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PHARMACOTHERAPIES FOR ADULTS WITH ALCOHOL USE DISORDERS: A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS

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Abstract

Background: We aimed to determine medications' comparative efficacy and safety for adults with alcohol use disorders.

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Methods: We searched eleven electronic data sources for randomized clinical trials with at least 4 weeks of treatment reporting on alcohol consumption (total abstinence and reduced heavy drinking), dropouts, and dropouts due to adverse events. We conducted network meta-analyses using random-effects, frequentist models, and calculated summary rate ratios (RRs) with 95% confidence intervals (CIs).

Results: We included 156 trials (N = 27,334). Nefazodone (RR = 2.11; 95% CI, 1.42–3.13), aripiprazole (RR = 1.97; 95% CI, 1.36–2.88), carbamazepine (RR = 1.85; 95% CI, 1.03–3.32), and nalmefene (RR = 1.17; 95% CI, 1.01–1.35) were associated with the most dropouts. Baclofen (RR = 0.83; 95% CI, 0.70–0.97) and pregabalin (RR = 0.63; 95% CI, 0.43–0.94) caused fewer dropouts than placebo. Nalmefene (RR = 3.26; 95% CI, 2.34–4.55), fluvoxamine (RR = 3.08; 95% CI, 1.59–5.94), and topiramate (RR=2.18; 95% CI, 1.36–3.51) caused more dropouts from adverse events over placebo. Gamma-hydroxy-butyrate (RR = 1.90; 95% CI, 1.03–3.53), baclofen (RR = 1.80; 95% CI, 1.39–2.34), disulfiram (RR = 1.71; 95% CI, 1.39–2.10), gabapentin (RR = 1.66; 95% CI, 1.04–2.67), acamprosate (RR = 1.33; 95% CI, 1.15–1.54), and oral naltrexone (RR = 1.15; 95% CI, 1.01–1.32) improved total abstinence over placebo (Fig. 3C). For reduced heavy drinking, disulfiram (RR = 0.19; 95% CI, 0.10–0.35), baclofen (RR = 0.72; 95% CI, 0.57–0.91), acamprosate (RR = 0.78; 95% CI, 0.70–0.86), and oral naltrexone (RR = 0.81; 95% CI, 0.73–0.90) were efficacious against placebo.

Conclusions: The current meta-analyses provide evidence that several medications for AUDs are effective and safe and encourage the expanded use of these medications in the clinical setting. Our review found that acamprosate (2–3 g/d), disulfiram (250–500 mg/d), baclofen (30 mg/d), and oral naltrexone (50 mg/d) had the best evidence for improving abstinence and heavy drinking for patients with AUD.

Keywords

alcohol; alcohol use disorder; meta-analysis; network meta-analysis; pharmacotherapy

Alcohol use disorder (AUD) is one of the most prevalent substance use disorders globally (following tobacco), causing more than 2 million deaths annually.[1] AUD management is multimodal, involving a combination of psychosocial and pharmacological approaches.2 However, only a third of patients with AUD enter treatment, and only 10% receive AUD-specific pharmacotherapy; these estimates are much lower in many other countries.2 In patients with moderate to severe AUD, guidelines have recommended naltrexone, acamprosate, and disulfiram as first-line interventions.[2] Although there is good evidence for these agents over placebo for a range of AUD outcomes, there are fewer head-to-head comparisons or indirect comparisons across existing treatments.[3]

Regrettably, previous reviews have reported that 38% to 70% of patients with AUD treated with acamprosate or naltrexone do not benefit or only partially benefit from a trial with one of these medications.[4] To date, the comparative safety, and efficacy of several off-label, alternative pharmacotherapies-topiramate, gabapentin, baclofen, and ondansetron, for example-is unclear, particularly in adolescent, pregnant, older adult, or more complex patient populations (eg, those with concurrent medical, mental health, and substance use disorders). Although there is a need for larger, multi-site trials to confirm preliminary

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findings from multiple small randomized clinical trials (RCTs), particularly those looking at combination treatments, they are unlikely to occur.

There have been several AUD reviews and meta-analyses.[5–12] However, there remain gaps in knowledge for several reasons. First, previous reviews have not accounted for emerging AUD pharmacotherapies, newer trials, or head-to-head comparisons between agents.

Second, AUD treatment guidelines have been based on older literature, and there is a need to re-examine and update previous reviews and treatment guidelines. Finally, newer and more sophisticated techniques for comparative effectiveness research exist, such as network meta-analysis (NMA), a multiple treatments meta-analysis.[13] NMAs can synthesize direct and indirect evidence, draw new insights from existing data, and inform clinical guideline development. NMA offers several advantages over classical meta-analyses, including the ability to compare multiple treatments simultaneously (rather than using a fixed comparator) and the ability to rank treatments, which enables an appraisal of the comparative performance of agents in the network.

Therefore, the objectives of this systematic review and NMA are to evaluate the comparative efficacy, safety, and acceptability of AUD pharmacotherapies for promoting continuous total abstinence and reduced-risk drinking. We hypothesized that naltrexone, acamprosate, and disulfiram would show the most consistent efficacy and safety across treatments, given their established presence in AUD treatment and practice guidelines.

METHODS

Protocol and Registration

We registered our study protocol with the PROSPERO database of systematic reviews (CRD42021236612). In addition, we adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses for NMAs,[14] included as a checklist (Appendix 1, http://links.lww.com/JAM/A342).

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Eligibility Criteria

We defined our study eligibility using the populations-interventions-comparators-outcomes study design (PICO) framework.

- Population: Adults with AUD per the Diagnostic and Statistical Manual of Mental Disorders or other criteria. We included all patients regardless of AUD severity, comorbidity, age, gender, nationality, setting of care, or prior treatment history.
- Interventions: Any medication used to treat AUD, including naltrexone, acamprosate, disulfiram, baclofen, and others. Control interventions included placebo, other medications, or nonpharmacological/behavioral interventions.
- Outcomes: Alcohol consumption (total abstinence and reduced heavy drinking, defined as having 4 or 5 standard drinks in 1 sitting for females and males,

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respectively), withdrawal from trials, and withdrawal from trials due to adverse events.

- Studies: RCT or controlled clinical trials reporting eligible outcomes. We excluded nonadult samples, other study designs, and studies shorter than 4 weeks (as this was not considered enough time to treat AUD, per previous reviews).[12]

Information Sources and Search

We consulted a librarian, searching 9 electronic databases and registries for published and unpublished studies through February 2021 (Appendix 2, http://links.lww.com/JAM/A342). We also examined prior review articles and the bibliographies of included records for additional studies.

Study Selection

Two investigators independently reviewed each title and abstract and the full-text versions of articles deemed potentially relevant using Covidence, an electronic review manager.[15] We resolved discrepancies by consensus.

Data Collection Process and Data Items

We extracted relevant PICOS characteristics and appraised the study-level risk of bias using piloted forms in Covidence before transferring to a Microsoft Excel spreadsheet. Extracted variables included population characteristics (sample size, age, sex), intervention and comparator group details (name, dose, frequency, and route of administration), outcomes, and study design details (trial type, duration, location).

The Geometry of the Network

Network geometry was presented by graphing network plots, where each treatment represented a “node” and lines between nodes represent direct comparisons between treatment pairs.

Risk of Bias Within Included Studies

Using the Cochrane Collaboration tool for RCTs,[16] we appraised 6 key domains of bias: randomization, allocation concealment, blinding of participants, blinding of investigators, selective reporting, and attrition. Two reviewers assessed each domain and determined an overall grade (high, low, or unclear risk). Differences were resolved by consensus.

Summary Measures

As all outcomes were dichotomized, we calculated the summary rate ratio (RR) and its corresponding 95% confidence interval (95% CIs). RRs less than 1 with 95% CIs not crossing 1 indicated treatment significantly reduced the parameter of interest relative to the control. All summary measures were for total differences from the comparator condition over the entire course of treatment.

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Planned Methods of Analysis

Per previous NMAs, we used the netmeta package from R Studio (version 3.5.1) to conduct frequentist random-effects networks.[17] We extracted all outcomes using the intention-to-treat principle. To rank treatments, we calculated P-scores, which consider the effect size point estimate and precision and signify the mean extent of certainty that a treatment is better than the competing treatments.[18] Per previous reviews, we did not combine medications with similar mechanisms or in the same drug class to determine which medications have evidence supporting associations with improved outcomes.

Assessment of Inconsistency and Risk of Bias Across Studies

Per NMA guidelines, we assessed transitivity (the extent of network heterogeneity) and consistency (the degree of agreement between direct and indirect comparisons).[19] To measure transitivity, we measured I2 (the percentage of [tau]2 [total between-study variation] not due to random error), considering at least 50% significant values.[20,21] Per the Grading of Recommendations Assessment, Development, and Evaluation guidelines,[22] we downgraded the strength of evidence in the presence of high heterogeneity, bias in the Cochrane instrument, imprecision, or sensitivity to the inclusion or exclusion of additional data. Using Egger's test, we evaluated funnel plot asymmetry to detect possible publication bias.[23]

RESULTS

Study Selection

We identified 7784 unique reports from all electronic databases, and after title/abstract screening, there were 576 full-text articles for review. In total, 156 RCTs met inclusion criteria (Fig. 1).

Study Characteristics

Across the 156 RCTs, there were 27,334 participants (mean age 44 years, 74% male) and 37 unique treatment comparisons (Fig. 2, Appendix 3,http://links.lww.com/JAM/A342). The most encountered medications were oral naltrexone (n = 54), acamprosate (n =35), baclofen (n =14), disulfiram (n = 13), topiramate (n =12), nalmefene (n =9), gabapentin (n = −6), and extended-release naltrexone (n = 4). Most RCTs occurred in the United States (n = 69), used DSM criteria for AUD diagnosis (n = 127), and offered adjunctive psychotherapies (n = 92). The most provided modalities were individual supportive therapy (n = 20) and cognitive behavioral therapy (n = 18). The median trial duration was 12 weeks (range, 4–52). A handful of included trials were pilot studies (n = 16); however, the majority (n = 79) were multicentre RCT, and almost all of them took place in outpatient settings (n = 153). Few studies (n = 17) included persons with co-occurring substance use or psychiatric disorders, including cocaine dependence (n = 5), depression (n = 2), and tobacco use disorder (n = 2). Most studies (n = 97) required abstinence before commencing treatment.

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Risk of Bias Within Studies

The risk of bias profiles for each study is outlined in Appendix 4, http://links.lww.com/JAM/A342. Most studies were adequately randomized (84%), double-blinded (81%), and reported mechanisms for concealing treatment allocation (82%). However, attrition exceeded 20% in most studies (69%), and attrition was unbalanced (i.e., there was at least a 10% difference in attrition between study arms) in 37% (n = 55) of studies. Roughly one-third of studies did not fully report outcomes (30%). Trial registrations were identified for only a few studies (22%), and most RCTs had an unclear risk of selective reporting (79%). Most studies (75%) reported a mechanism for measuring treatment adherence, and most (77%) reported funding sources. Consequently, the overall risk of bias was high in most trials (97%).

Results of Individual Studies and Synthesis of Results

Dropouts—Nefazodone (RR = 2.11; 95% CI, 1.42–3.13), aripiprazole (RR = 1.97; 95% CI, 1.36–2.88), carbamazepine (RR = 1.85; 95% CI, 1.03–3.32), and nalmefene (RR = 1.17; 95% CI, 1.01–1.35) were associated with the most dropouts. Baclofen (RR = 0.83; 95% CI, 0.70–0.97) and pregabalin (RR = 0.63; 95% CI, 0.43–0.94) caused fewer dropouts than placebo (Fig. 3A).

Dropouts Due to Adverse Events—Nalmefene (RR = 3.26; 95% CI, 2.34–4.55), fluvoxamine (RR = 3.08; 95% CI, 1.59–5.94), and topiramate (RR = 2.18; 95% CI, 1.36–3.51) caused more dropouts from adverse events over placebo (Fig. 3B).

Abstinence—Gamma-hydroxy-butyrate (RR = 1.90; 95% CI, 1.03–3.53), baclofen (RR = 1.80; 95% CI, 1.39–2.34), disulfiram (RR = 1.71; 95% CI, 1.39–2.10), gabapentin (RR = 1.66; 95% CI, 1.04–2.67), acamprosate (RR = 1.33; 95% CI, 1.15–1.54), and oral naltrexone (RR = 1.15; 95% CI, 1.01–1.32) improved total abstinence over placebo (Fig. 3C).

Heavy Drinking—For reduced heavy drinking, disulfiram (RR = 0.19; 95% CI, 0.10–0.35), baclofen (RR = 0.72; 95% CI, 0.57–0.91), acamprosate (RR = 0.78; 95% CI, 0.70–0.86), and oral naltrexone (RR = 0.81; 95% CI, 0.73–0.90) were efficacious against placebo (Fig. 3D).

Exploration for Inconsistency and Risk of Bias Across Studies

There was greater evidence of intransitivity for abstinence and heavy drinking than dropouts and dropouts due to adverse events. Still, inconsistency estimates were high for dropouts from adverse events, abstinence, and heavy drinking (Table 1). In addition, we found evidence suggestive of publication bias (based on funnel plot asymmetry) for dropouts from adverse events and heavy drinking (Table 1; Appendices 5, http://links.lww.com/JAM/A343, 6, and 7, http://links.lww.com/JAM/A342). For these reasons, we downgraded the strength of evidence for each of the 4 primary outcomes.

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DISCUSSION

Summary of Evidence

The present NMA reviewed 156 RCTs, 27,334 participants, and 5 decades of AUD research. Naltrexone, disulfiram, and acamprosate were the most extensively studied agents and had the most consistent evidence for their efficacy. By contextualizing our results into the broader literature, we hope that our findings support ongoing AUD knowledge translation efforts.

Naltrexone and Acamprosate

Prior meta-analyses support naltrexone and acamprosate as first-line AUD treatment.5–12 In the present NMA, we found roughly similar efficacy for both agents in reducing heavy drinking and promoting abstinence. Previous studies suggest high cravings and a family history of AUD seem to predict naltrexone response while having an abstinence treatment goal, baseline anxiety, no family history of AUD, and older age of AUD onset (>40 years) improve acamprosate efficacy.[24] RCT evidence also demonstrates that targeted naltrexone can reduce heavy drinking when taken before drinking or significant cravings.[25] As targeted naltrexone shows similar efficacy and fewer adverse events than daily-dosed naltrexone, it may be a practical approach in patients with lower adherence, significant side effects, or those not meeting full AUD criteria.[26] Monthly intramuscular injections of extended-release naltrexone are available and seem to improve adherence, treatment retention, abstinence, and cravings in AUD.[27] Given the dual efficacy of naltrexone in opioid use disorder, this formulation may be suited for co-occurring diagnoses and in criminal justice settings.

Disulfiram

In the present meta-analysis, we found an effect of disulfiram on abstinence and heavy drinking. Whereas the previous meta-analysis by Skinner et al. found no evidence of superiority in blinded studies, the findings from open-label studies suggested it was a safe and efficacious treatment.[28] However, in their meta-analysis,[28] all outcomes were pooled, whereas the present meta-analysis stratified outcomes by abstinence and heavy drinking. Still, although double-blinding in RCTs mitigates several biases, disulfiram's effectiveness depends directly upon the patient's anticipations.[29] Considering these differences, the literature on the efficacy of disulfiram for AUD has been inconsistent. For example, a blinding-stratified meta-analysis of 22 trials demonstrated disulfiram's efficacy in open-label RCTs under structured, supervised conditions.[28] In a follow-up study, disulfiram's efficacy appeared to wane in unsupervised settings.[30] Still, patients benefiting from disulfiram may differ from the average AUD patient. Overall, disulfiram seems to work best under supervised settings and could be suggested for motivated patients with AUD committed to abstinence in general, especially if they would take it in front of a significant other.[26]

Topiramate

Two previous meta-analyses of topiramate found low-to-modest quality evidence for its use in AUD.[7,12] Topiramate was not significantly better than oral naltrexone or acamprosate. Moreover, despite its efficacy, topiramate was poorly tolerated, causing approximately

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twice as many adverse events leading to discontinuation than placebo in the present NMA, primarily from cognitive impairment and sedation.

Gabapentin

Despite its common use in treating AUD, our analyses did not identify a significant effect of gabapentin for heavy drinking, but did find a significant effect for improving abstinence (RR = 1.66; 95% CI, 1.04–2.67). Of note, the only RCT involving extended-release gabapentin, which we included in the present NMA, did not demonstrate efficacy over placebo for any AUD outcomes.[31]

Baclofen

Although early baclofen RCTs indicated potent AUD efficacy, previous reviews have found differing evidence across AUD outcomes. The discrepancies between our findings and previous reviews likely stem from methodological differences, including dosing issues, as European studies have tended towards using higher doses than U.S. studies. For example, Bschor et al. pooled any primary outcome across 14 baclofen RCTs, combining cumulative abstinence duration, percentage of abstinent days, heavy drinking outcomes, and liver enzyme elevations in 1 analysis.[32] The 2018 Cochrane review of baclofen for AUD only involved 5 trials for abstinence,[8] whereas the present study identified 16 RCTs spanning a range of outcomes. Minozzi et al. also defined heavy drinking differently, using the percentage change in the number of heavy drinking days.[8] Baclofen can cause several side effects, including vertigo, drowsiness, paresthesias, muscle rigidity.[8] However, our NMA found lower pooled dropout rates for baclofen participants than placebo.

Future Directions

Unfortunately, AUD pharmacotherapies remain severely underutilized, with 1 study showing that only 0.4% of public drug plan beneficiaries with AUD filled a prescription for naltrexone or acamprosate.[33] Future AUD research can fill gaps in optimal pharmacotherapy duration, treatments for special populations, maintenance, and dose titration strategies, and ways to enhance pharmacotherapy utilization. Although most clinical practice guidelines recommend at least 6 months of treatment and others suggest indefinite treatment, there is a need to determine the optimal pharmacotherapy duration. AUD treatment in special populations, including youth and pregnant individuals, is another research priority. Adolescent AUD treatment emphasizes psychosocial treatment alone, yet nearly 80% resume drinking within 12-month of psychosocial therapy alone.[34] There are also concerns that untreated adolescent AUD can progress to severe alcohol-related harms in adulthood.[35] Pilot studies of naltrexone for youth with moderate to severe AUD reported significant reductions in overall alcohol consumption, cravings, heavy drinking, and lower cravings over disulfiram.[36,37]

Although there are no RCTs on AUD pharmacotherapies in pregnant individuals, case reports point to potential benefits from gabapentin, naltrexone, or acamprosate. In addition, clinical practice guidelines emphasize considering the relative teratogenicity of untreated AUD and some AUD pharmacotherapies when counseling pregnant patients. For example, topiramate is contraindicated in pregnancy due to its association with cleft palate, whereas

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disulfiram is contra-indicated due to potential severe disulfiram-alcohol reactions to the fetus.[38]

Although abstinence has been the traditional goal of AUD treatment, reduced risk drinking may be a more appropriate target for many patients.[39] Unfortunately, there is a shortage of efficacy data for the latter. One prior meta-analysis found no robust evidence for available pharmacotherapies to reduce total alcohol consumption in nonabstinent patients with AUD.[40] However, 2 studies have shown that patients with AUD are more likely to achieve self-identified treatment goals than goals set for them,[41,42] emphasizing patient-centered treatment.

Strengths and Limitations

To our knowledge, the present NMA is the most comprehensive review of AUD pharmacotherapies. Compared to previous reviews, the present NMA considered all treatment settings, included a larger study yield, more RCTs, and a larger breadth of off-label pharmacotherapies.

However, our study also has limitations. First, we combined studies spanning different treatment settings, medication doses, duration of treatment, AUD severity, comorbidity status (eg, AUD and depression), treatment goal (abstinence or harm reduction), and delivery of psychosocial co-interventions. Given the lack of standardized protocols for RCTs investigating AUD, this heterogeneity was, to a certain extent, unavoidable and not a specific limitation of this review. We selected the random-effects model to account for higher between-study heterogeneity, which assumes that different studies estimate different parameters.[43] Finally, we determined whether these sources of potential heterogeneity had a significant influence on our conclusions via sensitivity analyses, stratifying each network by potential effect modifying characteristics. Fortunately, effect sizes did not change significantly.

Second, we mixed higher-quality studies with lower-quality ones, which could overinflate the benefits of small pilot studies exploring off-label agents. As we included more studies than previous reviews, smaller, lower-quality trials may have been overrepresented. However, most studies were of similar quality per the Cochrane risk of bias, suggesting no large differences in study quality in the networks.

Thirdly, despite an extensive search across published and unpublished literature, we may have missed relevant RCTs, given the appearance of potential publication bias in 2 of our secondary outcomes. However, the statistical significance of funnel plot symmetry only suggests publication bias and may be caused by other reasons, such as small sample sizes or selective reporting. Consequently, publication bias and selective reporting are potential limitations of this review.

CONCLUSIONS

The current meta-analyses provide evidence that several medications for AUDs are effective and safe and encourage the expanded use of these medications in the clinical setting. Our

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review found that acamprosate (2–3 g/d), disulfiram (250–500 mg/d), baclofen (30 mg/d), and oral naltrexone (50 mg/d) had the best evidence for improving abstinence and heavy drinking for patients with AUD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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AB wrote the initial draft of the work and managed revision feedback from the other authors. All the authors contributed to the design of this study, the interpretation of the data, subsequent manuscript drafts (and revisions) and gave final approval for submission.

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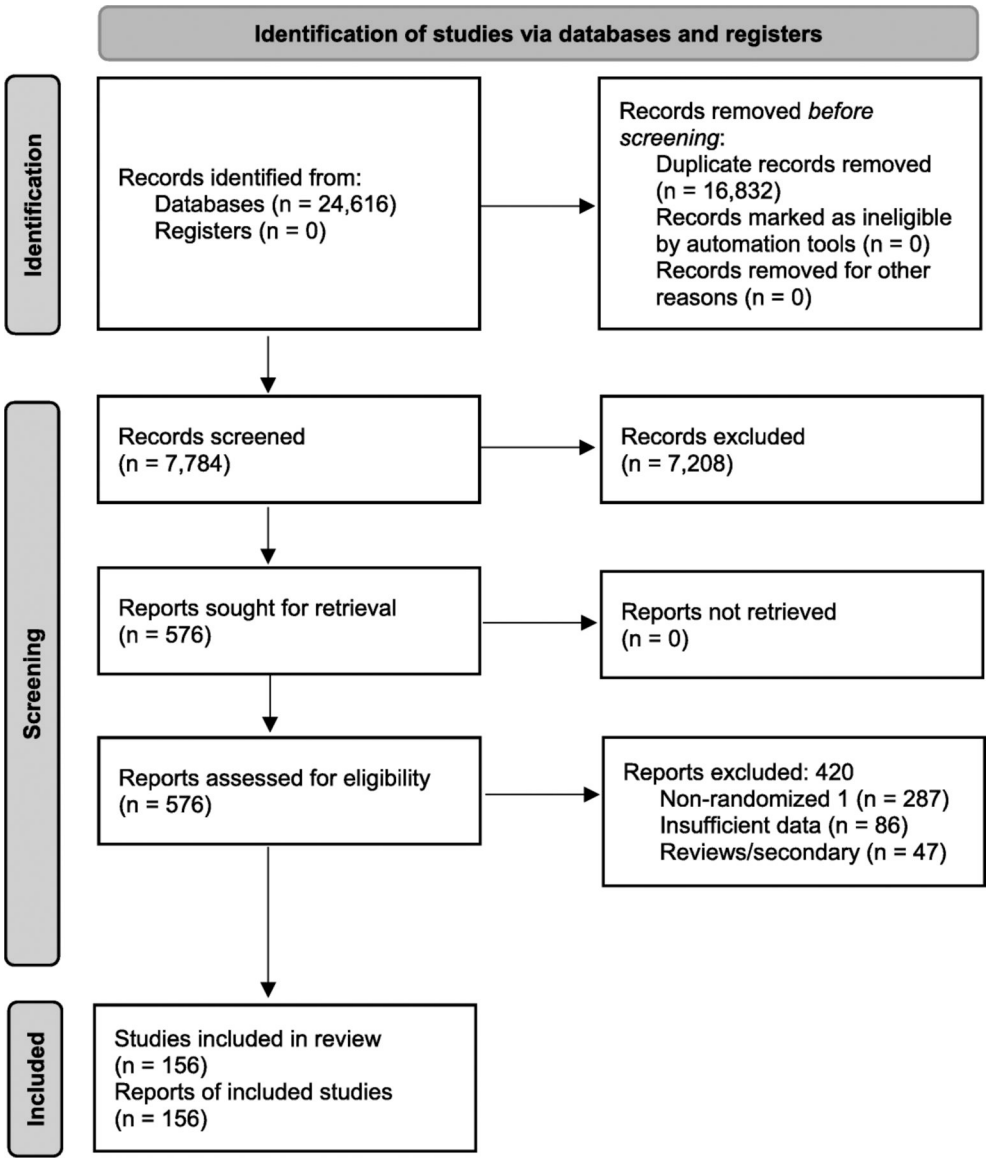

FIGURE 1.

PRISMA flow diagram. PRISMA indicates Preferred Reporting Items for Systematic Reviews and Meta-analyses

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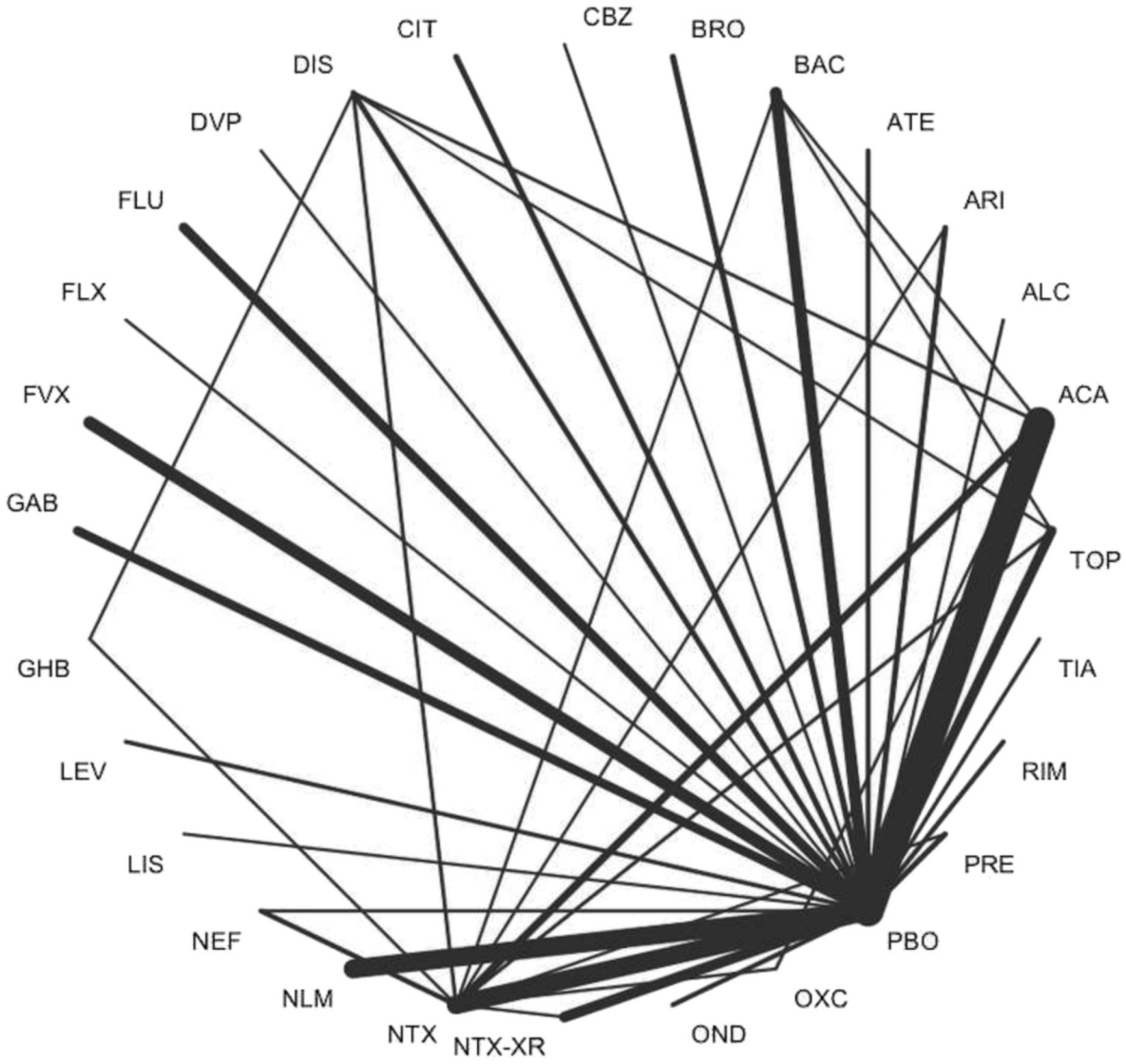

FIGURE 2.

Network plot of eligible pharmacotherapy comparisons across all studies for dropouts. Line width corresponds to the number of trials comparing pharmacotherapy pairs. ACA indicates acamprosate; ALC, acetyl-L-carnitine; ARI, aripiprazole; ATE, atenolol; BAC, baclofen; BRO, bromocriptine; CBZ, carbamazepine; CIT, citalopram; DIS, disulfiram; DVP, divalproex; FLU, flupenthixol; FLX, fluoxetine; FVZ, fluvoxamine; GAB, gabapentin; GHB, gamma-hydroxybutyrate; LEV, levetiracetam; LIS, lisuride; NEF, nefazodone; NLM, nalmefene; NTX, naltrexone; NTX-XR, naltrexone extended-release; OND, ondansetron; OXC, oxcarbazepine; PBO, placebo; PRE, pregabalin; RIM, rimonabant; TIA, tiapride; TOP, topiramate.

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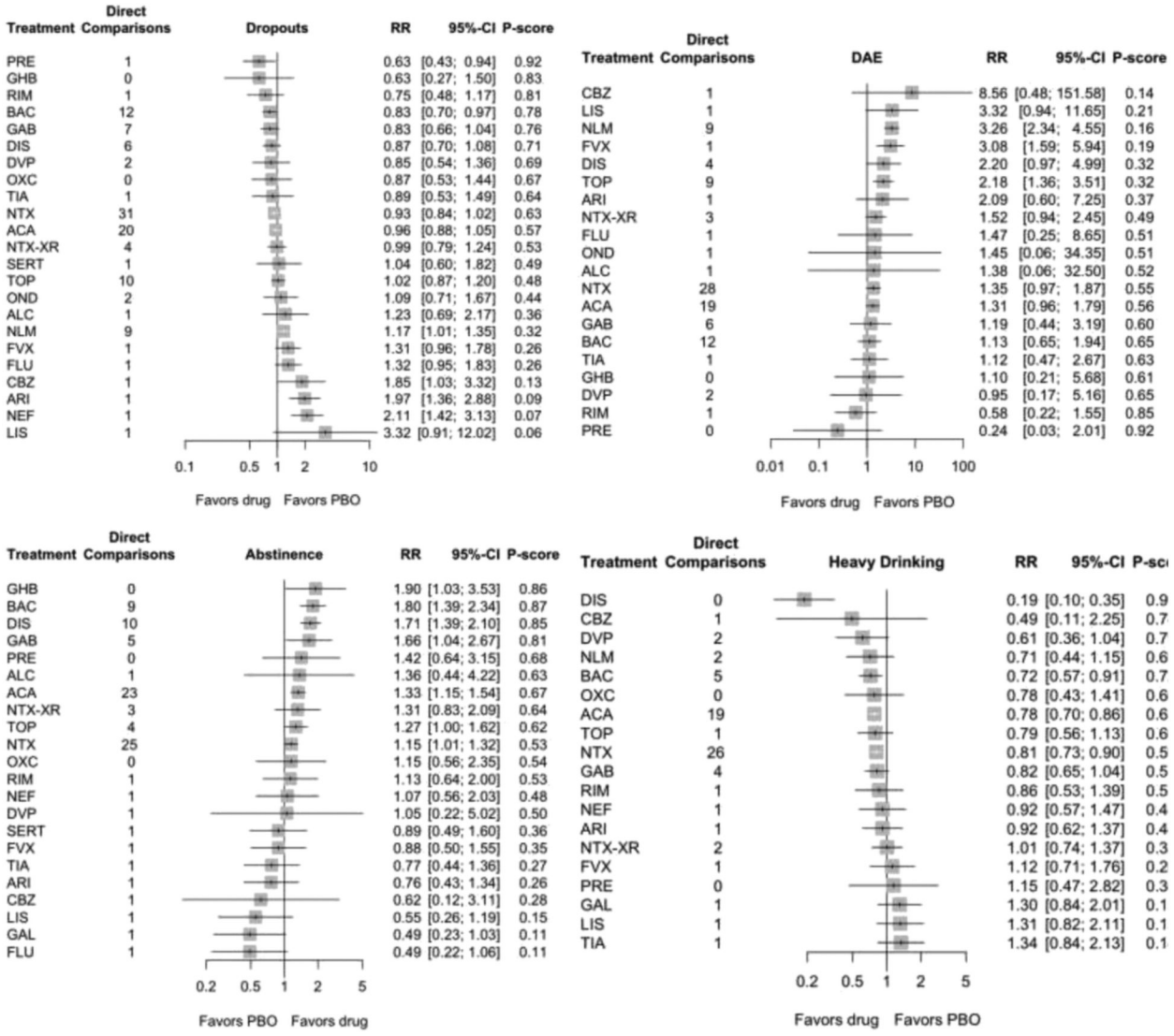

FIGURE 3.

Forest plot for networkmeta-analysis across randomized controlled trials of pharmacotherapies for alcohol use disorder for (A) Dropouts; (B) Dropouts from Adverse Events [DAE]; (C) Abstinence; and (D) Heavy Drinking. ACA indicates acamprosate; ALC, acetyl-L-carnitine; ARI, aripiprazole; ATE, atenolol; BAC, baclofen; BRO, bromocriptine; CBZ, carbamazepine; CIT, citalopram; DAE, dropouts due to adverse events; DIS, disulfiram; DVP, divalproex; FLU, flupenthixol; FLX, fluoxetine; FVZ, fluvoxamine; GAB, gabapentin; GAL, galantamine; GHB, gamma-hydroxybutyrate; LEV, levetiracetam; LIS, lisuride; NEF, nefazodone; NLM, nalmefene; NTX, naltrexone; NTX-XR, naltrexone extended-release; OND, ondansetron; OXC, oxcarbazepine; PBO, placebo; PRE, pregabalin; RIM, rimonabant; TIA, tiapride; TOP, topiramate.

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TABLE 1

Network Meta-analysis Summary for Outcomes

Outcome	*k*	n	*M*	T^2	I^2	*Q* between	*P*	Egger
Dropouts (any)	120	28	134	0.02	33.9%	24.92	0.20	0.45
Dropouts (adverse)	85	24	93	0.05	8.2%	23.94	0.02	0.04
Abstinence	96	27	104	0.07	56.5%	27.07	0.03	0.09
Heavy drinking	76	23	84	0.03	65.1%	27.75	<0.01	<0.01

K = number of studies; n = number of treatments; M = number of comparisons; T^2 = total variation; I^2 = proportion of total variation not due to random error, $Q_{between}$ = Cochrane Q coefficient for inconsistency; *P* = statistical significance for $Q_{between}$; Egger = statistical significance for funnel plot asymmetry.