Oregon State University College of Pharmacy
Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-945-5220 | **Fax** 503-947-1119

Oregon Health Authority

Alcohol Use Disorder Treatment: Abbreviated Class Review

Month/Year of Review: July 2014 **End date of literature search:** June 2014
Drugs Included: Acamprosate (Campral®), disulfiram (Antabuse®), and naltrexone injectable and oral (Vivitrol®, Revia®)

Current Management: Naltrexone depot injection (Appendix 1) is non-preferred with prior authorization criteria to expand access to opioid addiction treatment, allow for use in alcohol use disorder until a subsequent full evidence review can be presented, deny for use in pain and for below the line indications.

Research Questions:

- What is the comparative efficacy and safety evidence comparing different pharmacologic treatment options for alcohol use disorder?
- What is the efficacy and safety evidence of different pharmacologic treatment options for alcohol use disorder when compared to placebo or active control?
- Are there subgroups of patients where one treatment option may be more effective or safer?

Conclusions:

- There is moderate level of evidence from five meta-analyses, that oral naltrexone reduced the chance of relapses measured by return to heavy drinking (NNT = 13)[1], any drinking (NNT = 25)[1], drinking days and reduced heavy drinking days, drinking days or number of drinks per drinking days[1–5] One meta-analysis indicated naltrexone increased the chance of abstinence compared with placebo with psychosocial co-interventions (OR: 1.46, 95% CI [1.07, 2.00]; p = 0.00182)[3] and one analysis[4] suggested oral naltrexone was associated with a significant decrease in risk of relapse to heavy drinking in non-abstinent drinkers compared to placebo (NNT = 8)[4].
- There is moderate level of evidence from four meta-analyses, that acamprosate reduced the risk of relapse to heavy drinking after detoxification in alcohol dependent patients compared to placebo.[1,4,6] It significantly reduced the risk of any drinking with NNT of 9[6] or 10[1], significantly reduced the risk of relapse to heavy drinking with NNT of 9[4], significantly reduced the risk of first drinking after abstinence with NNT of 7[4], and in non-abstinent drinkers there was no significant difference in risk of heavy drinking between acamprosate and placebo (RR 0.98, 95% CI: 0.94, 1.02)[4].
- There is moderate level of evidence[1,6] that there is no statistically significant difference between acamprosate and oral naltrexone (50-100mg/day) for consumption outcomes (return to any drinking RR 1.03 (95% CI 0.96 to 1.10); cumulative abstinence duration MD 2.98 (95% CI -7.45 to 13.42); return to heavy drinking RR 1.04 (95% CI 0.95 to 1.15))[6]after detoxication from analyses on head-to-head comparisons.
- There is low strength of evidence that naltrexone injection decreases return to any drinking and return to heavy drinking, and insufficient evidence for percent drinking days.

- There is moderate level of evidence that the side effects of naltrexone and acamprosate were mainly gastrointestinal and sedative effects[1,2]. In head-to-head studies, the risk of headache was higher for naltrexone than for acamprosate (risk difference -0.06; 95% CI: -0.15, 0.03)[1].
- There is moderate level of evidence from one meta-analysis that men and women did not differ on any measure of acamprosate efficacy, safety, or tolerability.[7]
- There is low quality evidence suggesting supervised disulfiram has some beneficial effect on short-term abstinence and days until relapse when compared to placebo, nothing or other abstinence-supportive treatments.[1,8] There is insufficient evidence that dilsulfiram improves return to heavy drinking, percent of days drinking, quality of life or function, or mortality.
- There is insufficient evidence comparing depot injection of naltrexone to oral naltrexone form for efficacy and safety.
- There is insufficient evidence with any treatment on improving health outcomes, including accidents, injuries, quality of life, function, or mortality.

Recommendations:

- Combine the alcohol dependence agents and opioid dependence into one PDL class. Oral naltrexone and acamprosate should be considered for inclusion on PDL based on moderate level evidence to support the similar efficacy and safety for the treatment of alcohol use disorder.
- Maintain injectable naltrexone as a treatment option for those patients unable or unwilling to take oral therapy or are not likely to adhere with oral naltrexone therapy.
- Maintain naltrexone depot injection prior authorization criteria (Appendix 1).
- Designate disulfiram as non-preferred and grandfather clients for 12 months.

Reason for Review:

Naltrexone depot injection was recently reviewed for its role in the treatment of opioids dependence. There are several agents including naltrexone available for the treatment of alcohol use disorder. However none of these agents are currently on the Preferred Drug List (PDL). This review will examine their place in therapy for PDL placement.

Background:

Alcohol use disorder is a cluster of somatic, behavioral and physical symptoms, which are classified as mild, moderate and severe categories based upon the presence of a pre-defined list of symptoms.[9] Alcohol misuse is a widespread psychiatric disorder with lifetime prevalence estimates of 7-12.5% in most Western countries.[10,11] In the United States, about 18 million people have an alcohol use disorder.[12] Alcohol use disorder is reported to be the third leading preventable cause of death in the US, which results in significant morbidity and approximately 88,000 deaths annually. Excessive alcohol use is responsible for 2.5 million years of potential life lost (YPLL) annually, or an average of about 30 years of potential life lost for each death.

Although abstinence is the ultimate outcome for the treatment of alcohol use disorder, goals such as decreasing the drinking incidence, shortening the course, reducing episode severity, and preventing relapse are essential. Recently reduction in the frequency of heavy drinking was recognized as the major

factor for decreasing disease burden and improving quality of life.[13] Traditionally the most recognized strategy for the treating alcohol use disorder was specialty treatment programs using psychosocial therapy.[14] However using psychotherapy without an adjunct pharmacological treatment gives a poor clinical outcome, with up to 70% of patients resuming drinking within a year.[2,15,16] Medications currently approved by the Food and Drug Administration (FDA) for the treatment of alcohol use disorder include disulfiram, naltrexone and acamprosate.

The Substance Abuse and Mental Health Services Administration (SAMHSA) provides robust and comprehensive treatment guidelines/protocols for the management of alcohol disorder. Its treatment Improvement Protocol (TIP) 49[17] recognizes three pharmacological options: disulfiram, naltrexone, and acamprosate.

Disulfiram

Disulfiram was the first medication approved by the FDA to treat chronic alcohol dependence. Disulfiram is an alcohol-aversive or alcohol-sensitizing agent, which causes an acutely toxic physical reaction when mixed with alcohol. Disulfiram inhibits the liver enzyme aldehyde dehydrogenase. Alcohol intake during treatment leads to the accumulation of acetaldehyde, which possibly causes the disulfiram-ethanol reaction in the form of increased pulse and respiration, tachycardia, facial flushing, nausea, committing, hypotension, and cardiovascular collapse in the worst case.[18] Disulfiram has only limited clinical utility for patients with high motivation, good health and good cooperation. Even in highly motivated individuals, disulfiram may only partially improve alcohol-dependent patients in some aspects such as drinking frequency and amount of alcohol consumption[19].

Naltrexone

Oral naltrexone was approved by the FDA in 1994 for the treatment of alcohol use disorder. It reduces both the rewarding effects of alcohol and the craving for it. In 2010 an extended-release, monthly, intramuscular injection of naltrexone (Vivitrol®) was approved by the FDA to overcome the documented poor compliance with the oral product. Naltrexone is a highly effective opioid antagonist that binds to mu-receptors. Consequently the endorphins released as a result of alcohol drinking can no longer stimulate the opioid receptors and cause euphoria.[20] Patients notice the futility of drinking and limit their intake of alcohol.

Acamprosate

The exact mechanism of action of acamprosate has not been clearly established, but it is thought that it interacts with the glutamate neurotransmitter system, reducing and normalizing the pathologic glutamatergic hyperactivity that occurs during protracted withdrawal from alcohol. It is hypothesized that this normalization leads to a reduction of common symptoms of protracted, or post-acute, withdrawal such as insomnia, anxiety, and restlessness—symptoms that may contribute to a patient's return to alcohol use.[21,22] It was also proposed that patients who returned to drinking while taking acamprosate drank less, and less frequently, than those taking placebo.[23]

Methods:

A MEDLINE Ovid search was conducted using the terms: alcohol dependence, alcohol use disorder, disulfiram, acamprosate and naltrexone. The search was limited to meta-analysis, English language, and to studies conducted in humans in the last 10 years. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, Oregon Evidence-based Practice Center, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs (VA) and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were searched for high quality and relevant systematic reviews. The AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

Systematic Reviews and Meta-analyses: (See Appendix 2 for abstract)

Medical Treatment of Alcohol Use Disorder

AHRQ (2014 report)[1] conducted a systematic review and meta-analysis of the efficacy, comparative effectiveness, and harms of medications (both FDA-approved and others) for adults with alcohol-use disorders, and to evaluate the evidence from primary care settings. The review included 130 studies. Most patients met criteria for alcohol dependence; mean ages were in the 40s. Moderate strength of evidence (SOE) found both acamprosate and oral naltrexone are effective for improving alcohol consumption outcomes NNT 12 and 20, respectively). For return to heavy drinking, evidence did not support the efficacy of acamprostae. Oral naltrexone was efficacious for return to heavy drinking (NNT 12). There was low SOE that injectable naltrexone is efficacious for reducing percentage of heavy drinking days. For acamprosate and naltrexone including both oral and IM forms, numbers needed to treat (NNT) to prevent one person from returning to any drinking were 10 and 25, respectively (moderate strength of evidence (SOE)). NNT to prevent one person from returning to heavy drinking was 13 for naltrexone (moderate SOE). The meta-analyses of 3 head-to-head trials found no statistically significant difference between acamprosate and oral naltrexone (50-100mg/day) for consumption outcomes after detoxication (moderate SOE). Compared with placebo, patients treated with acamprosate had a higher risk of anxiety, diarrhea, and vomiting. Those treated with naltrexone had a higher risk of dizziness, nausea, and vomiting. In head-to-head studies, the risk of headache was higher for naltrexone than for acamprosate (risk difference -0.06; 95% CI: -0.15, 0.03). Evidence was insufficient to determine comparative effectiveness of medications for subgroups. The authors concluded that acamprosate and naltrexone including both oral and IM forms have the best evidence of efficacy for improving alcohol consumption outcomes for patients with alcohol dependence; and that head-to-head trials have not consistently established superiority of one medication over the others. Thus, other factors may contribute to medication choices, such as frequency of administration, potential adverse events, coexisting symptoms, and availability of treatments.

Miller PM et. al. (2011)[5] performed a systematic review to examine the efficacy of pharmacological interventions alone or in combination with brief psychosocial interventions for the treatment of alcohol dependence in primary care and specialist medical settings. Eighty-five RCTs (18,937 participants) were included in the review. Follow-up ranged from 12 weeks to 15 months.

Disulfiram (11 RCTs): Nine trials were used to draw conclusions as two used a method of administration without proven efficacy. One of the nine trials had lower potential for bias. It was unclear whether disulfiram was an effective intervention. There were mixed findings for all comparisons with placebo and active interventions. Some outcome measures showed a statistically significant benefit and others did not.

Naltrexone (31 RCTs): Seventeen trials were judged to have a lower potential for bias. Oral Naltrexone was superior to placebo in most trials (25 trials), but no difference or mixed findings were found in some (five trials). Naltrexone combined with sertraline (an antidepressant) was effective in one trial that

included participants with alcohol dependence and depression but not in another trial where the participants were not depressed. The two trials included depot injections and both found statistically significant benefit compared to placebo injections.
Acamprosate (24 RCTs): Fifteen trials were rated as having a low potential for bias. There were mixed findings in 11 trials that compared acamprosate with placebo. Six of these trials found some benefits for acamprosate and five trials found either no significant differences or mixed findings. There were mixed findings for the combination of acamprosate and naltrexone (two trials). One trial found no difference with naltrexone compared with other medications. The other trials found acamprosate to be less effective than naltrexone (one trial) and disulfiram (two trials). Adjunctive psychosocial interventions (11 RCTs): Most studies of pharmacological interventions summarised above included adjunctive psychosocial interventions. Eleven trials examined this separately and seven were judged to be of low risk of bias. There were mixed findings concerning the benefits of adjunctive psychosocial treatment. The authors concluded although effects are modest, pharmacological treatment for alcohol dependence with brief support or more intensive psychosocial interventions can be effective in primary care and specialist settings. Overall the review lacks clarity for the inclusion criteria and the lack of detail provided for outcome data mean that the authors' conclusions may not be reliable.

Acamprosate and Naltrexone Reviews:

Meta-analysis by Rösner S et. al (Jan. 2008)[4] included 21 RCTs evaluating acamprosate (n=5,280) and 20 RCTs evaluated oral naltrexone at 50mg/day (n=2,182). The primary review outcomes were: return to any drinking (defined as the first drink after a period of continuous abstinence); and return to heavy drinking (as defined in individual studies). Secondary review outcomes included days drinking per week, quantity consumed per day, time to first drink, time to first relapse and gamma-glutamyl transpeptidase (GGT) level. Naltrexone studies used a drug dose of 50 mg/day. All studies used psychosocial co-interventions concurrently for all groups. Treatment duration ranged from 51 days to one year. The mean age of patients was between 36 and 58 years. The risk of having a first drink after abstinence was reduced significantly with acamprosate compared to placebo (RR 0.84, 95% CI: 0.78, 0.91; NNT 8) and with naltrexone compared to placebo (RR 0.93, 95% CI: 0.88, 0.99; NNT 17). Significant heterogeneity was found for both analyses: $p<0.00001$, I^2 83.6% for acamprosate; and $p=0.08$, I^2 33.8% for naltrexone. The risk of relapse to heavy drinking was significantly reduced with acamprosate compared to placebo (RR 0.82, 95% CI: 0.73, 0.92; NNT 9) and for naltrexone compared to placebo (RR 0.80, 95% CI: 0.71, 0.91; NNT 8). Significant heterogeneity was found for both analyses ($p<0.0001$, I^2 75.5% for acamprosate and $p< 0.0001$, I^2 64.6% for naltrexone). For non-abstinent drinkers there was no significant difference in the risk of heavy drinking between acamprosate and placebo (RR 0.98, 95% CI: 0.94, 1.02), but the risk of heavy drinking was significantly reduced with naltrexone compared to placebo (RR 0.88, 95% CI: 0.80, 0.96; NNT to prevent one additional relapse to heavy drinking was nine). The funnel plot was asymmetrical suggesting the potential for publication bias, but Begg's test showed no significant evidence ($p=0.09$ and 0.31 for the two main analyses). The authors concluded abstinence rates were significantly increased by both naltrexone and acamprosate, but only naltrexone was associated with a significant decrease in the risk of relapse to heavy drinking in non-abstinent drinkers.

Disulfiram

Jørgensen,CH., et al (2011).[8] This systematic review included eleven randomized controlled trials (RCTs) with a total of 1,527 patients. The review compared disulfiram treatment with placebo, none or other abstinence-supportive treatments. Overall, 6 studies reported a significantly better effect on abstinence for patients treated with disulfiram. Six of 9 studies measuring secondary outcomes reported that patients treated with disulfiram had significantly more

days until relapse and fewer drinking days, respectively. The quality of the included studies was moderate. Heterogeneity was significant in most of the meta-analyses, but statistically significant results were found regarding the effect of disulfiram versus placebo over 12 months and unsupervised disulfiram versus other or no treatment. The vast majority of statistically significant studies were of shorter duration, while only 3 studies of 12 months were significant regarding more days until relapse and/or reduction in drinking days. The authors concluded supervised treatment with disulfiram has some effect on short-term abstinence and days until relapse as well as number of drinking days when compared with placebo, none, or other treatments for patients with alcohol dependency or abuse. Long-term effect on abstinence has not been evaluated yet. The authors suggested the need for more homogeneous and high-quality studies in the future regarding the efficacy of disulfiram.

Naltrexone

Cochrane Review by Rösner et al. (October 2010)[2]

The aim of this systematic review was to evaluate the effectiveness and tolerability of opioid antagonists (i.e. naltrexone/nalmefene) compared to placebo or active control in the treatment of alcohol dependence. A minimum of four weeks daily treatment was required to ensure an adequate implementation of the intervention. To allow clinically relevant conclusions on treatment stability, post-treatment evaluations had to include at least 12 weeks of observation. The study end-points of the primary effectiveness outcomes including, return to heavy drinking, return to any drinking, or drinking days were considered as constitutive for effectiveness conclusions. Based on a total of 50 RCTs with 7,793 patients, naltrexone including both oral (43 RCTs) and IM (4 RCTs) forms reduced the risk of heavy drinking versus the placebo group, RR 0.83 (95% CI 0.76 to 0.90) and decreased drinking days by about 4%, MD -3.89 (95% CI -5.75 to -2.04). Side effects of naltrexone were mainly gastrointestinal problems (e.g. nausea: RD 0.10; 95% CI 0.07 to 0.13) and sedative effects (e.g. daytime sleepiness: RD 0.09; 95% CI 0.05 to 0.14). Based on a limited study sample, the effects of injectable naltrexone and nalmefene missed statistical significance. Effects of industry-sponsored studies, RR 0.90 (95% CI 0.78 to 1.05) did not significantly differ from those of non-profit funded trials, RR 0.84 (95% CI 0.77 to 0.91) and the linear regression test did not indicate publication bias (P = 0.765). The authors concluded naltrexone based on analysis on both forms appears to be an effective and safe strategy in alcoholism treatment. Even though the sizes of treatment effects might appear moderate in their magnitudes, these should be valued against the background of the relapsing nature of alcoholism and the limited therapeutic options currently available for its treatment.

Meta-analysis by Jarosz et.al. (May 2013)[3]

The objective of this article was to review the clinical effectiveness of oral naltrexone as an adjunct therapy to psychotherapy for the treatment of alcohol dependency. This meta-analysis included 2,427 patients in 17 RCTs with a short-term observation period (12–16 weeks), which constitutes the core of the meta-analysis. Based on the results of the meta-analysis, naltrexone increased the chance of abstinence and reduced the chance of relapse in alcohol-dependent patients. The OR of abstinence rate was 1.46, 95% CI [1.07, 2.00] and reached statistical significance (p =.00182). The OR of relapse was 0.48, 95% CI [0.36, 0.64], demonstrating statistical significance (p <.0001) in favor of naltrexone. No statistically significant differences between groups in terms of efficacy and safety assessment were observed for medium and long observational periods. The authors acknowledge that the studies included in this analysis differ with respect to type of psychotherapy reported. Moreover, the same type of psychotherapy modality can differ in its structure and intensity.

They concluded oral naltrexone (50 mg once daily) is an effective and safe therapy for the treatment of alcohol-dependent patients who are simultaneously undergoing psychotherapy.

Acamprosate

The Cochrane Review by Rösner S et. al (Sept. 2010)[6] Twenty-two RCTs with 6,915 participants fulfilled the criteria of inclusion and were included in the review. Compared to placebo, acamprosate was shown to significantly reduce the risk of any drinking, RR 0.86 (95% CI 0.81 to 0.91); NNT 9 (95% CI 6.66 to 14.28) and to significantly increase the cumulative abstinence duration MD 10.94 (95% CI 5.08 to 16.81). Diarrhea was the only side effect that was more frequently reported under acamprosate than placebo RD 0.11 (95% 0.09 to 0.13); NNT 9 (95% CI 7.69 to 11.11). Effects of industry-sponsored trials RR 0.88 (95% 0.80 to 0.97) did not significantly differ from those of non-profit funded trials RR 0.88 (95% CI 0.81 to 0.96). In addition, the linear regression test did not indicate a significant risk of publication bias (p = 0.861). The meta-analytic integrations based on head-to-head comparisons between acamprosate and oral naltrexone (50-100mg/day) did not indicate a superiority of one or the other drug (return to any drinking RR 1.03 (95% CI 0.96 to 1.10); cumulative abstinence duration MD 2.98 (95% CI -7.45 to 13.42); return to heavy drinking RR 1.04 (95% CI 0.95 to 1.15)). The authors concluded acamprosate appears to be an effective and safe treatment strategy for supporting continuous abstinence after detoxification in alcohol dependent patients. The authors recognized the treatment effect sizes appear to be rather moderate, and they recommended the use of acamprosate should be valued against the background of the relapsing nature of alcoholism and taking into consideration of the limited therapeutic options currently available for its treatment.

Special Population: Sex-specific Meta-analysis

Mason B et. al. (March 2012)[7]: The objective of this study was to assess sex-specific differences in the efficacy, safety, and tolerability of acamprosate compared to placebo in the treatment of women and men with alcohol dependence. A sex-specific meta-analysis was conducted based on individual patient data. Individual records were obtained from 1,317 women and 4,794 men who participated in 22 eligible studies conducted in 18 countries. A meta-analyses of the data found a significant beneficial effect of acamprosate relative to placebo across all 4 efficacy end points: an incremental gain of 10.4% (95% CI 7.1 to 13.7, $p < 0.001$) in percentage of abstinent days, an incremental gain of 11.0% (7.4 to 14.6, $p < 0.001$) in percentage of no heavy drinking days, an odds ratio of 1.9 (1.6 to 2.2, $p < 0.001$) for rate of complete abstinence, and an odds ratio of 1.9 (1.6 to 2.3, $p < 0.001$) for rate of no heavy drinking, over the study duration. Acamprosate was also associated with significantly higher rates of treatment completion ($p = 0.004$) and medication compliance ($p < 0.001$) than placebo. Men and women did not differ on any measure of acamprosate efficacy, safety, or tolerability. The authors concluded that acamprosate has a significant effect compared with placebo in improving rates of abstinence and no heavy drinking in both women and men with alcohol dependence. Further, acamprosate was associated with significantly higher rates of treatment completion and medication compliance than placebo among both women and men and had a comparable safety and tolerability profile.

Treatment guidelines:

National Institute for Health and Clinical Excellence (NICE) released guidelines on diagnosis, assessment and management of harmful drinking and alcohol dependence in 2011.[24] The NICE guidelines recommended using benzodiazepines such as diazepam or chlordiazepoxide for assisted withdrawal. After a

successful withdrawal, consider offering 1) acamprosate or oral naltrexone in combination with an individual psychological intervention (cognitive behavioral therapies, behavioral therapies or social network and environment-based therapies) focused specifically for alcohol miseuse or 2) offering Disulfiram in combination with a psychological intervention to users who have a goal of abstinence but acamprosate and oral naltrexone are not suitable or prefer disulfiram and understand the relative risk of taking the drug.

VA/DoD 2009 updated treatment guideline on substance abuse have the following recommendations on pharmacotherapy for alcohol dependence:[25] 1)routinely consider oral naltrexone, an opioid antagonist, and/or acamprosate for patients with alcohol dependence (level A); 2)medications should be offered combined with addiction-focused counseling(level A); 3)Injectable naltrexone should be considered when medication adherence is a significant concern in treating alcohol dependence and should be combined with addiction-focused counseling (level A); 4)if patient does not respond to one of the approved medications, a trial on one of the other approved medications is warranted; 5) because of the risk of significant toxicity and limited evidence of effectiveness, risk and benefits of disulfiram should be considered and disulfiram should only be used when abstinence is the goal and when combined with addiction-focused counseling (level B). The informed consent discussion with the patient should be documented.

World Federation of Societies of Biological Psychiatry (WFSBP) released guidelines for the treatment of alcoholism in 2008.[26] Among the medications used as relapse prevention, disulfiram has level C strength of evidence on its efficacy whereas both acamprosate and naltrexone have level A grading. The guidelines also recognized the value of using pharmacotherapy in conjunction with psychosocial treatment to increase abstinence rates and relapse rates.

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Appendix 1: Vivitrol Prior Authorization Criteria

Naltrexone Extended Release Inj. (Vivitrol)

Goal(s):

- Promote safe and cost effective therapy for the treatment of alcohol and opioid dependence.

Length of Authorization: Initial – 3 months; Renewal – one year

Covered Alternatives: Acamprosate, naltrexone tablets, disulfiram

Approval Criteria		
1. What is the diagnosis?	Record ICD-9 code	
2. Does the member have a diagnosis of alcohol dependence (DSM-IV-TR) or alcohol use disorder (AUD; DSM5)?	**Yes:** Go to #3.	**No:** Go to #4
3. Has the requesting prescriber provided documentation and/or confirmation of abstinence from alcohol as assessed by the provider and/or objective testing?	**Yes:** Go to #6	**No:** Deny, medical appropriateness. Patients must have demonstrated alcohol abstinence prior to administration.
4. Does the member have a diagnosis of opioid dependence (DSM-IV-TR) or opioid use disorder (OUD; DSM5)?	**Yes:** Go to #5	**No:** Deny, medical appropriateness. Naltrexone extended release injection is only approved for alcohol and opioid dependence.
5. Has the patient tried and failed other oral agents for the treatment of opioid dependency (buprenorphine, methadone) **OR** Is the patient unable to take oral therapy or d~~D~~oes the patient require injectable therapy due to adherence issues?	**Yes:** Go to #6	**No:** Deny, medical appropriateness.

Approval Criteria		
6. Is the member part of a comprehensive treatment program for substance abuse that includes a psychosocial support system?	**Yes:** Go to #7	**No:** Deny, medical appropriateness. Naltrexone extended release injection therapy must be part of a comprehensive treatment program including psychosocial support.
7. Has the patient received any opioid prescription within the last 30 days from a prescriber other than the requesting provider based on prescription claims history?	**Yes:** Notify requesting provider of the opioid prescriber, drug, dose, prescription date and the day supply; Go to #8.	**No:** Go to #8
8. Has the patient abstained from the use of any opioids for at least 7 to 10 days, including street opioids such as heroin or prescription opioids as assessed by the provider and/or objective testing?	**Yes:** Approve for 3 months for initial therapy, 12 months for continuation therapy	**No:** Deny, medical appropriateness. Patient must be opioid free for 7 to 10 days prior to administration to minimize risk of acute opioid withdrawal syndrome.

Appendix 2: Abstract of Selected Systemic Reviews and Meta-analyses

1. **Pharmacotherapy for adults with alcohol use disorders in outpatient settings: A systematic review and meta-analysis.**
Jonas DE, Amick HR, Feltner C, et al. *JAMA*. 2014;311(18):1889-1900.

Abstract

Importance: Alcohol use disorders cause substantial morbidity and early mortality yet remain greatly undertreated. Medications are considerably underused.

Objective: To conduct a systematic review and meta-analysis of the benefits and harms of medications (US FDA-approved and others) for adults with alcohol use disorders.

Data Sources: PubMed, Cochrane Library, PsycINFO, CINAHL, EMBASE, FDA website, and clinical trials registries (January 1, 1970, to March 1, 2014).

Study Selection: Two reviewers selected randomized clinical trials (RCTs) with at least 12 weeks' duration that reported eligible outcomes and head-to-head prospective cohort studies reporting health outcomes or harms.

Data Extraction and Synthesis: We conducted meta-analyses using random-effects models and calculated numbers needed to treat for benefit (NNTs) or harm (NNHs).

Main Outcomes and Measures: Alcohol consumption, motor vehicle crashes, injuries, quality of life, function, mortality, and harms.

Results: We included 122 RCTs and 1 cohort study (total 22,803 participants). Most assessed acamprosate (27 studies, n = 7519), naltrexone (53 studies, n = 9140), or both. The NNT to prevent return to any drinking for acamprosate was 12 (95% CI, 8 to 26; risk difference [RD], -0.09; 95% CI, -0.14 to -0.04) and was 20 (95% CI, 11 to 500; RD, -0.05; 95% CI, -0.10 to -0.002) for oral naltrexone (50 mg/d). The NNT to prevent return to heavy drinking was 12 (95% CI, 8 to 26; RD -0.09; 95% CI, -0.13 to -0.04) for oral naltrexone (50 mg/d). Meta-analyses of trials comparing acamprosate to naltrexone found no statistically significant difference between them for return to any drinking (RD, 0.02; 95% CI, -0.03 to 0.08) or heavy drinking (RD, 0.01; 95% CI, -0.05 to 0.06). For injectable naltrexone, meta-analyses found no association with return to any drinking (RD, -0.04; 95% CI, -0.10 to 0.03) or heavy drinking (RD, -0.01; 95% CI, -0.14 to 0.13) but found an association with reduction in heavy drinking days (weighted mean difference [WMD], -4.6%; 95% CI, -8.5% to -0.56%). Among medications used off-label, moderate evidence supports an association with improvement in some consumption outcomes for nalmefene (heavy drinking days per month: WMD, -2.0; 95% CI, -3.0 to -1.0; drinks per drinking day: WMD, -1.02; 95% CI, -1.77 to -0.28) and topiramate (% heavy drinking days: WMD, -9.0%; 95% CI, -15.3% to -2.7%; drinks per drinking day: WMD, -1.0; 95% CI, -1.6 to -0.48). For naltrexone and nalmefene, NNHs for withdrawal from trials due to adverse events were 48 (95% CI, 30 to 112) and 12 (95% CI, 7 to 50), respectively; risk was not significantly increased for acamprosate or topiramate.

Conclusions and Relevance: Both acamprosate and oral naltrexone were associated with reduction in return to drinking. When directly compared with one another, no significant differences were found between acamprosate and naltrexone for controlling alcohol consumption. Factors such as dosing frequency, potential adverse events, and availability of treatments may guide medication choice.

2. **The Efficacy of Disulfiram for the Treatment of Alcohol Use Disorder.**
Jørgensen, C. H., Pedersen, B. and Tønnesen, H. (2011), Alcoholism: Clinical and Experimental Research, 35: 1749–1758. doi: 10.1111/j.1530-0277.2011.01523.x

Abstract

Background: Alcohol use disorders (AUD) involving hazardous, harmful, and addictive misuse of alcohol are widespread in most parts of the world. The aim of this study was to review the effect of disulfiram in the treatment of patients with AUD. The effect of disulfiram was evaluated according to the primary outcome of an intake of alcohol below 30 and 20 g/d for men and women, respectively, as well as secondary outcomes such as days until relapse, alcohol intake, and numbers of drinking days.

Methods: A systematic review of the literature was conducted using MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL).

Results: Eleven randomized controlled trials were included with a total of 1,527 patients. They compared disulfiram treatment with placebo, none or other abstinence-supportive treatments. Overall, 6 studies reported of a significant better effect on abstinence for patients treated with disulfiram. Six of 9 studies measuring secondary outcomes reported that patients treated with disulfiram had significantly more days until relapse and fewer drinking days, respectively. The quality of the included studies was moderate. Heterogeneity was significant in most of the meta-analyses, but valid results were found regarding the effect of disulfiram versus placebo over 12 months and unsupervised disulfiram versus other or no treatment. The vast majority of significant studies were of shorter duration, while only 3 studies of 12 months were significant regarding more days until relapse and/or reduction in drinking days.

Conclusions: Supervised treatment with disulfiram has some effect on short-term abstinence and days until relapse as well as number of drinking days when compared with placebo, none, or other treatments for patients with alcohol dependency or abuse. Long-term effect on abstinence has not been evaluated yet. However, there is a need for more homogeneous and high-quality studies in the future regarding the efficacy of disulfiram.

3. **Opioid antagonists for alcohol dependence.**
Rösner S, Hackl-Herrwerth A, Leucht S, Vecchi S, Srisurapanont M, Soyka M. Cochrane Database of Systematic Reviews 2010, Issue 12. Art. No.: CD001867. DOI: 10.1002/14651858.CD001867.pub3.

Abstract
Background: Alcohol dependence belongs to the globally leading health risk factors. Therapeutic success of psychosocial programs for relapse prevention is moderate and could be increased by an adjuvant treatment with the opioid antagonists naltrexone and nalmefene.

Objectives: To determine the effectiveness and tolerability of opioid antagonists in the treatment of alcohol dependence.

Search methods: We searched the Cochrane Drugs and Alcohol Group (CDAG) Specialized Register, PubMed, EMBASE and CINAHL in January 2010 and inquired manufacturers and researchers for unpublished trials.

Selection criteria: All double-blind randomised controlled trials (RCTs) which compare the effects of naltrexone or nalmefene with placebo or active control on drinking-related outcomes.

Data collection and analysis: Two authors independently extracted outcome data. Trial quality was assessed by one author and cross-checked by a second author.

Main results: Based on a total of 50 RCTs with 7793 patients, naltrexone reduced the risk of heavy drinking to 83% of the risk in the placebo group RR 0.83 (95% CI 0.76 to 0.90) and decreased drinking days by about 4%, MD -3.89 (95% CI -5.75 to -2.04). Significant effects were also demonstrated for the secondary outcomes of the review including heavy drinking days, MD - 3.25 (95% CI -5.51 to -0.99), consumed amount of alcohol, MD - 10.83 (95% CI -19.69 to -1.97) and gamma-glutamyltransferase, MD - 10.37 (95% CI -18.99 to -1.75), while effects on return to any drinking, RR 0.96 (95 CI 0.92 to 1.00) missed statistical significance. Side effects of naltrexone were mainly gastrointestinal problems (e.g. nausea: RD 0.10; 95% CI 0.07 to 0.13) and sedative effects (e.g. daytime sleepiness: RD 0.09; 95% CI 0.05 to 0.14). Based on a limited study sample, effects of injectable naltrexone and nalmefene missed statistical significance. Effects of industry-sponsored studies, RR 0.90 (95% CI 0.78 to 1.05) did not significantly differ from those of non-profit funded trials, RR 0.84 (95% CI 0.77 to 0.91) and the linear regression test did not indicate publication bias (P = 0.765).

Authors' conclusion: Naltrexone appears to be an effective and safe strategy in alcoholism treatment. Even though the sizes of treatment effects might appear moderate in their magnitudes, these should be valued against the background of the relapsing nature of alcoholism and the limited therapeutic options currently available for its treatment.

4. **Naltrexone (50 mg) Plus Psychotherapy in Alcohol-Dependent Patients: A Meta-Analysis of Randomized Controlled Trials.**
Jarosz J, Miernik K, Wąchal M, Walczak J, Krumpl G. *Am J Drug Alcohol Abuse*. 2013;39(3):144-160. doi:10.3109/00952990.2013.796961.

Abstract

Background: Alcoholism is a chronic and potentially fatal disease. One of the therapeutic options is pharmacotherapy with the opioid antagonist naltrexone in combination with psychotherapy,

Objectives: The objective of this review was to compare the clinical effectiveness of naltrexone (50 mg/day) versus that of a placebo in alcohol-dependent patients receiving psychotherapy.

Methods: The clinical effectiveness of the treatment was assessed in accordance with the principles of systematic review, as outlined in the Cochrane Collaboration guidelines (Cochrane Reviewer's Handbook) and the guidelines of the Polish Agency for Health Technology Assessment (AHTAPol).

Results: Statistical significances in favor of the treatment modality were found in both the percentage of patients maintaining total abstinence and the percentage of relapsed patients.

Conclusion: The analysis herein demonstrates that for short (12–16 weeks) period of treatment, a combination of naltrexone administration and psychotherapy results in high clinical efficacy with a safety profile comparable to that of the placebo in the treatment of alcohol-dependent patients. The side effects of naltrexone treatment are usually mild and transient.

5. **Naltrexone for the treatment of alcoholism: a meta-analysis of randomized controlled trials.**
Srisurapanont M, Jarusuraisin N. *Int J Neuropsychopharmacol Off Sci J Coll Int Neuropsychopharmacol CINP*. 2005;8(2):267-280. doi:10.1017/S1461145704004997.

Abstract

Many trials of naltrexone have been carried out in alcohol-dependent patients. This paper is aimed to systematically review its benefits, adverse effects, and discontinuation of treatment. We assessed and extracted the data of double-blind, randomized controlled trials (RCTs) comparing naltrexone with placebo or other treatment in people with alcoholism. Two primary outcomes were subjects who relapsed (including heavy drinking) and those who returned to drinking. Secondary outcomes were time to first drink, drinking days, number of standard drinks for a defined period, and craving. All outcomes were reported for the short, medium, and long term. Five common adverse effects and dropout rates in short-term treatment were also examined. A total of 2861 subjects in 24 RCTs presented in 32 papers were included. For short-term treatment, naltrexone significantly decreased relapses [relative risk (RR) 0.64, 95% confidence interval (CI) 0.51-0.82], but not return to drinking (RR 0.91, 95% CI 0.81-1.02). Short-term treatment of naltrexone significantly increased nausea, dizziness, and fatigue in comparison to placebo [RRs (95% CIs) 2.14 (1.61-2.83), 2.09 (1.28-3.39), and 1.35 (1.04-1.75)]. Naltrexone administration did not significantly diminish short-term discontinuation of treatment (RR 0.85, 95% CI 0.70-1.01). Naltrexone should be accepted as a short-term treatment for alcoholism. As yet, we do not know the appropriate duration of treatment continuation in an alcohol-dependent patient who responds to short-term naltrexone administration. To ensure that the real-world treatment is as effective as the research findings, a form of psychosocial therapy should be concomitantly given to all alcohol-dependent patients receiving naltrexone administration.

6. **Acamprosate for alcohol dependence.**
Rösner S, Hackl-Herrwerth A, Leucht S, Lehert P, Vecchi S, Soyka M. Cochrane Database of Systematic Reviews 2010, Issue 9. Art. No.: CD004332. DOI: 10.1002/14651858.CD004332.pub2.

Abstract

Background: Alcohol dependence is among the main leading health risk factors in most developed and developing countries. Therapeutic success of psychosocial programs for relapse prevention is moderate, but could potentially be increased by an adjuvant treatment with the glutamate antagonist acamprosate.

Objectives: To determine the effectiveness and tolerability of acamprosate in comparison to placebo and other pharmacological agents.

Search methods: We searched the Cochrane Drugs and Alcohol Group (CDAG) Specialized Register, PubMed, EMBASE and CINAHL in January 2009 and inquired manufacturers and researchers for unpublished trials.

Selection criteria: All double-blind randomised controlled trials (RCTs) which compare the effects of acamprosate with placebo or active control on drinking-related outcomes.

Data collection and analysis: Two authors independently extracted data. Trial quality was assessed by one author and cross-checked by a second author. Individual patient data (IPD) meta-analyses were used to verify the primary effectiveness outcomes.

Main results: 24 RCTs with 6915 participants fulfilled the criteria of inclusion and were included in the review. Compared to placebo, acamprosate was shown to significantly reduce the risk of any drinking RR 0.86 (95% CI 0.81 to 0.91); NNT 9.09 (95% CI 6.66 to 14.28) and to significantly increase the cumulative abstinence duration MD 10.94 (95% CI 5.08 to 16.81), while secondary outcomes (gamma-glutamyltransferase, heavy drinking) did not reach statistical significance. Diarrhea was the only side effect that was more frequently reported under acamprosate than placebo RD 0.11 (95% 0.09 to 0.13); NNTB 9.09 (95% CI 7.69 to 11.11). Effects of industry-sponsored trials RR 0.88 (95% 0.80 to 0.97) did not significantly differ from those of non-profit funded trials RR 0.88 (95% CI 0.81 to 0.96). In addition, the linear regression test did not indicate a significant risk of publication bias (p = 0.861).

Authors' conclusions: Acamprosate appears to be an effective and safe treatment strategy for supporting continuous abstinence after detoxification in alcohol dependent patients. Even though the sizes of treatment effects appear to be rather moderate in their magnitude, they should be valued against the background of the relapsing nature of alcoholism and the limited therapeutic options currently available for its treatment.

7. **Acamprosate supports abstinence, naltrexone prevents excessive drinking: evidence from a meta-analysis with unreported outcomes.**
Rösner S, Leucht S, Lehert P, Soyka M. *J Psychopharmacol Oxf Engl*. 2008;22(1):11-23. doi:10.1177/0269881107078308.

Abstract

Two pharmacological agents have repeatedly been shown to be efficacious for relapse prevention in alcohol dependence: The putative glutamate-antagonist acamprosate and the opioid-antagonist naltrexone. Clinical evidence for both drugs is based on various outcome criteria. Whereas for acamprosate primarily abstinence maintenance has been demonstrated, studies with naltrexone have mostly emphasised the prevention of heavy drinking. The remaining effects of both drugs are not always reported; accordingly the corresponding database is fragmentary. Thus, the primary objective of the present meta-analysis was to complete the efficacy profiles for acamprosate and naltrexone and to compare them with each other. Unreported results, requested from the study investigators and the drug manufacturers, were integrated in the computation of effect sizes. For the meta-analysis, emphasis was placed on the conceptual distinction between having a first drink and returning to heavy drinking. Naltrexone was found to have a significant effect on the maintenance of abstinence as well as the prevention of heavy drinking. Acamprosate was shown only to support abstinence; it did not influence alcohol consumption after the first drink. When the efficacy profiles of the two

drugs were compared, acamprosate was found to be more effective in preventing a lapse, whereas naltrexone was better in preventing a lapse from becoming a relapse. The superiority of either one drug or over the other one cannot be determined as a general rule, it rather depends on the therapeutic target. Benefits in the treatment of alcohol dependence might be optimized by matching the efficacy profiles of specific antidipsotropics with the motivational status of alcohol-dependent patients.

8. **Acamprosate for alcohol dependence: a sex-specific meta-analysis based on individual patient data.**
Mason BJ, Lehert P. *Alcohol Clin Exp Res*. 2012;36(3):497-508. doi:10.1111/j.1530-0277.2011.01616.x.

Abstract

Background: It is unknown whether women derive comparable benefits and have a similar safety and tolerability profile as men from acamprosate, a widely prescribed drug for the maintenance of abstinence in alcohol dependence. The objective of this study was to assess sex-specific differences in the efficacy, safety, and tolerability of acamprosate in the treatment of women and men with alcohol dependence.

Methods: A sex-specific meta-analysis was conducted based on individual patient data (IPD). Data were obtained from double-blind, randomized controlled trials with quantitative drinking measures in patients with alcohol dependence receiving oral acamprosate or placebo. Sources included PubMed, PsychInfo, and Cochrane electronic databases; reference lists from retrieved articles and presentations at professional meetings; and direct access to authors and companies who provided IPD.

Results: Individual records were obtained from 1,317 women and 4,794 men who participated in 22 eligible studies conducted in 18 countries. IPD meta-analyses found a significant beneficial effect of acamprosate relative to placebo across all 4 efficacy end points: an incremental gain of 10.4% (95% CI 7.1 to 13.7, $p < 0.001$) in percentage of abstinent days, an incremental gain of 11.0% (7.4 to 14.6, $p < 0.001$) in percentage of no heavy drinking days, an odds ratio of 1.9 (1.6 to 2.2, $p < 0.001$) for rate of complete abstinence, and an odds ratio of 1.9 (1.6 to 2.3, $p < 0.001$) for rate of no heavy drinking, over the study duration. Acamprosate was also associated with significantly higher rates of treatment completion ($p = 0.004$) and medication compliance ($p < 0.001$) than placebo. Men and women did not differ on any measure of acamprosate efficacy, safety, or tolerability.

Conclusions: This sex-specific IPD meta-analysis provides evidence that acamprosate has a significant effect compared with placebo in improving rates of abstinence and no heavy drinking in both women and men with alcohol dependence. Further, acamprosate was associated with significantly higher rates of treatment completion and medication compliance than placebo among both women and men and had a comparable safety and tolerability profile.

9. **Medical treatment of alcohol dependence: a systematic review.**
Miller PM, Book SW, Stewart SH. *Int J Psychiatry Med*. 2011;42(3):227-266.

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 U.S. 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.