Table S1 Search Strategy

PubMed from Jan 2022- Jan 2025:

Search	Query	Result
#1	Alcoholism[Mesh]	81,920
#2	Drinking Behaviour[Mesh]	87,764
#3	Alcohol-Related Disorder[Mesh]	124,319
#4	Abuse*[Title/Abstract] OR addict*[Title/Abstract] OR disorder*[Title/Abstract] OR drink*[Title/Abstract] OR consumption[Title/Abstract] OR treatment[Title/Abstract] OR management[Title/Abstract] OR	9,644,492
#5	Acamprosate[Mesh]	684
#6	Acamprosate[Title/Abstract]	900
#7	Disulfiram[Mesh]	3,849
#8	Disulfiram[Title/Abstract]	3,948
#9	Naltrexone[Mesh]	8,913
#10	Naltrexone[Title/Abstract]	8,244
#11	Randomized controlled trial[Publication Type]	628,016
#12	Controlled clinical trial[Publication Type]	718,744
#13	Trial*[Title/Abstract]	1,459,137
#14	RCT[Title/Abstract]	39,933
#15	Random*[Title/Abstract]	1,579,133
#16	placebo[Title/Abstract]	261,184
#17	(“2022/01/01”[Date – Publication] : “2024/12/31”[Date – Publication])	4,670,556
#18	#1 OR #2 OR #3	188,431
#19	#5 OR #6 OR #7 OR #8 OR #9 OR #10	16,823
#20	#11 OR #12 OR #13 OR #14 OR #15 OR #16	2,579,252
#21	#4 AND #17 AND #18 AND #19 AND #20	71

Cochrane library

Search	Query	Result
#1	Alcohol [Mesh]	46657
#2	Drinking Behaviour [Mesh]	6076
#3	Alcohol Related Disorders [Mesh]	7401
#4	"Abuse" or "Addict" or "dependent" or " disorder" or "drink" or "consumption" or "treatment" or "management" [Tiltle/Abstract]	1267085
#5	Acamprose [Mesh]	202
#6	Acamprose [Title/ Abstract]	1
#7	Disulfiram [Mesh]	197
#8	Disulfiram [Title/ Abstract]	342
#9	Naltrexone [Mesh]	1736
#10	Naltrexone [Title/ Abstract]	2959
#11	Randomizzed controlled trial [Publication Type]	0
#12	Controlled Clinical Trial [Publication Type]	0
#13	Trial [Title/Abstract]	1202130
#14	RCT [Title/Abstract]	43367
#15	Random [Title/ Abstract]	1311635
#16	Placebo [Title/ Abstract]	401491
#17	#1 OR #2 OR #3	555888
#18	#11 OR #12 OR #13 OR #14 OR #15 OR #16	1617214
#19	#5 OR #6 OR #7 OR #8 OR #9 OR #10	3330
#20	#4 AND #17 AND #18 AND #19	721
#21	Exclude review and other reports	52

Embase:

Search	Query	Result
#1	'alcoholism'/exp OR 'alcoholism'	180,780
#2	'alcohol use disorder'/exp OR 'alcohol use disorder'	154,600
#3	#1 OR #2	182,818
#4	'acamprosate'/exp OR 'acamprosate'	3,140
#5	'disulfiram'/exp OR 'disulfiram'	11,382
#6	'naltrexone'/exp OR 'naltrexone'	20,271
#7	#4 AND #5 AND #6	1,197
#8	#3 AND #7	1,111
#9	'randomized controlled trail (topic)'	284,175
#10	#8 and #9	94

Table S2 Reasons for exclusion after full text screening

No.	Title/Author	Reason for exclusion
1	Wenzel et al 2024 [1]	Not the intervention of interest
2	Dali et al 2024 [2]	Not the intervention of interest
3	Bernstein et al 2024 [3]	Not the intervention of interest
4	NCT06175507 [4]	No outcome
5	Schacht et al 2022 [5]	Not the intervention of interest
6	Tsui et al 2024 [6]	Not the outcome of interest
7	Wallach et al 2022 [7]	Not an RCT
8	NCT05748639 [8]	Not the intervention of interest
9	NCT06471686 [9]	Not the outcome of interest
10	Morley et al 2024 [10]	Not the outcome of interest
11	Waddell et al 2022[11]	Not the outcome of interest
12	Simpson et al 2024 [12]	Not the outcome of interest
13	Stryhn et al 2022 [13]	Not the intervention of interest
14	Santos et al 2023 [14]	Insufficient data for quantitative synthesis

- Note the intervention of interest: The study tested or used a different intervention than the one the reviewers are interested in analysing.
- Note the outcome of interest: the study does not report or measure the specific outcomes or effects that the review is focused on (i.e., the return to any level of drinking and the return to heavy drinking)
- Not an RCT: excluded study designs other than RCTs
- Insufficient data for quantitative synthesis: study did not provide the necessary dichotomous outcome data (e.g., number of participants who returned to any level of drinking or to heavy drinking), which are required to calculate risk ratios (RR) and 95% confidence intervals (CI)

Table S3 Characteristics of studies included

Author, year	Intervention with dose	Setting	Follow-up	Age range	Co-intervention	Risk of bias
Lhuintre 1985 [15]	ACAM 1000 to 2250mg (N=42) PLBO (N=43)	France	13	40-43	Meprobamate for first month	H
Lhuintre 1990 [16]	ACAM 1332mg (N=279) PLBO (N=290)	France	12	42-43	Psychotherapy allowed	U
Pelc 1992 [17]	ACAM 1332 to 1998mg (N=55) PLBO (N=47)	Belgium	26	43	Supportive psychotherapy	H
Paille 1995 [18]	ACAM 1300mg (N=188) ACAM 2000mg (N=173) PLBO (N=177)	France	78	43	Supportive psychotherapy 100% Hypnotics 6 to 7% Anxiolytics 8 to 12% Antidepressants 8 to 9%	M
Whitworth 1996 [19]	ACAM 1332 or 1998mg (N=224) PLBO (N=224)	Austria	104	42	NA	M
Sass 1996 [20]	ACAM 1332 to 1998mg (N=136) PLBO (N=136)	Germany	96	41-42	Counselling/ psychotherapy	M
Poldrugo 1997 [21]	ACAM 1332 to 1998mg (N=122) PLBO (N=124)	Italy	52	43-45	Community-based rehabilitation program with group sessions, alcohol education, community meetings	M
Pelc 1997 [22]	ACAM 1332mg (N=63) ACAM 1998mg (N=63) PLBO (N=62)	Belgium	13	NR	Counselling, social support when needed	M
Geerlings 1997 [23]	ACAM 1332 to 1998mg (N=128) PLBO (N=134)	Belgium	52	40-42	ACAM: benzodiazepines 5% PLBO: benzodiazepines 6%	M
Besson 1998 [24]	ACAM 1300 to 1998mg (N=55) PLBO (N=55)	Switzerland	108	42	Routine counselling 100% Voluntary disulfiram 22-24%	M
Tempesta 2000 [25]	ACAM 1998mg (N=164)	Italy	39	46	Medical and behavioural	M

	PLBO (N=166)				counselling	
Chick 2000 [26]	ACAM 1998mg (N=289) PLBO (N=292) NALT Oral 50mg (N=85) PLBO (N=79)	UK	24	43	Usual psychosocial outpatient treatment program	M
Gual and Lehert 2001 [27]	ACAM 1998mg (N=147) PLBO (N=141)	Spain	26	41	NA	M
Baltieri and De Andrade 2004 [28]	ACAM 1998mg (N=40) PLBO (N=35)	Brazil	24	18-60	Alcoholics Anonymous encouraged	M
Mason 2006 [29]	ACAM 2000mg (N=258) ACAM 3000mg (N=83) PLBO (N=260)	US	32	44-45	Brief abstinence-oriented protocol-specific counselling and self-help materials	L
Berger 2013 [30]	ACAM 1998mg (N=51) PLBO (N=49)	US	12	48	Brief structured behavioural intervention from primary care physician	M
Higuchi 2015 [31]	ACAM 1998mg (N=163) PLBO (N=164)	Japan	48	52	Individual therapy, group therapy, and/or self-help group	M
Fuller 1986 [32]	DISL 250mg (N=202) CTRL (N=403)	US	52	41-42	Counselling (loosely defined) % NA	M
Fuller and Roth 1979 [33]	DISL 250mg (N=43) CTRL (N=85)	US	52	43	Counselling (unspecified)	M
Petrakis 2005 [34]	DISL 250mg (N=66) NALT Oral 50mg (N=59) PLBO (N=64)	US	12	47	Psychiatric treatment as usual	H (DISL vs PLBO) M (NALT vs PLBO)
O'Malley 1992 [35]	NALT Oral 50mg (N=52) PLBO (N=52)	US	38	41	See arms	M
Volpicelli 1995 [36]	NALT Oral 50mg (N=54) PLBO (N=45)	US	12	NR	Outpatient treatment program and group therapy	U
Volpicelli 1997 [37]	NALT Oral 50mg (N=48) PLBO (N=49)	US	12	38-39	Counselling	M
Oslin 1997 [38]	NALT 100mg on Monday and Wednesday, 150mg on Friday (N=21) Placebo (N=23)	US	12	58	Group therapy and case manager	M
Anton 1999 [39]	NALT Oral 50mg (N=68) PLBO (N=63)	US	12	41-44	Cognitive Behavioural Therapy	M

Lee 2001 [40]	NALT Oral 50mg (N=35) PLBO (N=18)	Singapore	12	45	Intensive inpatient rehabilitation program, post discharge therapy encouraged	H
Krystal 2001 [41]	NALT Oral 50mg for 12 months (N=209) NALT Oral 50mg for 3 months then PLBO (N=209) PLBO (N=209)	US	12 or 52	49	12-step facilitation	M
Morris 2001 [42]	NALT Oral 50mg (N=55) PLBO (N=56)	Australia	12	47	Group psychoeducation and social support	M
Gastpar 2002 [43]	NALT Oral 50mg (N=84) PLBO (N=87)	Germany	12	43	Psychosocial treatment	M
Ahmadi and Ahdmadi 2002 [44]	NALT Oral 50mg (N=58) PLBO (N=58)	Iran	12	43	Individual counselling	U
Guardia 2002 [45]	NALT Oral 50mg (N=101) PLBO (N=101)	Spain	12	NR	Psychosocial	M
Balldin 2003 [46]	NALT Oral 50mg (N=56) PLBO (N=62)	Sweden	26	48-51	None	L
Killeen 2004 [47]	NALT Oral 50mg (N=54) PLBO (N=43)	US	12	37	Several types and intensities	M
O'Malley 2007 [48]	NALT Oral 50mg (N=57) PLBO (N=50)	US	12	40	CBCST, based on manualized approach used in Project MATCH	M
O'Malley 2008 [49]	NALT Oral 50mg (N=34) PLBO (N=34)	US	16	40	Medical Management	M
Baltieri 2008 [50]	NALT Oral 50mg (N=49) PLBO (N=54)	Brazil	12	44-45	Psychosocial	H
Oslin 2008 [51]	NALT Oral 100mg (N=120) PLBO (N=120)	US	24	41	None	M
Pettinati 2010 [52]	NALT Oral 100mg (N=49) PLBO (N=39)	US	14	43	Cognitive Behavioural Therapy	M
Kranzler 2004 [53]	NALT Injection 150mg (N=158) PLBO injection (N=157)	US	12	44	Motivational Enhancement Therapy	M
Garbutt 2005 [54]	NALT Injection 380mg (N=205) NALT Injection 190mg (N=210) PLBO (N=209)	US	26	45	BRENDA Standardized Supportive Therapy	M
HEAVY DRINKING						
Chick 2000 [26]	ACAM 1998mg (N=289) PLBO (N=292)	UK	24	43	Usual psychosocial outpatient treatment program	M
Monti 2001 [55]	NALT Oral 50mg (N=64)	US	52	39	Brief physician outpatient contacts	M

	PLBO (N=64)				(intensive therapy occurred prior to medication portion of trial)	
Latt 2002 [56]	NALT Oral 50mg (N=56) PLBO (N=51)	Australia	26	45	No extensive psychosocial interventions	M
Huang 2005 [57]	NALT Oral 50mg (N=20) PLBO (N=20)	Taiwan	14	38-43	Weekly individual psychotherapy sessions	H
Brown 2009 [58]	NALT Oral 50mg (N=20) PLBO (N=23)	US	12	41	CBT	H
ALK21−014 2011 [59]	NALT injection 380mg every 4 weeks (N=152) PLBO (N=148)	Germany	12	46	NR	M
Kiefer 2003 [60]	ACAM 1998 (N=40) NALT ORAL 50MG (N=40) PLBO (N=40) ACAM 1998 + NALT ORAL 50MG (N=40)	Germany	12	46	Group therapy	L
Morley 2006 [61]	ACAM 1998mg (N=55) NALT Oral 50mg (N=53) PLBO (N=61)	Australia	12	45	All offered 4-6 sessions of manualized compliance therapy Uptake/attendance NR	L
Anton 2006 [62]	ACAM 3000mg (N=303) NALT Oral 100mg (N=309) NAAC (N=305) PLBO (N=309)	US	68	44	As randomized, community support group participation (like AA) encouraged	L
Wölwer 2011 [63]	ACAM 1998mg (N=124) PLBO (N=125)	Germany	24(52)	46	NR	M
Mann 2012 [64]	ACAM 1998 mg (N=172) NALT Oral 50mg (N=169) PLBO (N=85)	Germany	12	45	Medical management	M
Anton 2005 [65]	NALT 50mg (N=80) PLBO (N=80)	US	12	43-45	CBT and MET as randomized	M

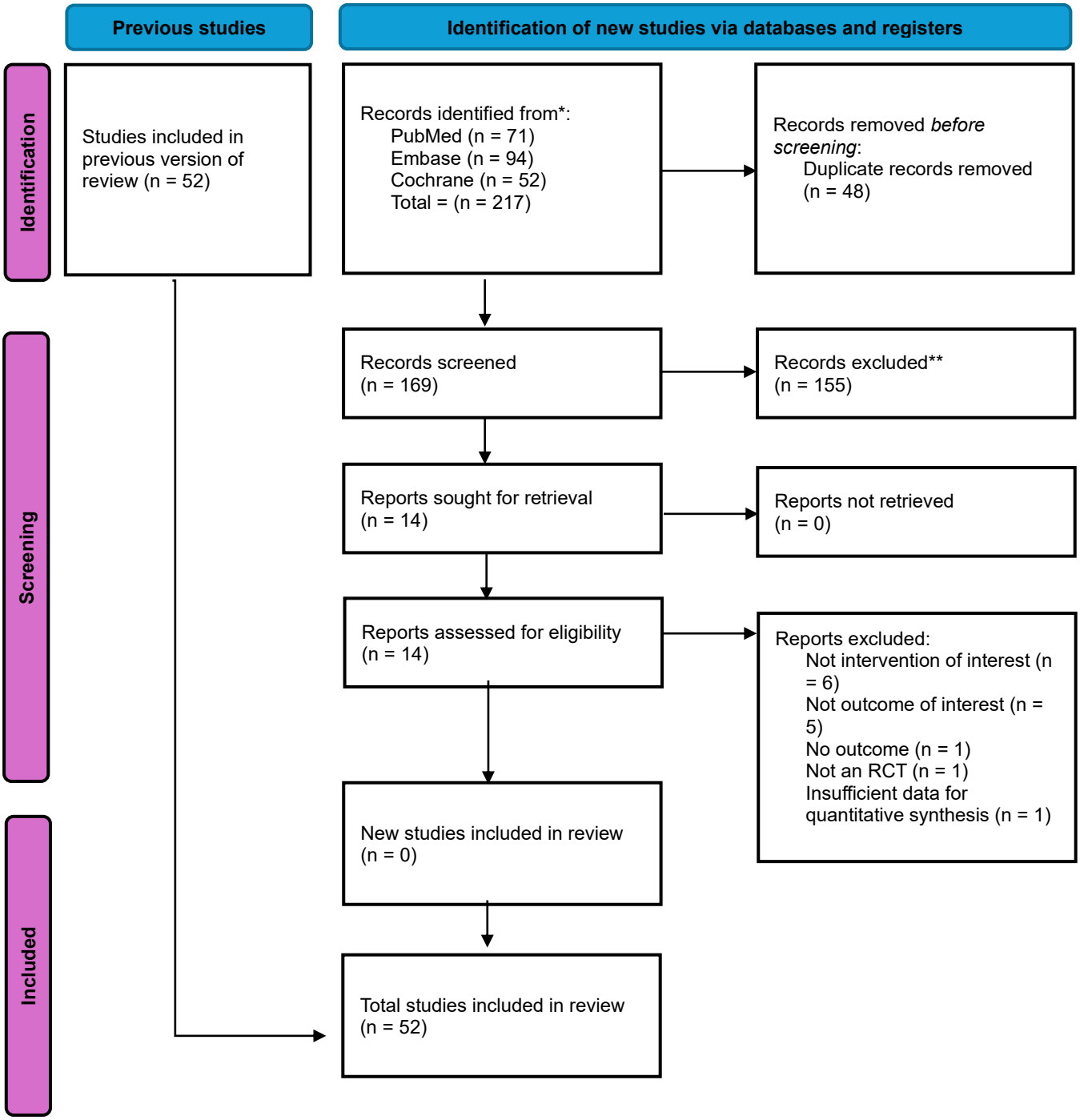
ACAM, Acamprosate; CBCST, Cognitive Behavioural Coping Skills Therapy; CBT, Cognitive behavioural therapy; CTRL, Control; DISL, Disulfiram; H, High; L, Low; M, Moderate; MET, motivational enhancement therapy; NA, Not applicable; NAAC, Combination of acamprosate and naltrexone; NALT, Naltrexone; NR, Not reported; PLBO, Placebo; U, Unsure

Table S4 Quality of evidence: primary outcome

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
ACAM:NAAC	1	No concerns	Some concerns	Some concerns	No concerns	No concerns	Some concerns	Low
ACAM:NALT	1	Some concerns	Some concerns	Some concerns	No concerns	No concerns	Some concerns	Low
ACAM:PLBO	16	Some concerns	Some concerns	Some concerns	No concerns	Some concerns	Some concerns	Moderate
DISL:PLBO	2	Some concerns	Some concerns	Some concerns	No concerns	No concerns	No concerns	Low
NAAC:NALT	1	No concerns	Some concerns	Some concerns	No concerns	No concerns	Some concerns	Low
NAAC:PLBO	1	No concerns	Some concerns	Some concerns	No concerns	No concerns	Some concerns	Low
NALT:PLBO	21	Some concerns	Some concerns	Some concerns	No concerns	No concerns	Some concerns	Moderate
ACAM:DISL	0	Some concerns	Some concerns	Some concerns	No concerns	Some concerns	No concerns	Low
DISL:NAAC	0	Some concerns	Some concerns	Some concerns	No concerns	No concerns	No concerns	Low
DISL:NALT	0	Some concerns	Some concerns	Some concerns	No concerns	Some concerns	No concerns	Low

ACAM, Acamprosate; DISL, Disulfiram; NAAC, Combination of acamprosate and naltrexone; NALT, Naltrexone; PLBO, Placebo

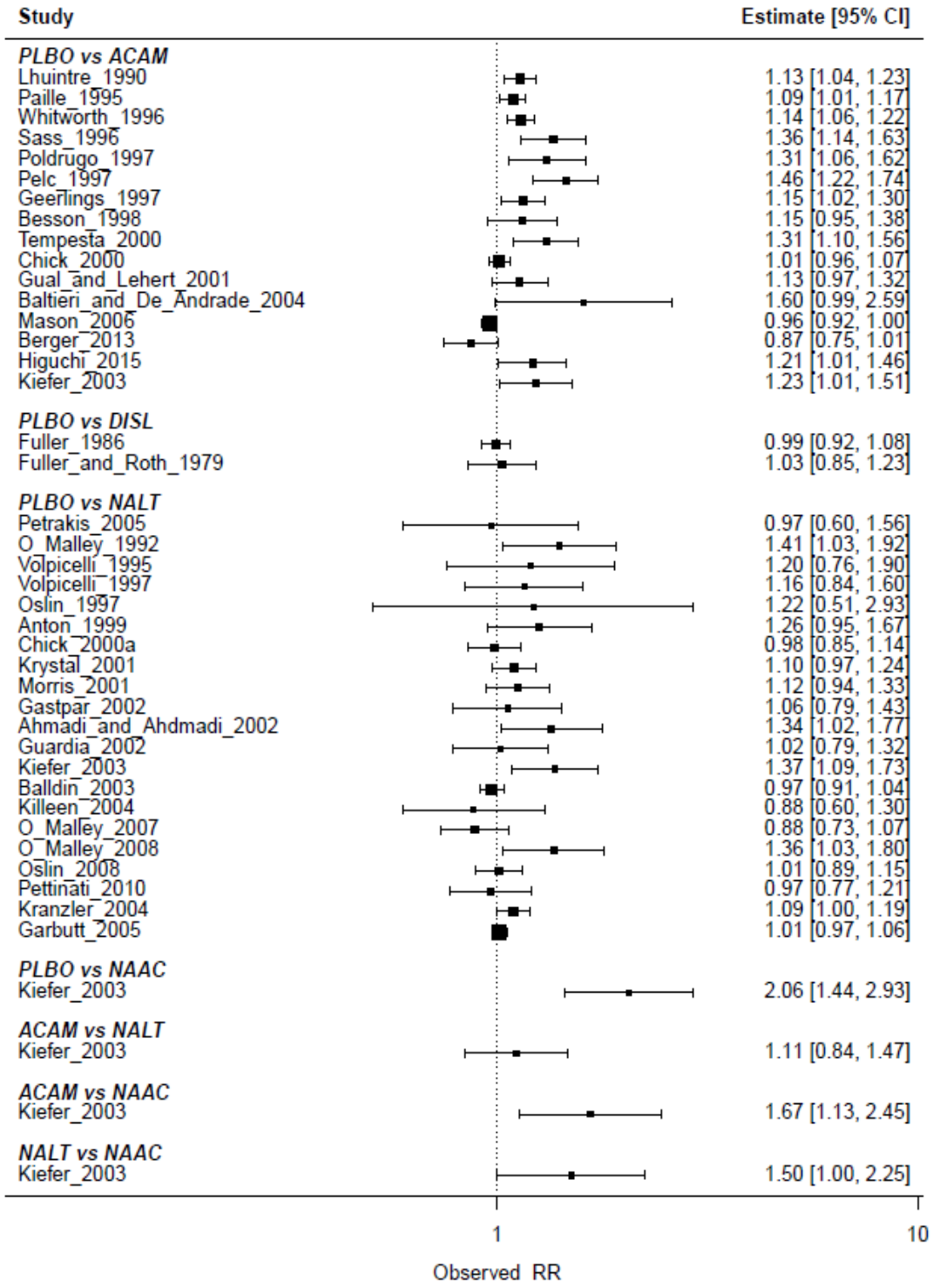
Fig. S1 PRISMA Flow diagram



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

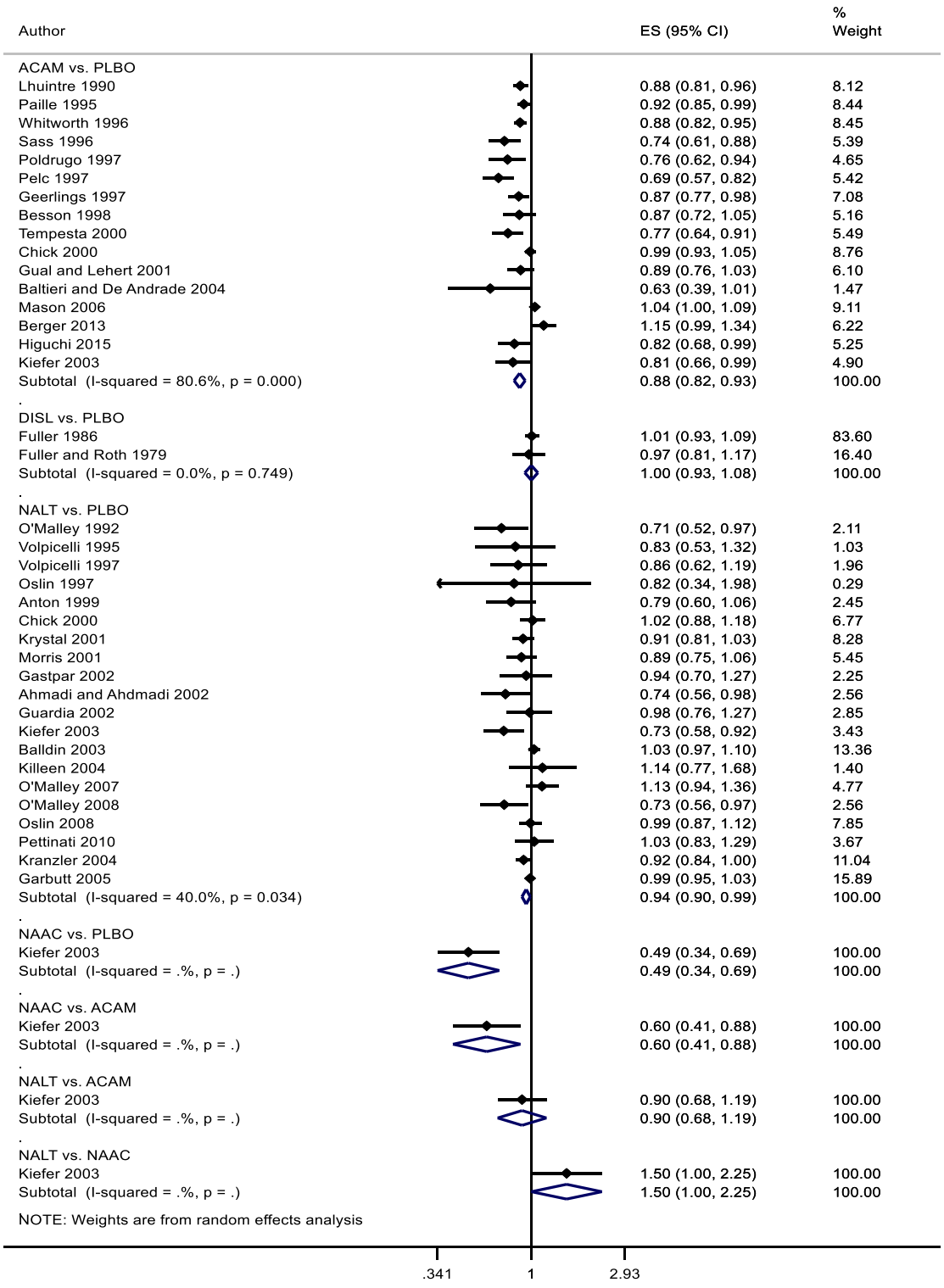
**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

Fig. S2 Individual study results size with 95% confidence intervals



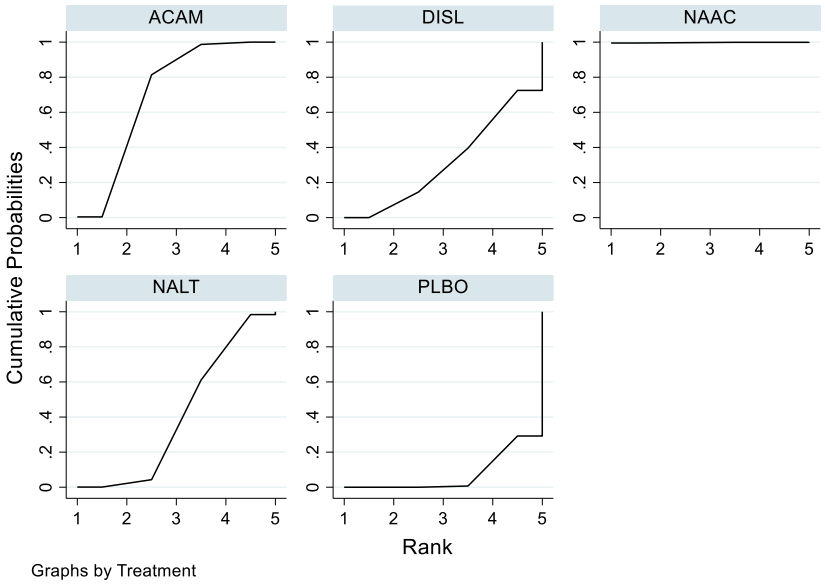
Abbreviations: ACAM, acamprosate; DISL, disulfiram; NALT, naltrexone; NAAC, combination of acamprosate and naltrexone; PLBO, placebo; RR, risk ratio

Fig. S3 Pairwise meta-analysis: Return to any drinking



Abbreviations: ACAM, acamprosate; DISL, disulfiram; ES, effect size; NALT, naltrexone; NAAC, combination of acamprosate and naltrexone; PLBO, placebo

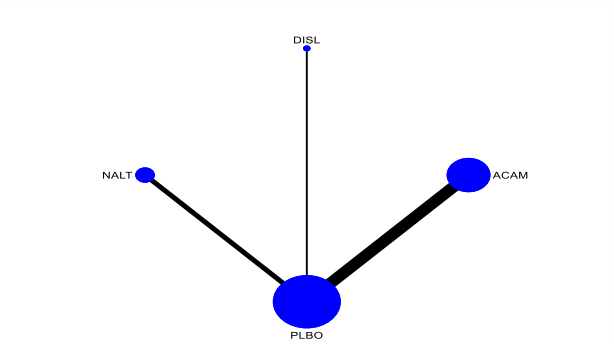
Fig. S4 SUCRA plot: Return to any drinking



Treatm~t	SUCRA	PrBest	MeanRank
PLBO	7.5	0.0	4.7
ACAM	70.1	0.4	2.2
DISL	31.7	0.0	3.7
NAAC	99.7	99.5	1.0
NALT	41.0	0.1	3.4

Abbreviations: ACAM, acamprosate; DISL, disulfiram; NALT, naltrexone; NAAC, combination of acamprosate and naltrexone; PLBO, placebo; SUCRA, Surface under the cumulative ranking curve

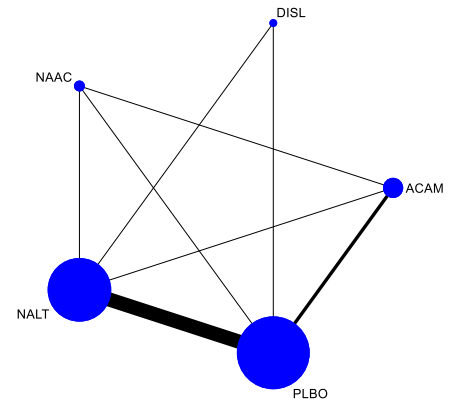
Fig. S5 Subgroup analysis: more than 12 weeks



Comparisons available	RR (95% CI)	SUCRA rank
ACAM vs PLBO	0.86 (0.80 to 0.91)	0.97
DISL vs PLBO	0.99 (0.85 t0 1.16)	0.29
NALT vs PLBO	0.95 (0.86 to 1.05)	0.51
NAAC vs PLBO	NA	NA

Abbreviations: ACAM, acamprosate; CI, confidence interval; DISL, disulfiram; NA, not applicable; NALT, naltrexone; NAAC, combination of acamprosate and naltrexone; PLBO, placebo; ROB, risk of bias; RR, risk ratio; SUCRA, Surface under the cumulative ranking curve

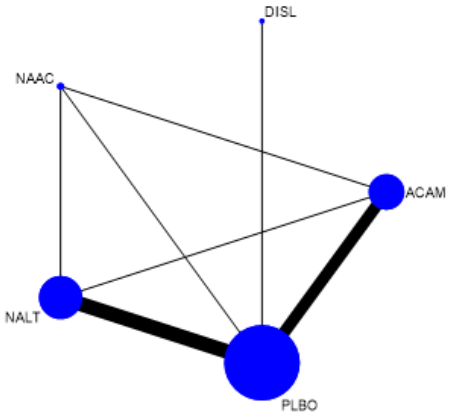
Fig. S6 Subgroup analysis: with 12 weeks



Comparisons available	RR (95% CI)	SUCRA rank
ACAM vs PLBO	0.93 (0.82 to 1.02)	0.34
DISL vs PLBO	0.62 (0.37 t0 1.06)	0.77
NALT vs PLBO	0.92 (0.86 to 0.99)	0.41
NAAC vs PLBO	0.53 (0.33 to 0.77)	0.92

Abbreviations: ACAM, acamprosate; CI, confidence interval; DISL, disulfiram; NALT, naltrexone; NAAC, combination of acamprosate and naltrexone; PLBO, placebo; ROB, risk of bias; RR, risk ratio; SUCRA, Surface under the cumulative ranking curve

Fig. S7 Sensitivity analysis: excluding high ROB trials



Comparisons available	RR (95% CI)	SUCRA rank
ACAM vs PLBO	0.93 (0.82 to 1.02)	0.34
DISL vs PLBO	0.62 (0.37 t0 1.06)	0.77
NALT vs PLBO	0.92 (0.86 to 0.99)	0.41
NAAC vs PLBO	0.53 (0.33 to 0.77)	0.92

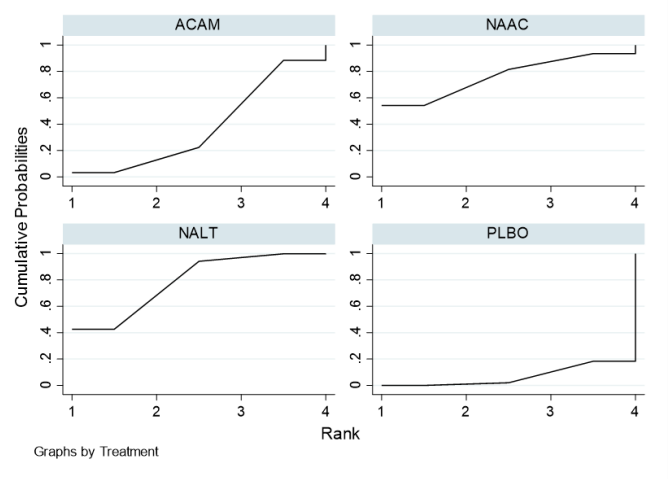
Abbreviations: ACAM, acamprosate; CI, confidence interval; DISL, disulfiram; NALT, naltrexone; NAAC, combination of acamprosate and naltrexone; PLBO, placebo; ROB, risk of bias; RR, risk ratio; SUCRA, Surface under the cumulative ranking curve

Fig. S8 NMA results for return to heavy drinking

ACAM			
1.10 (0.90,1.34)	**NAAC**		
1.08 (0.97,1.21)	0.99 (0.82,1.19)	**NALT**	
0.95 (0.86,1.05)	0.87 (0.71,1.06)	0.87 (0.80,0.95)	**PLBO**

Abbreviations: ACAM, acamprosate; NALT, naltrexone; NAAC, combination of acamprosate and naltrexone; PLBO, placebo

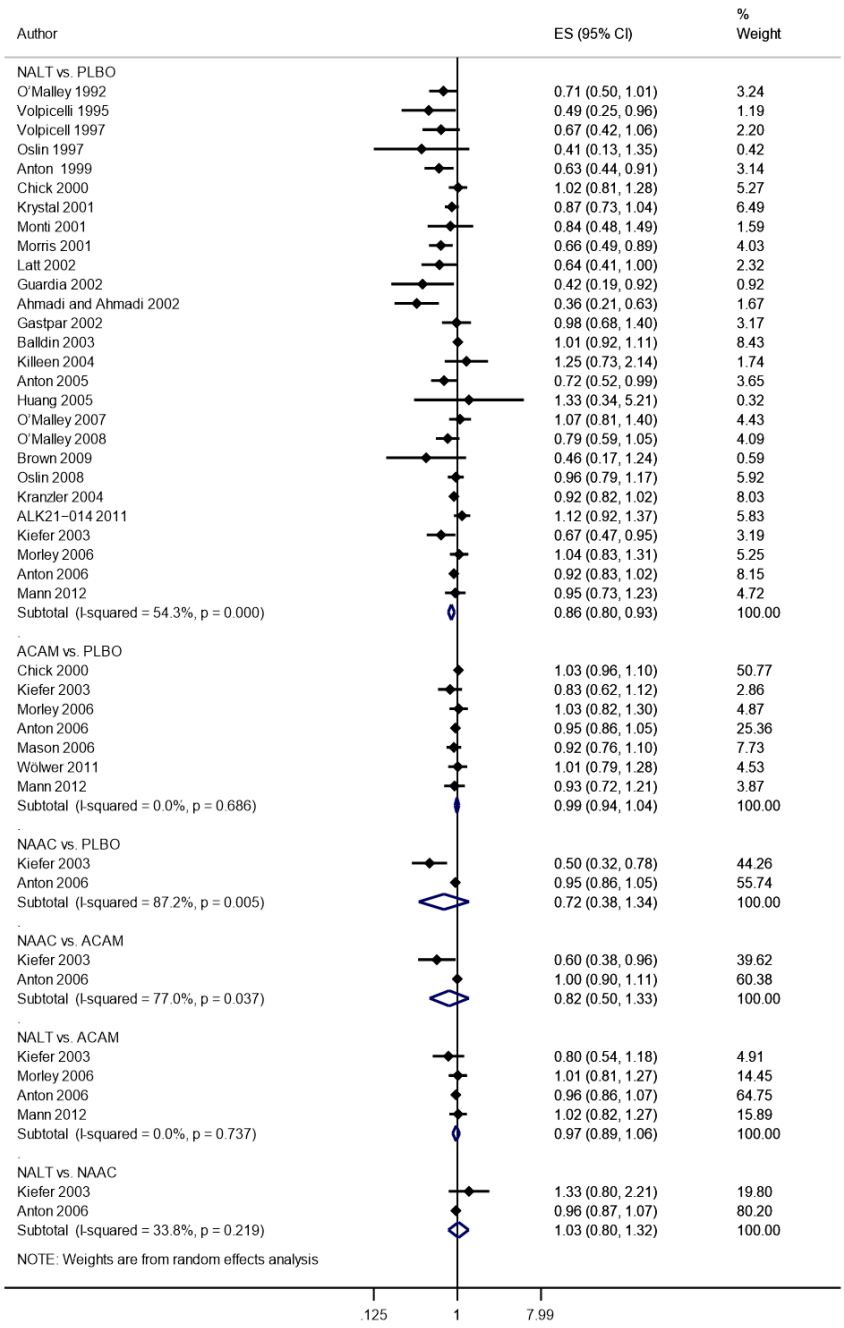
Fig. S9 SUCRA plot for return to heavy drinking



Treatm~t	SUCRA	PrBest	MeanRank
PLBO	6.8	0.0	3.8
ACAM	38.0	3.3	2.9
NAAC	76.4	54.1	1.7
NALT	78.8	42.6	1.6

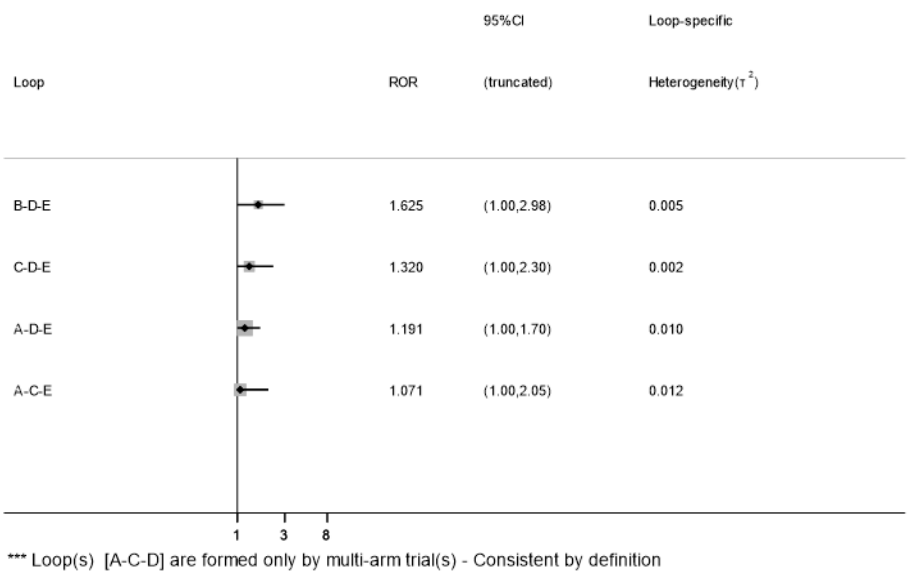
Abbreviations: ACAM, acamprosate; NALT, naltrexone; NAAC, combination of acamprosate and naltrexone; PLBO, placebo; SUCRA, Surface under the cumulative ranking curve

Fig. S10 pairwise meta-analysis for return to heavy drinking



Abbreviations: ACAM, acamprosate; ES, effect size; NALT, naltrexone; NAAC, combination of acamprosate and naltrexone; PLBO, placebo

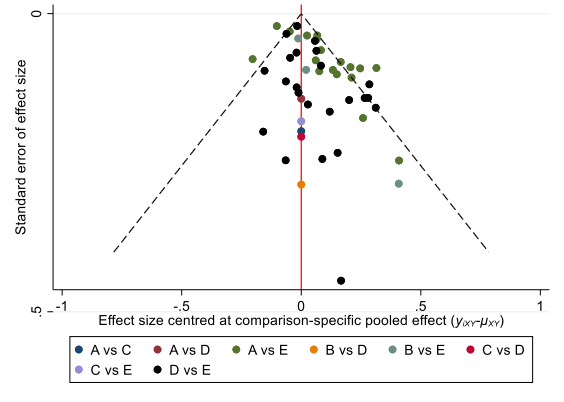
Fig. S11 Loop-specific inconsistency assessment for primary outcome



ROR = Ratio of two odds ratios

Loop-specific approach considers only triangular (formed by three treatments all compared with each other) and quadratic (formed by four treatments that each one is compared exactly with two other treatments in the loop) loops. In this case, 4 one triangular loops are formed. An example of a loop includes values of high inconsistency (e.g. mean RoR larger than 2) meaning that the direct estimate can be twice as large as the indirect estimate or the opposite (the indirect estimate is twice the direct). In this case all ROR values are close to 1.

Fig. S12 Comparison adjusted funnel plot primary outcome

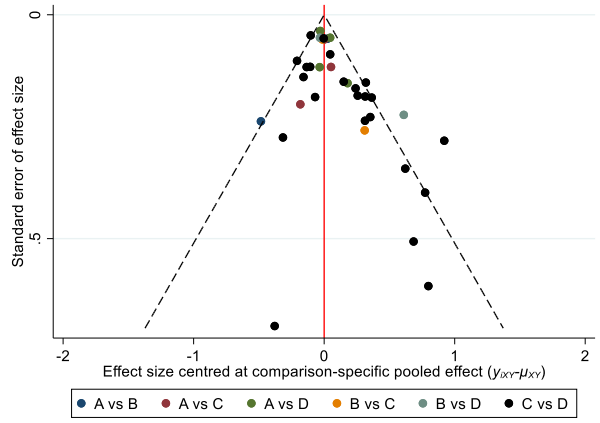


Treatments used

A:	ACAM
B:	DISL
C:	NAAC
D:	NALT

Abbreviations: ACAM, acamprosate; DISL, disulfiram; NALT, naltrexone; NAAC, combination of acamprosate and naltrexone

Fig. S13 Comparison adjusted funnel plot secondary outcome




```
Treatments used
   A:                              ACAM
   B:                              NAAC
   C:                              NALT
   D (reference):                  PLBO
```

Abbreviations: ACAM, acamprosate; NALT, naltrexone; NAAC, combination of acamprosate and naltrexone; PLBO, placebo

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1. Wenzel K, Thomas J, Carrano J, Stidham J, Fishman M. A pilot randomized controlled trial of medication adherence therapy: Psychosocial leverage using a significant other (MAT-PLUS) for individuals on extended-release naltrexone. J Subst Use Addict Treat. 2024 Aug;163:209366.

2. Dali G, Logge W, Kranzler H, Hurzeler T, Gallagher H, Haber P, et al. Comparative effects of topiramate and naltrexone on neural activity during anticipatory anxiety in individuals with alcohol use disorder. Alcohol Alcohol Oxf Oxfs [Internet]. 2024;60(1). Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02776861/full

3. Y Bernstein E, Magane KM, Dukes KA, Palfai TP, Lee JH, Saitz R, et al. Correlates of post-hospitalization naltrexone adherence for alcohol use disorder. Drug Alcohol Depend. 2024 Dec 1;265:112470.

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