Original Investigation

Pharmacotherapy for Adults With Alcohol Use Disorders in Outpatient Settings

A Systematic Review and Meta-analysis

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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.

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Alcohol use disorders (AUDs) are common, cause substantial morbidity, and result in 3-fold increased rates of early mortality (eTable 1 in the Supplement).[1-8] Treating AUDs is difficult but may be aided by using medications. Pharmacotherapy for AUDs was initiated in the 1950s and consisted only of disulfiram (Antabuse). In the 1990s, naltrexone (oral and intramuscular formulations) and acamprosate were approved by the US Food and Drug Administration (FDA) (eTable 2 in the Supplement).

Fewer than one-third of patients with AUDs receive treatment,[6] and only a small percentage (<10%) receive medications to assist in reducing alcohol consumption. To evaluate the benefits and harms of medications for the treatment of adults with AUDs, we conducted a systematic review. A larger, more comprehensive technical report for the Agency for Healthcare Research and Quality was prepared (eTable 3 in the Supplement).[9] This article summarizes findings from the larger report on the efficacy of various medications used for the treatment of AUDs in reducing alcohol intake or improving health outcomes and on the adverse effects of these medications.

Methods

We developed and followed a standard protocol. A technical report that details methods, search strategies, and additional information is available online.[9]

Data Sources and Searches

We searched PubMed, the Cochrane Library, PsycINFO, CINAHL, and EMBASE from January 1, 1970, to October 11, 2013, for the technical report; we updated searches through March 1, 2014, for this article. An experienced Evidence-based Practice Center (EPC) librarian ran all searches; another EPC librarian peer-reviewed them. We manually searched reference lists of pertinent reviews and trials for relevant citations that our searches missed.

We searched for unpublished studies using ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform, and the FDA website. In addition, the Scientific Resource Center of the Agency for Healthcare Research and Quality requested unpublished studies and data from manufacturers.

Study Selection

We included studies enrolling adults with AUDs that evaluated an FDA-approved medication or any of 23 off-label medications for at least 12 weeks in an outpatient setting. Studies were required to assess one of the following outcomes: (1) consumption—return to any drinking, return to heavy drinking, drinking days, heavy drinking days (≥4 drinks per day for women; ≥5 for men), drinks per drinking day; (2) health outcomes—accidents (ie, motor vehicle crashes), injuries, quality of life, function, and mortality; or (3) adverse effects.

Double-blind randomized clinical trials (RCTs) comparing one of the medications with placebo or another medication were eligible. Prospective cohort studies that compared 2 medications were eligible if they reported a health outcome. For adverse effects, the following designs were eligible if they compared 2 drugs of interest: nonrandomized or open-label trials, subgroup analyses from trials, prospective cohort studies, and case-control studies.

Two investigators independently reviewed each title and abstract. Studies marked for possible inclusion by either reviewer underwent dual, independent full-text review. If reviewers disagreed, we resolved conflicts by consensus.

Data Extraction and Risk of Bias Assessment

We used structured data extraction forms to gather relevant data from each article. All data extractions were reviewed for completeness and accuracy by at least 2 investigators.

To assess the risk of bias of studies, we used predefined criteria based on established guidance.[10,11] We included questions about adequacy of randomization, allocation concealment, similarity of groups at baseline, blinding, attrition, validity and reliability of measures, whether intention-to-treat (ITT) analysis was used, methods of handling missing data, and fidelity. We rated the studies as low, medium, high, or unclear risk of bias.[10,11] Two independent reviewers assessed risk of bias for each study. Disagreements were resolved by consensus.

Data Synthesis and Analysis

We conducted meta-analyses of RCTs using random-effects models.[12] For continuous outcomes, we used weighted mean differences (WMDs) and 95% CIs. For binary outcomes, we calculated risk differences (RDs) between groups and 95% CIs. We did not include studies rated as high or unclear risk of bias in our main analyses but included them in sensitivity analyses. When possible, we conducted post hoc subgroup analyses to assess whether pooled results differed for studies rated as low risk of bias. We calculated the I^2 statistic to assess statistical heterogeneity.[13,14] We examined potential sources of heterogeneity by analysis of subgroups defined by patient population (eg, US vs non-US studies). Analyses were conducted using the metan, metafunnel, and metabias commands in Stata version 11.1 (StataCorp). Statistical significance was assumed when 95% CIs of pooled results did not cross 0. All testing was 2-sided. We calculated numbers needed to treat (NNTs) and numbers needed to harm (NNHs) when pooled RDs found a statistically significant result. When appropriate[15,16] (eg, ≥10 studies in a meta-analysis), we assessed for publication bias by visually examining funnel plots and using the Begg-Mazumdar[17] test. None of the funnel plots or statistical tests indicated concern for publication bias. When quantitative synthesis was not appropriate (eg, insufficient numbers of similar studies), we synthesized the data qualitatively.

We graded the strength of evidence as high, moderate, low, or insufficient based on established guidance.[18] The approach incorporates 4 key domains: risk of bias, consistency, directness, and precision. Two reviewers assessed each domain for each outcome and determined an overall grade. Differences were resolved by consensus.

We did not combine medications with similar mechanisms or in the same drug class in our analyses because we

aimed to determine which medications (not classes) have evidence supporting associations with improved outcomes. For example, nalmefene is an opioid receptor antagonist like naltrexone, but we analyzed them separately.

Results

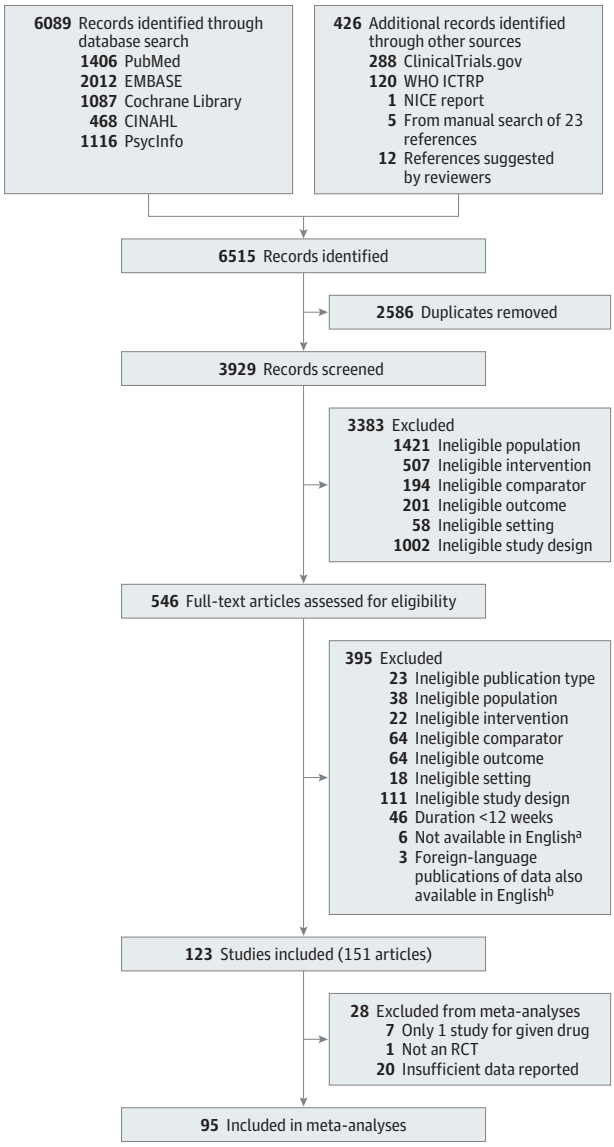
We included 151 articles reporting on 123 studies (**Figure 1**). Of these, one was a prospective cohort study[29]; the rest were RCTs; the total number of participants was 22 803. Characteristics of included studies are shown in eTable 4 in the Supplement. Most studies assessed acamprosate (27 studies, n = 7519), naltrexone (53 studies, n = 9140), or both. Sample sizes ranged from 21 to 1383. Treatment duration ranged from 12 to 52 weeks. Mean age was usually in the 40s. All participants met criteria for alcohol dependence in the vast majority of trials. Most studies enrolled patients after detoxification or required a period of sobriety (at least 3 days). Studies typically included psychosocial co-interventions; thus, effect sizes reflect the added benefits of medications beyond those of psychosocial interventions and placebo. The largest trial, COMBINE,[30] randomized 1383 treatment-seeking patients to receive medical management with naltrexone (plus 1 placebo), acamprosate (plus 1 placebo), both, or 2 placebos, with or without a combined behavioral intervention or to receive a combined behavioral intervention only (no pills).

We included 22 placebo-controlled trials of acamprosate, 4 of disulfiram, and 44 of naltrexone. For medications used off-label, we included 1 placebo-controlled trial for each of the following: aripiprazole, atomoxetine, desipramine, fluvoxamine, gabapentin, imipramine, olanzapine, ondansetron, and paroxetine. We included multiple placebo-controlled trials for baclofen, buspirone, citalopram, fluoxetine, nalmefene, quetiapine, sertraline, topiramate, valproic acid, and varenicline. We 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).

Consumption Outcomes

Acamprosate and naltrexone were associated with improvement in consumption outcomes (**Table 1**, **Figure 2**, and **Figure 3**). To prevent 1 person from returning to any drinking, the NNTs were 12 (95% CI, 8 to 26; 16 trials, n = 4847) and 20 (95% CI, 11 to 500; 16 trials, n = 2347) for acamprosate and oral naltrexone (50 mg/d), respectively. For return to heavy drinking, acamprosate was not associated with improvement, whereas oral naltrexone (50 mg/d) was associated with improvement with an NNT of 12 (95% CI, 8 to 26; 19 trials, n = 2875). For injectable naltrexone, our meta-analyses found no statistically significant association with return to any drinking or return to heavy drinking but found an association with reduction in heavy drinking days (WMD −4.6%; 95% CI, −8.5% to −0.56%; 2 trials, n = 926). Evidence from well-controlled trials of disulfiram does not adequately support an association with preventing return to any drinking or improvement in other alcohol consumption outcomes (Table 1). The largest disulfiram trial (n = 605) reported fewer drinking days for participants who returned to drinking and had a complete set of assessments.[32] Results of sensitivity analyses that included studies rated as high or unclear risk of bias were similar to the results of our main analyses (eFigures 1 and 2 in the Supplement).

Figure 1. Disposition of Articles



RCT indicates randomized clinical trial; WHO, World Health Organization.
[a]The following studies were unavailable in English (this information is from the English-language abstracts): Barrias et al,[19] 1997 (Portuguese): study of acamprosate; no other details available in English; Huang et al,[20] 2002 (Chinese): 12-week randomized trial of naltrexone vs placebo; n = 45; Krupitski et al,[21] 1994 (Russian): study (unspecified design) of baclofen vs sibazon vs amitriptyline vs placebo; n = 90; Ladewig et al,[22] 1993 (German): 6-month double-blind period of year-long trial of acamprosate vs placebo; number of patients unspecified; Castro et al,[23] 2009 (Portuguese): 12-week double-blind RCT of naltrexone vs placebo; n = 71; and Roussaux et al,[24] 1996 (French): double-blind RCT (duration unspecified) of acamprosate vs placebo; n = 127.
[b]The following non-English studies reported results identical to the results reported in the English-language study publications: Geerlings et al, 1995,[25] Kiefer et al, 2003,[26] and Sass et al,[27] 1996.

Table 1. Summary of Findings and Strength of Evidence From Trials Assessing Efficacy of FDA-Approved Medications for Alcohol Use Disorders

Medication	Outcome	No. of Studies	No. of Participants[a]	Results Effect Size (95% CI)[b]	NNT (95% CI)[c]	Strength of Evidence
Acamprosate	Return to any drinking	16	4847	RD: −0.09 (−0.14 to −0.04)	12 (8 to 26)	Moderate
	Return to heavy drinking	7	2496	RD: −0.01 (−0.04 to 0.03)	NA	Moderate
	% DDs	13	4485	WMD: −8.8 (−12.8 to −4.8)	NA	Moderate
	% HDDs	1	100	WMD: −2.6 (−11.4 to 6.2)	NA	Insufficient
	Drinks per DD	1	116	WMD: 0.4 (−1.8 to 2.6)	NA	Insufficient
	Accidents or injuries	0	0	NA	NA	Insufficient
	QoL or function	1	612	NSD	NA	Insufficient
	Mortality	8	2677	7 events (acamprosate) vs 6 events (placebo)	NA	Insufficient
Disulfiram	Return to any drinking	2	492	RD: −0.04 (−0.11 to 0.03)	NA	Low
	Return to heavy drinking	0	0	NA	NA	Insufficient
	% DDs	2	290	NSD[d]	NA	Insufficient
	% HDDs	0	0	NA	NA	Insufficient
	Drinks per DD	0	0	NA	NA	Insufficient
	Accidents or injuries	0	0	NA	NA	Insufficient
	QoL or function	0	0	NA	NA	Insufficient
	Mortality	0	0	NA	NA	Insufficient
Naltrexone, 50 mg oral	Return to any drinking	16	2347	RD: −0.05 (−0.10 to −0.002)	20 (11 to 500)	Moderate
	Return to heavy drinking	19	2875	RD: −0.09 (−0.13 to −0.04)	12 (8 to 26)	Moderate
	% DDs	15	1992	WMD: −5.4 (−7.5 to −3.2)	NA	Moderate
	% HDDs	6	521	WMD: −4.1 (−7.6 to −0.61)	NA	Moderate
	Drinks per DD	9	1018	WMD: −0.49 (−0.92 to −0.06)	NA	Low
Naltrexone, 100 mg oral	Return to any drinking	3	946	RD: −0.03 (−0.08 to 0.02)	NA	Low
	Return to heavy drinking	2	858	RD: −0.05 (−0.11 to 0.01)	NA	Low
	% DDs	2	858	WMD: −0.9 (−4.2 to 2.5)	NA	Low
	% HDDs	2	423	WMD: −3.1 (−5.8 to −0.3)	NA	Low
	Drinks per DD	1	240	WMD: 1.9 (−1.5 to 5.2)	NA	Insufficient
Naltrexone injection	Return to any drinking	2	939	RD: −0.04 (−0.10 to 0.03)	NA	Low
	Return to heavy drinking	2	615	RD: −0.01 (−0.14 to 0.13)	NA	Low
	% DDs	1	315	WMD: −8.6 (−16.0 to −1.2)	NA	Insufficient
	% HDDs	2[e]	926	WMD: −4.6 (−8.5 to −0.56)	NA	Low
	Drinks per DD	0	0	NA	NA	Insufficient
Naltrexone (any dose)	Accidents or injuries	0	0	NA	NA	Insufficient
	QoL or function	4	1513	Some conflicting results[f]	NA	Insufficient
	Mortality	6	1738	1 event (naltrexone) vs 2 events (placebo)	NA	Insufficient

Abbreviations: DD, drinking day; FDA, US Food and Drug Administration; HDD, heavy drinking day; NA, not applicable; NNT, number needed to treat; NSD, no statistically significant difference; QoL, quality of life; RD, risk difference; WMD, weighted mean difference.

[a] Includes only studies rated as low or medium risk of bias that were included in the main analyses; these numbers do not include studies rated as high or unclear risk of bias that were only included in sensitivity analyses.

[b] Negative effect sizes favor intervention over placebo/control. For dichotomous outcomes, RDs show the absolute difference between groups for the outcome. For example, the RD of −0.09 for acamprosate compared with placebo for return to any drinking indicates that 9% fewer participants treated with acamprosate (than with placebo) returned to any drinking. For continuous outcomes, the WMDs represent the mean difference between groups; they are the same units as the outcome specified. For example, a WMD of −8.8 for acamprosate compared with placebo for percentage of drinking days indicates 8.8% fewer drinking days over the course of treatment for those treated with acamprosate than for those who received placebo.

[c] NA entry for NNT indicates that the RD (95% CI) was not statistically significant, so we did not calculate a NNT, or that the effect measure was not one that allows direct calculation of NNT (eg, WMD).

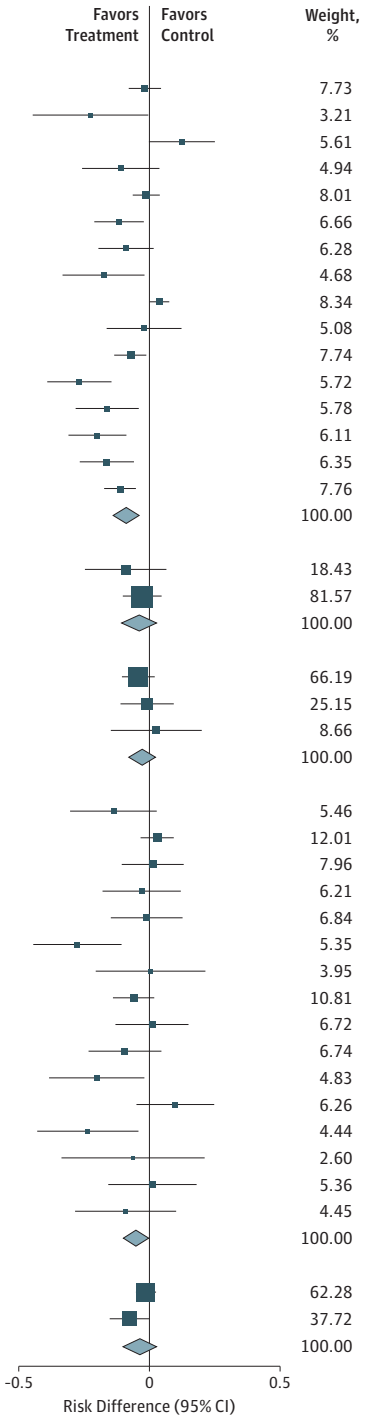
[d] One study (n = 128) reported similar percentages and no significant difference[31]; the other reported that disulfiram was favored among the subset of participants (162/605 participants) who drank and had a complete set of assessment interviews, but it did not report this outcome for the full randomized sample.[32] Overall, evidence was insufficient due to imprecision, inconsistency, and indirectness.

[e] Contains data from personal communication (B. Silverman, November 14, 2013).

[f] Unable to pool data. Two studies found no significant difference between naltrexone- and placebo-treated participants.[33,34] One study reported that patients receiving injectable naltrexone, 380 mg/d, had greater improvement on the mental health summary score than those receiving placebo at 24 weeks (8.2 vs 6.2, $P = .04$).[35] One study measured alcohol-related consequences and reported that more participants who received placebo (n = 34) had at least 1 alcohol-related consequence than those who received naltrexone (n = 34): 76% vs 45%, $P = .02$.[36]

Figure 2. Return to Any Drinking for Selected Medications Compared With Placebo

Source	Duration, wk	Risk of Bias	Treatment Group Events, No.	Treatment Group No Events, No.	Control Group Events, No.	Control Group No Events, No.	Risk Difference (95% CI)	Weight, %
Acamprosate								
Anton et al,[30] 2006	16	Low	244	59	254	55	-0.02 (-0.08 to 0.04)	7.73
Baltieri et al,[47] 2004	12	Med	15	25	21	14	-0.22 (-0.45 to -0.00)	3.21
Berger et al,[46] 2013	12	Med	48	3	40	9	0.12 (-0.00 to 0.25)	5.61
Besson et al,[48] 1998	51	Med	41	14	47	8	-0.11 (-0.26 to 0.04)	4.94
Chick et al,[49] 2000	24	Med	254	35	260	32	-0.01 (-0.06 to 0.04)	8.01
Geerlings et al,[51] 1997	26	Med	96	32	116	18	-0.12 (-0.21 to -0.02)	6.66
Gual et al,[45] 2001	26	Med	92	49	109	38	-0.09 (-0.19 to 0.02)	6.28
Kiefer et al,[39] 2003	12	Low	30	10	37	3	-0.17 (-0.33 to -0.02)	4.68
Mason et al,[37] 2006	24	Low	328	13	240	20	0.04 (0.00 to 0.08)	8.34
Morley et al,[38] 2006	12	Low	44	11	50	11	-0.02 (-0.16 to 0.12)	5.08
Paille et al,[52] 1995	51	Med	294	67	157	20	-0.07 (-0.13 to -0.01)	7.74
Pelc et al,[53] 1997	13	Med	74	52	53	9	-0.27 (-0.39 to -0.14)	5.72
Poldrugo et al,[54] 1997	26	Med	63	59	84	40	-0.16 (-0.28 to -0.04)	5.78
Sass et al,[28] 1996	48	Med	75	61	102	34	-0.20 (-0.31 to -0.09)	6.11
Tempesta et al,[55] 2000	26	Med	87	77	115	51	-0.16 (-0.27 to -0.06)	6.35
Whitworth et al,[56] 1996	52	Med	183	41	208	16	-0.11 (-0.17 to -0.05)	7.76
Subtotal: $I^2 = 80.8\%$; $P < .001$							-0.09 (-0.14 to -0.04)	100.00
Disulfiram								
Fuller et al,[31] 1979	52	Med	34	9	37	5	-0.09 (-0.25 to 0.07)	18.43
Fuller et al,[32] 1986	52	Med	164	38	167	32	-0.03 (-0.10 to 0.05)	81.57
Subtotal: $I^2 = 0.0\%$; $P = .48$							-0.04 (-0.11 to 0.03)	100.00
Naltrexone (100 mg/d oral)								
Anton et al,[30] 2006	16	Low	241	68	254	55	-0.04 (-0.10 to 0.02)	66.19
Oslin et al,[57] 2008	24	Med	95	25	96	24	-0.01 (-0.11 to 0.09)	25.15
Pettinati et al,[58] 2010	14	Med	39	10	30	9	0.03 (-0.15 to 0.20)	8.66
Subtotal: $I^2 = 0.0\%$; $P = .69$							-0.03 (-0.08 to 0.02)	100.00
Naltrexone (50 mg/d oral)								
Anton et al,[59] 1999	12	Med	36	32	42	21	-0.14 (-0.30 to 0.03)	5.46
Balldin et al,[60] 2003	24	Low	55	1	59	3	0.03 (-0.03 to 0.09)	12.01
Chick et al,[50] 2000	12	Med	70	15	64	15	0.01 (-0.11 to 0.13)	7.96
Gastpar et al,[61] 2002	12	Med	41	43	45	42	-0.03 (-0.18 to 0.12)	6.21
Guardia et al,[62] 2002	12	Med	53	48	54	47	-0.01 (-0.15 to 0.13)	6.84
Kiefer et al,[39] 2003	12	Low	26	14	37	3	-0.28 (-0.44 to -0.11)	5.35
Killeen et al,[63] 2004	12	Med	30	21	21	15	0.00 (-0.21 to 0.22)	3.95
Krystal et al,[64] 2001	12	Med	255	163	140	69	-0.06 (-0.14 to 0.02)	10.81
Morley et al,[38] 2006	12	Low	44	9	50	11	0.01 (-0.13 to 0.15)	6.72
Morris et al,[65] 2001	12	Med	43	12	49	7	-0.09 (-0.23 to 0.05)	6.74
O'Malley et al,[66] 1992	12	Med	27	24	38	14	-0.20 (-0.38 to -0.02)	4.83
O'Malley et al,[67] 2007	12	Med	49	8	38	12	0.10 (-0.05 to 0.25)	6.26
O'Malley et al,[36] 2008	16	Med	22	12	30	4	-0.24 (-0.43 to -0.04)	4.44
Oslin et al,[68] 1997	12	Med	6	15	8	15	-0.06 (-0.34 to 0.21)	2.60
Petrakis at al,[69] 2005	12	Med	21	38	22	42	0.01 (-0.16 to 0.18)	5.36
Volpicelli et al,[70] 1997	12	Med	27	21	32	17	-0.09 (-0.28 to 0.10)	4.45
Subtotal: $I^2 = 46.4\%$; $P = .02$							-0.05 (-0.10 to -0.00)	100.00
Naltrexone injection								
Garbutt et al,[44] 2005	26	Med	388	27	198	11	-0.01 (-0.05 to 0.03)	62.28
Kranzler et al,[71] 2004	12	Med	130	28	141	16	-0.08 (-0.15 to 0.00)	37.72
Subtotal: $I^2 = 58.5\%$; $P = .12$							-0.04 (-0.10 to 0.03)	100.00

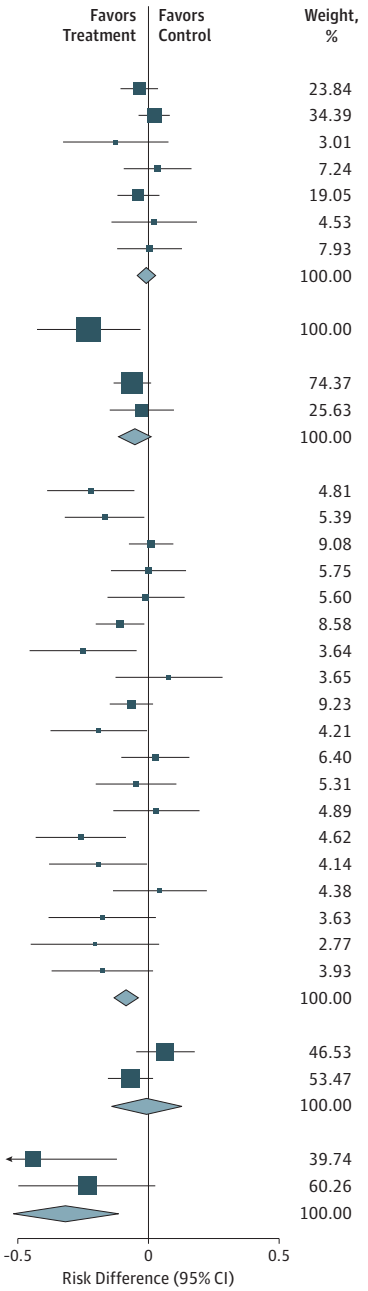


Weights are from random-effects analysis. Size of data markers reflects study weight. Med indicates medium.

Post hoc subgroup analyses by risk of bias (separating studies rated as low risk of bias) did not reveal any notable differences or were underpowered to find differences for most outcomes and medications (eFigures 3 through 10 in the Supplement). However, the subgroup analysis for return to any drinking for acamprosate compared with placebo showed a decreasing effect size from high/unclear (RD, −0.13; 95% CI, −0.20 to −0.06; 3 trials, n = 757) or medium (RD, −0.11; 95% CI, −0.16 to −0.06, 12 trials, n = 3438) to low (RD, −0.02; 95% CI, −0.09 to 0.05, 4 trials, n = 1409) risk of bias (eFigure 3 in the Supple-

Figure 3. Return to Heavy Drinking for Selected Medications Compared With Placebo

Source	Duration, wk	Risk of Bias	Treatment Group Events, No.	Treatment Group No Events, No.	Control Group Events, No.	Control Group No Events, No.	Risk Difference (95% CI)	Weight, %
Acamprosate								
Anton et al,[30] 2006	16	Low	211	92	226	83	-0.04 (-0.11 to 0.04)	23.84
Chick et al,[49] 2000	24	Med	246	43	242	50	0.02 (-0.04 to 0.08)	34.39
Kiefer et al,[39] 2003	12	Med	25	15	30	10	-0.13 (-0.33 to 0.08)	3.01
Mann et al,[40] 2013	12	Med	89	83	41	44	0.04 (-0.09 to 0.16)	7.24
Mason et al,[37] 2006	24	Low	143	198	119	141	-0.04 (-0.12 to 0.04)	19.05
Morley et al,[38] 2006	12	Low	40	15	43	18	0.02 (-0.14 to 0.19)	4.53
Wolwer et al,[73] 2011	24	Med	65	59	65	60	0.00 (-0.12 to 0.13)	7.93
Subtotal: I^2 = 0.0%; P = .67							-0.01 (-0.04 to 0.03)	100.00
Nalmefene								
Mason et al,[41] 1999	12	Med	26	44	21	14	-0.23 (-0.43 to -0.03)	100.00
Naltrexone (100 mg/d oral)								
Anton et al,[30] 2006	16	Low	207	102	226	83	-0.06 (-0.13 to 0.01)	74.37
Oslin et al,[57] 2008	24	Med	73	47	76	44	-0.03 (-0.15 to 0.10)	25.63
Subtotal: I^2 = 0.0%; P = .61							-0.05 (-0.11 to 0.01)	100.00
Naltrexone (50 mg/d oral)								
Anton et al,[59] 1999	12	Med	26	42	38	25	-0.22 (-0.39 to -0.05)	4.81
Anton et al,[72] 2005	12	Med	33	48	46	34	-0.17 (-0.32 to -0.02)	5.39
Balldin et al,[60] 2003	24	Low	53	3	58	4	0.01 (-0.07 to 0.10)	9.08
Chick et al,[50] 2000	12	Med	57	28	53	26	-0.00 (-0.14 to 0.14)	5.75
Gastpar et al,[61] 2002	12	Med	34	50	36	51	-0.01 (-0.16 to 0.14)	5.60
Guardia et al,[62] 2002	12	Med	8	93	19	82	-0.11 (-0.20 to -0.02)	8.58
Kiefer et al,[39] 2003	12	Low	20	20	30	10	-0.25 (-0.45 to -0.05)	3.64
Killeen et al,[63] 2004	12	Med	21	30	12	24	0.08 (-0.13 to 0.28)	3.65
Krystal et al,[64] 2001	12	Med	183	235	105	104	-0.06 (-0.15 to 0.02)	9.23
Latt et al,[74] 2002	12	Med	19	37	27	24	-0.19 (-0.37 to -0.01)	4.21
Mann et al,[40] 2013	12	Med	86	83	41	44	0.03 (-0.10 to 0.16)	6.40
Monti et al,[75] 2001	12	Med	16	48	19	45	-0.05 (-0.20 to 0.11)	5.31
Morley et al,[38] 2006	12	Low	39	14	43	18	0.03 (-0.13 to 0.20)	4.89
Morris et al,[65] 2001	12	Med	28	27	43	13	-0.26 (-0.43 to -0.09)	4.62
O'Malley et al,[66] 1992	12	Med	24	28	34	18	-0.19 (-0.38 to -0.01)	4.14
O'Malley et al,[67] 2007	12	Med	39	18	32	18	0.04 (-0.14 to 0.22)	4.38
O'Malley et al,[36] 2008	16	Med	22	12	28	6	-0.18 (-0.38 to 0.03)	3.63
Oslin et al,[68] 1997	12	Med	3	18	8	15	-0.20 (-0.45 to 0.04)	2.77
Volpicelli et al,[70] 1997	12	Med	17	31	26	23	-0.18 (-0.37 to 0.02)	3.93
Subtotal: I^2 = 43.7%; P = .02							-0.09 (-0.13 to -0.04)	100.00
Naltrexone injection								
ALK21-014[76]	12	Med	90	62	78	70	0.07 (-0.05 to 0.18)	46.53
Kranzler et al,[71] 2004	12	Med	122	36	132	25	-0.07 (-0.16 to 0.02)	53.47
Subtotal: I^2 = 72.2%; P = .06							-0.01 (-0.14 to 0.13)	100.00
Valproic acid								
Brady et al,[42] 2002	12	Med	5	9	12	3	-0.44 (-0.77 to -0.12)	39.74
Salloum et al,[43] 2005	24	Med	12	15	17	8	-0.24 (-0.50 to 0.03)	60.26
Subtotal: I^2 = 0.0%; P = .33							-0.32 (-0.52 to -0.11)	100.00



Weights are from random-effects analysis. Size of data markers reflects study weight. Med indicates medium.

ment). Although the confidence intervals for pooled estimates of all subgroups overlapped, the pooled estimate for the low risk of bias subgroup was not statistically significant, and the 2 studies[30,37] rated as low risk of bias that contributed the largest number of events found lack of efficacy for acamprosate.

Our meta-analyses of head-to-head RCTs comparing acamprosate with naltrexone[30,38-40] found no statistically significant difference between the 2 medications (**Table 2**). COMBINE was one of the RCTs.[30] It found that patients receiving medical management with naltrexone, a combined behavioral intervention, or both had better drinking outcomes than those who received placebo, but acamprosate showed no evidence of efficacy.

For the vast majority of medications used off-label, evidence was either insufficient to determine whether they are associated with reduced consumption or evidence suggested that they are not (eTable 5 in the Supplement). We found some exceptions (eTable 5, Figure 3). For topiramate, evidence sup-

Table 2. Summary of Findings and Strength of Evidence From Double-Blind Randomized Clinical Trials Directly Comparing Acamprosate and Naltrexone[a]

Outcome	No. of Studies	No. of Participants[b]	Results Effect Size (95% CI)[c]	Strength of Evidence
Return to any drinking	3	800	RD: 0.02 (−0.03 to 0.08)	Moderate
Return to heavy drinking	4	1141	RD: 0.01 (−0.05 to 0.06)	Moderate
% DDs	2	720	WMD: −2.98 (−13.4 to 7.5)	Low

Abbreviations: DD, drinking day; RD, risk difference; WMD, weighted mean difference.

[a] We did not include rows in this table for outcomes that we graded as insufficient strength of evidence (percentage heavy drinking days, drinks per DD, accidents or injuries, quality of life or function, and mortality).

[b] Includes only studies rated as low or medium risk of bias included in the main analyses; these numbers do not include studies rated as high or unclear risk of bias that were included in sensitivity analyses.

[c] Negative effect sizes favor acamprosate over naltrexone.

ports an association with fewer drinking days (WMD, −6.5%; 95% CI, −12.0% to −1.0%; 2 trials,[77,78] n = 541), heavy drinking days (WMD, −9.0%; 95% CI, −15.3% to −2.7%; 3 trials,[77-79] n = 691), and drinks per drinking day (WMD, −1.0; 95% CI, −1.6 to −0.48; 3 trials,[77-79] n = 691). For nalmefene, evidence supports an association with fewer heavy drinking days per month (WMD, −2.0; 95% CI, −3.0 to −1.0; 2 trials,[80,81] n = 806) and drinks per drinking day (WMD, −1.02; 95% CI, −1.77 to −0.28; 3 trials,[41,82,83] n = 608). Finally, limited evidence from 2 small RCTs[42,43] (total n = 88), one enrolling people with bipolar disorder, supports an association between valproic acid and improvement in some consumption outcomes.

Health Outcomes

We found insufficient direct evidence from RCTs to determine whether or not treatment with medications leads to improvement in health outcomes (Table 1 and eTable 5 in the Supplement). Very few trials reported health outcomes, and the included trials were not designed or powered to assess health outcomes: they typically focused on consumption outcomes. COMBINE reported some evidence of improvement in quality of life with naltrexone plus behavioral intervention (on the physical health scale from the 12-item Short Form health survey, version 2), but the difference between groups did not reach a clinically meaningful threshold.[33]

Adverse Effects

There was insufficient evidence regarding many potential adverse events precluding determination of risks associated with these medications. In most cases, inadequate precision (ie, wide confidence intervals that contained clinically distinct conclusions) resulted in our inability to arrive at conclusions about medication risk. For most of the specific adverse events, point estimates favored placebo (ie, more adverse events with medications), but differences were not statistically significant. In head-to-head studies, the risk of withdrawal due to adverse events was not significantly different between acamprosate and naltrexone, but the risks of headache and vomiting were slightly higher for those treated with naltrexone (eTable 6 in the Supplement).

Compared with placebo, patients treated with naltrexone or nalmefene had a higher risk of withdrawal from trials due to adverse events (NNH, 48; 95% CI, 30 to 112; 17 trials, n = 2743; and NNH, 12; 95% CI, 7 to 50; 5 trials, n = 2054, respectively); we found no significant difference for acamprosate or topiramate. Compared with placebo, patients treated with acamprosate had a higher risk of anxiety (NNH, 7; 95% CI, 5 to 11; 2 trials, n = 624), diarrhea (NNH, 11; 95% CI, 6 to 34; 12 trials, n = 2978), and vomiting (NNH, 42; 95% CI, 24 to 143; 4 trials, n = 1817); those treated with naltrexone had a higher risk of dizziness (NNH, 16; 95% CI, 12 to 28; 13 trials, n = 2675), nausea (NNH, 9; 95% CI, 7 to 14; 24 trials, n = 4655), and vomiting (NNH, 24; 95% CI, 17 to 44; 9 trials, n = 2438); those treated with nalmefene had a higher risk of dizziness (NNH, 7; 95% CI, 5 to 10; 4 trials, n = 1944), headache (NNH, 26; 95% CI, 15 to 143; 3 trials, n = 1401), insomnia (NNH, 10; 95% CI, 8 to 17; 5 trials, n = 2049), nausea (NNH, 7; 95% CI, 5 to 11; 5 trials, n = 2049), and vomiting (NNH, 17; 95% CI, 11 to 48; 3 trials, n = 1679); and those treated with topiramate had a higher risk of cognitive dysfunction (NNH, 12; 95% CI, 7 to 84; 2 trials, n = 521), paresthesias (NNH, 4; 95% CI, 3 to 7; 3 trials, n = 691), and taste abnormalities (NNH, 7; 95% CI, 5 to 15; 2 trials, n = 477) (eTable 7 in the Supplement).

Discussion

When used in conjunction with psychosocial co-interventions, addition of several medications resulted in better alcohol consumption outcomes. Acamprosate and oral naltrexone (50 mg/d) have the best evidence supporting their benefits. Trials comparing these medications have not established a difference in outcomes between them.

When clinicians decide to use one of the medications, a number of factors may help with choosing which medication to prescribe, including the medication's efficacy, administration frequency, cost, adverse events, and availability. In some health systems, these medications may not be on the formulary. Acamprosate is given 3 times daily and is somewhat less convenient to use than oral naltrexone that only requires 1 daily tablet. Acamprosate is contraindicated with severe renal impairment and oral naltrexone is contraindicated with acute hepatitis, liver failure, concurrent opioid use, or an anticipated need for opioids.[84]

Because of its long-standing availability, clinicians may be more familiar with disulfiram than naltrexone or acamprosate. However, well-controlled trials of disulfiram did not show overall reductions in alcohol consumption. In a subgroup analysis of the largest disulfiram trial,[32] there were fewer drinking days for patients who returned to drinking and had a complete set of assessments. This suggests that disulfiram may benefit some AUD patients. However, none of the disulfiram trials

evaluated supervised medication delivery, potentially underestimating the benefits of the drug when used in supervised treatment programs.

The evidence from trials was insufficient to make any conclusions about improved health outcomes attributable to pharmacotherapy of AUDs. Epidemiologic studies consistently relate high average alcohol consumption and heavy per-occasion use to increased risks for health problems. These include cancers (eg, mouth, esophagus, colon, liver, and breast); cognitive impairment; liver cirrhosis; chronic pancreatitis; stroke; depression; suicide; and injuries and violence.[5,85-91] Given the epidemiologic evidence for adverse health consequences of heavy alcohol use, improved health outcomes should occur with AUD treatment. A recent modeling study estimated that increasing treatment coverage to 40% of all people with alcohol dependence in the European Union would reduce alcohol-attributable mortality by up to 13%.[92] Several AUD treatment combinations including pharmacotherapy, when compared with placebo plus medical management, reduced costs from health care, arrests, and motor vehicle accidents in a cost analysis of the COMBINE trial.[93]

Applicability of Findings

All participants met criteria for alcohol dependence in most of the studies we reviewed. Based on the studies' time period, they used *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*) Third Edition or Fourth Edition criteria for alcohol dependence. The Fifth Edition, *DSM-5*, was released in 2013 and describes a single AUD category measured on a continuum from mild to severe (eTable 1 in the Supplement). *DSM-5* no longer has separate categories for alcohol abuse and dependence.[94,95] Using *DSM-5* terminology, most participants in the studies we reviewed likely had moderate to severe AUDs. As a consequence, applicability of our findings regarding pharmacological treatment for AUDs to patients with mild disorders is uncertain. The mean age of participants was generally in the 40s. We did not find evidence to confirm or refute whether treatments are likely to be more or less beneficial for older or younger subgroups, different sex groups, racial or ethnic minorities, smokers or nonsmokers, and those with certain coexisting conditions.[9]

The majority of placebo-controlled trials assessing acamprosate were conducted in Europe (16/22) and a minority were conducted in the United States (4/22). In contrast, the opposite occurred for naltrexone: 27 of 44 trials were conducted in the United States and 8 of 44 were carried out in Europe. The few US-based acamprosate studies did not find it to be efficacious. The European trials of acamprosate typically identified patients from inpatient settings or treatment programs, whereas the US-based trials recruited patients using advertisements and referrals. Differences in how patients were recruited into the trials might have resulted in populations with differing AUD severity and differing potential for benefit.

Most studies required patients to abstain for at least a few days prior to initiating medication. Medications for AUDs are generally recommended for maintenance of abstinence. Acamprosate and injectable naltrexone are only approved for use in patients who have established abstinence. However, some studies enrolled patients who were not yet abstinent and reported reduced heavy drinking with naltrexone[44,96] or acamprosate.[45]

Applicability to Primary Care Settings

The US Preventive Services Task Force recommends screening adults for alcohol misuse.[97] Screening will inevitably identify some individuals with AUDs. Clinicians must then decide whether to refer to specialized treatment or intervene within their practice. Like primary care–based behavioral counseling interventions for risky drinking, implementing pharmacotherapy and psychosocial interventions for AUDs may require formal protocols, staffing (eg, multidisciplinary team-based care), support systems, and additional provider and staff training.[86,98] Some experts advocate chronic care management, a systematic approach to treatment and follow-up similar to how the health care system approaches heart failure, diabetes, and other chronic diseases.[99]

Barriers to prescribing medications for AUDs in primary care may include lack of familiarity with the medications, lack of confidence in their effectiveness, or inability to provide suitable psychosocial co-interventions—eg, because of competing demands or insufficient practice resources, personnel, or training. Historically, primary care providers have referred patients with AUDs for specialized treatment. However, these medications are underutilized,[100,101] and many patients may not be willing to pursue or may not have access to specialized treatment. Thus, offering treatment through primary care has the potential to reduce morbidity for many patients with AUDs.

We found scant evidence from primary care settings. One trial (n = 100) that recruited participants primarily by advertisement in 2 family medicine settings found no significant treatment effect for acamprosate.[46] The only other trial meeting our inclusion criteria conducted in primary care settings compared nalmefene with placebo in 15 sites (about half were primary care) in Finland.[83] It found no significant difference in percentage of drinking days but reported a lower percentage of heavy drinking days (18.1% vs 29.7%, $P = .02$) and fewer drinks per drinking day (WMD, −1.0; 95% CI, −2.0 to −0.02) for patients treated with nalmefene than for those who received placebo.

Some included studies conducted in non-primary care settings used interventions that could be adapted for delivery in primary care. For example, in the COMBINE study,[30] providers delivered a medical management intervention comprised of up to 9 manual-guided counseling visits (at weeks 0, 1, 2, 4, 6, 8, 10, 12, and 16). The first visit was approximately 45 minutes, and follow-up visits were about 20 minutes each. Medical management included advice for reducing drinking, inquiries about medication adverse effects, and emphasis on the importance of adherence. Participants were encouraged to attend support groups available in the community (eg, Alcoholics Anonymous). The *Medical Management Treatment Manual* provides direction for clinicians to provide medical management, a combined behavioral intervention, and medical treatment with naltrexone or acamprosate as provided in the COMBINE trial.[102]

Regarding implementation of treatment programs for AUDs in primary care, we identified 4 other publications that did not meet our inclusion criteria (because of study design or comparators) that have important implications.[103-106] Although these studies found conflicting results, they demonstrate approaches to managing AUDs in primary care. Further details of these studies are available in the eDiscussion in the Supplement. In general, the interventions involve formal clinic structure, staffing, and protocols. They used variations of chronic care management, multidisciplinary team-based care, and care coordination between primary care and mental health providers.

Limitations

We only considered trials with at least 12 weeks of treatment. Longitudinal studies have found that shorter treatment periods may yield misleading conclusions about benefits, due to fluctuations in drinking typical of the course of AUDs.[107,108] Next, we did not assess how medications and psychosocial interventions compare with each other. Our review focused on studies assessing benefits and harms of medications and how they compare with other medications, and our findings reflect the added benefits of medications beyond those of psychosocial co-interventions. Studies used a variety of different psychosocial co-interventions. This heterogeneity limits our certainty about the benefits of medications when used alone (with no co-intervention) or when added to a particular psychosocial intervention. Further, we did not specifically assess benefits for patients without a goal of abstinence.

We combined studies that included populations with a dual diagnosis (eg, alcohol dependence and depression) and those that did not in our meta-analyses. To determine whether this potential population heterogeneity had a significant influence on our conclusions, we conducted sensitivity analyses for acamprosate and naltrexone, stratifying by whether or not studies reported enrolling a dual diagnosis population (data in full report[9]). Effect sizes did not change significantly.

Most studies were rated as medium risk of bias. We rated few studies as low risk of bias (8/123 included studies; 4/27 studies assessing acamprosate; and 4/53 studies assessing naltrexone). Most studies rated as medium, rather than low, risk of bias lacked complete reporting of information about several of the following: randomization sequence generation, allocation concealment, fidelity, adherence, or outcome assessor masking. For most outcomes and medications, our post hoc subgroup analyses separating studies rated as low risk of bias did not suggest notable differences or were underpowered to find differences. But a subgroup analysis for return to any drinking for acamprosate showed that the pooled effect of the studies rated as low risk of bias found no significant difference between acamprosate and placebo. Possible explanations include population differences (eg, severity, country), other heterogeneity, no true association between acamprosate and return to drinking (ie, the effect found in overall pooled analyses represents bias), random error, or a combination of these factors. The 2 studies (out of 4) rated as low risk of bias that contributed by far the largest number of events were both conducted in the United States and relied on advertisements and referrals to identify participants. In contrast, the vast majority of the 15 studies rated as medium, high, or unclear risk of bias were conducted in European countries (1 was in the United States and 1 in Brazil) and typically identified patients from inpatient settings or treatment programs. It is possible that this resulted in populations with differing AUD severity and differing potential for benefit or that having gone through a program may increase adherence to treatments and improve potential for benefit.

In addition, publication bias and selective reporting are potential limitations. However, funnel plots did not raise concern for publication bias, and we searched for unpublished studies and unpublished outcomes and did not find direct evidence of either of these biases.

Conclusions

Both acamprosate and oral naltrexone (50 mg/d) were associated with reduction in return to drinking. They have the best evidence for improving alcohol consumption outcomes for patients with AUDs. Head-to-head trials have not established superiority of either medication. Among medications used off-label, moderate evidence supports an association with improvement in some consumption outcomes for nalmefene and topiramate.

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