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REVIEW PAPER

The comparative efficacy of FDA-approved drugs for management of alcohol use disorder – a network meta-analysis

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ABSTRACT

Introduction and aim. Alcohol use disorder (AUD) represents a significant and lasting public health challenge affecting millions of people around the world. Currently, the US FDA has approved naltrexone, disulfiram, and acamprosate for AUD; however, their comparative effectiveness remains uncertain. This study aimed to evaluate the comparative efficacy of FDA-approved medications for AUD.

Material and methods. A comprehensive search of PubMed, the Cochrane Library, and Embase was performed up to January 2025. Eligible studies were randomized controlled trials of at least 12 weeks in duration, enrolling adults with AUD and investigating one or more FDA-approved medications, individually or in combination. The Cochrane Risk of Bias 2 (ROB 2) tool was used to assess study quality. A frequentist random-effects network meta-analysis (NMA) was performed. The primary and secondary outcomes were the return to any level of drinking and the return to heavy drinking, respectively.

Analysis of the literature. Fifty-two trials were included. Compared to placebo, acamprosate (risk ratio, RR, 0.87 [95% CI, 0.82-0.92]), naltrexone (0.93 [0.88-0.99]) and a combination of acamprosate and naltrexone (NAAC) (0.52 [0.35-0.76]) all statistically significantly reduced the risk of return to any type of drinking. Based on SUCRA rankings, NAAC (SUCRA = 0.99) was ranked first for efficacy. For the secondary outcome, only naltrexone (RR, 0.87 [0.80-0.95]) was found to be effective.

Conclusion. When combined with psychosocial interventions, naltrexone and acamprosate demonstrated superior efficacy compared to placebo. Furthermore, the combination of the two medications led to significantly better results.

Keywords. acamprosate, alcohol use disorder, disulfiram, meta-analysis, naltrexone, randomized controlled trial

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The list of abbreviations:

AUD alcohol use disorder, **ACAM** – acamprosate, **CI** confidence interval, **CINeMA** confidence in Network Meta Analysis, **DISL** disulfiram, **NAAC** – combination of acamprosate and naltrexone, **NALT** naltrexone, **NMA** – network meta-analysis, **PLBO** placebo, **RCTs** – randomized controlled trials RCTs, risk ratio, **SUCRA** – surface under the cumulative ranking curve

Introduction

Alcohol use disorder (AUD) is a prevalent and debilitating common behavioral health condition characterized by impaired control over alcohol consumption, leading to frequent sessions of uncontrolled drinking.[1] It poses a significant global health challenge, affecting a large proportion of the population and contributing to more than 2 million deaths annually.[2] According to estimates, individuals with AUD have a mortality risk 3-4 times higher compared to those without AUD.[3] However, the risk is reduced by half in AUD patients who receive treatment and successfully reduce their consumption of alcohol, when compared to that of those who persist with heavy drinking.[4] The principal aim in treating AUD is to enable individuals to attain and maintain abstinence, or to significantly decrease alcohol use and the accompanying behavioral harms. AUD management has several components, including a combination of behavioral interventions and pharmacotherapy. The pharmacological regimens for AUD include FDA-approved and recommended (off-label) medications. Currently, the US FDA has authorized the use of disulfiram, naltrexone, and acamprosate for this condition. Although these medications have shown promising results in clinical trials, as demonstrated by several systematic reviews and meta-analyses,[5–10] their relative efficacy is not well established.

Although the conventional meta-analysis approach is valuable, it has limitations. It can only compare two interventions at a time and is restricted to those evaluated in direct head-to-head trials. In contrast, network meta-analysis (NMA) is an advanced statistical technique that simultaneously compares several interventions utilizing evidence which is both direct and indirect. This approach offers a more comprehensive understanding of the comparative efficacy of various interventions for AUD.[11] Recent NMAs of clinical trials have assessed the comparative efficacy of various pharmacological interventions,[12,13] including treatments not yet recommended by any guidelines (ie, off-label drugs). Additionally, these NMAs included clinical trials with treatment durations shorter than 12 weeks, as many of the off-label interventions were tested over relatively brief time periods. Longitudinal research has suggested that studies with short durations of medications can produce erroneous conclusions about effectiveness due to the observed variability in alcohol consumption behavior patterns.[5] Consequently, the inclusion criteria for clinical trials in this analysis stipulate a minimum treatment period of at least twelve weeks thereby ensuring reliable findings, as was observed in a recent pairwise meta-analysis.[5]

Aim

Therefore, to address this gap, the present study conducts a systematic review and NMA of randomized controlled trials (RCTs) to determine the comparative effectiveness of FDA-approved treatments for AUD, with a focus on trials with durations of not less than 12 weeks. This study provides updated and robust evidence to help clinicians in selecting the most effective FDA-approved pharmacological interventions for people with AUD.

Material and methods

This review protocol was prospectively registered with (https://osf.io/5zfsg). The study adhered to the PRISMA guidelines, specifically the extension designed for systematic reviews that incorporate network meta-analyses.[14]

Data source and search strategy

We conducted an updated search from January 2022 to January 2025 in PubMed, the Cochrane Register of Controlled Trials (CENTRAL) and Embase to identify additional studies published since the last search date of a prior systematic review on this topic conducted by McPheeters et al.[5] Manual screening of reference lists from published systematic reviews was also performed. To ensure a comprehensive and systematic approach, search strategies were designed in accordance with the Population, Intervention, Comparator and Study Design (PICOS) framework, using a combination of indexing terms and free-text keywords.

Study selection

All RCTs with not less than 12 weeks of treatment duration that enrolled adults with AUD, regardless of comorbid conditions, and investigated an FDA approved drug (disulfiram, acamprosate, or naltrexone),[15] alone or in combination compared to control, no treatment, or another FDA-approved medication in outpatient clinics were included. The primary outcome was relapse, that is, the return to drinking, measured by the number of people who had relapsed with respect to any drinking at the end of the study.[16] The secondary outcome was the return to heavy drinking.[16] Relapse or return to any drinking was defined as the intake of any quantity of alcohol during the follow-up period. The return to heavy drinking was defined as consuming 4 or more drinks per day for women and 5 or more drinks per day for men.

Details of the search strategy are available in Table S1. Two reviewers (F.T. and A.H.) independently screened

the titles and abstracts to assess initial relevance. The full text articles were retrieved and reviewed to determine final eligibility. Any disagreements were addressed by discussion with a third reviewer (SV). We did not consider conference abstracts. Language restrictions were not applied during the study selection process.

Data extraction

Two reviewers (S.S. and F.T.) independently extracted data using a standardized extraction template. The number of participants initially randomly assigned to each study arm was recorded for all results. Data analysis was conducted regardless of the original authors' analytical approach.[17] Risk of bias was independently evaluated by two reviewers (C.J. and C.F.) using predefined criteria informed by established methodological guidance.[18,19] A third reviewer adjudicated any disagreements between the two reviewers. The risk of bias for each study was assessed and classified as low, medium, high, or unclear was assigned to each study.

Data synthesis and statistical analysis

For direct comparisons, conventional pairwise meta-analyses were conducted using a DerSimonian and Laird random-effects model to calculate pooled risk ratios (RRs) with 95% confidence intervals (CIs).[20] When more than one trial contributed to a comparison, heterogeneity was assessed using the I^2 statistics. To integrate both direct and indirect evidence, a frequentist random-effects network meta-analysis (NMA) with a consistency model was employed.[11] The network was anchored on a shared comparator, typically placebo or control. The consistency of the network was examined through a global inconsistency test using the design-by-treatment interaction model[21] and a loop-specific method.[22] Summary effects of the NMA were reported along with predictive intervals to help interpret findings in the context of observed heterogeneity.[11] To rank treatments by their relative efficacy, the surface under the cumulative ranking curve (SUCRA) were calculated.[23] Higher SUCRA scores (which can range from 0 to 1) indicated that an intervention is more likely to be better than those with lower scores. Possible small-study effects were investigated using comparison adjusted funnel plots. For the primary outcome, subgroup analyzes were performed according to the duration of follow-up (at least 12 weeks and more than 12 weeks). To assess the robustness of our results, we performed a sensitivity analysis by excluding trials of high risk of bias for the primary outcome. For statistical analysis, we used Stata version 16.0 (StataCorp, College Station, TX, USA).

Strength of evidence

We evaluated the certainty of evidence from NMA using the online software Confidence in Network Meta-Analysis (CINeMA) (https://cinema.ispm.unibe.ch/#rob [accessed January 2025]). The certainty was categorized into four levels: high, moderate, low, and very low. For the primary outcome, classification was performed across six methodological domains: reporting bias, within-study bias, , incoherence, heterogeneity, indirectness, and imprecision.[24,25] Two independent reviewers (SK, JC) performed the assessment of certainty of evidence, and in cases where there were discrepancies unresolved through discussion, a further reviewer (S.V.) was involved to reach a final consensus.

Analysis of the literature

The study search and selection process is illustrated in the PRISMA flow chart (Fig. S1). Our new search identified 169 citations following exclusion of duplicates. Following the selection of the title and abstract, 14 articles were retrieved for full text evaluation, but none met the eligibility criteria. The justifications for exclusion are reported in Table S2. Fifty-two studies[26–77] reporting primary or secondary outcomes were identified from previous reviews.[5] The characteristics of these studies are detailed in Table S3. Of the 52 studies, 4 were carried out in Asia, 2 in South America, 22 in North America, and 21 in Europe. Treatment durations varied between 12 and 52 weeks, while sample sizes ranged from 18 to 403 participants. The recruitment strategies employed in the studies involved a variety of approaches, including enrolling participants through treatment programs, using advertisements, receiving referrals, or employing a combination of these methods. Among the 52 studies, 40 (76.92%) included psychosocial cointerventions, whereas the remaining studies did not clearly report whether such cointerventions were used. Most studies (50 out of 52) used placebo as the comparator. Based on the risk of bias assessment (Table S3), 5 studies were rated as low risk, 38 as moderate and 7 as high. The risks of bias were unclear.

Primary outcome: return to any drinking

Thirty-seven RCTs (9474 patients) gave dichotomous data on the probability of returning to drinking. Five interventions have been included in the NMA (the network plot is shown in Fig. 1). The total number of comparisons of pairs with direct data was seven. Across the entire network, 7,160 events were recorded. The size of individual study results with 95% confidence intervals grouped by treatment comparison are given in Fig. S2.

NMA indicated that compared to placebo, acamprosate (RR, 0.87 [95% CI, 0.82 to 0.92]), naltrexone (RR, 0.93 [95% CI, 0.88 to 0.99]), and a combination of acamprosate and naltrexone (that is, NAAC) (RR, 0.52 [95% CI, 0.35 to 0.76]) were associated with a statistically significant reduction in the risk of relapse (return to any drinking) (Fig. 2). On the contrary, disulfiram did

not differ significantly from placebo (RR, 0.95 [95% CI, 0.82 to 1.12]). Comparative analyses between different interventions (Fig. 2) revealed that NAAC statistically significantly reduced the risk of relapse compared to disulfiram (RR, 0.54 [95% CI, 0.36 to 0.82]), acamprosate (RR, 0.59 [95% CI, 0.41 to 0.88]) and naltrexone (RR, 0.56 [95% CI, 0.38 to 0.82]). Comparison between acamprosate and naltrexone did not show statistically significant differences (RR, 1.67 [95% CI, 1.14 to 2.24]). The results of network meta-analyses resembled those obtained using standard pairwise meta-analyses (Fig. 2 and Fig. S3). Among the statistically significant comparisons in NMA illustrated in Figure 2, the 95% prediction intervals excluded the null value only in three comparisons (NAAC vs. disulfiram, NAAC vs acamprosate, and NAAC vs naltrexone) (Fig. 3). According to SUCRA rankings, NAAC (SUCRA = 0.99) had the highest probability of being the most effective, followed by acamprosate (SUCRA=0.70), naltrexone (SUCRA = 0.41) and disulfiram (SUCRA=0.31) (Fig. S4).

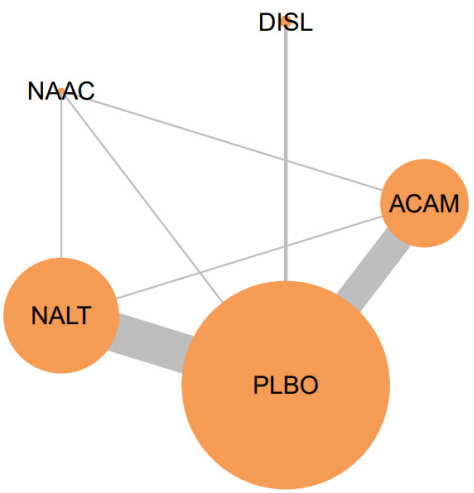

Fig. 1. Network plot for primary outcome (Notes: lines between nodes represent direct comparisons from head-to-head trials. The size reflects the number of studies for each intervention, while the thickness of the connecting lines corresponds to the number of trials that compare two strategies, ACAM acamprosate, DISL – disulfiram, NALT naltrexone, NAAC – combination of acamprosate and naltrexone, PLBO placebo)

In a subgroup analysis that included trials with follow-up of more than 12 weeks, only acamprosate demonstrated statistically significant differences compared to control (RR, 0.86 [95%CI, 0.80 to 0.92]) (Fig. S5). No trials comparing NAAC with placebo or any other interventions were included in this subgroup analysis. The subgroup analysis that included trials with a 12-week follow-up yielded findings similar to the primary analysis, except for the results regarding acamprosate. Due to the limited number of trials that evaluated acamprosate, the finding regarding its comparison to placebo was no longer statistically significant (Fig. S6). The sensitivity analysis that excluded studies with high risk of bias yielded results consistent with the primary analysis (Fig. S7).

ACAM	NA	NA	NA	0.88 (0.82, 0.93)
0.91 (0.78,1.07)	**DISL**	NA	NA	1.00 (0.93, 1.08)
1.67 (1.14,2.46)	1.84 (1.22,2.77)	**NAAC**	NA	NA
0.93 (0.86,1.01)	1.02 (0.87,1.20)	0.56 (0.38,0.82)	**NALT**	0.94 (0.90, 0.99)
0.87 (0.83,0.93)	0.96 (0.82,1.12)	0.52 (0.36,0.77)	0.94 (0.88,0.99)	**PLBO**

Fig. 2. Primary outcome: summary of findings from both pairwise and network meta-analysis (the top-right portion displays pairwise meta-analysis results, while the bottom left shows network meta-analysis results for the primary outcome, results are reported as risk ratios (RR) with 95% confidence intervals, for both pairwise and network analyses, an RR<1 suggests that treatment in the top-left position is more effective; RR>1 indicates the opposite, orange shaded results indicate statistical significance, ACAM acamprosate, DISL – disulfiram, NALT naltrexone, NAAC – combination of acamprosate and naltrexone, PLBO placebo)

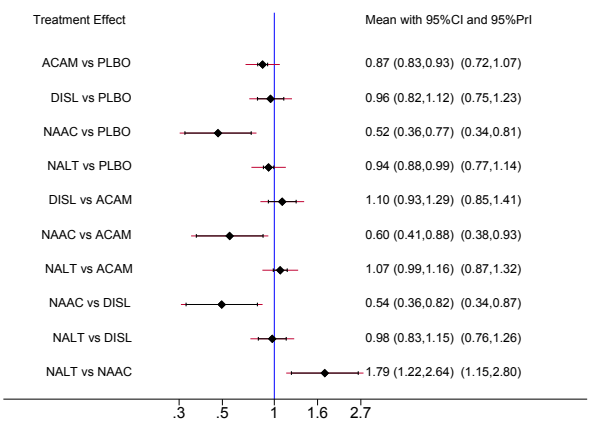

Fig. 3. Treatment effects among comparisons in NMA (reported as mean with 95% CI and 95% PrI, ACAM acamprosate, DISL – disulfiram, NALT naltrexone, NAAC – combination of acamprosate and naltrexone, PLBO placebo)

Secondary outcome: return to heavy drinking

Thirty RCTs (7012 patients) provided dichotomous data on the probability of returning to drinking. The network meta-analysis incorporated four treatment interventions, as illustrated in Fig. 4. Disulfiram was not tested in any of the trials included in the network. Six direct treatment comparisons available in the included trials, with a total of 3,992 events reported within the network.

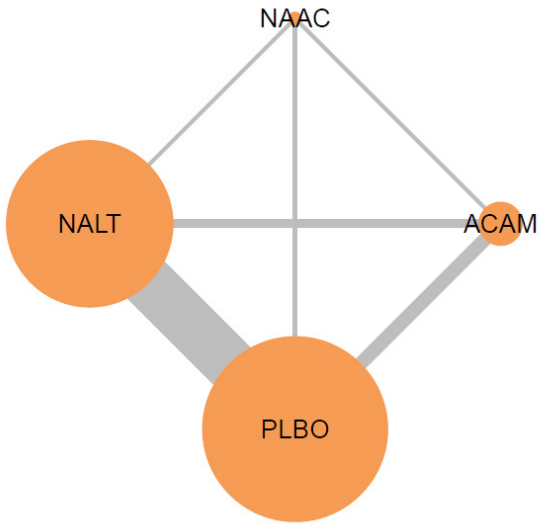

Fig. 4. Network plot for secondary outcome (Notes: lines between nodes represent direct comparisons from head-to-head trials. The size reflects the number of studies for each intervention, while the thickness of the connecting lines corresponds to the number of trials comparing ACAM – acamprosate, DISL – disulfiram, NALT naltrexone, NAAC – combination of acamprosate and naltrexone, PLBO placebo)

NMA suggested that indicated that naltrexone was associated with a statistically significant reduction in the risk of relapse compared to placebo (i.e., return to heavy drinking) (RR, 0.87 [95%CI, 0.80 to 0.95]). No statistically significant differences were observed for acamprosate (RR, 0.95 [95%CI, 0.86 to 1.04]) and NAAC (RR, 0.87 [95%CI, 0.71 to 1.06]) compared to placebo (Fig. S8). The comparative evaluation of efficacy across the different interventions did not demonstrate statistically significant superiority of one intervention over the others (Fig. S8). The SUCRA plot showed that naltrexone (SUCRA=0.79) was ranked first for efficacy followed by NAAC (SUCRA = 0.76) and acamprosate (SUCRA=0.38) (Fig. S9). The results of network meta-analyses resembled those obtained using standard paired meta-analyses (Fig. S10).

Network consistency and small study effects

For all results, the global test for inconsistency based on the design-by-treatment interaction model did not detect any significant inconsistency in the network (primary result: p = 0.22; secondary outcome: p = 0.75). Similarly, the loop-specific approach revealed no notable signs of inconsistency between the comparisons (Fig. S11). However, comparison-adjusted funnel plots (Figs. S12 and S13) suggested the possible presence of small-study effects.

Certainty of evidence

Applying CINeMA to the NMA, the certainty of evidence for all comparisons was determined to be low. Both direct and indirect evidence were also classified as low quality due to wide confidence intervals in the imprecision section. Further details on the quality of evidence can be found in Table S4.

Discussion

AUD is a significant public health problem, affecting millions of individuals and imposing a substantial economic burden on communities. The FDA has approved three medications for the treatment of AUD: naltrexone, acamprosate and disulfiram. Recent evidence from a systematic review and meta-analysis indicates that the FDA-approved medications acamprosate and naltrexone, but not disulfiram, are effective in decreasing the likelihood of returning to any alcohol consumption compared to placebo.[5] However, the previous systematic review is limited to a comparison of two interventions at a time, focusing on those evaluated in direct head-to-head trials. This study used an NMA of RCTs to comprehensively assess the comparative effectiveness of FDA-approved drugs for AUD. The findings of this review were based on trials with treatment durations of at least 12 weeks or more , as shorter follow-up periods may not adequately reflect long-term drinking patterns. The NMA results suggest that naltrexone, acamprosate, and their combination were all effective compared to placebo in reducing the likelihood of relapsing with alcohol consumption. In contrast, disulfiram did not show a statistically significant benefit in reducing the risk of relapse compared to placebo. These findings, when compared to placebo, are consistent with results from previous systematic reviews.[5] In addition, the results of NMA also suggest that combined use of acamprosate and naltrexone appeared to be the most effective intervention in reducing the risk of relapse compared to placebo and other individual FDA-approved medications for AUD.

The results of NMA suggest that acamprosate was ranked as the most effective medication compared to naltrexone in reducing the probability of relapsing to any alcohol consumption when examining the two individually. In contrast, naltrexone was the only FDA-approved intervention found to be effective in the likelihood of relapsing to reduce heavy drinking. This finding should be noted with caution, as the network had a relatively limited number of trials and sample sizes for the outcome of reducing heavy drinking for acamprosate compared to the data available for naltrexone. The available evidence suggests that acamprosate and naltrexone have shown comparable efficacy in improving outcomes such as the percentage of drinking and heavy drinking days.[5]

Previous reviews have reported that although serious side effects did not differ significantly between groups,

mild side effects such as dizziness were observed with naltrexone and gastrointestinal problems such as diarrhoea, nausea, and vomiting were reported with both naltrexone and acamprosate compared to placebo.[9,10] Oral naltrexone offers a simpler dosing regimen, requiring only a single daily dose, while acamprosate typically involves taking two tablets three times a day.[78] Acamprosate is not recommended for individuals with severe kidney dysfunction, while naltrexone is to be avoided by patients with liver failure, acute hepatitis, or those currently taking opioids. Therefore, selecting the most suitable medication should hinge on a comprehensive evaluation of the patient's clinical profile, encompassing their preference, compliance capabilities, co-existing medical conditions or contraindications, associated costs, and a thorough assessment of the potential risks and benefits.

Disulfiram has long been an FDA-approved treatment for AUD since the 1950s, underscoring its long-standing role in the management of this condition. However, the effectiveness in treating alcohol dependence has been a topic of considerable debate.[79] The efficacy of disulfiram is based on closely monitored administration and patient adherence, factors that can be difficult to sustain in practical clinical settings. Current evidence provides limited support for the effectiveness of disulfiram compared to naltrexone or acamprosate, which is consistent with the results of our NMA.

NMA evidence suggests that naltrexone in combination with acamprosate may offer potential advantages over the administration of either drug individually for the treatment of AUD, though the strength of this evidence is low because only a limited number of clinical trials were available for inclusion in the analysis. As an opioid receptor antagonist, the mechanism involves disrupting the cycle of enhanced activation of opiate receptors induced by alcohol consumption.[80] Alternatively, acamprosate is believed to work by regulating glutamatergic and GABAergic neurotransmitters systems; thus the aim is to restore the neurochemical balance disrupted by chronic alcohol exposure, which can aid in reducing alcohol relapse.[81] Studies have suggested that combining these two medications may offer synergistic effects by targeting these different aspects of alcohol dependence.[82] The existing evidence supports the tolerability of combining acamprosate and naltrexone in the management of AUD.[83] However, minor side effects, such as nausea, were observed to occur more frequently with the combined therapy compared to individual drug administration.[84] The long-term efficacy of combination therapy with naltrexone and acamprosate, with or without additional behavioral interventions, compared to monotherapy remains to be determined. Further research should be carried out to determine the optimal dosage and order of administration when using acamprosate and naltrexone together for AUD.

Treatment of AUD includes initial detoxification phase followed by rehabilitation. Relapse prevention is a key component of rehabilitation, during which these medications are used primarily alongside psychosocial interventions or with individual or group counseling. Currently, in many settings, the use of antidepressants and anxiolytics after the detoxification phase is limited, with a greater emphasis on psychosocial interventions, counseling, and ongoing support. However, acamprosate and naltrexone may have potential to reduce alcohol intake among individuals experiencing co-occurring depressive disorders. Although these medications are not specifically intended for treating depressive disorders, it is unclear how combination therapy may affect preexisting depressive conditions in these patients. To maximize the effectiveness of treatment and minimize potential risks, several important factors should be considered when selecting patients for combination therapy with naltrexone and acamprosate in the treatment of AUD. These factors include the severity of AUD, history of relapse, history of alcohol consumption, co-occurring mental and other health conditions, the potential for drug interactions and costs. A thorough evaluation of these factors allows healthcare providers to determine the suitability of combination therapy with naltrexone and acamprosate combination therapy and tailor treatment plans to the individual needs of the patient.

The limitations of this study warrant careful consideration. Firstly, this NMA encompassed studies with participants who experienced both alcohol dependence and depression, as well as those without these comorbid conditions together. Consequently, the relevance of these findings to individuals with alcohol dependence only warrants further clarification. Second, selective reporting of outcomes across studies may introduce bias. Third, the interpretation of findings should account for variations in study designs, intervention doses and dosage forms, patient populations, and outcome measured across included trials. Due to limited data, no subgroup analyzes could be performed exploring the influence of these factors on treatment outcomes. Fourth, the meta-analysis was limited in evaluating the comparative safety of the interventions due to insufficient safety data. Specifically, the small sample sizes and low number of adverse events across the included studies precluded robust NMA for safety outcomes. Future research should prioritize the collection and reporting of detailed safety data to facilitate more comprehensive risk-benefit assessments. Furthermore, the interpretation of the interactions between pharmacotherapy and psychotherapy, including cognitive interventions warrants consideration, as evidence suggests that psychotherapy reinforces the effects of medication. All study participants all received some type of concurrent psychosocial

interventions as a component of the overall treatment approach. The skills learned in therapy to avoid or manage alcohol triggers may have helped reduce drinking and self-reported cravings in treatment groups. Further research should be conducted on how psychosocial interventions and pharmacotherapy interact.

Conclusion

Our NMA offers a thorough synthesis of existing evidence, revealing the comparative efficacy of FDA-approved medications for AUD. In conjunction with psychosocial interventions, both naltrexone and acamprosate demonstrated increased efficacy compared to placebo. A combination of these two medications resulted in significantly improved therapeutic outcomes. However, more research is necessary to determine the optimal dosing strategy that maximizes therapeutic efficacy while minimizing the risk of adverse effects when these agents are used in combination. Additionally, future research should emphasize long-term results and the identification of patient characteristics that predict treatment response.

Declarations

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Author contributions

Conceptualization, S.V. and S.K..; Methodology, S.V. and S.K.; Software, S.V.; Validation, S.V., C.J. and S.K.; Formal Analysis, S.KV. and C.J.; Investigation, F.T., A.H., and C.F.; Data Curation, F.T., A.H., C.J., S.S. and C.F.; Writing – Original Draft Preparation, S.V. and S.K.; Writing – Review & Editing, F.S., S.S., P.A., and C.M.; Visualization, S.K.; Supervision, S.V. Project Administration, S.K..

Conflicts of interest

The authors have no competing interests to disclose.

Data availability

All data used in this study were obtained from existing randomized controlled trials and systematic reviews. Detailed sources are provided in the appendix. Additional data can be shared upon reasonable request.

Ethics approval

No ethical approval was required for this study, as it is a systematic review without direct involvement of human or animal subjects.

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