0, 0.09)	0.454	0.561
Number of cigarettes smoked per week	312 (170, 468)	491 (491, 491)	233 (102, 388)	275 (202, 490)	0.446	0.096
Longest consecutive non-smoking days	0.5 (0, 3)	0 (0, 0)	1 (0, 7)	1 (0,3)	0.489	0.182

[a] MA response defined by at least 3 MA-negative urine tests out of a possible 4 at the end of Stage 1 (weeks 5–6) and at the end of Stage 2 (weeks 11–12).

[b] MA responders versus MA non-responders.