International Journal of Neuropsychopharmacology (2008), **11**, 1–14. Copyright © 2007 CINP
doi:10.1017/S1461145707007778

ARTICLE

CINP

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

Bankole A. Johnson[1], Nassima Ait-Daoud[1], Ahmed M. Elkashef[2], Edwina V. Smith[2], Roberta Kahn[2], Francis Vocci[2], Shou-Hua Li[2], Daniel A. Bloch[3] and the Methamphetamine Study Group*

[1] *Department of Psychiatry and Neurobehavioral Sciences, University of Virginia, Charlottesville, VA, USA*
[2] *Division of Pharmacotherapies and Medical Consequences of Drug Abuse, National Institute on Drug Abuse, National Institutes of Health, Bethesda, MD, USA*
[3] *Department of Health Research and Policy, Division of Biostatistics, Stanford University School of Medicine, Stanford, CA, USA*

Abstract

Methamphetamine dependence is an increasing public health problem in the United States. No efficacious medication for methamphetamine dependence has been developed. As ondansetron, a 5-HT_3 receptor antagonist and modulator of cortico-mesolimbic dopamine function, has been shown to reduce some of the rewarding effects of d-amphetamine in animal and human laboratory studies, we decided to test whether it would be superior to placebo at reducing methamphetamine use. In a preliminary, multi-site, randomized, double-blind, 8-wk controlled trial, 150 methamphetamine-dependent men and women received ondansetron (0.25 mg, 1 mg, or 4 mg b.i.d.) or placebo. Participants were assessed on several measures of methamphetamine use including urine methamphetamine level up to three times per week. As a psychosocial adjunct to the medication condition, cognitive behavioural therapy also was administered three times per week. Ondansetron was well tolerated and was less likely than placebo to be associated with serious adverse events. Nevertheless, none of the ondansetron doses was superior to placebo at decreasing any of the measures of methamphetamine use, withdrawal, craving, or clinical severity of methamphetamine dependence. Our preliminary results do not support the utility of ondansetron, at the doses tested, as a treatment for methamphetamine dependence. These findings should be viewed in light of the possibility that a less intensive cognitive behavioural therapy regimen might have yielded more positive results in this initial phase II trial exploring for the efficacy of ondansetron.

Received 17 March 2006; Reviewed 27 June 2006; Revised 30 January 2007; Accepted 19 March 2007; First published online 1 May 2007

Key words: Clinical trial, cognitive behavioural therapy, humans, methamphetamine dependence, ondansetron.

Introduction

In the United States, methamphetamine abuse is a major health problem (U.S. Department of Health and Human Services, 2005), particularly in the Pacific and western states (Anglin et al., 1998; Galloway et al., 1996). Recently, methamphetamine abuse has become of substantial concern in other regions of the nation. Results from the Substance Abuse and Mental Health Services Administration showed that the number of individuals who had sampled methamphetamine during their lifetime increased from 4.9 million in 1996 to an estimated 12 million in 2004 (U.S. Department of Health and Human Services, 1997, 2005). Among high-school seniors in 2004, the rate of methamphetamine use was about 3.4%, with 6.2% reporting lifetime use (Johnston et al., 2006). Further, the increased availability and production of methamphetamine in

Address for correspondence: B. A. Johnson, D.Sc., M.D., Ph.D., Alumni Professor and Chairman, Department of Psychiatry and Neurobehavioral Sciences, University of Virginia, PO Box 800623, Charlottesville, VA 22908-0623, USA.
Tel.: 434-924-5457 *Fax*: 434-244-7565
E-mail: bankolejohnson@virginia.edu
* Investigators in the Methamphetamine Study Group are listed in the Appendix.

diverse areas of the country, particularly rural areas, have prompted added concern about the proliferation of its use (Office of National Drug Control Policy, 2000). High rates of methamphetamine abuse also have been reported in other parts of the world including Great Britain (Klee, 1992, 1997), Japan (Suwaki, 1991; Suwaki et al., 1997), and Australia (Hando and Hall, 1994, 1997; Makkai and McAllister, 1993; Shearer et al., 2001). In Great Britain, methamphetamine abuse is considered of greater public health consequence than cocaine, especially in relation to the spread of HIV infection (Klee, 1997). In Japan, of the 20 000 drug offences reported each year, about 90% have been attributed to the Stimulants Control Law that specifically governs the use of methamphetamines (Yamamoto, 2004). In Australia, amphetamines are the second most frequently used drugs, after cannabis (Shearer et al., 2001).

The lack of efficacious pharmacological treatment for methamphetamine users has far-reaching health ramifications in terms of the consequences from continued drug use and increased potential for transmitting HIV as a generation of new users is engaging in highly risky sexual activities under its influence (Colfax and Shoptaw, 2005). Consequently, the development of effective treatments for methamphetamine abuse or dependence has become a pressing concern for the national and global drug abuse treatment community.

Despite a decade of intensive research, an efficacious pharmacotherapy for stimulant dependence remains elusive, with a noted lack of controlled clinical trials to test promising compounds for the treatment of methamphetamine abuse or dependence (Ling and Shoptaw, 1997; Vocci and Ling, 2005).

The reinforcing effects of methamphetamine associated with its abuse liability are mediated principally through facilitated cortico-mesolimbic dopamine (DA) neurotransmission (Carboni et al., 2001; Chevrette et al., 2002; Koob and Nestler, 1997; Lorrain et al., 1999). Hence, one novel approach would be to test whether the 5-HT_3 antagonist ondansetron, a modulator of cortico-mesolimbic DA function, would be an efficacious treatment for methamphetamine dependence. Currently, ondansetron is approved by the U.S. Food and Drug Administration for the prevention of nausea, particularly in those receiving chemotherapy (Rubenstein et al., 2006). Evidence supporting ondansetron's potential efficacy as a treatment for methamphetamine dependence includes (a) animal studies showing that ondansetron can attenuate: hyperlocomotion in the rat induced by intra-accumbens injection of DA (Bradbury et al., 1985) and other hyper-dopaminergic behaviours (Shankar et al., 2000), and 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), and (b) human laboratory studies showing that ondansetron can diminish some of the d-amphetamine-mediated increases in positive subjective mood and euphoria (Grady et al., 1996; Silverstone et al., 1992a) and anorexia (Silverstone et al., 1992b). Taken together, these animal and human laboratory studies demonstrated enough potential efficacy, in our view, to provide the rationale for pursuing a clinical trial.

In the present 8-wk, double-blind, preliminary, multi-site clinical trial, we sought to determine whether ondansetron (0.25 mg, 1 mg, and 4 mg orally b.i.d.) would be more efficacious than placebo as a treatment for methamphetamine dependence.

Methods

Participants

We enrolled 150 men and women who had been diagnosed with methamphetamine dependence according to DSM-IV criteria (APA, 1994). During the 2-wk baseline period, enrolled participants also had to provide 4–6 urine samples; at least one of the minimum of four samples had to test positive for the presence of methamphetamine. Participants were treatment-seeking individuals at least 18 years of age who had agreed to attend the clinic three times per week for monitoring and psychosocial intervention. They were in good physical health as determined by physical and laboratory examinations (i.e. haematological assessment, biochemistry, and urinalysis), including electrocardiographic studies.

We excluded individuals currently dependent, as defined by DSM-IV criteria, on any psychoactive substance besides methamphetamine, nicotine, or marijuana, and those with physiological dependence on alcohol or a sedative-hypnotic, e.g. a benzodiazepine requiring medical detoxification. We also excluded individuals with current diagnoses of anxiety, affective, or psychotic disorders. We did not study individuals who: were mandated by the courts to be treated for methamphetamine 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 2 months of enrolment, were asthmatic, or had AIDS.

We received ethics approval from the institutional review board at each of the six participating sites, which included: The University of Texas Health Science Center at San Antonio; Lutheran Hospital, Des Moines, Iowa; University of Hawaii at Manoa; South Bay Treatment Center, San Diego, California; University of Missouri-Kansas City, and Matrix Institute on Addictions, Costa Mesa, California. The multi-centre study was coordinated by the University of California, Los Angeles, Integrated Substance Abuse Programs. Study participants were recruited between August 2002 and July 2003 by newspaper, television, or radio advertisements.

General procedures

At baseline (weeks −4 to 0), after obtaining written informed consent, we assessed participants on: (a) physical health – medical history, physical examination, vital signs (i.e. blood pressure, pulse, and temperature), 12-lead electrocardiogram, haematological and biochemical laboratory studies including drug testing, breath alcohol concentration, urine pregnancy test, infectious disease panel, rapid plasma reagin, forced expiratory volume in 1 s, optional HIV test, HIV risk-taking behaviour scale (Darke et al., 1991), and adverse events; (b) psychiatric diagnosis – structured clinical interview for DSM-IV (First et al., 1994); (c) measures of addiction severity and depression – addiction severity index 'lite' form (ASI-Lite) and Hamilton depression rating scale (HAMD) on one occasion, and (d) measures of methamphetamine or other drug use and its sequelae – brief substance craving scale (BSCS; Mezinskis et al., 1998), clinical global impression – observer (CGI-O; National Institute of Mental Health, 1976), and clinical global impression – self (CGI-S; National Institute of Mental Health, 1976) on two occasions, and the methamphetamine withdrawal questionnaire (MAWQ) (an instrument created for this study) and substance use report (SUR; Sobell et al., 1980) on 4–6 occasions. Additionally, during the 2-wk baseline period, participants were required to provide 4–6 urine specimens – at least one of which had to be positive for the presence of methamphetamine – to satisfy an eligibility criterion for participation in the double-blind treatment phase. If a subject failed to provide a minimum of four completed MAWQs and at least four urine specimens – including one positive for urine methamphetamine – within the required 2-wk period, the baseline period was extended until the subject met the requirements in any consecutive 14-d period but within 4 wk before randomization.

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, and vital signs, along with the measures of methamphetamine use and its sequelae – BSCS, CGI-O, and CGI-S, which were performed once per week throughout the 8-wk treatment phase, and the SUR and MAWQ, which were assessed three times per week (although the MAWQ was conducted just once per week after the first 2 wk). Additionally, vital signs were checked weekly, and the other physical checks and HAMD were repeated at week 4. At termination (i.e. the end of week 8), the physical examination, vital signs, SUR, breath alcohol concentration, adverse events, urine methamphetamine, creatinine, and toxicology screens, BSCS, CGI-S, CGI-O, MAWQ, haematology and blood chemistries, medical urinalysis, pregnancy, ASI-Lite, HIV risk-taking behaviour scale, electrocardiogram, concomitant medications, cognitive function tests, and HAMD were assessed. At week 12, a post-treatment follow-up visit was conducted as a safety measure, during which we ascertained measures of methamphetamine or other drug use and its sequelae, as well as adverse events.

Participants received $10 as compensation for each visit in which a urine specimen was provided, plus $25 for the study termination interview and the week 12 follow-up assessment.

Study design and randomization plan

We conducted a double-blind, placebo-controlled, randomized, four-arm, dose-ranging study comparing three dose levels of ondansetron (0.25 mg, 1 mg, and 4 mg b.i.d.) and placebo administered to methamphetamine-dependent outpatients (Figure 1).

Stratified randomization was used to balance treatment groups with respect to diagnosis of alcohol abuse (women $\leqslant$3 drinks/d vs. >3 drinks/d, men $\leqslant$5 drinks/d vs. >5 drinks/d), age at onset of methamphetamine use [early onset (<18 yr) vs. late onset ($\geqslant$18 yr)], and frequency of methamphetamine use [current high (>10 d of use in the last 30 d) vs. low ($\leqslant$10 d of use in the last 30 d)]. Age at onset of methamphetamine use was selected as a stratum based on the premise that age of onset was shown to be an important predictive variable of treatment response in a previous stimulant trial (Sigmon et al., 1999). The randomization process was performed by computer at the National Institute on Drug Abuse (NIDA) data coordinating centre. Treatment assignments were

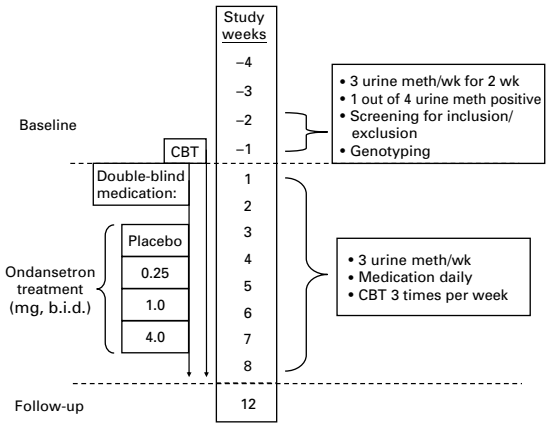

Figure 1. Study design. CBT, Cognitive behavioural therapy; meth, methamphetamine.

provided by NIDA to the study pharmacist at each participating site for distribution of the investigational agent.

Medication: procurement, preparation, and dosing

The study medication was prepared and supplied by Murty Pharmaceuticals, Inc. (Lexington, KY, USA) to the investigational sites in 1-oz bottles labelled with the protocol number, random dose code, and expiry date. Each bottle contained 20 size-1 opaque gelatin capsules (i.e. a 10-d supply) consisting of placebo or 0.25 mg, 1 mg, or 4 mg ondansetron. Each local site research pharmacist, who had no contact with participants or clinical staff and maintained the double-blind dose codes for individual participants, labelled the appropriate bottle – based upon the random dose code assigned to the patient – with the subject's study identification number, the subject's letter identification code, the words 'Study Week X', where X was the study week number (i.e. 1–8), and instructions for use. From weeks 1–8, we dispensed study medication (placebo, 0.25 mg, 1 mg, or 4 mg b.i.d.) in a double-blind fashion.

Psychosocial treatment

Cognitive behavioural therapy (CBT), an effective psychosocial intervention for the treatment of stimulant dependence (Huber et al., 1997; Rawson et al., 2002; Shoptaw et al., 1994), was provided to all patients as a method for enhancing protocol compliance and teaching skills to prevent relapse. CBT was delivered to all participants in 90-min group sessions, three times per week from weeks 1–8, by trained master's-level and doctoral-level therapists. During these sessions, emergency counselling and referral services were provided as needed. All therapy sessions were audiotaped and a random selection reviewed to monitor therapist drift and ensure adherence to proper procedures.

Monitoring procedures

Two procedures were implemented to ensure adequate monitoring of participants' safety. First, we established an independent Data and Safety Monitoring Board that met regularly to evaluate the conduct of the trial. Second, an independent medical monitor was appointed by NIDA to supervise the data collection process and to monitor adverse events reporting.

Primary outcome measures

The first primary outcome variable for each subject was the weekly proportion of methamphetamine-free urine samples. Three urine collection days were scheduled per calendar week. The weekly methamphetamine-free sample was recorded as: '0' if all three urine samples in the week were negative (<300 ng/ml); '1' if the proportion of weekly methamphetamine-free samples was between 0.67 and 0.75, inclusive; '2' if the proportion of weekly methamphetamine-free samples was between 0.33 and 0.5, inclusive, and '3' if the proportion of weekly methamphetamine-free samples was 0.

The other three primary outcome measures were mean $\log_{10}$ urine methamphetamine level, self-reported non-methamphetamine use days, and success vs. failure with achieving at least three consecutive weeks of abstinence.

Secondary outcome measures

Six secondary outcome measures were selected for study. These included: clinical severity of methamphetamine dependence – CGI-O, CGI-S, and ASI-Lite subscale score; withdrawal – MAWQ; craving – BSCS, and study retention.

Statistical analysis

Descriptive variables were characterized as their mean $\pm$ S.D. For inferential analyses, each primary and secondary outcome measure was analysed using appropriate methods for the intention-to-treat population. The general analytical 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 methamphetamine use in the last 30 d ($\leqslant$10 and $>$10), age at onset of methamphetamine use

[actual age or categorical (young vs. old)], gender, diagnosis of attention deficit disorder, baseline severity of depression (HAMD score $\leqslant 15$ 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 longitudinal data, this involved the use of generalized estimating equations (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.

Results

Participants

From Table 1, it can be seen that the participants' demographic and alcohol and methamphetamine use characteristics at baseline, by study group, were similar. Participants were mostly male ($n=96$, 64%), White ($n=109$, 73%), and employed ($n=96$, 64%) and had on average a 12th-grade education, with a mean age of 36.1 ± 8.7 (S.D.) years. All were dependent on methamphetamine, and the average number of days of methamphetamine use in the 30 d prior to enrolment ranged from 17.2 to 19.3.

Primary outcome measures

A methamphetamine-free study week was defined as a week in which all non-missing urine samples in the week were methamphetamine-free. The percentage of missing urine samples across all groups was 44.19% (placebo 46.83%, ondansetron 0.25 mg b.i.d. 43.24%, ondansetron 1 mg b.i.d. 41.52%, ondansetron 4 mg b.i.d. 43.97%). The differences in linear slopes of percentage of participants with a methamphetamine-free study week among treatment groups over the active treatment period were analysed using generalized estimating equations. On fitting the slopes, we allowed for differences in mean proportions at baseline (intercept). There were no statistically significant differences among any of the slopes (all p values >0.05) (Figure 2).

Further, there were no statistically significant differences (all p values >0.05) among the groups on the mean $\log_{10}$ urine methamphetamine level (Figure 3), self-reported non-methamphetamine-use days (Figure 4), or rates of success vs. failure in self-reported achievement of at least three consecutive weeks of abstinence (placebo 34.8% vs. 65.2%, ondansetron 0.25 mg b.i.d. 24.3% vs. 75.7%, ondansetron 1 mg b.i.d. 24.1% vs. 75.9%, ondansetron 4 mg b.i.d. 23.7% vs. 76.3%).

Secondary outcome measures

There were no statistically significant differences among the study groups in the scales of clinical severity of methamphetamine dependence (i.e. CGI-O and CGI-S) and withdrawal (i.e. MAWQ) (data not shown) or in the rate of change in BSCS score ($p=0.63$) (Figure 5). For the comparison of pretreatment vs. post-treatment ASI-Lite subscale scores, the salient findings were that: the average decline in the drug score was significantly less negative for the ondansetron (0.25 mg b.i.d.) group compared with placebo ($p=0.04$); the average improvement in the employment score was greater for the ondansetron (0.25 mg b.i.d.) group compared with placebo ($p=0.02$), and the average decline in the psychiatric score was greater for the placebo group compared with the ondansetron (4 mg b.i.d.) group ($p=0.04$). After correction for multiple comparisons, none of these hypothesis tests remained statistically significant. None of the between-group comparisons for the other ASI-Lite subscales achieved statistical significance.

Treatment retention

Retention was defined as the provision of at least one urine sample during the eighth week of treatment. At study end, retention rates were: placebo 54.3%, ondansetron 0.25 mg b.i.d. 51.4%, ondansetron 1 mg b.i.d. 62.1%, and ondansetron 4 mg b.i.d. 50%. No difference was detected in time to last urine sample among the four groups (log rank test, $p=0.51$). (See Figure 6 for the subject disposition during the study.)

Adverse events

From Table 2, it can be seen that ondansetron was well tolerated, and adverse events were more likely to be reported in the placebo group compared with two of the three ondansetron treatment groups. Serious adverse events were more likely in the placebo group than in ondansetron-treated participants. Of the three serious adverse events reported in those receiving ondansetron, only two of these occurred while subjects were on medication. One event was of a 45-yr-old woman with right upper quadrant abdominal pain who was discharged 2 d later and given Pepcid®. The

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

Variable	Placebo ($n=46$)	Ondansetron treatment group			Total ($n=150$)
		0.25 mg ($n=37$)	1 mg ($n=29$)	4 mg ($n=38$)	
Age, yr*[a]	36.7 (9.8)	37.3 (9.0)	35.9 (6.7)	34.3 (8.2)	36.1 (8.7)
Sex distribution†[a]					
Male	29 (63)	25 (68)	22 (76)	20 (53)	96 (64)
Female	17 (37)	12 (32)	7 (24)	18 (47)	54 (36)
Race†[a]					
White	35 (76)	29 (78)	19 (66)	26 (68)	109 (73)
Hispanic	7 (15)	2 (5)	6 (21)	4 (11)	19 (13)
Black	1 (2)	0 (0)	1 (3)	1 (3)	3 (2)
Asian or Pacific Islander	3 (7)	6 (16)	3 (10)	7 (18)	19 (13)
Height, cm*[b]	173.7 (10.5)	173.8 (10.0)	172.5 (9.7)	170.7 (10.6)	172.8 (10.2)
Weight, kg*[b]	80.4 (18.7)	82.7 (18.2)	80.6 (16.6)	82.2 (22.4)	81.4 (19.1)
Years of education*[a]	12.7 (1.9)	12.5 (2.0)	13.3 (1.7)	13.2 (1.6)	12.9 (1.8)
Employment in last 30 d†[a]					
Full-time	18 (39)	22 (59)	7 (24)	13 (34)	60 (40)
Part-time	9 (20)	5 (14)	13 (45)	9 (24)	36 (24)
Student	1 (2)	0 (0)	0 (0)	1 (3)	2 (1)
Retired/disabled	1 (2)	0 (0)	0 (0)	1 (3)	2 (1)
Homemaker	2 (4)	1 (3)	0 (0)	1 (3)	4 (3)
Unemployed	14 (30)	9 (24)	9 (31)	13 (34)	45 (30)
In controlled environment	1 (2)	0 (0)	0 (0)	0 (0)	1 (1)
Occupational category†[c]					
Management	3 (7)	4 (11)	2 (7)	4 (11)	13 (9)
Administrative	3 (7)	3 (8)	6 (21)	2 (5)	14 (9)
Clerical/sales	12 (26)	6 (16)	4 (14)	10 (26)	32 (21)
Skilled manual	15 (33)	14 (38)	9 (31)	11 (29)	49 (33)
Semi-skilled	5 (11)	3 (8)	6 (21)	6 (16)	20 (13)
Unskilled	8 (17)	5 (14)	2 (7)	5 (13)	20 (13)
Homemaker	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
Student/disabled/none	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
Marital status†[a]					
Legally married	3 (7)	11 (30)	6 (21)	6 (16)	26 (17)
Living with a partner but unmarried	4 (9)	1 (3)	2 (7)	2 (5)	9 (6)
Widowed	1 (2)	0 (0)	0 (0)	1 (3)	2 (1)
Separated	2 (4)	1 (3)	3 (10)	3 (8)	9 (6)
Divorced	18 (39)	7 (19)	6 (21)	9 (24)	40 (27)
Never married, not living with a partner	18 (39)	17 (46)	12 (41)	17 (45)	64 (43)
Adult attention deficit disorder†[d]					
Yes	5 (11)	1 (3)	1 (3)	5 (13)	12 (8)
No	41 (89)	36 (97)	28 (97)	32 (84)	137 (91)
Data missing	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)
Depression (HAMD total score >15)†[e]					
Yes	6 (13)	3 (8)	4 (14)	1 (3)	14 (9)
No	39 (85)	33 (89)	25 (86)	37 (97)	134 (89)
Data missing	1 (2)	1 (3)	0 (0)	0 (0)	2 (1)
HAMD total score at baseline*[e]	6.7 (5.5)	6.8 (6.0)	6.8 (6.1)	7.2 (4.7)	6.9 (5.5)

Table 1 (*cont.*)

Variable	Placebo ($n=46$)	Ondansetron treatment group: 0.25 mg ($n=37$)	1 mg ($n=29$)	4 mg ($n=38$)	Total ($n=150$)
Diagnosis of alcohol abuse or dependence†[f]					
Yes	3 (7)	4 (11)	4 (14)	4 (11)	15 (10)
No	43 (93)	33 (89)	25 (86)	34 (89)	135 (90)
Age at onset of alcohol use*[g]	15.9 (3.5)	15.7 (2.7)	15.3 (3.7)	14.7 (3.4)	15.4 (3.3)
Days of alcohol use in last 30 d*[h]	3.9 (8.1)	8.1 (11.0)	4.4 (7.3)	4.2 (7.1)	5.1 (8.6)
Age at onset of methamphetamine use†[g]					
<18 yr	15 (33)	12 (32)	8 (28)	10 (26)	45 (30)
$\geqslant 18$ yr	31 (67)	25 (68)	21 (72)	28 (74)	105 (70)
Age at onset of methamphetamine use, yr*[g]	21.8 (7.7)	22.9 (8.5)	21.5 (6.6)	21.3 (5.7)	21.9 (7.2)
Days of methamphetamine use in last 30 d†[h]					
$\leqslant 10$	10 (22)	10 (27)	6 (21)	9 (24)	35 (23)
>10	36 (78)	26 (70)	23 (79)	29 (76)	114 (76)
Data missing	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
Days of methamphetamine use in last 30 d*[h]	18.9 (8.8)	17.2 (10.1)	17.9 (8.5)	19.3 (8.7)	18.4 (9.0)
Lifetime years of amphetamine use*[c]	11.8 (8.7)	12.8 (7.0)	11.4 (8.2)	10.8 (7.6)	11.7 (7.9)
Amphetamine route of administration†[c]					
Oral	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)
Nasal	6 (13)	5 (14)	6 (21)	5 (13)	22 (15)
Smoking	29 (63)	24 (65)	17 (59)	26 (68)	96 (64)
Non-intravenous injection	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)
Intravenous injection	8 (17)	7 (19)	6 (21)	4 (11)	25 (17)
Data missing	3 (7)	0 (0)	0 (0)	2 (5)	5 (3)
Dollars spent on drugs in last 30 d*[c]	714.1 (2929.2)	523.0 (840.8)	208.6 (248.3)	249.5 (356.0)	451.5 (1688.1)
Number of lifetime drug abuse treatments*[c]	2.5 (3.8)	1.2 (1.9)	0.9 (1.3)	1.4 (1.7)	1.6 (2.6)
Addiction severity index composite scores*[c]					
Medical	0.1 (0.2)	0.1 (0.3)	0.1 (0.3)	0.1 (0.2)	0.1 (0.2)
Employment	0.4 (0.2)	0.3 (0.3)	0.4 (0.3)	0.5 (0.3)	0.4 (0.3)
Alcohol	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)
Drug	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)
Legal	0.2 (0.2)	0.2 (0.2)	0.2 (0.3)	0.2 (0.2)	0.2 (0.2)
Family relations	0.3 (0.3)	0.2 (0.2)	0.3 (0.3)	0.2 (0.2)	0.2 (0.2)
Psychiatric	0.2 (0.2)	0.2 (0.2)	0.2 (0.2)	0.2 (0.2)	0.2 (0.2)

HAMD, Hamilton depression rating scale.

* Values represent mean (S.D.).

† Values represent *n* (%).

Sources: [a] demographics form; [b] physical examination form; [c] addiction severity index 'lite' form; [d] attention deficit disorder form; [e] HAMD form; [f] structured clinical interview for DSM-IV form; [g] quantity and frequency interview form; [h] timeline follow-back form.

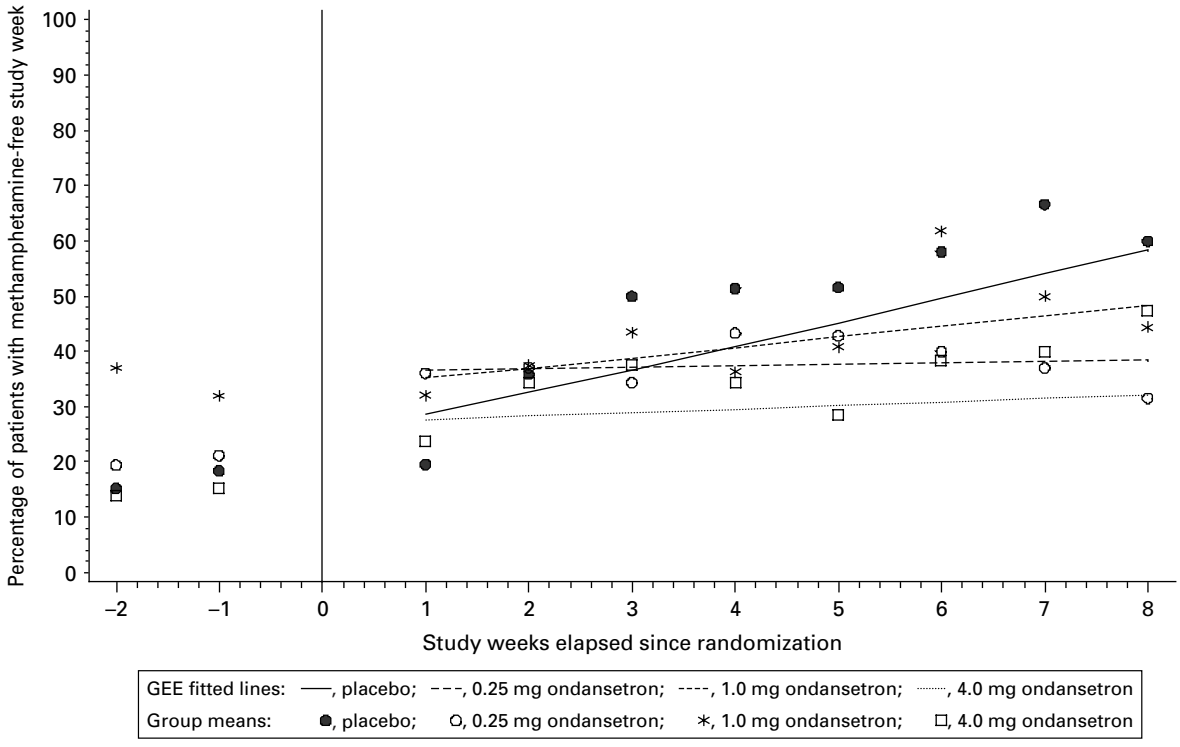

Figure 2. Percentage of participants with a methamphetamine-free study week. Data are presented as group means and generalized estimating equations (GEE) fitted lines.

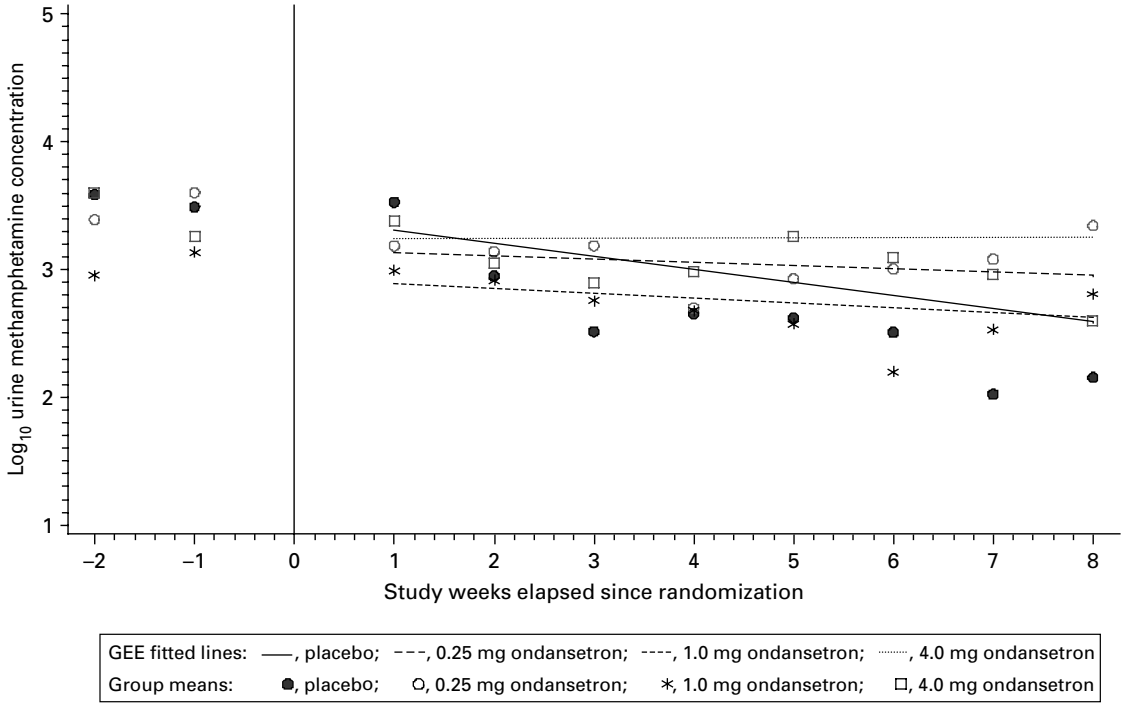

Figure 3. Mean $\log_{10}$ urine methamphetamine level. Data are presented as group means and generalized estimating equations (GEE) fitted lines.

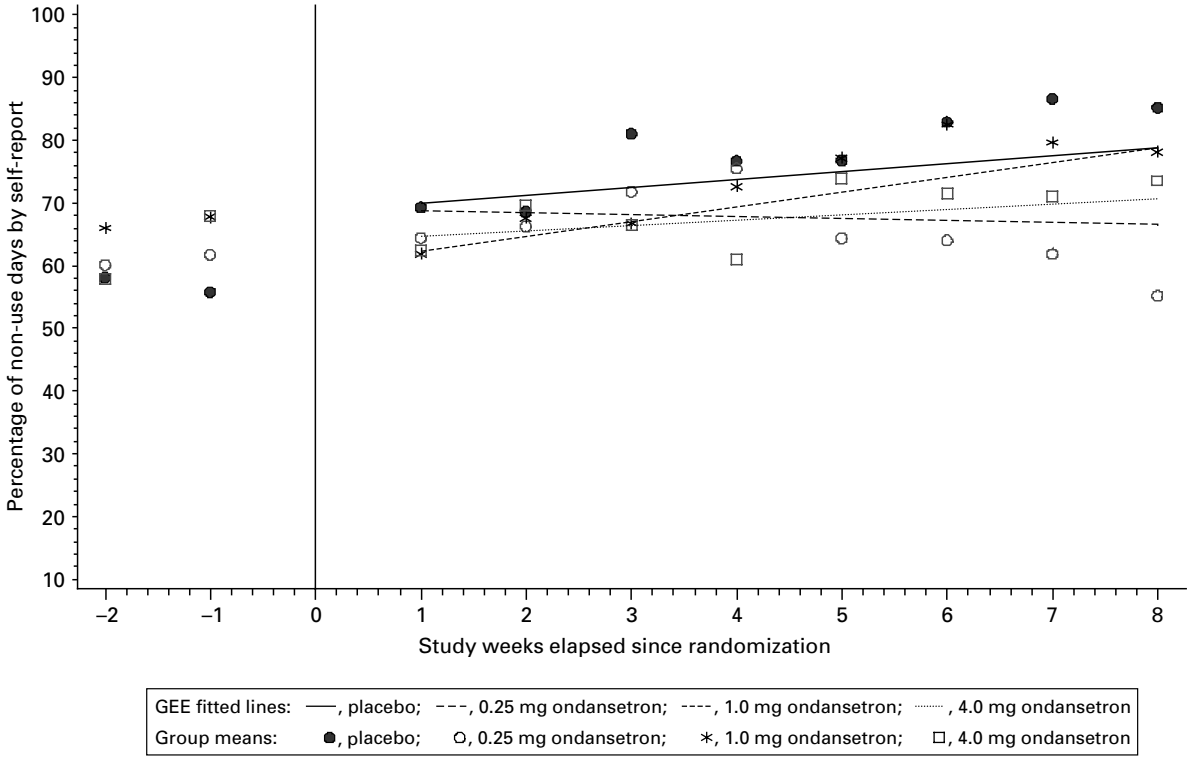

Figure 4. Percentage of self-reported non-methamphetamine-use days. Data are presented as group means and generalized estimating equations (GEE) fitted lines.

other event was of a 46-yr-old man who had a scalp rash and pyrexia, for which he received antibiotics as an outpatient. Over the course of the study, 13 subjects had a QTc interval on the electrocardiogram greater than 450 ms (upper bound cut-off at intake was 400 ms), and five of them were in the placebo group; hence, this adverse event was not particularly related to ondansetron treatment.

Discussion

Our results showed that ondansetron was not superior to placebo as a treatment agent for methamphetamine dependence. We considered five potential reasons for these results.

First, we considered the possibility that because of the relatively short half-life of ondansetron (~5.2 h) (Lam et al., 2004) and our adherence to a twice-daily dosing regimen to maximize compliance, it is plausible that a more frequent dosing strategy would have been needed to demonstrate a therapeutic effect. Nevertheless, we were not persuaded by this premise as the chronicity of dosing would have ensured measurable ondansetron levels for most of the study duration.

Second, we considered the possibility that a higher ondansetron dose might have been efficacious as a treatment for methamphetamine dependence. Certainly, due to ondansetron's favourable adverse event profile and high tolerability, it would be possible to test much higher doses. We thought, however, that this would, at best, yield a modest outcome consistent with the previous findings in the human laboratory, i.e. that even an aggressive dosing strategy with ondansetron has only a partial effect to antagonize d-amphetamine-mediated reinforcing effects (Grady et al., 1996; Silverstone et al., 1992a).

Third, we considered the possibility that there might be a differential response to ondansetron treatment by clinical subtype. We, therefore, conducted exploratory analysis based upon the concept of an age of onset with which a differential response was obtained in the treatment of alcohol dependence (Johnson et al., 2000). Although these data are not reported here, we were unable to find evidence of a differential treatment response by age of onset. Nevertheless, we did not think that this undermined the concept of clinical subtyping but rather that it perhaps more aptly related to our relative lack of understanding, in the methamphetamine field

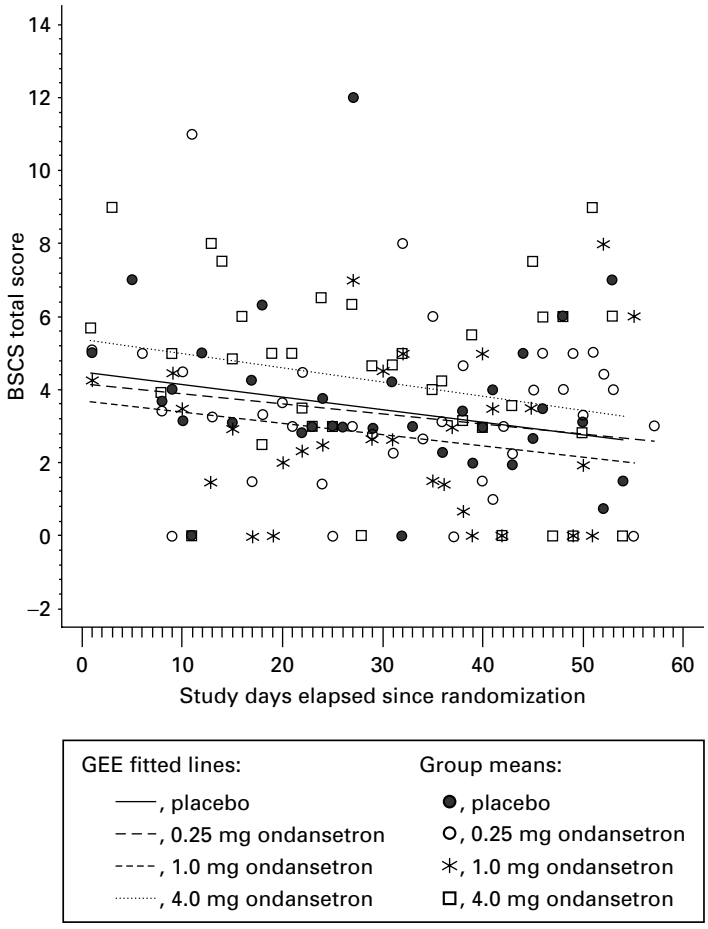

Figure 5. Rate of change in brief substance craving scale (BSCS) score among the study groups. Data are presented as group means and generalized estimating equations (GEE) fitted lines.

compared with the alcoholism field, of where to make the distinction. Further, it could be argued not only that the discriminating age that we chose was exploratory and did not have pathophysiological significance but also that other criteria for subtyping might be more important. More epidemiological research in this area might help to clarify the issue.

Fourth, we considered the possibility that genetic differences might be associated with differential treatment response to ondansetron. This premise is currently under exploration, but because of the relatively small sample size of this trial, it will need to be examined as part of a meta-analytical data analysis, which is beyond the scope of this report.

Fifth, we considered the possibility that one reason for the lack of demonstration of ondansetron's efficacy might have been the highly intensive nature of the CBT that we used. In other words, fewer CBT sessions may have been more revealing in an initial phase II trial to explore for the efficacy of ondansetron. Indeed, ondansetron does not reduce methamphetamine intake within the context of a highly intensive CBT programme. Presumably, this might pave the way for other investigators who wish to test the efficacy of ondansetron as an adjunct to less intensive psychosocial interventions for treating methamphetamine-dependent individuals.

We did have some additional caveats to the interpretation of our data. These included the relatively high dropout rate (50/155, or 32.3%), the relatively small sample size, and the relatively short length of the trial (8 wk rather than 12 wk). Greater retention, especially with high medication compliance, might have increased our chances of detecting an ondansetron treatment effect. Longer time in treatment also might have increased the likelihood of finding efficacy for ondansetron in methamphetamine-dependent individuals.

Table 2. Numbers of subjects with treatment-emergent adverse events (AEs)

	Treatment-emergent AEs				Treatment-emergent serious AEs			
Ondansetron treatment group …	Placebo	0.25 mg	1 mg	4 mg	Placebo	0.25 mg	1 mg	4 mg
AE	($n=46$)	($n=37$)	($n=29$)	($n=38$)	($n=46$)	($n=37$)	($n=29$)	($n=38$)
Headache	14	11	9	14	2	0	1	0
Back pain	10	6	5	2	0	0	0	0
Nasopharyngitis	5	5	1	7	0	0	0	0
Arthralgia	4	6	2	2	0	1	0	0
Fatigue	4	1	1	5	0	0	0	0
Nausea	3	3	2	3	1	0	0	0
Toothache	5	2	2	2	0	0	0	0
Insomnia	1	2	3	4	0	0	0	0
Depressed mood	3	0	2	4	0	0	0	0
Sore throat	3	0	3	3	0	0	0	0
Constipation	1	1	2	4	0	0	0	0
Diarrhoea	3	2	2	1	0	0	0	0
Influenza	3	2	0	3	0	0	0	0
Pain in limb	3	0	2	2	0	0	0	0
Abdominal pain – upper	2	0	1	3	0	0	1	0
Dizziness (excluding vertigo)	0	2	2	2	0	0	0	0
Laceration	1	2	1	2	0	0	0	0

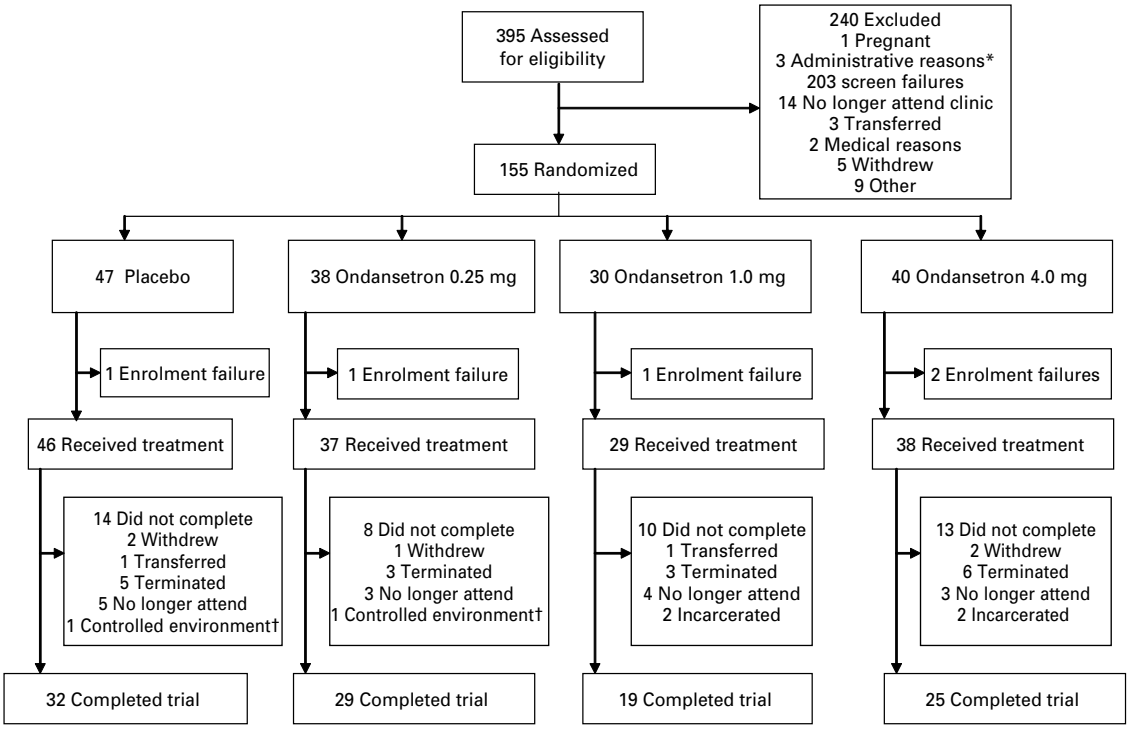

Figure 6. Trial flow diagram of methamphetamine-dependent participants, by ondansetron treatment group.
* 'Administrative reasons' was used when a subject missed six consecutive visits and was, therefore, terminated from the study. † 'Controlled environment' refers to in-patient hospitalization or other restricted setting (excluding incarceration, which was a separate category).

A final caveat pertains to our rationale for the choice of ondansetron doses. To expand upon our point emphasized in the third paragraph of the Discussion (see above), the dose of 4 mg was based on earlier human laboratory studies (Grady et al., 1996; Silverstone et al., 1992a,b). The smaller doses were determined by scalar $\times 4$ reductions to produce a 64-fold therapeutic range. We thought that such a large therapeutic range would enable us to detect ondansetron effects. We might, however, have needed a larger dose of ondansetron to maximize efficacy. The side-effects were low; thus, safety and tolerability would not be likely to have been compromised by a carefully selected, larger dose.

In summary, ondansetron treatment was safe and well tolerated among methamphetamine-dependent individuals receiving treatment. Nevertheless, our results do not support the utility of ondansetron, at the doses tested, as a treatment for methamphetamine dependence.

Appendix. The Methamphetamine Study Group

Name	Role	Site	Current title and affiliation
Richard A. Rawson, Ph.D.	Coordinating Center Principal Investigator	University of California, Los Angeles, Integrated Substance Abuse Programs	Associate Professor, Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, Los Angeles, California
Dennis Weis, M.D.	Site Principal Investigator	Powell Chemical Dependency Center, Lutheran Hospital, Des Moines, Iowa	Medical Director, Powell Chemical Dependency Center, Lutheran Hospital, Des Moines, Iowa
William F. Haning, III, M.D.	Site Principal Investigator	University of Hawaii at Manoa, Honolulu	Associate Professor, Department of Psychiatry, University of Hawaii at Manoa, Honolulu, Hawaii
Joseph Mawhinney, M.D.	Site Principal Investigator	South Bay Treatment Center, San Diego, California	Medical Director, South Bay Treatment Center, San Diego, California
Jan L. Campbell, M.D.	Site Principal Investigator	University of Missouri-Kansas City	Associate Professor, Department of Psychiatry, University of Missouri-Kansas City, Kansas City, Missouri
Roger A. Donovick, M.D.	Site Principal Investigator	Matrix Institute on Addictions, Costa Mesa, California	Assistant Professor, Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, Los Angeles, California
Thomas F. Newton, M.D.	Coordinating Center Subinvestigator	University of California, Los Angeles, Integrated Substance Abuse Programs	Professor, Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, Los Angeles, California
Michael McCann, M.A.	Site Subinvestigator	Matrix Institute on Addictions, Costa Mesa, California	Associate Director, Matrix Institute on Addictions, Costa Mesa, California
Charles W. Gorodetsky, M.D., Ph.D.	Site Subinvestigator	University of Missouri-Kansas City	Consultant in Pharmaceutical Medicine, Kansas City, Missouri
Barry S. Carlton, M.D.	Site Subinvestigator	University of Hawaii at Manoa, Honolulu	Associate Professor, Department of Psychiatry, University of Hawaii at Manoa, Honolulu, Hawaii
Walter Ling, M.D.	Coordinating Center Subinvestigator	University of California, Los Angeles, Integrated Substance Abuse Programs	Professor, Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, Los Angeles, California

Acknowledgements

We are grateful to the National Institute on Drug Abuse for its support through contracts N01DA-9-8101 (awarded to The University of Texas Health Science Center at San Antonio) and N01DA-0-8804 (awarded to the University of California, Los Angeles). We also thank Robert H. Cormier, Jr. for his assistance with manuscript preparation.

Statement of Interest

None.

References

Anglin MD, Kalechstein A, Maglione M, Annon J, Fiorentine R (1998). *Epidemiology and Treatment of Methamphetamine Abuse in California: A Regional Report*. Rockville, MD: National Evaluation Data and Technical Assistance Center (NEDTAC), Center for Substance Abuse Treatment (contract no. 270-94-001).

APA (1994). *Diagnostic and Statistical Manual of Mental Disorders* (4th edn). Washington, DC: American Psychiatric Association.

Bradbury AJ, Costall B, Kelly ME, Naylor RJ, Smith JA (1985). Biochemical correlates of motor changes caused by the manipulation of dopamine function in the substantia nigra of the mouse. *Neuropharmacology 24*, 1155–1161.

Carboni E, Spielewoy C, Vacca C, Nosten-Bertrand M, Giros B, Di Chiara G (2001). Cocaine and amphetamine increase extracellular dopamine in the nucleus accumbens of mice lacking the dopamine transporter gene. *Journal of Neuroscience 21*, RC141 (1–4).

Chevrette J, Stellar JR, Hesse GW, Markou A (2002). Both the shell of the nucleus accumbens and the central nucleus of the amygdala support amphetamine self-administration in rats. *Pharmacology, Biochemistry, and Behavior 71*, 501–507.

Colfax G, Shoptaw S (2005). The methamphetamine epidemic: implications for HIV prevention and treatment. *Current HIV/AIDS Reports 2*, 194–199.

Costall B, Domeney AM, Naylor RJ, Tyers MB (1987). Effects of the 5-HT3 receptor antagonist, GR38032F, on raised dopaminergic activity in the mesolimbic system of the rat and marmoset brain. *British Journal of Pharmacology 92*, 881–894.

Darke S, Hall W, Heather N, Ward J, Wodak A (1991). The reliability and validity of a scale to measure HIV risk-taking behaviour among intravenous drug users. *AIDS 5*, 181–185.

Di Chiara G, Imperato A (1988). Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. *Proceedings of the National Academy of Sciences USA 85*, 5274–5278.

First MB, Spitzer RL, Gibbon M, Williams JBW (1994). *Structured Clinical Interview for DSM-IV Axis I Disorders – Patient Edition* (*SCID-I/P, Version 2.0*). New York: New York State Psychiatric Institute, Biometrics Research Department.

Galloway GP, Newmeyer J, Knapp T, Stalcup SA, Smith D (1996). A controlled trial of imipramine for the treatment of methamphetamine dependence. *Journal of Substance Abuse Treatment 13*, 493–497.

Grady TA, Broocks A, Canter SK, Pigott TA, Dubbert B, Hill JL, Murphy DL (1996). Biological and behavioral responses to D-amphetamine, alone and in combination with the serotonin3 receptor antagonist ondansetron, in healthy volunteers. *Psychiatry Research 64*, 1–10.

Hando J, Hall W (1994). HIV risk-taking behaviour among amphetamine users in Sydney, Australia. *Addiction 89*, 79–85.

Hando J, Hall W (1997). Patterns of amphetamine use in Australia. In: Klee H (Ed.), *Amphetamine Misuse: International Perspectives on Current Trends* (pp. 81–110). Amsterdam, The Netherlands: Harwood Academic Publishers.

Huber A, Ling W, Shoptaw S, Gulati V, Brethen P, Rawson R (1997). Integrating treatments for methamphetamine abuse: a psychosocial perspective. *Journal of Addictive Diseases 16*, 41–50.

Johnson BA, Roache JD, Javors MA, DiClemente CC, Cloninger CR, Prihoda TJ, Bordnick PS, Ait-Daoud N, Hensler J (2000). Ondansetron for reduction of drinking among biologically predisposed alcoholic patients: a randomized controlled trial. *Journal of the American Medical Association 284*, 963–971.

Johnston LD, O'Malley PM, Bachman JG, Schulenberg JE (2006). *Monitoring the Future: National Survey Results on Drug Use, 1975–2005. Volume I, Secondary School Students* (NIH Publication No. 06-5883). Bethesda, MD: National Institute on Drug Abuse.

Klee H (1992). A new target for behavioural research – amphetamine misuse. *British Journal of Addiction 87*, 439–446.

Klee H (1997). Amphetamine misusers in contemporary Britain: the emergence of a hidden population. In: Klee H (Ed.), *Amphetamine Misuse: International Perspectives on Current Trends* (pp. 19–34). Amsterdam, The Netherlands: Harwood Academic Publishers.

Koob GF, Nestler EJ (1997). The neurobiology of drug addiction. *Journal of Neuropsychiatry and Clinical Neurosciences 9*, 482–497.

Lam YWF, Javors MA, Ait-Daoud N, Roache JD, Johnson BA (2004). Relative bioavailability of an extemporaneous ondansetron 4-mg capsule formulation versus solution. *Pharmacotherapy 24*, 477–481.

Liang KY, Zeger SL (1986). Longitudinal data analysis using generalized linear models. *Biometrika 73*, 13–22.

Ling W, Shoptaw S (1997). Integration of research in pharmacotherapy for addictive disease: where are we? Where are we going? *Journal of Addictive Diseases 16*, 83–102.

Lorrain DS, Arnold GM, Vezina P (1999). Mesoaccumbens dopamine and the self-administration of amphetamine. *Annals of the New York Academy of Sciences 877*, 820–822.

Makkai T, McAllister I (1993). *Patterns of Drug Use in Australian Society*. Canberra: Australian Government Printing Services.

McBride WJ, Li TK (1998). Animal models of alcoholism: neurobiology of high alcohol-drinking behavior in rodents. *Critical Reviews in Neurobiology 12*, 339–369.

Mezinskis J, Dyrenforth S, Goldsmith RJ, Cohen M, Somoza E (1998). Craving and withdrawal symptoms for various drugs of abuse. *Psychiatric Annals 28*, 577–583.

National Institute of Mental Health (1976). CGI clinical global impressions. In: Guy W (Ed.), *ECDEU Assessment for Psychopharmacology* (revised) (pp. 217–222). Rockville, MD: National Institute of Mental Health.

Office of National Drug Control Policy, National Institute of Justice (2000). *Methamphetamine Interagency Task Force – Final Report: Federal Advisory Committee*. Washington, DC: Office of National Drug Control Policy and National Institute of Justice.

Rawson RA, Huber A, McCann M, Shoptaw S, Farabee D, Reiber C, Ling W (2002). A comparison of contingency management and cognitive-behavioral approaches during methadone maintenance treatment for cocaine dependence. *Archives of General Psychiatry 59*, 817–824.

Rubenstein EB, Slusher BS, Rojas C, Navari RM (2006). New approaches to chemotherapy-induced nausea and vomiting: from neuropharmacology to clinical investigations. *Cancer Journal 12*, 341–347.

Sellers EM, Higgins GA, Sobell MB (1992). 5-HT and alcohol abuse. *Trends in Pharmacological Sciences 13*, 69–75.

Shankar RP, Karan RS, Handu SS, Bhargava VK (2000). Effect of the 5-HT3 receptor antagonist ondansetron on amphetamine-induced hyperactivity and stereotypy in rats. *Indian Journal of Physiology and Pharmacology 44*, 355–358.

Shearer J, Wodak A, Mattick RP, Van Beek I, Lewis J, Hall W, Dolan K (2001). Pilot randomized controlled study of dexamphetamine substitution for amphetamine dependence. *Addiction 96*, 1289–1296.

Shoptaw S, Rawson RA, McCann MJ, Obert JL (1994). The Matrix model of outpatient stimulant abuse treatment: evidence of efficacy. *Journal of Addictive Diseases 13*, 129–141.

Sigmon SC, Higgins ST, Badger GJ (1999). Relation of age of cocaine initiation to drug use severity and treatment outcome. In: Harris LS (Ed.), Problems of Drug Dependence 1999: Proceedings of the 61st Annual Scientific Meeting, Acapulco, Mexico, The College on Problems of Drug Dependence, Inc. *NIDA Research Monograph 180*, 216.

Silverstone PH, Johnson B, Cowen PJ (1992a). Does ondansetron attenuate amphetamine-induced behaviour in human volunteers? *Psychopharmacology 107*, 140–141.

Silverstone PH, Oldman D, Johnson B, Cowen PJ (1992b). Ondansetron, a 5-HT3 receptor antagonist, partially attenuates the effects of amphetamine: a pilot study in healthy volunteers. *International Clinical Psychopharmacology 7*, 37–43.

Sobell MB, Maisto SA, Sobell LC, Cooper AM, Cooper T, Sanders B (1980). Developing a prototype for evaluating alcohol treatment outcome studies. In: Sobell LC, Sobell MB, Ward E (Eds.), *Evaluating Alcohol and Drug Abuse Treatment Effectiveness: Recent Advances* (pp. 129–150). New York: Pergamon Press.

Suwaki H (1991). Methamphetamine abuse in Japan. *NIDA Research Monograph 115*, 84–98.

Suwaki H, Fukui S, Konuma K (1997). Methamphetamine abuse in Japan: its 45 year history and the current situation. In: Klee H (Ed.), *Amphetamine Misuse: International Perspectives on Current Trends* (pp. 199–214). Amsterdam, The Netherlands: Harwood Academic Publishers.

U.S. Department of Health and Human Services (1997). *Preliminary Results from the 1996 National Household Survey on Drug Abuse*. Rockville, MD: Substance Abuse and Mental Health Services Administration (SAMHSA), Office of Applied Studies.

U.S. Department of Health and Human Services (2005). *Methamphetamine Use, Abuse, and Dependence: 2002, 2003, and 2004. The National Survey on Drug Use and Health (NSDUH) Report, September 16, 2005*. Rockville, MD: Substance Abuse and Mental Health Services Administration (SAMHSA), Office of Applied Studies.

Vocci F, Ling W (2005). Medications development: successes and challenges. *Pharmacology & Therapeutics 108*, 94–108.

Yamamoto J (2004). Recent trends of drug abuse in Japan. *Annals of the New York Academy of Sciences 1025*, 430–438.