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Moderators of Varenicline Treatment Effects in a Double-Blind, Placebo-Controlled Trial for Alcohol Dependence: an Exploratory Analysis

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Abstract

Objectives—To explore if varenicline (Chantix[®]) showed more efficacy in treating certain subgroups of patients. In a recent multi-site trial, varenicline was shown to be effective in reducing drinking in alcohol dependent patients, both smokers and nonsmokers. Given the heterogeneity among alcohol dependent patients, secondary analyses were conducted to determine if certain subgroups responded more favorably than others to treatment with varenicline.

Methods—Data were drawn from a Phase 2 randomized, double-blind, placebo-controlled multi-site 13-week trial of varenicline in alcohol dependent patients (Litten et al., 2013). Seventeen moderator variables were selected for exploratory testing on the basis of theoretical and scientific interest.

Results—Of the 17 moderator variables assessed, four were statistically significant, including cigarettes per day reduction, treatment drinking goal, years drinking regularly, and age of patient. Two other variables—the type of adverse events experienced by patients and the severity of alcohol-related consequences—appeared to moderate the varenicline treatment effect at borderline statistical significance. Individuals who reduced the number of cigarettes per day experienced a significant effect from varenicline in reducing drinking, whereas those who did not change or who increased their number of cigarettes observed no beneficial effect. Reviewing the moderators related to severity, varenicline appeared to have greater efficacy than placebo among less severely-dependent patients.

Conclusions—Varenicline appears to be more efficacious in certain subgroups, particularly in those who reduced their smoking and in the “less severe” patient. Additional studies are warranted to confirm the results of these exploratory analyses.

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Keywords

Alcohol Dependence; varenicline; Chantix[®]; randomized placebo-controlled clinical trial; moderator subgroup

INTRODUCTION

During the past two decades, progress has been made in developing medications to treat alcohol dependence. Currently, there are four U.S. Food and Drug Administration (FDA)-approved pharmacotherapies for the treatment of alcohol dependence: disulfiram (Antabuse[®]), oral naltrexone (Revia[®]), acamprosate (Campral[®]), and the injectable suspension formulation of naltrexone (Vivitrol[®]). In addition, nalmefene (Selincro[®]) recently has been approved by the European Medicines Agency (EMA). Despite these advances, because of the heterogeneity that exists among the alcohol dependent population, none of these medications have been found to be effective for everyone and in every circumstance. Thus, it is a high priority to discover and develop new effective medications to treat this complex disorder.

Varenicline (Chantix[®]) (Pfizer, New York) is a partial agonist at the $\alpha 4\beta 2$ and a full agonist at the $\alpha 7$ nicotinic acetylcholine receptors (Mihalak et al., 2006; Nocente et al., 2013). It is FDA-approved for use as an aid in smoking cessation. Varenicline also appears to affect alcohol-drinking behavior. Several preclinical studies found varenicline effective in reducing drinking in rodents and baboons (Steensland et al., 2007; Bito-Onon et al., 2011; Wouda et al., 2011; Nocente et al., 2013; Kaminski and Weerts, 2014). In a human laboratory study, McKee et al., (2009) reported that varenicline reduced alcohol consumption, craving, and the reinforcing effects of alcohol in heavy drinkers who also were smokers. In addition, two small clinical studies found that varenicline reduced heavy drinking and alcohol craving in people who drank heavily and were smokers as well as in people who were alcohol dependent (Fucito et al., 2011; Mitchell et al., 2012). In another preliminary study, Plebani et al (2013) reported that varenicline reduced craving and improved mood in alcohol dependent patients (Plebani et al., 2013). The results of our recent multi-site clinical trial showed that varenicline was effective in reducing percent heavy drinking days (PHDD), drinks per day (DPD), drinks per drinking day (DPDD), and alcohol craving in alcohol dependent patients, regardless of their smoking status (Litten et al., 2013).

Given the heterogeneity among alcohol dependent patients, it is not surprising that pharmacotherapies may have differential effects for certain patient subgroups or populations. Understanding the moderators that influence the effectiveness of treatment may help identify those patients who will benefit the most from a particular medication. Several moderators have been explored in previous randomized clinical trials for alcohol dependence, such as gender (Bond et al., 2010; Greenfield et al., 2010), family history of alcoholism (Capone et al., 2011; Rohsenow et al., 2007), age of alcoholism onset (Kranzler et al., 2012; Rohsenow et al., 2007), severity of the alcohol dependence syndrome (Kampman et al., 2007), cigarette smoking (Fucito et al., 2012), comorbid marijuana use

(Rohsenow et al., 2007), baseline treatment goal (Mason et al., 2006), and medication adherence (Zweben et al., 2008).

Our recent multi-site study (Litten et al., 2013) collected data on a wide range of patients and enabled us to further explore the potential moderators that may influence varenicline's efficacy in the treatment of alcohol dependence. A total of 17 variables were selected for this exploratory secondary analysis on the basis of theoretical and scientific interest (Table 1). These included 14 baseline characteristics: (1) gender, (2) age, (3) years of drinking regularly, (4) parental problem drinking, (5) treatment drinking goal, (6) DPD during 28 days pre-screening and (7) DPD during 7 days pre-randomization, (8) pre-randomization reducer in DPD, (9) number of alcohol dependence criteria endorsed in the MINI assessment at screening, (10) the withdrawal criterion endorsed (MINI), (11) alcohol craving score (PACS) measured in Week 1 (Flannery et al., 1999), (12) alcohol consequence score (ImBIBe, a revised and abbreviated form of the DrInC [Miller, 1995; Werner et al., 2008]) measured in Week 1, (13) blood level of gamma-glutamyl transpeptidase (GGT) tested at screening, and (14) marijuana-positive urine test results at screening; and 3 variables observed during the treatment period: (1) varenicline-consistent adverse event (AE), (2) medication compliance, and (3) change in average number of cigarettes smoked per day (cigs/day) from Week 1 to Week 13 among smokers only.

METHODS

Study Design

The study design has been covered extensively elsewhere (Litten et al., 2013) and is briefly described in the following paragraphs. The Phase 2 double-blind, placebo-controlled trial was conducted at 5 sites over a 13-week period. Randomized patients (n=200) included 142 men and 58 women diagnosed with past year alcohol dependence according to the *Diagnostic and Statistical Manual, 4th edition Text Revision (DSM-IV-TR)* (American Psychiatric Association, 1994) and assessed by the MINI International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). Patients were eligible for the study if they were at least 18 years of age; reported drinking an average of at least 28 standard drinks per week for women or 35 drinks per week for men during the 28-day period prior to consent and the 7-day period prior to randomization; and did not reduce the total number of drinks per week by more than 50% between the 28-day period prior to consent and the 7-day period prior to randomization.

Patients were randomly assigned, in a 1:1 ratio, to receive either varenicline or placebo using a permuted stratified block randomization procedure. The stratification variables were clinical site and regular smoking (≥ 10 versus < 10 cigarettes smoked per day for the past week) (Gonzales et al, 2006). Six in-clinic visits (randomization and at the beginning of Weeks 2, 4, 6, 10 and 14) and 8 telephone visits (Weeks 3, 5, 7, 8, 9, 11, 12, and 13) were conducted.

The medication was dispensed to patients using a double-blind method, at regularly scheduled visits over the 13 weeks. Varenicline or an identical matching placebo was supplied in 0.5 mg over-encapsulated tablets. The amount was titrated from a starting dose

of 0.5 mg, taken once a day on Days 1 to 3 to 0.5 mg, taken twice a day, on Days 4 to 7. A target dose of 1 mg, taken twice daily, was maintained during Weeks 2–13. Patients who discontinued medication were allowed to remain in the study and participate in study assessments. Dosage compliance was verified by comparing the patient’s self-report with the number of pills removed from the blister pack. Besides medications, all patients were required to view *Take Control*—a novel computerized bibliotherapy platform derived from the National Institute on Alcohol Abuse and Alcoholism’s (NIAAA’s) self-help approach, *Rethinking Drinking* (NIAAA, 2009). *Take Control* consists of 6 modules. Patients were asked to view a single module at each clinic visit.

Drinking Measures

Drinking measures were captured via the Time-Line Followback and Form 90 interview methodology and procedures (Sobell and Sobell, 1992; Miller, 1996). One standard drink is 0.5 ounces of absolute alcohol, which is equivalent to 10 ounces of beer, 4 ounces of wine, or 1 ounce of 100-proof liquor. The a priori primary efficacy endpoint was PHDD, which was measured weekly during the maintenance phase of the study (Weeks 2–13). A “heavy drinking day” was defined as having 4 or more drinks per drinking day for women and 5 or more drinks per drinking day for men. A priori secondary efficacy endpoints included DPD, DPDD, and percent very heavy drinking days (PVHDD), which were measured weekly during Weeks 2 to 13. Alcohol craving was measured using the Penn Alcohol Craving Scale (PACS) in Weeks 5, 9, and 13. A “very heavy drinking day” was defined as having 8+ drinks for women or 10+ drinks for men in a single drinking day.

Definitions of Selected Moderator Variables for Secondary Analysis

Years of drinking regularly was calculated as current age minus age of onset of drinking regularly (“age when first started drinking alcohol regularly at least 3 times per month”). *Parental problem drinking* was established if the patient reported having either a father or mother with an alcohol problem. Patients’ *treatment drinking goal* was dichotomized as the desire to achieve total abstinence and never drink again vs. other outcomes (such as to drink occasionally when feeling the urge strongly, to become abstinent temporarily, to drink in a controlled manner, or to have no particular goal). *Pre-randomization reducers* were those participants who reduced their average number of drinks per day during the 28-day period before screening and the 7-day period before randomization.

Varenicline-consistent AEs included nausea, abnormal dreams, and constipation. Litten and colleagues (2013) found these three AEs to be significantly greater in the varenicline group compared with the placebo group. These three AEs also were the most common side-effects listed in varenicline’s (Chanix) package insert (<https://www1.pfizerpro.com/hcp/chantix/safety#cae>). The AE variable was selected to determine if the varenicline effect persisted even among patients who might have believed -- because they did not experience the side-effects listed in the consent forms -- that they were receiving a placebo rather than the active medication. *Good medication compliance* was defined as a self-reported total intake of >305 pills from Weeks 2 to 13, approximating the consumption of more than 90% of the prescribed medication. Previously, smoking status (smoker versus non-smoker) was not found to be a significant moderator of varenicline’s treatment effect (Litten et al., 2013). In

the present study, however, smokers were further stratified into those who reduced their smoking during treatment versus those who increased or remained the same. Reducers were patients who reported smoking fewer cigarettes per day in Week 13 than in Week 1.

Exploratory analyses of prior alcohol pharmacotherapy trials suggest that treatment effect also may be influenced by the “severity” of the alcohol dependence syndrome (Kampman et al., 2007). There is no single universally-accepted measure of “severity.” Therefore, 8 severity-related baseline measures were tested in the current study, including number of alcohol dependence criteria endorsed (MINI), past-year history of alcohol withdrawal syndrome (MINI alcohol dependence criterion), two measures of self-reported alcohol consumption (DPD during the 28-day period prior to screening and during the 7-day period prior to randomization), alcohol craving (PACS), years of drinking regularly, GGT, and alcohol-related consequence (ImBIBe score).

Statistical Analysis

As before, all secondary analyses were conducted using a modified intention-to-treat (mITT) population comprising all randomized patients who took at least one dose of medication and provided valid post-randomization outcome data (n=197) (per Litten et al., 2013). Per Litten et al. (2013) the primary outcome was PHDD. Additional analyses were conducted on secondary outcomes (DPD, DPDD, PVHDD, and PACS) to corroborate the results of the primary outcome. All outcomes were analyzed using a repeated-measures mixed effects model with covariates treated as fixed effects and patients treated as the random effect. An unstructured covariance matrix best fit the data and was used to model the correlations between repeated measures among patients. Least-square means (LSMEANs), standard errors (SEs), and 95% confidence intervals (CIs) were calculated for each treatment group and were derived from fully adjusted models on untransformed outcomes (to facilitate clinical interpretation) during the maintenance period. The fully adjusted models included the following covariates: treatment group (varenicline vs. placebo), week (from 2 to 13), site, treatment drinking goal (total abstinence vs. other), alcohol craving (PACS score), baseline value of the outcome (computed during the 28-day period before the first screening visit), a treatment group by week interaction, and the interaction term(s) between the treatment group and the selected moderator variable (the main interest of the analyses). Treatment goal and PACS were included as covariates because they were correlated with drinking outcome and because they were used covariates in the models presented in our main paper (Litten et al., 2013). For the craving outcome (PACS), the treatment-drinking goal was excluded as a covariate because it was not correlated with PACS. No imputation was made for missing drinking data as prior sensitivity analyses revealed similar results were obtained when missing data were handled in two ways: a) by imputing missing data as heavy drinking days and b) by using multiple imputation (Litten et al., 2013).

To facilitate interpretation, continuous moderator variables were dichotomized based on clinically meaningful cutoffs when possible (i.e., GGT = elevated vs. non-elevated based on the cutoff levels predetermined by the testing laboratories). For variables where clinically meaningful cutoffs are not established, we dichotomized variables based on results from loess curves for the varenicline and placebo groups on the outcome, average PHDD in

Weeks 2–13, by the continuous moderator variable (data not shown). The cutoffs were selected to maximize the observed difference in treatment effects between subgroups while maintaining a sufficient sample size for each subgroup (i.e., age >45 [44th percentile]; years drinking regularly > 28 [~48th percentile]; had an average of more than 7 drinks for women and 9 drinks for men per day during the 28 days prior to screening [27th and 35th percentile for women and men, respectively] and the 7 days prior to randomization [37th and 45th percentile for women and men, respectively]; 6–7 criteria of alcohol dependence criteria endorsed [78th percentile]; PACS > 20 [68th percentile]; and ImBIBe > 22 [~66th percentile]). This data-driven dichotomization approach could increase the Type 1 error rate and potentially overestimate the true moderation effects, for which additional clinical trials are necessary to confirm or refute.

For all statistical tests, $p < 0.05$ (two-tailed) was considered statistically significant. The effect of varenicline relative to placebo on the 5 measured outcomes (PHDD, DPD, DPDD, PVHDD, and PACS) was tested by 17 moderator variables, resulting in a total of 85 post hoc subgroup analyses. Therefore, up to 4 statistically significant interaction tests could occur by chance alone (Wang et al., 2007). For the primary outcome (PHDD), which is the focus of this paper, up to 1 of the 17 moderator variables could be expected to interact significantly with treatment by chance alone. As this was an exploratory analysis, no correction was made for multiple inferential tests. Data were analyzed with SAS version 9.2 (SAS Institute, Inc., Cary, NC).

RESULTS

Of the 461 patients who consented for the study, 200 were randomized to receive either varenicline ($n = 99$) or placebo ($n = 101$). Descriptions of screen failures, discontinuations, medication compliance, trial participation, and baseline characteristics were detailed previously (Litten et al., 2013). As indicated in that paper, patients in both groups had statistically similar baseline values.

Among the 14 baseline characteristics assessed as moderators of the varenicline treatment effect, significant interactions were found for three variables: age, years of drinking regularly, and treatment drinking goals (Table 1). Age and years of drinking regularly were moderators that favored greater efficacy for varenicline among older patients and those who had been drinking regularly for a longer time. Specifically, varenicline and placebo had similar weekly PHDD among patients < 45 years of age (48.5 vs. 47.7, respectively; $p = .90$) and < 28 years drinking regularly (49.3 vs. 47.9, respectively; $p = .82$); yet varenicline had 17.8 less PHDD than placebo for patients > 45 years of age (30.4 vs. 48.1, respectively; $p < .001$) and 20.4 less PHDD than placebo for patients > 28 years drinking regularly (27.1 vs. 47.5, respectively; $p < .001$). Treatment drinking goal had a disordinal interaction. The varenicline group had 18.0 less PHDD than the placebo group among patients with a non-abstinent goal (44.8 vs. 62.8, respectively; $p < .001$), yet showed no significant difference in PHDD compared with the placebo group among patients with a goal of total abstinence (36.9 vs. 28.2, respectively; $p = .29$).

Baseline alcohol consequence score (ImBIBe) appeared to moderate the varenicline treatment effect at borderline statistical significance (interaction term $p = .07$). Specifically, varenicline had significantly greater efficacy than placebo among patients with less alcohol-related consequences (38.3 vs. 53.7, respectively; $p = .01$), whereas there was no significant difference in efficacy among patients with more consequences (38.8 vs. 37.0, respectively; $p = .81$). Similar patterns were observed across all other drinking outcomes, unless noted otherwise in Table 1.

Among the variables observed during the treatment period, varenicline showed more efficacy than placebo in patients who did not experience any AEs (35.5 vs. 65.1, respectively; $p = .04$) and among patients who experienced varenicline-consistent AEs (34.5 vs. 52.5, respectively; $p = .01$); whereas there was no significant difference in efficacy among patients who reported other adverse events (45.0 vs. 43.6, respectively; $p = .84$). Varenicline efficacy did not vary by medication compliance during the maintenance period (interaction term $p = .55$).

Previously, varenicline significantly reduced PHDDs in both smokers and non-smokers (Litten et al., 2013). To better understand the varenicline efficacy among smokers only, we further subdivided this group into those who reduced their number of cigarettes by the end of the trial (Week 13) versus those who increased or did not change their cigarette consumption. Smokers who reduced their cigarette consumption and who took varenicline, compared with placebo, showed significant efficacy on reducing PHDD (36.1 vs. 55.4, respectively; $p = .04$). Conversely, smokers whose cigarette consumption remained the same or increased during the study period experienced a nonsignificant increase in PHDD with varenicline (68.3 vs. 51.6, respectively; $p = .15$) (Table 1). A significant interaction was detected between the treatment group and this moderator for PHDD outcome ($p < .02$) as well as other drinking outcomes—DPD ($p < .0001$), DPDD ($p < .001$), and PVHDD ($p < .0001$)—but was not observed for craving (data not shown).

Although not statistically significant, 5 moderator variables had at least a 10% difference in the varenicline-placebo LSMEAN differences that were obtained within the moderator subgroups. This difference can be considered “clinically meaningful” and corresponded to a moderator-by-treatment-group interaction significance level of $p < 0.25$. Since these results are not statistically significant and were obtained without statistical correction for multiple tests, they are merely “suggestive” and should not be interpreted with the same rigor as those that are statistically significant. Specifically, varenicline appeared to have greater efficacy than placebo among less severely-dependent patients—those with less alcohol consumption during the 7 days prior to randomization (i.e., drinks per day = 7/9 for women/men, respectively; $p = .15$) and less alcohol craving (PAC score = 20; $p = .16$). In addition, varenicline had greater efficacy among those patients who a) tested positive for marijuana during screening ($p = .17$), b) did not reduce their drinking prior to randomization ($p = .17$), and c) did not have a parental history of problem drinking ($p = .24$). Similar patterns were observed for these moderators on all other drinking outcomes and, in some cases, were statistically significant. For instance, alcohol craving was a statistically significant moderator on the drinks per drinking day outcome ($p = .05$) and marijuana use was a statistically significant moderator on most drinking outcomes ($p < .05$) (data not shown).

DISCUSSION

A previous multisite trial of varenicline (Litten et al., 2013), found that the medication significantly reduced measures of alcohol use, including percent heavy drinking days (primary measure), drinks per day, and drinks per drinking day. In this article, exploratory analyses were conducted to determine if varenicline's efficacy varied by baseline characteristics or other variables observed during treatment.

One of the most significant findings was the interaction between the medication and the moderator, cigarettes per day. Smokers who reduced the number of cigarettes per day experienced a significant positive effect on drinking from varenicline, whereas smokers whose cigarettes per day increased or stayed the same experienced a negative benefit on drinking from varenicline. This result, although statistically significant and provocative, should be interpreted cautiously given the small sample size, particularly among the varenicline patients who did not change or who increased their cigarettes per day. Varenicline, like FDA-approved medications to reduce drinking, appears to work better in some patients rather than in others. This wide response can be directly linked to the heterogeneity of alcohol use disorder (AUD). It is possible that the effect varenicline has on the nicotinic receptors is the same basic mechanism that reduces both drinking and smoking. For example, it has been hypothesized that varenicline works through the nicotinic receptors to increase dopamine release in the nucleus accumbens, altering the rewarding effect of the addictive substance, be it alcohol or nicotine (Feduccia et al., 2012; Wu et al., 2014). Thus, individuals who experienced no effect in reducing smoking also may experience no effect on drinking, whereas the opposite occurs for those who experience a reduction in cigarettes per day. This finding was supported by the exploratory analysis. Interestingly, those patients taking varenicline who did not change or who increased their number of cigarettes per day appeared to drink more than the placebo group. Given the finding that varenicline appears to drive reductions in both drinking and smoking in some, but not all smokers, future studies might investigate nicotinic acetylcholine receptor (nAChR) single nucleotide polymorphisms (SNPs) as potential moderators of varenicline's treatment effect.

Three additional moderators also were statistically significant: treatment drinking goals, years drinking regularly, and age. The strongest effect was observed with treatment drinking goals. Those patients who entered the trial with a non-abstinent goal had 18 less PHDD in the varenicline group than in the placebo group, whereas those with an abstinent goal exhibited the opposite effect: 8.7 greater PHDD in the varenicline group versus the placebo group. Interestingly, most of the patients in the trial (72%) did not have the goal of permanent abstinence, perhaps because the study's inclusion criteria stipulated that patients could not reduce their total number of drinks per week by more than 50% between the 28-day period before consent and the 7-day period before randomization. Finally, patients who 45 years of age or older, and who were drinking regularly for a longer period of time also had a stronger response from varenicline.

These three moderators, as well as others that were suggestive of a moderation effect, indicated that lower alcohol severity was associated with a more favorable response to varenicline. For example, patients with the non-abstinent drinking goal had a lower ImBIBe

score, indicating fewer alcohol-related consequences, less alcohol consumption, and better mental health measures (data not shown). Furthermore, it has been suggested that people with severe alcohol dependence are more likely to have a goal of abstinence than a goal to reduce drinking to safe levels (Dawson et al., 2005). Also, in the present study, older patients and those who had been drinking regularly for a longer time consumed less alcohol than their younger counterparts and those who had been drinking regularly for a shorter time, respectively. These subgroups also exhibited fewer alcohol-related consequences, which is consistent with lower severity. In addition, although not statistically significant ($p = .07$), patients who had fewer alcohol-related consequences experienced a greater benefit from varenicline than those patients with more alcohol-related consequences. The patients with fewer alcohol-related consequences were drinking less pre-randomization, had a lower craving for alcohol, and non-elevated GGT levels; and they experienced a reduction in PHDD values from varenicline compared with those who reported a greater number of alcohol-related consequences. Several other moderators (i.e., baseline alcohol consumption, alcohol craving [PACS] score, and GGT), though not statistically significant (p 's $.15$), were more likely to show a varenicline treatment effect in the categories associated with lower severity; however this pattern was not found in two other moderators related to severity (i.e., alcohol withdrawal criterion and the number of alcohol dependence criteria on the MINI).

As noted above, patients with less severe alcohol dependence appear to exhibit a greater response to varenicline than those with a higher severity. One possible reason may be that alcohol dependence involves more components of addiction at higher severity levels. Varenicline is a partial agonist at the $\alpha 4\beta 2$ nicotinic receptor; and although it exhibits to a lesser degree, it is a partial agonist at the $\alpha 3\beta 2$ and $\alpha 6\beta 2$ receptors and a full agonist at the $\alpha 7$ and $\alpha 3\beta 4$ nicotinic receptors (Mihalak et al., 2006; Grady et al., 2010). The exact mechanism(s) underlying the nicotinic effects on alcohol seeking and drinking behavior remains unclear (Feduccia et al., 2012). What is clear, however, is that alcohol dependence is a complex disease with many proposed components underlying this behavioral disorder. This includes positive reinforcement (reward), negative reinforcement (negative symptoms/stress), incentive salience, craving, habituation, impaired inhibitory control, and social processes (Litten et al., 2012). The current analysis suggests that although varenicline reduces drinking in alcohol dependent patients, as the severity of dependence increases, and perhaps as more components of the addiction response are realized, the overall effects of varenicline are reduced (Koob, 2013). A similar observation was reported with serotonin reuptake inhibitors. For instance, Kranzler et al. (1996 and 2011) and Pettinati et al. (2004) independently found that sertraline and fluoxetine were more effective in alcoholics with less severe dependence compared with those who experienced greater severity. Further studies are needed to replicate these findings and, if replicated, evaluation will be needed to better explain the underlying mechanism of these findings.

In the current analysis, patients who reported adverse effects consistent with the varenicline label were more likely to have a significant and positive effect from the medication (a difference of 18 PHDD between the varenicline and placebo groups). Interestingly, those who reported adverse effects not consistent with the medication's label showed no benefit from the medication. We might speculate that patients who took varenicline and experienced varenicline-consistent adverse events knew they were taking the medication, and thus,

expected that taking the drug caused those adverse reactions. However, because the placebo group experienced similar adverse events, it seems likely that the patients in this group would have the same expectation. Indeed, when asked to guess after completion of the trial what medication they thought they had taken during the trial, similar percentages of patients in both the varenicline and placebo groups who experienced varenicline-consistent adverse events thought they had taken varenicline (54.5% vs. 53.6%, respectively; $p = .93$). Because both groups had similar adverse event profiles and expectations, this suggests that varenicline had a true pharmacological effect.

Although not statistically significant ($p = .17$), patients who did not reduce their drinking from the 28-day period before screening to the 7-day period before randomization had a greater effect from varenicline than those who reduced their drinking during this period (19.8 PHDD difference between varenicline and placebo groups in non-reducers compared with 6.3 PHDD difference in reducers). This effect is similar to that reported for the recent nalmefene trial where patients who did not reduce their drinking prior to randomization benefitted more from the medication (Gual et al., 2013). A possible explanation is that those in the reducer group were more likely to respond to the placebo than those in the non-reducer group (PHDD = 44.3 vs. 58.7, respectively; see Table 1). Alternatively, the non-reducers had less severe alcohol dependence than the reducers (i.e., lower baseline alcohol consumption, fewer alcohol-related consequences, and less craving), which may account for the greater effect of varenicline in non-reducers.

Finally, it is intriguing that, although not statistically significant ($p = .17$), patients who tested positive for marijuana use before randomization, but who were not marijuana dependent) had a substantial effect from varenicline (26 PHDD difference between varenicline and placebo compared with 8.2 PHDD difference among non-marijuana users). The underlying mechanism is unclear, although recent research has shown a relationship between the cannabinoid CB1 receptor and nicotine addiction (Le Foll et al., 2014). These results should be viewed with caution, however, as the percentage of patients who tested positive for marijuana at screening was small, only 13%, and thus, additional research is needed to further explore this finding.

CONCLUSIONS

Results from a recent multisite clinical trial showed that varenicline reduced drinking in alcohol dependent patients, both smokers and nonsmokers. Upon exploratory analyses, subgroups of patients were identified that were more responsive to varenicline than others. These subgroups included patients who experienced a decrease in the number of cigarettes they consumed per day during the study period, who reported a treatment goal of non-abstinence, who were older, and who reported drinking regularly for a longer period of time. After analyzing several other treatment moderators, a pattern emerged suggesting that varenicline may be more efficacious in patients with less severe alcohol dependence. Because these are only exploratory analyses, with no statistical adjustment for multiple testing, future studies are needed to confirm these findings.

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Table 1

Adjusted Mean Percent Heavy Drinking Days (Weeks 2–12) by Treatment Group and Moderator

Moderator	Subgroup	Placebo		Varenicline		LSMEANs		Moderator* Treatment Interaction p-value	Patterns in Treatment Effects: Consistency of Other Outcomes with PHDD	Moderator* Treatment Interaction p-values for Other Outcomes ^d	
		N	LSMean	95% CI	N	LSMean	95% CI				Difference
Baseline Characteristics											
Treatment Drinking Goal	Other	73	62.8	55.3 – 70.3	69	44.8	37.2 – 52.5	-18.0	5.3	0.00	All p>.05
	Total Abstinence	28	28.2	16.5 – 39.9	27	36.9	24.9 – 48.9	8.7	8.3	0.29	
Years Drinking Regularly	28	54	47.9	39.1 – 56.6	44	49.3	39.9 – 58.8	1.5	6.2	0.82	All p<.05, except DPDD (p=.10)
	>28	47	47.5	38.0 – 57.1	52	27.1	18.0 – 36.2	-20.4	6.2	0.00	
Age	45	50	47.7	38.6 – 56.8	38	48.5	38.1 – 59.0	0.8	6.7	0.90	All p<.05, except PVHDD (p=.37), DPDD (p=.36)
	>45	51	48.1	38.8 – 57.5	58	30.4	21.6 – 39.2	-17.8	6.0	0.00	
Alcohol Consequences (ImBIBe) Score ^b	22	72	53.7	45.4 – 62.0	60	38.3	29.6 – 47.0	-15.4	5.5	0.01	All p>.05
	>22	29	37.0	25.2 – 48.7	35	38.8	27.6 – 50.0	1.8	7.8	0.81	
Drinks per Days (7 days pre-randomization)	7/9 women/men	43	41.6	31.5 – 51.6	41	24.3	14.0 – 34.6	-17.3	6.7	0.01	All p>.05
	>7/9 women/men	58	52.1	43.7 – 60.5	55	47.5	38.6 – 56.4	-4.6	5.8	0.43	
Alcohol Craving (PACS) Score	20	69	45.4	36.2 – 54.6	63	30.9	22.1 – 39.7	-14.5	5.6	0.01	All p>.05, except DPDD (p=.05)
	>20	32	53.9	41.0 – 66.9	33	52.9	39.7 – 66.2	-1.0	7.8	0.90	
Marijuana Use	No	89	47.0	39.7 – 54.3	82	38.8	31.2 – 46.4	-8.2	4.9	0.10	All p<.05, except DPD (p=.05), PACS (p=.20)
	Yes	12	58.4	40.3 – 76.5	14	32.4	15.7 – 49.2	-26.0	12.2	0.03	
Pre-Randomization Reducer (DPD)	No	31	58.7	46.5 – 70.8	28	38.9	26.7 – 51.1	-19.8	8.2	0.02	All p>.05
	Yes	70	44.3	36.4 – 52.2	68	38.0	29.9 – 46.0	-6.3	5.4	0.24	
Parental Problem Drinking	No	51	48.6	39.2 – 58.1	44	32.7	22.8 – 42.6	-16.0	6.5	0.01	All p>.05
	Yes	50	47.9	38.7 – 57.0	52	42.5	33.2 – 51.8	-5.4	6.4	0.40	
Gender	Female	32	47.8	36.6 – 59.1	25	30.3	17.5 – 43.0	-17.6	8.4	0.04	All p>.05
	Male	69	48.6	40.5 – 56.7	71	40.5	32.5 – 48.5	-8.1	5.4	0.13	
Withdrawal (MINI)	No	59	43.5	34.4 – 52.5	61	36.9	28.4 – 45.5	-6.5	5.8	0.26	All p>.05

Moderator	Subgroup	Placebo			Varenicline			LSMEANS			Moderator* Treatment Interaction p-value	Patterns in Treatment Effects: Consistency of Other Outcomes with PHDD	Moderator* Treatment Interaction p-values for Other Outcomes ^d
		N	LSMean	95% CI	N	LSMean	95% CI	Difference	SE	p			
	Yes	42	54.2	44.3 – 64.1	35	38.7	27.8 – 49.7	-15.5	7.2	0.03			
Drinks per Day (28 days pre-screening)	7/9 women/men	37	43.4	32.4 – 54.5	28	26.9	14.2 – 39.6	-16.5	7.7	0.03			
	>7/9 women/men	64	50.5	42.2 – 58.8	68	42.3	34.1 – 50.6	-8.2	5.5	0.14		All p>.05	
GGT	Non-Elevated	66	49.9	41.5 – 58.3	62	36.8	28.1 – 45.5	-13.1	5.7	0.02			
	Elevated	35	45.6	34.8 – 56.5	34	40.1	29.0 – 51.1	-5.6	7.6	0.47		All p>.05	
# Alcohol Dependence Criteria	3–5	79	48.4	40.4 – 56.3	73	38.6	30.7 – 46.4	-9.8	5.2	0.06			
	6–7	22	48.1	34.1 – 62.0	23	35.5	21.8 – 49.2	-12.6	9.5	0.19		All p>.05	
Variables Observed During the Treatment Period													
Change in Cigarettes per Day (among Smokers) ^c	No change or increase	22	51.6	38.3 – 65.0	9	68.3	49.5 – 87.1	16.7	11.4	0.15			
	Reduction	16	55.4	41.3 – 69.6	27	36.1	24.2 – 48.0	-19.3	9.2	0.04		All p<.01, except PACS (p=.69)	
Varenicline-Consistent Adverse Event (AE)	No AE	11	65.1	46.1 – 84.1	9	35.5	14.8 – 56.1	-29.6	14.1	0.04			
	Other AE	60	43.6	35.2 – 52.0	32	45.0	33.3 – 56.7	1.4	7.0	0.84		All p>.05	
	Varenicline-Consistent AE	30	52.5	40.9 – 64.1	55	34.5	25.8 – 43.2	-18.0	7.1	0.01			
Compliance	305 pills taken	28	53.8	41.3 – 66.4	20	38.7	23.6 – 53.7	-15.2	9.5	0.11			
	>305 pills taken	73	46.5	38.6 – 54.4	76	37.8	30.2 – 45.3	-8.7	5.2	0.09		All p>.05	

Abbreviations: LSMEANS=least squares means; CI=confidence interval; PHDD=percent heavy drinking days; PVHDD=percent very heavy drinking days; PACS=Penn Alcohol Craving Scale; DPDD=drinks per drinking day; DPD=drinks per day; rand=randomization; GGT=gamma-glutamyl transpeptidase

Note: moderators with a statistically significant treatment interaction are shaded in gray.

^a Other outcomes include percent very heavy drinking days, drinks per day, drinks per drinking day, and the Penn Alcohol Craving Scale

^b ImBiBe missing 1 subject in varenicline group

^c Change in Cigarettes per Day (among Smokers) missing 3 placebo subjects and 1 varenicline subject