The Impact of Varenicline on Alcohol Consumption in Subjects With Alcohol Use Disorders:

Systematic Review and Meta-Analyses

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ABSTRACT

Objective: Varenicline has been shown to be safe and effective in improving abstinence in smokers. However, results from randomized, placebo-controlled trials using varenicline for alcohol use disorders (AUDs) are inconsistent. The present systematic review and meta-analyses aimed to ascertain whether varenicline improves drinking-related outcomes in subjects with AUDs.

Data Sources: Ovid, Embase, and Scopus databases were queried using the search terms *varenicline*, *alcoholism*, *alcohol-related disorders*, and *drinking behavior* for English-language publications until August 29, 2019, of randomized, placebo-controlled trials in humans.

Study Selection: A total of 197 articles were identified by the literature search. Studies of subjects with heavy drinking or alcohol dependence/AUD that reported alcohol use–related outcomes were examined.

Data Extraction: Weighted mean difference (WMD), standardized mean difference (SMD), and 95% CIs were calculated. The primary outcome of interest was percentage of heavy drinking days. Secondary outcomes included the number of drinks per drinking day, percentage of days abstinent, and change in alcohol craving.

Results: Ten studies (n = 731, 66.6% male, 55.1% smokers) were included in the systematic review. In meta-analyses, no significant differences in percentage of heavy drinking days (n = 597; WMD = −1.09; 95% CI, −4.86 to 2.69; I^2 = 22%), number of drinks per drinking day (n = 570; WMD = −0.71; 95% CI, −1.44 to 0.03; I^2 = 0%), or percentage of days abstinent (n = 439; WMD = 3.89; 95% CI, −1.25 to 9.02; I^2 = 0%) were noted with varenicline use. Overall risk of bias was low. A statistically significant decrease in craving was observed (n = 436; SMD = −0.63; 95% CI, −1.18 to −0.08; I^2 = 84%).

Conclusions: In the present systematic review and meta-analyses, varenicline was shown to reduce alcohol craving but not improve drinking-related outcomes in subjects with AUDs.

J Clin Psychiatry 2020;81(2):19r12924

To cite: Gandhi KD, Mansukhani MP, Karpyak VM, et al. The impact of varenicline on alcohol consumption in subjects with alcohol use disorders: systematic review and meta-analyses. *J Clin Psychiatry*. 2020;81(2):19r12924.

To share: https://doi.org/10.4088/JCP.19r12924

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Alcohol use disorders (AUDs) are highly comorbid with tobacco use; 35%–60% of individuals with AUDs report smoking tobacco.[1–3] Mechanistically, both substances influence the nicotinic acetylcholine receptors in the mesolimbic dopaminergic system, which mediates the experience of reward. Both alcohol and nicotine modulate α_4/β_2-nicotinic acetylcholine receptors in the ventral tegmental area leading to dopamine release in the nucleus accumbens.[4,5]

Varenicline is an α_4/β_2-nicotinic receptor partial agonist that significantly improves abstinence in smokers without significant increase in neuropsychiatric adverse events.[6] Preclinical studies[3,5] suggest that varenicline may also reduce alcohol craving and alcohol use.

Prior clinical studies[7–9] examining the efficacy of varenicline in AUDs utilized protocols involving ad libitum drinking in circumstances when alcohol was made freely available. These studies demonstrated mixed results; some showed a decrease in ad libitum drinking with varenicline, while others showed no significant change. The populations studied varied in these investigations. McKee et al,[7] in a study of nondependent heavy drinkers, found that varenicline reduced alcohol self-administration as well as craving and subjective reinforcing effects of alcohol, whereas Ray et al[9] observed no significant decrease in drinking with varenicline alone in a heavy-drinking population with comorbid nicotine dependence. Verplaetse et al[8] studied a population with AUDs using 1-mg and 2-mg doses of varenicline; the lower dose varenicline was ineffective in reducing heavy drinking, and the 2-mg dose resulted in an improvement in alcohol craving but not consumption. In a small open label trial conducted by Hays et al[10] in smokers recovering from alcohol dependence, varenicline increased smoking cessation and did not adversely impact ongoing alcohol abstinence. Thus, overall, the results of studies that examined the impact of varenicline on ad libitum drinking were conflicting, with some evidence of greater efficacy at higher doses of the medication.

To further examine the question of whether varenicline results in meaningful improvements in alcohol-related outcomes, we performed a systematic review and meta-analyses of all randomized placebo-controlled trials that evaluated the effects of varenicline in subjects with *DSM-IV*–defined alcohol dependence, *DSM-5*–defined AUDs, or heavy drinking as defined by National Institute

Clinical Points

- Alcohol and tobacco use disorders are highly comorbid. Varenicline use reduces smoking; however, results of studies utilizing varenicline to reduce alcohol use have been mixed.
- The present meta-analyses show that while varenicline reduces alcohol craving, it does not improve measures of alcohol consumption. Clinicians should use other strategies to reduce alcohol use in patients with comorbid alcohol and tobacco use disorders.

on Alcohol Abuse and Alcoholism (NIAAA) criteria.[11–13] Our aim was to determine whether varenicline improved drinking-related outcomes in these subjects compared to placebo, measured by percentage of heavy drinking days. Secondary outcomes assessed included number of drinks per drinking day, percentage of days abstinent, and change in alcohol craving. We also attempted to ascertain whether patient characteristics such as sex, smoking status, or severity of AUD moderated the effects of varenicline on alcohol use–related outcomes.

METHODS

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[14] for the present systematic review and meta-analyses.

Search Strategy and Selection Criteria

An independent librarian performed a systematic search of the literature and verified the strategy with the authors prior to conducting the search. The search was later updated from an initial end date of December 17, 2018, to August 29, 2019, to ensure inclusion of all appropriate articles. Databases queried were Ovid (initially 1946 to December 17, 2018, then to August 29, 2019), Embase (initially 1988 to December 17, 2018, then to August 29, 2019), and Scopus (initially 1996 to December 17, 2018, then to August 29, 2019). Search terms used were *varenicline*, *alcoholism*, *alcohol-related disorders*, and *drinking behavior*. References of research articles were manually reviewed to ensure no trials were missed. Studies were included if they were double-blind, randomized, placebo-controlled trials conducted in human subjects diagnosed with heavy drinking, alcohol dependence, or an AUD. Studies were included only if they reported alcohol use–related outcomes. Excluded studies were those that were not performed in human subjects, review articles, nonrandomized or not placebo-controlled trials, or those that inadequately reported drinking-related outcomes.

Study Selection and Data Extraction

All titles and abstracts were independently reviewed by two authors (B.P.K. and K.D.G.) to identify articles of interest. Any discrepancy was resolved by discussion with a third author (M.P.M.). Following the initial review, full-length articles were examined to assess for eligibility. The data from articles that met inclusion criteria were extracted by two authors of the current report (K.D.G. and B.P.K). The respective corresponding authors of articles were contacted in requests for further information for publications in which data were not available for abstraction. In addition, the authors of the present report obtained publicly available unpublished data for trials registered at ClinicalTrials.gov when available.

Outcomes

Qualifying studies reported multiple outcomes in various formats. A majority of studies reported percentage of heavy drinking days, which was the primary outcome of interest. The NIAAA recommends the use of percentage of heavy drinking days as a primary efficacy endpoint for alcohol trials, and it is accepted as a primary outcome for phase 3 trials of alcohol pharmacotherapies by the US Food and Drug Administration (FDA).[15,16] Secondary outcomes that were assessed when available included number of drinks per drinking day and percentage of days abstinent. In addition, a few studies reported changes in alcohol craving over time, and these differences were also analyzed as a secondary outcome.

Risk of Bias Assessment

The Cochrane Collaboration Risk of Bias tool was used to assess the risk of bias within and between individual studies. Risk of bias was assessed based on random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias (see Supplementary Figures 1 and 2).

Statistical Analysis

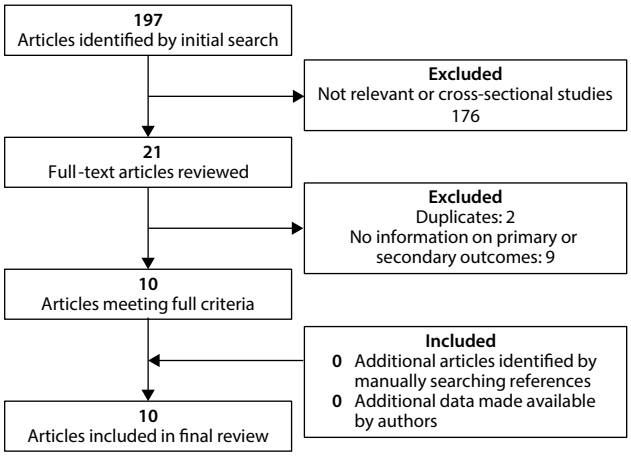
As the primary and secondary outcomes of interest were continuous measures, weighted mean differences (WMDs) and 95% CIs were calculated. Given the varied craving scales utilized across studies, standardized mean difference (SMD) was used in craving scale outcome calculations. The DerSimonian and Laird random effects model was utilized to pool effect size of included studies. Since only a small number of studies ultimately met inclusion criteria, publication bias could not be assessed. Heterogeneity was assessed using the I^2 statistic. All statistical analyses were conducted using RevMan version 5.3.[17]

RESULTS

Search Results

The initial literature search yielded 197 abstracts. After initial review, full texts of 21 articles were considered. Of these, 10 studies met all the criteria for inclusion in the systematic review (Figure 1). Studies excluded were those that did not report drinking-related outcomes (number of heavy drinking days, abstinent days, or drinks per drinking day) or that measured changes in alcohol self-administration only under controlled conditions. Data for the meta-analyses

Figure 1. PRISMA Flow Diagram Outlining Study Selection



could be abstracted from 8 studies[18,20–26]; 6 of these included information on heavy drinking days, 6 reported data on percentage of days abstinent, and 5 provided a measure of the number of drinks per drinking day. An additional 4 studies reported changes in alcohol craving. Results from the 2 studies that met inclusion criteria for the systematic review but did not provide data in a manner that could be utilized for the meta-analyses are presented separately. Detailed review of references did not yield any further articles; other study authors were contacted, but no additional data were made available. Data for inclusion in the meta-analyses were obtained from ClinicalTrials.gov for 1 study.[21]

Characteristics of Included Studies

All 10 studies included in the systematic review were parallel-group, randomized, placebo-controlled trials using varenicline, with a total of 731 subjects, of whom 66.6% were male and 55.1% were smokers. All investigations recruited volunteers without medical complications and with either heavy drinking or alcohol dependence/AUD, with or without nicotine use or dependence. One study[22] enrolled patients with schizophrenia; all other studies excluded patients with non–nicotine-related psychiatric comorbidities. All studies recruited patients from the community. Methods used for recruitment varied but included print or radio advertisements and internet postings. Supplementary Figures 1 and 2 show assessment of risk of bias. Eight trials reported allocation concealment; 7 studies were conducted with intention-to-treat analysis. One study[23] reported findings for men and women separately. All included studies used a varenicline dose of 2 mg/d (Table 1). A summary of findings from these studies is shown in Supplementary Table 1.

Impact of Varenicline on Percentage of Heavy Drinking Days

Six studies (n = 597)[18–21,23,24] reported the percentage of heavy drinking days in varenicline versus placebo groups. Meta-analysis of the impact of varenicline on percentage heavy drinking days revealed no significant difference between varenicline and placebo groups and little heterogeneity between studies (WMD = −1.09; 95% CI, −4.86 to 2.69; I^2 = 22%) (Figure 2).

Impact of Varenicline on Drinks per Drinking Day

Meta-analysis of 6 studies (n = 570)[18,20–26] that reported the number of drinks per drinking day showed no significant difference between varenicline and placebo groups, with minimal heterogeneity between studies (WMD = −0.71; 95% CI, −1.44 to 0.03; I^2 = 0%) (Figure 3).

Impact of Varenicline on Percent Days Abstinent

Meta-analysis of 5 studies (n = 439)[18,20–22,25] that recorded the percentage of days abstinent demonstrated no significant difference in subjects on varenicline compared to placebo; minimal heterogeneity was found among the studies (WMD = 3.89; 95% CI, −1.25 to 9.02; I^2 = 0%) (Supplementary Figure 3).

Impact of Varenicline on Craving Scale Scores

In the 4 studies (n = 436)[18,19,21,24] that evaluated craving via scale measures (Penn Alcohol Craving Scale or Obsessive Compulsive Drinking Scale), a statistically significant decrease in craving scores in varenicline versus placebo groups was observed, with significant heterogeneity noted among the studies (SMD = −0.63; 95% CI, −1.18 to −0.08; I^2 = 84%) (Figure 4).

Four studies[19,20,24,26] that were included in these meta-analyses recruited patients who were not specifically seeking treatment for their alcohol use. Repeat analysis including only studies with treatment-seeking populations showed no differences in any of the outcomes (results not shown).

Two studies included in this systematic review reported results in a format that did not allow for inclusion in the meta-analyses. One study[27] recruited patients with alcohol dependence and reported that varenicline at a dose of 2 mg resulted in an improvement in craving but not in alcohol use–related outcomes. The other study,[26] also utilizing varenicline at 2 mg, in patients with heavy drinking and smoking noted a decrease in the total number of drinks and the number of drinks per week in patients receiving the medication but reported none of the aforementioned primary or secondary outcomes. This study did not report a difference in craving.

We were unable to examine the potential moderating effects of patient characteristics and severity of alcohol use on the efficacy of varenicline. One study[23] included in the meta-analyses found decreased efficacy of varenicline in reducing alcohol use in women compared to men; however, inconsistent reporting of sex-stratified results in the other studies limited our ability to analyze sex as a potential moderator. Some investigations included only smokers with comorbid alcohol use, while others included both smokers and nonsmokers. Severity of AUD likewise differed between studies from heavy drinking to a diagnosis of alcohol dependence. Smoking-related outcomes were reported inconsistently across the studies, and although

Table 1. Characteristics of Studies Included in the Systematic Review[a]

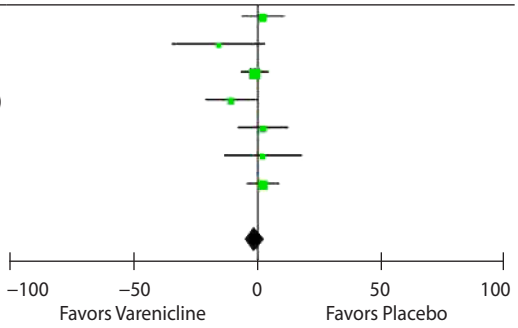
Study	N	Female Subjects, %	Subject Characteristics	Blinding Status	Follow-Up Duration	Subjects Who Were Smokers, %	Varenicline Dose
O'Malley et al (2018)[23]	131	29.8	Healthy adult smokers with alcohol dependence	Triple-blind	17 wk	100	2 mg
Hurt et al (2018)[20]	33	36.3	Healthy adult smokers with alcohol dependence	Triple-blind	6 mo	100	2 mg
De Bejczy et al (2015)[18]	160	38	Healthy adults with alcohol dependence	Quadruple-blind	6 mo	Not reported	2 mg
Schacht et al (2014)[24]	35	43	Healthy adults with alcohol dependence	Double-blind	None	43	2 mg
Plebani et al (2013)[27]	40	15	Healthy adults with alcohol dependence	Double-blind	1 wk	Varenicline: 47.3 Placebo: 38.0	2 mg
Meszaros et al (2013)[22]	10	30	Adults with schizophrenia or schizoaffective disorder and nicotine dependence and alcohol dependence	Triple-blind	1 mo	100	2 mg
Litten et al (2013)[21]	200	30	Healthy adults with alcohol dependence	Quadruple-blind	2 wk	Varenicline: 38.1 Placebo: 41	2 mg
Mitchell et al (2012)[26]	64	40.6	Healthy adult smokers with heavy drinking	Triple-blind	1 mo	100	2 mg
Fucito et al (2011)[19]	30	40	Healthy adult smokers with heavy drinking	Double-blind	None	100	2 mg
Pfeifer and Fehr (2019)[25]	28	13.33	Adults with alcohol and nicotine use disorder and desire to abstain from alcohol who had completed alcohol withdrawal therapy	Double-blind	12 wk	100	2 mg

[a]All studies included in the systematic review were placebo-controlled randomized clinical trials.

Figure 2. Subgroup Analysis of Percentage of Heavy Drinking Days in Those Receiving Varenicline Versus Placebo

Study or Subgroup	Varenicline Mean	Varenicline SD	Varenicline Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random (95% CI)
de Bejczy et al[18]	51	28.3	86	49	28.2	85	15.2%	2.00 (–6.47 to10.47)
Fucito et al[19]	22.7	17.5	15	38	31.2	15	4.1%	–15.30 (–33.40 to 2.80)
Hurt et al[20]	7.9	8.3	16	9.1	7.2	17	28.4%	–1.20 (–6.52 to 4.12)
Litten et al[21]	37.9	35.91	96	48.4	35.37	101	11.8%	–10.50 (–20.46 to –0.54)
O'Malley et al[23,a]	63	23	45	61	25	47	12.1%	2.00 (–7.81 to 11.81)
O'Malley et al[23,a]	65	23	19	63	25	20	5.7%	2.00 (–13.07 to 17.07)
Schacht et al[24]	60	10.8	18	58	8.4	17	22.7%	2.00 (–4.39 to 8.39)
Total (95% CI)			**295**			**302**	**100.0%**	**–1.09 (–4.86 to 2.69)**

Heterogeneity: $\tau^2 = 5.68$; $\chi^2_6 = 7.73$ ($P = .26$); $I^2 = 22\%$
Test for overall effect: $Z = 0.56$ ($P = .57$)

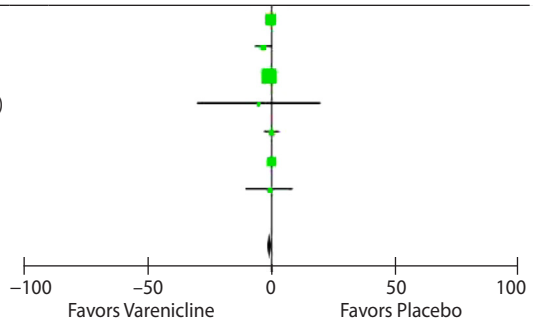


[a]The study by O'Malley et al[23] is included twice to show separate results for the two groups in the study.
Abbreviation: IV = inverse variation.

Figure 3. Subgroup Analysis of Number of Drinks per Drinking Day in Those Receiving Varenicline Versus Placebo

Study or Subgroup	Varenicline Mean	Varenicline SD	Varenicline Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random (95% CI)
de Bejczy et al[18]	3	5.08	86	3.42	4.3	85	26.9%	–0.42 (–1.83 to 0.99)
Hurt et al[20]	5.7	3.9	16	9	5.3	17	5.3%	–3.30 (–6.46 to –0.14)
Litten et al[21]	5.8	4.21	96	6.8	4.01	101	40.5%	–1.00 (–2.15 to 0.15)
Meszaros et al[22]	8	17	5	13	21	5	0.1%	–5.00 (–28.68 to 18.68)
O'Malley et al[23a]	8	5	19	8	4	20	6.6%	0.00 (–2.85 to 2.85)
O'Malley et al[23a]	9	4	45	9	4	47	20.0%	0.00 (–1.64 to 1.64)
Pfeifer et al[25]	21	12.1	15	22.1	12.2	13	0.7%	–1.10 (–10.13 to 7.93)
Total (95% CI)			**282**			**288**	**100.0%**	**–0.71 (–1.44 to 0.03)**

Heterogeneity: $\tau^2 = 0.00$; $\chi^2_6 = 4.08$ ($P = .67$); $I^2 = 0\%$
Test for overall effect: $Z = 1.89$ ($P = .06$)

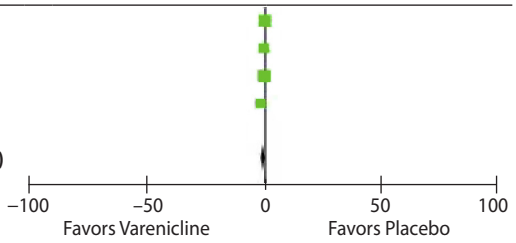


[a]The study by O'Malley et al[23] is included twice to show separate results for the two groups in the study.
Abbreviation: IV = inverse variation.

Figure 4. Subgroup Analysis of Standard Mean Differences in Craving Scale (Penn Alcohol Craving Scale or Obsessive Compulsive Drinking Scale) Scores in Those Receiving Varenicline Versus Placebo

Study	Varenicline Mean	Varenicline SD	Varenicline Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Standardized Mean Difference IV, Random (95% CI)
de Bejczy et al[18]	4.54	15.96	86	6.18	14.74	85	30.0%	−0.11 (−0.41 to 0.19)
Fucito et al[19]	6.41	1.92	15	7.71	2.59	15	20.9%	−0.55 (−1.29 to 0.18)
Litten et al[21]	9.9	4.9	99	11.6	4.92	101	30.3%	−0.34 (−0.62 to −0.07)
Schacht et al[24]	5	1.08	18	7.2	1.05	17	18.8%	−2.02 (−2.85 to −1.19)
Total (95% CI)			**218**			**218**	**100.0%**	**−0.63 (−1.18 to −0.08)**

Heterogeneity: $\tau^2 = 0.24$; $\chi^2_3 = 18.29$ ($P = .0004$); $I^2 = 84\%$
Test for overall effect: $Z = 2.24$ ($P = .02$)



Abbreviation: IV = inverse variation.

not a primary aim of this study, we noted that smoking cessation rates significantly improved in these patients with AUD.

DISCUSSION

Summary

The present systematic review and meta-analyses of 10 randomized placebo-controlled trials examining the effects of varenicline compared to placebo on measures of alcohol use in subjects with heavy drinking or alcohol dependence/AUD did not demonstrate improvements in most drinking-related outcomes. To our knowledge, the present comprehensive systematic review and meta-analyses are the first to evaluate the effectiveness of varenicline on all major alcohol use–related outcomes. We found no evidence that varenicline decreased the percentage of heavy drinking days or the number of drinks consumed per drinking day or increased number of days abstinent. Reported alcohol craving decreased with use of varenicline.

Varenicline and Alcohol Consumption

A majority of trials included in this review reported percentage of heavy drinking days; some studies reported drinks per drinking day and percentage of days abstinent. The results of the meta-analyses were consistent across all of these measures and showed no significant changes with the use of varenicline compared to placebo. Alcohol use at light, medium, and heavy levels of drinking is associated with significant morbidity and all-cause mortality, even in those who do not fulfill criteria for an AUD.[28] Although abstinence has been considered the goal of AUD treatment, reductions in drinking to low-risk levels are associated with marked improvements in physical and mental health markers.[29] Alcohol-related harm increases in a linear fashion with the frequency of heavy drinking episodes, and there is a heightened risk of mortality with higher alcohol consumption.[30] The percentage of heavy drinking days, number of drinks per drinking day, and percentage of days abstinent from alcohol are thus useful indicators of morbidity and mortality risk in those with AUDs.[30] Varenicline did not appear to improve these practical measures of harm associated with alcohol use in the current systematic review and meta-analyses.

Varenicline and Craving

Craving can be understood as an intense subjective desire to use a substance and is part of the *DSM-5* diagnostic criteria for substance use disorders.[13] Medication-assisted treatments for AUDs promote abstinence (acamprosate, naltrexone) or decrease the risk of relapse by preventing heavy drinking (naltrexone).[31] Acamprosate and naltrexone also reduce alcohol craving.[32–34] In our meta-analyses, varenicline did result in a reduction in alcohol craving. However, there was significant heterogeneity in the studies that were included in this analysis, and only a small number of studies reported data on craving. Despite improvements in craving, none of the alcohol consumption–related outcomes improved. While some studies[35] have shown that craving could be a risk factor for alcohol relapse, other studies[36–38] have not reported an association between craving and subsequent relapse. Thus, on the basis of the current data, it appears that improvements in craving following varenicline use do not necessarily translate into a reduction in alcohol consumption in subjects with AUDs.

Strengths and Limitations

The current systematic review and meta-analyses are, to our knowledge, the first to evaluate the effects of varenicline compared to placebo on meaningful drinking-related outcomes in subjects with AUDs. The included studies had limited heterogeneity with regard to the main outcomes assessed. Multiple alcohol consumption–related outcomes were examined. We included all data that were publicly available on the impact of varenicline on alcohol use–related measures.

The present systematic review and meta-analyses must be viewed in light of some limitations. Although sex and amount of alcohol consumption were known, and close to half the included participants had comorbid AUD and tobacco use disorder, data were not reported in a manner in which we could examine whether patient factors such as sex, severity of AUD, and smoking status exerted a moderating effect on alcohol use–related outcomes. Furthermore, inconsistent

clinical subgroup classification and reporting of results limited comparisons between studies, and some data could not be included in the meta-analyses. The findings may have been different if unpublished data had been available; however, the consistent results across studies and low heterogeneity among studies reporting the main outcomes suggest that different findings are unlikely. Heterogeneity among studies reporting alcohol craving was high, very likely due to the small number of studies reporting craving-related outcomes, and these findings need to be confirmed in future well-designed studies.

Future Directions

The question regarding whether there are specific patient populations and clinical characteristics that might influence the response to varenicline remains open. A single study[23] indicated possible sex-related differences in response. Currently available data were not reported in a manner in which we could examine differential response based on sex. Future studies should aim to overcome this shortcoming. Additionally, other clinical characteristics such as smoking status and severity of alcohol use could influence treatment response. Reporting of measures in the included studies did not render it feasible to evaluate the moderating effects of these clinical factors. Future investigations should aim to report outcomes in a standardized fashion and should explicitly examine whether these clinical characteristics influence treatment response. The impact of varenicline on drinking-related outcomes in subpopulations with AUDs such as those with comorbid psychiatric conditions also requires further study.

CONCLUSIONS

Alcohol and drug use, especially the use of alcohol and tobacco, is a major cause of physical disease burden.[39] Alcohol and tobacco use and dependence commonly co-occur and may have common underlying genetic mechanisms.[3,40] Current FDA-approved treatments (naltrexone, acamprosate, disulfiram) for AUDs result in improvements in only a minority of patients. Thus, there is an ongoing need for improved pharmacotherapies for AUDs. Despite promising preclinical and mixed clinical results of varenicline in the treatment of AUD, the current systematic review and meta-analyses did not find benefits from varenicline in reducing alcohol consumption. Future research should examine whether varenicline may be more effective in certain subpopulations.

Submitted: May 22, 2019; accepted September 17, 2019.

Published online: February 25, 2020.

Potential conflicts of interest: The authors have no conflicts of interest to declare.

Funding/support: No funding was received for this research or manuscript.

Previous presentation: Poster previously presented at the Research Society on Alcoholism Annual Meeting; June 22–26, 2019; Minneapolis, Minnesota.

Supplementary material: Available at PSYCHIATRIST.COM

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Supplementary Material

Article Title: The Impact of Varenicline on Alcohol Consumption in Subjects With Alcohol Use Disorders: A Systematic Review and Meta-Analysis

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DOI Number: https://doi.org/10.4088/JCP.19r12924

List of Supplementary Material for the article

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4. Table 1 — Results of interest included in the systematic review

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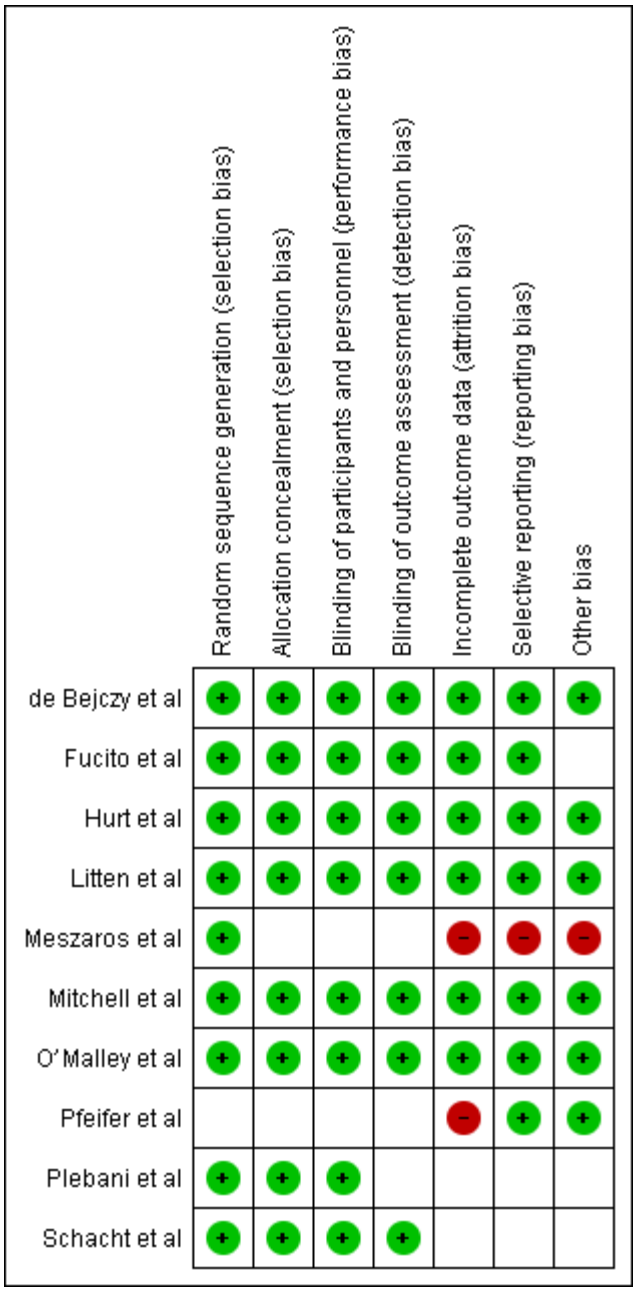
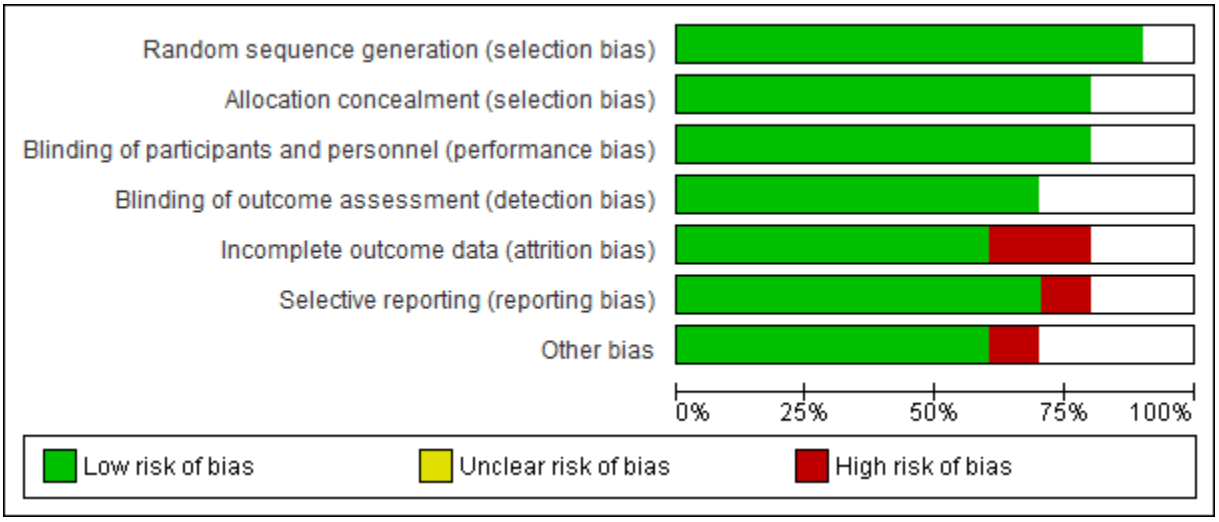
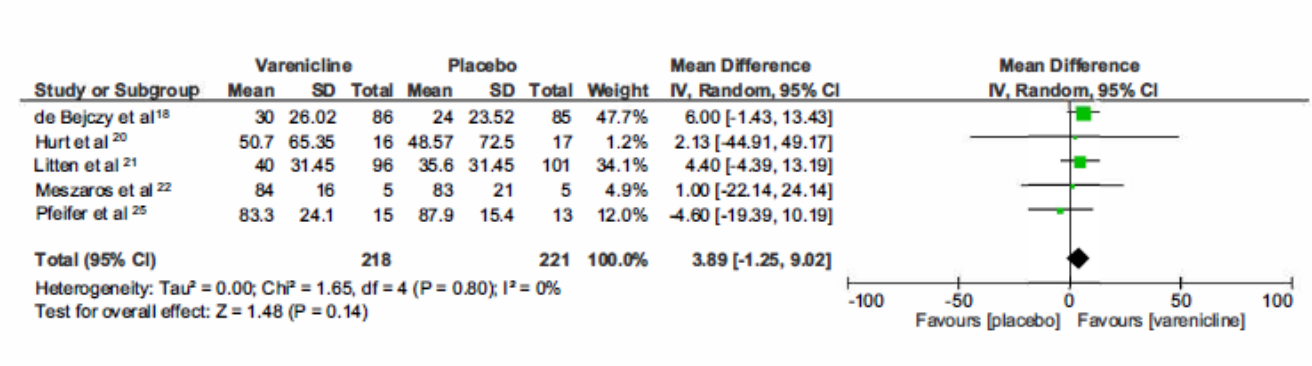


Supplementary Figure 1: Risk of bias table



Supplementary Figure 2: Risk of bias graph



Supplementary Figure 3: Subgroup analysis of number of days abstinent in those receiving varenicline versus placebo

Supplementary Table 1. Results of interest included in the systematic review

Author and date of Publication	Percentage heavy drinking days-varenicline (SD)	Percentage heavy drinking days- placebo (SD)	Drinks per drinking day-varenicline (SD)	Drinks per drinking day-placebo (SD)	Percentage days abstinent-varenicline	Percentage days abstinent-placebo
O'Malley et al (2018)[23]	Men: 63 (26) Women: 65 (23)	Men: 61 (25) Women: 63 (25)	Men: 9 (4) Women: 8 (5)	Men: 9 (4) Women: 8 (4)	Not reported	Not reported
Hurt et al (2018)[20]	Week 12: 7.9 (8.3) Week 24: 7.8 (8.5)	Week 12: 9.1 (7.2) Week 24: 8.8 (7.5)	5.7 (3.9)	9.0 (5.3)	50.7 (65.35)	48.57 (72.5)
De Bejczy et al (2015)[18]	51 (28.3)	49 (28.2)	3 units[a]	3.42 units[a]	30 (26.02)	24 (23.52)
Schacht et al (2014)[24]	60 (5)	58 (8)	Not reported (no effect)	Not reported (no effect)	Not reported (no effect)	Not reported (No data reported, authors state no change was observed)
Plebani et al (2013)[27]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Meszaros et al (2013)[22]	Not reported	Not reported	Standard drinks per week: 8 (17)	Standard drinks per week: 13 (21)	84 (16)	83 (21)
Litten et al (2013)[21]	37.9 (35.91)	48.4 (35.37)	5.8 (SE 0.43)	6.8 (SE 0.42)	40 (SE 3.21)	35.6 (SE 3.13)
Mitchell et al (2012)[26]	Not reported	Not reported	Average consumed through week 12: Mean 177.04 (SE 28.86)	Average consumed through week 12: Mean 277.5 (SE	Not reported	Not reported

				41.9)		
Fucito et al (2011)[19]	Not reported	Not reported	Reported no change	Reported no change	Not reported	Not reported
Pfeifer and Fehr (2019)[25]	Not reported	Not reported	reduction of 11.3 (11.1)	reduction of 1.3 (9.1)	83.3 (24.1)	87.9 (15.4)

[a]Study defined 1 unit of alcohol as 13 grams.

Abbreviations: SD=Standard deviation; SE=Standard error