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Varenicline for tobacco-dependence treatment in alcohol-dependent smokers: A randomized controlled trial

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ABSTRACT

Background: Tobacco use is prevalent among persons with alcohol abuse and dependence. Varenicline has been shown to be the most effective pharmacotherapy for smoking cessation and may decrease alcohol consumption. The purpose of this study was to evaluate the efficacy of 12 weeks of varenicline for increasing smoking abstinence rates in smokers with alcohol abuse or dependence.

Methods: Participants were eligible for enrollment if they were 18 years or older, smoked 10 or more cigarettes per day for at least 6 months, had current alcohol abuse or dependence, and were interested in quitting smoking. Participants were randomly assigned to receive 12 weeks of varenicline 1 mg twice daily or matching placebo. The primary end point was 7-day point prevalence smoking abstinence at week 12.

Results: The 7-day point prevalence smoking abstinence rate at 12 weeks was significantly higher with varenicline (n = 16) than placebo (n = 17) (43.8% vs 5.9%; $P = .01$). At 24 weeks, the 7-day point prevalence smoking abstinence rate was still significantly higher with varenicline than placebo (31.3% vs 0%; $P = .02$). At 12 weeks, mean (SD) drinks per drinking day was significantly lower with varenicline than placebo (5.7 [3.9] vs 9.0 [5.3] drinks; treatment effect estimate, −2.8 [90% CI, −6.6 to −1.0]). Adverse events were minor and comparable to varenicline clinical trials.

Conclusions: Varenicline is safe and efficacious for increasing smoking abstinence rates in smokers with alcohol abuse or dependence. Varenicline may decrease alcohol consumption in this population of smokers.

1. Introduction

Alcohol dependence is an important and prevalent public health problem affecting approximately 7% of the adult population of the United States (Substance Abuse and Mental Health Services Administration, 2015). Persons with alcohol abuse or dependence who actively seek treatment have long-term alcohol abstinence rates of 40% to 60%. Because of a high smoking prevalence and more frequent smoking, those with an alcohol use disorder are at increased risk for adverse health consequences from tobacco (Falk et al., 2006; Hurt et al., 1996). Smokers with alcohol abuse or dependence are less likely to quit smoking and have low abstinence rates when they do attempt to quit (Hughes and Kalman, 2006). Among smokers with alcohol abuse or dependence who are able to achieve alcohol abstinence, ongoing smoking increases the risk of relapse to alcohol use (Dawson, 2000).

Varenicline is 1 of 7 first-line medications currently available in the United States for treating tobacco dependence (Cahill et al., 2012; Clinical Practice Guideline Treating Tobacco Use, Dependence Update Panel Liaisons Staff, 2008; Jorenby et al., 2006). Varenicline is the most efficacious monotherapy for increasing smoking abstinence rates, with proven superiority over bupropion SR and nicotine-replacement therapy (Anthenelli et al., 2016; Cahill et al., 2012; Jorenby et al., 2006). In addition to helping smokers to stop smoking, varenicline has also been shown to decrease alcohol consumption in both animal models and human trials (Litten et al., 2013; Mitchell et al., 2012; Randall et al., 2015). Although some randomized trials have included participants who are in long-term stable recovery from alcohol abuse or dependence, active problem drinking has been an exclusion criterion for these early trials (Hays et al., 2011; Hays et al., 2009).

The goal of the current pilot study was to evaluate the efficacy of varenicline in smokers with current alcohol abuse or dependence. We hypothesized that 12 weeks of treatment with varenicline would be

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more effective than placebo for decreasing tobacco dependence rates, nicotine withdrawal symptoms, and alcohol consumption in this population.

2. Methods

The Mayo Clinic Institutional Review Board approved the study, which was preregistered at Clinical Trials.gov (NCT01347112) before recruitment and enrollment began. We recruited participants from the general population in the Rochester, Minnesota, area. Enrollment took place between July 2011 and April 2013. The study followed the CONSORT guidelines.

2.1. Participants

Participants were recruited through radio advertisements (74.9%), word of mouth (10.7%), Internet postings (5.9%), flyers (3.2%), and television advertisements (3.7%). Persons were eligible to participate if they: 1) were aged 18 years or older; 2) smoked on average 10 or more cigarettes per day for 6 months or more; 3) had alcohol dependence or abuse as assessed by the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998) and the physician investigator; 4) were currently drinking; and 5) were interested in quitting smoking.

Persons were excluded from study participation if: 1) they had a cardiac condition (angina, myocardial infarction, or coronary angioplasty within the past 3 months), an untreated cardiac dysrhythmia, kidney disease, or cancer; 2) they had psychosis, bipolar disorder, or unstable or untreated moderate or severe depression as assessed by the Center for Epidemiologic Studies-Depression scale (Radloff, 1977); 3) they had current nonspecific suicidal thoughts as defined by the Columbia-Suicide Severity Rating Scale (Posner, 2007) or had ever made a suicide attempt; 4) they had a varenicline allergy; 5) another member of their household was already participating in the study; 6) they were undergoing current treatment with another investigational drug within the past 30 days; 7) they had untreated hypertension or a baseline blood pressure higher than 180 mm Hg systolic or 100 mm Hg diastolic; 8) they were currently using a tobacco-dependence treatment involving a drug, behavioral intervention, or both; or 9) they were concurrently using another nicotine product other than cigarettes. Women of childbearing potential or women who were pregnant, breastfeeding, or likely to become pregnant and who were not willing to use contraception during the medication phase of the trial also were excluded.

2.2. Medication

Participants were randomly assigned to varenicline or placebo for 12 weeks, with follow-up at 6 months. Pharmacy personnel dispensed study medication into containers labeled with study identification numbers. Study participants, investigators, and pharmacy staff were blinded to treatment assignment. Participants assigned to varenicline started at a dosage of 0.5 mg once daily for 3 days, which increased to 0.5 mg twice daily for days 4–7, and then to a target dosage of 1 mg twice daily for 11 weeks. Participants assigned to placebo received identical-appearing tablets with the same dosing instructions. Participants set a *target quit day* for the eighth day of the study.

2.3. Study schedule

All interested persons called our clinical research center and completed a telephone prescreen. If they passed the telephone prescreen, they were invited to attend a one-on-one consent visit. If verified to be eligible for study participation, participants signed a written consent form and completed a baseline visit, at which time random assignment occurred, study drug was dispensed, brief counseling took place, and study assessments were completed. Participants were randomly assigned using a computer-generated sequence in a 1:1 ratio using Medidata Balance (Medidata Solutions, Inc). All participants received a personalized program consisting of brief behavioral counseling sessions ($\approx$10 min) during in-person clinic follow-up visits, based on the "Smoke Free and Living It" manual (Croghan et al., 2012). Clinic study visits occurred every week for weeks 1–4 and every other week for weeks 6–12. This was followed by an in-person visit 1 week after the end of treatment (week 13), 2 telephone calls at weeks 16 and 20, and a final end-of-study in-person visit at week 24.

2.4. Measures

Sociodemographic characteristics, smoking and alcohol history information, and the Mini-International Neuropsychiatric Interview for alcohol and drug dependence (Sheehan et al., 1998) were collected at baseline. Tobacco dependence was measured with the Fagerström Test for Nicotine Dependence (Fagerstrom and Schneider, 1989; Heatherton et al., 1991). The Timeline Followback method from the consent/screen visit to the baseline visit was used to collect alcohol use (Sobell and Sobell, 1992). Vital signs, expired air CO, and alcohol levels using breath testing were collected at every study visit before any intervention. Participants also completed the Minnesota Nicotine Withdrawal Symptoms measure (Hughes, 2007). Adverse events (AEs) and concomitant medication data were collected at every study visit by querying the participants with a reference point of "since your last visit." Data collection in this study used electronic data capture through Mayo Clinic Medidata Rave (Medidata Solutions, Inc).

2.5. Study end points

We used the same study end points for smoking that we used in a previous study (Ebbert et al., 2014). Seven-day point prevalence smoking abstinence rate was the primary study end point, which was defined in this study as self-reported, CO-confirmed, zero tobacco (chewing or smoking) use in the preceding week. A measured expired CO level ($\leq$8 parts per million) was used to confirm the smoking abstinence status reported by the participant. A secondary end point for smoking was 7-day point prevalence smoking abstinence at weeks 12 and 26. *Prolonged smoking abstinence* was defined if participants self-reported an answer of "no" to both questions: 1) Since 14 days after your target quit date, have you used any tobacco on each of 7 consecutive days? and 2) Since 14 days after your target quit date, have you used any tobacco on at least 1 day in each of 2 consecutive weeks?

A secondary end point for alcohol use was the decrease in the number of *heavy drinking days* ($\geq$5 standard alcohol drinks/day for men and $\geq$4 for women) during the final month of the treatment phase (weeks 9 through 12). Alcohol-use outcomes, collected at every visit, were determined using the Timeline Followback method for the 28-day period before the given visit. For weeks 12 and 24, alcohol-use outcomes for persons who discontinued the study before the given visit were imputed using the data for the 28-day period before the last study visit they attended.

2.6. Statistical analysis

Data are presented as mean (SD) for continuous variables and frequency (percentage) for nominal variables. Tobacco-use outcomes were analyzed using an intention-to-treat approach. For these analyses, any participant who missed a visit was classified as *smoking* for that assessment. For all tobacco abstinence outcomes, groups were compared by using the Fisher exact test, and 1-tailed P values are reported. For the primary end point, a 1-tailed P value < 0.20 was considered sufficient to suggest that a larger phase III study should be pursued (Rubinstein et al., 2005; Ratain and Sargent, 2009; Gan et al., 2010). Alcohol-use outcomes were analyzed using analysis of covariance, with treatment (varenicline vs placebo) as the independent variable and the baseline value of the given alcohol-use variable included as a covariate. To be