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A pilot trial of olanzapine for the treatment of cocaine dependence

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Abstract

Background: Multiple lines of evidence suggest both dopaminergic and serotonergic involvement in the reinforcing effects of cocaine. Medications such as olanzapine, which block dopamine D2 receptors, as well as serotonin receptors 5HT2A and 5HT2C may be able to reduce cocaine use in cocaine dependent patients by reducing the euphoric effects of cocaine and attenuating cocaine craving. *Methods:* This was a 12-week, double blind, placebo controlled, pilot trial involving 30 cocaine dependent subjects. Subjects received either olanzapine (10 mg/day) or identical placebo. Outcome measures included treatment retention, qualitative urine benzoylecgonine tests, cocaine craving, clinical global impression scores, and results from the addiction severity index. *Results:* Treatment retention was slightly, but significantly, better in the placebo-treated subjects. Placebo-treated subjects were more likely to be abstinent from cocaine during the trial compared to olanzapine-treated subjects, based on urine benzoylecgonine results. Olanzapine was not superior to placebo in any outcome measure. *Conclusions:* The results of this trial do not support the usefulness of olanzapine for the treatment of cocaine dependence. In fact, olanzapine may worsen cocaine treatment outcome.

Keywords: Cocaine; Olanzapine; Clinical trial; Double-blind

1. Introduction

Multiple studies have suggested that increases in extracellular dopamine mediate the acute reinforcing effects of cocaine (Dworkin and Smith, 1988; Roberts et al., 1980; Goeders et al., 1986; Koob et al., 1987). Medications able to block dopamine receptors may be able to reduce cocaine craving and assist cocaine dependent patients achieve abstinence in outpatient treatment. Preclinical trials of dopamine antagonists have demonstrated their ability to alter cocaine self-administration in several animal models (Kuhar et al., 1991; Richardson et al., 1994; Bourland and French, 1995). Olanzapine has been specifically found to reduce cocaine self-administration in rodents (Meil and Schechter, 1997; Rasmussen et al., 2000). Dopamine antagonists may be able to reverse behavioral sensitization seen with chronic cocaine administration (Tella, 1994). Sensitization to cocaine may be an important component of drug craving and the loss of control over cocaine use seen in cocaine dependent patients.

Studies of the effects of dopamine antagonists on the euphoric effects of cocaine and on cue-induced craving in humans have been promising. Newton et al. found that the atypical antipsychotic risperidone, given at a dose of 2 mg daily for 5 consecutive days, reduced the euphoric effects of a 40 mg dose of experimentally-administered intravenous cocaine (Newton et al., 2001). Berger et al. demonstrated that the dopamine antagonist haloperidol significantly decreased anxiety and cocaine craving elicited by exposure to conditioned cues of prior cocaine use (Berger et al., 1996). Finally, Smelson reported that risperidone diminished cue-induced cocaine craving (Smelson et al., 1997).

Only a few clinical trials of dopamine antagonists to reduce cocaine use have been undertaken. The results of

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these trials have been mixed, with some reports of significant problems with neuroleptic-induced side effects (Gawin et al., 1989; Kumor et al., 1986; Gawin et al., 1996). Olanzapine may be superior to traditional neuroleptics for the treatment of cocaine dependence due to its less severe side effect profile (Leucht et al., 1999; Berk et al., 1999). In addition, its ability to block 5HT2A and 5HT2C receptors may also reduce cocaine craving and reinforcement. In two separate trials the blockade of 5HT2 receptors reduced cocaine-induced hyperactivity in rodents (McCreary and Cunningham, 1999; O'Neill et al., 1999). Although recent data has suggested that antagonism of 5HT2A receptors and 5HT2C receptors may have opposing influences on cocaine effects in animal models (McMahon and Cunningham, 2001). The current pilot study was intended to obtain more data regarding the safety, tolerability and potential efficacy of olanzapine for reducing cocaine use in cocaine dependent subjects prior to conducting a large controlled clinical trial.

2. Methods

2.1. Subjects

The subjects were 30 DSM-IV cocaine dependent men and women between the ages of 18 and 60. Psychiatric diagnoses were obtained by a board-certified addiction psychiatrist (KK) through a clinical interview. Subjects were required to have self-reported at least $100 worth of cocaine use in the month prior to entry. Medical screening included a complete medical history and physical examination conducted by a certified nurse practitioner. Baseline laboratory testing included a chemistry screen, complete blood count, urinalysis, and a 12 lead EKG. Women received urinary pregnancy testing prior to starting medications, and at monthly intervals throughout the study.

Subjects dependent on any additional drug except nicotine and alcohol were excluded. Cocaine dependent subjects also dependent on alcohol were excluded if the alcohol dependence was severe enough to require benzodiazepines for detoxification. Psychiatric exclusion criteria included psychosis, dementia and the use of other psychotropic medications. Medical exclusion criteria included unstable medical illnesses and a history of hypersensitivity to olanzapine.

2.2. Measures

The primary outcome measure for this trial was qualitative urine benzoylecgonine tests (UBT) obtained twice weekly. Urine collection was not observed but urine sample temperature was monitored. Samples less than 90°, or greater than 100° Fahrenheit were not accepted. Samples were analyzed for benzoylecgonine by fluorescent polarization assay. Samples containing equal to or greater than 300 ng/ml of benzoylecgonine were considered to be positive.

Secondary outcome measures for the trial included treatment retention, which was measured by the number of evaluation sessions attended. Severity of addictive problems was measured by the addiction severity index (ASI) (McLellan et al., 1992) which was administered 4 times; at baseline, 4 weeks after starting medications, 8 weeks after starting medications, and at the end of the trial. The study physician rated illness severity and improvement weekly using the Clinical Global Impression (CGI) Scale (Guy, 1976). Cocaine craving was measured weekly using the Brief Substance Craving Scale (Somoza et al., 1995). Cocaine withdrawal symptoms were measured at each visit using the Cocaine Selective Severity Assessment (Kampman et al., 1998). Mood and anxiety symptoms were measured at baseline and at the end of the study using the Hamilton Depression Rating Scale and Hamilton Anxiety Rating Scale (Hamilton, 1959, 1967).

Safety measures included assessment of adverse events weekly using a modified version of the Systematic Assessment of Treatment Emergent Effects (SAFTEE) (Rabkin et al., 1992). Subjects were screened for extrapyramidal side effects, akathisia and tardive dyskinesia weekly. Specific measurement of akathisia was accomplished using the Barnes Akathisia Scale (Barnes, 1989). Tardive dyskinesia was screened using the Abnormal Involuntary Movement Scale (AIMS) (Guy, 1976) and extra-pyramidal side effects were screened using the Simpson Angus Scale (Simpson and Angus, 1970).

2.3. Procedures

Subjects were treatment-seeking cocaine users recruited at the University of Pennsylvania Treatment Research Center (TRC). The TRC recruits through advertisement in the local media as well as through professional referrals. Patients entering the trial were not involved in any other type of addiction treatment elsewhere. All subjects signed informed consent prior to participation in the trial after trial procedures were explained to them by an investigator. The study was reviewed and approved by the Institutional Review Board (IRB) of the University of Pennsylvania. Subjects were reimbursed $5 at each visit for completing all research procedures; at the last visit they received $30 because of the greater number of research procedures done at the end of the study. Subjects received an additional $5 each week for returning the previous week's medication package in order to facilitate the pill-count compliance check. If needed, two transit tokens were provided at each visit.

Eligible subjects entered a 12-week trial that included a 1-week baseline phase during which all pre-treatment measures were obtained and subjects began psychosocial treatment. Subjects were required to attend 2 visits during this week to be eligible to receive study medications. Eligible subjects were randomized to receive either olanzapine or placebo using urn randomization (Stout et al., 1994). Characteristics used in the urn randomization process included gender, initial urine toxicology results and baseline cocaine withdrawal symptom severity measured by scores on the CSSA. In the second week of the study, subjects received either olanzapine 2.5 mg daily or identical placebo. The dose of olanzapine was increased to 5 mg during study week 3 and increased to 10 mg daily during week 4. It remained at 10 mg daily until the last week of the medication phase (week 12) when it was reduced to 5 mg daily. Subjects were evaluated 2 times weekly throughout the baseline and medication phases of the trial.

In addition to medication or placebo, participants received twice-weekly individual cognitive-behavioral therapy utilizing a Cognitive-Behavioral Coping Skills Therapy (CBT) manual. The CBT therapy manual and supporting materials were developed for the National Institute on Alcohol Abuse and Alcoholism Project MATCH (Kadden et al., 1995). The basic format was accepted, although specific procedures were adapted for treatment of cocaine dependence by our group. Therapy was provided by Master's level therapists with additional training in CBT.

2.4. Statistical analysis

Baseline measures between the olanzapine and placebo groups were compared using t-tests for continuous variables and χ^2-tests for dichotomous variables. The number of sessions attended for each group during the trial was compared using the Mann–Whitney U-test. Urine toxicology results were compared in Generalized Estimating Equations (GEE) models (Diggle et al., 1994). Secondary outcome measures gathered over several time points were compared using linear mixed effects models. The models used to compare the groups on the primary and secondary outcome measures generally included the pre-treatment version of the response as a covariate, together with treatment group, and a linear time effect. The two-way interactions among these covariates were also considered for inclusion by examining P-values of regression coefficients for the GEE models and Akaike's Information Criterion (Littell et al., 1996) comparisons of overall model fit for the mixed effects models. The pre-treatment response was not included in the models for the General Improvement Scale from the CGI, where improvement is measured from baseline and no baseline version is administered, and the UBT results, where all but two of the 30 subjects (one from each group) provided a positive UBT in the week prior to randomization. For the GEE models for the UBT results, an auto-regressive 1 structure was used for the working correlation matrix. For the mixed effects models, a random intercept and time effect were used. In the analyses of the secondary measures, the scales from the ASI, CGI, and Hamilton Anxiety and Depression Scales were all log transformed prior to the analyses, to reduce levels of skewness. In general, there were few significant effects. In the descriptions below, we report only the medication effects, and other significant effects, from the final model.

3. Results

3.1. Baseline demographic and drug use

There were no significant differences between the two medication groups in any of the baseline demographic or drug use variables (Table 1). On average, subjects were about 40 years old. Most of the subjects were African–American men and most smoked crack cocaine. Because our clinic is located in West Philadelphia, where the majority of cocaine users are African–American, crack smoking men, this sample was representative of treatment seeking cocaine users in our area. On average, subjects had used cocaine between 11 and 14 days in the month prior to treatment. During the baseline week most subjects continue to use cocaine as evidenced by the fact that in both groups 12/15 subjects

Table 1
Subject characteristics, expressed as percents or means (standard deviation)

Variable	Olanzapine ($N = 15$)	Placebo ($N = 15$)
Age, years	42.00 (6.26)	40.58 (5.79)
% Male	80%	67%
Race		
African–American	100%	86%
Caucasian	0%	7%
Native American	0%	7%
Years of education	11.93 (1.53)	12.73 (1.83)
Days of alcohol use in past 30 days	4.00 (5.74)	8.27 (9.65)
Days of cocaine use in past 30 days	11.93 (9.32)	13.20 (8.74)
Years of cocaine use, lifetime	13.20 (7.61)	11.07 (4.26)
Number of prior treatments	3.00 (3.74)	2.07 (2.40)
Route of cocaine use		
Intranasal	20%	0%
Smoked	73%	100%
Intravenous	7%	20%

had a positive UBT when they received their first dose of study medications.

3.2. Treatment retention

Very few subjects were lost to follow-up. Twenty-seven of the 30 randomized subjects completed the final visit, 14/15 in the placebo group and 13/15 in the olanzapine group ($\chi^2 = 0.370$, df = 1, ns). However, treatment retention, measured by the number of visits attended, did differ significantly. Because of skew, the number of visits attended was analyzed nonparametrically. The median number of sessions attended by the placebo-treated subjects (22) was significantly greater than the median number of visits attended by the olanzapine-treated subjects (18) (Mann–Whitney *U*-test $Z = -2.178$, $N = 30$, $P = 0.029$).

3.3. Urine Benzoylecgonine Test Results

For the UBT results, there was a significant ($P = 0.01$) time by medication group interaction: the estimated odds of a positive UBT increased by 4% (OR = 1.036; 95% CI = (0.975, 1.068)) between visits for the olanzapine group, and decreased by 6% (OR = 0.944; 95% CI = (0.920, 0.968)) for the placebo group. So, rates of positive UBTs in the placebo group tended to decrease over the 12 weeks, while the rates in the olanzapine group stayed fairly constant (Fig. 1).

3.4. Results from the Addiction Severity Index and mood and anxiety symptoms

There was little change in the ASI scales over the 12 weeks (Table 2). Only days of cocaine use in the last 30 days showed a significant change over time ($t = -2.21$, $P = 0.03$). There were no medication effects on any of the scales. There were no significant medication effects on either Hamilton Anxiety Scale ($t = -0.31$, $P = 0.76$), or on Hamilton Depression Scale ($t = -0.65$, $P = 0.52$) (Table 2).

3.5. Results from the clinical global impression

The CGI was used by the study physician to rate both the overall severity of cocaine dependence and improvement since baseline (Table 3). There was no medication effect on either general severity ($t = -0.85$, $P = 0.40$) or improvement since baseline ($t = -1.32$, $P = 0.20$). There was no change on general severity over the 12 weeks, but improvement from baseline scores declined slightly, showing slight improvement from baseline in both groups ($t = -1.86$, $P = 0.06$).

3.6. Results from BSCS

The BSCS divides cocaine craving into three domains: intensity, duration and frequency. Each domain is measured on a 0–4 likert scale (Table 3). Although these measures are 0–4 likerts, their distributions were reasonably symmetric, and were appropriate for the

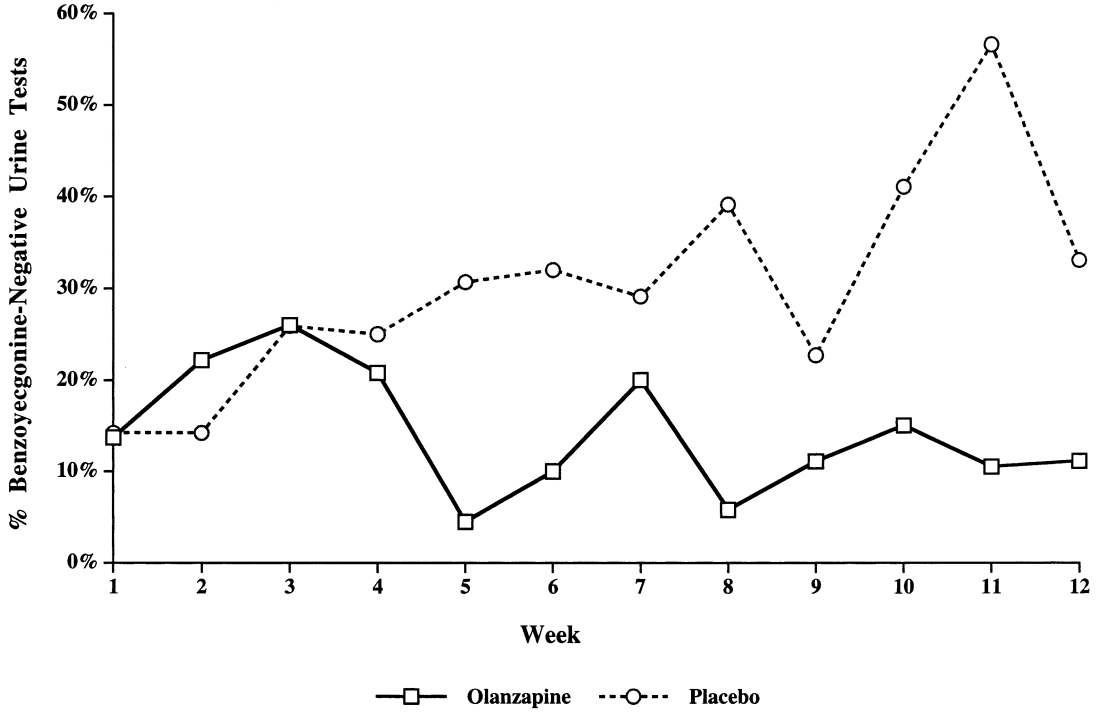

Fig. 1. Weekly mean % Benzoylecgonine-negative urine tests.

Table 2
Results from the ASI and Hamilton scales

Variable	Olanzapine		Placebo		Time Effects[a]		Medication Effects[a]	
	Baseline mean (S.D.)	End of study mean (S.D.)	Baseline mean (S.D.)	End of study mean (S.D.)	*t*	*P*	*t*	*P*
Days cocaine use/ past 30 days	11.93 (9.32)	6.62 (8.97)	13.2 (8.74)	4.43 (5.56)	−2.21	0.03	−1.50	0.15
Money spent on drugs/past 30 days	564 (678)	290 (545)	276 (224)	72 (95)	−1.49	0.14	0.27	0.79
Drug composite	0.227 (0.055)	0.169 (0.094)	0.237 (0.077)	0.149 (0.090)	1.74	0.09	1.63	0.11
Alcohol composite	0.056 (0.069)	0.052 (0.091)	0.124 (0.131)	0.109 (0.111)	1.84	0.07	0.59	0.68
Employment composite	0.781 (0.303)	0.610 (0.334)	0.675 (0.295)	0.676 (0.285)	1.67	0.10	0.58	0.57
Family social composite	0.190 (0.245)	0.293 (0.308)	0.197 (0.253)	0.071 (0.130)	1.00	0.32	1.10	0.28
Medical composite	0.130 (0.292)	0.315 (0.322)	0.238 (0.323)	0.201 (0.287)	1.34	0.19	−0.42	0.68
Psychiatric composite	0.143 (0.171)	0.108 (0.180)	0.165 (0.167)	0.049 (0.125)	−0.81	0.42	−1.42	0.17
Legal composite	0.087 (0.172)	0.035 (0.085)	0.057 (0.142)	0.064 (0.165)	−0.59	0.56	1.67	0.11
Hamilton Depression Rating Scale	11.93 (8.65)	2.67 (3.23)	9.93 (8.43)	3.86 (5.53)	NA	NA	−0.65	0.52
Hamilton Anxiety Rating Scale	5.80 (4.90)	1.58 (1.83)	4.93 (3.97)	2.36 (3.48)	NA	NA	−0.31	0.76

[a] Linear, mixed effects regression model ASI from baseline, weeks 4, 9 and 12 with baseline values included as covariates, 24-item Hamilton Depression Rating Scale and Hamilton Anxiety Rating Scale from baseline and week 12 with baseline values included as covariates. No time effects were calculated for the Hamilton scales.

Table 3
Results from CSSA, BSCS, and CGIO, means shown with (standard deviation)

	CSSA[a] (scale 0–112)		BSCS frequency (scale 0–4)		BSCS intensity (scale 0–4)		BSCS duration (scale 0–4)		CGIO improvement (scale 0–7)		CGIO severity (scale 0–7)	
Week	Olanzapine	Placebo	Olanzapine	Placebo	Olanzapine	Placebo	Olanzapine	Placebo	Olanzapine	Placebo	Olanzapine	Placebo
1	19.2 (15.2)	19.2 (12.2)	1.86 (1.2)	1.93 (0.9)	1.79 (1.3)	1.80 (0.9)	1.71 (1.2)	1.93 (1.0)	na	na	4.93 (1.0)	5.13 (1.1)
2	17.3 (8.6)	12.6 (7.2)	1.53 (0.8)	2.07 (1,0)	1.87 (1.0)	2.00 (1.2)	1.60 (1.0)	2.00 (1.0)	3.36 (1.0)	3.43 (1.0)	4.47 (1.1)	4.71 (1.0)
3	16.6 (9.8)	14.4 (9.1)	1.58 (0.7)	1.71 (1.0)	1.75 (1.0)	1.64 (1.1)	1.58 (0.80)	1.71 (1.0)	2.67 (1.2)	2.42 (1.0)	3.58 (1.1)	3.58 (1.2)
4	18.2 (17.8)	13.8 (6.1)	1.46 (1.0)	1.47 (0.9)	1.62 (1.1)	1.27 (0.9)	1.38 (1.2)	1.33 (0.8)	2.85 (0.9)	2.47 (1.1)	3.62 (1.3)	3.67 (1.3)
5	14.3 (11.4)	13.8 (11.1)	1.21 (0.8)	1.83 (1.1)	1.29 (0.8)	1.62 (1.0)	1.43 (1.0)	1.85 (1.0)	3.17 (0.9)	2.54 (1.1)	4.00 (1.3)	3.54 (1.4)
6	14.7 (11.2)	11.2 (8.9)	1.85 (0.8)	1.38 (1.0)	1.77 (0.9)	1.31 (1.2)	1.92 (0.8)	1.15 (1.0)	2.75 (1.1)	2.08 (1.1)	3.83 (1.3)	3.08 (1.3)
7	11.8 (6.4)	12.2 (7.8)	1.30 (0.7)	1.54 (0.9)	1.30 (0.7)	1.46 (1.1)	1.4 (0.8)	1.54 (1.0)	2.87 (1.0)	2.23 (1.2)	4.00 (1.5)	3.31 (1.2)
8	12.2 (5.0)	11.5 (10.4)	1.33 (0.9)	1.58 (1.4)	1.33 (0.9)	1.42 (1.2)	1.33 (0.9)	1.58 (1.4)	3.33 (0.8)	2.25 (1.2)	4.78 (1.4)	3.33 (1.8)
9	10.3 (5.6)	11.8 (9.4)	1.40 (0.8)	1.08 (1.1)	1.60 (1.0)	1.08 (1.3)	1.40 (0.8)	1.00 (1.0)	2.78 (1.2)	2.18 (1.0)	3.61 (1.5)	3.18 (1.5)
10	13.8 (7.7)	9.8 (8.7)	1.27 (0.9)	0.92 (0.9)	1.45 (1.1)	0.83 (0.8)	1.36 (1.0)	1.00 (1.0)	2.73 (1.1)	2.55 (1.1)	4.18 (1.8)	3.82 (1.5)
11	8.6 (5.2)	9.3 (6.7)	1.40 (0.5)	1.0 (0.9)	1.10 (0.3)	1.00 (1.2)	1.10 (0.3)	0.69 (0.7)	2.70 (1.1)	2.23 (1.2)	3.90 (1.5)	3.31 (1.4)
12	14.4 (9.7)	8.8 (6.5)	1.30 (0.8)	1.0 (0.9)	1.30 (0.8)	1.00 (1.0)	1.00 (0.9)	1.00 (0.9)	2.63 (0.7)	2.31 (1.2)	3.50 (1.4)	3.38 (1.6)

[a] CSSA scores are weekly means (standard deviation).

mixed effects models. In each case the scales showed a significant decline over the 12 weeks: duration ($t = -3.16$, $P = 0.002$); frequency ($t = -2.94$, $P = 0.004$), and intensity ($t = -2.93$, $P = 0.004$). There was no medication effect on either duration ($t = -0.04$, $P = 0.97$), frequency ($t = 0.50$, $P = 0.62$), or intensity ($t = -0.39$, $P = 0.7$).

3.7. Results from CSSA

Cocaine withdrawal severity was measured by scores on the CSSA (Table 3). There was no medication effect on CSSA scores ($t = -0.75$, $P = 0.46$), but there were significant main effects of time ($t = 2.52$, $P = 0.01$) and baseline score ($t = 6.71$, $P < 0.0001$), and their interaction ($t = -3.44$, $P = 0.0006$). Thus, cocaine withdrawal severity measured by scores on the CSSA declined over time in both groups with greater declines noted among subjects with higher baseline CSSA scores.

3.8. Medication adherence

Medication adherence was measured by pill count. Both groups showed good adherence, with no significant difference in adherence between groups. The average percentage of prescribed pills taken by the olanzapine-treated subjects was 84.5% compared to 89.3% in placebo-treated subjects ($t = 0.629$, df = 28, ns).

3.9. Safety analyses

3.9.1. Adverse events

Olanzapine was well tolerated. Adverse events were recorded by a modified version of the SAFTEE. This instrument allowed for the spontaneous reporting of adverse events as well as specifically screening for seven adverse events known to be associated with olanzapine. Adverse events reported included: weight gain (40%), drowsiness (40%), constipation (13%), dizziness (10%), dry mouth (7%), nausea (7%), restlessness (7%) and urticaria (3%). Adverse events were mainly mild and evenly distributed between the olanzapine and placebo groups. There were no significant differences noted in the occurrence of any adverse event between the two groups. There were no medication associated serious adverse events reported. On average olanzapine-treated subjects gained slightly less weight during the trial compared to placebo-treated subjects. Olanzapine-treated subjects gained, on average, 2.86 lbs during the trial compared to 3.93 lbs gained, on average, by the placebo-treated subjects ($t = 0.272$, df = 27, $P = 0.788$).

3.9.2. Movement disorders

Screening for abnormal movements using the AIMS revealed no treatment emergent abnormal movements. Screening for akathisia using the Barnes Akathisia Rating Scale revealed no cases of akathisia determined by a score of two or more on the Global Clinical Assessment of Akathisia. Five subjects, all receiving olanzapine, reported restlessness at one visit. However, this restlessness was transient and resolved by the next week without a change in dose. One placebo subject was noted to have abnormal movements but this was attributed to a familial dyskinesia. There were no significant extrapyramidal side effects associated with olanzapine as measured by scores on the Simpson Angus Scale. Only two olanzapine subjects reported treatment emergent mild rigidity that resolved within 1–2 weeks without a change in dose. Overall, olanzapine use resulted in no occurrence of movement disorders typically associated with antipsychotic medications.

3.9.3. Missing data

Although 27/30 subjects completed the study there were a number of missed visits resulting in missing data. The data most affected by missed visits were the UBT. One hundred sixty-seven urine samples out of 750 or 22.3% of the urine samples were missing. In order to determine if missing data might affect interpretation of the study results, the number of urine samples submitted was correlated with baseline demographic and drug use variables as well as outcome variables including ASI results. The number of urine samples submitted did not correlate significantly with any baseline demographic or drug use variable. The number of urine samples submitted did not correlate significantly with any outcome measure except the psychiatric composite score ($r = -0.445$, $P = 0.020$, $N = 27$).

To further assess the sensitivity of our analyses to missing data, we used a pattern-mixture approach (Little, 1994; Hedeker and Gibbons, 1997) to test for differences in regression relationships across observed patterns of missed data. As our sample size is small, we used the number of missed visits as a (continuous) indicator of pattern, rather than considering discrete indicators such as the time of drop out. We reran each of the analyses described above, including a main effect term for number of missed visits, and an interaction term between number of missed visits and medication group (Hedeker and Gibbons, 1997). These additional terms did not attain significance (even at the 10% level) for any of the analyses, suggesting that the missing data are ignorable. For the cocaine urines, we also reran the analyses with all missing visits coded as dirty, and found that the results did not change.

4. Discussion

This study was a rapid screening trial intended to determine if olanzapine showed any promise for the

treatment of cocaine dependence. We found that, although olanzapine was well tolerated in cocaine dependent subjects, it did not appear to have efficacy. In the primary outcome measure, cocaine abstinence measured by qualitative UBT, placebo-treated subjects were significantly more likely to remain abstinent from cocaine compared to olanzapine-treated subjects. In addition, olanzapine was not superior to placebo in any of the secondary outcome measures including self-reported cocaine use, cocaine craving, mood and anxiety symptoms, and measures taken from the ASI. Moreover, we found that placebo-treated subjects attended more evaluation visits than did olanzapine-treated subjects.

Despite the fact that olanzapine was well tolerated among our subjects, it should be kept in mind that olanzapine does have serious side effects including weight gain and diabetes and that these side effects alone may limit its usefulness. In this trial, subjects treated with olanzapine did not gain more weight on average than placebo-treated subjects. This may have been due to the fact that the olanzapine-treated subjects were more likely to continue using cocaine during the trial. None of the olanzapine-treated subjects developed diabetes. Despite the fact that olanzapine-treated subjects did not report more side effects, we cannot rule out the possibility that the increased dropout rate seen among olanzapine-treated subjects may have been due to unreported side effects.

The fact that olanzapine was associated with more cocaine use and worse treatment retention compared to placebo may be attributed its effects on dopamine receptors. The results of this trial could be considered predictable based on some animal models of cocaine self-administration in which pre-treatment with dopamine antagonists show increased cocaine self-administration (Corrigall and Coen, 1991; Hubner and Morton, 1991; Caine and Koob, 1994). This is thought to be due to the reduced effects of cocaine as a result of dopamine antagonism. Such an increase in cocaine self-administration is usually seen in models in which the dose of cocaine is relatively high and the demands placed on the animal to obtain cocaine are relatively low (Hubner and Morton, 1991; Caine and Koob, 1994). This animal model may be an appropriate one for this trial, which was conducted in an environment in which cocaine was readily available, relatively inexpensive, and subjects used cocaine mainly in a binges during which large amounts of cocaine were consumed. Whether or not individual subjects used more cocaine during each episode of cocaine use after they were treated with olanzapine could not be determined with the relatively insensitive measures of quantity of cocaine use we employed in this trial.

Another explanation for the worse outcome among olanzapine-treated subjects may be a worsening of cocaine withdrawal symptoms due to blockade of dopamine receptors. In animals, abrupt cessation of cocaine administration is associated with reduced dopaminergic activity and changes in brain reward thresholds thought to model the post-cocaine depression and irritability seen in humans. Markou and Koob (1991) examined brain reward thresholds in cocaine withdrawn rats using intracranial self-stimulation (ICSS) thresholds. During withdrawal from a cocaine binge, ICSS threshold were elevated compare to pre-drug baseline levels and to control animal thresholds. This was thought to reflect an anhedonic state. The magnitude and duration of this anhedonic state was proportional to the amount of cocaine consumed during the binge. This elevation in ICSS threshold was reversed with the administration of the dopamine agonist bromocriptine (Markou and Koob, 1992).

In humans, chronic cocaine use has been associated with diminished dopaminergic neurotransmission which may underlie impaired hedonic function and increased craving (Dackis and O'Brien, 2002). As a dopamine antagonist, olanzapine may worsen this hedonic dysregulation and this may have made it difficult for olanzapine-treated subjects to remain abstinent. However, if olanzapine had any effects on hedonic dysregulation these effects were too subtle to be observed in measures of mood and anxiety or in measures of cocaine withdrawal symptoms. Scores on the Hamilton Depression Rating Scale, the Hamilton Anxiety Rating Scale and the CSSA were not significantly different in olanzapine-treated subjects compared to placebo-treated subjects.

Results from at least one trial of atypical antipsychotics for patients with both cocaine dependence and schizophrenia have shown positive results. Risperidone was found to be effective in reducing craving and relapse among cocaine dependent schizophrenics in an open trial (Smelson et al., 2002). It may be that the effects of the atypical antipsychotics on symptoms of schizophrenia, particularly the negative symptoms of schizophrenia, may make these medications useful for cocaine dependent patients with schizophrenia.

The current study has several weaknesses. First, the number of subjects included was small. As a result, the sample may not be representative of all cocaine users in all treatment centers. For example, almost all the subjects were African–American men who were fairly heavy cocaine users, and almost all of the subjects continued to use cocaine during the baseline week. Therefore, the results may not be generalizable to other populations of cocaine users with less severe cocaine dependence or to cocaine dependent patients who are able to achieve some measure of abstinence prior to starting medications. Finally, the dose of olanzapine selected was well below the maximum safe dose of

olanzapine, and perhaps a higher dose would have yielded different results.

Despite its flaws, this trial was able to yield important data regarding the ability of olanzapine to influence outcome in the outpatient treatment of cocaine dependence. In none of the several outcomes measured was there even a suggestion that olanzapine was superior to placebo, and in two important measures, treatment retention and urine toxicology results, placebo was superior to olanzapine. Thus, based on the results of this trial, olanzapine does not appear to be promising for the treatment of cocaine dependence. Moreover, in actively using cocaine dependent patients, olanzapine may worsen cocaine treatment outcome.

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