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Efficacy and acceptability of varenicline for alcoholism: A systematic review and meta-analysis of randomized-controlled trials

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ABSTRACT

Background: Current pharmacological treatment for alcoholism remains unsatisfactory. While there have been several clinical trials investigating the efficacy and safety of the therapeutic use of varenicline in alcoholism, no definitive review of this topic has been carried out. This systematic review aimed to determine the efficacy and acceptability of the use of varenicline in treating alcoholism.

Methods: This systematic review included double-blinded, randomized, placebo-controlled trials reporting heavy drinking days, amount of alcohol consumption, overall dropouts, or dropouts due to adverse events. We searched PubMed, Scopus, Web of Science, ClinicalTrials.gov, and the Cochrane Library in January 2019. We independently selected the trials and assessed the quality of included studies. We calculated standardized mean differences on heavy drinking days and the amount of alcohol consumption. We calculated the relative risks for dropout rate. All data were pooled using random-effects models.

Result: This systematic review included nine double-blind, randomized, placebo-controlled trials (N = 585). The study duration ranged from 4 to 13 weeks. Varenicline therapy was not superior to placebo in decreasing heavy drinking days but significantly superior to placebo in decreasing alcohol consumption. There were no statistically significant differences between groups on dropout rates due to any reason or due to adverse events.

Conclusion: Varenicline therapy is effective in decreasing alcohol consumption over a period of time. It may be an option for decreasing heavy drinking days in patients with alcoholism. It is a well-accepted medication for alcoholism. More studies are needed to determine if varenicline is effective in decreasing heavy drinking.

1. Introduction

Alcoholism is a common mental disorder and leads to an increase of physical and psychiatric morbidities, disability, and mortality (Popova et al., 2016; Rehm, 2011; Vancampfort et al., 2016). Due to its chronic course and frequent relapses, intensive biological, psychological, and social interventions are mandatory to lengthen the abstinence duration and prevent relapses. A variety of medication has been shown to play an important role in decreasing alcohol consumption and severity of alcohol dependence.

Over the past two decades, only slow progress has been made in developing medication for the treatment of alcohol dependence (Shen, 2018). The U.S. Food and Drug Administration (FDA) has approved only four medications for the treatment of alcohol dependence: oral disulfiram, naltrexone, acamprosate, and an injectable suspension formulation of naltrexone (Substance Abuse and Mental Health Services Administration, 2015). Although these medications are helpful in reducing heavy drinking days and alcohol consumption, their long-term efficacy remains unsatisfactory. While short-term treatment of naltrexone for alcoholism decreases the risk of alcohol relapse by 36%, about 36% of those taking naltrexone may discontinue this medication in the first 12 weeks (Srisurapanont and Jarusuraisin, 2005)

Several lines of evidence suggest that varenicline may have a beneficial effect on reducing alcohol consumption. Varenicline is a potent partial agonist at α6β2, a partial agonist of the α4β2, and a full agonist at the α7 nicotinic acetylcholine receptors (nAChRs) (Bordia et al., 2012; Mihalak et al., 2006). It has been shown to decrease smoking behavior and is FDA-approved for use as an aid in smoking cessation. Its partial agonism at α6β2 and α4β2 receptors are related to the reinforcing effects of nicotine and to maintaining smoking behavior (Bordia et al., 2012).

Generally, tobacco and alcohol were found to have reciprocal influences. Verplaetse and McKee (2017) suggested that alcohol increases the craving for smoking, decreases the time to initiate smoking, and

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increases smoking self-administration. Reciprocally, tobacco and nicotine increase alcohol craving, decrease subjective effects of alcohol, and increase alcohol consumption.

Although the mechanism used by the drugs is still unclear, a number of studies into the action of varenicline in alcoholism have been carried out. Several findings suggested that the engagement or lack of engagement of nicotinic acetylcholine receptors were related to alcohol drinking behavior (Erwin and Slaton, 2014; Feduccia et al., 2014; Holgate et al., 2018). In a placebo-controlled study, varenicline appeared to reduce the feelings of happiness and excitement when anticipating alcohol reward (Vatsalya et al., 2015). A functional magnetic resonance imaging study also found that heavy drinkers receiving varenicline tended to have a lower reaction of left amygdala in responding to fearful faces (Gowin et al., 2016). Several clinical trials have found that varenicline was associated with reduced consumption of both tobacco and alcohol, decreasing alcohol craving, and has also been related to improved cognitive performance (Roberts et al., 2017; Roberts and McKee, 2018).

Due to its therapeutic possibilities, there have been a number of clinical trials investigating the effects of varenicline in patients with problematic alcohol drinking. Understanding the effects of varenicline on alcoholism would be helpful to determine its position in being a treatment option for alcoholism. We, therefore, proposed to carry out a systematic review to examine the efficacy and acceptability of varenicline in patients with alcoholism.

2. Materials and methods

2.1. Inclusion criteria

Only the double-blinded, randomized, placebo-controlled trials were considered. Based on the PICO model (Higgins and Green, 2011), the key characteristics of included studies were as follows: i) patients – people with problematic alcohol use; ii) intervention – varenicline; iii) comparator – placebo; and iv) outcome - efficacy (i.e., heavy drinking, alcohol consumption) and acceptability (i.e., dropout rate). The present quantitative analysis included only the studies lasting more than two weeks.

Problematic alcohol use was defined as alcohol abuse, alcohol dependence, and alcohol use disorder meeting the diagnostic criteria of DSM-IV, DSM-IV-TR and ICD-10 systems (American Psychiatric Association, 2013; First et al., 2002; World Health Organization, 1992). The number of heavy drinking days at the endpoint was chosen as the primary outcome of efficacy because this has been specified by researchers and patients in most RCTs as the most pertinent parameter in determining the efficacy of treating alcoholism (Sobell et al., 2003; World Health Organization, 2018). The second outcome measures of interest were the number of alcohol consumed in terms of standard drinks for a defined period (eg. week, study duration). Overall dropout rate and dropout rate due to adverse events were considered as an index of acceptability. For any outcome assessed more than once in a particular term, we extracted results obtained at the farthest points of follow-up after receiving varenicline and placebo treatment.

2.2. Data sources and searches

Four electronic database searches included Pubmed, Scopus, Web of Science, ClinicalTrials.gov and the Cochrane Library in January 2019. Keywords used for searching were (varenicline OR chantix OR champix) and (alcohol) (see Appendix 1 for the full details of searches). No language restriction was applied. The bibliographical manager (Zotero 5.0.58) and the systematic review web application (rayyan.qcri.org) were used to store, remove the duplicates, and select the randomized, placebo-controlled trials. The references of included articles and review articles were then searched for citations of potentially relevant published and unpublished research. When data required for the meta-analysis were missing, either the first or corresponding authors were contacted for additional information.

2.3. Study selection

Two authors (AO and MS) reviewed the trial searches and independently identified the trials meeting the inclusion criteria. We included double-blinded, randomized, and placebo-controlled trials. Concomitant psychosocial interventions for problematic alcohol use were allowed. Trials conducted in in- or out-patient settings in any country were included. If there was a discrepancy between authors on the selection of trials both authors would discuss and make a consensus on the study inclusion.

2.4. Data extraction and quality assessment of included trials

Both authors independently assessed the methodological quality of included studies as described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins and Green, 2011). The risk of bias tool enables the assessment of potential risk of bias and classifies each risk into three categories (low, high, or unclear). Seven aspects that were assessed included: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Any discrepancy was resolved by discussion between reviewers.

Trial characteristics and the data relevant to the reviewed outcomes were extracted and recorded in a data record form. In addition to the characteristics of included studies both reviewers also independently extracted the specified outcomes (i.e., heavy drinking days, alcohol consumption, overall dropout, and dropouts due to adverse events). As the treatment or the controlled groups of some studies were divided into several subgroups (mostly due to the differences in concomitant treatment), a continuous outcome of these subgroups could not be combined as an outcome of the whole group. In this case, the outcomes of the subgroup receiving the most rigorous treatment, e.g. the recommended doses of treatment, were used as representative of that group.

2.5. Statistical analysis

A standardized mean difference (SMDs) with 95% confidence interval (CI) was used to synthesize the outcomes of heavy drinking days and alcohol consumption because these outcomes were likely to be measured by various units (e.g. number and decrease in heavy drinking days, standard drinks per week, per month, or per drinking day). Missing outcomes were handled using recommendations drawn from the special topics in statistics described in the Cochrane Handbook for Systematic Reviews for Interventions (Higgins and Green, 2011). For data reported in graphical form in the first instance we contacted the authors for the precise data.

For the dichotomous outcome of dropout rates we calculated the relative risks (RRs) with 95% CI. The data synthesis was done on an intention-to-treat basis. As the results obtained from a random-effect model of data synthesis might be more generalized, this model was used throughout the review for calculating RRs and SMDs (DerSimonian and Laird, 2015). The effect sizes (SMDs) were interpreted as follows: 0.2 = small; 0.5 = medium; and 0.8 = large (Cohen, 1992).

The consistency of data was examined by looking at the graphical display of the results and also by using an I-square (I^2) (Higgins et al., 2003). As recommended, an I^2 of 75% or more indicates a high inconsistency of data. The meta-analysis and publication bias were performed using Review Manager 5.3 and Jamovi 0.9.1, respectively. We reported the results of this systematic review as recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklists (Moher et al., 2009).

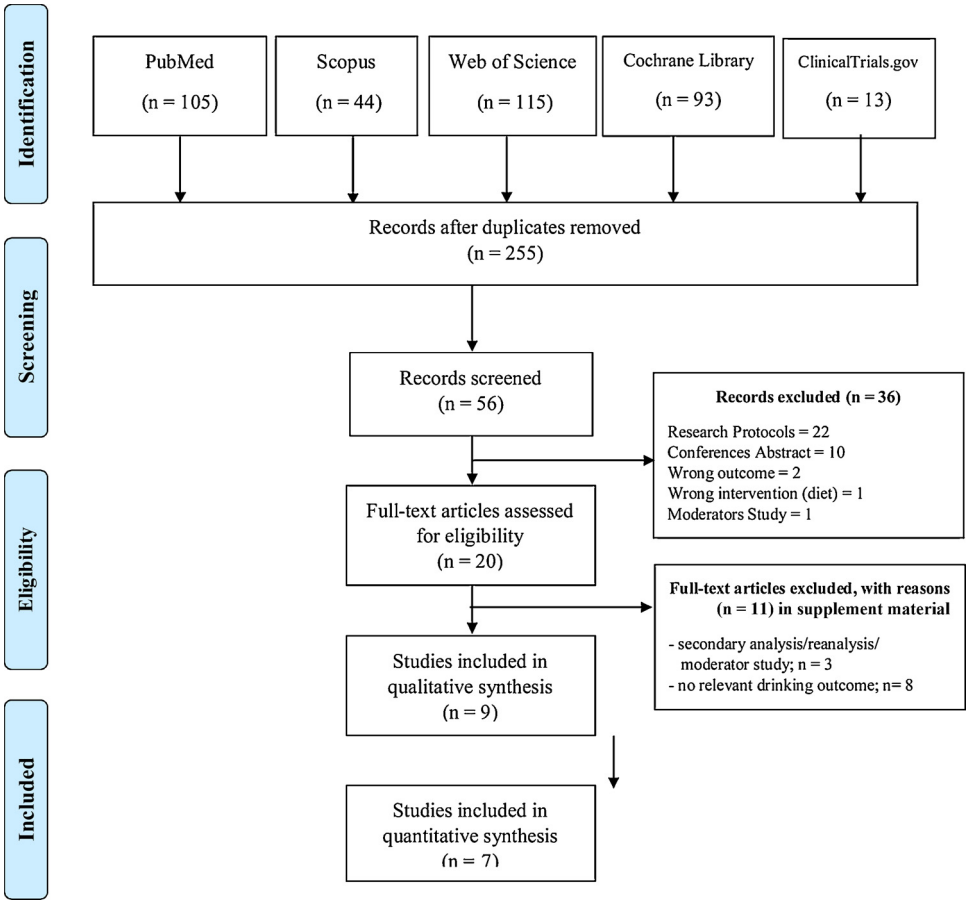

Fig. 1. Article selection flow diagram.

3. Results

3.1. Study inclusion and characteristics

After screening the abstracts and removing duplicates, we found 56 studies that were relevant to the inclusion criteria. Of the 36 studies that were excluded in the abstract screening process, 22 studies were research protocols, 10 studies were conferences abstracts, 2 studies had no outcome that was pre-defined by the reviewers, 1 study was a moderator study, and 1 study was not the intervention in which we were interested (see Fig. 1). Eleven more articles were excluded after a full-text review because 8 did not report any one of the four pre-defined outcomes, 1 was a reanalysis study, 1 was a moderator study, and 1 was a secondary analysis (please see supplement material). Finally, nine studies were included in the full-text article assessment for eligibility, and no high risk of bias was found. (see Fig. 2) These nine studies were double-blind, randomized, placebo-controlled studies and were included in this systematic review (de Bejczy et al., 2015; Fucito et al., 2011; Hurt et al., 2018; Litten et al., 2013; Meszaros et al., 2013; Mitchell et al., 2012; O'Malley et al., 2018; Plebani et al., 2013; Schacht et al., 2014).

Eight studies were conducted in the USA and 1 study in Sweden (see Table 1). All studies were published in English. The total number of subjects included in this review was 585. Of those, 280 were assigned to the varenicline-treated group. All trials diagnosed the subjects by using either the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, DSM-IV-TR, DSM-5), the Mini International Neuropsychiatric Interview (MINI), or International Classification of Diseases 10th (ICD-10). Table 1 shows the characteristics of the included studies. The duration of the studies was between 4 and 13 weeks, with sample sizes between 10 and 200 participants. The mean age of the study population was between 25 and 55.6 years. The included studies reported various outcomes of alcohol consumption, including drinks per day, drinks per drinking day, drinks per week and cumulative drinks.

We excluded two studies from the quantitative analysis because one study reported the outcomes in graph (Plebani et al., 2013) and another one had too short study duration (2 weeks) (Schacht et al., 2014). We extracted the data on an intention-to-treat basis.

3.2. Efficacy in treating alcoholism

Five studies reported the outcome of heavy drinking days (de Bejczy et al., 2015; Fucito et al., 2011; Hurt et al., 2018; Litten et al., 2013; O'Malley et al., 2018) (see Fig. 3a). Varenicline was not significantly superior to placebo in decreasing heavy drinking days. (SMDs = -0.14, 95% CI -0.33–0.05, p = 0.15, I^2 = 15%, 5 RCTs, n = 551). The funnel plot of this outcome showed no evidence of publication bias.

Five studies reported the outcome of alcohol consumption (de Bejczy et al., 2015; Hurt et al., 2018; Litten et al., 2013; Meszaros et al., 2013; Mitchell et al., 2012) (see Fig. 3b). Varenicline was significantly superior to placebo in decreasing alcohol consumption. (SMDs = -0.37, 95% CI -0.66 to -0.07, p = 0.02, I^2 = 49%, 5 RCTs, n = 465).

In the study reporting the average drinks per day, the average drinks per drinking day, the drinking day, and the heavy drinking day after varenicline discontinuation for 24 weeks, the authors found that varenicline was significantly superior to placebo as regards those outcomes (Hurt et al., 2018). Another study reported the outcome of efficacy after extended pretreatment study for 4 weeks, including the titration period (Fucito et al., 2011). A study in schizophrenia patients with problematic alcohol use also suggested that the varenicline group consumed less alcohol than placebo group (Meszaros et al., 2013). However, due to the small sample size of this later study, the statistical power was

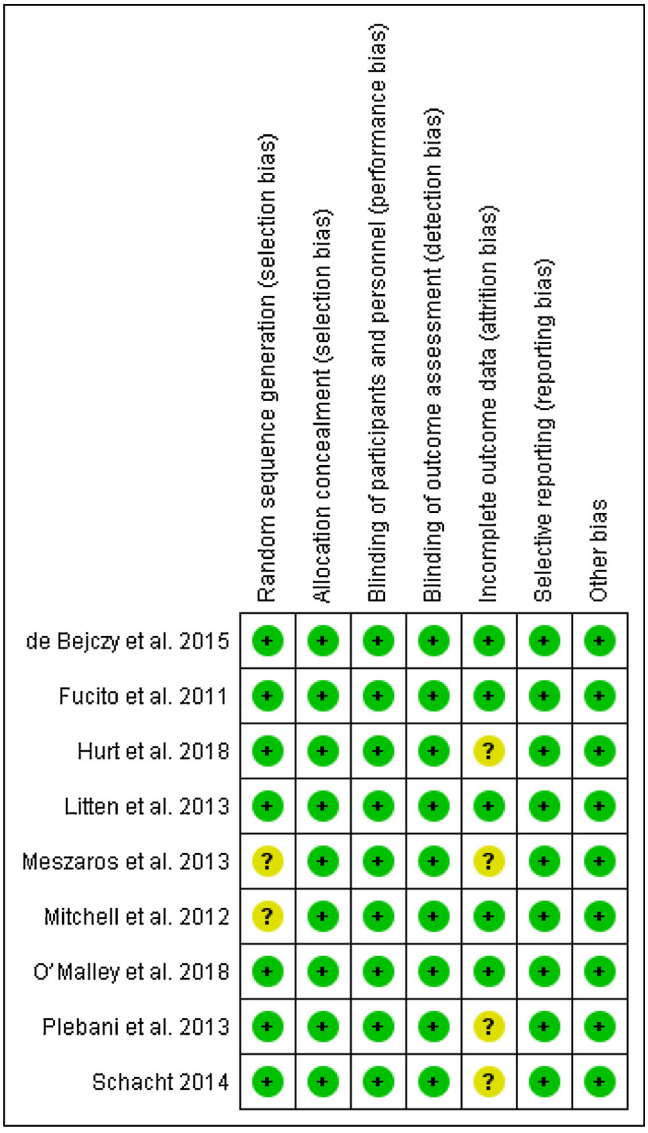

Fig. 2. Risk of bias assessment using criteria for judging risk of bias from the Cochrane Handbook for Systematic Reviews of Interventions.

inadequate to detect the efficacy of varenicline in reducing alcohol drinking.

3.3. Acceptability

We excluded a study that did not report the outcome of dropouts (Fucito et al., 2011). Dropout rate was reported in six studies and were included in the present meta-analysis. (de Bejczy et al., 2015; Hurt et al., 2018; Litten et al., 2013; Meszaros et al., 2013; Mitchell et al., 2012; O'Malley et al., 2018). The total number in participants for this outcome was 609. Both dropout rate due to any reason and dropouts due to adverse events were not significantly different with the RR of 0.82 (95% CI 0.53–1.26, p = 0.36, I^2 = 54%, 6 RCTs, n = 626) (see Fig. 3c) and the RR of 1.70 (95% CI 0.64–4.51, p = 0.28, I^2 = 35%, 6 RCTs, n = 626) (see Fig. 3d), respectively.

4. Discussion

This comprehensive meta-analysis of RCTs focusing on the efficacy and acceptability of varenicline for treating alcoholism. While varenicline is effective for decreasing alcohol consumption, it is not effective for reducing heavy drinking days. The SMD of -0.37 suggests that varenicline has a moderately sized effect for reducing alcohol consumption. The low dropout rates due to any reason and due to adverse events suggest that varenicline is highly accepted and tolerable.

In comparison to a recent systematic review of varenicline for alcoholism (Erwin and Slaton, 2014), our systematic review included more trials and participants. In addition, it includes studies with a high methodological quality by including those using a double-blindness design, clearly defined diagnostic systems and mostly low risk of bias. However, both the previous and present systematic reviews found that varenicline is effective for reducing alcohol consumption.

Varenicline may be as effective as some other medications approved or used for the treatment of alcoholism. As approved by FDAs in many countries, several findings suggest that naltrexone is effective for reducing heavy drinking and craving, and acamprosate can promote alcohol abstinence (Maisel et al., 2013). Naltrexone in an oral and injectable form is reported to have a small and medium sized effect respectively on the reduction heavy drinking. No statistically significant difference for heavy drinking is found when comparing acamprosate to naltrexone (Jonas et al., 2014). As regards alcohol consumption, a previous meta-analysis demonstrated that 50 mg of oral naltrexone had a medium sized effect in reducing drinks per drinking day, and acamprosate has no effect in alcohol consumption (Jonas et al., 2014). Two recent meta-analyses also reported that baclofen and topiramate had a large effect size in decreasing alcohol consumption and superior to naltrexone and acamprosate in treating alcohol use disorder (Blodgett et al., 2014; Palpacuer et al., 2018). The present findings showed that varenicline had a medium effect for reducing alcohol consumption. Taken together, varenicline may have no role in the reduction of heavy drinking. However, it would be an alternative medication for decreasing alcohol consumption.

The present findings support previous clinical trials into participants with alcoholism. Although the mechanism of varenicline on treatment of alcoholism is not yet clear, growing evidence in neurobiology, such as neuroimaging, suggests that varenicline reduces cue-elicited activation of the bilateral anterior cingulate cortex and left nucleus accumbens in heavy-drinking smokers (Ray et al., 2015) and reduces cue-elicited activation of the orbitofrontal cortex, a neural substrate of alcohol cue reactivity (Schacht et al., 2013). Furthermore, another study suggests that varenicline produces a moderate and constant level of dopamine release both in the mesolimbic pathway and in the prefrontal cortex. Thus, this may reduce alcohol craving, seeking, and consumption (Nocente et al., 2013).

There are several limitations to the present analysis. Firstly, some data was presented only in graphs (Plebani et al., 2013). For this kind of data, we attempted to get the data from the original authors but could not receive the figure data. The data of this study therefore could not include in the meta-analysis. Secondly, there were also few studies and a small sample size and several differences in patient populations, which could generate heterogeneity. Thirdly, most studies included in our meta-analysis were carried out for the duration of between 4 and 13 weeks only while longer term studies may give more pertinent findings, particularly as regards relapse behavior. Finally, the sample size of the studies included in the meta-analysis was also small. For the non-significant differences of some outcomes, type II error due to the small sample size could not be excluded.

Since most participants included in the present systematic review had a smoking comorbidity, one should be cautious in generalizing the present findings to patients with alcoholism without smoking. Furthermore, almost all included studies also provided psychosocial interventions, such as motivational interviewing and smoking cessation counseling, so the efficacy of varenicline therapy found in this review reflects the combination of varenicline and a psychosocial treatment model. Not giving an effective psychosocial intervention to those treated with varenicline is, therefore, unjustified because the efficacy of varenicline monotherapy is not yet known. In addition, as reported above, varenicline in most studies was, at best, modestly effective.

Table 1
Characteristics of RCTs comparing varenicline with placebo or other treatment in people with alcoholism.

Study	Methods	Participants	Intervention	N	Age	Outcomes	Timepoint of measure
Studies included in the quantitative analysi							
Fucito et al., 2011	Double-blinded, PBO controlled, 4 weeks of pretreatment phase study + 4 weeks of active treatment in USA	- Heavy-drinking smokers seeking smoking cessation - Exceeding maximum weekly drinking limits every week within the past 4 weeks (i.e., > 7 drinks/week for women, > 14 drinks/week for men) ; maximum daily drinking limits on at least one occasion within the past 4 weeks (i.e., > 3 drinks/day for women, > 4 drinks/day for men) - smoking ≥5 cigarettes/day ≥ 3 days/week, having fewer than 3 months of smoking abstinence within the past year	VAR (2 mg/d) 4 weeks pretreatment + 4 weeks VAR active treatment + SCC 4 weeks of PBO + 4 weeks VAR active treatment + SCC	15 15	Total, mean (SD) = 43.17 (8.12)	**Heavy drinking days** PBO-controlled pretreatment phase (4 weeks) VAR < PBO Active treatment phase (8wk) mean change extended VAR(8wk) > standard VAR (4wk)	Week 4 of pretreatment PBO-controlled
Mitchell et al., 2012	Double-blind, PBO-controlled, 12-wk study in the USA	– Outpatients aged 21-59 years, nontreatment-seeking heavy drinkers who also smoke – Alcohol consumption (≥7 drinks/week for women and ≥14 drinks/week for men). – Cigarette smoking (≥10 cigarettes/week) Non-treatment seeking	VAR (2 mg/d) 12 weeks + GT PBO twice daily, 12 weeks + GT	33 31	VAR, median (range) = 25 (21-59) PBO, median (range) = 29 (21-44)	**Alcohol consumption**: *cumulative drinks* all completers n = 34; VAR < PBO all subjects randomized n = 58; VAR < PBO	Measured at wk 3-11
Meszaros et al., 2013	Double-blind, PBO-controlled, 8-wk study in the USA	- Patients with schizophrenia or schizoaffective disorder and co-occurring nicotine and alcohol dependence using DSM-IV, no age specified - smoked at least 20 cigarettes per day and drank at least 7 standard alcoholic drinks over the 7 days before intake. - patients expressed a desire to quit drinking and smoking	VAR (2 mg/d) 8 weeks + MI PBO twice daily, 8 weeks + MI	5 5	VAR, mean (SD) = 42 (7) PBO, mean (SD) = 44(7)	**Alcohol consumption**: *drinks per week Mean decrease* VAR > PBO	Measured at wk 2-8
Litten et al. 2013	Double-blind, PBO-controlled, 13-wk study in the USA (multicenter study)	- Aged at least 18 years, DSM-IV-TR or MINI were used in diagnosis. - at least 28 standard drinks per week for females or 35 drinks per week for males during the 28-day period prior to consent and the 7-day period prior to randomization - 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 - blood alcohol content (BAC) of 0.000 upon providing study consent - nicotin dependence not excluded	VAR 2 mg/d, 13 weeks + NCBT PBO twice daily, 13 weeks + NCBT	97 101	VAR, mean (SD) = 46.0 (11.0) PBO, mean (SD) = 45.0 (12.3)	**Percent heavy drinking days** VAR LS mean < PBO LS mean LS mean difference = 10.4 **Alcohol consumption**: *Drinks per day* VAR LS mean < PBO LS mean LS mean difference = 0.9	Measured at wk 2-13
de Bejczy et al. 2015	Double-blind, PBO-controlled, 12-wk study in Sweden (multicenter study)	- Age 30 to 70 years, meet the DSM-IV criteria for alcohol dependence meeting ≥3 of 7 criteria for alcohol dependence obtained by DSM-IV-TR - ≥20; heavy drinking days (HDD) during the last 60 days HDD defined as ≥5 drinks of 13 g alcohol per day for men and ≥4 drinks per day for women without any serious physical or mental disorders - nicotin dependence not excluded	VAR 2 mg/d, 12 weeks N random (n PP) no specific PSI PBO twice daily, 12 weeks N random (n PP) no specific PSI	77 (51) 83 (64)	VAR, mean (SE) = 54.6 (1.00) PBO, mean (SE) = 55.6 (0.88)	**Proportion of Heavy drinking day** ITT mean VAR = ITT Mean PBO PP mean VAR = ITT mean PBO **Alcohol consumption:** *drink per drinking day* ITT mean VAR = ITT mean PBO PP mean VAR = PP mean PBO	Measure at wk2-12

(*continued on next page*)

Table 1 (*continued*)

Study	Methods	Participants	Intervention	N	Age	Outcomes	Timepoint of measure
Hurt et al., 2018	Double-blind PBO-controlled, 12-wk study in the USA	- 18 years or older, alcohol-dependent smoker using MINI - smoked 10 or more cigarettes per day for at least 6 months, had current alcohol abuse or dependence, and were interested in quitting smoking.	VAR 2 mg/d, 12 weeks + BBC PBO twice daily, 12 weeks + BBC	16 17	VAR, mean (SD) = 40.2 (11.9) PBO, mean (SD) = 38.8 (10.4)	**Heavy drinking day** 12 wk VAR < PBO 24 wk VAR < PBO Alcohol consumption: *drinks per drinking day* 12 wk VAR < PBO 24 wk VAR < PBO	Measure at wk2-12, Follow-up at wk24
O'Malley et al., 2018	Double-blind, PBO-controlled, 12-wk study in the USA	- Aged 18 to 70 years who met alcohol-dependence criteria, according to the *DSM-IV-TR* and who reported heavy drinking 2 or more times a week for the previous 90 days and 7 or fewer consecutive days of abstinence prior to intake - 5 or more cigarettes, carbon monoxide level of 6 ppm or greater, or plasma cotinine level of 40 ng/ml or greater to nondaily smoking	VAR 2 mg/d, 16 weeks + MM PBO twice daily, 16 weeks + MM	64 67	Total, mean (SD) = 42.7 (11.7)	**Percentage of heavy drinking day** VAR LS mean = PBO LS mean	Measure at wk1-16
Studies included in the qualitative analysis							
Plebani et al., 2013	Double-blind, PBO-controlled, 12-wk study in the USA	- Patients diagnosed alcohol dependence by using DSM-IV-TR criteria for and reported drinking on at least 12 of the past 30 days, no age specified	VAR (2 mg/d) 12 weeks + MM PBO twice daily, 12 weeks + MM	19 21	VAR, mean (SD) = 44.8(12.3) PBO, mean (SD) = 48.1(10.5)	**Heavy drinking days per week** VAR numbers of heavy drinking days < PBO; PBO group having an average of 1.95 times more heavy drinking days per week.	Measured at wk 2-12
Schacht, 2014	Double-blind, PBO-controlled, 13-wk study in the USA	- Aged 21 to 60, to report consuming at least 20 drinks per week - meet *DSM-IV* Alcohol dependence, not currently be seeking treatment for their drinking. - nicotin dependence not excluded	VAR 2 mg/d, 2 weeks -PSI not mentioned PBO twice daily, 2 weeks -PSI not mentioned	18 17	VAR, mean (SD) = 26.8 (4.3) PBO, mean (SD) = 33.7 (12.0)	**Percent Heavy drinking day** VAR = PBO **Alcohol consumption:** *drink per drinking day* VAR = PBO	Measured at wk 1-2

VAR Varenicline **PBO** Placebo **ITT** intention-to-treat **PP** per protocols **LS mean** least square mean **wk** week/weeks **USA** United States of America **SCC** smoking cessation counseling **GT** group therapy **MI** motivational interview **MM** medical management **NCBT** novel computerized bibliotherapy **PSI** psychosocial intervention **BBC** brief behavioral counseling **MINI** Mini-International Neuropsychiatric Interview **DSM** Diagnostic and Statistical Manual of Mental Disorders.

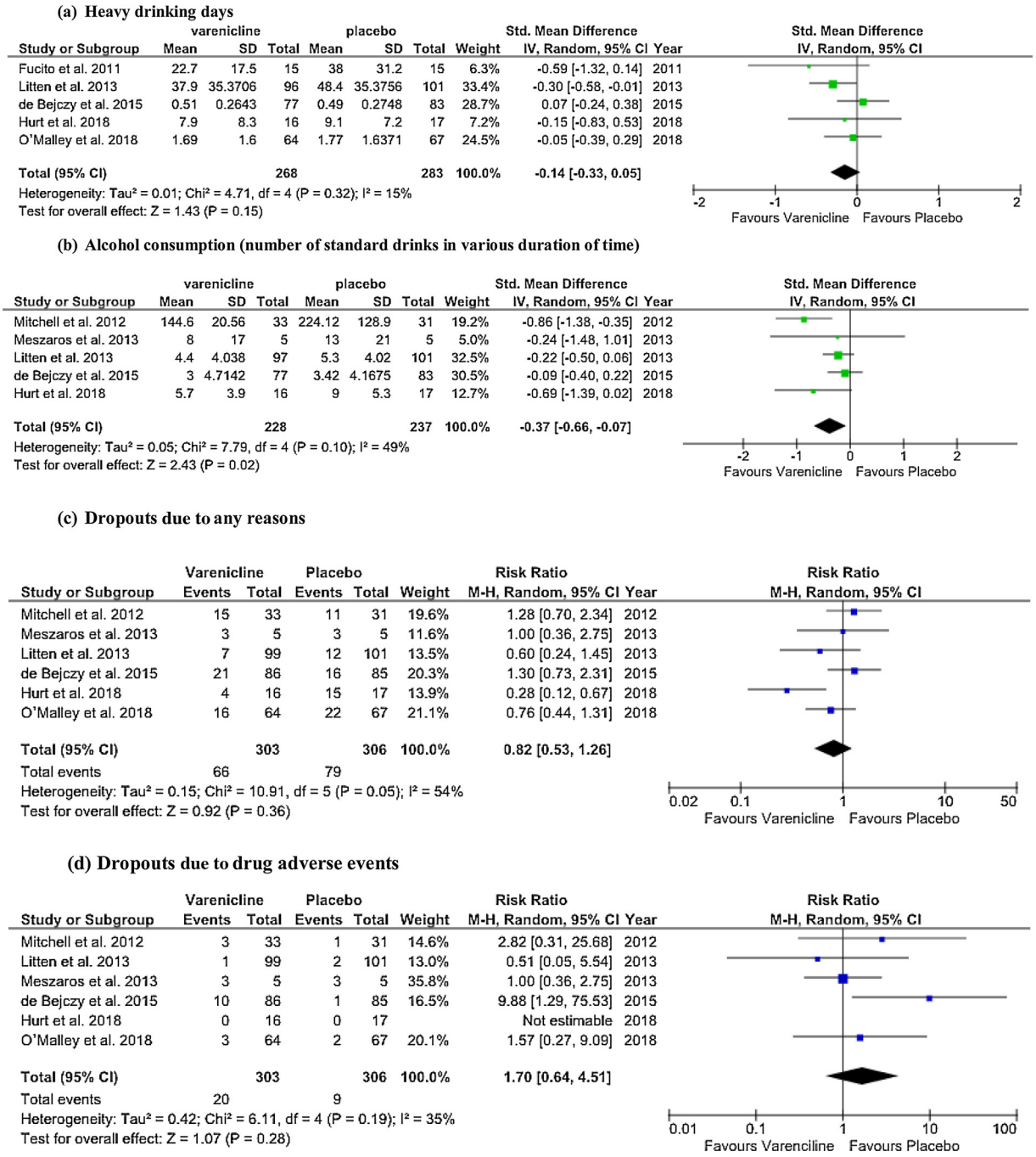

Fig. 3. Short-term comparisons between varenicline and placebo in respect of subjects with endpoint heavy drinking days and alcohol consumption.

Future studies should be carried out for a longer duration (> 13 weeks) and with a larger sample size. Despite the chronic course of alcoholism, only one study with a small number of participants reported the longer-term efficacy at 24 weeks. In terms of acceptability, although partial agonism of α4β2 nAChR by varenicline is expected to increase the incidence of psychiatric adverse events via dopaminergic pathways (Crunelle et al., 2010), varenicline therapy is unlikely to result in high dropout rates. However, more details of the physical and psychiatric adverse events should be further investigated in order to clarify the acceptability of the prescription of varenicline in this population. The drinking outcomes of this study are subjective (heavy drinking day, alcohol consumption from timeline followback method assessment), future studies should include some biomarkers of alcohol abuse such as gamma-glutamyl transferase (GGT), aspartate amino-transferase (AST) or alanine amino-transferase (ALT) (Jastrzębska et al., 2016).

5. Conclusion

This systematic review and meta-analysis provide evidence that varenicline may be beneficial in decreasing alcohol consumption over a period of time. More studies may be needed to determine its efficacy in decreasing heavy drinking days. As a medication with high acceptability and tolerability, varenicline may be an option for patients with alcoholism who want to decrease alcohol consumption or those who cannot tolerate other medications for alcoholism. Further studies are warranted.

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Contributors

AO and MS conceived the idea of this work, searched and extracted the data, analyzed and interpreted the data, and drafted the article. SL conceived the idea of this work, analyzed and interpreted the data, and drafted the article. All authors have read and approved the final manuscript.

Declaration of Competing Interest

Srisurapanont M has received grants and honorarium Lundbeck and Sumitomo Dainippon Pharma. Awirut Oon-aroma and Surinporn Likhitsathaina have had no conflict of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugalcdep.2019.107631.

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