Multisite, Randomized, Double-Blind, Placebo-Controlled Pilot Clinical Trial to Evaluate the Efficacy of Buspirone as a Relapse-Prevention Treatment for Cocaine Dependence

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ABSTRACT

Objective: To evaluate the potential efficacy of buspirone as a relapse-prevention treatment for cocaine dependence.

Method: A randomized, double-blind, placebo-controlled, 16-week pilot trial was conducted at 6 clinical sites between August 2012 and June 2013. Adult crack cocaine users meeting *DSM-IV-TR* criteria for current cocaine dependence who were scheduled to be in inpatient/residential substance use disorder (SUD) treatment for 12–19 days when randomized and planning to enroll in local outpatient treatment through the end of the active treatment phase were randomized to buspirone titrated to 60 mg/d (n = 35) or placebo (n = 27). All participants received psychosocial treatment as usually provided by the SUD treatment programs in which they were enrolled. Outcome measures included maximum days of continuous cocaine abstinence (primary), proportion of cocaine use days, and days to first cocaine use during the outpatient treatment phase (study weeks 4–15) as assessed by self-report and urine drug screens.

Results: There were no significant treatment effects on maximum continuous days of cocaine abstinence or days to first cocaine use. In the female participants (n = 23), there was a significant treatment-by-time interaction effect ($\chi^2_1 = 15.26$, $P < .0001$), reflecting an increase in cocaine use by those receiving buspirone, relative to placebo, early in the outpatient treatment phase. A similar effect was not detected in the male participants (n = 39; $\chi^2_1 = 0.14$, $P = .70$).

Conclusions: The results suggest that buspirone is unlikely to have a beneficial effect on preventing relapse to cocaine use and that buspirone for cocaine-dependent women may worsen their cocaine use outcomes.

Trial Registration: ClinicalTrials.gov identifier: NCT01641159

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In 2010, over 1 million people in the United States were abusing or dependent on cocaine,[1] and in Europe, cocaine use has increased significantly in recent years.[2] Although psychosocial interventions for cocaine dependence can help, treatment dropout followed by relapse to cocaine use is high. Despite extensive work, there still is no US Food and Drug Administration (FDA)–approved treatment for cocaine dependence.[3] Preclinical research has found that dopamine D_3 receptor antagonists can reduce the rewarding effects of cocaine and reinstatement of cocaine seeking.[4–6] In addition, imaging research suggests that dopamine D_3 receptors may be up-regulated in stimulant abusers.[7] Buspirone is an FDA-approved treatment for generalized anxiety disorder with little abuse potential[8] and a well-established safety profile.[9] Buspirone has long been established to be a 5-HT_{1A} agonist,[8] but in more recent years has been determined to be a dopamine D_3[10,11] and D_4 antagonist[11] as well. Buspirone has been found to significantly decrease cocaine-cue reinstatement in rats,[12] and both acute[11,13] and chronic[14] buspirone have been found to decrease cocaine self-administration in rhesus monkeys.

On the basis of the preclinical data showing the ability of buspirone to decrease cocaine reinstatement and self-administration, combined with buspirone's favorable safety profile, a clinical trial, A Randomized Controlled Evaluation of Buspirone for Relapse-Prevention in Adults with Cocaine Dependence (BRAC), was conducted by the National Institute on Drug Abuse National Drug Abuse Treatment Clinical Trials Network to test the efficacy of buspirone as a cocaine dependence treatment. Prior research suggests that stimulant-dependent patients vary substantially in their response to dopaminergic agents,[15] and thus testing for subgroups for whom buspirone might be differentially effective was planned for in the trial.[16] One subgroup of interest in this regard is gender, given evidence that gender plays a significant role in dopaminergic function and response to dopaminergic agents.[17–23] Specific to cocaine, research has found that male monkeys who become dominant have an increase in dopamine D_2/D_3 receptors and evidence less vulnerability to the reinforcing effects of cocaine, whereas female monkeys who become dominant also have an increase in dopamine D_2/D_3 receptors but evidence *more* vulnerability to cocaine's reinforcing effects.[24]

As described elsewhere,[16] BRAC was designed to be a 2-stage process in which a pilot trial would first be completed to obtain information needed to address important operational aspects critical to the design of the full-scale clinical trial (medication tolerability, adherence, missing data rates, eligibility criteria, etc). The results from the pilot, including an evaluation of gender effects, are reported in the present article.

Clinical Points

- There is currently no FDA-approved medication for the treatment of cocaine dependence.
- Buspirone, which is an FDA-approved treatment for generalized anxiety disorder, may have a significant negative effect on cocaine use outcomes in cocaine-dependent women.
- Buspirone does not appear to be an effective relapse prevention treatment for cocaine dependence.

METHOD

Study Design

BRAC was a 16-week, double-blind, placebo-controlled, intent-to-treat (ITT) trial. Dose titration was completed in an inpatient/residential setting, which allowed an evaluation of buspirone as a relapse-prevention treatment and, based on the potential relapse rate of 65%–72%,[25–27] also of its ability to curtail ongoing cocaine use. Eligible participants were randomly assigned to buspirone or matching placebo and scheduled to receive study medication and to attend 2 research visits per week throughout the active treatment phase, which began with randomization and ended on day 7 of study week 15. A single visit was scheduled in week 16 to complete retrospective data for week 15. The trial was conducted at 6 substance use disorder (SUD) treatment programs between August 2012 and June 2013. The study was registered on ClinicalTrials.gov (identifier: NCT01641159).

Participants

Recruitment was primarily from patients seeking inpatient/residential treatment at a participating site; secondary recruitment methods included advertising and direct community promotions, such as networking with community professionals. Eligible participants were adults who were scheduled to be in inpatient/residential SUD treatment for 12–19 days when randomized and were planning to enroll in local outpatient treatment through the end of the active treatment phase. Participants were required to meet *DSM-IV-TR* criteria for current cocaine dependence, to have used crack cocaine a minimum of 4 times in the 28 days prior to inpatient/residential admission, and to report that their typical pattern of use was at least once per week. Study eligibility was limited to crack cocaine users in the interest of increasing sample homogeneity. Exclusion criteria included a medical or psychiatric condition potentially making participation unsafe, taking psychotropic medication or a medication with which buspirone could have a potentially dangerous interaction, and meeting criteria for current opioid dependence; additional criteria for women were pregnancy, breastfeeding, or unwillingness to use adequate birth control. 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

The small sample size for this pilot trial necessitated selecting a single dose of buspirone to be evaluated; the dose evaluated, 60 mg, is the highest FDA-approved dose for treating generalized anxiety disorder. Participants were randomly assigned to buspirone (60 mg per day) or matching placebo in a 1:1 ratio stratified by site and baseline cocaine use frequency (< 10 days or ≥ 10 days in the 28 days prior to inpatient/residential admission). Dose escalation was completed over a 10-day period under observation on an inpatient/residential unit in daily divided doses starting with 10 mg on study days 1–3, 20 mg on study days 4–6, 40 mg on study days 7–9, and 60 mg on day 10. Participants who were unable to reach the 60-mg dose or needed a dose reduction from 60 mg due to tolerability were maintained on 15 mg, 30 mg, or 45 mg, whichever was the highest dose tolerated. All participants received psychosocial treatment as usually provided by the inpatient/residential and outpatient programs in which they are enrolled (ie, treatment as usual [TAU]). For the inpatient/residential phase, the minimum allowable TAU was at least 1 therapeutic activity daily (including milieu therapy) for 12–19 days. For the participants' postdischarge treatment, the minimum allowable TAU was at least 1 hour of individual or group therapeutic activity per week through study week 15.

During the 15-week treatment phase, participants were scheduled to attend 2 research visits per week for efficacy and safety assessments. Participants were reimbursed for transportation, inconvenience, and time; a participant attending all 31 postrandomization research visits earned $955. To help assure good medication adherence with buspirone's required twice-daily dosing, all participants could also earn monetary rewards through contingency management for opening their medication bottle within 6 hours of a prescribed dose time (ie, 3 hours before or after the dose was to be taken). The Med-ic eCAP system (Information Mediary Corporation, Ottawa, Ontario), which is a medication bottle with a microchip that records the times and dates of bottle opening, was used to track medication bottle openings. The contingency management plan involved a relatively quick escalation of reinforcement earnings as a strategy to promote consistent opening of the medication bottle, with resets to initial reinforcement values for failing to open the bottle as scheduled. A participant who was fully adherent throughout the 15-week active treatment phase could earn a total of $798.50. Reinforcements were provided in the form of retail gift cards (minimum $5 value), with the provision of cash for reinforcements less than $5. The buspirone and placebo participants earned a mean of $453.10 (SD = 187.81) and $427.40 (SD = 209.62), respectively.

Measures

The primary outcome was the maximum days of continuous cocaine abstinence during the outpatient treatment phase (eg, study weeks 4–15), as assessed by urine drug screen (UDS) and self-report. A rapid UDS 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 a commercially available adulterant test. Self-report of substance use was assessed using the timeline follow-back (TLFB) method,[28] which is a widely employed and well-validated method. Cocaine abstinence was determined by aggregating TLFB and UDS results into a single binary daily composite use indicator. More specifically, an algorithm was developed to combine UDS and TLFB for classifying each day and follows the general principle that a UDS covers a 4-day look-back period spanning days –3 to 0, where day 0 is when the urine is donated. A positive UDS for which the associated TLFB reports are negative will result in "correcting" TLFB days to be cocaine use days. Assumptions are also required for assigning missing UDS dates in scenarios when a UDS is missing. Details on the rules for assigning a day of collection for missing UDS and for combining TLFB and UDS while accounting for missing UDS results have been published elsewhere.[16]

Secondary outcomes included proportion of cocaine use days and days to first cocaine use as assessed by UDS and TLFB during the outpatient treatment phase. Safety was assessed through adverse event (AE) reporting and suicide risk assessments. Medication adherence measures included pill counts, participant self-reported adherence, and Med-ic eCAP data. Finally, a biological measure of adherence was obtained for participants in the buspirone arm. Specifically, urine samples were collected weekly during the treatment period and shipped to the Analytic Division of the University of California San Francisco School of Pharmacy Drug Studies Unit for analysis. The samples from the buspirone group were assayed for the buspirone metabolite 1-pyrimidinylpiperazine (1-PP) using a liquid chromatography/mass spectrometry method.

Data Analysis

All analyses were completed on the ITT sample using SAS, Version 9.3 (SAS Institute, Inc; Cary, North Carolina). Statistical tests were conducted at a 5% type I error rate (2-sided) for all measures. The overall rate of missed visits was only 4.4%. Missing data for the primary outcome and days to first use variables were imputed as being positive for cocaine use, while analysis of the proportion of cocaine use days ignored missing data. The primary outcome variable (maximum days of continuous cocaine abstinence) was tested for a treatment effect using a gamma generalized linear regression. Daily composite cocaine use indicators were tested for treatment and treatment-by-time effects using a logistic generalized mixed model regression. For graphs of daily composite cocaine use, daily percentages were pooled into weekly percentages to improve the clarity of presentation. Days to first cocaine use was tested for a treatment effect using a Cox proportional hazards regression. The days-to-first-use survival graphs display the by-treatment survival probability distributions as estimated using Kaplan-Meier calculations on raw data. For each outcome, the respective regression was performed using all ITT participants and then repeated using female ITT participants and using male ITT participants. All regressions used baseline proportion of self-reported cocaine use days as a covariate.

RESULTS

Participants and Disposition

As shown in Figure 1, 379 candidates were prescreened, 100 provided written consent and were screened, and 62 were randomly assigned to buspirone (n = 35) or placebo (n = 27). Approximately 94% of participants completed the 15-week active treatment period, 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 for the sample as a whole or within gender subgroup. The sample was approximately 63% male and 73% African American, and the mean age was 46 years (Table 1).

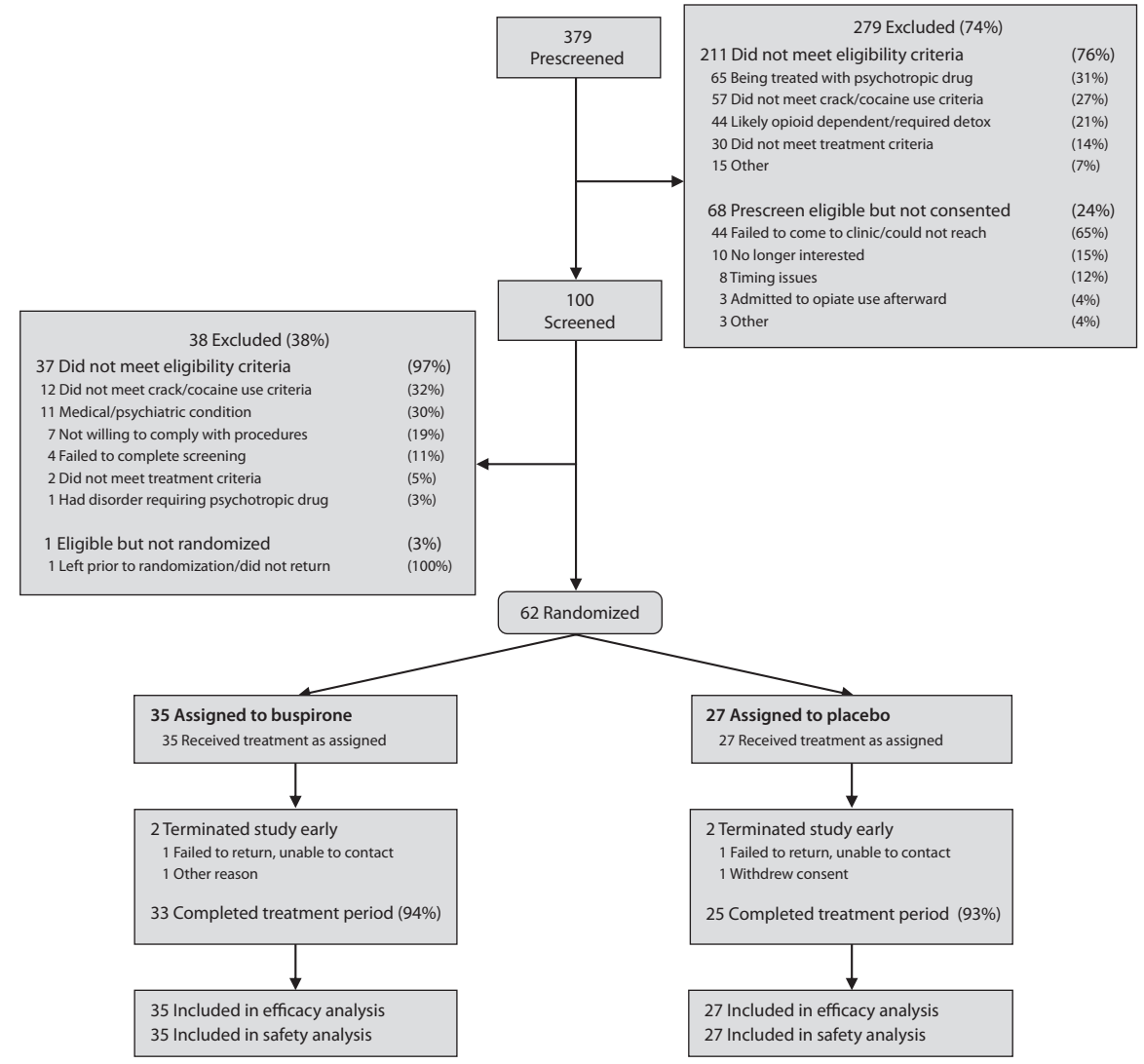
Medication Adherence

Medication adherence and tolerability did not differ significantly between treatment groups for the sample as a whole or within gender subgroup (Table 2). Study participants self-reported taking a mean of 89.8% of the prescribed pills over the course of the study, and participants took a mean of 95.0% of the pills dispensed based on pill count. On the basis of the Med-ic eCAP data, a mean of 84.5% of the scheduled twice-daily bottle openings occurred across the study participants. The overall mean rate of urine screens positive for 1-PP in the buspirone group was 81.5% across study participants over all study weeks (Table 2). During the first 7 weeks of the trial, a mean of 93.6% of urine screens were positive for 1-PP in the buspirone participants overall, with rates of 95.5% and 92.8% in the female and male subgroups. All study participants reached the target dose (60 mg/d), and approximately 89% of participants were maintained at the target dose.

Efficacy Outcomes

All participants. The mean maximum number of days of continuous cocaine abstinence among all participants (n = 62) was 39.7 (SD = 31.4) for the buspirone group and 42.1 (SD = 31.1) for the placebo group, which was not a statistically significant difference ($\chi^2_1 = 0.05$, $P = .82$). In contrast, there was a significant treatment-by-time interaction for proportion of cocaine use days ($\chi^2_1 = 6.06$, $P = .01$). A review of the associated graph (Figure 2A) indicates that this effect reflects a relative increase in use by the buspirone group early in the outpatient treatment phase (ie, weeks 5–8). Kaplan-Meier curves for the probability of maintaining abstinence from cocaine as a function of treatment are provided in Figure 2B; there was no statistically significant treatment effect on days to first cocaine use ($\chi^2_1 = 0.15$, $P = .70$).

Figure 1. Participant Disposition



Women. The mean maximum number of days of continuous cocaine abstinence among women (n = 23) was 37.7 (SD = 32.5) for the buspirone and 52.0 (SD = 32.9) for the placebo participants, which was not a statistically significant difference ($\chi^2_1 = 1.80$, $P = .18$). In contrast, there was a significant treatment-by-time interaction for proportion of cocaine use days ($\chi^2_1 = 15.26$, $P < .0001$). A review of the associated graph (Figure 2C) indicates that this effect reflects a relative increase in cocaine use by the buspirone group early in the outpatient treatment phase (ie, weeks 4–10). There was a trend for a significant treatment effect on days to first cocaine use ($\chi^2_1 = 3.20$, $P = .067$), reflecting the tendency for quicker relapse to cocaine use in the buspirone, relative to placebo, participants (Figure 2D).

Men. The mean maximum number of days of continuous cocaine abstinence among men (n = 39) was 40.5 (SD = 31.6) for the buspirone and 34.3 (SD = 28.1) for the placebo participants, which was not a statistically significant difference ($\chi^2_1 = 3.06$, $P = .08$). There was no significant treatment effect ($\chi^2_1 = 0.01$, $P = .91$) or treatment-by-time interaction ($\chi^2_1 = 0.14$, $P = .70$) for proportion of cocaine use days (Figure 2E). Finally, there was no statistically significant treatment effect on days to first cocaine use ($\chi^2_1 = 1.40$, $P = .24$; Figure 2F).

Safety Outcomes

The occurrence of treatment-emergent adverse events (TEAEs) related to study medication was significantly higher in the buspirone group relative to the placebo group (Table 3). Within gender subgroups, the occurrence of TEAEs related to study medication was significantly higher in the buspirone, relative to placebo, group in the women but not in the men (Table 3). One AE, dizziness, occurred at a rate of 5% or more in the buspirone group, and at a statistically significantly higher rate than in the placebo group in the sample overall ($P = .0005$) and in the women ($P = .005$); there was a trend for greater dizziness in the buspirone than the placebo group in the men ($P = .057$). There was no evidence

Table 1. Participant Demographic and Baseline Characteristics as a Function of Treatment Group and Gender

	All Participants			Women			Men		
Characteristic	Buspirone (n = 35)	Placebo (n = 27)	Total (N = 62)	Buspirone (n = 11)	Placebo (n = 12)	Total (n = 23)	Buspirone (n = 24)	Placebo (n = 15)	Total (n = 39)
Age, mean (SD), y	44.4 (7.6)	47.3 (6.6)	45.6 (7.3)	41.5 (8.0)	46.8 (5.8)	44.3 (7.3)	45.7 (7.1)	47.7 (7.3)	46.5 (7.2)
Gender, male, n (%)	24 (68.6)	15 (55.6)	39 (62.9)						
Race, n (%)									
African American	26 (74.3)	19 (70.4)	45 (72.6)	8 (72.7)	10 (83.3)	18 (78.3)	18 (75.0)	9 (60.0)	27 (69.2)
Caucasian	8 (22.9)	6 (22.2)	14 (22.6)	3 (27.3)	1 (8.3)	4 (17.4)	5 (20.8)	5 (33.3)	10 (25.6)
Other/mixed	1 (2.9)	2 (7.4)	3 (4.8)	0 (0.0)	1 (8.3)	1 (4.3)	1 (4.2)	1 (6.7)	2 (5.1)
Ethnicity, Hispanic, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Marital status, n (%)									
Married	3 (8.6)	5 (18.5)	8 (12.9)	2 (18.2)	1 (8.3)	3 (13.0)	1 (4.2)	4 (26.7)	5 (12.8)
Separated/divorced/widowed	15 (42.9)	5 (18.5)	20 (32.3)	6 (54.5)	3 (25.0)	9 (39.1)	9 (37.5)	2 (13.3)	11 (28.2)
Never married	17 (48.6)	17 (63.0)	34 (54.8)	3 (27.3)	8 (66.7)	11 (47.8)	14 (58.3)	9 (60.0)	23 (59.0)
Education, mean (SD), y	11.5 (2.0)	11.8 (1.4)	11.6 (1.8)	10.6 (2.2)	11.6 (1.8)	11.1 (2.0)	11.9 (1.9)	12.0 (1.1)	11.9 (1.6)
Employment, n (%)									
Full-time	8 (22.9)	6 (22.2)	14 (22.6)	0 (0.0)	1 (8.3)	1 (4.3)	8 (33.3)	5 (33.3)	13 (33.3)
Part-time	7 (20.0)	8 (29.6)	15 (24.2)	3 (27.3)	3 (25.0)	6 (26.1)	4 (16.7)	5 (33.3)	9 (23.1)
Other	20 (57.1)	13 (48.1)	33 (53.2)	8 (72.7)	8 (66.7)	16 (69.6)	12 (50.0)	5 (33.3)	17 (43.6)
Days with cocaine use in the 28 days preadmission, mean (SD)	16.4 (8.0)	14.4 (7.1)	15.5 (7.6)	18.6 (8.4)	16.1 (6.5)	17.3 (7.4)	15.4 (7.8)	13.1 (7.4)	14.5 (7.6)

Table 2. Summary of Medication Adherence and Tolerability

	All Participants			Women			Men		
	Buspirone (n = 35)	Placebo (n = 27)	Total (N = 62)	Buspirone (n = 11)	Placebo (n = 12)	Total (n = 23)	Buspirone (n = 24)	Placebo (n = 15)	Total (n = 39)
Medication adherence									
Buspirone/placebo pills taken, %, mean (SD)									
Self-report[a]	88.7 (21.6)	91.2 (17.0)	89.8 (19.7)	78.2 (32.5)	96.2 (4.5)	87.6 (24.0)	93.5 (12.5)	87.2 (22.0)	91.1 (16.8)
Pill count[b]	94.4 (9.6)	95.8 (5.2)	95.0 (8.0)	92.2 (12.6)	97.1 (3.0)	94.7 (9.1)	95.5 (8.0)	94.8 (6.4)	95.2 (7.3)
Bottle openings, %, mean (SD)	84.5 (22.0)	84.4 (20.5)	84.5 (21.2)	76.2 (31.1)	92.0 (7.9)	84.5 (23.1)	88.3 (15.6)	78.4 (25.4)	84.5 (20.2)
Urine samples positive for 1-PP, %, mean (SD)	81.5 (25.4)	…	…	82.4 (27.3)	…	…	81.0 (25.1)	…	…
Medication tolerability									
Reached maximum buspirone/placebo dose, n (%)	35 (100.0)	27 (100.0)	62 (100.0)	11 (100.0)	12 (100.0)	23 (100.0)	24 (100.0)	15 (100.0)	39 (100.0)
Sustained maximum buspirone/placebo dose, n (%)	31 (88.6)	24 (88.9)	55 (88.7)	10 (90.9)	11 (91.7)	21 (91.3)	21 (87.5)	13 (86.7)	34 (87.2)

[a]Self-reported adherence was calculated as (total milligrams taken)/(total milligrams prescribed) expressed as a percentage.
[b]Pill count adherence was calculated as (pills dispensed – pills returned – pills reported lost)/(pills dispensed – expected pills returned) expressed as a percentage. In cases in which participants failed to return their medication bottles, those bottles were excluded from the analysis.
Abbreviation: 1-PP = 1-pyrimidinylpiperazine.

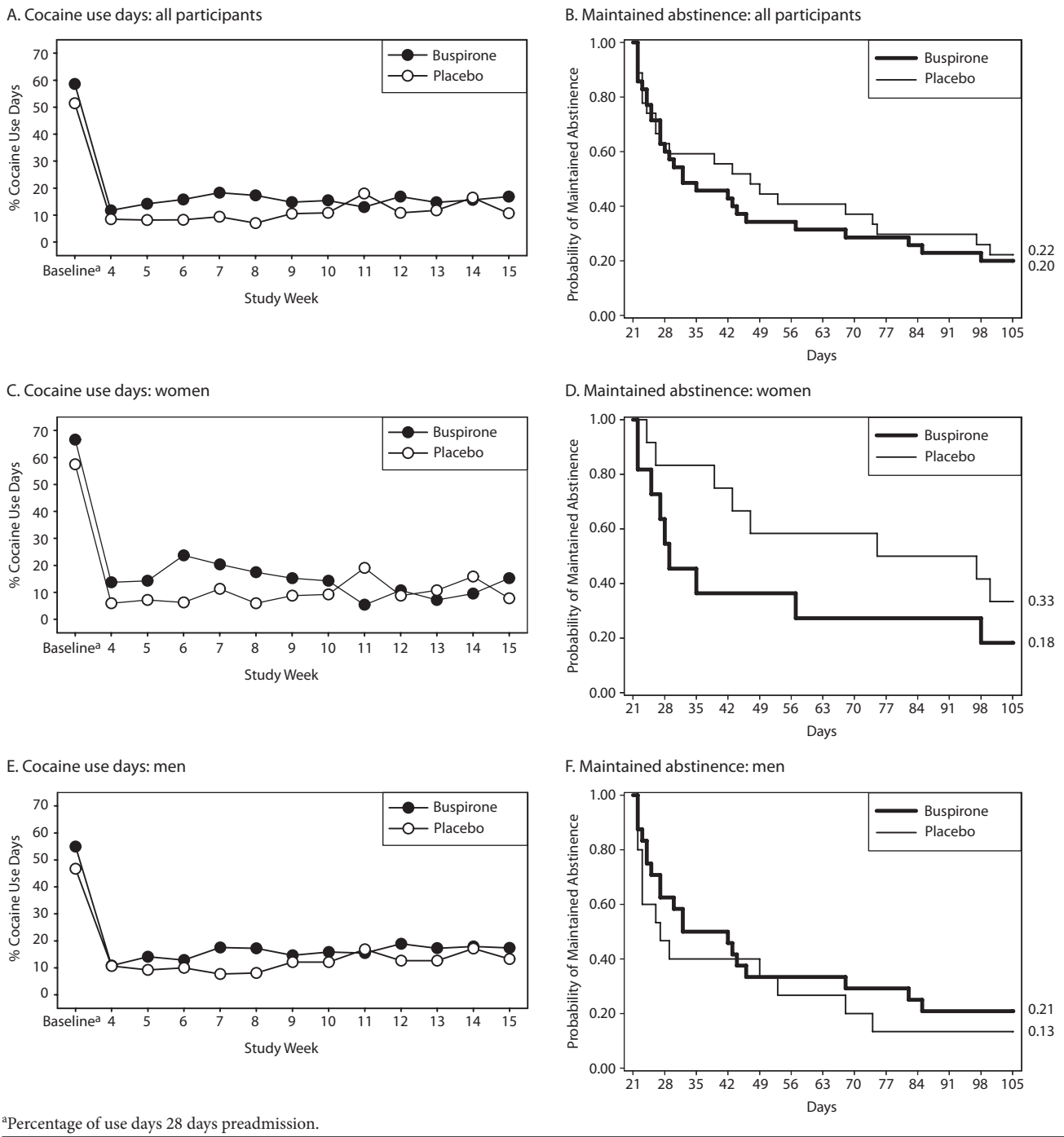
of an increased risk for suicidal ideation in the buspirone group. Three participants, all of whom were in the buspirone arm, experienced a treatment-emergent serious adverse event (SAE). The 3 events, which were rated as unrelated to the study medication, entailed inpatient hospital admissions for lower respiratory tract infection (n = 1), chest pain (n = 1), and pneumonia (n = 1).

DISCUSSION

This pilot trial was the first to evaluate buspirone as a relapse-prevention treatment for cocaine dependence. The pilot was successful in demonstrating the feasibility of conducting a large-scale trial based on enrollment, dose escalation tolerability, and adherence. The study, however, even with small numbers and counter to prediction, suggests that buspirone had no beneficial effect on relapse to cocaine use and had a significant negative effect on proportion of cocaine use days in female participants. This suggests that the use of buspirone in cocaine-dependent women may worsen their cocaine use outcomes, although, given the small sample of women in the trial (n = 23), this finding would need to be replicated before being given significant consideration clinically. The results for the male participants revealed no significant buspirone treatment effect, which suggests that buspirone is not an effective cocaine dependence treatment for males, but, again, based on the small sample of men in the trial (n = 39), this finding would also need to be replicated prior to concluding that buspirone is not effective.

The results from the present pilot trial are inconsistent with preclinical studies finding that buspirone significantly

Figure 2. Proportion of Cocaine Use Days and Kaplan-Meier Curves for Maintaining Cocaine Abstinence as a Function of Treatment Arm for Women, Men, and All Participants



[a]Percentage of use days 28 days preadmission.

decreases cocaine-cue reinstatement in rats[12] and that both acute[11,13] and chronic[14] buspirone decrease cocaine self-administration in rhesus monkeys. Of import, these preclinical studies have been completed only with males, and, thus, the discrepancy between the preclinical and present study results may reflect, in part, gender differences in dopaminergic function and dopaminergic agent response.[17–23] The present results are consistent with a small (N = 35) 12-week double-blind, placebo-controlled trial[29] evaluating the association between impulsivity, severity of cocaine use, and buspirone treatment, which found no significant treatment effect of buspirone on cocaine use outcomes.

The present study had several strengths. First, this trial was conducted at 6 sites, which enhances the generalizability of the results. Another study strength is that it was conducted with individuals seeking treatment at SUD treatment programs, and, thus, the results are likely generalizable to individuals in treatment for stimulant-dependence disorders.[30] Other strengths include the very high retention and good medication adherence rates. The small sample size

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

	All Participants (N = 62)			Women (n = 23)			Men (n = 39)		
TEAE	Buspirone (n = 35)	Placebo (n = 27)	*P* Value[b]	Buspirone (n = 11)	Placebo (n = 12)	*P* Value[b]	Buspirone (n = 24)	Placebo (n = 15)	*P* Value[b]
Any TEAE[c]	33 (94.3)	21 (77.8)	.0689	11 (100.0)	11 (91.7)	1.0000	22 (91.7)	10 (66.7)	.0846
TEAEs related to study medication[d]	22 (62.9)	8 (29.6)	.0094	9 (81.8)	4 (33.3)	.0361	13 (54.2)	4 (26.7)	.0920
Any serious TEAE	3 (8.6)	0 (0.0)	.2504	1 (9.1)	0 (0.0)	.4783	2 (8.3)	0 (0.0)	.5142
Discontinued medication due to TEAEs	0 (0.0)	0 (0.0)	…	0 (0.0)	0 (0.0)	…	0 (0.0)	0 (0.0)	…
Most frequent TEAEs[e] by MedDRA preferred term									
Nervous system disorders									
Dizziness	15 (42.9)	1 (3.7)	.0005	6 (54.5)	0 (0.0)	.0046	9 (37.5)	1 (6.7)	.0574
Somnolence	3 (8.6)	2 (7.4)	1.0000	2 (18.2)	1 (8.3)	.5901	1 (4.2)	1 (6.7)	1.0000
Infections and infestations									
Nasopharyngitis	8 (22.9)	4 (14.8)	.4268	1 (9.1)	1 (8.3)	1.0000	7 (29.2)	3 (20.0)	.7110
Bronchitis	2 (5.7)	1 (3.7)	1.0000	1 (9.1)	0 (0.0)	.4783	1 (4.2)	1 (6.7)	1.0000
Influenza	3 (8.6)	0 (0.0)	.2504	2 (18.2)	0 (0.0)	.2174	1 (4.2)	0 (0.0)	1.0000
Gastrointestinal disorders									
Nausea	8 (22.9)	2 (7.4)	.1642	3 (27.3)	2 (16.7)	.6404	5 (20.8)	0 (0.0)	.1359
Diarrhea	2 (5.7)	1 (3.7)	1.0000	0 (0.0)	1 (8.3)	1.0000	2 (8.3)	0 (0.0)	.5142
Dyspepsia	2 (5.7)	1 (3.7)	1.0000	2 (18.2)	0 (0.0)	.2174	0 (0.0)	1 (6.7)	.3846
Musculoskeletal and connective tissue disorders									
Back pain	5 (14.3)	2 (7.4)	.4550	2 (18.2)	2 (16.7)	1.0000	3 (12.5)	0 (0.0)	.2713
Arthralgia	2 (5.7)	1 (3.7)	1.0000	1 (9.1)	0 (0.0)	.4783	1 (4.2)	1 (6.7)	1.0000
Pain in extremity	2 (5.7)	1 (3.7)	1.0000	1 (9.1)	1 (8.3)	1.0000	1 (4.2)	0 (0.0)	1.0000
Respiratory, thoracic, and mediastinal disorders									
Pulmonary congestion	2 (5.7)	0 (0.0)	.5003	1 (9.1)	0 (0.0)	.4783	1 (4.2)	0 (0.0)	1.0000
Sinus congestion	2 (5.7)	0 (0.0)	.5003	0 (0.0)	0 (0.0)	…	2 (8.3)	0 (0.0)	.5142
Weight increased	2 (5.7)	1 (3.7)	1.0000	2 (18.2)	1 (8.3)	.5901	0 (0.0)	0 (0.0)	…
Insomnia	2 (5.7)	0 (0.0)	.5003	0 (0.0)	0 (0.0)	…	2 (8.3)	0 (0.0)	.5142

[a]Values expressed as n (%).
[b]*P* values are from either Fisher exact test or Pearson χ^2, depending on marginal frequency counts.
[c]TEAEs are adverse events defined as a new illness, or an exacerbation of a preexisting condition, occurring between the first dose of study drug and 1 week after the last dose of study drug.
[d]TEAE rated as possibly, probably, or definitely related to treatment.
[e]TEAEs presented here were reported by > 5% of buspirone group and at a greater rate than by the placebo group, in the full sample (N = 62).

of the present trial is a significant limitation in that small trials do not provide accurate estimates of treatment effect,[31] nor was this study adequately powered to detect differences in efficacy outcomes, since its primary goal was to address important operational aspects that would be applied to a second, larger trial. However, the results from this pilot trial do not provide a strong rationale for conducting a larger follow-up trial. Evaluation of a single dose of buspirone is another potential limitation of the present trial. There is evidence that buspirone's affinity for D_3 and D_4 receptors is comparable to its affinity for 5-HT_{1A} receptors, and thus standard clinically effective doses would likely affect D_3 and D_4.[32] The dose evaluated in this trial, 60 mg, is the highest FDA-approved dose for treating generalized anxiety disorder and, thus, would be expected to occupy D_3 and D_4 receptors. Still, an evaluation of other doses of buspirone might have produced different results from those observed in this trial. In conclusion, the results from the present trial suggest that buspirone is not an effective relapse-prevention treatment for cocaine dependence and may have a significant negative effect on cocaine use outcomes in cocaine-dependent women.

Drug names: buspirone (BuSpar and others).
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