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Medical Treatment of Alcohol Dependence: A Systematic Review

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Abstract

Objective—To summarize published data on pharmacologic treatments for alcohol dependence alone and in combination with brief psychosocial therapies that may be feasible for primary care and specialty medical settings.

Methods—We conducted electronic searches of published original research articles and reviews in MEDLINE, SCOPUS, CINAHL, Embase, and PsychINFO. In addition, hand searches of reference lists of review articles, supplemental searches of internet references and contacts with experts in the field were conducted. Randomized controlled studies published between January, 1960 and August, 2010 that met our inclusion/exclusion criteria were included.

Results—A total of 85 studies, representing 18,937 subjects, met our criteria for inclusion. The evidence base for oral naltrexone (6% more days abstinent than placebo in the largest study) and topiramate (prescribed off-label) (e.g., 26.2% more days abstinent than placebo in a recent study) is positive but modest. Acamprosate shows modest efficacy with recently abstinent patients, with European studies showing better results than US ones. The evidence-base for disulfiram is equivocal. Depot naltrexone shows efficacy (25% greater reduction in rate of heavy drinking vs. placebo, in one of the largest studies) in a limited number of studies. Some studies suggest that patients do better with extensive psychosocial treatments added to medications while others show that brief support can be equally effective.

Conclusions—Although treatment effects are modest, medications for alcohol dependence, in conjunction with either brief support or more extensive psychosocial therapy, can be effective in primary and specialty care medical settings.

Index Words

Alcoholism; naltrexone; acamprosate; disulfiram; topiramate

Alcohol dependence is a major progressive disease with a lifetime prevalence of 12.5% and an estimated annual economic cost (in 2007 dollars) in the United States of \$235 billion

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dollars.^{1–2} Heavy alcohol use causes or exacerbates a number of medical conditions including hypertension, diabetes, cardiovascular disease, digestive disease, depression, liver disease, and oral and pharyngeal cancer.³ In U.S. general hospitals ~ 7% of patients have an active alcohol use disorder.⁴ Studies show that ~20% of primary care patients drink excessively.⁵

While the U.S. Preventive Services Task Force (USPSTF) recommends screening and brief counseling to reduce alcohol misuse by adults in primary care settings, this recommendation only applies to hazardous (more than 7 drinks per week or more than 3 drinks per occasion for women, and more than 14 drinks per week or more than 4 drinks per occasion for men) and harmful (physical, social, or psychological harm from alcohol use) drinking and not those who meet DSM-IV criteria for alcohol dependence.⁶ With the availability of alcoholism medications (e.g., naltrexone, disulfiram, acamprosate), evidence suggests that alcohol dependence may be effectively treated in primary and specialty care medical settings.^{7–8} The current National Institute on Alcohol Abuse and Alcoholism (NIAAA) guidelines for alcohol screening and intervention propose the use of alcoholism pharmacotherapy and chronic disease management by physicians for their alcohol dependent patients.⁹

Increased treatment options for alcohol dependent patients in medical settings are critical, since only 13% receive specialized addiction treatment, and only 24% seek any kind of help, including Alcoholics Anonymous.¹⁰ Accordingly, the objective of this systematic review is to summarize published data on pharmacologic treatments alone and in combination with brief psychosocial interventions for maintaining abstinence or preventing relapse to heavy drinking. This review differs from currently available reviews on drug therapy for alcoholism in that it (1) summarizes data on multiple drug therapies rather than focusing on only one medication, (2) is a formal systematic review in its approach, and (3) interprets evidence-based findings primarily for practicing clinicians.

METHODS

Literature Search and Study Selection

In August, 2010, we conducted (1) electronic searches of published and “in press” original research articles and reviews in MEDLINE, Embase, SCOPUS, CINAHL, and PsycINFO, (2) hand searches of reference lists of review articles, (3) supplemental searches of internet references and (4) searches by contacting experts in the field. Time periods of searches included 1960 to August, 2010. Search terms included alcohol abuse, alcohol dependence, alcohol use disorder, alcoholics, alcoholism, alcohol pharmacotherapy, naltrexone, acamprosate, topiramate, disulfiram, antidepressants, ondansetron, nalmefene, serotonergic agents, brief intervention, and physician intervention. Specific inclusion and exclusion criteria are included in Table 1.

Study Selection

Two authors independently reviewed all titles and abstracts to identify relevant articles. Articles that met inclusion/exclusion criteria were independently abstracted by the two authors. Discrepancies were resolved by repeated review and discussion, with the principal author serving as the final arbiter to resolve conflict. The flow diagram in Figure 1 shows an overview of the study selection process.

Assessment for Potential Bias

Two authors independently rated each study using the Jadad scale, which focuses on the authors’ description of randomization, blinding, and study withdrawals.¹¹ Studies rated 4 or

5 by both independent raters were categorized as “Less Potential for Bias” while those receiving a 1, 2 or 3 were labeled “Higher Potential for Bias.” It is important to note that the Jadad assessment does not evaluate all sources of bias (e.g., as may arise in data analysis or reporting of the study results). Discrepancies were resolved by repeated review and discussion, with the principal author serving as the final arbiter to resolve conflict.

RESULTS

Our searches identified 85 randomized controlled trials (RCTs), representing 18,937 subjects, that met all inclusion/exclusion criteria and underwent full text review. Results are presented separately for each medication and also those including medication/psychosocial interactions. Some studies evaluated the efficacy of more than one active medication and are included in more than one section.

Tables 2 through 7 list studies for each medication, providing first author, year of publication, Jadad score, number of subjects, length of follow-up, and results.

Disulfiram

Disulfiram (Antabuse®), FDA-approved to treat alcohol dependence in 1951, interferes with the metabolism of alcohol, by inhibiting aldehyde dehydrogenase, and produces flushing, nausea, palpitations, and other severe reactions if drinking occurs. A total of 11 RCTs that evaluated the efficacy of disulfiram met our criteria for inclusion. Of these, two studies, although methodologically sound, investigated disulfiram tablets implanted in the abdomen.^{12–13} Since evidence is lacking for the bioavailability of implanted disulfiram tablets,¹⁴ results of these studies were not included in our conclusions. Of the remaining nine RCTs, only one study was rated in the “Less Potential for Bias” category. This study compared a placebo with two doses of disulfiram, one “active” 250 mg dose and one “inactive” 1 mg dose.¹⁵ No significant differences were found between disulfiram and placebo on any alcohol consumption measure. It might be noted that drug ingestion was unsupervised and the authors found a significant relationship between compliance and abstinence.

Eight other studies were judged to be in the “Higher Potential for Bias” category. These studies compared disulfiram either with placebo or with acamprosate, naltrexone, or topiramate. The two studies comparing disulfiram with placebo found significant reductions in alcohol consumption. Fuller, et al.¹⁶, in a Veterans Administration Cooperative Study, reported significantly fewer drinking days over a one year time period but no differences in total abstinence or time to first drink.. Chick, et al.¹⁷ found significant increases in number of abstinent days (100 for disulfiram vs. 69 for placebo over 6 months) and change in 6-month alcohol consumption. In both of these studies, close relatives were actively involved in the patient’s treatment, with disulfiram ingestion being supervised daily in the Chick study.

Three studies compared supervised disulfiram to oral naltrexone, with results favoring disulfiram in two studies.^{18–19} The third study, with blinded naltrexone and blinded placebo but open-label disulfiram, found that all active medications had better alcohol outcomes than placebo, with no advantage to combined medications.²⁰

Two studies included an acamprosate comparison group, with one comparing supervised disulfiram with acamprosate and another comparing disulfiram with acamprosate alone and naltrexone alone. Both of these studies favored disulfiram.^{19, 21} The one study that compared supervised disulfiram with topiramate found disulfiram to be significantly more effective than topiramate in delaying the onset of relapse (133 days vs. 79 days).²² After 9

months of treatment, 90% of disulfiram patients were abstinent compared to 56% for topiramate.

Topiramate

The anti-epileptic topiramate (Topamax®), although not FDA-approved for alcohol dependence, targets both the GABA and glutamate brain pathways and reduces alcohol craving. Four topiramate studies met our criteria for inclusion. Of these, 3 were categorized as having “Less Potential for Bias.”^{23–25} All three studies found topiramate to be superior to placebo on all drinking measures. In the largest of these studies, Johnson, et al.²⁵ found that topiramate, compared to placebo, decreased percentage of heavy drinking days (mean difference of 16.19%; CI, 10.79% – 21.60%) and all other drinking outcome measures. One of these three studies also included a naltrexone comparison group.²³ In that study, topiramate was superior to placebo but not to naltrexone. Naltrexone did not differ statistically from placebo.

A fourth study, rated as “Higher Potential for Bias,” compared topiramate with naltrexone and found no difference by treatment.²⁶ Abstinence did not differ by treatment at 3 or 6 months. No placebo group was included.

Antidepressants

Seven RCTs focusing on selective serotonin reuptake inhibitors (SSRIs) met our criteria and all were rated as having “Less Potential for Bias.” Four compared sertraline to placebo (one with alcohol dependent subjects with comorbid PTSD, two included subjects with comorbid major depression, and one included alcoholic subjects with lifetime depression).^{27–30} Three of these studies failed to show significant differences in any of several drinking outcomes by treatment group. One (which included adjunctive cognitive behavior therapy) found sertraline to result in fewer drinks per drinking day but no differences in time to first drink, time to first heavy drinking day or in abstinence rates.²⁷ Kranzler, et al.³¹ compared fluoxetine versus placebo and found no significant medication effects on drinking measures.³¹

Two recent studies investigated sertraline in combination with naltrexone. Farren, et al.³² found that, although there were trends toward favoring a sertraline/naltrexone combination compared to a placebo/naltrexone combination, no statistically significant differences were evident. Conversely, with alcohol dependent patients with comorbid depression, Pettinati, et al.³³ found greater total abstinence (54%) when naltrexone and sertraline were used in combination. The combined abstinence rate for sertraline alone, naltrexone alone, and placebo was only 24%. The combination of naltrexone and sertraline also led to significantly better outcomes on % of subjects not drinking heavily, time to relapse, and time to any drinking.

One study investigated the tricyclic antidepressant, desipramine, versus placebo, stratified on depression.³⁴ During the 6 month study there was a decreased relapse for desipramine relative to placebo. The interaction between depression and medication was not significant.

Two studies found that quetiapine, an antipsychotic mood stabilizer, as an adjunct to lithium or divalproex with alcohol dependent patients with bipolar I disorder did not result in reduction in drinking outcome measures.^{35–36}

Acamprosate

Acamprosate (Campral®) was FDA-approved for the treatment of alcohol dependence in 2004. While its mechanism is not entirely understood evidence suggests that it interacts with

the glutamate neurotransmitter system, reducing protracted (post-acute) withdrawal symptoms including insomnia, restlessness, and anxiety. A total of 24 RCTs evaluating acamprosate met our inclusion/exclusion criteria. Of these, 15 were rated as having “Less Potential for Bias.”^{7, 37–51} Eleven compared acamprosate to placebo, three included naltrexone as a comparison group in addition to placebo, and one had a disulfiram comparison group.

Results of the eleven placebo comparison studies were mixed. Six studies showed changes in drinking outcomes favoring acamprosate.^{47–51} For example, Pelc, et al⁴⁷ compared 1332 mg/day and 1998 mg/day of acamprosate with placebo in a 90 day trial. Both levels of acamprosate led to better cumulative abstinence duration (51.9 days, 56.6 days vs 34.3 days), time to first relapse (55.5 days, 56.3 days vs. 15 days), and total abstinence (41%, 41% vs. 15%) than placebo. Poldrugo⁴⁸ found that the percentage of patients with continuous abstinence after 6 months of treatment was almost double for the acamprosate group (40.7%) compared to the placebo group (20.8%).

Five other studies either had mixed results or showed no significant differences between acamprosate and placebo. Using 2 g and 3 g of acamprosate versus placebo, Mason found no significant differences in % alcohol free days or quantity/frequency of drinking. Post-hoc analyses, however, revealed a significantly higher percentage of abstinent days for acamprosate over placebo in subjects who were abstinent at baseline. At the end of a 6 month study, Gual⁴¹ found significantly higher cumulative days abstinent and days from last relapse in the acamprosate group but abstinence throughout the trial was not statistically significant. Three other studies found no significant differences between acamprosate and placebo on any drinking outcome measure.^{17, 40, 46}

Of three studies comparing acamprosate to both placebo and naltrexone, Kiefer, et al⁴² found, in a 12 week trial, that acamprosate was superior to placebo on abstinence (~28% vs. ~8%) and on no relapse to heavy drinking days (~40% vs. ~28%). Both acamprosate and naltrexone were equally effective and their combination was superior to acamprosate alone but not naltrexone alone. However, in two large multi-center RCTs, Anton, et al⁷ in the Combine Study in the United States and Morley, et al in Australia,⁴⁵ found no effect for acamprosate over placebo. In addition, the Combine study showed no advantage of the combination of acamprosate and naltrexone. Morley’s Australian study found neither acamprosate nor naltrexone were superior to placebo except in the case of subjects with low baseline dependence and depression, for which the efficacy of naltrexone was supported for relapse prevention.

Of the 8 studies rated as “Higher Potential for Bias,” results were similarly mixed. In four of these studies comparing acamprosate to placebo, acamprosate was superior to placebo.^{52–56} In three studies comparing acamprosate to other medications, two found disulfiram to be superior to acamprosate and one found naltrexone to be superior to acamprosate.

Finally, one study that is particularly relevant to the focus of this review, compared open label acamprosate to standard care alone in primary care settings.⁵⁷ Cumulative abstinence over one year was higher in the acamprosate group than the standard care group, but, the absence of a placebo control group limits the implications of this naturalistic study.

It might be noted that there is a trend for European studies to show positive results while US studies are more mixed or negative. Mason has observed that these trials differed on several variables (e.g., a significantly larger number of US subjects, compared to European subjects, had not discontinued drinking prior to randomization), all of which are considered predictors of poor treatment outcomes in clinical trials.⁵⁸

Naltrexone

Oral naltrexone (ReVia[®]; Depade[®]), FDA-approved for alcohol dependence in 1994, and extended-release injectable naltrexone (Vivitrol[®]), approved in 2006, block opioid receptors, inhibiting rewarding effects of alcohol and reducing craving. By far, naltrexone is the most researched medical treatment for alcohol dependence. A total of 33 naltrexone RCTs met our criteria for inclusion in this review.^{7, 18–20, 23, 26, 32–33, 39, 42, 45, 59–80} Of these, the majority investigated oral naltrexone, with two focusing on depot naltrexone.

Of the 31 studies of oral naltrexone, 17 received a “Less Potential for Bias” rating. Fifteen of these compared naltrexone with a placebo. Of these, the majority, 12 studies, found naltrexone to be significantly superior to placebo on drinking outcomes. Three others found naltrexone to be no better than placebo.^{23, 68, 73} One of these negative studies was the multicenter Veterans Affairs Naltrexone Cooperative Study which included patients with chronic, severe alcohol dependence, the majority of whom had family histories of alcoholism.⁶⁸ Another negative study targeted women with eating disorders.⁷³

Two other studies evaluated the combined effects of oral naltrexone and sertraline, an SSRI antidepressant. In non-depressed alcohol dependent subjects, Farren, et al.³² did not find evidence for the superiority of the combination over naltrexone alone. Pettinati, et al.,³³ however, found that, with depressed alcohol dependent subjects, the naltrexone/sertraline combination resulted in a higher abstinence rate (53.7%) than either naltrexone alone (21.3%), sertraline alone (27.5%), or placebo (23.1%).

Two studies evaluated depot naltrexone, a more recent form of naltrexone that is administered in monthly injections. Kranzler, et al.⁶⁷ evaluated monthly depot injections for 3 months versus placebo injections. Time to first drinking day and number of abstinent days (52.8 vs. 45.6) favored naltrexone. In a larger and longer (6 months) multisite study, Garbutt, et al.⁶¹ found a 25% and 17% (based on doses of 380 mg vs 190 mg) decrease in number of heavy drinking days for the naltrexone group compared to the placebo group.

Fifteen remaining studies were rated “Higher Potential for Bias.”^{18–20, 26, 62, 64–66, 72, 74–76, 78–79, 81–83} The majority of these investigations supported the efficacy of naltrexone over placebo. Two produced mixed results.^{72, 82} One, without a placebo control group, found that disulfiram was superior to naltrexone and another found naltrexone and acamprosate to be comparable (again, no placebo control).^{18–19}

Less Studied Medications

Seven RCTs examined the efficacy of a number of less studied drugs. All of these received a “Less Potential for Bias” rating. Two investigations evaluated baclofen, a GABA_B receptor agonist that may reduce withdrawal symptoms and inhibit cravings, versus placebo with one (using patients with liver cirrhosis) finding an advantage to baclofen and another (using outpatient volunteers) finding no difference compared to placebo.^{84–85} Three other projects studied nalmefene, an opioid receptor agonist that can lessen cravings and reduce the reinforcing properties of alcohol, with two finding reduction in heavy drinking days compared to placebo and one finding no difference with a placebo.^{86–88} Many of the subjects in one of these positive studies were primary care patients treated with the medication plus simple medical management.⁸⁷ Two studies found ondansetron, a 5-HT₃ receptor antagonist that can block the rewarding effects of alcohol, effective compared to placebo.^{89–90} Other less studied medications, with only one otherwise eligible RCT identified, were not included in this review (refer to Exclusion Criteria in Table 1).

Medication/Psychosocial Intervention Interaction

The question of whether brief psychosocial or supportive interventions add to the efficacy of alcohol dependence medications has received some research attention, although it is limited. In the vast majority of studies described above, all subjects, both active medication and placebo, received some type of adjuvant psychological intervention. Eleven studies have examined this issue separately in medication trials, with seven being judged as having “Less Potential for Bias.” Results of four of these seven studies conclude that either cognitive behavior therapy (CBT), coping skills training, communication skills training, or broad spectrum treatment (a combination of CBT, Motivational Enhancement Therapy (MET), community reinforcement approaches, and 12-step methods), in combination with naltrexone, significantly improved drinking outcomes compared to either naltrexone alone or naltrexone with brief motivational support or standard medical care.^{60, 74, 91–92} The remaining three of the seven, including the large multicenter COMBINE study, showed that minimal support in the presence of naltrexone was as effective as medication with more intensive psychosocial intervention.^{7, 93–94} All three studies are relevant to alcoholism treatment in primary care since, in addition to medication, one used medical management (MM) (a supportive, compliance-focused intervention potentially adaptable to primary care settings), another treated a cohort of primary care patients with low intensity support, and another included infrequent consultation with a physician. Of the four studies rated “Higher Potential for Bias,” one showed naltrexone plus coping skills training superior to naltrexone plus supportive therapy and three showed no significant advantage to adding extensive psychosocial treatments to naltrexone or acamprosate over brief support.^{64, 72, 95–96} In fact, O’Malley, et al.⁷² found that primary care management (PCM) plus naltrexone produced comparable results to cognitive behavior therapy (CBT) plus naltrexone in the short term (10 weeks) and produced better results in terms of maintenance of improvement over time.

Discussion

Research findings on the efficacy of medical treatments for alcohol dependence are generally mixed. While overall treatment effects for these medications have been quite modest, it is clear that some alcohol dependent patients will benefit from pharmacotherapy. Unfortunately for clinical practice, objective clinical predictors of individual treatment response to specific medications are currently unavailable.

Nevertheless, our review found several evidence-based results that support a role for alcohol dependence treatment in medical settings. First, the one study with the highest Jadad score, showed no advantage for disulfiram over placebo using an unsupervised disulfiram protocol. However, the majority of studies found that supervised disulfiram is more effective than placebo, with some evidence that it may be more efficacious than naltrexone, acamprosate, and topiramate. Compliance is a major problem with disulfiram and daily supervision of ingestion appears to be an essential key to clinical success. Second, evidence suggests that topiramate is an efficacious treatment for alcohol dependence, although the number of studies is small. Third, there is little evidence to support the use of antidepressants (either SSRIs or tricyclics) for alcohol dependence although one recent RCT found the combination of sertraline and naltrexone more effective with depressed alcoholics than naltrexone alone. Fourth, acamprosate may increase abstinence, although studies show mixed results, with some larger multisite studies in the US (e.g., the Combine Study) showing no advantage over placebo and European studies showing more favorable results (possibly due to differences in subject populations). However, taken as a whole, this review as well as a recent Cochrane review⁹⁷, suggests modest efficacy with abstinent alcoholics (i.e., those who were able to abstain for at least a few days prior to initiating medication). Fifth, a majority of studies support the efficacy of oral naltrexone over placebo. Injectable naltrexone shows efficacy but the number of studies are limited. Sixth, while some studies

suggest that patients do better with extensive psychosocial treatments added to medications, others show that brief support (as would be appropriate in most medical settings) can be equally effective.

In medical settings, current research suggests either oral naltrexone, , topiramate (used off-label), or acamprosate (with abstinent patients) as the initial pharmacotherapy consideration in patients without contraindications to their use. Disulfiram can be considered with motivated, abstinent patients if daily supervision of ingestion is feasible. Brief compliance-oriented support should accompany medication treatment although some patients may require more extensive adjunctive psychosocial treatment. Systematic evidence on specific populations that may or may not require more extensive psychosocial interventions is lacking. There is evidence to suggest, however, that, in the absence of the availability of intensive psychological help, medication plus brief support from a medical provider can lead to clinical improvement.

While these conclusions are based on a comprehensive search of the literature, it should be noted that non-English language articles and unpublished papers were excluded. Also, article screening, data abstraction, and Jadad ratings were not blinded, which may introduce a potential bias. However, there is evidence that blinding does not alter reviews of this nature.⁹⁸

The challenge in producing conclusions from a review of this nature is the heterogeneity of the patient populations under study. Variations in severity of dependence, genetic polymorphisms, gender, psychiatric comorbidities, and history of alcohol dependence may influence treatment response. Indeed, recent evidence indicates that genetic factors may predict treatment response to naltrexone.⁹⁹

Another major difficulty in comparing studies is the lack of uniformity of drinking outcome measures. In addition, definitions for outcomes such as “heavy drinking days” or “relapse” vary from study to study. The need for consensus on the most clinically relevant drinking outcome measures and a standardized format for reporting these data is essential. In addition, a potential limitation of published clinical trials on treatment of alcohol dependence is the limited length of follow-up (refer to Tables 2 – 7). Follow-up of all these studies is problematic since many are of only a three to six month duration. In particular, longer-term effects on morbidity and mortality should be investigated in future studies but, as yet, have not been quantified.

Most studies include some type of psychosocial treatment along with medications but often such treatments are not described in detail, with little information on frequency and duration of treatment. Too few studies are available that examine the separate effects of these treatments on medication efficacy. Overall, pharmacotherapy for alcohol dependence in primary and specialty care settings appears to be feasible and has the potential to improve patient outcomes. Unfortunately, while alcohol medications with brief interventions have demonstrated efficacy, few trials have been conducted in primary care. Issues that require further study include the identification of patients who are most likely to respond to certain medications, whether medication alone (i.e., without even brief psychosocial interventions) can be effective, compliance problems, and adoption and implementation issues in busy medical practice settings.

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Figure 1.
Article Selection

Table 1**Inclusion and Exclusion Criteria for Literature Search**

Inclusion Criteria	Exclusion Criteria
English language randomized controlled trials	Non-English language articles
Evaluation of alcoholism pharmacotherapy alone or in combination with brief psychosocial intervention	A medication for which only one RCT is reported
Inclusion of an identical placebo control group if evaluating only one medication	Studies other than randomized controlled trials
Alcohol consumption as primary outcome	Secondary analyses of randomized control trials in which the major outcome of interest was not alcohol consumption
Subject sample with diagnosis of alcohol dependence using well-established diagnostic criteria or valid clinical instruments (i.e., DSM-IV- R or ICD-10 diagnostic dependence criteria, Structured Clinical Interview for DSM-IV (SCID), Composite International Diagnostic Interview (CIDI), Substance Dependence Severity Scale (SDSS))	Sample size inadequate to detect at least a moderate treatment effect on the primary alcohol consumption outcome (e.g., studies using a subject sample of less than 30 per group for a continuous outcome were excluded)
Subjects 18 years of age or older	
Brief (<30 minutes) adjunctive psychosocial treatments applicable to or adaptable to general or specialty medical setting	

Table 2

Disulfiram

Primary Outcome	Source	JADAD	Sample Size	Length of Follow up	Intervention	Comparison
Significant	Chick J, 1992	3	126	6 months	Disulfiram	Vitamin C
Insufficient	Abstinent days, total drinks over 6 months Usual weekly intake, total drinks last month of study, days since last drink at end of study					
Significant	De Sousa A, 2004	3	100	1 year	Disulfiram	Naltrexone
Insufficient	Disulfiram group greater 1 year abstinence, more abstinent days, greater time to first relapse, and fewer drinks per occasion Days to first drink					
Significant	De Sousa AA, 2005	2	100	8 months	Disulfiram	Acamprosate
Insufficient	Disulfiram group with decreased relapse to heavy drinking, greater time to relapse, and longer time to first drink Drinks per drinking occasion, total abstinent days					
Significant	De Sousa AA, 2008	3	100	9 months	Disulfiram	Topiramate
Insufficient	Disulfiram group with decreased relapse to heavy drinking and greater days to relapse, and greater days until first drink Abstinent days					
Significant	Fuller RK, 1979	4	128	1 year	Disulfiram, 250 mg daily	Disulfiram, 1 mg or Riboflavin 50 mg
Insufficient	None reported Abstinence, percent drinking days					
Significant	Fuller RK, 1986	3	605	1 year	Disulfiram, 250 mg daily	Disulfiram 1 mg or Riboflavin 50 mg
Insufficient	Total drinking days was stratified by those who completed all assessments (where disulfiram 250 mg was superior) and those who did not complete all assessments (where there were no differences) Abstinence for one year, time to first drinking day					
Significant	Johnsen J, 1991	4	76	300 days	Disulfiram, 1 gram subcutaneous implant	Placebo implant
Insufficient	None reported Days to first drink, reduction in average alcohol use					
Significant	Laaksonen E, 2008	1	243	52 weeks	Naltrexone or Acamprosate or supervised Disulfiram	N/A
Insufficient	Supervised disulfiram better than naltrexone or acamprosate at time to first heavy drinking day, days to first drink, number of abstinent days, average weekly alcohol intake None reported					

Primary Outcome	Source	JADAD	Sample Size	Length of Follow up	Intervention	Comparison
	Petrakis IL, 2005	3	254	12 weeks	Naltrexone and counseling or Naltrexone and Disulfiram and counseling	Placebo and counseling
Significant	Drinking days per week less for active medication vs placebo, consecutive days of abstinence more for active medication vs placebo					
Insignificant	Percent days abstinent, percent heavy drinking days, total abstinence, no difference between groups on active medication					
	Petrakis IL, 2006	4	254	12 weeks	Naltrexone and counseling or Naltrexone and Disulfiram and counseling	Placebo and counseling
Significant	Percent of heavy drinking days less for active medication vs placebo, consecutive days of abstinence more for active medication vs placebo					
Insignificant	Total abstinence, no difference between groups on active medication					
	Petrakis I, 2007	3	254	12 weeks	Naltrexone and counseling or Naltrexone and Disulfiram and counseling	Placebo and counseling
Significant	Drinking days per week less for active medication vs placebo, consecutive days of abstinence more for active medication vs placebo					
Insignificant	Percent heavy drinking days, total abstinence, no difference between groups on active medication					
	Wilson, A, 1980	3	90	48 weeks	Disulfiram implant	Placebo implant and no implant
Significant	Days abstinent greater for disulfiram implant and placebo implant as compared to no implant					
Insignificant	None reported					

Table 3

Topiramate

Primary Outcome	Source	JADAD	Sample Size	Length of Follow up	Intervention	Comparison
Significant	Baltieri DA, 2008	5	155	12 weeks	Topiramate	Naltrexone
Insufficient	Time to relapse, cumulative abstinence days, and heavy drinking weeks					
Insufficient	Abstinence, time to relapse, cumulative abstinence days, and heavy drinking weeks vs naltrexone					
Significant	De Sousa AA, 2008	3	100	9 months	Disulfiram	Topiramate
Insufficient	Disulfiram group with decreased relapse to heavy drinking and greater days to relapse, and greater days until first drink					
Insufficient	Abstinence days					
Significant	Florez G, 2008	1	102	6 months	Topiramate	Naltrexone
Insufficient	None reported					
Insufficient	Abstinence, moderate drinking without associated problems					
Significant	Johnson BA, 2003	4	150	12 weeks	Topiramate	Placebo
Insufficient	Drinks per day, drinks per drinking day, percent heavy drinking days, percent days abstinent					
Insufficient	None reported					
Significant	Johnson BA, 2007	5	371	14 weeks	Topiramate	Placebo
Insufficient	Percent heavy drinking days					
Insufficient	None reported					
Significant	Narayana WCPL, 2008	2	129	1 year	Acamprosate or Naltrexone or Topiramate	N/A
Insufficient	Sustained abstinence better for topiramate than other two medications					
Insufficient	None reported					

Table 4

Antidepressants

Primary Outcome	Source	JADAD	Sample Size	Length of Follow up	Intervention	Comparison
Significant	Brady KT, 2005	4	94	12 weeks	Sertraline	Placebo
Insufficient	None reported					
Insufficient	Percent drinking days, drinks per day, drinks per drinking day, heavy drinking days					
Significant	Farren CK, 2009	4	113	10 weeks	Naltrexone and Sertraline	Naltrexone and placebo
Insufficient	None reported					
Insufficient	Time to first drink, time to first heavy drinking					
Significant	Kranzler HR, 1995	3	101	12 weeks	Fluoxetine plus counseling	Placebo plus CBT
Insufficient	None reported					
Insufficient	Weeks to first drink, weeks to first heavy drinking day					
Significant	Kranzler HR, 2000	3	183	11 weeks	Naltrexone and counseling or Nefazodone and counseling	Placebo and counseling
Insufficient	None reported					
Insufficient	Abstinence, time to first drink, time to first heavy drinking episode, drinking frequency, drinks per day, heavy drinking frequency					
Significant	Kranzler HR, 2006	4	328	10 weeks	Sertraline and counseling	Placebo and counseling
Insufficient	None reported					
Insufficient	Percent days abstinent, drinks per week					
Significant	Mason BJ, 1996	4	71	6 months	Desipramine	Placebo
Insufficient	Time to relapse					
Insufficient	None reported					
Significant	Moak DH, 2003	4	82	12 weeks	Sertraline and counseling	Placebo and counseling
Insufficient	Drinks per drinking day					
Insufficient	Percent days abstinent					
Significant	O'Malley SS, 2008	4	101	16 weeks	Naltrexone and counseling or Naltrexone and Sertraline and counseling	Placebo and counseling
Insufficient	Total abstinence, naltrexone alone vs placebo					
Insufficient	Time to first heavy drinking day					

Primary Outcome	Source	JADAD	Sample Size	Length of Follow up	Intervention	Comparison
Significant	Pettinati HM, 2001	4	100	14 weeks	Sertraline	Placebo
Insufficient	Percent days drinking less for sertraline among subjects without lifetime depression Weeks in relapse, total abstinence					
Significant	Pettinati HM, 2010	5	170	14 weeks	Naltrexone and Placebo or Sertraline and Placebo, or Naltrexone and Sertraline (all subjects had counseling)	Placebo and counseling
Insufficient	Total abstinence greater and time to relapse longer for naltrexone and sertraline group then for other three groups None reported					
Significant	Powell BJ, 1995	4	216	6 months	Nortriptyline or Bromocriptine	Placebo
Insufficient	Fewer drinking days for nortriptyline group only among subjects with antisocial personality disorder Longest period of total abstinence					
Significant	Stedman, 2010	4	362	12 weeks	Quetiapine plus Lithium or Divalproex	Placebo plus Lithium or Divalproex
Insufficient	None reported Mean change in proportion of heavy drinking days					
Significant	Wetzel H, 2004 counseling (GC)	3	242	15 months	Nefazodone and either CBT or less intensive counseling (GC)	Placebo and either CBT or less intensive
Insufficient	Nefazodone and GC had more drinks per drinking occasion and more total alcohol consumed than the three other treatment groups Relapse rate, cumulative abstinence, drinking days, and number of relapses					

Table 5

Acamprosate

Primary Outcome	Source	JADAD	Sample Size	Length of Follow up	Intervention	Comparison
Significant	Anton RF, 2006	5	1383	16 weeks	Naltrexone, or Acamprosate with or without two types of counseling (CBI or MM)	Placebo
Insufficient	Higher % abstinent days in naltrexone + MM, CBI + MM and placebos, or both naltrexone and CBI+MM; Naltrexone reduced risk of heavy drinking days with MM but not CBI					
Insufficient	None reported					
Significant	Baltieri DA, 2003	4	75	24 weeks	Acamprosate	Placebo
Insufficient	Continuous abstinence					
Insufficient	None reported					
Significant	Baltieri DA, 2004	3	75	24 weeks	Acamprosate	Placebo
Insufficient	Abstinence					
Insufficient	None reported					
Significant	Besson J, 1998	4	118	360 days	Acamprosate	Placebo
Insufficient	Abstinence at 1 year					
Insufficient	None reported					
Significant	Chick J, 2000	5	581	6 months	Acamprosate	Placebo
Insufficient	Decreased alcohol craving					
Insufficient	Continuous abstinence					
Significant	De Sousa AA, 2005	2	100	8 months	Disulfiram	Acamprosate
Insufficient	Disulfiram group with decreased relapse to heavy drinking, greater time to relapse, and longer time to first drink					
Insufficient	Drinks per drinking occasion, total abstinent days					
Significant	De Wildt WAJM, 2002	3	248	28 weeks	Acamprosate	Acamprosate with counseling
Insufficient	None reported					
Insufficient	Total number of days abstinent, rates of continuous abstinence, abstinence during last 6 wks of treatment, time to first relapse, number of drinks per drinking day					
Significant	Gual A, 2001	4	296	180 days	Acamprosate	Placebo
Insufficient	Cumulative abstinent days					
Insufficient	None reported					

Primary Outcome	Source	JADAD	Sample Size	Length of Follow up	Intervention	Comparison
Significant	Hammarberg, 2004	4	70	6 months	Acamprosate and more intensive counseling	Acamprosate and less intensive counseling
Insufficient	None reported					
	Heavy drinking, cumulative number of drinking days, number of days to first drink, biomarkers					
Significant	Kiefer F, 2003	5	160	12 weeks	Naltrexone, Acamprosate, or Naltrexone and Acamprosate	Placebo
Insufficient	Active treatment groups had lower relapse to heavy drinking than placebo and longer time to first drinking					
	None reported					
Significant	Kiritze-Topor P, 2004	3	422	1 year	Acamprosate	Standard care
Insufficient	Alcohol Related Problem Questionnaire score at study end, change from baseline, number of subjects with no alcohol related problems					
	None reported					
Significant	Laaksonen E, 2008	1	243	52 weeks	Naltrexone or Acamprosate or supervised Disulfiram	N/A
Insufficient	Supervised disulfiram better than naltrexone or acamprosate at time to first heavy drinking day, days to first drink, number of abstinent days, average weekly alcohol intake					
	None reported					
Significant	Lhuire JP, 1985	3	85	3 months	Acamprosate	Placebo
Insufficient	Continuous abstinence					
	None reported					
Significant	Mason BJ, 2006	4	601	6 months	Acamprosate and counseling	Placebo and counseling
Insufficient	None reported					
	Percent of alcohol-free days					
Significant	Morley KC, 2006	5	169	12 weeks	Naltrexone or acamprosate	Placebo
Insufficient	None reported					
	Time to relapse, time to first drink, total alcohol consumption, cumulative abstinence					
Significant	Namkoong K, 2003	5	142	8 weeks	Acamprosate and counseling	Placebo and counseling
Insufficient	None reported					
	Continuous abstinence, relapse rate, percent days abstinent, percent heavy drinking days, drinks per drinking day					
Significant	Narayana WCPL, 2008	2	129	1 year	Acamprosate or Naltrexone or Topiramate	N/A
Insufficient	Sustained abstinence better for topiramate than other two medications					
	None reported					

Primary Outcome	Source	JADAD	Sample Size	Length of Follow up	Intervention	Comparison
Significant	Paille FM, 1995	3	538	12 months	Acamprosate and counseling	Placebo and counseling
Insufficient	Continuous abstinence at 6 months, days to first drink					
Insufficient	Continuous abstinence at 3, 9 and 12 months, days to first drink comparing acamprosate 1.3 gm to placebo					
Significant	Pelc I, 1997	4	188	6 months	Acamprosate and counseling	Placebo and counseling
Insufficient	Cumulative abstinence, total abstinence					
Insufficient	None reported					
Significant	Poldrugo F, 1997	4	246	6 months	Acamprosate	Placebo and counseling
Insufficient	Abstinence at 1, 3, and 6 months, relapse at 1, 3, and 6 months, total abstinence for 180 days					
Insufficient	None reported					
Significant	Rubio G, 2001	3	157	12 months	Naltrexone and counseling	Acamprosate and counseling
Insufficient	Total abstinence relapse rate, days to relapse, drinks per drinking day cumulative days abstinent					
Insufficient	Days to first drink					
Significant	Soyka M, 1994	1	272	48 weeks	Acamprosate	Placebo
Insufficient	Total abstinence					
Insufficient	None reported					
Significant	Soyka M, 2002	1	753	24 weeks	Acamprosate with different types of counseling	N/A
Insufficient	None reported					
Insufficient	Time to first relapse, abstinence rates					

Table 6

Naltrexone

Primary Outcome	Source	JADAD	Sample Size	Length of Follow up	Intervention	Comparison
Significant	Anton RF, 1999	4	131	12 weeks	Naltrexone	Placebo
Insufficient	Time to relapse, percent days abstinent, average drinks/drinking day					
Insufficient	None reported					
Significant	Anton RF, 2006	5	1383	16 weeks	Naltrexone or Acamprosate with or without counseling (MM and/or CBI)	Counseling (MM and/or CBI) with or without Placebo
Insufficient	Higher % abstinent days in naltrexone and MM, CBI and MM and placebo, or naltrexone and CBI and MM, naltrexone reduced risk of heavy drinking days with MM but not CBI					
Insufficient	Decreased heavy drinking on acamprosate vs placebo alone, with naltrexone, or CBI, or naltrexone and CBI					
Significant	Ballin J, 2003	4	118	6 months	Naltrexone with counseling	Placebo with counseling
Insufficient	Percent heavy drinking days lower for naltrexone group, time to first heavy drinking					
Insufficient	Percent drinking days, abstinence rate					
Significant	Baltieri DA, 2008	5	155	12 weeks	Topiramate	Naltrexone
Insufficient	Time to relapse, cumulative abstinent days, and heavy drinking weeks					
Insufficient	Abstinence, time to relapse, cumulative abstinent days, and heavy drinking weeks vs naltrexone					
Significant	Chick J, 2000	4	172	12 weeks	Naltrexone	Placebo
Insufficient	None reported					
Insufficient	Time to first heavy drinking					
Significant	Davidson D, 2007	2	149	3 months	Naltrexone and 1 of two types of counseling (either BST or MET)	None
Insufficient	Percent days abstinent greater for BST then MET					
Insufficient	None reported					
Significant	Davidson D, 2007	3	146	24 weeks	Naltrexone for 24 weeks	Naltrexone 12 weeks then Placebo 12 weeks
Insufficient	None reported					
Insufficient	Percent days abstinent, percent heavy drinking days					
Significant	De Sousa A, 2004	3	100	1 year	Disulfiram	Naltrexone
Insufficient	Disulfiram group greater 1 year abstinence, more abstinent days, greater time to first relapse, and fewer drinks per occasion					
Insufficient	Days to first drink					

Primary Outcome	Source	JADAD	Sample Size	Length of Follow up	Intervention	Comparison
Significant	Farren CK, 2009	4	113	10 weeks	Naltrexone and Sertraline	Naltrexone and Placebo
Insignificant	None reported Time to first drink, time to first heavy drinking					
Significant	Florez G, 2008	1	102	6 months	Topiramate	Naltrexone
Insignificant	None reported Abstinence, moderate drinking without associated problems					
Significant	Garbutt JC, 2005	5	899	6 months	Monthly Naltrexone injection	Monthly Placebo injection
Insignificant	Decrease in heavy drinking days None reported					
Significant	Gastpar M, 2002	3	171	12 weeks	Naltrexone	Placebo
Insignificant	None reported Days to first heavy drinking episode					
Significant	Guardia J, 2002	4	202	12 weeks	Naltrexone	Placebo
Insignificant	Return to heavy drinking None reported					
Significant	Heinala P, 2001	3	121	12 weeks	Naltrexone with coping skills or with supportive therapy	Placebo with coping skills or with supportive therapy
Insignificant	Relapse to heavy drinking in coping skills group Relapse to heavy drinking in supportive therapy group					
Significant	Kiefer F, 2003	5	160	12 weeks	Naltrexone, Acamprosate, or Naltrexone and Acamprosate	Placebo
Insignificant	Active treatment groups had lower relapse to heavy drinking than placebo and longer time to first drinking None reported					
Significant	Killeen TK, 2004	3	145	12 weeks	Naltrexone and counseling	Placebo and counseling
Insignificant	None reported Percent days drinking, drinks/drinking day, drinks/day, heavy drinking days, time to first heavy drinking					
Significant	Kranzler HR, 2000	3	183	11 weeks	Naltrexone and counseling or Nefazodone and counseling	Placebo and counseling
Insignificant	None reported					

Primary Outcome	Source	JADAD	Sample Size	Length of Follow up	Intervention	Comparison
Insufficient	Abstinence, time to first drink, time to first heavy drinking episode, drinking frequency, drinks per day, heavy drinking frequency					
	Kranzler HR, 2004	4	315	3 months	Monthly Naltrexone injection	Monthly Placebo injection
Significant	Time to first drinking day, total abstinence, number of abstinent days					
Insufficient	Time to first heavy drinking day, any heavy drinking, number of heavy drinking days					
	Krystal JH, 2001	4	627	12 months	Naltrexone for 12 months or Naltrexone for 3 months followed by Placebo for 9 months	Placebo for 12 months
Significant	None reported					
Insufficient	Time to relapse, relapse rate, percent of drinking days, drinks per drinking day					
	Laaksonen E, 2008	1	243	52 weeks	Naltrexone or Acamprostate or supervised disulfiram	N/A
Significant	Supervised disulfiram better than naltrexone or acamprostate at time to first heavy drinking day, days to first drink, number of abstinent days, average weekly alcohol intake					
Insufficient	None reported					
	Latt NC, 2002	4	107	12 weeks	Naltrexone	Placebo
Significant	Relapse rate, time to relapse					
Insufficient	Drinking days per week; Mean alcohol consumption; Mean craving scores					
	Longabaugh R, 2009	5	174	24 weeks	Naltrexone for 6 months plus counseling	Naltrexone for 3 months plus counseling
Significant	Time to first drink and time to first heavy drinking day					
Insufficient	None reported					
	Monti PM, 2001	4	165	12 weeks	Naltrexone and counseling	Placebo and counseling
Significant	Heavy drinking days, fewer drinks on drinking days for 12 weeks but not for 9 months thereafter fewer relapse days, fewer heavy drinking days at 6 & 12 months (among medication compliant subjects)					
Insufficient	All subjects (compliant and non-compliant), no difference in relapse					
	Morley KC, 2006	5	169	12 weeks	Naltrexone or Acamprostate	Placebo
Significant	None reported					
Insufficient	Time to relapse, time to first drink, total alcohol consumption, cumulative abstinence					
	Morris PL, 2001	4	111	12 weeks	Naltrexone	Placebo
Significant	Relapse rate					
Insufficient	Time to relapse, time to first drink					

Primary Outcome	Source	JADAD	Sample Size	Length of Follow up	Intervention	Comparison
Significant	Narayana WCPL, 2008	2	129	1 year	Acamprosate or Naltrexone or Topiramate	N/A
Insufficient	Sustained abstinence better for topiramate than other two medications					
Insufficient	None reported					
Significant	O'Malley SS, 2003	2	197	34 weeks	Naltrexone and 1 of two types of counseling (either CBT or PCM)	Placebo and 1 of two types of counseling (either CBT or PCM)
Insufficient	Percent days abstinent greater for CBT vs PCM, persistent heavy drinking less for naltrexone vs placebo in PCM group					
Insufficient	Persistent heavy drinking not different between PCM and CBT; total percent days abstinent not different between PCM and CBT, maintaining low level of heavy drinking (i.e., <2 heavy drinking days in a 28 day period) not different between naltrexone and placebo in the CBT group					
Significant	O'Malley SS, 2007	4	103	12 weeks	Naltrexone and counseling	Placebo and counseling
Insufficient	None reported					
Insufficient	Time to first drinking day, time to first day of heavy drinking, % of participants who continued to meet criteria for alcohol dependence					
Significant	O'Malley SS, 2008	4	101	16 weeks	Naltrexone and counseling or Naltrexone and Sertraline and counseling	Placebo and counseling
Insufficient	Total abstinence, naltrexone alone vs placebo					
Insufficient	Time to first heavy drinking day					
Significant	Oslin DW, 2002	3	183	9 months	Naltrexone or Placebo in older subjects	Naltrexone or Placebo in younger subjects
Insufficient	Time to relapse					
Insufficient	None reported					
Significant	Oslin DW, 2008	4	240	24 weeks	Naltrexone and counseling (CBT)	Naltrexone and other counseling (BRENDA or medication clinic model)
Insufficient	Number of days of any alcohol use, any drinking or heavy drinking during month, number of days of heavy drinking					
Insufficient	None reported					
Significant	Petrakis IL, 2005	3	254	12 weeks	Naltrexone and counseling or Naltrexone and Disulfiram and counseling	Placebo and counseling
Insufficient	Drinking days per week less for active medication vs placebo, consecutive days of abstinence more for active medication vs placebo					
Insufficient	Percent days abstinent, percent heavy drinking days, total abstinence, no difference between groups on active medication					
Significant	Petrakis IL, 2006	4	254	12 weeks	Naltrexone and counseling or Naltrexone and Disulfiram and counseling	Placebo and counseling
Insufficient	Percent of heavy drinking days less for active medication vs placebo, consecutive days of abstinence more for active medication vs placebo					
Insufficient	Total abstinence, no difference between groups on active medication					

Primary Outcome	Source	JADAD	Sample Size	Length of Follow up	Intervention	Comparison
	Petrakis I, 2007	3	254	12 weeks	Naltrexone and counseling or Naltrexone and Disulfiram and counseling	Placebo and counseling
Significant	Drinking days per week less for active medication vs placebo, consecutive days of abstinence more for active medication vs placebo					
Insignificant	Percent heavy drinking days, total abstinence, no difference between groups on active medication					
	Pettinati HM, 2010	5	170	14 weeks	Naltrexone and counseling or sertraline and counseling or naltrexone and sertraline and counseling	Placebo and counseling
Significant	Total abstinence greater for naltrexone and sertraline group then for other three groups, time to relapse longer (days) for naltrexone and sertraline group than for the other three groups					
Insignificant	None reported					
	Rubio G, 2001	3	157	12 months	Naltrexone and counseling	Acamprosate and counseling
Significant	Total abstinence relapse rate, days to relapse, drinks per drinking day cumulative days abstinent					
Insignificant	Days to first drink					
	Rubio G, 2002	1	60	12 weeks	Naltrexone and counseling	Counseling alone
Significant	Number of heavy drinking days at 12 month follow up, total number of drinks during follow up phase (12 weeks–12 months)					
Insignificant	Days drinking, drinks per drinking day, having at least one day of heavy drinking during initial 12 weeks and at 12 month follow up, time to first heavy drinking day during initial 12 weeks					
	Volpicelli JR, 1992	4	70	12 weeks	Naltrexone and counseling	Placebo and counseling
Significant	Drinking days per week, relapse rate, time to relapse					
Insignificant	Abstinence					

Table 7

Less Studied Medications

Primary Outcome	Source	JADAD	Sample Size	Length of Follow up	Intervention	Comparison
Significant	Addolorato G, 2007	5	148	12 weeks	Baclofen	Placebo
Insufficient	Total abstinence, number of abstinent days					
Insufficient	None reported					
Significant	Anton RF, 2008	3	295	12 weeks	Aripiprazole	Placebo
Insufficient	None reported					
Insufficient	Percent days abstinent					
Significant	Garbutt JC, 2010	5	80	12 weeks	Baclofen	Placebo
Insufficient	None reported					
Insufficient	Percent heavy drinking days					
Significant	Johnson BA, 2000	4	321	12 weeks	Ondansetron	Placebo
Insufficient	In early onset alcoholics on 4 mg/kg dose, all drinking measures improved (drinks/day, drinks/drinking day, % days abstinent, total days abstinent)					
Insufficient	None reported					
Significant	Karhuvaara S, 2007	4	403	28 weeks	Nalmefene	Placebo
Insufficient	Mean number of heavy drinking days					
Insufficient	None reported					
Significant	Mason BJ, 1999	4	105	12 weeks	Nalmefene	Placebo
Insufficient	Relapse to heavy drinking					
Insufficient	None reported					
Significant	Sellers EM, 1994	4	71	6 weeks	Ondansetron	Placebo
Insufficient	Decreased drinks per drinking day when heavier drinkers were excluded					
Insufficient	None reported					