A multi-site, 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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Background and Significance

- Buspirone: a safe, FDA-approved treatment for GAD
  - A dopamine D_3 and D_4 antagonist, as well as a $5HT_{1A}$ agonist
  - Decreases cocaine-cue reinstatement in rats, and cocaine self-administration in rhesus monkeys
- Based on the promising pre-clinical data and safety profile, a trial was planned to evaluate buspirone as a relapse-prevention treatment
  - Pilot study completed first to provide information for designing full-scale clinical trial

Study Design

- Double-blind, placebo-controlled, ITT trial
- Conducted at 6 substance use disorder (SUD) treatment programs
- Randomized to buspirone (60 mg/day) or matching placebo, 1:1, stratified: site, cocaine use in prior 28 days (<10 days or ≥ 10 days)
- Participants received study medication and attended two weekly research visits through the end of week 15

Study Design

Study medication initiated in inpatient/residential setting

- Evaluation of buspirone as a relapse-prevention treatment
- With expected post-discharge relapse rate of 65% - 72% also allowed evaluation of buspirone's ability to curtail on-going cocaine use
- Maximize medication adherence

Study Inclusion Criteria

- Adults (18+) meeting DSM-IV-TR criteria for current cocaine dependence (12 mo) willing to comply with study procedures
- Must report using crack cocaine ≥ 4 times within the 28 days prior to inpatient/residential admission; typical pattern of use is at least once a week
- Enrolled in an inpatient/residential program and scheduled to be in setting for 12-19 days when randomized, planning to enroll in outpatient treatment through study week 15

Study Exclusion Criteria

- meeting DSM-IV-TR criteria for current opioid dependence (12 mo)
- taking psychotropic medication or having a medical or psychiatric condition that would make participation unsafe or difficult
- taking a medication that could adversely interact with buspirone
- significant suicidal/homicidal risk
- Women: pregnancy, breastfeeding or unwilling to use an adequate method of birth control

Study Medication: Dose Escalation

Buspirone/Placebo Dose Escalation	
Study Day	**Dose (mg)**
1 -3	10 mg (5 am, 5 pm)*
4 - 6	20 mg (10 am, 10 pm)
7 - 9	40 mg (20 am, 20 pm)
10	60 mg (30 am, 30 pm)

**The am dose on study day 1 may occur as late as 2:30 pm, with the second dose at least 8 hours later*

Contingency Management (CM)

- CM to increase medication adherence – bottle opening within +/- 3 hours of scheduled dose
- The CM plan involved a relatively quick escalation of the reinforcement value to promote consistent opening of the medication bottle
- A perfectly adherent participant earned $798.50 in retail gift cards/cash

Outcome Measures

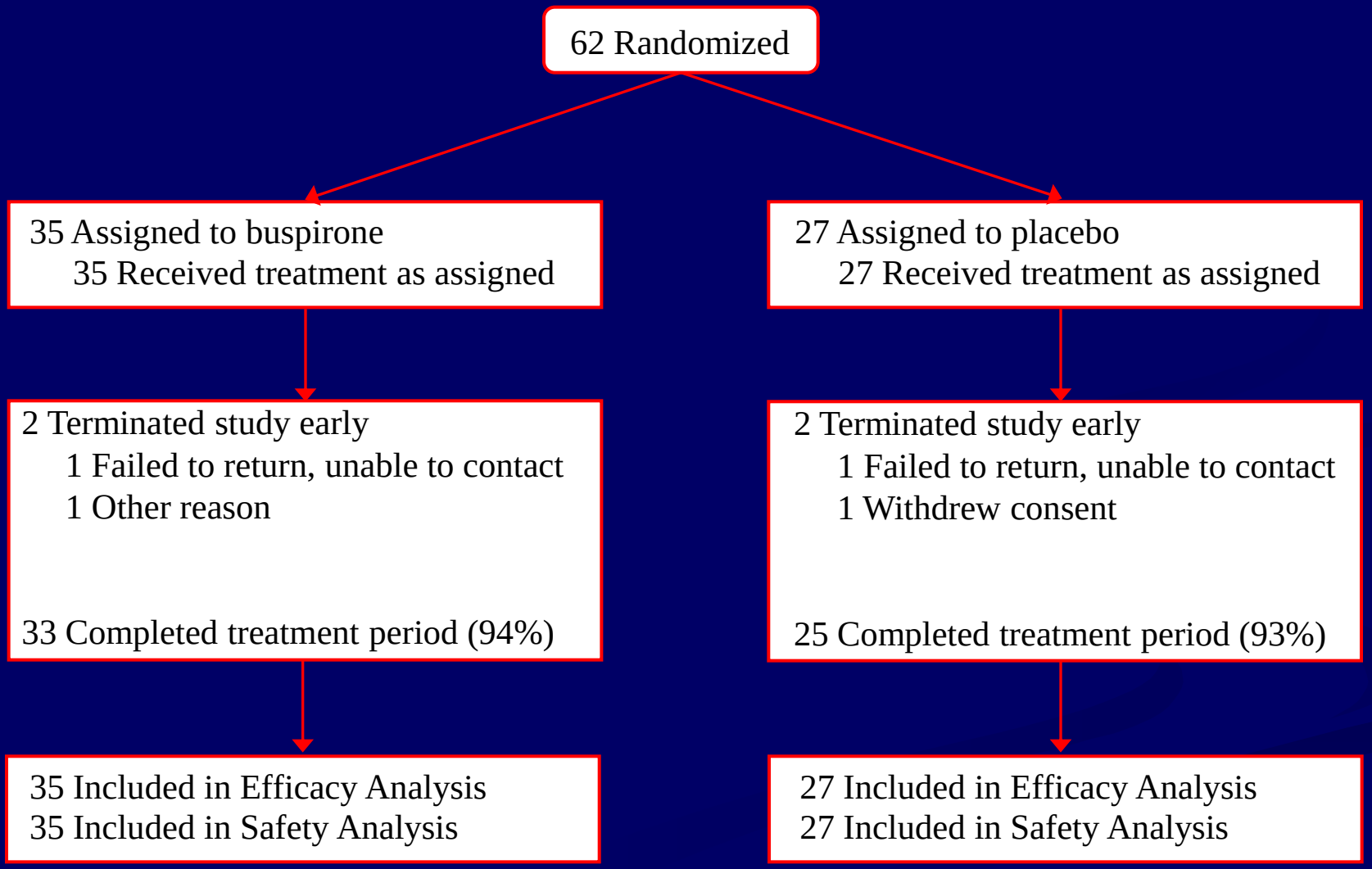
- Primary: Maximum days of continuous cocaine abstinence during the outpatient phase (study weeks 4-15)
- Secondary: Time to first cocaine use; Cocaine use days
- Determined by a combination of self-report, obtained by the timeline follow-back (TLFB) procedure, and qualitative urine drug screen (UDS) assessments

Medication Adherence/Safety Measures

- Adherence:
  - Self-report and pill counts
  - Medication events monitoring system (MEMS)
  - Buspirone: 1-PP (weekly urine sample)

- Safety:
  - Adverse Events (AEs)
  - Vital signs

Participant Disposition



Participant Demographics

	Buspirone (N=35)	Placebo (N=27)
Age	44.4	47.3
Males (%)	68.6	55.6
Race/Ethnicity (%)		
African-American	74.3	70.4
Caucasian	22.9	22.2
Other	2.9	7.4
Hispanic	0.0	0.0

Medication Adherence

	Buspirone (N=35)	Placebo (N=27)
Proportion taken		
Self report	89%	91%
Pill count	94%	96%
MEMS	85%	84%

- Proportion of urines positive for 1-PP:
  - 81% positive (weeks 2-15)
  - ≥ 90% positive weeks 2-7

Safety/Tolerability

- The adverse events occurring at a significantly higher rate in the buspirone arm have been observed in past trials with buspirone
- Rate of buspirone discontinuation comparable to, or lower than, rates reported in prior buspirone trials
- Dose escalation and 60 mg dose well tolerated

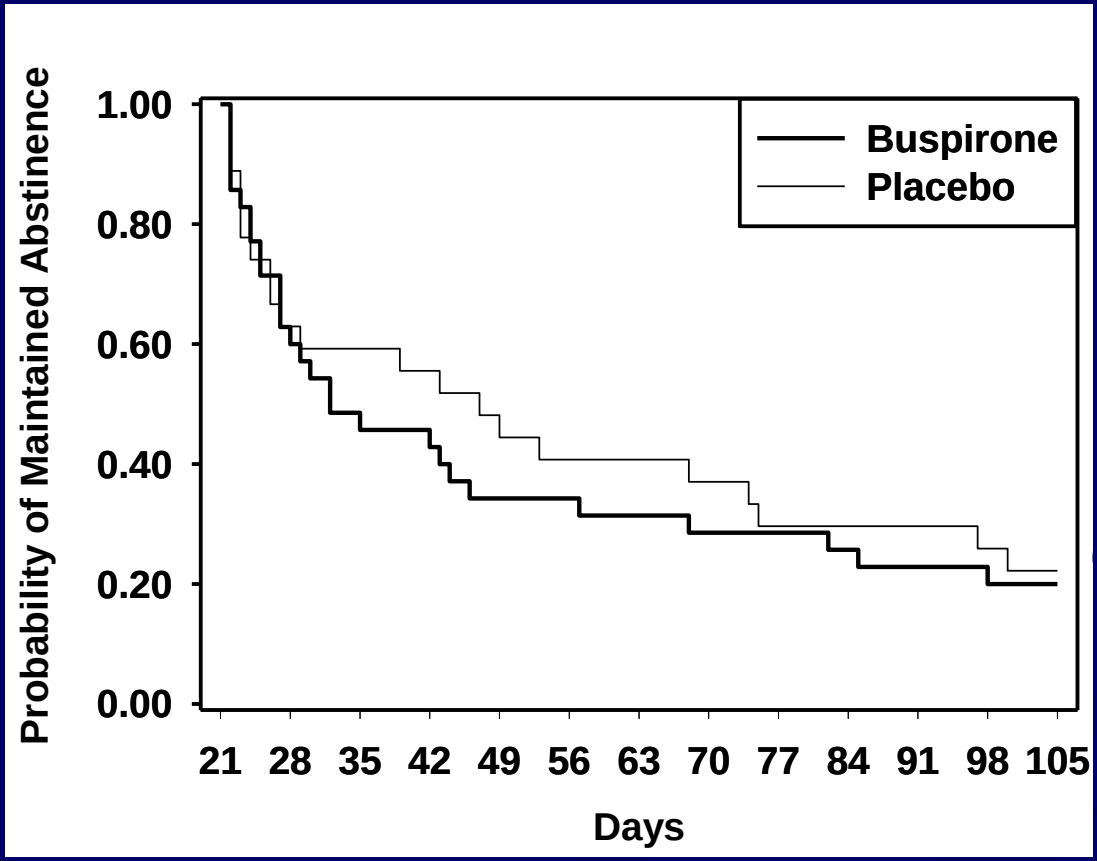
Primary Outcome - Maximum Days of Continuous Cocaine Abstinence

- No significant treatment effect (X^2_1=0.05, p=.82)

Buspirone (N=35)	Placebo (N=27)
39.7 (31.4)	42.1 (31.1)

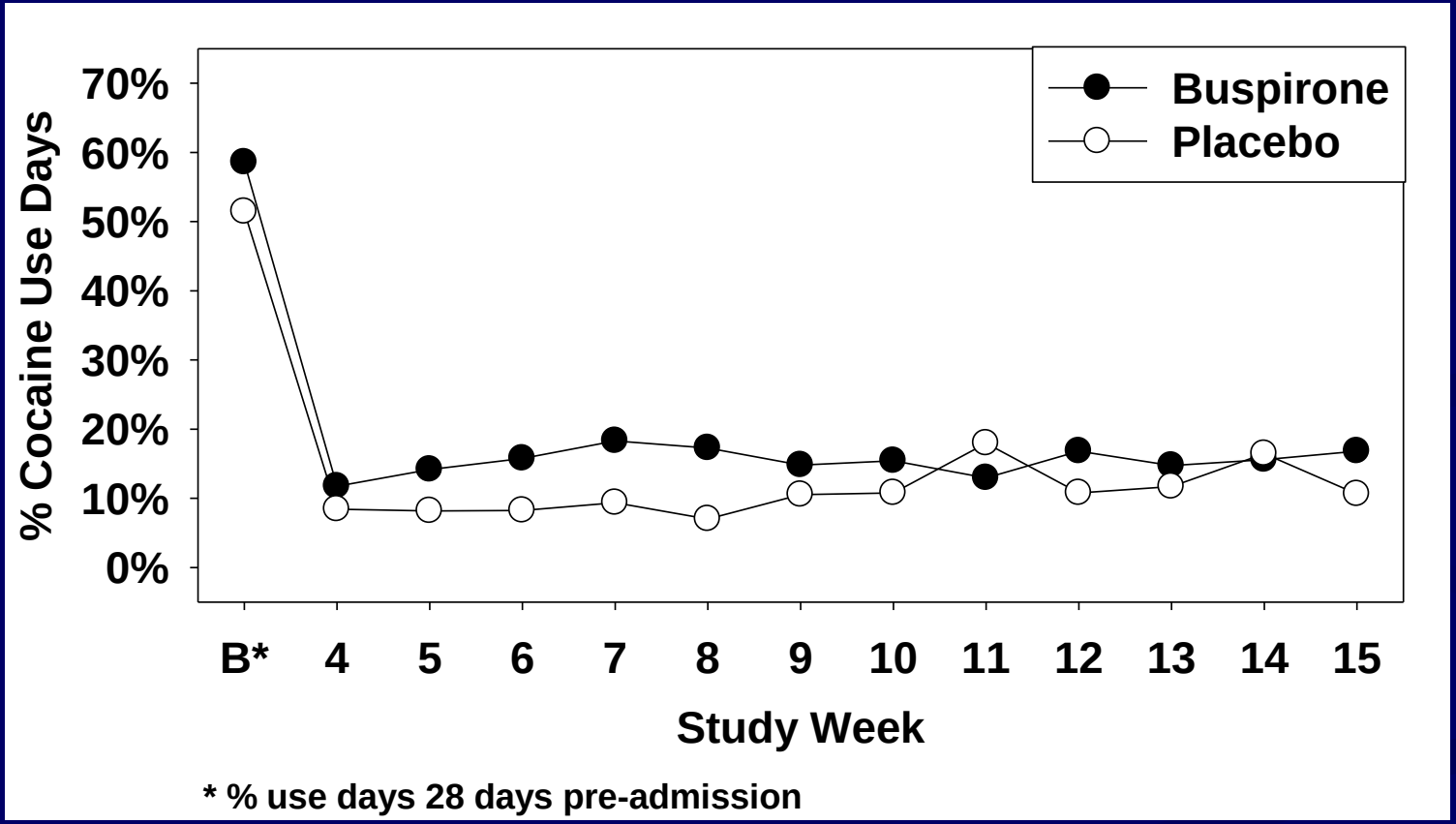
Days to First Cocaine Use

- No significant treatment effect (X^2_1=0.15, p=.70)



Proportion of Cocaine Use Days

- Significant treatment x time effect (X^2_1=6.06, p=.01)



Subgroup of Interest: Gender

- Pre-clinical buspirone studies completed only in males
- Evidence that gender plays a significant role in DA function (Poth et al., 2010; Riccardi et al., 2011)
- Male monkeys who become dominant have an increase in DA D_2/D_3 receptors and evidence less vulnerability to the reinforcing effects of cocaine
- Female monkeys who become dominant also have an increase in DA D_2/D_3 receptors but evidence more vulnerability to cocaine (Nader et al., 2012)

Primary Outcome as a Function of Treatment and Gender

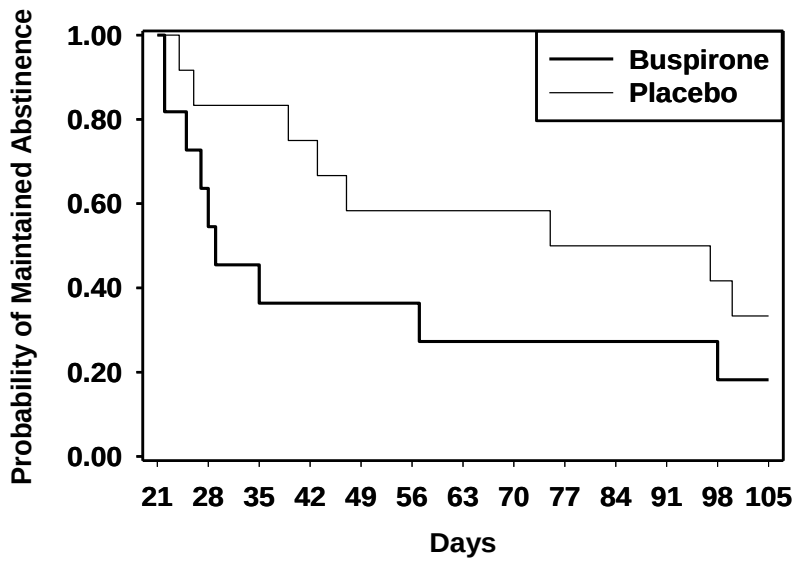
- The sample size for gender analyses limited – n=23 for females and n=39 for males

- No significant treatment effect for females or males on maximum days of continuous cocaine abstinence

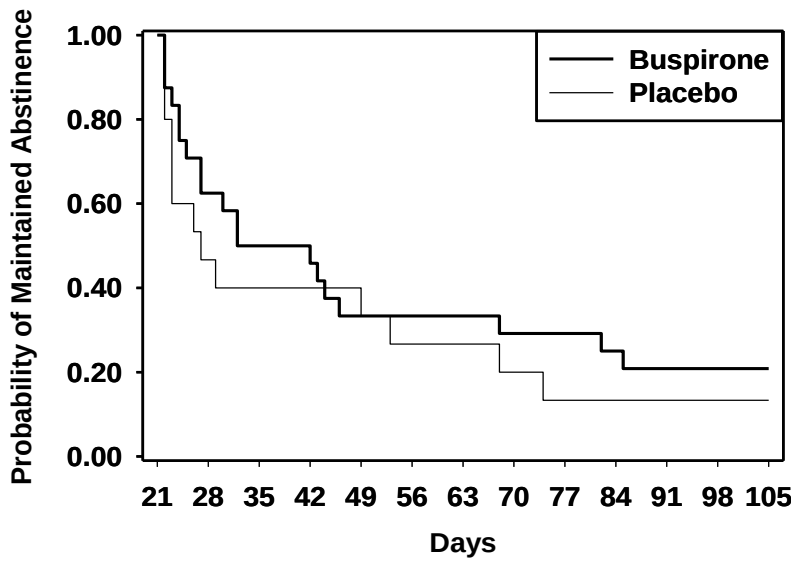
Days to First Cocaine Use by Treatment & Gender

- Females: Treatment (X^2=3.20, p=.067)
- Males: Treatment (X^2=1.40, p=.24)

Females (N=23)

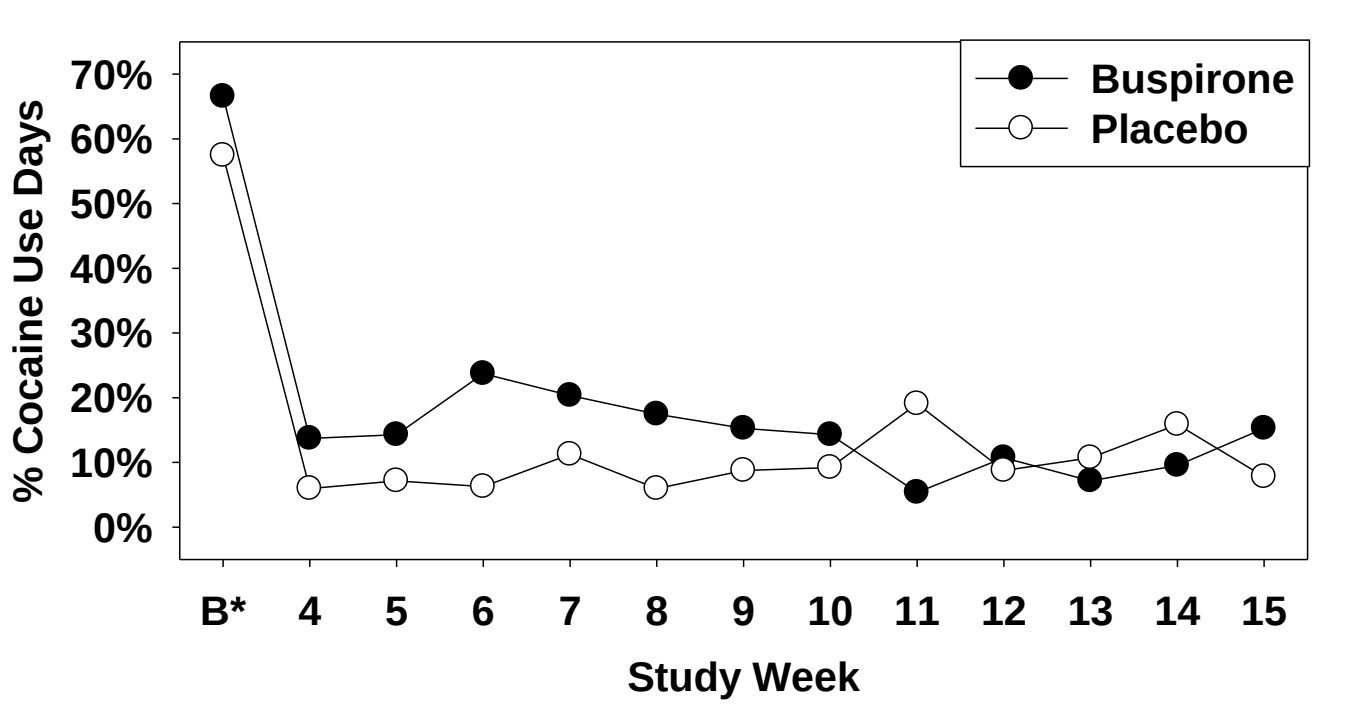


Males (N=35)



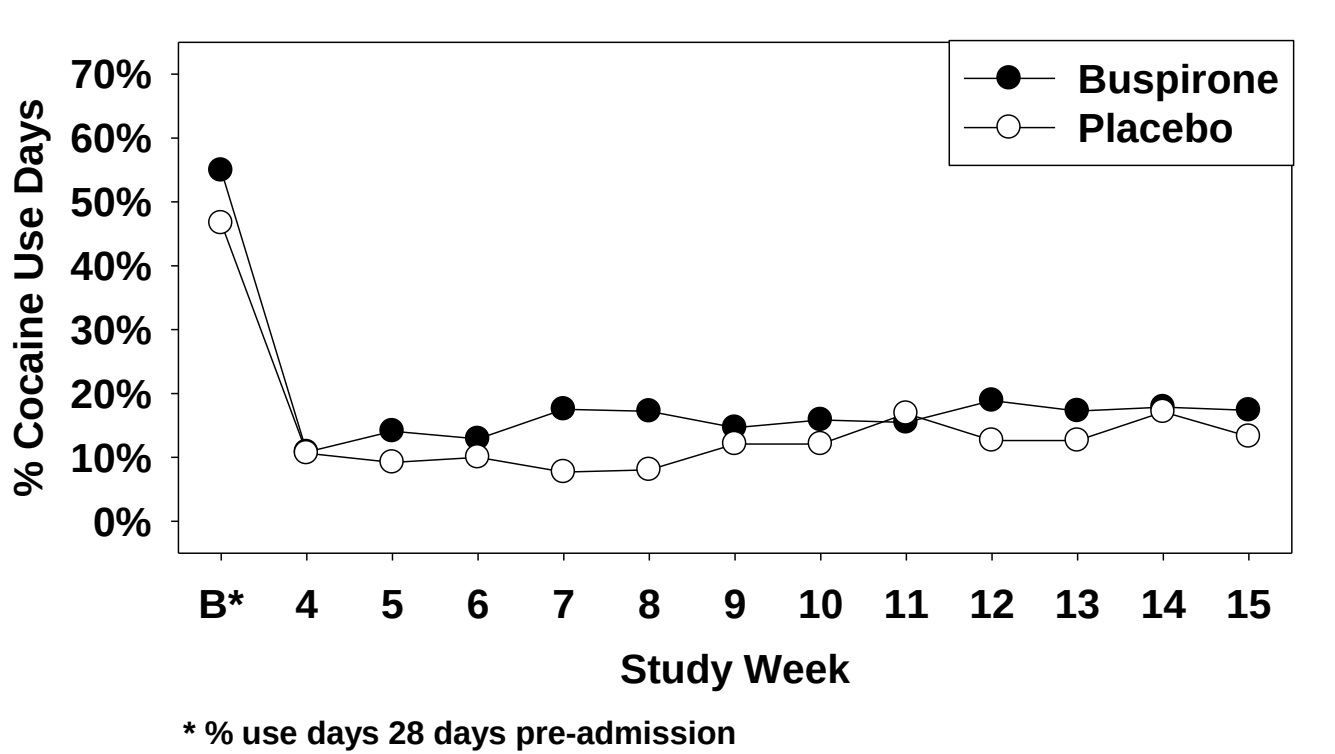
Proportion of Cocaine Use Days (Females)

- Significant treatment x time effect (X^2_1=15.26, p<.0001)



Proportion of Cocaine Use Days (Males)

- No Significant treatment (p=.91) or treatment x time (p=.70) effect



Discussion

- This pilot trial was the first to evaluate buspirone as a relapse-prevention treatment for cocaine dependence
- Results revealed no beneficial effect of buspirone on relapse and a significant negative effect on cocaine-use days in women
- These findings are inconsistent with pre-clinical research, conducted only with males
- Results consistent with findings of no significant buspirone effect on ongoing cocaine use in a small outpatient trial

Discussion

- Study strengths:
  - High completion rate (94%)
  - Medication adherence was good
  - Low rate of missed visits (4.4%)

- Primary limitation:
  - Small sample size

Conclusions

- Buspirone does not appear to be an effective relapse prevention treatment for cocaine dependence and may have a significant negative effect on cocaine-use outcomes in cocaine-dependent women

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