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Short communication

Results from a pilot clinical trial of varenicline for the treatment of alcohol dependence

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ABSTRACT

Background: Alcohol use, abuse and dependence remain a pressing public health problem. Based on its mechanism of action, varenicline seemed to be a likely candidate for treating alcohol dependence.
Methods: Alcohol dependent subjects ($n = 40$) were enrolled in a 13-week double-blind placebo controlled clinical trial. Subject visits were once per week. At each visit, subjects were tested for breath alcohol levels, provided self-report data on alcohol and nicotine use, and on mood and craving. In addition, subjects received once a week medical management (MM).
Results: There was no difference between varenicline and placebo treated groups on any of the drinking outcomes. Compared to placebo-treated subjects, varenicline treated subjects had decreased rates of alcohol craving and cigarette smoking, as well as greater mood improvements during the later part of the study (weeks 6–13). In addition, among subjects who were cigarette smokers, those treated with varenicline were significantly less likely to report heavy drinking during the trial.
Conclusions: Although varenicline was not significantly more effective than placebo at reducing drinking during the trial, its effects on alcohol craving and mood suggest that future investigation of the mechanism of action of varenicline, as well as additional clinical studies may be warranted. In particular, the findings regarding the influence of smoking status on heavy drinking among varenicline-treated subjects should be investigated in future studies.

1. Introduction

Varenicline 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). 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, which may be key in reducing alcohol withdrawal and craving during early alcohol abstinence, as α7 receptors are implicated in the neural reward circuitry activated by alcohol use (Mihalak et al., 2006; Bowers et al., 2005). Varenicline's ability to occupy the α7 and α4β2 nicotinic receptors, blocking alcohol's effects on those receptors, should reduce the euphoric and reinforcing effects of alcohol ingested during varenicline treatment. Support for this comes from the non-specific nAChR antagonist mecamylamine, which attenuates the reinforcing effects of alcohol, reducing alcohol consumption in animal models (Larsson and Engel, 2004). Mecamylamine studies in humans have shown that social drinkers treated with mecamylamine experience less euphoria and stimulating effects from alcohol than normal (Chi and de Wit, 2003) as well as decreases in the reinforcing effects of alcohol, and BAL decreases (Blomqvist et al., 2002). However, as mecamylamine causes autonomic side effects it is an impractical treatment for alcohol dependence.

A promising study examining the impact of varenicline on alcohol self-administration in rats showed a decrease in ethanol self-administration with acute administration of varenicline at doses of both 1 mg/kg and 2 mg/kg (Steensland et al., 2007). As testing of sucrose self-administration showed no decrease with varenicline, varenicline appears to be a highly specific target for alcohol-derived reinforcement. A human laboratory study examining the effects of varenicline on drinking behavior among heavy drinking smokers also showed reduced alcohol self-administration during varenicline treatment, as well as reduced alcohol craving (McKee et al., 2009). Taken together, the findings from these

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seminal studies make a strong case for testing varenicline clinically for the treatment of alcohol dependence in humans.

2. Methods

2.1. Subjects

We randomized 40 treatment-seeking participants from the greater metropolitan Philadelphia area to participate in this trial. The University of Pennsylvania Human Investigations Committee (IRB) approved the protocol as well as all print advertisements that were used for recruitment. Subjects provided written informed consent to participate in the trial. Subjects met Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) criteria for alcohol dependence and reported drinking on at least 12 of 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, were taking psychotropic medications or agents that could interact with varenicline, or had abnormal baseline laboratory findings. Pregnant and breastfeeding women were excluded and women of childbearing potential were only randomized if they agreed to use acceptable birth control methods.

2.2. Study design

The primary study objective was to evaluate the efficacy of varenicline treatment for alcohol dependence based on self-reported use, gathered using the Time-Line Follow Back (TLFB). A screening period (3–4 visits) included a comprehensive medical history, physical examination, clinical laboratory studies, vital signs and a 12-lead electrocardiogram (ECG), and was repeated at the end of the study after discontinuation of study medications. Current alcohol 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 ($n = 19$), or matching placebo ($n = 21$) for the 12-week treatment course. A research pharmacist generated the allocation sequence, assigned group participation, and was solely aware of the medication assignment code that was only available for emergency access. Research personnel who enrolled, treated, and assessed the patients were unaware of patient assignments. Urn randomization was used to stratify patients across the experimental conditions based on gender, race and cigarette smoking status. The study physician dispensed study medications (varenicline and matched placebo provided by Pfizer for use in this study) on a weekly basis in blister packs that contained a 9-day supply to cover missed visits. Patients were paid $5 for each returned blister pack to facilitate accurate pill counts. Study medications were initiated at .5 mg/day and titrated (0.5 mg o.d. for days 1–3, 0.5 mg b.i.d. for days 4–7), up to the full dose (1 mg b.i.d.) by the end of the first week. Subjects were reduced to 1 mg/day for the final week of medication during the study.

Subjects attended one clinic visit per week and provided breath samples during each visit, which assessed recent drinking. TLFB data on all drinking and other drug use were collected at each visit, as were data on mood, adverse events, concomitant medications, and global improvement. Individual, manual-guided MM was provided once weekly (total of 12 sessions). Safety data was also collected at each visit, including blood pressure, pulse, temperature, body weight, urine testing for other substances and adverse events.

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

The primary measure of efficacy was alcohol use based on self-reported alcohol use collected using the TLFB (Sobell and Sobell, 1995). Our secondary efficacy measures included self-reported smoking behavior; mood as measured by the Hamilton Anxiety Scale (Ham A; Hamilton, 1959) and Hamilton Depression Scale (Ham D; Hamilton, 1967), global improvement as measured by the nurse-rated Clinical Global Impression-Objective Scale (CGI-O; Guy, 1976), and the Clinical Global Impression Scale-Subjective Scale (CGI-S; Guy, 1976), as well as alcohol craving s measured by the Penn Alcohol Craving Scale (PACS; Flannery et al., 1999). Additional clinical and psychosocial characteristics were assessed at baseline and at end of study with the Addiction Severity Index (ASI; McLellan et al., 1992).

2.4. Attendance contingencies

Subjects were encouraged to attend all visits through use of attendance contingencies. Subjects earned payments on an escalating scale for attendance and completion of all visit requirements.

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. The number of sessions attended for each group during the trial was compared by using a t-test. Self-reported drinking results, as gathered by the TLFB, were compared by the generalized estimating equations (GEE; Diggle and Kenward, 1994), using Poisson models for counts of drinking and heavy drinking days, and logistic regression models for absence/presence binary indicators of drinking. In the GEE model, the pre-treatment 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 were considered for inclusion by examining the p-values of regression coefficients for the GEE model. For the GEE model for the drinking outcomes, a compound symmetry structure was used for the working correlation matrix.

Table 1
Baseline demographics.

	Varenicline	Placebo
Male (%)	78.9	90.5
African American (%)	57.9	28.6
Age (years)	44.8(12.3)	48.1(10.5)
Days of alcohol use in past 30 days	18.4(8.8)	17.6(9.1)
$ spent for alcohol in past 30 days	197(152)	165(137)
Years of alcohol use, lifetime	18.7(10.7)	21.2(12.0)
ASI Composite Alcohol Score	0.61(0.16)	0.60(0.15)
ASI Composite Employment Score	0.52(0.32)	0.46(0.27)
ASI Composite Legal Score	0.04(0.11)	0.02(0.08)
ASI Composite Family/Social Score	0.18(0.23)	0.14(0.20)
ASI Composite Psychiatric Score	0.06(0.10)	0.08(0.14)
ASI Composite Medical Score	0.16(0.30)	0.14(0.24)

3. Results

3.1. Baseline demographics

On the whole, the two study groups, varenicline and placebo, were very similar in demographics and baseline use characteristics (see Table 1). There were more African American subjects in the varenicline group as compared to the placebo group ($p = 0.06$).

3.2. Alcohol use results (TLFB)

There were no significant group effects for weekly days of alcohol use (beta = log(rate) = −0.14, exp(beta) = rate = 0.87, $\chi^2(1) = 0.18$, $p = 0.67$) or for presence/absence of alcohol use (beta = logodds ratio = −0.16, exp(beta) = odds ratio = 0.86, $\chi^2(1) = 0.07$, $p = 0.80$). The varenicline group had slightly lower numbers of heavy drinking days (Fig. 1a; beta = −0.67, exp(beta) = 0.51, $\chi^2(1) = 0.2.71$, $p = 0.10$), corresponding to the placebo group having an average of 1.95 times more heavy drinking days per week. There was no significant effect for presence/absence of heavy drinking (beta = −0.86, OR = 0.42, $\chi^2(1) = 1.98$, $p = 0.16$), although the varenicline group was less than half as likely as the placebo group to have heavy drinking in a given week.

3.3. Cigarette smoking results (TLFB)

At baseline smokers in the placebo group ($n = 8$) smoked an average of 15.01 (SD = 12.42) cigarettes per smoking day, while the varenicline-treated smokers ($n = 9$) averaged 13.88 (SD = 6.75), with no significant difference between the groups ($\chi^2(1) = 0.03$, $p = 0.87$). During treatment, smokers in the placebo group smoked an average of 13.99 (SD = 11.57) cigarettes per smoking day while the smokers in the varenicline group smoked an average of 8.79 (SD = 7.13), again with no significant difference between the groups ($\chi^2(1) = 1.26$, $p = 0.21$). Repeated measures negative binomial models comparing baseline and the treatment phase showed a significant group by time interaction for cigarettes per smoking day ($\chi^2(1) = 4.52$, $p = 0.03$), with a greater reduction for the smokers in the varenicline group.