

# A preliminary randomized, double-blind, placebo-controlled study of the safety and efficacy of ondansetron in the treatment of cocaine dependence

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## Abstract

Prior studies have demonstrated inefficacy among dopamine receptor antagonists for treating cocaine dependence. An alternative approach would be to investigate the ability of indirect inhibitors of cortico-mesolimbic dopamine release, such as the 5-HT<sub>3</sub> receptor antagonist ondansetron, to reduce cocaine's reinforcing effects. We hypothesized that ondansetron might be more efficacious than placebo at reducing cocaine intake and promoting abstinence in cocaine-dependent individuals. In a pilot randomized, double-blind, 10-week controlled trial, 63 treatment-seeking, cocaine-dependent men and women received ondansetron (0.25 mg, 1.0 mg, or 4.0 mg twice daily) or placebo. Up to three times per week, participants were assessed on several measures of cocaine use, including urine benzoylecgonine. Cognitive behavioral therapy was administered weekly. Ondansetron was well tolerated, causing no serious adverse events. The ondansetron 4.0 mg group had the lowest dropout rate among all treatment groups and a greater rate of improvement in percentage of participants with a cocaine-free week compared with the placebo group ( $p=0.02$ ), whereas the ondansetron 1.0 mg group had a lower rate of improvement in percentage of weekly mean non-use days than did placebo recipients ( $p=0.04$ ). These results suggest the possibility of a non-linear dose–response function, with evidence supporting efficacy for the 4.0 mg group.

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## 1. Introduction

Cocaine dependence and its psychiatric, social, and economic sequelae constitute a major public health problem in the US (Mendelson and Mello, 1996). While behavioral and psychosocial interventions have remained the mainstay of treatment, high relapse rates are typical (Di Ciano and Everitt, 2002), and medical treatments directed at treating the underlying pathophysiology of cocaine-taking offer the promise of greater efficacy. Yet, despite almost two decades of scientific effort, no medication has been approved by the Food and Drug Administration for the treatment of cocaine dependence.

Cortico-mesolimbic dopamine (DA) neurons mediate the reinforcing effects of cocaine that are associated with its abuse liability (Weiss and Porrino, 2002). Nevertheless, the obvious approach of using direct DA receptor antagonists in the treatment of cocaine dependence has not been fruitful (Kreek et al., 2002). While the reasons for this inefficacy are not well understood, it is plausible that central monoaminergic pathways exhibit high adaptability and compensatory mechanisms (Hemby et al., 1997), thereby reversing any early treatment effects or therapeutic gains of direct DA antagonists. In any case, poor compliance with direct DA receptor antagonists, due to their propensity to induce unpleasant adverse events (e.g., extrapyramidal symptoms) by non-selectively altering baseline DA function, limits their practical utility as treatment for cocaine dependence. Hence, an alternative scientific approach is needed. Logically, such an approach should include examination of the

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efficacy of indirect inhibitors of cortico-mesolimbic function, rather than direct DA antagonists, in the treatment of cocaine dependence.

Serotonin-3 (5-HT<sub>3</sub>) receptors co-localized with gamma-amino-butyric acid interneurons are indirect inhibitors of cortico-mesolimbic DA release (Bloom and Morales, 1998). It is, therefore, of scientific interest that 5-HT<sub>3</sub> receptor antagonists such as ondansetron, presumably by attenuating the suprabasal release of cortico-mesolimbic DA, have been shown to reduce the reinforcing effects of a variety of abused drugs including alcohol and amphetamines (Costall et al., 1987; Di Chiara and Imperato, 1988; McBride and Li, 1998; Sellers et al., 1992). Direct study of the anti-reinforcing effects of 5-HT<sub>3</sub> antagonists on cocaine-taking has, however, yielded some equivocal results. While 5-HT<sub>3</sub> antagonists reduce cocaine-induced extracellular DA release (Kankaanpaa et al., 1996; McNeish et al., 1993) and locomotion (Kankaanpaa et al., 1996; McNeish et al., 1993; Reith, 1990; Svingos and Hitzemann, 1992), they do not appear to attenuate cocaine-induced self-administration (Kankaanpaa et al., 1996; Lane et al., 1992; McNeish et al., 1993; Peltier and Schenk, 1991; Reith, 1990; Svingos and Hitzemann, 1992). Nevertheless, 5-HT<sub>3</sub> antagonists have been reported to reduce conditioned place preference for cocaine (Suzuki et al., 1992) cf. (Cervo et al., 1996), diminish the development of behavioral tolerance and sensitization to cocaine following a period of acute withdrawal (King et al., 1998) by down-regulation of 5-HT<sub>3</sub> receptors in the nucleus accumbens (King et al., 1999), and decrease discomfort or post-cessation anxiety following psychostimulant withdrawal (Costall et al., 1990a,b). In humans, the 5-HT<sub>3</sub> antagonist, ondansetron, also has been shown to inhibit right orbitofrontal cortex increases in neuronal activation and cerebral blood flow in recently withdrawn cocaine addicts (Adinoff, 2004). It is, therefore, reasonable to propose that when considered with the preclinical data (King et al., 2000), ondansetron might aid the restoration of normative DA function during the period of recent withdrawal from cocaine use, and thus decrease the potential for relapse to drug-taking. Taken together, these data suggest that 5-HT<sub>3</sub> antagonists such as ondansetron might impair the maintenance of preference for cocaine and reduce the likelihood of relapse to cocaine following cessation of its use.

As a proof-of-concept test of this hypothesis, we conducted a pilot randomized, double-blind, 10-week controlled, dose-ranging trial to determine whether ondansetron (0.25 mg, 1.0 mg, or 4.0 mg twice daily) would be more efficacious than placebo at reducing cocaine intake and promoting abstinence among cocaine-dependent individuals.

## 2. Methods

### 2.1. Participants

We enrolled 63 men and women with a primary diagnosis of cocaine dependence according to the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV) (American Psychiatric Association, 1994). During a 2-week baseline period, enrolled participants also had to provide up to six urine samples (three per week); at least one out of a minimum of four samples had

to test positive for the major cocaine metabolite, benzoylecgonine (BE). We included individuals with secondary diagnoses of alcohol, caffeine, tobacco, marijuana, or amphetamine abuse or dependence as long as the participants could provide urine samples free of these and other drugs and an alcohol-free breath sample without exhibiting any physical signs of withdrawal at the time of enrollment. Other forms of drug dependence were excluded. Participants were treatment-seeking individuals  $\geq 18$  years of age who had agreed to attend the clinic three times per week for monitoring and once during one of those visits for psychosocial intervention. They were in good physical health as determined by physical and laboratory examinations (i.e., hematological assessment, biochemistry, and urinalysis) including electrocardiographic studies. We excluded individuals with current diagnoses of bipolar or psychotic disorders or other Axis I disorders requiring treatment, including major depression. We also did not study individuals who were mandated by the courts to be treated for cocaine dependence, were pregnant or not using an acceptable form of contraception (i.e., oral contraceptive, hormonal or surgical implant, sterilization, or spermicide and barrier), were taking psychotropic medication that could interfere with ondansetron, were using opiate substitutes within 6 months of enrollment, were asthmatic, or had AIDS.

Ethics approval was provided by the institutional review board at The University of Texas Health Science Center at San Antonio (UTHSCSA). Participants were recruited between July 2001 and September 2002 by newspaper, television, or radio advertisements.

### 2.2. General procedures

Within 1 month prior to randomization, participants provided written informed consent and began a screening and baseline period. Their physical health was assessed by medical history, physical examination, vital signs (i.e., blood pressure, pulse, and temperature), 12-lead electrocardiogram, laboratory studies (including hematology, chemistry, drug testing, breath alcohol concentration, urine pregnancy test, infectious disease panel, and optional HIV test), and adverse events. Psychiatric diagnoses were determined by the structured clinical interview for DSM-IV (First et al., 1994), and the measure of cocaine use was the cocaine timeline follow-back (Sobell and Sobell, 1992). Drug-related symptoms and sequelae were assessed by the substance use inventory (SUI) (Sobell et al., 1980), cocaine selective severity assessment (Kampman et al., 1998), cocaine craving questionnaire-now (Tiffany et al., 1993), brief substance craving scale (Mezinskis et al., 1998), clinical global impression-observer (National Institute of Mental Health, 1976), clinical global impression-self (National Institute of Mental Health, 1976), sensation-seeking scale (Zuckerman and Link, 1968), and Barratt impulsivity scale (Barratt, 1965). During the screening and baseline period, participants reported to the clinic 3 days per week, and study entrance criteria – which were made known to the participants – required them to provide four to six urine samples during the 14 days prior to randomization, at least one of which had to be positive for cocaine (i.e., BE). Even if the first urine was positive for BE, an attempt was made to collect all six samples. Participants who failed to provide the required four urine specimens – including at least one positive specimen for BE – during their first 2 weeks were allowed another 16 days to meet this criterion (i.e., for such participants, the baseline period was extended to 30 days).

We enrolled eligible participants for double-blind treatment at the beginning of week 1 after a review of the diagnostic, physical health-related, and urine drug screen data. At that visit, we also collected data on adverse events, concomitant medications, vital signs, cocaine selective severity assessment, clinical global impression-observer, clinical global impression-self, brief substance craving scale, SUI, urine BE, and creatinine, with the latter three being measured two to three times per week. All the measures were repeated weekly for 7 weeks (i.e., through week 8). Additionally, all the physical health-related checks were repeated at weeks 4 and 8. The weekly study requirements were completed during the first visit each week, except for cognitive behavioral therapy (CBT), which could be scheduled on a second or third visit. Participants received US\$ 10 as compensation for each visit, plus an extra US\$ 10 bonus if they came in for all three visits in a week. Double-blind treatment was concluded at the end of week 8. At week 12, a post-treatment follow-up visit was conducted to ascertain cocaine timeline follow-back, adverse events, concomitant medications, SUI, urine BE, and creatinine.

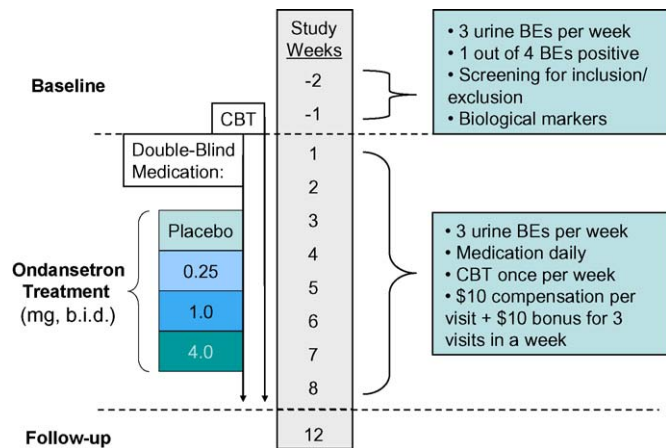


Fig. 1. Study design. BE: benzoylcegonine test; CBT: cognitive behavioral therapy.

### 2.3. Study design and randomization plan

This was a double-blind, placebo-controlled, randomized, four-arm, dose-ranging study comparing three dose levels of ondansetron (0.25 mg, 1.0 mg, and 4.0 mg twice daily) with placebo administered to cocaine-dependent outpatients (see Fig. 1).

Stratified randomization was used to balance treatment groups with respect to diagnosis of alcohol abuse/dependence, age at onset of cocaine use [early onset (<18 years) versus late onset ( $\geq$ 18 years)], and frequency of cocaine use [current high use (>18 days of use in the last 30 days) versus current low use ( $\leq$ 18 days of use in the last 30 days)]. Alcohol abuse/dependence diagnosis was an important stratum because alcohol abuse is highly comorbid in this population and ondansetron may affect cocaine use indirectly through changes in alcohol use. Age at onset of cocaine use was also selected as a stratum as this was an important variable in a previous trial (Sigmon et al., 1999). The randomization process was performed by computer at the National Institute on Drug Abuse data coordinating center. Treatment assignments were provided to the study pharmacist at UTHSCSA for investigational agent preparation.

### 2.4. Medication: procurement, preparation, and dosing

Ondansetron was purchased from GlaxoSmithKline as 8-mg tablets. These were crushed and formulated into size 1 opaque gelatin capsules containing cornstarch plus 0.25 mg, 1 mg, or 4 mg of ondansetron by the research pharmacist at UTHSCSA; placebo capsules contained only cornstarch. Our procedures for the reconstitution of ondansetron tablets into gelatin capsules have been validated previously (Lam et al., 2004). The research pharmacist had no contact with participants or clinical staff and maintained the double-blind dose codes for individual participants. From weeks 1 to 8, we dispensed study medication (placebo, 0.25 mg, 1 mg, or 4 mg twice daily) in a double-blind fashion using blister packs labeled with identification, study visit number, and date. The returned packs at each weekly visit were used to calculate the pill count.

### 2.5. Psychosocial treatment

CBT, an effective psychosocial intervention for the treatment of cocaine dependence (Covi et al., 2002; Maude-Griffin et al., 1998), was provided to all participants as a method for enhancing protocol compliance and teaching skills to prevent relapse. CBT was delivered to all participants in 1-h sessions each week from weeks 1 to 8 by trained doctoral-level therapists, who followed a standardized manual developed at the Boston Behavioral Treatment Training Center at Boston University. During these sessions, emergency counseling and referral services were provided. Up to four emergency crisis management sessions were provided if needed. All therapy sessions were audiotaped and a random selection reviewed to monitor therapist drift and to ensure adherence to the format of procedures in the manual.

### 2.6. Reporting of adverse events

Adverse event case report forms were filled out each week by a nurse or physician who saw and spoke with the patient. A study physician conducted a weekly review of the case report forms, and if an adverse event was recorded on a form, he or she met with the patient to discuss it. The study physician used his or her best judgment to determine not only the severity of an adverse event but also the relatedness of the event to the medication, according to the known pharmacology and toxicology of the medication, the timing of the event after administration of the medication, and whether or not there could be alternative explanations for the event.

### 2.7. Monitoring procedures

The research team members, including the principal investigator, co-investigators, nurse practitioner, project coordinator, database manager, and physicians involved in the study, met weekly to discuss the progress of the study and to address any issues pertaining to research and database procedures (e.g., data collection and data entry). Discussions also dealt with recruitment, enrollment, adverse events, and any safety procedures for handling and minimizing the occurrence of such adverse events.

### 2.8. Primary outcome measures

Three primary outcome measures were selected to test the efficacy of various doses of ondansetron in reducing cocaine use: (1) weekly mean proportion of cocaine non-use days as assessed by self-reported use and confirmed by urine BE determination, (2) weekly proportion of cocaine-free urine specimens over the 8 weeks of treatment, and (3) number of cocaine-free urine specimens provided over the 8 weeks of treatment.

The proportion of cocaine non-use days was selected as a primary outcome measure based on a recommendation resulting from a meeting of the College on Problems of Drug Dependence on April 28–29, 1999. Cocaine use and non-use days were defined by participants' self-reported use, confirmed or disproved by quantification of urine BE. For the primary efficacy response, each day of the 8-week study period was coded as either a use or a non-use day based on self-reports and on the urine BE data. Three urine collection days were scheduled per calendar week. The first day of week 1 and the last day of week 8 on which the participant received the investigational agent were not scored as use or non-use days because of the scoring rules. Thus, each participant had a maximum of 54 study days over the course of the 8-week study.

Due to the pharmacokinetics of cocaine and BE, carryover from previous cocaine use would be difficult to distinguish in the laboratory from new use. The rules enunciated by Preston et al. (1997), modified to meet the conditions of this study (Rules 1–5 below), facilitated classification of each assessment day as use or non-use. "New use" was indicated if the participant reported new use (Rule 0) or if the participant's self-report claimed no new use but any of the following applied: an increase in cocaine metabolite concentration over the concentration of the preceding urine specimen to any value  $>300$  ng/ml (Rule 1); cocaine metabolite concentration  $>300$  ng/ml and greater than half the concentration measured in the preceding urine specimen (Rule 2); cocaine metabolite concentration  $>300$  ng/ml in the first urine specimen collected in the study (Rule 3); the previous urine specimen was collected more than two calendar days before a urine specimen with cocaine metabolite concentration  $>300$  ng/ml (Rule 4); or creatinine  $<20$  mg/dl and cocaine metabolite/creatinine ratio increased since the previous specimen (cocaine metabolite does not have to be  $>300$  ng/ml) (Rule 5). Assessment days occasionally could be  $<48$  h apart in this study. For this reason, the Preston et al. (1997) rules were modified to delete reference to a previous urine specimen collected  $\geq 48$  h earlier.

Self-report gave preliminary determination of each day as a use or non-use day. Non-use days were confirmed or disproved by the urine BE data as follows: (1) the participant reported no new use since the last urine BE or within the preceding 72 h (whichever was the shorter time frame), but urine BE showed new use, in which case we scored the preceding day as a use day, (2) self-reported days of non-use were considered as missing if not followed by a urine BE assessment within 7 days; in the case of obtaining urine within 7 days, data also were considered as missing if the concordance rate between self-report and

urine BE for the individual was <70%, and (3) self-reported use was accepted in all cases.

The percentage of non-concordance between self-reported use and urine BE data was calculated for each study participant as the percentage of the number of days that were scored as use days based on urine BE data overruling self-report (according to criteria in #1 immediately above) divided by the total number of urine samples analyzed, as follows: (a) percent non-concordance = non-concordant use days/total urine samples analyzed  $\times$  100%, and (b) percent concordance = 100 – percent non-concordance. The concordance rate of <70% was established as a self-report data verification factor based on a survey of data sets from recently completed National Institute on Drug Abuse studies showing that mean concordance rates ranged from 70% to 90%.

The second primary outcome measure for each participant was the weekly proportion of cocaine-free urine samples, defined as those having urine BE levels <300 ng/ml. Three urine collection days were scheduled per calendar week. The weekly cocaine-free sample was recorded as “0” if all three urine BE levels in the week were <300 ng/ml. It was recorded as “1” if the proportion of weekly cocaine-free samples was between 0.67 and 0.75, inclusive. It was recorded as “2” if the proportion of weekly cocaine-free samples was between 0.33 and 0.5, inclusive. It was recorded as “3” if the proportion of weekly cocaine-free samples was 0.

The third primary outcome measure for each participant was the total number of cocaine-free urine specimens (BE <300 ng/ml) provided over the 8-week study period.

### 2.9. Statistical analysis

Descriptive variables were characterized as their mean  $\pm$  standard deviation. For inferential analyses, each primary and secondary outcome measure was analyzed using appropriate methods for the intent-to-treat population. The general analytic strategy was to determine whether there was a differential effect of ondansetron dose compared with placebo. The individual effects, if any, of ondansetron dose level, number of days of cocaine use in the last 30 days ( $\leq 18$  and  $>18$ ), age at onset of cocaine use [actual age or categorical (young versus old)], gender, diagnosis of attention deficit disorder, baseline severity of depression (24-item Hamilton depression rating scale score  $\leq 15$  and  $>15$ ), and their first-order interactions on the primary treatment effects were determined where numbers permitted it. We did not attempt to determine the effect of two or more of these variables acting together. For normally distributed data, this involved the use of generalized estimating equations (GEE) (Liang and Zeger, 1986) to fit a line to the outcomes that allowed for possible differences among study arms in mean response at randomization (end of baseline, defined as time “0”) as well as for differences among study arms in slopes of time over the active treatment period. Hence, the slopes represented the rate of change over the post-randomization period. For non-normally distributed data, the appropriate categorical test was used. All statistical tests were two-sided at a 5% Type I error rate.

## 3. Results

### 3.1. Participants

Table 1 shows the participants’ demographic and alcohol and cocaine use characteristics at baseline, by ondansetron treatment group. No significant demographic characteristics differed between groups. The ondansetron 4.0 mg group did, however, appear to include participants with the most severe psychopathology related to alcohol and cocaine consumption. Briefly, the participants were mostly male ( $n = 55$ ; 87%), Hispanic ( $n = 28$ ; 44%), and employed full-time ( $n = 36$ ; 57%), and had on average a 12th-grade education and a mean  $\pm$  S.D. age of  $36.1 \pm 8.0$  years. All were dependent on cocaine; the average number of days of cocaine use in the 14 days prior to enrollment ranged from 5.1 to 8.3.

### 3.2. Primary outcome measures

The differences between treatment groups in linear slopes of weekly mean proportion of non-use days over the active treatment period were analyzed using GEE. On fitting the slopes, we allowed for differences in mean proportions at baseline (intercept). The ondansetron 0.25 mg and 1.0 mg groups had a higher percentage of non-use days than the ondansetron 4.0 mg and placebo groups at baseline. No difference was detected between slopes of the ondansetron 0.25 mg or 4.0 mg group and the placebo group (both  $p$ -values  $> 0.66$ ). The rate of increase (i.e., slope) of the percentage of non-use days for the ondansetron 1.0 mg group was significantly lower than that for the placebo group ( $p = 0.04$ ).

Table 2 shows the percentage of participants with a cocaine-free study week (defined as a week in which all urine BE samples in the week are <300 ng/ml), by study week and ondansetron treatment group. Data were fitted by GEE assuming a logistic model. Fig. 2 is the plot of the percentage of participants with a cocaine-free study week along with the GEE fitted lines. No difference in linear slope (logistic scale) was detected between the ondansetron 0.25 mg or 1.0 mg group and the placebo group ( $p > 0.55$ ). The ondansetron 4.0 mg group, however, showed a significantly better rate of change (slope) for cocaine-free weeks than did the placebo group ( $p = 0.02$ ).

As there were differences between groups in the average number of urine specimens provided during the 8-week treatment period (range, 7.63–10.42), we examined the percentage of cocaine-free urine specimens. No difference was detected among the four groups in the percentage of cocaine-free urine specimens during the treatment period (non-parametric Kruskal–Wallis test,  $p = 0.56$ ).

### 3.3. Treatment retention

The dropout rate in the ondansetron 4.0 mg group (53%) was the lowest among all four treatment groups. The dropout rate for the ondansetron 0.25 mg, 1.0 mg, and placebo groups combined was over 65% at the end of the study. The ondansetron 1.0 mg and 4.0 mg groups had the lowest (12) and highest (19) numbers of participants, respectively, who received treatment following randomization. No between-group contrasts achieved statistical significance.

### 3.4. Medication compliance

Medication compliance rate (number of tablets prescribed/number of tablets taken  $\times$  100) was similar across all treatment groups: 73.3%, 75.6%, 70.7%, and 70.3% for the placebo, ondansetron 0.25 mg, ondansetron 1.0 mg, and ondansetron 4.0 mg groups, respectively.

### 3.5. Adverse events

From Table 3, it can be seen that ondansetron was well tolerated, and the only side effect reported significantly more frequently than with placebo was constipation. That is, increased

Table 1  
Baseline demographic characteristics and drug use histories of cocaine-dependent participants, by treatment group

Variable	Ondansetron treatment group				
	Placebo (n = 16)	0.25 mg (n = 16)	1.0 mg (n = 12)	4.0 mg (n = 19)	Total (n = 63)
Age (years) <sup>a,b</sup>	36.1 (6.6)	32.6 (9.1)	38.3 (10.9)	37.6 (5.2)	36.1 (8.0)
Sex distribution <sup>c,b</sup>					
Male	14 (88)	15 (94)	12 (100)	14 (74)	55 (87)
Female	2 (13)	1 (6)	0 (0)	5 (26)	8 (13)
Race <sup>c,b</sup>					
White	4 (25)	9 (56)	5 (42)	6 (32)	24 (38)
Hispanic	9 (56)	6 (38)	6 (50)	7 (37)	28 (44)
Black	2 (13)	1 (6)	1 (8)	6 (32)	10 (16)
Other	1 (6)	0 (0)	0 (0)	0 (0)	1 (2)
Height (cm) <sup>a,d</sup>	173.4 (9.4)	174.5 (8.4)	175.7 (7.3)	173.1 (10.9)	174.0 (9.2)
Weight (kg) <sup>a,d</sup>	84.7 (16.5)	83.8 (21.4)	89.3 (19.0)	80.0 (21.3)	83.9 (19.6)
Years of education <sup>a,b</sup>	12.7 (2.3)	12.1 (2.1)	13.7 (1.8)	12.6 (1.4)	12.7 (1.9)
Depression (Hamilton depression rating scale total score >15) <sup>c,e</sup>					
Yes	3 (19)	2 (13)	1 (8)	2 (11)	8 (13)
No	13 (81)	14 (88)	11 (92)	17 (89)	55 (87)
Hamilton depression rating scale total score at baseline <sup>a,e</sup>	7.8 (6.2)	7.6 (6.6)	5.8 (6.0)	6.8 (6.0)	7.1 (6.1)
Diagnosis of alcohol abuse or dependence <sup>c,f</sup>					
Yes	7 (44)	5 (31)	5 (42)	6 (32)	23 (37)
No	9 (56)	11 (69)	7 (58)	13 (68)	40 (63)
Age at onset of alcohol use (years) <sup>a,g</sup>	16.5 (2.9)	17.3 (3.7)	17.0 (3.8)	15.8 (2.4)	16.6 (3.2)
Days of alcohol use in last 30 days <sup>a,b</sup>	11.4 (10.2)	8.9 (10.7)	10.9 (8.3)	12.4 (9.9)	11.0 (9.8)
Age at onset of cocaine use (years) <sup>a,g</sup>	24.3 (6.6)	24.5 (8.2)	26.4 (12.4)	23.5 (6.3)	24.5 (8.2)
Days of cocaine use in last 30 days <sup>a,b</sup>	17.8 (10.2)	16.5 (9.9)	13.3 (8.9)	18.8 (9.0)	16.9 (9.5)
Lifetime years of cocaine use <sup>a,h</sup>	11.2 (7.9)	7.5 (7.7)	9.9 (7.0)	12.7 (5.6)	10.5 (7.2)
Cocaine route of administration <sup>c,h</sup>					
Intranasally	8 (50)	8 (50)	6 (50)	6 (32)	28 (44)
By smoking	8 (50)	4 (25)	2 (17)	11 (58)	25 (40)
Intravenously	0 (0)	4 (25)	4 (33)	2 (11)	10 (16)
Dollars spent on drugs in last 30 days <sup>a,h</sup>	1070.6 (997.3)	704.4 (717.6)	633.3 (692.3)	540.0 (384.3)	734.3 (732.2)
Number of lifetime drug abuse treatments <sup>a,h</sup>	0.2 (0.4)	1.2 (2.7)	1.0 (1.5)	1.2 (2.2)	0.9 (1.9)

Note: Few individuals had secondary diagnoses other than alcohol or nicotine abuse or dependence, and the frequency did not differ by treatment group (data not shown).

<sup>a</sup> Values represent mean (standard deviation).

<sup>b</sup> Source: Demographics form.

<sup>c</sup> Values represent *n* (%).

<sup>d</sup> Source: Physical examination form.

<sup>e</sup> Source: Hamilton depression rating scale form.

<sup>f</sup> Source: Structured clinical interview for DSM-IV form.

<sup>g</sup> Source: Quantity and frequency interview form.

<sup>h</sup> Source: Addiction severity index form.

Table 2  
Percentage of participants with a cocaine-free study week based on urine benzoylecgonine

Ondansetron treatment group	Baseline study week		Study week								Baseline	Weeks 1–8
	–2	–1	1	2	3	4	5	6	7	8		
Placebo	0 (11)	33.33 (6)	12.5 (16)	6.25 (16)	15.38 (13)	7.14 (14)	20 (10)	22.22 (9)	14.29 (7)	0 (5)	11.76	12.22
0.25 mg	23.08 (13)	40 (5)	18.75 (16)	23.08 (13)	18.18 (11)	22.22 (9)	0 (9)	25 (8)	42.86 (7)	50 (4)	27.78	22.08
1.0 mg	36.36 (11)	40 (5)	25 (12)	36.36 (11)	30 (10)	33.33 (9)	37.5 (8)	16.67 (6)	16.67 (6)	0 (4)	37.5	27.27
4.0 mg	5.88 (17)	28.57 (7)	0 (19)	0 (16)	11.76 (17)	7.14 (14)	16.67 (12)	27.27 (11)	33.33 (9)	40 (10)	12.5	13.89

Values not in parentheses represent the percentage of participants with a cocaine-free study week; i.e., all urine benzoylecgonine samples in that week were <300 ng/ml. Values in parentheses represent the sample size for that week. There was no difference between the 0.25 mg or 1.0 mg group and the placebo group on the rate of change over weeks 1–8 for the proportion of non-use days ( $P > 0.55$ , generalized estimating equations). The 4.0 mg group showed significant improvement from the placebo group on the rate of change over weeks 1–8 for cocaine-free week ( $P = 0.02$ , generalized estimating equations).

Table 3  
Adverse events

Adverse event	Ondansetron treatment group				
	Placebo (n = 16)	0.25 mg (n = 17)	1.0 mg (n = 13)	4.0 mg (n = 19)	Total (n = 65)
Headache NOS	6	7	4	9	26
Constipation	2	1	3	9*	15
Upper respiratory infection	3	3	2	7	15
Somnolence	2	2	2	3	9
Diarrhea NOS	2	4	1	1	8
Nausea	1	2	1	4	8
Abdominal pain NOS	1	2	0	3	6
Eye pain	2	3	0	1	6
Serious adverse event	0	1	0	0	1

Only 49 participants reported a total of 140 adverse events that were at least “remotely” related to the medication. Only one participant reported a serious adverse event, which was “definitely not” related to the medication. NOS: not otherwise specified.

\*  $P < 0.02$ .

constipation was reported for the ondansetron 4 mg group; this symptom did not require any specific medical treatment. No serious adverse events resulting from the medication were reported, and no deaths occurred.

#### 4. Discussion

Our results showed that ondansetron 4.0 mg twice daily was associated with a significantly greater rate of improvement in the percentage of participants with a cocaine-free week compared with placebo. This finding is made more notable by the fact that the ondansetron 4.0 mg group included the participants with the most severe patterns of cocaine use and psychopathology. Indeed, the effect size of the ondansetron 4.0 mg treatment response (data not shown) appears to be similar to the order of magnitude described for naltrexone in treating alcohol dependence (Kranzler and Van Kirk, 2001), thereby illustrating the practical and clinical significance of

our findings. In contrast, the ondansetron 1.0 mg group had a significantly lower rate of improvement than the placebo group in the percentage of weekly mean non-use days. Taken together, this would suggest the possibility of a non-linear dose–response function for ondansetron in treating cocaine dependence, with efficacy being seen at a high dose while a lower dose might be associated with some worsening in clinical condition. A non-linear dose–response characteristic for ondansetron has been described previously in both animal (Goudie and Leathley, 1990) and human (Sellers et al., 1994) studies. Regardless of the shape of the dose–response curve, these data suggest that at 4.0 mg or higher doses, ondansetron might be a promising medication for treating cocaine dependence.

Clearly, our results do have limitations that should lead to caution with their interpretation. These include the relatively high drop-out rate, the small sample size per treatment group, differences in sample size among treatment groups at randomization, and some baseline differences at randomization.

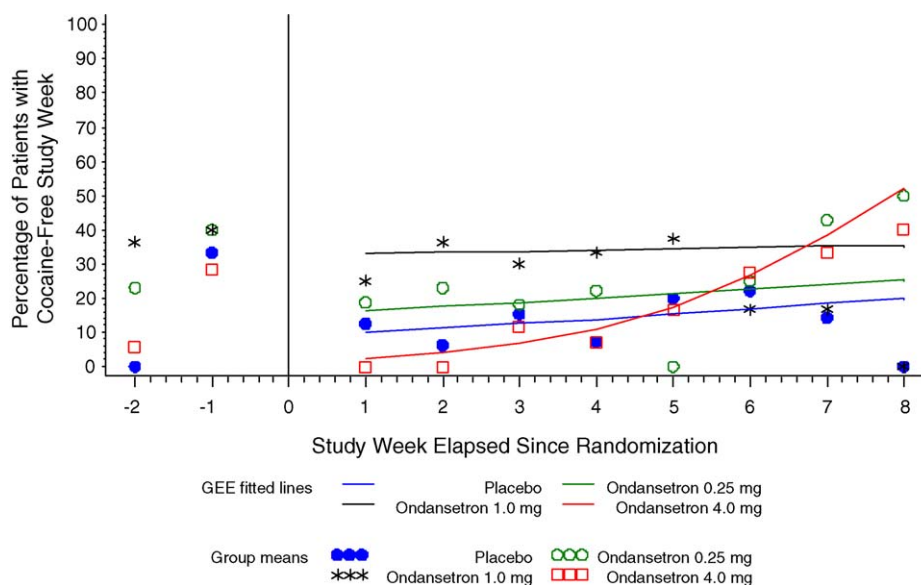


Fig. 2. Percentage of participants with a cocaine-free study week, as ascertained by the urine benzoyllecgonine test. Data are presented as group means and generalized estimating equations (GEE) fitted lines.

These limitations were brought about by the preliminary, dose-ranging nature of the study and by the fact that large cohorts are typically needed to balance treatment groups closely. Thus, it was not possible for us to determine whether or not certain factors, such as age at onset of alcohol or cocaine use, or both, may have influenced ondansetron treatment response.

Notably, ondansetron treatment was safe and well tolerated, with an unremarkable side-effect profile notwithstanding the minor incidence of constipation. This would suggest that if indeed there is a non-linear dose–response function for ondansetron in the treatment of cocaine dependence, future studies should test 4.0 mg or even higher doses to determine whether they would be associated with greater efficacy.

In summary, the results of this pilot study suggest that ondansetron 4.0 mg twice daily might be a promising candidate medication for treating cocaine dependence. Therefore, further larger scale, double-blind, controlled studies are needed to establish and extend these findings. Such studies would be particularly timely given the fact that there is, at present, no established pharmacotherapy for the treatment of cocaine dependence.

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