Varenicline for the Treatment of Alcohol Use Disorder: A Systematic Review and Meta Analysis

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Abstract

Objective: To assess the overall effectiveness of varenicline for the treatment of alcohol use disorder in adults according to three dependent variables: percent heavy drinking days, alcohol craving, and adverse events compared to a controlled study group.

Design: A systematic review of found literature and meta-analyses of the data reported.

Data Sources: ClinicalTrials.gov, PsycINFO, Sociological Abstracts, the Agricultural & Environmental Science Database, and the Biological Science Database.

Extraction: Percent heavy drinking days, alcohol craving scores, and the number of adverse events reported.

Conclusions: The evidence implies the effectiveness of varenicline for reducing the percent heavy drinking days and significantly reducing alcohol cravings in patients with alcohol use disorders. Adverse events likely to occur include abnormal dreams and nausea, different from the ones presented by Chantix. However, due to the small number of studies, more meta-analysis is needed.

Introduction

In the United States, $249 million are lost to alcohol "misuse" and over 88,000 people die due to alcohol related causes, annually (National Institute on Alcohol Abuse and Alcoholism, 2017). Globally, 3.3 million people die each year due to alcohol consumption alone (National Institute on Alcohol Abuse and Alcoholism, 2017). In 2015, the National Survey on Drug Use and Health revealed that 15.1 million adults above the age of 18 had an alcohol use disorder (AUD) or were unable to control or stop drinking alcohol despite social, financial, and health related consequences (National Institute on Alcohol Abuse and Alcoholism, 2017). While the population of adults with AUD (alcohol abuse or dependence) is larger than the three largest U.S. cities combined (United States Census, 2017), there are very few medications approved by the FDA (Food and Drug Administration) for the treatment of these disorders: disulfiram, naltrexone, and acamprosate (Katzung et al., 2012, p.396).

The three medications FDA approved to treat AUD each work in different ways and are known to have very unpleasant side-effects. Naltrexone acts as an opioid antagonist, that can help to reduce the "self administration" (Katzung et al., 2012, p.396-397) of alcohol, but still puts patients at an increased risk for liver damage, and cannot be used by those taking opioids. Acamprosate acts as "a weak NMDA-receptor antagonist and a $GABA_A$-receptor activator" (Katzung et al., 2012, p.397). Major side-effects include nausea, vomiting, diarrhea, and rash. Disulfiram causes an adverse reaction in patients when they consume alcohol by inhibiting aldehyde dehydrogenase. This allows for acetaldehyde to build up and cause "flushing, throbbing headache, nausea, vomiting, sweating, hypotension, and confusion" (Katzung et al., 2012, p.397) for up to 30 minutes after consuming alcohol. Alongside all of these side effects, compliance with the drugs are low, and participants are known to have many setbacks in regards to quitting drinking (Bouza et al., 2004; Whitworth et al., 1996; Wright and Moore, 1990).

Thus, there is a financial and social need for more safe and effective medication for the treatment of alcohol use disorder (National Institute of Health, 2017). One promising medication is varenicline. In 2006, varenicline was approved by the FDA as a smoking cessation aid (Katzung et al., 2012, p.110). Varenicline is a partial antagonist of α4β2 nAChRs (nicotinic receptors), it also has longer half-life than other medications. This, in-turn, prevents the dopamine response when nicotine is absorbed into the bloodstream (Katzung et al., 2012, p.110). Varenicline has also been used as a treatment for alcohol use disorders in many clinical trials (Plebani et al., 2013; Fucito et al., 2011; Litten et al., 2013; Hurt et al., 2018; O'Malley et al., 2018; Bejczy et al., 2015; Schacht et al., 2014; Roberts et al., 2017; Verplaetse et al., 2016; Vatsalya et al., 2015; Mitchell et al., 2012; Ray et al., 2014; McKee et al., 2009; Roberts & Mckee, 2018). This large number of studies of the effect of varenicline on adults with AUD presents the opportunity for a systematic review and meta analysis. In 2014, a systematic review of varenicline clinical trials for the treatment of AUD was conducted, but the studies were all too preliminary in their research and too few in number to conduct a meta analysis (Erwin & Slaton,

2014). Today, there are many more studies that have tested the combination of varenicline and alcohol use disorder, and many more so that have similar treatments, participants, and conditions in general. While a systematic review of varenicline clinical trials for the treatment of AUD is effective in understanding all of the literature available, it does not provide an empirical estimate of effect varenicline has in comparison to a controlled study arm.

Our objectives in this study was to perform a systematic review and statistical analysis of varenicline clinical trials for the treatment of alcohol use disorder, and to see if varenicline was and is effective in the treatment of AUD. With multiple studies producing different outcomes with different measures, a traditional narrative literature review may not be able to produce the best and most comprehensive conclusions. However, using a quantitative approach to explore the literature and conducting a statistical meta analysis of multiple clinical trials looking into the effect of varenicline on AUD, we are able to produce a better understanding of the overall estimated and true effect.

Our focus was on heavy drinking days, alcohol cravings, and the type and number of adverse events that occurred. Using heavy drinking days and alcohol cravings as outcome measures we are able to use characteristics of those with AUD, and judge the impact that varenicline has. In our final outcome measure we use adverse event data to understand if the benefits outweigh the risks and place our understanding of the effectiveness of varenicline within the context of the three FDA approved AUD medications.

Method

Literature search

The primary questions for our research were “Does varenicline help to reduce drinking and alcohol cravings in adults with alcohol use disorder?” and “What are the adverse effects of this medication when treating alcohol use disorder?” In-order to address these questions, we had to identify clinical trials using varenicline as a treatment for AUD and their subsequent study reports. The outcomes of the studies that we focused on were: percent heavy drinking days, alcohol cravings, and the number of adverse events. Percent heavy drinking days and alcohol cravings were chosen as outcomes in order to reflect the current requirements for diagnosis of alcohol use disorder according the DSM-V. (American Psychiatric Association, 2013).The DSM-V outlines AUD as problem drinking that results in compulsive drinking, inability to stop drinking, and a negative emotional response when not drinking (National Institute on Alcohol Abuse and Alcoholism, 2017; American Psychiatric Association, 2013). The DSM-V presents several questions to test if a subject has alcohol use disorder. Some of these questions ask subject if they have, “Had times when you ended up drinking more or longer, than you intended?...Wanted to drink so badly you could not think of anything else?” (American Psychiatric Association, 2013, p). Unlike the DSM-IV, the DSM-V combines both alcohol abuse and alcohol dependence into one disorder, alcohol use disorder, and includes alcohol craving as a

requirement for diagnosis. Thus, percent heavy drinking days and alcohol craving were useful and relevant outcome measures (National Institute on Alcohol Abuse and Alcoholism, 2016). Having met at least two of the requirements, this becomes an excellent measure for measuring the impact of AUD and the change caused by varenicline.

Information and data sources

Identifying studies started by using "ClinicalTrials.gov." In the website's search engine, we included the term "alcohol" in the "Condition or disease" field and "varenicline" in the "Other terms" field. This produced a list of 27 studies. From there, we selected only studies with results, producing a list of 13 clinical trials. Each of these clinical trials were examined for related published studies, whether or not they were using varenicline as a treatment for AUD, then the NCT clinical trial numbers were collected. Of the 13 trials identified, only 7 were included in further analysis (Ramchandani, 2016; Yale University, 2018; National Institute on Alcohol Abuse and Alcoholism, 2014; University of Pennsylvania, 2015; National Institute on Alcohol Abuse and Alcoholism, 2013; Mayo Clinic, 2018; National Institute on Alcohol Abuse and Alcoholism, 2013). The other trials were excluded for a number of reasons: one trial was excluded because it was not a placebo-controlled randomized trial (Mayo Clinic, 2011), another trial was excluded because varenicline was not used as a treatment (University of Iowa, 2017), two more studies were excluded because their outcomes were not one of the three previously mentioned (Yale University, 2018; Yale University 2018), one was excluded because it was a case study (Mayo Clinic, 2013), and the last study was excluded because its methods involved an ad libitum drinking period (National Institute on Alcohol Abuse and Alcoholism, 2018).

After conducting this preliminary search on ClinicalTrials.gov, a deeper search was done using ProQuest to explore the databases: PsycINFO, Sociological Abstracts, the Agricultural & Environmental Science Database, and the Biological Science Database. "Varenicline," "clinical trial*," and "alcohol*" were searched for in subject resulting in 44 results. These terms were included as we thought they would best describe our desired search results.

Another search was done using ProQuest to find studies in the databases: the Agricultural & Environment Science Database, the Biological Science Database, and MEDLINE. "Varenicline" (truncated with "*") and "alcoholism" (truncated with "*") were searched for in "All subjects & indexing." "cues OR 'cue reativ*' OR craving* or efficac* 'nicotinic acetylcholin*' OR 'nucleus accumbens'" was searched for in "Anywhere except full text" (* was used to truncate). Search terms were truncated in order to account for potential misspellings and very similar words with different endings that could still prove useful in answering our research question. This particular search produced 53 studies. When removing the search term "efficac*", 42 studies resulted.

After conducting the searches on the aforementioned databases, we sorted the studies based on our inclusion and exclusion criterias and the type of study. From an initial search, we

found 41 studies. 15 out of these studies were not clinical trials and were used for background information and included case studies, summaries and information about varenicline. Table 1 consists of the studies used in the background information.

Table 1: Studies used for Background information:

Study	**About**
Drobes & Thomas 1999	Alcohol Craving
Flannery et al. 1999	PACS
Mihalak et al. 2006	Mechanism of Varenicline
Erwin & Slaton 2014	Summary of Clinical Trials
Falk et al. 2008	Co-occurrence of alcohol and drug use
Falk et al. 2015	Analysis of Litten et al. 2013
Franck et al. 2009	Injury in patient with Underlying Liver disease
Hendrickson et al. 2010	Mechanism of Varenicline
Leeman et al. 2007	Review of Varenicline Trials
Nocente et al. 2013	Summary
Roche et al. 2016	Mechanisms of Treatment for Heavy drinking smokers
Rollema et al. 2007	Mechanism of Varenicline
Sprague et al. 2012	Case report about Drug-induced Liver injury
Staios et al. 2010	Summary
Ruth et al. 2014	Varenicline and Abnormal Sleep Related Events

Of the remaining studies, all were scientific experiments. Seven experiments were rejected because they were performed on animals including rats (Randall et al., 2015; Wouda et al., 2011; Steensland et al., 2007; Ericson et al., 2009; Bito-Onen et al., 2011), baboons (Kaminiski & Weerts, 2014) and larval zebrafish (Cousin et al., 2014). There were two studies where the clinical trial was performed on patients with depressive symptoms (Roberts et al., 2017) and schizophrenia (Meszaros et al., 2013): both were rejected because this did not match our exclusion criteria of not having patients with any psychological disorders since it is not representative of the general population. Another clinical trial was rejected because it tested the effect of varenicline with low dose naltrexone, which failed to answer our primary objective of testing the drug, Varenicline (Roberts et al., 2018). Two more clinical trials examined Varenicline as a treatment for tobacco dependence (Hays et al., 2010) and cocaine dependence (Plebani et al. 2012): these too were rejected since it did not fulfill our objective of testing Varenicline as a treatment for alcohol dependence. Another two clinical trials were rejected since they did not report any of the desired outcomes (Gowin et al., 2016; Childs et al., 2012). Table 2 lists the clinical trials that were rejected. Finally, we were left with 12 clinical trials which we

decided to use in our meta-analysis. Table 3 identifies the studies and the outcome measures that these studies were used for.

Table 2: Studies and Clinical Trials not used in Analysis:

Study	**About**
Bito-Onon et al. 2011	Study on Rats
Cousin et al. 2014	Study on Larval Zebrafish
Ericson et al. 2009	Study on Rats
Kaminski & Weerts 2014	Study on Baboons
Steensland et al. 2007	Study on Rats
Wouda et al. 2011	Study on Rats
Randall et al. 2015	Study on Rats
Hays et al. 2010	Clinical trial of Varenicline for Tobacco-dependence
Meszaros et al. 2013	Clinical trial on patients with Schizophrenia
Plebani et al. 2012	Clinical trial of Varenicline for Cocaine dependence
Roberts et al. 2018	Clinical trial of Varenicline with Naltrexone
Gowin et al. 2016	Clinical trial
Childs et al. 2012	Clinical trial
Roberts et al. 2017	Clinical trial on patients with Depressive Symptoms

Table 3: Studies and Clinical Trials Included in Analysis with Outcome:

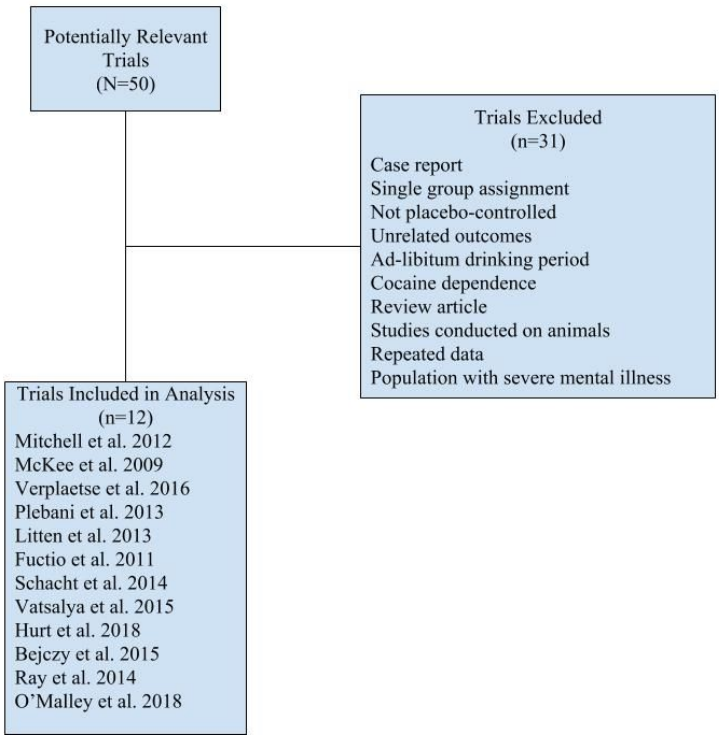
Study	**Outcome(s)**
Fucito et al. 2011	Percent Heavy Drinking Days, Adverse Events
Litten et al. 2013	Percent Heavy Drinking Days, Alcohol Craving, Adverse Events
Hurt et al. 2018	Percent Heavy Drinking Days, Adverse Events
O'Malley et al. 2018	Percent Heavy Drinking Days, Adverse Events
Bejczy et al. 2015	Percent Heavy Drinking Days, Alcohol Craving, Adverse Events
Schacht et al. 2014	Percent Heavy Drinking Days, Alcohol Craving
Vatsalya et al. 2015	Alcohol Craving, Adverse Events
Ray et al. 2014	Alcohol Craving
Plebani et al. 2013	Percent Heavy Drinking Days, Adverse Events
McKee et al. 2009	Alcohol Craving, Adverse Events
Mitchell et al. 2012	Adverse Events

Verplaetse et al. 2016	Adverse Events

Study selection

We chose the studies based on the following inclusion criteria: the studies must be written in English; all clinical trials are randomized, placebo-controlled, double-blind; all the subjects in the studies must be human and at least 18 years old; all studies must have subjects with alcohol use disorder; all studies must titrate varenicline to 2mg/day; the duration must be longer than a week; the sample size in each study must be larger than 20. Studies were excluded if they were case reports, a single group assignment, not placebo-controlled, unrelated outcomes, ad-libitum drinking periods, included participants with cocaine dependence, review articles, studies conducted on animals, using repeated data, or included participants with severe mental illness.

Figure 1: Selection Process: Inclusion and Exclusion



In addition to these, for the analysis of percent heavy drinking days, the studies must have reported either percent heavy drinking days or the number of heavy drinking days. For alcohol craving, the studies must have reported the measurement on an alcohol craving scale. For adverse events, we looked through all the studies that report any kinds of adverse events. We also looked at data which indicated the total number of non-serious and the total number of serious adverse events in the selected studies. We paid special attention to nausea, sleep

problems (vivid or abnormal dream), constipation, vomiting, which are the most common side effects suggested by Chantix™ (Pfizer, 2018), as well as the adverse events that are reported by most trials, such as headache, and flatulence.

Organization of studies and data extraction

All studies were organized according to the outcomes that were desired: percent heavy drinking days, alcohol craving, and/or adverse events. Data were then split into each of these outcomes according to two treatments: varenicline and placebo. For the varenicline group, participants were titrated to 2mg of varenicline. For the placebo group, participants were given identical looking pills to the varenicline group, but were in-fact sugar pills. If studies with the outcomes previously mentioned had other treatments, they were excluded in pooling of our data.

Once the studies had been organized, data was abstracted by three researchers. Differences in the data pulled were resolved between the three researchers. The variables collected from the studies reporting heavy drinking days or the percentage of heavy drinking days were: sample size, duration in weeks, the mean of the age, percentage male, whether the study was funded by pfizer, the percentage of participants seeking alcohol treatment or smoking treatment, and the mean number or percentage of heavy drinking days per week for each treatment group used in their analysis. The same was data was recorded for all of the other studies, except for percent heavy drinking days. Studies reporting alcohol craving had the mean alcohol craving recorded for each of the study arms used in analysis. Finally, studies that reported adverse events had the count of adverse events (total non-serious, total serious, nausea, sleep problems (vivid or abnormal dreams), headache, and flatulence) recorded. Additionally, the corresponding standard deviation for the outcome data was obtained. If only the standard error was available, it was transformed into a standard deviation using the sample size. For some studies the standard deviation was recorded for both genders, in this instance the standard deviations were combined.

When collecting whether or not a study was funded by Pfizer we first checked each of the articles to see if they had reported sponsorship by Pfizer. If they did, that data was recorded as a "Yes" for Pfizer funding. If studies reported that varenicline and the matching placebo pills were provided by Pfizer this was also considered a "Yes." Our justification for this inclusion was the cost of the medication and the size of the studies. It would cost roughly $4,000 to pay for 15 varenicline treatment group subjects in a 3 week study (Drugs.com).

Finally, when the data needed was not available from the reports found or ClinicalTrials.gov, software was used to extract data from the plots and graphs reported. This allowed us to get the best estimate possible for the effect and standard deviations (Olsen, Plot grab).

Study characteristics

Tables 5-7 presents study characteristics, including outcome data and demographic information about the studies used in the three outcomes measured.

Table 5: Percent Heavy Drinking Days Study Demographics and Outcomes

Study	Drug	Sample Size	Duration (weeks)	Age (mean)	Gender (% male)	Pfizer Funding	Alcohol Treatment Seeking (%)	Smoking Treatment Seeking (%)	PHDD[a] (%)	SD[b]
Bejczy et al. 2015	Placebo	83	12	55.6	59	Yes	NA[c]	NA[c]	49	20.42
Bejczy et al. 2015	Varenicline	77	12	54.6	65	Yes	NA[c]	NA[c]	51	18.12
Fucito et al. 2011	Placebo	15	3	43.47	53	No	0	100	38	31.99
Fucito et al. 2011	Varenicline	15	3	42.87	53	No	0	100	22.7	26.68
Hurt et al. 2018	Placebo	17	12	38.8	65	Yes	NA[c]	100	32.5	25
Hurt et al. 2018	Varenicline	16	12	40.2	63	Yes	NA[c]	100	28.21	31.07
Litten et al. 2013	Placebo	101	13	46	73.2	No	84	0	48.4	15.8
Litten et al. 2013	Varenicline	97	13	45	68.3	No	84	0	37.9	16.4
O'Malley et al. 2018	Placebo	67	16	42.1	70.14	Yes	100	0	9.78	25
O'Malley et al. 2018	Varenicline	64	16	43.59	70.3	Yes	100	0	11.02	25.15
Plebani et al. 2013	Placebo	21	13	48.1	90.5	Yes	100	NA[c]	17.29	4.43
Plebani et al. 2013	Varenicline	19	13	44.8	78.9	Yes	100	NA[c]	12.71	2.57
Schacht et al. 2014	Placebo	17	2	33.7	52.94	No	0	0	56.4	18.5
Schacht et al. 2014	Varenicline	18	2	26.8	61.11	No	0	0	59.2	23.2

a=Percent Heavy Drinking Days
b=Standard Deviation
c=Not Available

Table 6: Alcohol Craving Study Demographics and Outcomes

Study	Drug	Sample Size	Duration (weeks)	Age (mean)	Gender (% male)	Pfizer Funding	Alcohol Treatment Seeking (%)	Smoking Treatment Seeking (%)	Alcohol Craving Score	SD[a]	Scale
Bejczy et al. 2015	Placebo	83	12	55.6	59	Yes	NA[e]	NA[e]	6.18	1.57	OCDS[b]
Bejczy et al. 2015	Varenicline	77	12	54.6	65	Yes	NA[e]	NA[e]	4.54	1.69	OCDS[b]
Litten et al. 2013	Placebo	101	13	46	73.2	No	84	0	11.6	4.92	PACS[c]
Litten et al. 2013	Varenicline	97	13	45	68.3	No	84	0	9.9	4.92	PACS[c]
Mitchell et al. 2012	Placebo	33	12	25*	55	Yes	0	100	8.93	0.205	OCDS[b]
Mitchell et al. 2012	Varenicline	31	12	29*	65	Yes	0	100	6.64	0.389	OCDS[b]
Ray et al. 2014	Placebo	30	1	38.1	70	No	0	0	16.34	1.23	NA[e]
Ray et al. 2014	Varenicline	30	1	34.6	66.67	No	0	0	14.68	1.21	NA[e]
Schacht et al. 2014	Placebo	17	2	33.7	52.94	No	0	0	7.3	0.8	OCDS[b]
Schacht et al. 2014	Varenicline	18	2	26.8	61.11	No	0	0	4.9	0.7	OCDS[b]
Vatsalya et al. 2016	Placebo	22	3	37.9	92	Yes	0	NA[e]	26.82	17.35	AUQ[d]
Vatsalya et al. 2016	Varenicline	24	3	29.8	82	Yes	0	NA[e]	23.65	13.42	AUQ[d]

*=Median
a=Standard Deviation
b=Obsessive Complusive Drinking Scale
c=Penn Alcohol Craving Scale
d=Alcohol Urge Questionnaire
e=Not Available

Table 7: Adverse Events Study Demographics and Outcomes

Study	Drug	Sample Size	Duration (week)	Age (mean)	Gender (% Male)	Pfizer Funding	Alcohol Treatment Seeking (%)	Smoking Treatment Seeking (%)	Non-Serious Adverse Events (counts)	Serious Adverse Events (counts)
Bejczy et al. 2015	Placebo	83	12	55.6	59	Yes	NA*	NA*	NA*	NA*
Bejczy et al. 2015	Varenicline	77	12	54.6	65	Yes	NA*	NA*	NA*	NA*
Fucito et al. 2011	Placebo	15	3	43.47	53	No	0	100	14	0
Fucito et al. 2011	Varenicline	15	3	42.87	53	No	0	100	15	0
Hurt et al. 2018	Placebo	17	12	38.8	65	Yes	NA*	100	2	0
Hurt et al. 2018	Varenicline	16	12	40.2	63	Yes	NA*	100	5	0
Litten et al. 2013	Placebo	101	13	46	73.2	No	84	0	90	2
Litten et al. 2013	Varenicline	97	13	45	68.3	No	84	0	88	2
McKee et al. 2009	Placebo	10	1	35.3	80	Yes	0	0	4	NA*
McKee et al. 2009	Varenicline	10	1	34.2	80	Yes	0	0	3	NA*
Mitchell et al. 2012	Placebo	33	12	25	55	Yes	0	100	0	1
Mitchell et al. 2012	Varenicline	31	12	29	65	Yes	0	100	0	0
O'Malley et al. 2018	Placebo	67	16	42.1	70.14	Yes	100	0	46	0
O'Malley et al. 2018	Varenicline	64	16	43.59	70.3	Yes	100	0	47	2
Plebani et al. 2013	Placebo	21	12	48.1	90.5	Yes	100	0	19	0
Plebani et al. 2013	Varenicline	19	12	44.8	78.9	Yes	100	0	17	0
Vatsalya et al. 2015	Placebo	22	3	37.9	92	Yes	0	NA*	18	0
Vatsalya et al. 2015	Varenicline	24	3	29.8	82	Yes	0	NA*	21	0
Verplaetse et al. 2016	Placebo	20	1	34.2	75	Yes	0	0	NA*	NA*
Verplaetse et al. 2016	Varenicline	20	1	34.15	70	Yes	0	0	NA*	NA*

*=Not Available

Data analysis

Our data was synthesized using R software (version 1.1.419, 2017, RStudio, Inc., Vienna, Austria). In order to fully understand the impact that varenicline has on individuals with AUD, a meta analysis was conducted to produce a more well-rounded empirical measure of the effect of varenicline on the mean percent heavy drinking days, standardized mean alcohol craving scores, and the increase in odds of adverse events compared to placebo groups.

Random effects models were used for quantitative outcomes (i.e. percent heavy drinking days and alcohol cravings). The random effects model was chosen because our studies were not completely identical in methods and sample characteristics; this can produce unwanted variability (heterogeneity). The random effects model can help to account for the variability between and within studies and estimate that variability and give a better estimate of the overall effect of the studies (Viechtbauer, 2010, p.3). Heterogeneity and therefore the mean difference between the percent heavy drinking days in the varenicline treatment group and the control study group was estimated using an empirical Bayes method. The empirical bayes method was also used to estimate heterogeneity and standardized mean difference between alcohol craving scores in the varenicline treatment group and the control. A standardized mean difference was used instead of a raw mean difference, such as the one use for the outcome variable of percent heavy drinking days, because studies used different scales to measure alcohol cravings. This can be seen in Table 6. All of the scales used, the Penn Alcohol Craving Scales, the Obsessive Compulsive Drinking Scale, and the Alcohol Urge Questionnaire have high internal consistencies, and major the same outcome, and many other similarities (Flannery et al., 1999; Drobes & Thomas, 1999). So, the standardized mean difference becomes an effective meta analytic tool. The maximum likelihood method was used to estimate heterogeneity and to estimate the increase/decrease in the odds of adverse events between both treatment groups previously mentioned. For studies that had zero incidence, a standard half-integer transformation was applied.

Mixed effect models were also used to introduce covariates of interest. These covariates included duration in weeks, mean age, percent male, whether or not a study was funded by Pfizer, and the percentage of participants who were alcohol or smoking treatment seeking.

This was done using the “rma” and “rma.uni” programs within the “metafor” package. The output gave an estimate of the effect (mean difference, standard mean difference, and the log odds ratio), a 95% confidence interval, t-value with a corresponding p-value, and a statistical test for heterogeneity producing an I^2 value. The I^2 value can help us to determine the amount of heterogeneity or how much the results of each study varied. A t-test was chosen due to the smaller number of studies that did not quite match a normal distribution. A t-test does not require a large sample or a normal distribution. As well as the output from the “rma” and “rma.uni” programs, the “funnel.rma” and “forest.rma” programs were used to produce funnel and forest

plots to help with interpretation of heterogeneity, and to see the effect and effect size of each study and overall.

Results

Systematic Review

Percent heavy drinking days was an outcome in six studies. Heavy drinking day was defined as 4+ standard drinks per day for women and 5+ standard drinks per day for men. All studies reported percent heavy drinking days except one (Hurt et al. 2018), which reported heavy drinking days. Thus, to convert that to percent heavy drinking days, number of heavy drinking days was divided by 28 days (the time period). All the studies that were selected for the percent heavy drinking days outcome, regardless of drug being placebo or varenicline, showed a decrease in the percentage of heavy drinking days before and after the treatment. The average percent heavy drinking days before treatment was 65.58% in the varenicline group and 58.43% in the placebo group. After the treatment, the mean percent heavy drinking days in the varenicline group was 35.01% and 38.95% in the placebo group. There was an average decrease of 30.57% of heavy drinking days in the varenicline group and 19.48% in the placebo group after administration. Further, there was a difference in the amount of change in percentage heavy drinking days between studies depending on the study duration. Studies with duration of weeks 2 and 3 had an average decrease of 19.94% heavy drinking days in the varenicline group and 13.37% in the placebo group. While studies with a duration of more than 3 weeks had a decrease of 37.87% heavy drinking days in the varenicline group and 32.6% in the placebo group. Although the differences in the numbers are big, in order to identify any significant difference in studies based on duration, and other factors, conducting a meta-analysis was essential.

Alcohol craving was measured by five studies on different cravings scales. Two studies measured alcohol cravings using Obsessive Compulsive Drinking Scale (OCDS) (Schacht et al. 2014; Bejczy et al. 2015), one study used Penn Alcohol Craving Scale (PACS) (Litten et al. 2013), one study used Alcohol Urge Questionnaire (AUQ) (Vatsalya et al. 2015) and one was a general craving scale (Ray et al. 2014). In all studies in both the placebo and 2 mg varenicline group, the craving reduced after the treatment, except in the placebo group in Ray et al. 2014, the cravings increased. The baseline statistics for Vatsalya et al. 2015 were not available. However, excluding that, the mean decrease in alcohol craving was 7.74 in the varenicline group and 5.56 in the placebo group. To see if this difference across the treatment groups was in fact significant, a meta-analysis was necessary.

The adverse events that were studied were fatigue, nausea, flatulence, constipation, headache and abnormal/ vivid dreams, vomiting, and total number of serious and non-serious adverse events in all of these studies. Ten studies measured at least one of the adverse events. Table 4 shows the studies along with the type of adverse event it measured. Average percent of participants with total non-serious adverse events in the varenicline group is 62.8% while in the

placebo group is 59.4%. In terms of just the numbers this difference seems small and not significant, however in order to see if this difference was significant, a meta-analysis was conducted based on the count data.

Table 4: Studies in Adverse Events Analysis and type of Adverse Event:

Study	**Outcome(s)**
Fucito et al. 2011	Nausea, Fatigue, Headache, Abnormal Dreams, Constipation, Flatulence, Vomiting, Total Non-Serious Adverse Events, Total Serious Adverse Events
Litten et al. 2013	Nausea, Fatigue, Headache, Nasopharyngitis, Abnormal Dreams, Constipation, Vomiting, Total Non-Serious Adverse Events, Total Serious Adverse Events
Hurt et al. 2018	Nausea, Abnormal Dreams, Total Non-Serious Adverse Events, Total Serious Adverse Events
O'Malley et al. 2018	Nausea, Fatigue, Headache, Abnormal Dreams, Constipation, Flatulence, Vomiting, Total Non-Serious Adverse Events, Total Serious Adverse Events
Bejczy et al. 2015	Nausea, Fatigue, Headache, Nasopharyngitis, Abnormal Dreams
Vatsalya et al. 2015	Nausea, Headache, Constipation, Flatulence, Total Non-Serious Adverse Events, Total Serious Adverse Events
Plebani et al. 2013	Nausea, Headache, Abnormal Dreams, Total Non-Serious Adverse Events, Total Serious Adverse Events
McKee et al. 2009	Nausea, Abnormal Dreams, Constipation, Flatulence, Vomiting, Total Non-Serious Adverse Events
Mitchell et al. 2012	Nausea, Headache, Abnormal Dreams, Vomiting, Total Non-Serious Adverse Events, Total Serious Adverse Events
Verplaetse et al. 2016	Abnormal Dreams, Constipation, Flatulence

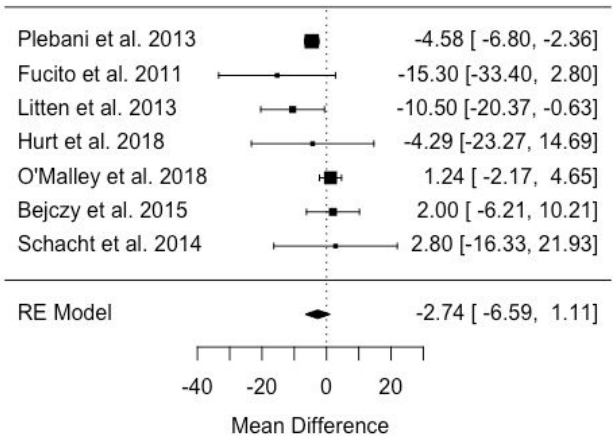
Meta-Analysis

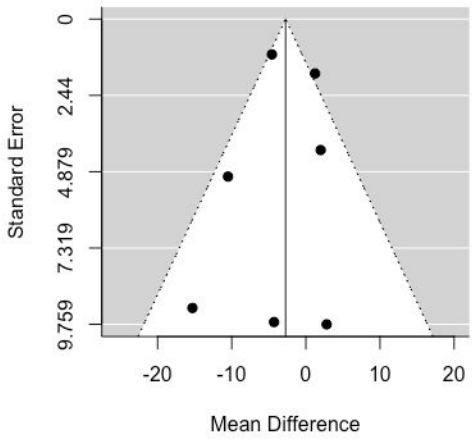
The three main dependent variables of interests in this analysis were the mean difference in percent heavy drinking days, standardized mean difference in alcohol cravings, and the difference in the number of counts for adverse events between varenicline treatment and control study arm. These variables were all treated as normally distributed. Seven studies (Bejczy et al.,

2015; Fucito et al., 2011; Hurt et al., 2018; Litten et al., 2013; O'Malley et al., 2018; Plebani et al., 2013; Schacht et al., 2014) were used for estimating the mean difference in percent heavy drinking days per week. Six studies (Bejczy et al., 2015; Litten et al., 2013; Mitchell et al., 2012; Ray et al., 2014; Schacht et al. 2014; Vatsalya et al. 2016) were included in our analysis and estimation of the standardized mean difference in alcohol craving scores between varenicline and control study groups. Finally, 10 studies (Bejczy et al., 2015; Fucito et al., 2011; Hurt et al., 2018; Litten et al., 2013; McKee et al., 2009; Mitchell et al., 2012; O'Malley et al. 2018; Plebani et al., 2013; Vatsalya et al., 2015; Verplaetse et al., 2016) were used to estimate the log odds ratio of adverse events between the varenicline and control study groups.

Percent Heavy Drinking Days

Our random effects model for percent heavy drinking days gave an estimate of -2.74 mean percent difference with a standard error of 1.964 in percent heavy drinking days between the varenicline and control study arms. The 95% confidence interval produced was between -7.54 and 2.07 mean percent difference. As stated early a t-test was used to understand if our mean difference estimate was in-fact a statistically significant. In this model, a t-value of -1.93 was found with a corresponding p-value of 0.2129. Thus, the mean difference between percent heavy drinking days for the treatment group of varenicline and the control group was not

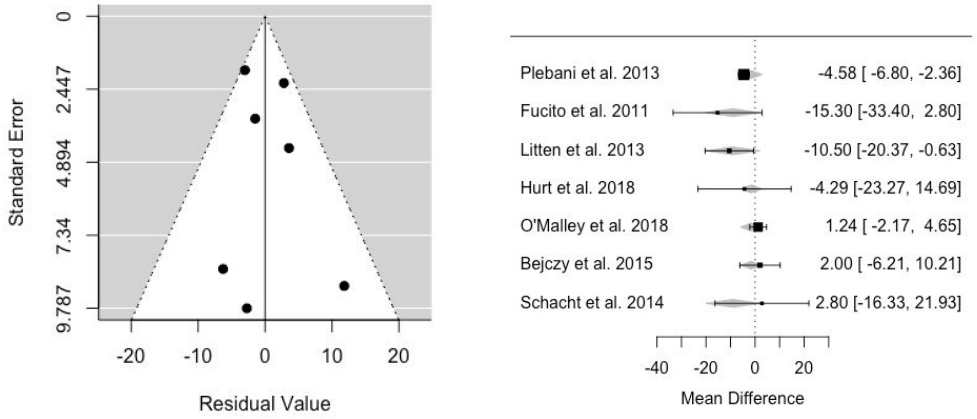




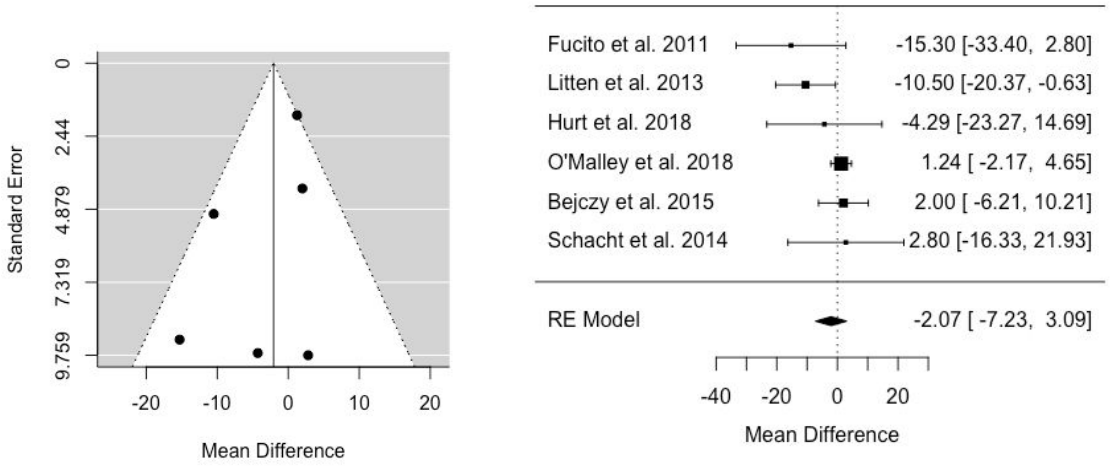
statistically significant at an alpha level of 0.05.

Finally, our I^2 value was 52.32%, meaning heterogeneity of the studies was moderate to substantial. This is also reflected within the funnel and forest plots. The funnel plot (left) shows no indication of publication bias and appears to the relatively normal.

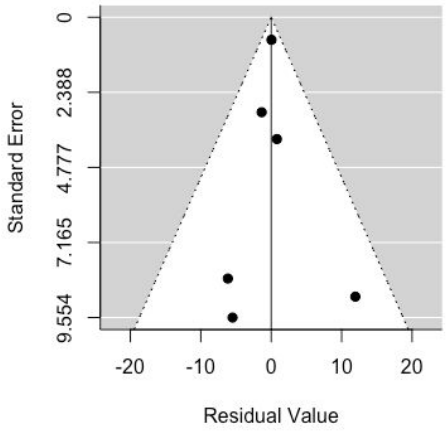
Mixed effect models for percent heavy drinking days were also conducted with covariates of duration, mean age, percent male, and pfizer funding. The duration, mean age, and percent male covariates were not considered significant with a p-value of 0.4441, 0.6279, and 0.7821, respectively. The pfizer covariate was the closest to being considered statistically significant with an alpha value of 0.20, it's p-value was 0.168. Introducing the pfizer funding covariate also change the estimate of the mean difference in percent heavy drinking days between the varenicline and placebo groups to -9.0285 with a standard error of 4.2997. Our new 95% confidence interval was -17.4557 to -0.6013. The updated t-test produced a t-value of -2.0998 and a p-value of 0.0898. With the Pfizer funding covariate, the I^2 value decreased to 37.08%, meaning that some of the covariate was able to account for some of heterogeneity amongst studies, reducing the I^2 value by 15.24%, this is reflected within both the funnel (left) and forest (right) plot.

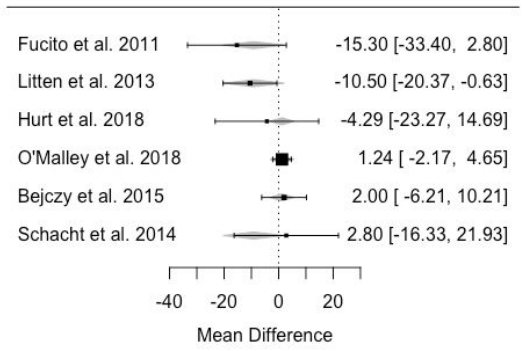


Another random effects model for percent heavy drinking days was done with all data retrieved from Plebani et al. 2013 removed. The data was removed because the way standard deviations were measured was different than the rest of the studies. The Plebani et al. study used a generalized linear model in-order to generate there desire data, which other studies did not. With the Plebani et al. data removed the estimate of the mean percent difference was -2.07% with a standard error of 2.6319%. The 95% percent confidence interval went from -8.835% to 4.696% mean difference. The t-test produced a t-value of -0.7863 with a corresponding p-value 0.4673. The I^2 value was reported to be 37.14%, this was considerably less than the model including Plebani et al. Meaning that due to the data retrieved from the Plebani et al. study produced a lot of the heterogeneity within the previous model.



More mixed effect models were conducted with the percent heavy drinking days, minus the Plebani et al. 2013 data. The same covariates previously mentioned were introduced to the model: duration in weeks, mean age of each study, percent male in each study, and whether or not a study was funded by Pfizer, the pharmaceutical company. Again, none of the covariates except for Pfizer funding were shown as close to statistically significant. Duration, age, and gender all produced large p-values of 0.498, 0.7747, and 0.7959, respectively. The pfizer funding covariate produced an estimated mean difference effect of 10.3483% with a standard error of 4.3278, a 95% confidence interval from -1.6676% to 22.3642%, and a t-value of 2.3911 with a corresponding p-value of 0.0751. The covariate also changed the estimated mean percent heavy drinking days difference between varenicline treatment and placebo treatment to -9.1475% with a standard error of 4.0272. Thus, this changed all other outputs from the model: the 95% confidence interval produced was from -20.3287% to 2.0337% and a t-value of -2.2715 with a corresponding p-value of 0.0856. Thus, with this covariate and the removal of the Plebani et al. 2013 data, both estimates of mean difference are statistically significant with an assumed alpha of 0.10. The mixed effect model including the Pfizer funding also produced an even lower I^2 value of 0%, meaning the heterogeneity between the studies was completely accounted for by the covariate.

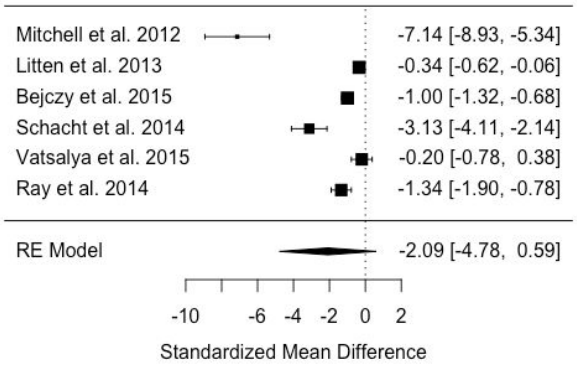


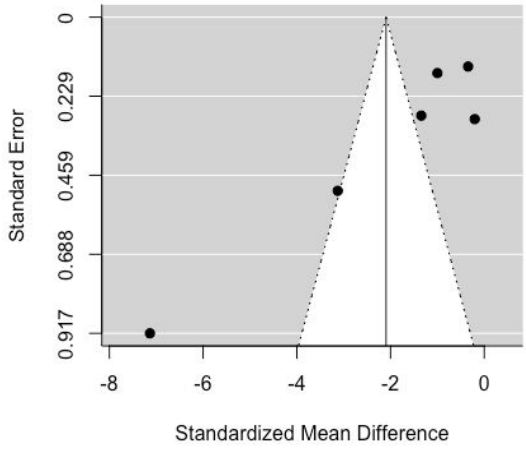


Alcohol Craving

Two random effects models were used to estimate the standardized mean difference between alcohol craving scores for the varenicline and control study arms. The first model included Mitchell et al. 2012, and the second did not. This was done due to the way that standard error was estimated for Mitchell et al. 2012. In the Mitchell et al.'s study, rather than solely comparing the final outcome groups, a matched-pair analysis was done to find the change from the beginning of the study to the end of the study in both study arms. This resulted in a standard error of the difference rather than the mean alcohol craving score for each group. Two models were conducted to see if there was a large enough difference when Mitchell et al. 2012 was included or excluded.

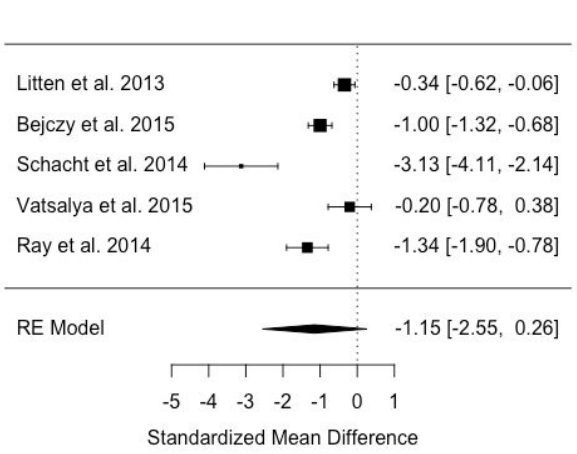
The random effects model that included Mitchell et al. 2012, produced an estimated standardized mean difference of -2.09 in alcohol craving between varenicline and placebo-controlled study groups with a standard error of 1.0462. The 95% confidence interval went from -4.7839 to 0.5946. A t-value of -2.002 with a corresponding p-value of 0.1016 was produced. The value of I^2 was 99.03%, meaning that there was considerable heterogeneity between the studies. The corresponding funnel and forests plots are shown below. The forest plot (left) shows that Mitchell, has extremely different results from the rest of the studies. This is also reflected in the funnel plot (right).

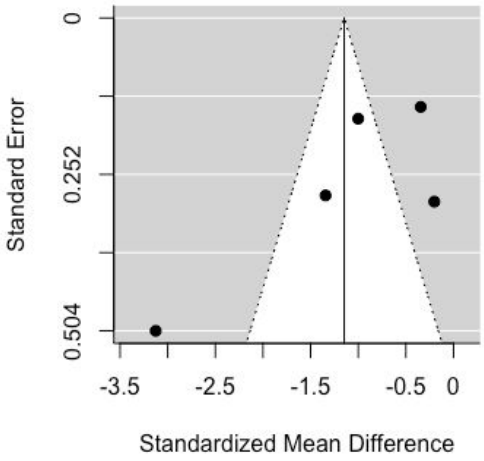




Another few mixed effect models were used to test our predetermined covariates of duration, age, gender, and Pfizer funding. None of these covariates were statistically significant. The duration, age, gender, and pfizer covariates produced p-values of 0.7155, 0.4839, 0.2163, and 0.6699.

The random effects model excluding Mitchell et al. 2012 estimated the standardized mean difference between alcohol craving scores for varenicline and the placebo-controlled study arms of the studies to be -1.1473 with a standard error of 0.5051. The model produced a 95% confidence interval from -2.5498 to 0.2552. A t-value of -2.2712 was produced with a corresponding p-value of 0.0856. The I^2 value was 95.88%. Again, the heterogeneity between studies reporting alcohol craving scores was extremely high. Mitchell et al. was excluded due to the fact that the way that the standard error was estimated compared to other studies (matched-pair study design). In comparison to the previous analysis, which included Mitchell et al., we can see a funnel plot that is bit more symmetrical, but still is very asymmetrical. This is likely due to a small number of studies for analysis.

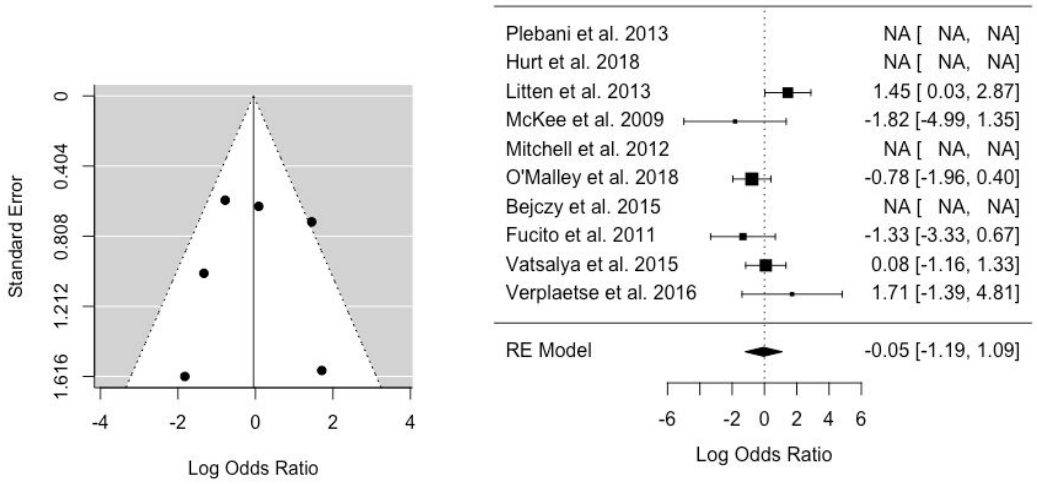




Adverse Events

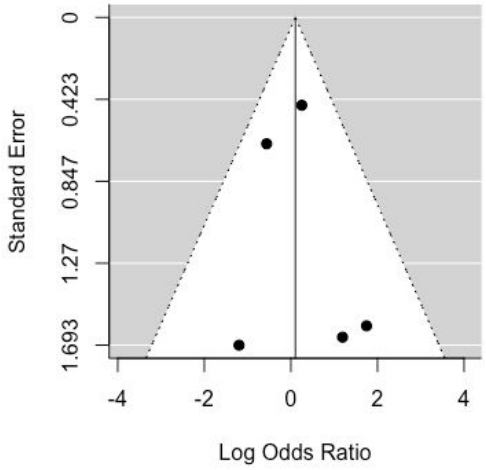
The random effects binomial models for adverse events were used to estimate the log odds ratio of adverse events occurring between the varenicline and control study arms of the selected studies. Studies with missing values were excluded, but the overall number of studies reporting adverse events, as seen above, was 10 (Bejczy et al., 2015; Fucito et al., 2011; Hurt et al., 2018; Litten et al., 2013; McKee et al., 2009; Mitchell et al., 2012; O'Malley et al., 2018; Plebani et al., 2013; Vatsalya et al., 2015; Verplaetse et al., 2016).

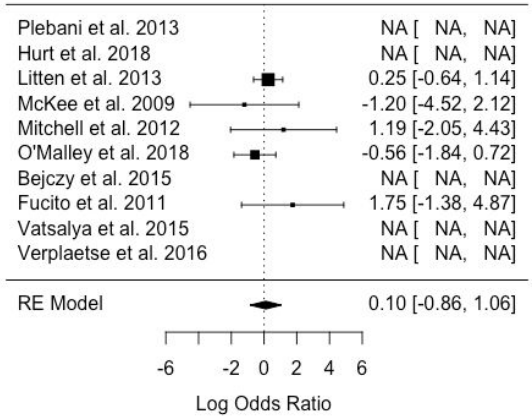
For constipation, the log odds ratio between varenicline and the placebo-controlled groups was estimated to be -0.0492 with a standard error of 0.444. Thus, the 95% confidence interval went from -1.1906 to 1.0923. To test the significance of this result a t-test was done. The t-value and p-value from this test were -0.1107 and 0.9162, respectively. The I^2 value was 40.62%. Thus, heterogeneity was just moderate and is reflected within the funnel (left) and forest plot (right). Plebani et al., Hurt et al., Mitchell et al., and Bejczy et al. studies were excluded from the analysis, because they did not report any data for the number of constipation events reported.



All covariates were tested and none were shown to be significant. The duration covariate produced a p-value of 0.7633, the age covariate produced a p-value of 0.873, gender produced a p-value of 0.5847, and the Pfizer funding covariate produced a p-value of 0.4868.

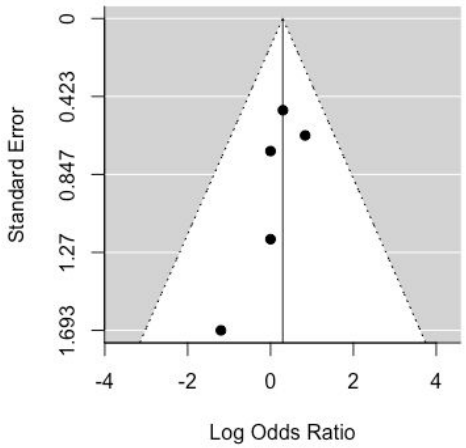
The log odds ratio estimated for the vomiting adverse event was 0.1034 with a standard error of 0.346. With this standard error, a 95% confidence from -0.8573 to 1.0641 was produced. The t-value for significance was 0.2987 producing a p-value of 0.78. The I^2 value was 0%, meaning there was little or no heterogeneity between studies. This can be shown in the funnel plot (left), where the studies are pretty much symmetrical about the middle vertical axis. Plebani et al., Hurt et al., Bejczy et al., Vatsalya et al., and Verplaetse et al. were excluded from the analysis, because they did not report any data about vomiting adverse events.

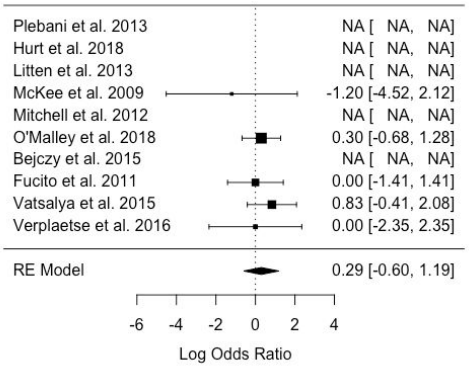




All covariates within mixed effects models for the vomiting adverse event were also not statistically significant at any reasonable alpha. The p-value for the duration covariate was 0.4697, the age covariate p-value was 0.3786, the gender covariate p-value was 0.3665, and the Pfizer funding covariate produced a p-value of 0.3182.

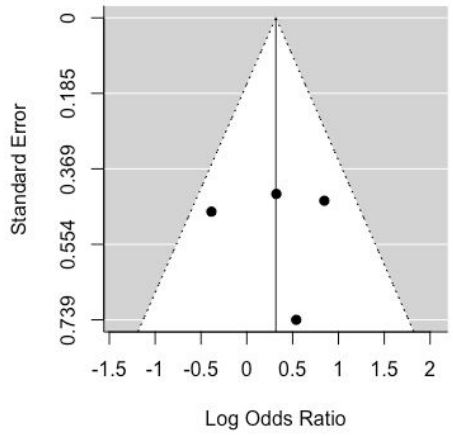
The log odds ratio estimated for flatulence between the study arms was 0.2945 with a standard error of 0.3208 which produced a 95% confidence interval of -0.5962 to 1.1853. In testing the significance of our result a t-value of 0.9181 was produced with a p-value of 0.4105. Finally, in testing the variance and heterogeneity an I^2 of 0% was produced, again there was no or very little heterogeneity amongst the studies. This is reflected within the funnel and forest plots below. Plebani et al., Hurt et al., Litten et al., Mitchell et al., and O'Malley et al. were excluded for missing data on flatulence adverse events.

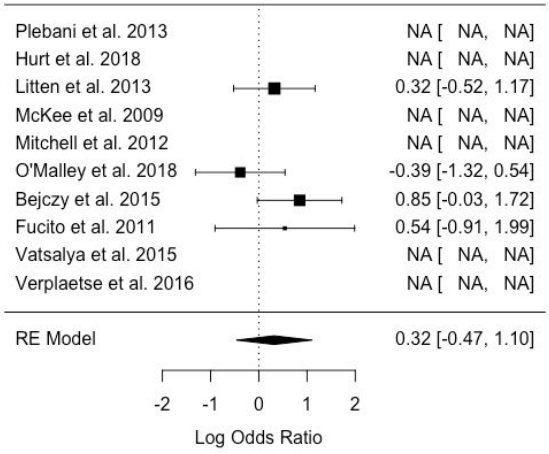




None of the covariates were significant for the flatulence adverse event. Duration produced a p-value of 0.9312, age produced a p-value of 0.6922, gender produced a p-value of 0.5239, and Pfizer funding produced a p-value of 0.6789.

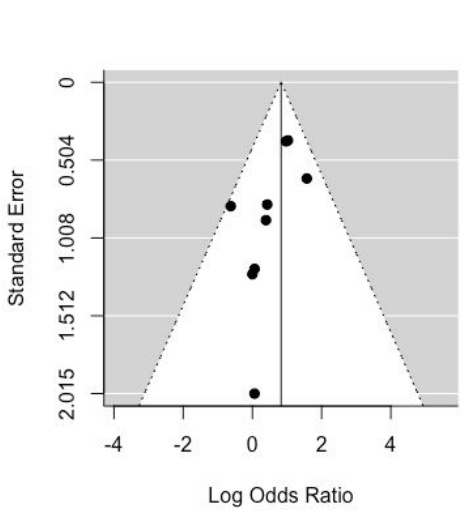
The log odds ratio estimated for fatigue between varenicline and place-controlled study arms was 0.317 with a standard error of 0.2464. This produced a 95% confidence interval that went from -0.4673 to 1.1013. Our t-test for significance produce a t-value of 1.2862 and a p-value of 0.2886. The I^2 produced was 3.38%, while this value was larger than previously mentioned I^2 values, there was still very little heterogeneity to be reported. Again, the funnel and forest plots below show the same result. Plebani et al., Hurt et al., McKee et al., Mitchell et al., Vatsalya et al., and Verplaetse et al. studies were all excluded from the analysis due no reports of fatigue.

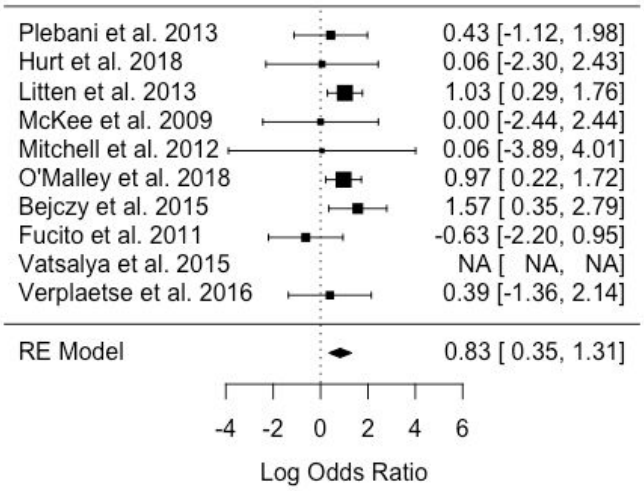




When the covariates of interest were introduced, none were significant. Duration had a p-value of 0.3894, age had a p-value of 0.2573, gender had a p-value of 0.3489, and the Pfizer covariate had a p-value of 0.8505.

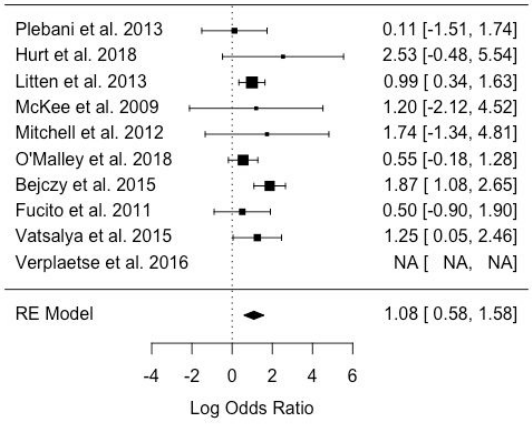
The model for estimating the log odds ratio of abnormal dreams for varenicline to placebo-controlled group produced an estimate of 0.8294 with a standard error of 0.2067. A 95% confidence interval from 0.3527 to 1.3062 was also produced. Finally, a t-test produced the t-value of 4.012 with a corresponding p-value of 0.0039. The I^2 produced was 0%, meaning little or no heterogeneity and was not important to understand the true effect size. The funnel and forest plots show the same result. Vatsalya et al. was excluded from this analysis due to missing reports of abnormal dream data.

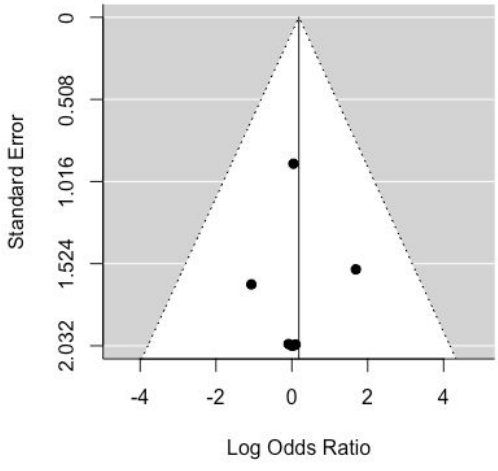




Duration, age, gender, and Pfizer funding covariates were all found to be not statistically significant producing p-values of 0.123, 0.1744, 0.7417, and 0.7179.

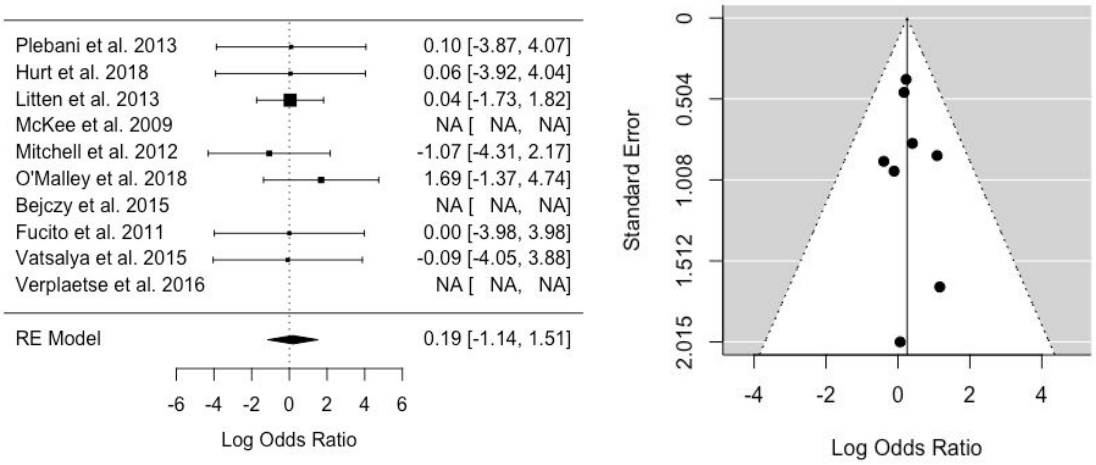
For nausea, a log odds ratio of 1.0837 was produced with a standard error of 0.217. The 95% confidence interval went from 0.5834 to 1.5841. The t-test produced a t-value of 4.9945 with a p-value of 0.0011. The I^2 produced was 18.44%, meaning that while there is some heterogeneity it is probably not that important in its impact on the true effect size. Only Verplaetse et al. was excluded from this analysis for missing data.





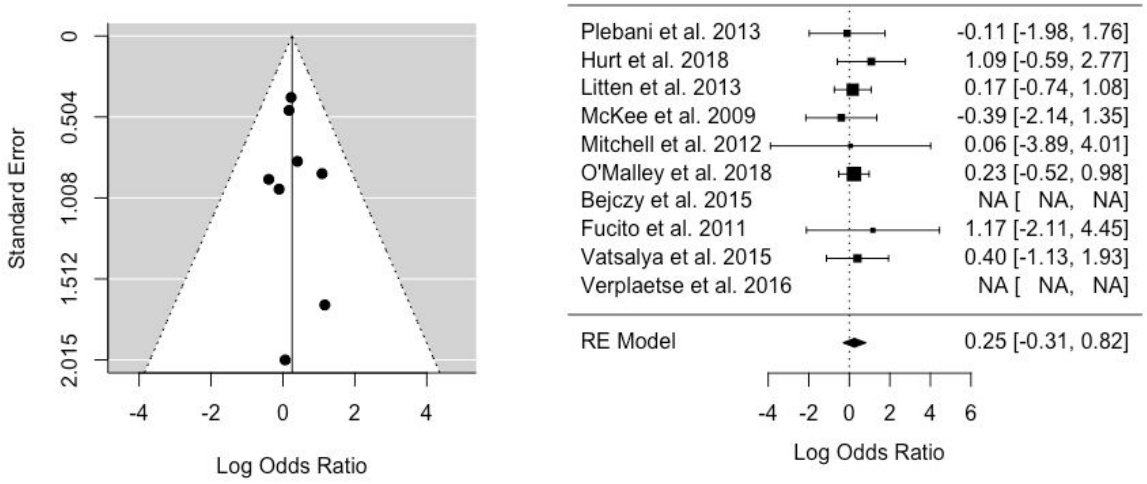
Once again, none of the covariates of interest were found to be statistically significant. Duration produced a p-value of 0.7857, age produced a p-value of 0.1847, gender produced a p-value of 0.422, and the Pfizer funding covariate produced a p-value of 0.5137.

The total serious adverse events log odds ratio produced was 0.1855 with a standard error of 0.5429, the 95% confidence interval went from -1.1431 to 1.5140, the t-value was 0.3416 with a p-value of 0.7443, and finally an I^2 of 0% was produced. The I^2 value indicates that the overall heterogeneity was very low, which is also shown by the symmetrical funnel plot. The forest plot also shows relatively equally confidence intervals. Studies missing serious adverse event data were excluded from the analysis including: McKee et al., O'Malley et al., and Verplaetse et al.



None of the covariates, duration, age, gender, and Pfizer funding, were found to be statistically significant with p-values of 0.5734, 0.9872, 0.7542, and 0.8186.

An log odds ratio of 0.2542 was estimated for the total non-serious adverse events between varenicline and the placebo-controlled group with a standard error of 0.2377. The log odds ratio 95% confidence interval was from -0.3079 to 0.8162. In testing the statistical significance, a t-value of 1.0692 with a p-value of 0.3204. The I^2 value produced was 0%. Again, this indicates that there was little to no heterogeneity between studies which is also supported by the symmetry of the funnel plot below.



Bejczy et al and Verplaetse et al. were excluded for not reporting the total number of non-serious adverse events. None of the covariates used in the mixed effects models were found to be significant. Duration, age, gender, and Pfizer funding all produced large p-values of 0.9165, 0.907, 0.4722, and 0.9938, respectively.

Discussion

Based on the statistical meta-analysis, varenicline appears to be effective in reducing alcohol cravings, but not actually reducing the percentage of heavy drinking days in patients with alcohol use disorders.

Examining the outcome of percent heavy drinking days, based on the results from the systematic review, this study provides evidence that the mean difference in average percent heavy drinking days between the varenicline treatment and control was 11.09%. However, a further statistical meta-analysis showed that there was not enough evidence to say that there is a significance difference in the mean difference in percent heavy drinking days at the 95% confidence level. Further, in the systematic review, even though duration (number of weeks of the experiment) seemed like it could be a confounding variable and help in improving the accuracy of the results of the difference in percent heavy drinking days, the meta-analysis revealed a of lack of significance. Similarly, other covariates —age, gender, and treatment seeking (alcohol and smoking)— did not show significance at the 95% confidence level. However, pfizer funding was significant at the 90% confidence level, allowing the conclusion that there was a significant difference in mean percent heavy drinking days between varenicline treatment and control study arm.

Next, for standardized mean difference in alcohol cravings, the systematic review showed a difference of a decrease of 2.18 across the two treatment groups. Confirming the small difference, the meta-analysis revealed that there was not enough evidence to conclude that there is a significant difference in the standardized mean difference in alcohol cravings at the 95% confidence level. However, the results were significant at the 90% confidence level, showing that Varenicline in fact resulted in a reduction of alcohol craving in users. The covariates of duration, age, gender, pfizer funding, and treatment seeking (alcohol and smoking) were not significant.

In order to get a holistic understanding of Varenicline as a drug, we also examined the adverse events. The adverse events were studied included fatigue, nausea, flatulence, constipation, headache and abnormal/ vivid dreams, and vomiting. These were either listed as side-effects of varenicline by Chantix™ (Pfizer, 2018) or by tallying were discovered to be the most commonly occuring side effects across all the 12 studies. Across these, the side effects of abnormal/ vivid dreams and nausea were significantly different between the Varenicline treatment and the control arm. Further, to see if there was a cumulative effect we also conducted a systematic review and meta-analysis on the total number of serious and non-serious adverse events in the selected 10 studies. There was a difference of 3.4% of average non-serious adverse events between the varenicline and the control group in the systematic review. The small difference indicates that the difference might be random and not significant— a statistical meta-analysis of non-serious adverse events as well as with covariates (age, duration, gender and pfizer funding) confirmed the hypothesis.

Several limitations must be taken into consideration when interpreting the results of the meta-analysis and the systematic review. We must consider the limited generalizability of the study since the population in the selected clinical trials do not accurately represent the true population of people with alcohol use disorders. Most of the sample were white, middle-aged men, without any mental illnesses. However, as stated by the National Institute of Alcohol Abuse and Alcoholism (National Institute of Alcohol Abuse and Alcoholism, 2002), psychiatric disorders are often a comorbidity associated with alcohol use disorders. Further, A National Survey on Drug Use and Health showed that the races in which drug abuse is most prevalent are Native Hawaiians or Other Pacific Islanders, American Indians or Alaska Natives, Blacks, Whites and Asians in descending order; the study also showed that ages 21-25 have the highest rates of heavy alcohol usage (U.S. Department of Health and Human Services, 2014). Another limitation is the disparity across the selected clinical trials of duration (the durations range from 1-16 weeks). Apart from this disparity, because the short durations of the studies, we do not know much about how effectively varenicline works in the long run or the relapse-rates in participants. Further, the short sample sizes of the studies, the differences in location (Bejczy et al. 2015 was conducted in Sweden) are also additional limitations. The disparity in the subjects seeking treatment for smoking and/or alcohol consumption across the trials could also lead to inaccurate conclusions. Further, the differences in the scales that measure alcohol cravings also undermine the overall findings of the meta-analysis. Studies had to be excluded because of missing or unavailable data (like standard error/ standard deviations), which could have changed the outcomes of the meta-analysis. Further, within the selected studies, some studies presented the data in the form of graphs; in order to extract the data from these studies, a statistical software PlotGrab (Olsen, Plot grab) was used, which might have led to slightly different numbers. Finally, the total number of studies, with all the data, used to conduct the meta-analysis (7 studies for percent heavy drinking days, 6 for alcohol craving and 10 for adverse events) were small in number, which might also lead to conclusions not reflective of the true results.

Predominantly, the strengths of the meta-analysis and the systematic review includes the fact that all the clinical trials used were randomized, placebo-controlled and double-blind. Also all studies titrated varenicline, and the placebo drug, up to 2 mg/ day. All studies (except Ray et al. 2014 and Verplaetse et al. 2016, which had slight variations) did so by asking the participants to take 0.5 mg/day during first three days, from the fourth day to the seventh day, and then adding up to 1 mg/day, and then increasing to 2 mg/day for the remaining days. Another key strength of this study is its well-balanced exploration into two important and different outcome measures, percent heavy drinking days and alcohol cravings, along with the adverse events of varenicline, especially the adverse events which aligned with those listed by Chantix™ (Pfizer, 2018).

Conclusions

In answering our question of how does varenicline impact those with AUD, we examined three outcomes: percent heavy drinking days, alcohol craving, and the number of adverse events. For percent heavy drinking days we found that there was no statistically significant difference between the treatment groups of varenicline and the placebo-controlled group without a covariate in the analysis, no matter if the Plebani et al. data was included or not. This could likely be due to the lower number of studies were able to include in our analysis, or simply due to the fact that varenicline does not have a statistically significant effect on the percentage of heavy drinking days per week for adults with alcohol use disorder. When the Pfizer funding covariate was added to our model resulting in a mixed effect model the statistical significance changed. These results were significant in comparison to an alpha value of 0.10. This alpha value can be considered reasonable due to the severity of the alcohol use disorder an adult has. With the Pfizer covariate in the analysis and the Plebani et al. data removed the varenicline group had an estimated 9% fewer percent heavy drinking days per week. When Pfizer funded the research there were about 10% fewer percent drinking days per week. This is interesting to note, because it shows the impact that a pharmaceutical company may have on changing the overall market for varenicline from not just smoking, but to alcohol use disorder. This suggests that there is a possibility that one, varenicline is able to reduce the percent of heavy drinking days an adult with alcohol use disorder engages in. It also suggests that Pfizer might be pushing research that shows this result to expand its market.

When it came the alcohol craving, the results were similar. When Mitchell et al. was included in the data the significance of the results were arguable, without Mitchell et al. the results were completely significant in comparison to an alpha of 0.10. When Mitchell et al. was included in the analysis the estimate of the effect of varenicline on alcohol craving was -2.09 on a standardized scale. What this meant is that varenicline was able to reduce the cravings for alcohol. When Mitchell et al. was excluded and the result was significant with an alpha of 0.10, the estimate was -1. This means that the effect was smaller, but interpreted as more likely to be significant. None of the covariates in the analysis appeared to be significant.

The only two adverse events that were statistically significant in their analysis were abnormal dreams and nausea. The estimate of the log odds ratio for abnormal dreams was estimated to be 0.8294. This means that your odds of having abnormal dreams are 0.19 percent higher when taking varenicline. The estimate of the log odds for nausea were 1.0837. Thus these means again that the odds of nausea when taking varenicline are higher than within the placebo group.

Ultimately, our meta analysis shows that there is certainly promise for varenicline as a treatment for alcohol use disorder. The percent heavy drinking days tend to decrease with varenicline. What is needed to confirm this is more studies, the same is true for alcohol craving. There are only a few adverse events that appear to be more likely when taken. This is all different than what the Chantix website presented. In-order to confirm our results, more

meta-analyses must be done. In the future, meta-analyses of this topic should look more into the other markers of AUD.

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