BEST in Mental Health
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Best Evidence Summaries of Topics in Mental Healthcare

BEST *in* MH *clinical question-answering service*

Question

In adults (>18 years old) with moderate to severe alcohol dependence, how effective are pharmacological treatments (in particular, oral naltrexone, disulfiram and acamprosate) compared to any other treatments, in improving consumption-related outcomes?

Clarification of question using *PICO* structure

Patients: adults (>18 years old) with moderate to severe alcohol dependence
Intervention: medication – oral naltrexone, disulfiram and acamprosate
Comparator: any other treatments
Outcome: consumption-related outcomes

Plain language summary

Limited evidence suggests that oral naltrexone and acamprosate are effective in improving consumption-related outcomes in alcohol dependent adults. However more high quality trials are needed to adequately assess the effectiveness of pharmacological treatments in this area.

Clinical and research implications

Evidence from one high quality systematic review indicated that oral naltrexone and acamprosate are similarly effective in improving consumption related outcomes in people with alcohol dependence. These results were partially supported by the findings of a second, smaller, poor quality systematic review. Evidence about the effectiveness of disulfiram was sparse and inconsistent.

More research needs to be done as to which subsets of service users these medications would be most appropriate for. The effects of different population characteristics (e.g. degree of dependence, genetic factors) in influencing the response to pharmacological treatment need to be examined further (1). Longer term follow-ups would mean that more data on health outcomes (e.g. morbidity, mortality) can be collected (1,2) and the true effect of the drug examined after its novelty effect has worn off. Jonas et al. suggests for more research to look at the benefits for those groups whose aim is controlled drinking, rather than total abstinence (2). Further research into how medications and psychosocial treatments compare with each other as well as combinations that could work well could be considered as well (1,2). Besides this, more studies on cost effectiveness and risk of side effects would be useful. NICE has also recommended for research into understanding and tackling non-compliance (3). Looking at the bigger picture, more research needs to go into preventative measures at the population level, in light of the deeply socially embedded drinking culture.

What does the evidence say?

Number of included studies/reviews (number of participants)

Two systematic reviews (SRs) by American authors were included. Miller et al. (2011) set out to sum up the published literature concerning pharmacotherapy for alcohol dependence in community and specialist settings, looking at 85 RCTS with a total of 18 937 subjects (1). Jonas et al. (2014) evaluated the benefits and harms of various medications used in outpatient settings (2). They included meta-analyses of placebo controlled trials for each of the three interventions specified for this evidence summary and of direct comparisons, where these were available(2).

Main findings

The smaller review (1) did not include a meta-analysis and summarised findings, for each medication, in terms of the proportion of studies finding a significant treatment effect; no numerical results were reported.

In the other SR that included a meta-analysis, both acamprosate and naltrexone were linked to a decrease in the return to any drinking with no statistically significant difference between the two (2). It found that for every 20 people treated with oral naltrexone, 1 person would not return to any drinking (NNT=20, 95% CI, 11 to 500; RD, -0.05, 95% CI -0.10 to -0.0002; 16 trials, n = 2347) (2). Naltrexone was also associated with an improvement in the abstinence from heavy drinking, with 1 person abstaining from heavy drinking for every 12 treated (NNT=12, 95% CI, 8 to 26; RD 0.09, 95% CI -0.13 to -0.04; 19 trials, n = 2875) (2). Acamprosate did not change the number that abstained from heavy drinking but was able to prevent 1 person from returning to any drinking for every 12 people treated (NNT=12, 95% CI, 8 to 26; RD, -0.09, 95% CI -0.14 to -0.04; 16 trials, n = 4847) (2). For those treated with disulfiram, the risk difference was small at -0.04 (2). The associated 95% confidence interval crossed the null (CI -0.11 to 0.03) (2), suggesting a high probability that the results were due to chance.

It should be noted that there was some overlap between the studies included in the two systematic reviews.

Authors conclusions

Jonas et al. concluded that overall, there were modest positive treatment effects with oral naltrexone and acamprosate (with neither superior to the other), while the effect of disulfiram was ambiguous (2). They suggested that decisions regarding medication be dictated by such issues as 'dosing frequency, potential adverse effects, and availability of treatments' (2). Miller et al. drew similar conclusions and suggested for acamprosate and naltrexone to be considered initially before disulfiram (1). They advocate that disulfiram is only suitable for those who are highly motivated and already abstinent and can be supervised in taking the tablet everyday (1).

Reliability of conclusions/Strength of evidence

The SR by Miller et al. did not clearly define a question to address and just set out to provide an overview of all published data. There was no indication that the authors made use of medical subject headings (MeSH) in their search, neither did they consider non-English language papers (1) which may have led to some critical studies being missed out in the search. Another flaw was the focus on only published information, leading to the possibility of the findings being affected by publication bias. Although two reviewers discussed conflicts in paper selection and assessment, the fact that the main author had the final say in the matter (1) leads one to question whether the finally selected studies and ratings primarily reflected the principal author's views.

Further, the SR did not conduct any meta-analyses to calculate summary effect estimates, which would have increased the power of the evidence, nor did they report numerical results for the individual included studies. What the authors did was assess the risk of bias in the papers using the Jadad scale. However, the scale has been criticised for only considering the randomisation, blinding and description of withdrawals and/or dropouts; and not all potential sources of bias such as poor allocation concealment or selective reporting of data (1). Moreover, the authors did not supply any reasoning for their scores. They did not greatly criticise the papers nor apply any weightings to them. With the mixed amount of evidence from the many studies found, it is hard to see how the authors came to their final conclusions.

The question addressed by Jonas et al. was not immediately clear because of the wide scope that it covered. However, an exhaustive breakdown of the questions that the review sought out to answer, with well-defined PICO terms, was provided in the separate, detailed review protocol.

A commendation of the study was the reviewers' endeavours to include unpublished data by making requests to manufacturers and searching the World Health Organisation (WHO) International Clinical Trials Registry platform as well as the Food and Drug Administration (FDA) website (2). The authors further tried to assess for publication bias using the Begg-Mazumdar method, which suggested no bias (2). The reviewers also made a well-reasoned decision for one of their inclusion criteria to be that treatment had to been given for at least 12 weeks to show a more reliable effect (2).

The authors conducted a meta-analysis of 95 of the RCTs and created forest plots on the risk difference of returning to any or heavy drinking for certain medications (2). I^2 tests were performed and there was found to be considerable heterogeneity in the studies looking at the risk difference in the return to any drinking for patients on acamprosate (2). Appropriately, the authors performed random-effects analysis to address this (2). However, they could have more deeply explored the potential sources of this heterogeneity.

The authors used the Agency for Healthcare Research and Quality (AHRQ) established guidance to assess risk of bias in studies, documenting support for their judgements (2). They recognised that most of the studies had a moderate risk of bias due to selective data reporting, and conducted subgroup analyses to compare the results between studies with low risk and high risk of bias (2). These analyses found little to no difference in the results, giving confidence in these results.

What do guidelines say?

NICE guidelines say the following for adults with alcohol dependence:

Interventions for moderate and severe alcohol dependence after successful withdrawal:

- After a successful withdrawal for people with moderate and severe alcohol dependence, consider offering acamprosate or oral naltrexone in combination with an individual psychological intervention (cognitive behavioural therapies, behavioural therapies or social network and environment-based therapies) focused specifically on alcohol misuse.
- After a successful withdrawal for people with moderate and severe alcohol dependence, consider offering acamprosate or oral naltrexone in combination with behavioural couples therapy to service users who have a regular partner and whose partner is willing to participate in treatment.
- After a successful withdrawal for people with moderate and severe alcohol dependence, consider offering disulfiram in combination with a psychological intervention to service users who:
    1. Have a goal of abstinence but for whom acamprosate and oral naltrexone are not suitable, or
    2. Prefer disulfiram and understand the relative risks of taking the drug. **CG115, pp23.**

Date question received: 04/07/2016
Date searches conducted: 04/07/2016
Date answer completed:

References

Systematic reviews

1. Miller PM, Book SW, Stewart SH. Medical Treatment of Alcohol Dependence: A Systematic Review. Int J Psychiatry Med. 2011;42(3):227–66.

2. Jonas DE, Amick HR, Feltner C, Bobashev G, Thomas K, Wines R, et al. Pharmacotherapy for adults with alcohol use disorders in outpatient settings: a systematic review and meta-analysis. JAMA. 2014 May 14;311(18):1889–900.

Guidelines

3. National Institute of Clinical Excellence (NICE). Alcohol-use disorders: diagnosis, assessment and management of harmful drinking and alcohol dependence [Internet]. 2010 [cited 2016 Jul 25]. Available from: https://www.nice.org.uk/guidance/cg115/resources/alcoholuse-disorders-diagnosis-assessment-and-management-of-harmful-drinking-and-alcohol-dependence-35109391116229

Results

Systematic reviews

Author (year)	Search date	Inclusion criteria	Number of included studies	Summary of results	Risk of bias
Jonas et al (2013)	March 2014	***Participants*****:** Included studies enrolling adults with alcohol use disorders (AUDs). ***Intervention*****:** FDA-approved medications (oral acamprosate 666 mg TID, oral disulfiram 250 to 500 mg per day, oral naltrexone 50 to 100 mg per day, intramuscular naltrexone injection 380 mg monthly), or any of 23 off-label medications used to manage AUDs. ***Comparator*****:** Placebo or other medication ***Outcome*****:** Alcohol consumption (return to any drinking, return to heavy drinking, drinking days, heavy drinking days (≥4 drinks per day for women or ≥5 drinks per day for men), drinks per drinking day), motor vehicle crashes, injuries, quality of life, function, mortality and harms. ***Study design*****:** Randomised controlled trial (RCTs); one cohort study was included.	123 studies (n=22803 participants) 95 RCTs include in the meta-analyses	The objective of this systematic review was to evaluate the benefits and harms of various medications used in outpatient settings, for adults with alcohol use disorders. This evidence summary only included results relating to placebo-controlled trials of oral naltrexone, disulfiram or acamprosate, comparisons between these drugs, or comparisons of one or more of these drugs with other pharmacological interventions. Most of the studies included in the review assessed acamprosate (27 studies, n=7519), naltrexone (53 studies, n=9140), or both. There were 22 placebo-controlled trials of acamprosate, 4 of disulfiram, and 44 of naltrexone. The review also included included 4 trials directly comparing acamprosate with naltrexone, 1 comparing disulfiram with naltrexone, and 4 comparing naltrexone with the off-label medications (aripiprazole, desipramine, paroxetine, sertraline, and topiramate).	The research objectives were clearly stated and appropriate inclusion criteria were defined. The searches were comprehensive and attempts were made to locate unpublished data. Data extractions were reviewed by at least 2 investigators. Study selection and risk of bias assessment was done by two independent reviewers. The methodological quality of included studies was

				Both acamprosate and naltrexone were linked to a decrease in the return to any drinking. For every 20 people treated with oral naltrexone (50 mg), 1 person would not return to any drinking (NNT=20 (95% CI: 11 to 500); absolute risk difference (RD), -0.05 (95% CI: -0.10 to -0.0002); 16 trials, n = 2347). Naltrexone (50 mg) was also associated with an improvement in the abstinence from heavy drinking, with 1 person abstaining from heavy drinking for every 12 treated (NNT=12 (95% CI: 8 to 26); RD 0.09 (95% CI: -0.13 to -0.04); 19 trials, n = 2875). Naltrexone (50 mg) was also associated with statistically significant reductions in the % drinking days, % heavy drinking days and number of drinks per drinking day, compared to placebo. Only three placebo-controlled trials assessed the effectiveness of 100 mg oral naltrexone; summary effect estimates for return to drinking, return to heavy drinking % drinking days and drinks per drinking day were not statistically significant. Acamprosate had no statistically significant effect on the numbers abstaining from heavy drinking but was able to prevent 1 person from returning to any drinking for every 12	assessed according to guidelines established by the Agency for Healthcare Research and Quality (AHRQ). A summary of the risk of bias of each study and the reasoning for this was included. I^2 calculations were used to assess heterogeneity. Meta-analyses were performed using random effects models where appropriate. Forest plots were created. Publication bias was assessed using the Begg-Mazumdar method.

				people treated (NNT=12 (95% CI: 8 to 26); RD, -0.09 (95% CI: -0.14 to -0.04); 16 trials, n = 4847). Acamprostate was also associated with a reduction in the % drinking days compared to placebo, but had no statistically significant effect on the % heavy drinking days or drinks per day. Only two placebo-controlled studies assessed disulfiram; the risk difference was not statistically significant at -0.04 (CI -0.11 to 0.03). There were no statistically significant differences between oral naltrexone and acamprosate, in terms of return to any drinking (3 studies), return to heavy drinking (4 studies) or % drinking days (2 studies). No consumption-related outcomes were reported for the trial comparing disulfiram with naltrexone, or the four trials comparing naltrexone with the off-label medications.	
Miller et al (2011)	August 2010	***Participants*:** Adults (≥18 years) with a 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)).	85 studies (n=18937 participants)	The objective of this systematic review was to summarise the published literature concerning pharmacotherapy for alcohol dependence in community and specialist settings. Only the literature concerning oral naltrexone, acamprosate and disulfiram is included in this evidence summary.	The research had a vague objective with wide scope. Inclusion and exclusion criteria were clearly stated.

		***Intervention*:** disulfiram, naltrexone, acomprosate, antidepressants, topiramate, or any other pharmacological intervention ***Comparator*:** Placebo or other medication ***Outcome*:** Alcohol consumption ***Study design*:** RCTs		9 RCTs evaluating the effectiveness of oral disulfiram were found. The only study which was rated as having low potential for bias found no significant difference in alcohol consumption measures between disulfiram and placebo. The remaining eight studies were rated as having higher potential for bias: two studies found significant reductions in alcohol consumption measures relative to placebo; three studies compared disulfiram to oral naltrexone of which two favoured disulfiram and one found no significant difference in alcohol consumption between the two interventions; two studies compared disulfiram to acamprosate and reported results favouring disulfiram; one study found disulfiram to be slightly more effective than topiramate in delaying the onset of relapse. 24 RCTs were found to have assessed acamprosate. 15 were deemed to have a lower potential of bias: 11 were placebo controlled trials, of which six reported consumption outcomes favouring acamprosate; 3 compared acamprosate to oral naltrexone and placebo, all found no difference between the treatments and two also found no effect relative to placebo; 1 compared acomprosate to disulfiram (see	Five databases were searched. Manual searching of reference lists, searches of internet references and searched through contact with experts was done. Searching was limited to English language papers and published data. Data extraction, inclusions assessment and quality assessment was done by two reviewers. The methodological quality of included studies was assessed using the Jadad scale.

				above). The eight studies rated as having higher potential for bias reported similarly mixed results. More studies were found to be assessing oral naltrexone, with 31 RCTs found, 17 of which were assessed to have a low risk of bias. Fifteen low risk of bias studies were placebo controlled trials 12 of these showed evidence for a beneficial effect of naltrexone on consumption outcomes. The studies rated as having higher risk of bias supported these findings. It should be noted that there was overlap between the studies included in this systematic review and those included in Jonas 2014.	A table summarising the characteristics of the included studies was provided, together with their Jadad scores, but no numerical results for individual studies or meta-analyses were reported.

Risk of bias

Systematic reviews

Author (year)	RISK OF BIAS				
	Inclusion criteria	**Searches**	**Review process**	**Quality assessment**	**Synthesis**
Jonas et al (2014)	☺	☺	☺	☺	☺
Miller et al (2011)	☺	☹	☺	☺	☹

☺Low risk ☹High risk ? Unclear risk

Search details

Source	Search Strategy	Number of hits	Relevant evidence identified
NICE	Alcohol dependence	8	1
MEDLINE	95. Medline; ((alcohol) AND (abuse* OR dependen* OR disorder* OR drink* OR consumption)).ti,ab; 99296 results. 96. Medline; ((alcohol) AND (abuse* OR dependen* OR disorder* OR drink* OR consumption)).ti,ab; 99296 results. 97. Medline; alcohol*.ti,ab 98. Medline; 95 OR 96 OR 97; 300252 results 100. Medline; exp ALCOHOL ABSTINENCE/ OR exp ALCOHOL DRINKING/ OR exp ALCOHOL-RELATED DISORDERS/ OR exp ALCOHOLICS/ OR exp ALCOHOLICS ANONYMOUS/ OR exp ALCOHOLISM/; 143125 results. 102. Medline; (acamprosate* OR campral*).ti,ab 103. Medline; (naltrexone* OR vivitrol* OR revia* OR nalmefene*).ti,ab 104. Medline; ((opiate* OR narcotic*) adj2 (antagon*)).ti,ab 107. Medline; (disulfiram* OR antabuse*).ti,ab; 2993 results. 108. Medline; exp NALTREXONE/; 6979 results. 109. Medline; exp DISULFIRAM/; 3242 results. 110. Medline; exp NARCOTIC ANTAGONISTS/ 111. Medline; 100 OR 102 OR 103 OR 104 OR 107 OR 108 OR 109 OR 110; 40420 results 112. 98 AND 111; 4106 results 113. Medline; 112 [Limit to: (Clinical Trial or Controlled Clinical Trial or Meta-analysis or Randomized Controlled Trial or Scientific Integrity Review)]; 646		
EMBASE	144. EMBASE; ((alcohol) AND (abuse* OR dependen* OR disorder* OR drink* OR consumption)).ti,ab; 136538 results. 146. EMBASE; alcohol*.ti,ab; 344399 results. 148. EMBASE; exp ALCOHOL ABSTINENCE/ OR exp ALCOHOL ABUSE/ OR exp ALCOHOL CONSUMPTION/ OR exp ALCOHOL USE DISORDER/ OR exp ALCOHOL WITHDRAWAL/; 120632 results. 151. EMBASE; 144 OR 146 OR 148; 375371 results. 152. EMBASE; (acamprosate* OR campral*).ti,ab; 946 results. 154. EMBASE; exp ACAMPROSATE/; 2067 results. 155. EMBASE; (naltrexone* OR vivitrol* OR revia* OR nalmefene*).ti,ab; 7396 results. 156. EMBASE; exp NALTREXONE/; 12058 results. 157. EMBASE; exp NALMEFENE/; 1089 results. 158. EMBASE; exp OPIATE ANTAGONIST/; 77399 results.		

	159. EMBASE; exp NARCOTIC ANTAGONIST/; 53718 results. 160. EMBASE; ((opiate* OR narcotic*) adj2 (antagon*)).ti,ab; 3667 results. 161. EMBASE; (disulfiram* OR antabuse*).ti,ab; 3209 results. 162. EMBASE; exp DISULFIRAM/; 7122 results. 163. EMBASE; 152 OR 154 OR 155 OR 156 OR 157 OR 158 OR 159 OR 160 OR 161 OR 162; 85831 results. 164. EMBASE; 151 AND 163; 6960 results. 166. EMBASE; 164 [Limit to: (Clinical Trials Clinical Trial or Randomized Controlled Trial or Controlled Clinical Trial) and Publication Year 2010-2016]; 320 results. 167. EMBASE; 164 [Limit to: (EBM-Evidence Based Medicine Meta Analysis or Systematic Review) and Publication Year 2010-2016]; 103 results.		
PsycINFO/CINAHL	114. PsycInfo; ((alcohol AND (abuse* OR dependen* OR disorder* OR drink* OR consumption)).ti,ab 115. PsycInfo; alcohol*.ti,ab; 107743 results. 116. PsycInfo; exp ALCOHOL ABUSE/ OR exp ALCOHOL DRINKING ATTITUDES/ OR exp ALCOHOL WITHDRAWAL/ OR exp ALCOHOLICS ANONYMOUS/ OR exp ALCOHOLISM/; 46027 results. 117. PsycInfo; 114 OR 115 OR 116; 110648 results. 122. PsycInfo; (acamprosate* OR campral*).ti,ab; 414 results. 124. PsycInfo; (naltrexone* OR vivitrol* OR revia* OR nalmefene*).ti,ab; 3006 results. 125. PsycInfo; ((opiate* OR narcotic*) adj2 (antagon*)).ti,ab; 1063 results. 127. PsycInfo; (disulfiram* OR antabuse*).ti,ab; 724 results. 129. PsycInfo; exp ACAMPROSATE/; 191 results. 130. PsycInfo; exp NALTREXONE/; 1684 results. 132. PsycInfo; exp NARCOTIC ANTAGONISTS/; 5248 results. 134. PsycInfo; exp DISULFIRAM/; 322 results. 135. PsycInfo; 122 OR 124 OR 125 OR 127 OR 129 OR 130 OR 132 OR 134; 7334 results. 136. PsycInfo; 117 AND 135; 1711 results. 143. PsycInfo; 136 [Limit to: Publication Year 2010-2016 and (Methodology Literature Review or Meta Analysis or Systematic Review or Treatment Outcome/Clinical Trial)]; 139 results.		

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