Varenicline in the Treatment of Alcohol Use Disorders

Beth L. Erwin, PharmD¹, and Rachel M. Slaton, PharmD²

Abstract

Objective: To summarize the efficacy and safety data for the use of varenicline in the treatment of alcohol use disorders. Data Sources: A literature search was conducted in PubMed, International Pharmaceutical Abstracts, and Cochrane Library (through May 2014). Key search terms included varenicline, alcohol, alcohol dependence, alcoholism, ethanol, and nicotinic acetylcholine receptor. Additional references were identified from literature citations. Study Selection and Data Extraction: Results were limited to clinical trials and case reports that discussed either the use of varenicline in alcohol drinking patients or adverse effects experienced with its use. Only English language studies in humans were reviewed. Data Synthesis: In all, 7 randomized, placebo-controlled clinical trials and 1 open-label study were identified that evaluated the impact of varenicline on various drinking-related end points. The studies were conducted in patients dependent on alcohol (n = 4), non-alcohol-dependent patients (n = 3), and patients with a history of alcohol dependence but who had been abstinent for at least 6 months (n = 1). The majority of the studies classified their participants as heavy drinkers; however, this definition varied across studies. Most studies included smokers, but 2 trials included both smokers and nonsmokers. Conclusions: Evidence supports the use of varenicline for the reduction of alcohol craving as well as for the reduction of overall alcohol consumption in patients with alcohol use disorders. However, it is not likely to improve abstinence rates. Although most of the data were derived from patients with concurrent nicotine dependence, the effects of varenicline appear to occur independent of baseline smoking status.

Keywords
varenicline, alcohol, alcohol dependence, alcoholism, ethanol, nicotinic acetylcholine receptor

Background

The term *alcohol use disorder* is a broad diagnostic classification that encompasses several alcohol-related disorders, including alcohol abuse and alcohol dependence.¹ The diagnostic criteria for alcohol use disorders is complex but usually involves the excessive use of alcohol, in either amount or duration, and is often associated with various behavioral and physical symptoms, including craving, tolerance, and withdrawal.² Approximately 8% of the US adult population suffers from an alcohol use disorder,² and the harmful use of alcohol is the leading risk factor for premature mortality in the United States.³ Because alcoholism can negatively affect both health and quality of life, it becomes important to explore new potentially effective treatment options for this disorder.⁷

Currently, the only Food and Drug Administration (FDA)-approved medications for the treatment of alcoholism in the United States are disulfiram, naltrexone, and acamprosate.⁴ Seven of these agents may be limited by adverse effects, and it is not uncommon for patients to experience relapse during treatment with these medications.⁵,⁸ Other medications under off-label investigation for treatment of alcohol dependence include baclofen, ondansetron, nalmefene, aripiprazole and topiramate. In addition, approximately 80% to 85% of alcohol-dependent patients are concurrent smokers,⁹ making any agent effective for both conditions simultaneously of great value in this population with historically low compliance rates.⁵ Varenicline, an FDA-approved smoking cessation aid currently marketed as Chantix, has recently been evaluated in numerous clinical trials for its proposed benefit in alcohol use disorders.⁵,⁷,¹¹-¹⁶ Its mechanism in nicotine dependence involves partial agonism of α4β2 nicotinic acetylcholine receptors (nAChRs) and full agonism of α7 nAChRs located in the ventral tegmental area of the brain, thus regulating the overall impact

¹University of Alabama at Birmingham (UAB) Hospital, Birmingham, AL, USA
²Samford University McWhorter School of Pharmacy, Birmingham, AL, USA

Corresponding Author:
Rachel M. Slaton, Samford University McWhorter School of Pharmacy, 800 Lakeshore Drive, Birmingham, AL 35229, USA.
Email: rslaton@samford.edu
of exogenous nicotine on dopaminergic pathways. Because modulation of nAChRs in the central nervous system can have broad downstream effects on the activity of dopamine and other neurotransmitters, varenicline has become a particular entity of interest for potential benefit in various other dependence disorders besides nicotine addiction and alcoholism, such as cocaine dependence and amphetamine dependence.

Although varenicline’s exact mechanism in alcohol use disorders is not fully understood, it is believed to exert its alcohol-deterrent effects by decreasing the release of dopamine in the nucleus accumbens, thus mitigating the rewarding effects associated with alcohol intake. In addition, chronic consumption of alcohol may lead to changes in the expression of nAChRs, making varenicline’s ability to occupy these receptors, providing a basal level of activation without causing symptoms of withdrawal, an attractive property. Varenicline was initially found to reduce alcohol seeking behavior and alcohol consumption in rats following both acute and chronic administration, providing support for its hypothesized efficacy in humans.

Varenicline has a number of beneficial characteristics that could potentially be used to promote its proposed role in the treatment of alcohol use disorders. The most notable advantage is its proven efficacy as a smoking cessation aid. A single agent that is able to treat 2 separate conditions is of value, not only because it reduces overall cost for the patient, but also because it reduces overall pill burden, increasing the likelihood of medication adherence. In addition, varenicline is considered to have a low potential for abuse—a desired characteristic for any pharmacotherapy used in illnesses with an addictive feature. Varenicline also has several advantageous pharmacokinetic properties, including 100% bioavailability regardless of concurrent food administration, few drug-drug interactions because of minimal hepatic metabolism, and a fairly rapid time to peak plasma concentrations. And finally, there is documentation that the smoking cessation effects of varenicline last for as long as 40 to 52 weeks after a standard 12-week treatment course. This potential for long-lasting efficacy would be of great value in alcohol-dependent patients who, compared with the general population, tend to have lower medication adherence rates.

Despite its possible benefit for alcohol-dependent patients, there is particular concern about the use of varenicline in individuals with mental health illnesses. Although the initial clinical trial data demonstrated no increased risk of mood- or behavior-related adverse effects, varenicline received a boxed warning highlighting its association with the occurrence of neuropsychiatric adverse events a few years after its approval in 2006. This warning was based on a number of reported cases of depression, suicidal ideation, psychosis, hostility, and abnormal behavior in both patients with and without preexisting psychiatric conditions. However, it is possible that some of these symptoms were mistaken for symptoms of nicotine withdrawal, which could theoretically result on initiation of varenicline for smoking cessation. The most commonly reported adverse effect of varenicline is nausea (16%-40%). Other adverse effects associated with its use, in decreasing order of incidence, include headache, insomnia, abnormal dreams, constipation, and vomiting. The Chantix package insert also advises prescribers to take into consideration any patient-specific cardiovascular diseases or risk factors before prescribing Chantix. Although varenicline may increase the frequency of certain cardiovascular events, the relationship between varenicline and cardiovascular events is not fully understood. Combined results from 15 clinical trials showed that those treated with varenicline had reduced cardiovascular mortality as well as all-cause mortality compared with placebo.

Current guidelines make no mention of varenicline’s potential therapeutic benefit in the treatment of alcohol use disorders. Likewise, the 3 official compendia for off-label uses contain no information on use of varenicline for this indication. Therefore, the purpose of this article is to evaluate the available evidence supporting the use of varenicline in alcohol use disorders. The efficacy and safety data from 8 clinical trials are summarized in Table 1.

### Literature Review

It was found that 7 randomized, double-blind, placebo-controlled clinical trials and 1 open-label study have assessed the impact of varenicline on various drinking-related end points in humans. Of these trials, 4 were conducted in patients dependent on alcohol, whereas the remaining 3 included only non-alcohol-dependent patients. One study evaluated patients with a history of alcohol dependence but who had been abstinent for at least 6 months. The majority of the studies classified their participants as heavy drinkers; however, this definition varied across studies. Only 2 trials included both smokers and nonsmokers, whereas all others were comprised solely of smokers.

The results from a multisite clinical trial (n = 200) published in 2013 showed that, over the 13-week treatment period, varenicline-treated alcohol-dependent patients had only 37.9% heavy-drinking days per week compared with 48.4% heavy-drinking days per week for placebo-treated alcohol-dependent patients (P = 0.03). In addition, drinks per day averaged 4.4 and 5.3 for the varenicline and placebo groups, respectively (P = 0.03). The average number of drinks per drinking day was also significantly lower for the varenicline group (P = 0.03). The calculated Penn Alcohol Craving Scale scores (5 questions [0 = Never; 6 = Always]; total score, 0-30) for the intervention and placebo groups were 9.9 and 11.6, respectively (P = 0.01). Neither the
Table 1. Studies Evaluating the Efficacy and Safety of Varenicline for the Treatment of Alcohol Use Disorders.

<table>
<thead>
<tr>
<th>Reference, Study Design</th>
<th>Drug Regimen &amp; Sample Size</th>
<th>Participants</th>
<th>End Points</th>
<th>Results</th>
<th>Importance</th>
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<tr>
<td>Litten et al&lt;sup&gt;6&lt;/sup&gt; (2013) R, DB, PC, PG</td>
<td>• VAR: week 1 titration phase; 1 mg bid for weeks 2-13 plus behavioral intervention</td>
<td>Past-year alcohol-dependent patients</td>
<td>PE: Percentage heavy drinking days (drinks/d ≥5 [men] or ≥4 [women]) measured weekly</td>
<td>Average weekly percentage heavy drinking days lower with VAR (mean difference, 10.4%; P &lt; 0.03 [d = 0.31]); no difference with regard to baseline smoking status</td>
<td>• VAR improved measures of alcohol use, with moderate effects, similar to those seen with agents FDA approved for treatment of alcohol dependence</td>
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<td>• PBO bid plus behavioral intervention n = 200</td>
<td>Previous 28-day drinking average: drinks/wk ≥35 (men) or ≥28 (women)</td>
<td>SEs: other drinking measures, alcohol craving (PACS), alcohol-related consequences, quality of life</td>
<td>VAR: fewer drinks/d (4.4 vs 5.3; P &lt; 0.03 [d = 0.29]), fewer drinks/drinking day (5.8 vs 6.8; P &lt; 0.03 [d = 0.26]), fewer percentage very heavy drinking days (17.6 vs 26.1%; P &lt; 0.047 [d = 0.25]), lower craving score (PACS 9.9 vs 11.6; P &lt; 0.01 [d = 0.33]). Treatment effects greatest during weeks 8-13 (d = 0.39-0.42)</td>
<td>• PE outcomes were independent of smoking status, and effects were greatest during the second half of treatment</td>
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<td>• Both smokers and nonsmokers included</td>
<td>Past-year alcohol-dependent patients</td>
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<td>• VAR did not increase the overall risk of psychiatric AEs</td>
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<td>Previous 28-day drinking average: drinks/wk ≥35 (men) or ≥28 (women)</td>
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<td>• Most of the AEs experienced were mild</td>
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<td></td>
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<td>Both smokers and nonsmokers included</td>
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<td>Limited by short duration; further studies needed to replicate findings</td>
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<td>Plebani et al&lt;sup&gt;15&lt;/sup&gt; (2013) R, DB, PC</td>
<td>• VAR: week 1 titration phase; 1 mg bid for weeks 2-12; 1 mg/d during week 13</td>
<td>Alcohol-dependent patients seeking treatment (most were non-heavy drinkers)</td>
<td>PE: self-reported alcohol use (weekly days of use, presence or absence of use)</td>
<td>VAR: greater decrease in ASI from week 0 to week 14 (−2.54, P = 0.02), lower Ham-D (P = 0.05) and PACS (P = 0.01) scores after week 6</td>
<td>• VAR reduced alcohol craving and improved mood</td>
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<td>• PBO: same as above n = 40</td>
<td>Reported drinking ≥12 of past 30 days</td>
<td>SEs: mood (Ham-A, Ham-D), global improvement (CGI-I, CGI-S), alcohol craving (PACS), clinical and psychosocial characteristics (ASI)</td>
<td>Baseline smokers in VAR group had lower rates of heavy drinking than those in the PBO group (P = 0.01); this did not differ for baseline nonsmokers</td>
<td>• VAR may be most beneficial for alcohol-dependent patients who smoke versus those who do not smoke</td>
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<td>No difference: self-reported alcohol use</td>
<td>Limited by short duration, small sample size, and self-reporting of abstinence; drinkers were not very heavy drinkers</td>
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<td>AEs: no difference in frequency; 1 report of PTSD-like event and 1 report of anxiety in VAR group</td>
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<tr>
<th>Reference, Study Design</th>
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</table>
| Meszaros et al\(^{12}\) (2013) R, DB, PC | • VAR: week 1 titration phase; 1 mg bid for weeks 2-8  
• PBO: same as above  
n = 10 | • Alcohol- and nicotine-dependent patients with schizophrenia  
• Smoked ≥20 cigarettes/d  
• Consumed ≥7 drinks in previous 7 days | • PEs: change in drinks/wk, cigarettes/wk, and percentage days abstinent from alcohol  
• SEs: alcohol and nicotine craving, measures of cognition and symptoms of schizophrenia | • No difference: decrease in number of drinks/wk (VAR 16.6 vs PBO 2.4; \(P = 0.38\) [\(d = 0.589\)]); decrease in alcohol craving (VAR 35% vs PBO 41%; \(P = 0.38\)), cigarette craving, cognition, symptoms of schizophrenia  
• AEs: higher rate of nausea and vomiting (3% vs 0%) and abdominal pain (3% vs 0%) in the VAR group | • Use of VAR in schizophrenic patients with codependence on alcohol and nicotine may be limited by GI AEs, rather than psychiatric AEs  
• Very small sample size (n = 5) and short duration; limited statistical power for end points but numerical differences encouraging |
| Mitchell et al\(^{5}\) (2012) R, DB, PC | • VAR: week 1 titration phase; 1 mg bid for weeks 2-11; week 12 down-titration  
• PBO: same as above  
• Follow-up: weeks 14 and 16  
n = 64 | • Non-alcohol-dependent heavy drinkers who smoked ≥10 cigarettes/wk  
• Seeking treatment for smoking only  
• Consumed ≥14 drinks/wk (men) or ≥7 drinks/wk (women) | • PEs: drinks/wk, alcohol craving/wk  
• SEs: cumulative cigarettes and drinks consumed, days abstinent from alcohol | • VAR: fewer drinks/wk from weeks 3-11 (\(P = 0.0001\)), fewer cumulative drinks (VAR 177.04 vs PBO 277.5; \(P = 0.029\))  
• No difference: days abstinent or cravings  
• No correlation between average drinks consumed/wk and average cigarettes smoked/wk  
• AEs: low occurrence rate, no difference between groups, DASS scores remained low | • VAR reduced alcohol consumption in heavy-drinking smokers not seeking treatment for alcohol abuse  
• VAR may play a greater role in reducing alcohol intake once drinking is initiated rather than affecting the initial urge to drink  
• No increased risk of AEs  
• Limited by small sample size and high drop-out rate |
| Childs et al\(^{16}\) (2012) R, DB, PC, CO | • VAR 2 mg or PBO followed by a drink of varying alcohol content  
• 6 Total sessions, each separated by ≥3 days  
n = 15 | • Healthy, non-alcohol-dependent heavy drinkers and nondependent smokers  
• Not seeking treatment for either substance  
• Consumed ≥10 drinks/wk with ≥1 binge episode/wk  
• Smoked ≤5 cigarettes/d | • Subjective effects of alcohol, heart rate, blood pressure, eye tracking  
• Before drinking: VAR increased feelings of “feel drug” (\(P < 0.001\)), “feel high” (\(P < 0.05\)), and dysphoria (\(P < 0.05\)); decreased craving-related measures (\(P = 0.01\)). VAR increased systolic (\(P < 0.05\)) and diastolic (\(P < 0.01\)) blood pressure and heart rate (\(P < 0.05\))  
• After drinking: VAR increased feelings of dysphoria after intake of PBO beverage and 0.4 g/kg alcohol but not after 0.8 g/kg of alcohol intake (\(P < 0.05\)). VAR attenuated “drug-liking” after 0.4 g/kg alcohol (\(P < 0.08\)). VAR alcohol-induced eye movements were diminished by VAR for alcohol intake of 0.8 g/kg only  
• AEs: VAR increased rates of nausea (\(P = 0.001\)) | • Acute pretreatment with VAR appears to reduce alcohol consumption by reinforcing alcohol’s undesired effects while diminishing its positive effects  
• Negative subjective effects occurred independently of nausea  
• VAR may prevent the progression from initial alcohol intake to binge drinking in non-nicotine-dependent heavy drinkers  
• Limited by small sample size but strengthened by objective measurements of physiological and subjective responses to alcohol |

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<tr>
<td>Fucito et al(^7) (2011) R, DB, PC</td>
<td>Extended pretreatment: 4 weeks VAR pretreatment followed by 4 weeks VAR treatment (VAR titration during week 1)</td>
<td>Heavy-drinking smokers with current or a history of alcohol dependence</td>
<td>Drinking end points: frequency and quantity of alcohol use, alcohol craving, subjective alcohol effects (stimulating and sedating)</td>
<td>Pretreatment phase: VAR decreased craving (VAR 1.59 vs PBO 0.29; (P = 0.03)); trend toward decreased heavy drinking days (38.1% vs 31%; (P = 0.06)) and increased subjective sedating effects of alcohol (VAR 2.92 vs PBO -7.09; (P = 0.01))</td>
<td>VAR reduced alcohol craving and demonstrated a medium to large effect size for reduced consumption in heavy-drinking smokers</td>
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<td>Usual pretreatment: 3 weeks PBO pretreatment followed by 5 weeks VAR treatment (VAR titration during week 4)</td>
<td>Smoked (\geq 5) cigarettes/d (\geq 3) days/wk with &lt;3 months abstinence in the past year</td>
<td>Smoking end points: frequency of smoking, abstinence</td>
<td>Post PC phase: receipt of extended VAR pretreatment decreased percentage heavy drinking days and reduced alcohol craving compared with usual pretreatment</td>
<td>It is possible that the increased sedating effects of alcohol experienced with VAR help reduce alcohol reinforcement</td>
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<td>VAR dose: 1 mg bid (n = 30)</td>
<td>Consumed (&gt;14) drinks/wk (men) or (&gt;7) drinks/wk (women) for the past 4 weeks, with (&gt;4) drinks/d (men) or (&gt;3) drinks/d (women) at least once</td>
<td>7-Day smoking abstinence rate of 31% (95% CI = 15-47) with a prolonged smoking abstinence rate of 28% (95% CI = 13-44)</td>
<td>Both phases: no difference in percentage days abstinent, drinks/drinking day, or stimulating effects of alcohol</td>
<td>VAR's full potential for reducing alcohol intake may not be reached for several weeks</td>
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<td>Pretreatment decreased cravings (calculated, (d = 0.5))</td>
<td>No difference in smoking outcomes</td>
<td>Pretreatment decreased cravings (calculated, (d = 0.5))</td>
<td>Limited by small sample size. Good external validity</td>
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<td>No significant AE; more nausea (67% vs 20%; (P = 0.03)) in VAR-treated patients. Adherence was similar between groups</td>
<td>No significant AE; more nausea (67% vs 20%; (P = 0.03)) in VAR-treated patients. Adherence was similar between groups</td>
<td>No significant AE; more nausea (67% vs 20%; (P = 0.03)) in VAR-treated patients. Adherence was similar between groups</td>
<td>VAR appears to promote smoking abstinence in tobacco-dependent patients with a history of alcohol abuse</td>
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<td>7-Day smoking abstinence rate of 31% (95% CI = 15-47) with a prolonged smoking abstinence rate of 28% (95% CI = 13-44)</td>
<td>No reports of alcohol use during study</td>
<td>VAR does not appear to promote relapse among recovering alcohol-dependent patients</td>
<td>Good external validity</td>
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<td>No reports of alcohol use during study</td>
<td>AE: 2 reports of unusual behavior change, 5 reports of either depression or anxiety symptoms, no reports of suicidal ideation or behavior; 5 AEs were of severe intensity but not defined as serious</td>
<td>Study limited by OL design and small sample size. Good external validity</td>
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<td>Hays et al(^{13}) (2010) OL</td>
<td>VAR: week 1 titration phase; 1 mg bid for weeks 2-12 (n = 32)</td>
<td>Smokers recovering from alcohol dependence (\geq 6) Months of abstinence from alcohol Past-year smoking average of (\geq 10) cigarettes/d</td>
<td>PE: Smoking abstinence rates at 7 days posttreatment</td>
<td>7-Day smoking abstinence rate of 31% (95% CI = 15-47) with a prolonged smoking abstinence rate of 28% (95% CI = 13-44)</td>
<td>VAR appears to promote smoking abstinence in tobacco-dependent patients with a history of alcohol abuse</td>
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<td>SE: Prolonged smoking abstinence</td>
<td>No reports of alcohol use during study</td>
<td>VAR does not appear to promote relapse among recovering alcohol-dependent patients</td>
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<td>McKee et al(^{14}) (2009) R, DB, PC</td>
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<td></td>
<td>• VAR: titrated to steady state (1 mg bid) over 7 days</td>
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<td>• PBO: same as above</td>
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<td>• On day 7, all received an alcohol priming drink, followed by a 2-hour session of self-administered alcohol</td>
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<td>n = 20</td>
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<td></td>
<td>• Non-alcohol-dependent heavy-drinking smokers</td>
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<td>• Consumed ≥14 drinks/wk (men) or ≥7 drinks/wk (women) in previous 30 days</td>
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<td>• Drinks/episode &gt;4 (men) or &gt;3 (women)</td>
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<td>• Smoked ≥10 cigarettes/d</td>
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<td>• Not seeking treatment for alcohol or nicotine dependence</td>
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<td>• BALs, alcohol craving, tobacco craving, drinks consumed, subjective effects of alcohol (mean of high, like, rush, feel-good, intoxicated), mood</td>
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<td>• After initial priming drink; VAR decreased craving and reinforcing effects of alcohol; no difference in tobacco craving, mood, or maximum BALs</td>
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<td>• Voluntary drinking period: VAR reduced total drinks consumed (resulting in lower BALs) and decreased subjective alcohol effects; VAR increased likelihood of remaining abstinent; no difference in mood</td>
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<td>• AEs: minimal; did not differ between groups</td>
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<td>• Heavy-drinking smokers not dependent on alcohol experienced beneficial alcohol-related outcomes when treated with short-term VAR</td>
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<td>• VAR’s effects on alcohol intake seem to be unrelated to its effects on nicotine</td>
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<td>• VAR was well tolerated and did not aggravate mental illness</td>
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Abbreviations: AE, adverse effect; ASI, Addiction Severity Index; BAL, blood alcohol level; d, treatment effect size (<0.1, trivial; 0.1-0.3, small; 0.3-0.5, moderate; >0.5, large); DASS, Depression, Anxiety, and Stress Scale; CGI-O, Clinical Global Impression Scale—Objective; CGI-S, Clinical Global Impression Scale—Subjective; CO, cross-over; CR, case report; DB, double blind; GI, gastrointestinal; Ham-A, Hamilton Anxiety Scale; Ham-D, Hamilton Depression Scale; OL, open label; PACS, Penn Alcohol Craving Scale; PBO, placebo; PC, placebo controlled; PE, primary end point; PG, parallel group; R, randomized; SE, secondary end point; VAR, varenicline.
percentage of days abstinent nor the percentage of patients abstinent was significantly different between the 2 groups. Because this study stratified patients according to baseline smoking status on randomization, it was able to examine the impact of smoking status on the drinking outcomes of varenicline therapy. The investigators found that outcomes did not differ significantly between baseline smokers and nonsmokers.6

Results from a second clinical trial (n = 40) evaluating various subjective and objective drinking measures were also published in 2013.15 The participants in this study did not have a diagnosis of alcohol dependence, and most were not considered to be heavy drinkers. Except for a greater number of African American participants in the varenicline group, baseline demographics were similar between the intervention and control groups. Weekly days of alcohol use and total heavy drinking days did not differ between the groups. However, among the subgroup of baseline smokers, varenicline resulted in a statistically significant lower rate of heavy drinking (P = 0.01). Varenicline-treated patients also had lower depression scores (P = 0.05) and alcohol craving scores (P = 0.01) during the second half of the 13-week treatment period.15

Another clinical trial (n = 64) assessed drinking outcomes during 12 weeks of varenicline therapy versus placebo therapy in a sample of non-alcohol-dependent heavy drinkers who were concurrent smokers.5 Separate analyses were conducted for study completers and for all participants randomized to treatment. All analyses illustrated a statistically significant difference in favor of varenicline for both the number of drinks consumed per week and the number of cumulative drinks consumed (P < 0.05 for all). The number of days absent did not differ between the groups, and there was a non-statistically significant trend toward decreased alcohol craving scores among study completers (P = 0.09). The drop-out rates for the intervention and placebo groups were 45.17% and 35.72%, respectively, and the majority of participants dropped out because of time- or travel-related issues rather than adverse effects.5

A crossover trial (n = 15) conducted in 2012 measured subjective effects of alcohol after an acute dose of varenicline.10 Participants attended 6 separate sessions in which they consumed an alcoholic drink containing either 0.0, 0.4, or 0.8 g/kg of alcohol 3 hours after receiving their respective dose of varenicline. Results from the postvarenicline, prealcohol period showed that varenicline increased participants’ ratings of dysphoria and “feel high” and had the opposite effect on ratings of “drug liking” and “want more drug” (P < 0.05 for all). These findings remained statistically significant after controlling for nausea. For the period following alcohol consumption, varenicline-treated participants experienced increased dysphoria after intake of the 0.0- and 0.4-g/kg concentrations of alcohol, whereas alcohol-induced eye movements were diminished by varenicline only after intake of the 0.8-g/kg concentration of alcohol (P < 0.01).16

One controlled clinical trial (n = 30) assessed both drinking and smoking outcomes associated with an extended pretreatment phase of varenicline.7 Alcohol-dependent, heavy drinking smokers were included, and patients were randomized to receive either 4 weeks of varenicline pretreatment followed by 4 more weeks of varenicline therapy or 3 weeks of placebo pretreatment followed by 5 weeks of varenicline therapy. During the placebo-controlled pretreatment phase, varenicline reduced alcohol craving scores (P = 0.03) and increased ratings of alcohol-induced sedation (P = 0.01). The percentage of heavy drinking days was 22.7% for the varenicline group and 38.0% for the placebo group; however, this difference was not statistically significant (P = 0.06). At the end of the 8-week treatment, alcohol craving scores remained significantly lower for patients pretreated with varenicline. These patients also reported significantly fewer heavy drinking days at weeks 4, 6, and 7. On the other hand, the difference in the number of drinks consumed was not significant (P > 0.03), and neither alcohol nor smoking abstinence rates differed between the extended and the usual pretreatment groups.7

One of the first controlled clinical trials conducted in humans to study the effects of varenicline on alcohol consumption and craving involved a group of 20 non-alcohol-dependent heavy drinking smokers assigned to receive either adequately titrated varenicline or placebo.14 On day 7, all patients received an alcoholic priming drink, which was followed by a 2-hour period of voluntary alcohol intake. Varenicline-treated patients reported decreased craving (P < 0.05) and decreased subjective (reinforcing) effects of alcohol (P < 0.05) after the initial priming drink. For the voluntary drinking period, varenicline-treated patients consumed significantly fewer drinks (P < 0.05), were more likely to decline additional drinks altogether (P < 0.03), and reported decreased subjective (reinforcing) effects of alcohol (P < 0.05). Mood outcomes were similar between groups.14

A very small placebo-controlled pilot trial (n = 10) in patients with schizophrenia with concurrent nicotine and alcohol dependence was conducted to determine varenicline’s effect on alcohol consumption and nicotine use in this distinct population.12 Because of the occurrence of adverse events and loss to follow-up, only 4 patients completed the 8-week study. The number of drinks consumed per week did not differ between participants of the 2 treatment groups (P = 0.58), and between-group differences in craving measures were also nonsignificant. However, the usefulness of these results is limited because of the study’s small sample size and inability to meet statistical power.12

An open-label study designed to evaluate smoking abstinence rates with varenicline therapy was conducted in 32
smokers with a history of alcohol dependence who were currently in recovery (median duration of alcohol abstinence of 36 months). A relevant outcome from this study was that none of the participants experienced alcohol relapse during the 12 weeks of smoking cessation treatment with varenicline. This is helpful information because of the concern that quitting smoking may incline former alcoholics to relapse. Although the lack of relapse during the study period could have been influenced by other factors, the use of varenicline in smokers who are also recovering alcoholics is encouraging.13,30

Two case reports involved the use of varenicline in patients diagnosed with alcohol dependence. Pirmoradi et al29 described the case of a 33-year-old man with a past medical history of alcohol dependence, hypertension, major depression, and hypothyroidism. He was a previous smoker with 2 months of cessation at the time of varenicline initiation, which was prescribed for smoking cessation maintenance. On day 7 of treatment, the patient experienced very concerning adverse effects: severe anxiety, nausea, vertigo, blurred vision, and dizziness. Varenicline was discontinued, and the adverse effects resolved over a 3-day period.29 Cocores and Gold30 describe a second case report of a 66-year-old woman with current diagnoses of alcohol dependence, depression, anxiety, panic, and peripheral neuropathy. She was prescribed varenicline for alcohol dependence and reported weight loss and improvements in energy, focus, memory, and mood, in addition to abstinence from alcohol after 1 week of therapy. These beneficial effects were maintained after 3 weeks, with a total weight loss during this time period of 10 pounds.30

Safety

Of the 7 placebo-controlled trials, 6 failed to show an increased rate of neuropsychiatric adverse events (eg, depression, anxiety, suicidal ideation or behavior, irritability, aggression, and change in behavior or cognitive function).6,7,11-16 The remaining trial contained 29 varenicline-treated patients, of whom 1 patient experienced both anger and aggression and another patient experienced both anger and agitation. However, both these patients tested positive for psychostimulant use.5 Out of 7 trials, 2 found no difference in the overall occurrence of adverse effects between the varenicline and placebo groups.14,15

Four trials demonstrated an increased rate of nausea in participants treated with varenicline; however, nausea was usually considered to be of mild intensity.6,7,12,16 The largest of the controlled clinical trials showed that in addition to nausea, varenicline was associated with an increased risk of abnormal dreams and constipation, but most of these adverse effects were categorized as mild, and none were defined as severe.6 In the open-label study by Hays et al,13 28% of the 32 patients reported nausea, 19% reported sleep disturbances, 16% reported abnormal dreams, 16% reported depression or anxiety, and 6% reported behavioral changes. Also, 5 patients reported experiencing psychiatric adverse events of severe intensity, none of which were suicidal ideation or behavior.13

Results from a recently published meta-analysis also failed to find an association between varenicline and neuropsychiatric adverse events.31 The investigators reanalyzed safety data from 17 placebo-controlled trials, with a combined total of 8027 participants, 1004 of whom had a baseline psychiatric disorder. They found no greater risk of depression, suicide, or aggression/agitation in varenicline-treated patients when compared with those treated with placebo. The side effect of nausea was, however, highly associated with the use of varenicline. The investigators also evaluated data from a Department of Defense observational study of more than 35,000 participants to compare the occurrence of psychiatric-related events in patients taking varenicline with those using nicotine replacement therapy. The results showed that nicotine replacement therapy was actually associated with higher rates of neuropsychiatric disorders than varenicline.31

Two cases of acute liver injury with varenicline have been reported in the literature.32,33 In both cases, male patients experienced nausea and vomiting within a week of beginning treatment with varenicline. In 1 patient, decreased appetite, weight loss, and malaise was also reported. Liver chemistries revealed elevated aspartate aminotransferase (AST; 868-1191 U/L), alanine aminotransferase (ALT; 657-1592 U/L), and alkaline phosphatase (183-254 U/L) as well as, in 1 case, elevated total bilirubin (12 mg/dL) and elevated international normalized ratio (1.3). Both patients developed significant hepatitis within 4 weeks. Following discontinuation of varenicline, the patient’s liver chemistry levels returned to normal within 2 and 4 months, respectively. In both cases, hepatic serologies revealed positive antibodies for hepatitis C virus.32,33 Both patients reported alcohol use, and 1 patient had an alcohol abuse history of 30 years that included consumption of >12 beers per day.32 Although varenicline has been found to be safe and effective at normal doses in patients with liver dysfunction,25 practitioners should be aware of postmarketing surveillance reports, so that patients can be adequately screened for risk factors before beginning treatment with varenicline.

A 12-week, open-label, pilot study of HIV-positive smokers receiving standard dose varenicline reported significant changes in ALT and diastolic blood pressure.34 In general, ALT increased by a mean of 10 IU/L in 17% of patients by week 12 (P = 0.011) and by 8 IU/L in 19% of patients by week 24 (P = 0.004). Diastolic blood pressure increased by a mean of 6 mm Hg at week 12 in 17% of patients (P = 0.001) and 4 mm Hg at week 24 in 11% of patients (P = 0.049), resulting in hypertension. Based on these findings, monitoring of liver enzymes and blood pressure in HIV-infected smokers is recommended.34
Discussion

Based on the trials discussed, off-label use of varenicline appears to be effective in improving drinking-related outcomes in patients with alcohol use disorders. Although most of the data were drawn from patients with concurrent nicotine dependence, 2 trials were able to report data specifically for alcohol-dependent nonsmokers. In the largest study, the beneficial effects of varenicline were apparent regardless of baseline smoking status, whereas the smaller study found that varenicline may be most beneficial for patients who smoke. In addition, one of the studies comprised entirely of smokers found no correlation between the alcohol-related and smoking-related effects of varenicline, indicating that these beneficial outcomes could occur independently of each other.

The drinking-related results of the 7 placebo-controlled trials are relatively consistent in regard to the efficacy of varenicline in alcohol use disorders; 4 trials showed a definite reduction in alcohol consumption with varenicline treatment, whereas a fifth trial demonstrated reduced consumption in the subgroup of smokers, and another showed that varenicline has the potential to reduce consumption based on its ability to increase alcohol’s negative effects and decrease its reinforcing effects. It is, however, important to keep in mind that in the majority of these studies, participants were considered to be heavy or very heavy drinkers, and thus, consumption-related outcomes with varenicline treatment may differ for individuals who consume lesser amounts of alcohol. Likely related to varenicline’s observed effects on alcohol consumption are its effects on alcohol craving. Of the 7 placebo-controlled trials, all but 1 demonstrated a statistically significant reduction in craving-related end points. This supports the proposed mechanism that varenicline exerts its effect by modulating neurotransmitters and pathways in the brain associated with reward and reinforcement.

In regard to abstinence rates, 1 trial found that abstinence rates were significantly greater for varenicline-treated patients, but this effect was only studied for a 2-hour period following administration of a priming drink. In contrast, 4 studies showed that varenicline did not increase the percentage of days patients abstained from alcohol, implying that varenicline may be more beneficial for limiting cumulative alcohol consumption following an initial drink rather than preventing initial alcohol consumption altogether. However, the lack of significant abstinence results may be related to patient-specific treatment goals regarding their alcohol consumption. The results from the study conducted by Litten et al, in which <30% of patients reported a desire for complete abstinence, provide support for this theory. On the other hand, Mitchell et al excluded individuals seeking treatment for alcohol dependence to eliminate bias and also to better isolate the effects resulting from treatment with varenicline.

Several limitations should be taken into consideration when interpreting the collective results of these trials. One is the limited generalizability of the results. All but one of the trials excluded patients with concurrent psychiatric illness or dependence on psychoactive substances other than alcohol or nicotine. This is important because it is not uncommon for patients with alcohol use disorders to have a concomitant psychiatric comorbidity or additional substance abuse. Another limitation is the lack of long-term efficacy data of varenicline in alcohol use disorders. Most of the studies discussed in this review assessed varenicline’s effects over a 12- or 13-week treatment phase and, thus, can provide no information in regard to the longevity of these effects posttreatment. It is possible that some of the outcomes reported to be nonsignificant, such as quality of life and alcohol-related consequences, would have emerged as significant had outcomes been assessed for a longer period of time and/or in a larger patient population. Further studies are needed to assess the posttreatment effects of varenicline as well as to determine the optimal duration of therapy in this specific population.

Other collective limitations of the trials reviewed include the relatively small sample sizes, the variability of scales used to measure alcohol-related end points, and the lack of head-to-head comparisons between varenicline and medications currently approved to treat alcohol dependence. In addition, trial methodology usually involves some sort of measure to promote or ensure medication compliance throughout the study. Therefore, the high adherence rates reported in these trials may not be reflective of those in the general population of patients with alcohol use disorders, which could affect observed drug efficacy when varenicline is used outside of clinical trials.

In general, strengths of the studies included use of robust study designs (randomized, double-blind placebo-controlled trials), standardized titration and dosing of varenicline, and consistent patient populations with a clearly defined number of drinks and/or cigarettes used per patient per day. Overall, varenicline was well tolerated by the majority of the study participants and provided a moderate treatment effect size (d = 0.3-0.5). The most commonly reported adverse effects (nausea, abnormal dreams, and constipation) were consistent with those listed in the product labeling and were generally mild. The overall lack of reported psychiatric adverse events was consistent with that found in the recently published large meta-analysis and thus provides some support for varenicline’s use in alcohol use disorders.
Disorders. They should not be completely ignored because they provide unique pieces of information regarding the safety of varenicline.

**Summary**

Alcohol use disorders are a large contributor to premature mortality in the United States, and there is a need for more effective treatment options for patients who struggle with these conditions. Because of its ability to modulate nAChRs and decrease the rewarding effects associated with alcohol intake, varenicline has been proposed as a potential treatment option for patients with alcohol use disorders. Efficacy results from the placebo-controlled clinical trials reviewed in this article vary according to the specific outcome measured. Varenicline is most likely to be effective for reducing overall alcohol consumption once drinking is initiated by decreasing alcohol craving and increasing the negative subjective effects of alcohol intake. These effects may be most significant for moderate to heavy drinkers. In contrast, varenicline is not likely to improve abstinence rates. Although varenicline has the unique advantage of a potential dual treatment effect in patients with concomitant nicotine dependence, evidence indicates that it may also improve drinking outcomes in patients who do not smoke. The studies failed to find an increased risk of psychiatric adverse events with varenicline therapy, but additional studies are needed in patients with baseline psychiatric comorbidities before these results can be extrapolated to the entire population of patients with alcohol use disorders. In conclusion, varenicline appears to be a generally safe and effective treatment option for patients with alcohol use disorders and could be considered for off-label use when standard therapies for alcohol dependence are contraindicated or prove ineffective or when patients would benefit from simultaneous treatment of nicotine dependence.

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