A Randomized Trial of Concurrent Smoking-Cessation and Substance Use Disorder Treatment in Stimulant-Dependent Smokers

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ABSTRACT

Objective: To evaluate the impact of concurrent treatments for substance use disorder and nicotine-dependence for stimulant-dependent patients.

Method: A randomized, 10-week trial with follow-up at 3 and 6 months after smoking quit date conducted at 12 substance use disorder treatment programs between February 2010 and July 2012. Adults meeting *DSM-IV-TR* criteria for cocaine and/or methamphetamine dependence and interested in quitting smoking were randomized to treatment as usual (n = 271) or treatment as usual with smoking-cessation treatment (n = 267). All participants received treatment as usual for substance use disorder treatment. Participants assigned to treatment as usual with concurrent smoking-cessation treatment received weekly individual smoking cessation counseling and extended-release bupropion (300 mg/d) during weeks 1–10. During post-quit treatment (weeks 4–10), participants assigned to treatment as usual with smoking-cessation treatment received a nicotine inhaler and contingency management for smoking abstinence. Weekly proportion of stimulant-abstinent participants during the treatment phase, as assessed by urine drug screens and self-report, was the primary outcome. Secondary measures included other substance/nicotine use outcomes and treatment attendance.

Results: There were no significant treatment effects on stimulant-use outcomes, as measured by the primary outcome and stimulant-free days, on drug-abstinence, or on attendance. Participants assigned to treatment as usual with smoking-cessation treatment, relative to those assigned to treatment as usual, had significantly better outcomes for drug-free days at 6-month follow-up ($\chi^2_1 = 4.09$, $P < .05$), with a decrease in drug-free days from baseline of −1.3% in treatment as usual with smoking-cessation treatment and of −7.6% in treatment as usual. Participants receiving treatment as usual with smoking-cessation treatment, relative to those receiving treatment as usual, had significantly better outcomes on smoking point-prevalence abstinence (25.5% vs 2.2%; $\chi^2_1 = 44.69$, $P < .001$; OR = 18.2).

Conclusions: These results suggest that providing smoking-cessation treatment to illicit stimulant-dependent patients in outpatient substance use disorder treatment will not worsen, and may enhance, abstinence from nonnicotine substance use.

Trial Registration: ClinicalTrials.gov identifier: NCT01077024

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Cigarette smoking, which accounts for 443,000 deaths annually in the United States,[1] has a prevalence rate of 49%–98% in illicit drug abusers, a rate substantially higher than the 19.8% rate in the general population.[2] Despite the pervasiveness and deadly consequences of smoking in addicted individuals,[3] smoking-cessation treatment is typically not provided in substance use disorder treatment programs due, in part, to concern that it might impact negatively on nonnicotine substance use outcomes.[4,5] Prochaska and colleagues[6] completed a meta-analysis of 19 studies in which the impact of smoking-cessation treatment on nonnicotine drug/alcohol use was assessed; the findings suggested that smoking-cessation treatment may actually improve substance use outcomes. However, the 19 studies analyzed included mainly alcohol-dependent, and, to a lesser extent, methadone-maintained participants; the potential impact of concurrent treatment for illicit stimulant and nicotine dependence is unknown.

Clinical and laboratory studies have established a link between cigarette smoking and nonnicotine stimulant abuse. The rate of smoking is 75%–80%[7–9] in cocaine abusers and 87% or higher in methamphetamine abusers,[10,11] and smoking is associated with more severe cocaine addiction.[7,12] Human laboratory studies have found that cocaine administration increases cigarette smoking[13,14] and that mecamylamine, a nicotine antagonist, reduces cue-induced cocaine craving,[15] while nicotine increases it.[16] The present trial addressed this research gap by evaluating the impact of concurrent substance use disorder treatment and smoking-cessation treatment in cocaine- and/or methamphetamine-dependent patients. Past research suggests that smoking-cessation rates in substance-abusing populations are poor[17,18] but that smoking-cessation rates can be improved by combining psychosocial and pharmacologic smoking-cessation interventions.[19,20] Therefore, the smoking-cessation treatment utilized in the present trial combined psychosocial interventions with US Food and Drug Administration–approved smoking

Clinical Points

- The prevalence of smoking in cocaine- and/or methamphetamine-dependent patients is ≥ 75%.
- Smoking-cessation treatment can significantly increase smoking abstinence in these patients.
- Intensive smoking-cessation treatment will not worsen, and may enhance, abstinence from nonnicotine substance use.

cessation medications. It was predicted that the concurrent provision of treatments for substance use disorder and smoking-cessation would improve, rather than worsen, stimulant-use outcomes.

METHOD

Study Design

This was a 10-week, intent-to-treat (ITT), 2-group randomized trial, with follow-up visits at 3 and 6 months after smoking quit date. The trial was conducted by the National Institute on Drug Abuse (NIDA) National Drug Abuse Treatment Clinical Trials Network (CTN) at 12 substance use disorder treatment programs between February 2010 and July 2012. The study was registered on ClinicalTrials.gov (identifier: NCT01077024). A full discussion of design considerations has been published previously.[21]

Participants

Recruitment was primarily from clinic patients entering treatment at a participating site; secondary recruitment methods included advertising and direct community promotions, such as networking with community professionals. Eligible participants were adults enrolled in outpatient substance use disorder treatment and interested in quitting smoking. Participants were required to meet *DSM-IV-TR* criteria for current cocaine or methamphetamine dependence, to smoke at least 7 cigarettes per day, to have a carbon monoxide (CO) level ≥ 8 ppm, and to have smoked cigarettes for at least 3 months. The decision to require 7 cigarettes per day was based on a prior trial completed by our group in which the more standard ≥ 10 cigarettes per day criterion was a primary reason for excluding African American, but not white, smokers. Exclusion criteria included a medical or psychiatric condition potentially making participation unsafe; current treatment for nicotine dependence; and, for women, pregnancy, breastfeeding, or unwillingness to use adequate birth control. Candidates were excluded if they had used tobacco products other than cigarettes in the past week, had all stimulant-positive urine drug screen results during screening/baseline, or were seeking or receiving opioid-agonist treatment. All participants were given a thorough explanation of the study and signed an informed consent form approved by the institutional review boards of the participating sites.

Procedures

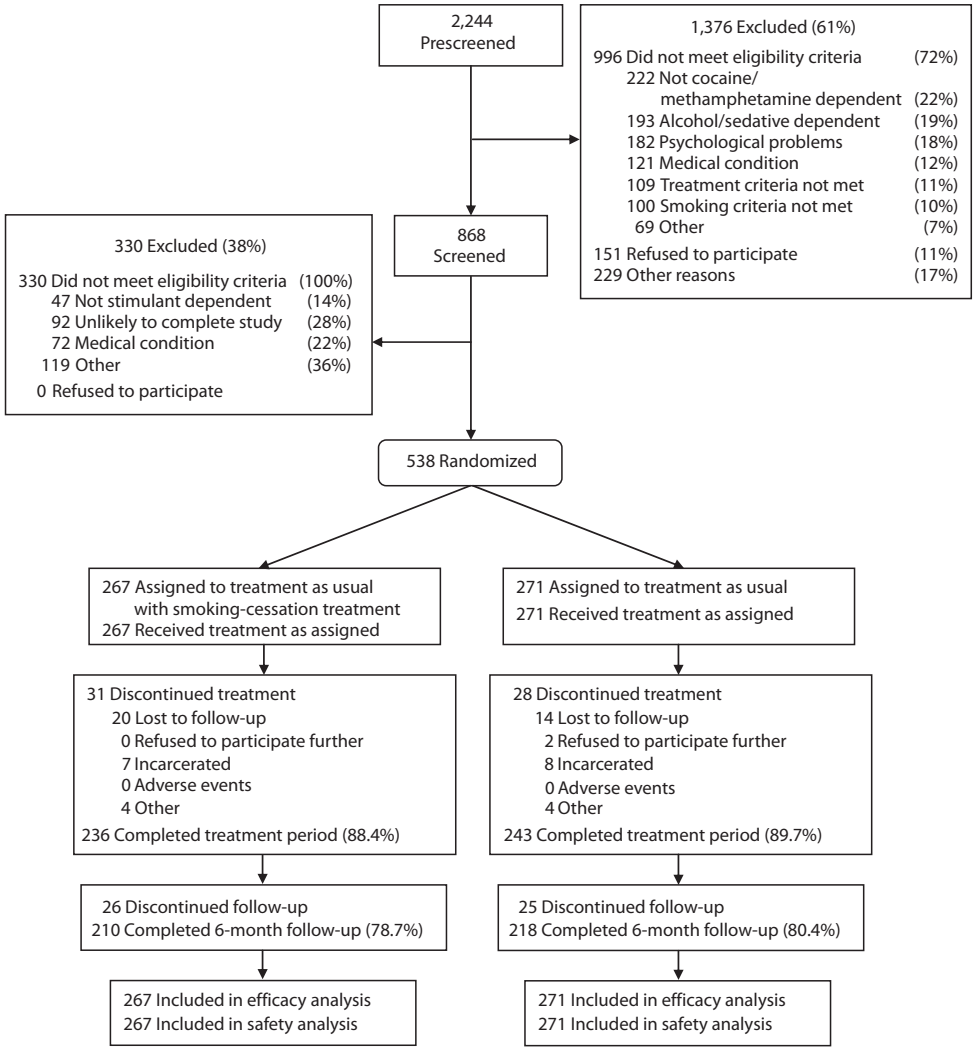
Participants were randomized to treatment as usual or treatment as usual with smoking-cessation treatment in a 1:1 ratio stratified by site and baseline urine drug screen results (stimulant-negative vs stimulant-positive). During the 10-week treatment phase, participants were scheduled to attend 2 research visits per week for efficacy and safety assessments, with identical assessments completed for participants assigned to treatment as usual and for those assigned to treatment as usual with smoking-cessation treatment. There were single follow-up visits at 3 months' and 6 months' post-quit date. Participants received $15 for shorter and $25 for longer weekly visits; at the week 10 longer visit, participants received an additional $25 because of the visit's larger assessment burden. Participants were reimbursed $40 per follow-up visit. Participants receiving treatment as usual with smoking-cessation treatment could also earn monetary rewards through the contingency management intervention.

Treatment

All participants received treatment for substance use disorder as typically provided by the study site, which consisted of at least 1 treatment session per week during the 10-week treatment phase. Participants assigned to treatment as usual with smoking-cessation treatment also received smoking-cessation treatment consisting of extended-release (XL) bupropion, nicotine inhaler, smoking-cessation counseling, and contingency management for smoking abstinence. Bupropion hydrochloride XL 150 mg (for dose escalation and taper) and 300-mg tablets, manufactured by GlaxoSmithKline, were used. The bupropion-XL dosing schedule was 150 mg/d for study days 1–3, 300 mg/d for study days 4 through week 10, and a 3-day dose taper of 150 mg following week 10. The NICOTROL inhaler, manufactured by Pfizer (New York, New York), was also used for the trial. Starting with the target quit date (study day 20) through week 10, participants assigned to treatment as usual with smoking-cessation treatment were prescribed 6–16 nicotine cartridges per day ad libitum; participants received a 3-week taper following week 10.

Participants assigned to treatment as usual with smoking-cessation treatment received weekly 10-minute smoking-cessation counseling sessions during study weeks 1–10, using the *Smoke Free and Living It*[22] manual. Interventionists were trained on the manual and certified after a successful mock session. All sessions were video recorded to monitor adherence; of the 283 sessions rated, 271 (95.8%) were rated as adherent. Prize-based contingency management (ie, using a fishbowl from which chips were drawn) was used to reinforce negative CO (ie, CO < 4 ppm) results by the participants assigned to treatment as usual with smoking-cessation treatment during the post-quit phase. In order to encourage continuous abstinence, the number of draws earned escalated with each consecutive week of abstinence and reset if evidence of smoking was obtained. The maximum number of draws that could be earned by a

Figure 1. Participant Disposition



participant was 110, which equates to approximately $380 in prizes.

Measures

The primary outcome was the weekly proportion of stimulant-abstinent participants during the treatment phase, as assessed by stimulant-negative urine drug screen and self-report of no stimulant use. A rapid urine drug screen system that screened for cocaine, methamphetamine, amphetamine, opioids, benzodiazepines, and marijuana was used to analyze the urine samples (Branan Medical Corporation, Irvine, California). To avoid falsification, urine samples were collected using temperature monitoring, and the validity of urine samples was checked with the use of a commercially available adulterant test. Self-report of substance use was assessed using the timeline follow-back method,[23,24] which is a widely employed and well-validated method.

Secondary outcomes included proportion of stimulant-abstinent participants at follow-up, proportion of drug-abstinent participants during active treatment and follow-up, stimulant-free and drug-free days during the active treatment phase and follow-up, smoking point-prevalence abstinence at the end of treatment and follow-up, and substance use disorder treatment attendance during the active treatment phase. Drug-abstinence was assessed by negative urine drug screen and self-report of no substance use (ie, alcohol and/or other nonnicotine substance use). Stimulant-free and drug-free days were assessed by the time line follow-back method. Smoking point-prevalence abstinence was assessed by self-report of not smoking in the previous 7 days, confirmed by a CO level < 8 ppm.[25] Treatment attendance was defined as the percentage of scheduled treatment hours attended as obtained from clinic records. Safety was assessed through adverse event reporting. Bupropion-XL adherence was assessed weekly via self-report and pill count; nicotine inhaler use was assessed weekly during the post-quit period via self-report and inhaler count.

Data Analysis

All analyses were completed on the ITT sample using SAS, version 9.1.3 (SAS Institute, Inc, Cary, North Carolina).

Table 1. Participant Demographic and Baseline Characteristics[a]

Characteristic	Treatment as Usual With Smoking-Cessation Treatment (n = 267)	Treatment as Usual (n = 271)	Total (n = 538)
Age, mean (SD), y	36.9 (10.0)	36.0 (10.1)	36.4 (10.0)
Male sex, n (%)	145 (54.3)	135 (49.8)	280 (52.0)
Race, n (%)			
African American	83 (31.2)	88 (32.5)	171 (31.8)
Caucasian	162 (60.9)	158 (58.3)	320 (59.6)
Other/mixed	22 (7.9)	25 (9.2)	47 (8.6)
Hispanic ethnicity, n (%)	34 (12.9)	33 (12.3)	67 (12.6)
Marital status, n (%)			
Married	32 (12.0)	26 (9.6)	58 (10.8)
Separated/divorced/widowed	89 (33.3)	104 (38.4)	193 (35.9)
Never married	146 (54.7)	141 (52.0)	287 (53.3)
Education, mean (SD), y	11.7 (1.9)	12.0 (1.9)	11.9 (1.9)
Employment, n (%)			
Full-time	74 (27.7)	86 (31.7)	160 (29.7)
Part-time	61 (22.8)	62 (22.9)	123 (22.9)
Other	132 (49.4)	123 (45.4)	255 (47.4)
Stimulant dependence diagnosis, n (%)			
Cocaine only	147 (55.1)	154 (57.0)	301 (56.1)
Methamphetamine only	102 (38.2)	107 (39.6)	209 (38.9)
Both cocaine and methamphetamine	18 (6.7)	9 (3.3)	27 (5.0)
Alcohol/nonstimulant diagnosis, n (%)[b]	120 (44.9)	121 (44.6)	241 (44.8)
Days/stimulant use at baseline (previous 28 d), mean (SD)	1.9 (4.9)	1.5 (3.7)	1.7 (4.3)
Stimulant-free (previous 28 d), n (%)	194 (72.7)	199 (73.4)	393 (73.0)
Days/drug use at baseline (previous 28 d), mean (SD)	4.2 (7.9)	3.5 (6.9)	3.8 (7.4)
Drug-free (previous 28 d), n (%)	155 (58.1)	164 (60.5)	319 (59.3)
Smoking history			
Fagerström score, mean (SD)	5.7 (2.3)	5.6 (2.1)	5.6 (2.2)
No. of smoking years, mean (SD)	20.3 (9.6)	19.0 (10.3)	19.7 (9.9)
No. of cigarettes/d, mean (SD)	16.7 (8.4)	16.0 (7.4)	16.3 (7.9)

[a]Demographic and baseline characteristics did not differ significantly between the treatment groups.
[b]A diagnosis of substance abuse or dependence. (The most common diagnoses were alcohol dependence at 14.7%, marijuana abuse at 13.8%, and alcohol abuse at 11.8%.)

Statistical tests were conducted at a 5% type I error rate (2-sided) for all measures. It has been recommended that effect sizes be provided rather than use of the Bonferroni procedure to adjust for multiple comparisons[26]; thus, effect sizes and 95% confidence intervals (CIs) are provided for each statistically significant treatment effect. Statistical models for longitudinal data included treatment, week, and treatment-by-week interaction effects. For each model, the baseline of the outcome measure being analyzed was a covariate that could be selected for inclusion in the model by the corrected Akaike information criterion as the optimizing criterion.

All repeated-measures regressions were random intercept mixed model (or generalized mixed model) regressions using participant as random effect. Regressions with binary response variables used logistic mixed models, and the remaining regressions used ordinary mixed models. Adverse events included all untoward events reported by the participants as well as clinically significant changes in vital signs. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 15) and tabulated by body system and preferred term, seriousness, and relationship to study medication. Adverse events were compared between treatment groups using Pearson χ^2 or the Fisher exact test, depending on marginal frequency counts.

The most conservative estimate for missing data was calculated, which was for missing urine samples, including those missed due to participants' failure to attend visits as well as due to technical issues. This estimate yielded a missing data rate of 13.8%. The approach taken to handling missing data depended on the outcome measure. For the primary outcome (stimulant abstinence), data for a week in which both urine samples were missing and the participant self-reported no illicit stimulant use were treated as missing. For a week in which 1 stimulant-free urine drug screen was produced, the second urine sample was missing, and the participant self-reported no illicit stimulant use or the self-report data were missing, data were imputed as stimulant-abstinent. For the smoking abstinence measure, missing days were coded as smoking days, which is a standard approach in smoking-cessation trials. Missing data for other measures were treated as missing.

RESULTS

Participants and Disposition

The sample disposition in Figure 1 shows that 2,244 candidates were prescreened, 868 consented and were screened, and 538 were randomized to treatment as usual with concurrent smoking-cessation treatment or treatment as usual. Approximately 89% of participants completed the 10-week active treatment period, 85% completed the 3-month follow-up, and 79.6% completed the 6-month follow-up, with no group differences on completion rate or reasons for noncompletion. No participant discontinued the study due to an adverse event. Demographic and baseline characteristics did not differ significantly between groups. The sample was approximately 52% male and 60% white, and participants were 36 years of age on average (Table 1). Approximately 56% of the sample were cocaine dependent, 39% were methamphetamine dependent, and 5% were dependent on both substances. The sample had a medium level of nicotine dependence as assessed by the Fagerström score, and, on average, smoked 16 cigarettes per day.

Smoking-Cessation Treatment Adherence

Table 2 provides adherence and tolerability data for the study medications. On the basis of pill count and self-report, approximately 93% of prescribed bupropion pills were taken. In contrast, the nicotine inhaler was used as prescribed by only 7.3% of participants according to self-report data and by 5.5% of participants according to cartridge count data. For smoking-cessation counseling, participants attended 8.6 of 10 possible sessions on average. For contingency management, 187 of the participants assigned to treatment as usual with concurrent smoking-cessation treatment earned at least 1 draw.

Table 2. Summary of Medication Adherence and Tolerability for Participants Assigned to Treatment as Usual With Smoking-Cessation Treatment

Medication Adherence	Self-Report	Pill/Cartridge Count
Percentage of bupropion taken, mean (SD)	92.4 (15.6)[a]	94.5 (14.9)[b]
Average no. of nicotine inhaler cartridges used per day (over all active treatment weeks), n (%)		
<1 Cartridge	139 (56.3)[c]	148 (62.2)[d]
1–3 Cartridges	69 (27.9)[c]	63 (26.5)[d]
4–5 Cartridges	21 (8.5)[c]	14 (5.9)[d]
≥6 Cartridges (as prescribed)	18 (7.3)[c]	13 (5.5)[d]
Tolerability of maximum bupropion dose, n (%)		
Reached maximum bupropion dose	258 (97.7)	NA
Sustained maximum bupropion dose	190 (72.0)	NA

[a]Self-reported adherence was calculated by dividing the number of milligrams reported taken by the number of milligrams prescribed and multiplying by 100.
[b]Pill count adherence was calculated by taking the number of pills dispensed minus the number returned or reported lost divided by the number of pills prescribed and multiplying by 100.
[c]Self-reported adherence was calculated by dividing the number of cartridges reported taken by the number of days assessed and multiplying by 100.
[d]Cartridge count adherence was calculated by dividing the number of used cartridges returned by the number of days assessed and multiplying by 100. Medication bottles/cartridges that participants failed to return were excluded from the analysis.
Abbreviation: NA = not applicable.

Efficacy Outcomes

Stimulant-use outcomes. The treatment groups did not differ significantly on the primary outcome measure of weekly proportion of stimulant-abstinent participants during active treatment, with nonsignificant treatment ($\chi^2_1 = 0.65$, $P = .42$) and treatment-by-week interaction ($\chi^2_1 = 0.86$, $P = .35$) effects. Overall, participants assigned to treatment as usual with smoking-cessation treatment averaged 77.2% stimulant-abstinent weeks compared to 78.1% stimulant-abstinent weeks for participants assigned to treatment as usual. There was a similar lack of significant treatment effect on stimulant abstinence at 3-month ($\chi^2_1 = 2.45$, $P = .12$) and 6-month ($\chi^2_1 = 0.10$, $P = .75$) follow-ups. For stimulant-free days, there were no significant treatment ($\chi^2_1 = 0.06$, $P = .80$) or treatment-by-week interaction ($\chi^2_1 = 0.24$, $P = .62$) effects for weekly proportion of stimulant-free days during active treatment and no significant treatment effect for stimulant-free days at 3-month ($\chi^2_1 = 0.63$, $P = .43$) and 6-month ($\chi^2_1 = 1.26$, $P = .26$) follow-ups.

Smoking outcomes. Point-prevalence abstinence rates were significantly higher in the group assigned to treatment as usual with smoking-cessation treatment compared to the group assigned to treatment as usual (Figure 2A) at week 10, (25.5% vs 2.2%; $\chi^2_1 = 44.69$, $P < .0001$; OR = 18.23 [95% CI, 7.78–42.69]), 3-month follow-up (19.1% vs 3.0%; $\chi^2_1 = 26.73$, $P < .0001$; OR = 7.58 [95% CI, 3.52–16.32]), and 6-month follow-up (13.1% vs 3.7%; $\chi^2_1 = 13.00$, $P = .0003$; OR = 3.81 [95% CI, 1.84–7.88]).

Other substance use disorder outcomes. Other substance use disorder outcomes included drug-abstinence, treatment attendance, and drug-free days. The treatment groups did not differ significantly on the weekly proportion of drug-abstinent participants during active treatment with nonsignificant treatment ($\chi^2_1 = 1.80$, $P = .18$) and treatment-by-week interaction ($\chi^2_1 = 1.55$, $P = .21$) effects. There was a similar lack of treatment effect on drug abstinence at 3-month ($\chi^2_1 = 1.35$, $P = .25$) and 6-month ($\chi^2_1 = 1.23$, $P = .27$) follow-ups. There were no significant treatment effects for substance use disorder treatment attendance during the active treatment phase, with nonsignificant treatment ($\chi^2_1 = 0.03$, $P = .86$) and treatment-by-week interaction ($\chi^2_1 = 1.52$, $P = .22$) effects.

Figure 2B displays baseline-corrected drug-free days as a function of treatment and time. Participants assigned to treatment as usual with smoking-cessation treatment, relative to those assigned to treatment as usual, tended to have better outcomes, with 10-week, 3-month, and 6-month changes in drug-free days from baseline being 0.5% vs −3.3%, 1.1% vs −3.3%, and −1.3% vs −7.6%, respectively. Statistically, there was a trend toward a significant treatment-by-week interaction effect ($\chi^2_1 = 3.61$, $P = .058$) during treatment, no significant treatment effect at 3-month follow-up ($\chi^2_1 = 2.44$, $P = .12$), and a significant treatment effect at 6-month follow-up ($\chi^2_1 = 4.09$, $P = .04$). The Cohen *d* for the 6-month effect is 0.22 [95% CI, 0.03–0.41], which is a small effect.

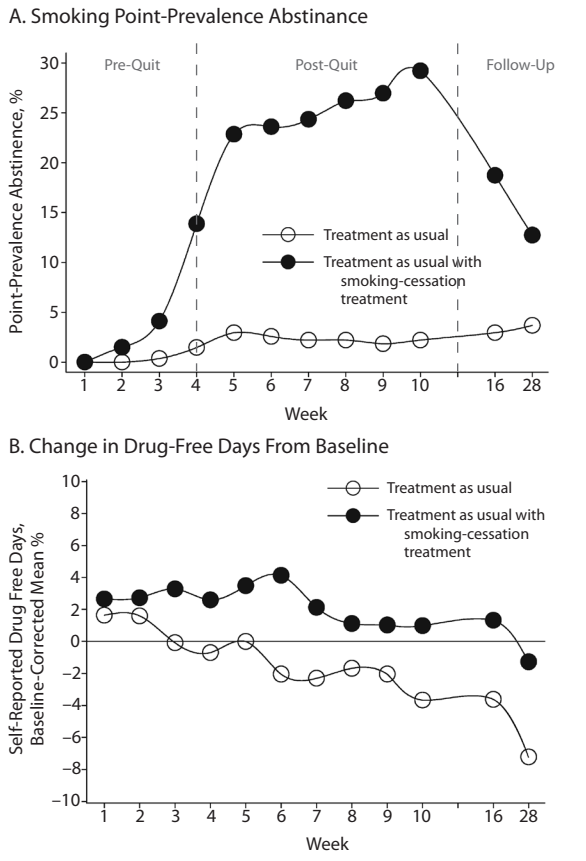
Safety Outcomes

The occurrence of treatment-emergent adverse events was significantly higher in the group receiving treatment as usual with smoking-cessation treatment relative to the treatment as usual group (Table 3). The adverse events occurring at a rate of 5% or more in the group receiving treatment as usual with smoking-cessation treatment and at a significantly higher rate than in the treatment as usual group were dry mouth, nausea, headache, anxiety, insomnia, and throat irritation. Twenty-three participants experienced a treatment-emergent serious adverse event, with no significant difference between arms (Table 3). Four participants experienced a medication-related serious adverse event, with 1 experiencing suicidal ideation and chest pain, 2 experiencing suicidal ideation, and 1 experiencing panic attacks.

DISCUSSION

This trial is the first to evaluate the impact of concurrently providing smoking-cessation and substance use disorder treatment to cocaine- and/or methamphetamine-dependent patients. We had predicted that treatment as usual concurrent with smoking-cessation treatment, relative to treatment as usual, would significantly improve stimulant-use outcomes. The results from ITT analyses indicate that stimulant use during active treatment and follow-up did not differ significantly between the treatment groups. This suggests that providing smoking-cessation treatment to cocaine- and/or methamphetamine-dependent patients in outpatient substance use disorder treatment does not affect stimulant-use outcomes. Alternatively, the findings might reflect a ceiling effect, given the relatively low rate of stimulant use (ie, participants averaged 77.6% weekly abstinence during treatment).

Figure 2. Nicotine and Drug-Use Outcomes as a Function of Treatment Group and Time



A secondary objective of the trial was to evaluate the impact of treatment as usual concurrent with smoking-cessation treatment, relative to treatment as usual, on other drug-abuse outcomes. The results suggest that there were no significant treatment effects for drug abstinence but that the participants receiving treatment as usual with smoking-cessation treatment, relative to those receiving treatment as usual, evidenced better outcomes for drug-free days, with a trend for a significant treatment difference during active treatment and a significant difference at 6-month follow-up. This finding is consistent with past research,[6,27] which has found that concurrent smoking cessation and substance use disorder treatment for alcohol use disorders can enhance abstinence from substance use. The results from our present study also revealed that substance use disorder treatment attendance did not differ significantly between the participants receiving treatment as usual with smoking-cessation treatment and those receiving treatment as usual. This finding is in contrast to a past smoking-cessation trial,[18] which found that, in nonmethadone maintenance sites, there was a significant decrease in substance use disorder treatment attendance in the participants receiving smoking-cessation treatment relative to those receiving treatment as usual. Given the larger sample size and site diversity of the present study, the present finding should help reassure community

Table 3. Summary of Treatment Emergent Adverse Events (TEAEs) by MedDRA-Preferred Term[a]

TEAE[b]	Treatment as Usual With Smoking-Cessation Treatment (n = 267)	Treatment as Usual (n = 271)	*P* Value
Any TEAEs, n (%)	195 (73.0)	157 (57.9)	.0002
TEAEs related to study medication, n (%)[c]	128 (47.9)	NA	
Discontinued bupropion XL due to TEAEs, n (%)	13 (4.9)	NA	
Discontinued nicotine inhaler due to TEAEs, n (%)	7 (2.6)	NA	
Most frequent TEAEs, n (%)[d]			
Psychiatric disorders			
Insomnia	21 (7.9)	3 (1.1)	.0001
Anxiety	20 (7.5)	5 (1.8)	.0019
Gastrointestinal disorders			
Nausea	18 (6.7)	7 (2.6)	.0220
Dry mouth	14 (5.2)	0 (0.0)	.0001
Headache	34 (12.7)	13 (4.8)	.0011
Throat irritation	16 (6.0)	0 (0.0)	< .0001
Any serious TEAE, n (%)	14 (5.2)	9 (3.3)	.2704
Serious TEAE related to study medication, n (%)[c]	4 (1.5)	NA	
Suicidal ideation	3	NA	
Panic attacks	1	NA	
Chest pain	1	NA	
Serious TEAE unrelated to study medication, n (%)	11 (4.1)	9 (3.3)	.6244
Cardiac disorders, n			
Angina pectoris	0	1	
Myocardial infarction	0	1	
Eye disorders: vision blurred	1	0	
Gastrointestinal disorders, n			
Abdominal pain upper	0	1	
Constipation	0	1	
Pancreatitis	0	1	
General disorders/administration site conditions, n			
Death	1	0	
Drug withdrawal syndrome	1	0	
Noncardiac chest pain	1	0	
Infections and infestations, n			
Appendicitis	0	1	
Pyelonephritis	1	0	
Sepsis	1	0	
Sinusitis	1	0	
Injury: tibia fracture, n	1	0	
Metabolism and nutrition disorder: dehydration, n	0	1	
Musculoskeletal and connective tissue disorder: exostosis, n	1	0	
Psychiatric disorders, n			
Depression	1	0	
Suicidal ideation	0	1	
Suicidal attempt	0	1	
Respiratory, thoracic, and mediastinal disorders: asthma, n	0	1	
Vascular disorders: hematoma, n	1	0	

[a]Terminology in MedDRA is the international medical terminology developed under the auspices of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. MedDRA is a registered trademark of the International Federation of Pharmaceutical Manufacturers and Associations.
[b]A TEAE was defined as a new illness or an exacerbation of a preexisting condition, with onset date postrandomization.
[c]A TEAE rated as possibly, probably, or definitely related to treatment.
[d]Reported by > 5% of participants assigned to treatment as usual with smoking-cessation treatment and at a statistically significantly ($P < .05$) greater rate than by the treatment as usual group.
Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, NA = not applicable, XL = extended release.

treatment providers who worry that providing smoking-cessation treatment concurrently with substance use disorder treatment might increase treatment drop out.

Another objective of the present trial was to evaluate the efficacy of treatment as usual with smoking-cessation treatment, relative to treatment as usual, in improving smoking-abstinence outcomes. The results suggest that treatment as usual with smoking-cessation treatment significantly improved smoking-abstinence outcomes for cocaine- and/or methamphetamine-dependent participants in outpatient substance use disorder treatment, as indicated by the odds ratio of 18.23 for treatment as usual with smoking-cessation treatment, compared to treatment as usual, for end-of-treatment point-prevalence abstinence rate. Still, the point-prevalence abstinence rate of 25.5% for treatment as usual with smoking-cessation treatment was somewhat modest and lower than rates of approximately 35% obtained in smoking-cessation trials completed in non–substance-abusing populations.[28–30] The present end-of-treatment point-prevalence abstinence rate does, however, compare favorably with point-prevalence abstinence rates from smoking-cessation trials completed in alcohol-dependent patients.[31,32] Smoking-cessation trials typically include longer term follow-up assessments. The final follow-up assessment for the present trial was at 6 months after smoking cessation for which the point-prevalence abstinence rate was 13.1% for the participants receiving treatment as usual with smoking-cessation treatment. As with the end-of-treatment point-prevalence abstinence rate, this is lower than the 6-month point-prevalence abstinence rate of approximately 26% reported for bupropion in past trials with non–substance-abusing populations,[30,33] but it is comparable to 6-month point-prevalence abstinence rates in trials with alcohol-dependent smokers.[31,32] Moreover, the odds ratio of 3.81 for treatment as usual with smoking-cessation treatment, compared to treatment as usual, at 6-month follow-up suggests that smoking-cessation outcomes over longer term follow-up can be significantly improved in stimulant-dependent patients in outpatient substance use disorder treatment.

The present study had several strengths. First, this trial was conducted at 12 sites, which enhances the generalizability of the results, and included a relatively large sample of stimulant-dependent participants. Another study strength is that it was conducted with individuals seeking treatment at substance use disorder treatment programs and, thus, the results are most likely generalizable to individuals in treatment for stimulant-dependence disorders.[34] Other strengths include the participants' high retention rate and strong adherence to smoking cessation counseling and their taking bupropion as prescribed. Thus, while adherence with the nicotine inhaler was poor, the participants assigned to treatment as usual with smoking-cessation treatment received important elements of effective smoking-cessation treatment.

A limitation of the present study was the use of a more intensive smoking-cessation intervention, composed of 2 medications and 2 psychosocial treatments, than could be implemented by many substance use disorder treatment programs outside the context of a clinical trial. Thus, the smoking interventions implemented in substance use disorder treatment programs may have less of an impact on smoking behavior than the smoking-cessation treatment provided in the present trial. Another limitation was the relatively high rate of stimulant abstinence, and, thus, the lack of significant effect of treatment as usual with smoking-cessation treatment, relative to treatment as usual, on stimulant abstinence may reflect a ceiling effect. A final limitation was the lack of a biomarker for medication adherence, and, thus, the reported adherence rates for bupropion most likely reflect upper limit estimates.

In conclusion, the present results demonstrate that providing smoking-cessation treatment to cocaine- and/or methamphetamine-dependent patients in outpatient substance use disorder treatment had no effect on stimulant-use outcomes, significantly improved smoking-abstinence outcomes, and did not significantly impact treatment attendance. Participants receiving treatment as usual with smoking-cessation treatment, relative to those receiving treatment as usual, had significantly better outcomes for drug-free days at 6-month follow-up. These results are consistent with findings from research[6,35] studying the impact of smoking-cessation treatment in other substance use disorder populations and add to a growing literature demonstrating that concurrent smoking-cessation and substance use disorder treatment can significantly improve smoking-abstinence outcomes and do not negatively impact nonnicotine outcomes.

Drug names: bupropion (Zyban and others).

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