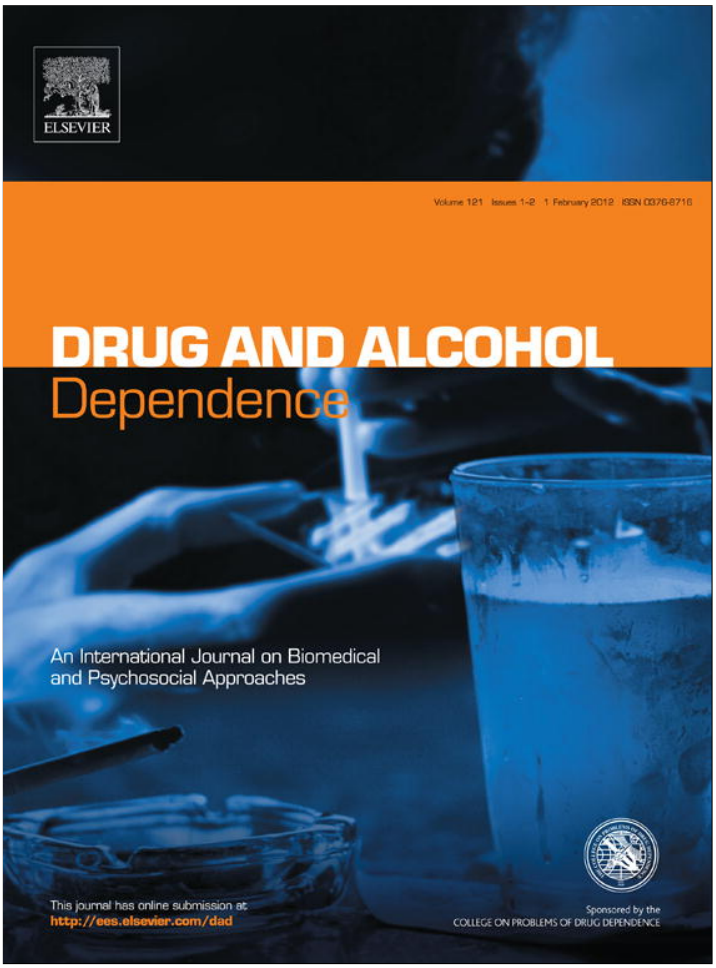

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Short communication

Results of an initial clinical trial of varenicline for the treatment of cocaine dependence

Jennifer G. Plebani*, Kevin G. Lynch, Qin Yu, Helen M. Pettinati, Charles P. O'Brien, Kyle M. Kampman

University of Pennsylvania, Department of Psychiatry, Treatment Research Center, 3900 Chestnut Street, Philadelphia, PA 19104, United States

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ABSTRACT

Background: Cocaine use, abuse and dependence remains a pressing public health problem. Based on its mechanism of action, varenicline, an alpha4beta2 partial agonist seemed to be a likely candidate for treating cocaine dependence.
Methods: Cocaine dependent participants ($n = 37$) were enrolled in a 9-week double-blind placebo controlled clinical trial. Varenicline was titrated up to a target dose of 1 mg BID during the first week of medication.
Results: Varenicline was associated with lower odds of cocaine use than placebo (OR = 2.02, $p = 0.08$), as measured by thrice-weekly urinalysis results. Compared to placebo-treated participants, varenicline treated participants had significantly decreased rates of cocaine reward, as measured by the Multiple Choice Procedure (MCP) ($p = 0.02$).
Conclusions: Varenicline appears to decrease cocaine use and reward, suggesting that further investigation of varenicline may be warranted.

1. Background

The role of the cholinergic system in cocaine abuse and dependence is complicated (c.f., Williams and Adinoff, 2008). Acetylcholine (Ach) directly influences glutamatergic and GABAergic effects on midbrain dopamine neurons, which effects striatal dopamine release (Grillner et al., 2000). Cocaine has been shown to increase ACh in the nucleus accumbens (NAc), likely through D1 induced stimulation (Williams and Adinoff, 2008). Cocaine also has non-dopaminergic effects on ACh, affecting both mAChR and nAChR directly, suggesting that acetylcholine may play a central role in cocaine dependence.

Varenicline (Chantix™) is a partial agonist for the α4β2 nicotinic acetylcholine receptor subtypes. It has demonstrated efficacy as a treatment for smoking cessation (Oncken et al., 2006; Nides et al., 2006) and relapse prevention (Tonstad et al., 2006). Based on varenicline's specific affinity for the nicotinic acetylcholine receptors that are implicated in cocaine reward circuitry (c.f., Schoffelmeer et al., 2002; Panagis et al., 2000), it appears to be a good candidate for treatment of cocaine dependence. In addition to its partial agonist activity at heteromeric α4β2 nicotinic acetylcholine receptors, varenicline has also been shown to be a full agonist at homomeric α7 nicotinic acetylcholine receptors (Mihalak et al., 2006).

Although Poling et al. (2010) did not see an effect for varenicline in their pilot trial among methdone-maintained subjects, the present study tests the potential clinical efficacy of varenicline for cocaine dependence in a population with only cocaine dependence.

2. Methods

2.1. Participants

Thirty-seven treatment-seeking participants from the greater metropolitan Philadelphia area were randomized to participate in this trial. The University of Pennsylvania Institutional Review Board (IRB) approved the protocol as well as all recruitment materials. Participants provided written informed consent to participate in the trial. Participants met Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) criteria for cocaine dependence and reported using at least $200 worth of cocaine in the past 30 days. Individuals were excluded from the study if they were dependent on any other substance (except nicotine) or had active and serious medical or psychiatric illness. Individuals with a history of bipolar disorder, taking psychotropic medications or agents that could interact with varenicline, or having abnormal baseline laboratory findings were also excluded. Pregnant and breastfeeding women were excluded and women of childbearing potential were only randomized if they agreed to use acceptable birth control methods. Due to concerns about varenicline exacerbating suicidal and homicidal behavior, individuals with a history of either (as measured by the SCID), as well as those with depression (evidenced by a Hamilton Depression Rating Score > 10) were excluded from the study.

2.2. Study design

This was a randomized, double-blind, placebo-controlled 9-week trial of varenicline for cocaine dependence. A 1-week screening period included a comprehensive

* Corresponding author. Tel.: +1 215 222 3200x152; fax: +1 215 386 5106.
E-mail address: plebani_j@mail.trc.upenn.edu (J.G. Plebani).

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medical history, physical examination, clinical laboratory studies, vital signs and a 12-lead electrocardiogram (ECG). The diagnosis of current cocaine dependence was established with a Structured Clinical Interview for DSM IV (SCID) (First et al., 1996), and other psychiatric disorders were ruled out with the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998). After screening, eligible patients were randomized to varenicline 2 mg/day ($n = 18$), or matching placebo ($n = 19$) for the 8-week treatment course. Study medications were initiated at 0.5 mg/day and titrated up to the full dose (2 mg/day) by the end of the first week. Participants were reduced to 1 mg/day for the final week of medication during the study.

Participants provided thrice-weekly urine samples which were analyzed for the major cocaine metabolite, benzoylecgonine (BE). Individual, manual-guided CBT (adapted for substance abuse) was provided once weekly (total of 8 sessions) (Carroll, 1998). Safety data were also collected weekly. In addition, patients' mood was assessed at visits by study staff to ensure no development of depression, suicidal ideation and/or homicidal behavior.

2.3. Outcome measures, schedule of assessments, and sample size

The primary measure of efficacy was cocaine use based on thrice-weekly semi-quantitative urine BE assays. Secondary efficacy measures included the nurse-rated Clinical Global Impression-Objective (CGI-O) Scale (Guy, 1976), and the Brief Substance Craving Scale (BSCS) (Somoza et al., 1995), the Cocaine Selective Severity Assessment (CSSA) (Kampman et al., 1998), Hamilton Anxiety Scale (Ham A) (Hamilton, 1959), Hamilton Depression Scale (Ham D) (Hamilton, 1967), and the Multiple Choice Procedure (MCP) (Griffiths et al., 1993), which were rated weekly, and the Timeline Follow-Back Interview (TLFB) (Sobell and Sobell, 1995) which was done at each study visit. Additional clinical and psychosocial characteristics were assessed at baseline, mid-study, and at end of study with the Addiction Severity Index (ASI) (McLellan et al., 1992).

2.4. Attendance contingencies

Participants were encouraged to attend all visits through use of attendance contingencies. Participants could earn draws from the "fishbowl" (c.f. Petry and Martin, 2002) for attendance and completion of all visit requirements. Participants earned draws for completing each visit, with bonus draws available for attending all three required visits in a given week. The values of the chips and their proportion in the fishbowl were as follows; 250 (50%) of chips worth $0 (Good Job!), 219 (43.8%) of chips worth $1, 30 (6%) of chips worth $25, and 1 (0.2%) worth $100. Earnings from the $1 draws were provided in cash at the same visit, earnings from $25 and $100 draws were provided in the form of gift cards of the subject's choosing.

2.5. Statistical analysis

Baseline measures between the varenicline and placebo groups were compared using t-tests for continuous variables and χ^2-tests for dichotomized variables. Urine toxicology results were compared by the generalized estimating equations (GEE) (Diggle and Kenward, 1994). GEE models were also used to compare secondary outcomes. In all GEE models, a pre-treatment version of the response was included as a covariate, together with the treatment group indicator, and a linear time effect. The two-way interactions between these covariates, and terms for higher order time effects, were considered for inclusion by examining the p-values of regression coefficients for the GEE model. A compound symmetry structure was used for the working correlation matrix.

3. Results

3.1. Baseline demographics and drug use

The two groups were very similar on most baseline characteristics (Table 1). There was a significant difference only for composite legal score between the varenicline and placebo groups ($F = 4.44$, $p = 0.04$).

3.2. Missing data

There were a relatively small number of missed visits resulting in missing data (see Fig. 1, top panel). Each group provided 77% of their scheduled treatment urines. Time to last visit was not significantly different between the groups ($F = 2.77$, $p = 0.10$).

3.3. Cocaine use (UDS)

For the cocaine use results, treating missing urines as cocaine-positive, and controlling for baseline use, the placebo group was about twice as likely to use cocaine as the varenicline group (OR = 2.02, 95% CI = (0.91, 4.48), $p = 0.08$) (Fig. 1, second panel). If missing urines are treated as ignored, the direction of the effect is the same, although the estimated effect is slightly smaller (OR = 1.86, 95% CI = (0.74, 4.70), $p = 0.19$).

Table 1
Study demographics.

	Varenicline	Placebo
Male (%)	69.57	75.00
African American (%)*	89	67
Days of alcohol use in past 30 days	1.56(1.46)	6.06(8.93)
Days of cocaine use in past 30 days	13.13(8.55)	15.39(10.21)
$ spent for drugs	534.38(516.42)	911.88(980.98)
Years of cocaine use, lifetime	11.67(7.39)	11.94(9.06)
ASI Composite Drug Score	0.22(0.04)	0.25(0.07)
ASI Composite Alcohol Score*	0.03(0.05)	0.08(0.10)
ASI Composite Employment Score	0.72(0.22)	0.66(0.26)
ASI Composite Legal Score	0.07(0.17)	0.07(0.13)
ASI Composite Family/Social Score	0.09(0.16)	0.11(0.14)
ASI Composite Psychiatric Score	0.07(0.14)	0.13(0.17)
ASI Composite Medical Score*	0.04(0.17)	0.20(0.36)

* $ps < 0.03$.

3.4. Secondary outcomes

Changes from baseline to mid study, baseline to end of the study, and mid study to end of the study were examined for the Addiction Severity Index (ASI). Varenicline-treated participants were more likely to have less days of alcohol use ($F = 5.98$, $p = 0.015$) from baseline to mid study, but there were no time by medication group interaction effects. Varenicline-treated participants were more likely to have lower ASI composite medical scores compared with placebo-treated participants from mid study to the end of the study ($F = 3.86$, $p = 0.05$), but there were no time by medication group interaction effects. Most measures showed significant improvement across the three timepoints, but no difference between groups. These included days of cocaine use, dollars spent on drugs, as well as composite drug, medical and psychiatric scores (all $ps \leq 0.05$).

As measured by the Multiple Choice Procedure (MCP), varenicline treated participants had significantly decreased rates of cocaine reward compared to placebo-treated participants ($p = 0.02$) (Fig. 1, third panel).

The Brief Substance Craving Scale (BSCS) composite measure combines three cocaine craving domains: intensity, duration and frequency. Cocaine craving showed a significant decline over the trial in both groups ($F = 20.34$, $p < 0.001$).

The Cocaine Selective Severity Assessment (CSSA) composite, a measure of cocaine withdrawal symptoms, showed a significant decline over the trial in both groups ($F = 8.42$, $p = 0.004$) (Fig. 1, bottom panel).

The Hamilton Depression Scale (HAM-D) examines depression intensity. Depression scores showed a significant decline over the trial in both groups ($F = 8.62$, $p = 0.003$). Varenicline-treated participants were more likely to have lower HAM-D scores compared with placebo group, but there was no significant difference between these two groups ($F = 0.01$, $p = 0.90$).

The severity and improvement scores for the Clinical Global Impression Scale (CGI) were treated as either continuous, dichotomized, or categorical (3 categories). If treated as continuous variables, CGI severity scores ($F = 46.07$, $p < 0.001$) and CGI improvement scores ($F = 37.11$, $p < 0.001$) changed significantly in both groups over time, with CGI severity decreasing and CGI improvement increasing, but there was no significant time by treatment interaction for CGI severity scores and CGI improvement scores. If CGI severity and improvement were dichotomized into low and

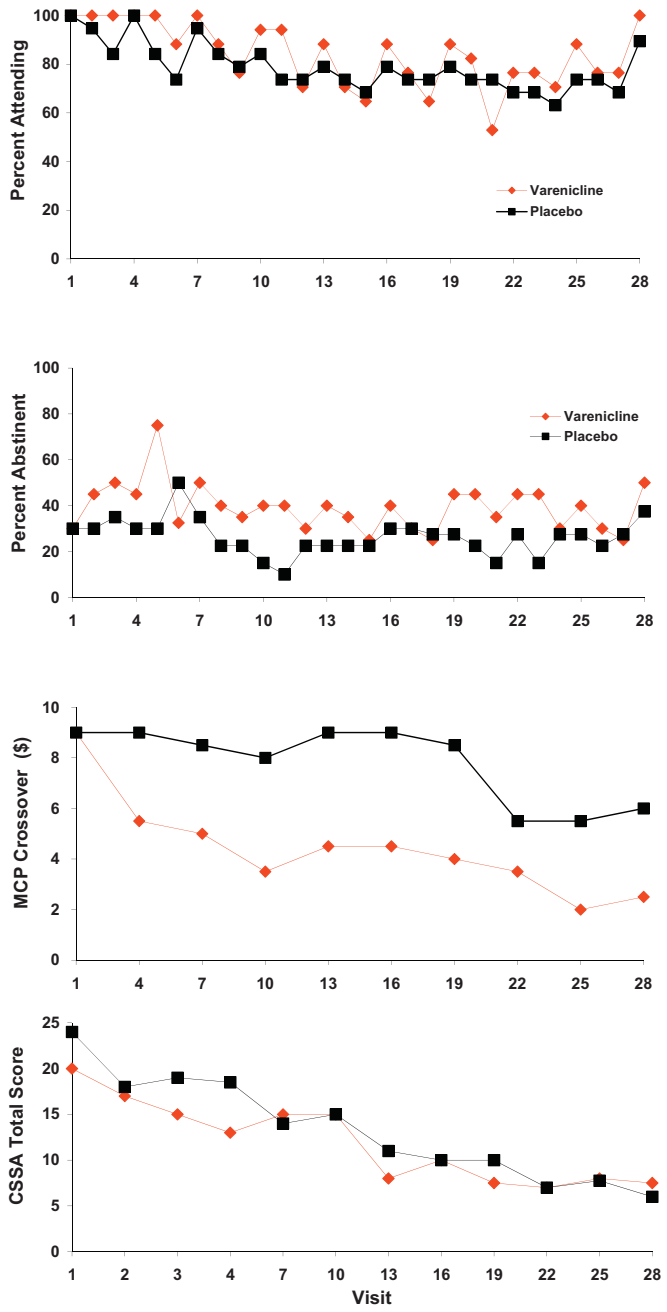

Fig. 1. Attendance rates for the varenicline and placebo groups. Both groups attended approximately 77% of visits, with no significant difference in time to last visit ($F = 2.77$, $p = 0.10$). Cocaine use results as measured by semi-quantitative benzoylecgonine levels. Varenicline treated participants had lower rates of cocaine use than did placebo-treated participants (OR = 2.02, $p = 0.08$). Results from the Multiple Choice Procedure (MCP), showing devaluation of cocaine over time in the varenicline-treated group, as compared to a fairly steady-state level in placebo-treated participants ($p = 0.02$). Results from the CSSA. Both varenicline and placebo-treated groups show significant decreases in craving from baseline to end of study ($p = 0.004$).

high categories, there was a significant time main effect for CGI severity ($F = 6.90$, $p = 0.009$) associated with a decreasing trend over time with no significant time by treatment group interaction. CGI improvement showed a significant increasing trend ($F = 25.19$, $p < 0.001$), but no significant time by treatment group interaction. If there were three categories (low, mild and high scores) for CGI severity and improvement, there was a decreasing trend for CGI severity ($F = 12.00$, $p < 0.001$). For CGI improvement, there was a significant increasing trend for CGI improvement ($F = 12.63$, $p < 0.001$); there was no significant interaction shown for time by treatment interaction.

4. Discussion

This study was a small preliminary trial, and thus was underpowered for anything less than large effects. However, our data suggest a small to moderate effect for varenicline on cocaine use. The MCP, a measure of cocaine reinforcement, showed significant improvement among varenicline treated participants as compared to placebo treated participants. Taken together, these findings suggest that varenicline should be studied further, both to assess its efficacy for treating cocaine dependence, as well as to examine its mechanism of action. Additional subjective measures showed improvements in cocaine craving, mood, and global functioning in both varenicline and placebo treated participants. As participants attended the majority of visits and therapy sessions, such improvements could be attributed to attendance and treatment participation for both groups. We were able to keep attendance rates high and collect approximately 80% of the urine samples for analysis, which is significantly higher than in prior studies. As such, we are confident that the cocaine use rates we found in this study accurately reflect actual use patterns.

Our findings are opposite those of Poling et al. (2010), who found no effect of varenicline for cocaine use among methadone-maintained opiate dependent participants. In the Poling study, the only measure of cocaine use in that study was urine toxicology, while the present study also has measures of craving and cocaine reinforcement, where effects greater than the abstinence effects were found.

The findings herein suggest that future studies of varenicline for cocaine may be warranted, including those involving varenicline's mechanism of action and potential alterations in cocaine-derived reinforcement.

Role of funding source

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Contributors

Dr. Plebani wrote the first draft of the manuscript, managed the literature searches and summaries of previous related work, and directed the data analysis. Drs. Plebani, Kampman, Pettinati and O'Brien designed the study. Dr. Lynch and Dr. Yu undertook the statistical analysis. All authors contributed to and have approved the final manuscript.

Conflict of interest

No conflict declared.

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