Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Definitions of Alcohol Use Disorders: Evolution of Terminology[a]

Term	Definition
Alcohol use disorder (DSM-5, 2013)[1] Levels of severity Mild: 2-3 Moderate: 4-5 Severe: ≥6	1. Alcohol is taken in larger amounts or over a longer period than intended 2. Persistent desire or unsuccessful efforts to cut down or control alcohol use 3. A great deal of time is spent in activities necessary to obtain alcohol, use alcohol, or recover from its effects 4. Craving, or a strong desire or urge to use alcohol 5. Recurrent alcohol use resulting in a failure to fulfill major role obligations at work, school, or home 6. Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol 7. Important social, occupational, or recreational activities are given up or reduced because of alcohol use 8. Recurrent alcohol use in situations in which it is physically hazardous 9. Alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by alcohol 10. Tolerance, as defined by either of the following: a) A need for markedly increased amounts of alcohol to achieve intoxication or desired effect b) A markedly diminished effect with continued use of the same amount of alcohol 11. Withdrawal, as manifested by either of the following: a) The characteristic withdrawal syndrome for alcohol b) Alcohol (or a closely related substance, such as a benzodiazepine) is taken to relieve or avoid withdrawal symptoms

Alcohol abuse (DSM-IV, 2000)[4]	A. A maladaptive pattern of alcohol use leading to clinically significant impairment or distress, as manifested by at least 1 of the following occurring within a 12-month period: (1) recurrent alcohol use resulting in a failure to fulfill major role obligations at work, school, or home (e.g., repeated absences or poor work performance related to alcohol use; alcohol-related absences, suspensions, or expulsions from school; neglect of children or household); (2) recurrent alcohol use in situations in which it is physically hazardous (e.g., driving an automobile or operating a machine when impaired); (3) recurrent alcohol-related legal problems (e.g., arrests for alcohol-related disorderly conduct); or (4) continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol (e.g., arguments with spouse about consequences of intoxication, physical fights). B. The symptoms have never met the criteria for alcohol dependence.
Alcohol dependence (DSM-IV, 2000)[4] (alcoholism, alcohol addiction)	A maladaptive pattern of alcohol use, leading to clinically significant impairment or distress, as manifested by at least 3 of the following occurring at any time in the same 12-month period: (1) tolerance, as defined by either of the following: (a) a need for markedly increased amounts of alcohol to achieve intoxication or desired effect; or (b) markedly diminished effect with continued use of the same amount of alcohol; (2) withdrawal, as manifested by either of the following: (a) the characteristic withdrawal syndrome for alcohol; or (b) alcohol (or a closely related drug) is taken to relieve or avoid withdrawal symptoms; (3) alcohol is often taken in larger amounts or over a longer period than was intended; (4) there is a persistent desire or unsuccessful efforts to cut down or control alcohol use; (5) a great deal of time is spent in activities necessary to obtain alcohol, use alcohol, or recover from its effects; (6) important social, occupational, or recreational activities are given up or reduced because of alcohol use; or

	(7) alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by alcohol (e.g., continued drinking despite recognition that an ulcer was made worse by alcohol consumption).
Harmful use (ICD-10, 1994)[2,3]	A pattern of drinking that is already causing damage to health. The damage may be either physical (e.g., liver damage from chronic drinking) or mental (e.g., depressive episodes secondary to drinking).

[a]The included literature used definitions from DSM-III or DSM–IV. DSM-5 (2013) describes a single alcohol use disorder category measured on a continuum from mild to severe, and no longer has separate categories for alcohol abuse and dependence.[1] Clinicians can also add "in early remission," "in sustained remission," "on maintenance therapy," and "in a controlled environment" to the diagnosis.

eTable 2. Medications that are FDA-approved for treating adults with alcohol dependence

Generic Drug Name	Mechanism	Dosing
Acamprosate	Thought to modulate hyperactive glutamatergic NMDA receptors	Oral: 666 mg 3 times per day
Disulfiram	Inhibits ALDH2, causing accumulation of acetaldehyde during alcohol consumption, which produces a variety of adverse effects such as nausea, dizziness, flushing, and changes in heart rate and blood pressure	Oral: 250 to 500 mg per day
Naltrexone	Opioid antagonist; competitively binds to opioid receptors and blocks the effects of endogenous opioids such as β-endorphin	Oral: 50 to 100 mg per day Intramuscular injection: 380 mg per month

Abbreviations: ALDH2 = aldehyde dehydrogenase; FDA = U.S. Food and Drug Administration; mg = milligram; NMDA = N-methyl-D-aspartate.

eTable 3. Questions for the full technical report (all six) and for this manuscript (1 through 3)

1	a: Which medications are efficacious for improving consumption outcomes for adults with AUDs in outpatient settings? b: How do medications for adults with AUDs compare for improving consumption outcomes in outpatient settings?
2	a: Which medications are efficacious for improving health outcomes for adults with AUDs in outpatient settings? b: How do medications for adults with AUDs compare for improving health outcomes in outpatient settings?
3	a: What adverse effects are associated with medications for adults with AUDs in outpatient settings? b: How do medications for adults with AUDs compare for adverse effects in outpatient settings?
4	Are medications for treating adults with AUDs effective in primary care settings?
5	Are any of the medications more or less effective than other medications for men or women, older adults, young adults, racial or ethnic minorities, smokers, or those with co-occurring disorders?
6	Are any of the medications more or less effective for adults with specific genotypes (e.g., related to polymorphisms of the mu-opioid receptor gene [OPRM1])?

Abbreviation: AUD = alcohol use disorder

eTable 4. Characteristics of included studies

Author, Year Trial Name	Arm Dose, mg/day (N)	Rx Dur, Wks (f-u)	Setting	Recruit-ment Method	Age, Yrs by arm[a]	% Non-white	% Fem	% With Co-occurring Condition	Co-intervention	Risk of Bias
Addolorato, 2007[14]	BAC 30 (42) Placebo (42)	12	University treatment and research center; Italy	People contacting alcohol treatment unit	49 (range 43-61) 50 (range 44-60)	NR	24-31	Liver cirrhosis 100 Hepatitis B 15 Hepatitis C 29	Routine psychological support 100%	Med
Ahmadi, 2002[15]; Ahmadi, 2004[16]	NTX 50 (58) Placebo (58)	12	Outpatient treatment; Iran	Self-referral	43 (10) 43 (9)	NR	0	NR	Individual counseling 100%	Un-clear
ALK21-014, 2011[17]	NTX inj 380 every 4 wks (152) Placebo (148)	12	Outpatient; Germany, Austria	NR	46 (9) 46 (8)	NR	20	NR	NR	Med
Anton, 1999[18]; Anton, 2001[19]	NTX 50 (68) Placebo (63)	12	Outpatient academic research center; U.S.	Ads, referrals for treatment-seekers	41 (10) 44 (10)	11-18	27-31	0	CBT 100%	Med
Anton, 2003[20]	ACA 3,000 + CBI + MM (9) ACA 3,000 + MM (9) NTX 100 + CBI + MM (9) NTX 100 + MM (9) Placebo + CBI + MM (9) Placebo + MM (8)[b]	16	11 U.S. academic sites	Ads, community resources, clinical referrals at 11 academic sites	ACA (any): 42 (11) NTX (any): 41 (7) PBO (any) 38 (7)	17 to 22	22 to 33	NR	As randomized	Med

Anton, 2004[21]	NALM 5 (68) NALM 20 (66) NALM 40 (68) Placebo (68)	12	Outpatient; U.S.	Ads, recruited as outpatients	45 (11) 46 (11) 44 (9) 45 (11)	6-15	22-33	NR	MET 100%	Med
Anton, 2005[22]	NTX 50+CBT (39) NTX 50+MET (41) Placebo+CBT (41) Placebo+MET (39)	12	Outpatient; U.S.	Ads, referred to clinical service	44 (8) 43 (10) 45 (11) 43 (9)	8-23	21-27	NR	CBT and MET as randomized	Med
Anton, 2006[23] Donovan, 2008[24] LoCastro, 2009[25] COMBINE	ACA 3,000+CBI + MM (151) ACA 3,000+MM (152) NTX 100+CBI+MM (155) NTX 100+MM (154) Placebo+CBI+MM (156) Placebo+MM (153)[b]	16 (68)	11 academic sites; U.S.	Ads, community resources, clinical referrals	45 (10) 44 (11) 45 (1) 44 (10) 43 (10) 44 (9)	23	31	NR	As randomized; Community support group participation (like AA) encouraged	Low
Anton, 2008[26]	ARI 2 to 30 (149) Placebo (146)	12	16 academic centers; U.S.	NR	47 (9) 47 (9)	15-16	25-38	NR	Enhanced CBT 100%	Med
Anton, 2011[27]	NTX 50 (50) Placebo (50) NTX 50+6 wks gabapentin, with 1,200 maximum dose (50)	16	Outpatient; U.S.	NR	44 (10) 43 (10) 47 (9)	13	18	NR	Used COMBINE's manual (CBT+MM+12-step techniques) 100%	Med

Balldin, 2003[28]	NTX 50+CBT (25) NTX 50+ST (31) Placebo+CBT (30) Placebo+ST (32)	26	10 sites outpatient; Sweden	Newspaper, outpatient treatment	50 (7) 48 (8) 50 (8) 51 (8)	NR	9-23	0	None	Low
Baltieri, 2004[29]	ACA 1,998 (40) Placebo (35)	12 (24)	Outpatient; Brazil	Patients seeking treatment at outpatient SA clinic	Full sample4 4 (8)	NR	0	0	AA encouraged	Med
Baltieri, 2008[30]; Baltieri, 2009[31]	NTX 50 (49) TOP target 200, maximum 400 (52) Placebo (54)	12	Outpatient; Brazil	NR	44 (7) 46 (9) 43 (9)	29	0	NR	Psychosocial 100%	High
Berger, 2013[32]	ACA 1,998 (51) Placebo (49)	12	U.S.; 2 outpatient primary care clinics	Provider referral and ads	47 (8) 48 (9)	9	38	NR	Brief structured behavioral intervention from primary care physician	Med
Besson, 1998[33]	ACA 1,300 to 1,998 (55) Placebo (55)	52 (108)	Outpatient; 3 psychiatric treatment centers; Switzerland	From inpatient treatment unit	42 43 (NR)	NR	20	0	Routine counseling 100% Voluntary DIS 22-24%	Med
Book, 2008[34]; Thomas, 2008[35]	PAR 10-60 (20) Placebo (22)	16	NR; U.S.	Ads	28 (7) 30 (8)	0-18	45-50	SAD 100 MDD approx. 10	None	Med
Brady, 2002[36]	VALP 1,500 (14) Placebo (15)	12	Outpatient; U.S.	Newspaper; several treatment settings	40 (8) 41 (10)	54	62	0	CBT	Med

Brady, 2005[37]	SERT 150 (49) Placebo (45)	12	Outpatient; U.S.	Ads, outpatient SA treatment programs	37 (8) 37 (9)	NR	43-49	PTSD 100 Depress-ive disorder 51 Anxiety disorder 38	CBT 100%	Med
Brown, 2008[38]	QUET titrated from 25 to 600 over 6 weeks (52) Placebo (50)	12	NR; U.S	From community	39 (10) 38 (9)	39	37	Bipolar 100	NR	High
Brown, 2009[39]	NTX 50 (20) Placebo (23)	12	Outpatient; university health center; U.S.	Newspaper ads, physician referral, flyers and brochures at clinics	40 (14) 42 (11)	26	49	Bipolar (current depressed or mixed mood) 100 Cannabis abuse 21 Cocaine abuse 12 Ampheta-mine abuse 7	CBT 100%	High
Chick, 2000[40]	ACA 1,998 (289) Placebo (292)	24	Outpatient; U.K.	Recruited from treatment programs	43 (NR) 44 (NR)	NR	16	0	Usual psychosocial outpatient program	Med
Chick, 2000[41]	NTX 50 (90) Placebo (85)	12	Outpatient; U.K.	From patients starting outpatient alcohol rehabilitatio n program	43 (8) 44 (10)	NR	25	0	“Usual psychosocial treatment program”	Med

Chick, 2004[42]	FLUV 100 to 300 (261) Placebo (260)	52	10 outpatient sites; U.K., Eire, Austria, Switzerland	NR	42 (10) 42 (9)	NR	35	NR	Psychosocial TAU at each site	Med
Cornelius, 1997[43] Cornelius, 1995[44]	FLUOX 20-40 (25) Placebo (26)	12	Inpatient psychiatric institute; U.S.	Recruited as inpatient	36 (10) 34 (10)	53	49	MDD 100%	Usual care: psychotherapy 100%	Med
Corrêa Filho, 2013[45]	OND 16 (50) Placebo (52)	12	University-based outpatient SA treatment center; Brazil	Enrollees in the SA treatment program at study site	44 (10) 42 (9)	60-73	0	NR	Standardized brief cognitive behavioral intervention	High
Coskunol, 2002[46]	SERT 100 (30) Placebo (29)	26	Inpatient (mean 1 month) followed by 6 months outpatient; SA treatment unit; Turkey	NR	44 (8) 44 (9)	NR	0	For eligibility, required no concurrent Axis I disorders	Thiamine 500 mg/day 100% Pyridoxone 500 mg/day 100% AA during inpatient 100%	Med
De Sousa, 2004[47]	DIS 250 (50) NTX 50 (50)	52	India; outpatient	Recruited as inpatients	46 (NR) 43 (NR)	NR	0	NR	Supportive group psychotherapy	High

De Sousa, 2005[48]	ACA 1,998 (50) DIS 250 (50)	35	India; outpatient, private psychiatric hospital	Patients undergoing detoxification	42 (NR) 43 (NR)	100	0	NR	Weekly supportive group psychotherapy offered	High
Fawcett, 2000[49]	BUS 40 (48) Placebo (52) Lithium 1,200 (56)	26	Outpatient; U.S.	Ad, referral, inpatient/ outpatient programs	39 (8) 40 (8) 41 (8)	16	0	Depression 48	Supportive therapy	Med
Florez, 2008[50]	NTX 50 (51) TOP 50-400 (51)	26	Outpatient SA clinic, referrals; Spain	Recruited when presenting for treatment	47 (9) 47 (9)	0	15	Personality disorders 27	Therapy based on Relapse Prevention Model 100%	High
Florez, 2011[51]	NTX 50 (91) TOP 200 (91)	26	Spain; Outpatient SA clinic, referrals	Recruited and screened when presenting for treatment	47 (9) 48 (10)	NR	15	Personality disorders 23	BRENDA 100% At least monthly meeting with psychiatrist 100%	High
Fogaca, 2011[52]	NTX 50 (20) Placebo (20) NTX 50+PUFA (20) PUFA (20)	12	Outpatient; Brazil	Newspaper and radio ads	NR	NR	0	NR	None	High
Fuller, 1979[53]	DIS 250 (43) DIS 1 (43) RIB 50 (42)	52	Outpatient; VA hospital; U.S.	Patients presenting to VA hospital requesting	Full sample 43 (9)	61	0	NR	Counseling (unspecified) 100%	Med

				treatment for alcoholism or patients admitted for alcohol-related illness						
Fuller, 1986[54]	DIS 250 (202) DIS 1 (204) RIB 50 (199)	52	Outpatient; 9 VAMCs; U.S.	Screened as inpatients in 7 centers and outpatients at 2	41 (11) 42 (10) 42 (10)	47	0	NR	Counseling (loosely defined) % NR	Med
Garbutt, 2005[55]; Pettinati, 2009[56]; Lucey, 2008[57]	NTX inj 380 every 4 weeks (208) NTX inj 190 every 4 weeks (210) Placebo (209)	26	Inpatient and outpatient, private and VA; U.S.	NR	45 (10) 45 (11) 45 (11)	17	32	NR	BRENDA standardized ST 100%	Med
Garbutt, 2010[58]	BAC 30 (40) Placebo (40)	12	Outpatient, details NR; U.S.	Newspaper and radio ads	48 (8) 50 (7)	4	45	NR	BRENDA 100%	Med
Gastpar, 2002[59]	NTX 50 (84) Placebo (87)	12	7 centers; Outpatient; Germany	Outpatient and inpatient recruitment	43 (10) 42 (10)	0	28	0	Psychosocial treatment	Med
Geerlings, 1997[60]	ACA 1,332 to 1,998 (128) Placebo (134)	26 (52)	Outpatient SA treatment centers;	Recruited from detox patients in same	40 (9) 42 (8)	NR	24	NR	ACA: benzodiazepines 5% Placebo:	Med

			Belgium, the Netherlands, and Luxem-bourg	centers					benzodiazepine s 6%	
George, 1999[61]	BUS 60 (25) Placebo (24)	52	Outpatient; U.S.	Recruited from inpatient research unit at NIAAA	Full sample 42 (range 20-61)	NR	0	0	Care of psychiatrist and nurse at posthospital clinic 100%	High
Gual, 2001[62]	ACA 1,998 (148) Placebo (148)	26	Outpatient; multicenter; hospitals; Spain	NR	41 (9) 41 (9)	NR	20-21	NR	NR	Med
Gual, 2003[63]	SERT 50-150 (44) Placebo (39)	24	1 center; Outpatient; Spain	Outpatient alcohol depen-dence treatment	46 (9) 47 (10)	NR	47	Depress-ion/ dysthymia 100	NR	Med
Gual, 2013[64] ESENSE 2	NALM 20 as-needed (358) Placebo (360)	24	Belgium, Czech Republic, France, Italy, Poland, Portugal, Spain; 57 sites	Referrals and ads	45 (11) 44 (11)	1	26-29	0	BRENDA	Med
Guardia, 2002[65]	NTX 50 (101) Placebo (101)	12	7 centers, Outpatient; Spain	Recruited treatment-seeking patients	NR	NR	25	NR	Psychosocial	Med

Guardia, 2004[66]	OLA 5-15 (29) Placebo (31)	12 (16)	Addictive behavior unit of a hospital psychiatry department; Spain	Treatment-seekers addictive behavior unit	43 (10) 44 (14)	NR	23-27	NR	CBT 100%	Med
Heinala, 2001[67]	NTX 50 daily for 12 weeks then targeted+CS (34) Placebo+CS (33) NTX 50 daily for 12 weeks then targeted+ST (29) Placebo+ST (25)	32	Outpatient; Finland	Ads	Full sample 46 (8)	NR	29	0	None	High
Huang, 2005[68]	NTX 50 (20) Placebo (20)	14	Alcoholism treatment unit of an inpatient psychiatric hospital; 1 week inpatient, remainder outpatient; Taiwan	Recruited as inpatients after admission for detox	38 (6) 43 (9)	100	0	NR	Weekly individual psychotherapy sessions 100%	High
Johnson, 2003[69] Ma, 2006[70]; Johnson, 2004[71]	TOP 25-300 (75) Placebo (75)	12	1 site; outpatient; U.S.	Newspaper	42 (9) 42 (9)	NR	28-40	0	None	Med

Johnson, 2004[72]	NTX inj 400 every 28 days (25) Placebo inj (5)	17	4 centers; outpatient; U.S., France, the Netherlands	NR	42 (9) 45 (8)	37	27	NR	Psychosocial support 100%	High
Johnson, 2007[73] Johnson, 2008[74]	TOP 50-300, mean 171 (183) Placebo (188)	14	17 academic sites; U.S.	From academic sites; by newspaper, radio, television ads	47 (9) 48 (9)	15	26-28	NR	BBCET 100%	Low
Kabel, 1996[75]	FLUOX 20-60 (15) Placebo (13)	15	Inpatient SA treatment; U.S.	Inpatient recruitment	Full sample 47 (9)	46	0	Cocaine use 14%	NR	High
Kampman, 2007[76]	QUET 400 (29) Placebo (32)	12	Outpatient; U.S.	Community referrals, media ads	Full sample 47 (9)	46	23	MDD 15 Antisocial personality disorder 11 PTSD 8 Panic disorder 5 Social phobia 5 GAD 3 OCD 2	BRENDA 100%	High
Kampman, 2013[77]	TOP 25-300[c] (83) Placebo (87)	12 (13)	Outpatient; U.S.	Treatment-seeking cocaine users	45 (7) 43 (8)	17	21	Cocaine depend-ence 100	Weekly individual CBCST	Med

Karhuvaara, 2007[78]	NALM 10 to 40 Targeted dose[d] (242) Placebo (161)	28[e]	15 sites[f]; Finland	Mainly by newspaper ads	50 (9) 49 (8)	0	19	NR	Some elements of BRENDA	Med
Kiefer, 2003[79] Kiefer, 2004[80] Kiefer, 2005[81]	ACA 1,998 (40) NTX 50 (40) Placebo (40) ACA 1,998+NTX 50 (40)	12	1 site, Outpatient; Germany	Inpatient withdrawal treatment	46 (8) 46 (8) 46 (11) 47 (10)	NR	26	0	Group therapy	Low
Killeen, 2004[82]	NTX 50+TAU (54) Placebo+TAU(43) TAU alone (48)	12	Outpatient community SA treatment center; U.S.	Clinic treatment seekers	38 (8) 36 (8) 38 (10)	24	37	Comorbid psychiatric disorder 51 Additional substance use disorder 35	Several types and intensities	Med
Kranzler, 1994[83]	BUS 15-60, mean 52.5 (31) Placebo (30)	12 (38)	Outpatient; university health center; U.S.	Ads	39 (9) 40 (10)	0-10	20-26	GAD 37 to 46 Anxiety disorder 50 to 52 MDD 25 to 27	CBT 100%	Med
Kranzler, 1995[84]	FLUOX 20-60, mean 47 (51) Placebo (50)	12 (38)	Outpatient clinic; U.S.	Ads	Full sample 40 (9)	5	20	Major depression 14%	Group psychotherapy 79% Individual psychotherapy 21%	Med
Kranzler, 2004[85]	NTX inj 150 once a month (185) Placebo inj (157)	12	Outpatient; U.S.	Ads, recruited as outpatients	44 (10) 44 (9)	17-18	33-37	NR	MET 100%	Med
Kranzler, 2009[86]	NTX 50 targeted (38)	12	Outpatient;	Media ads,	Full sample	3	42	Drug use disorder <1	Brief coping	Med

	NTX 50 once daily (45) Placebo targeted (39) Placebo once daily (41)		U.S.	local provider referral	49 (10)			Social phobia 3 Antisocial personality disorder 3 Dysthymic disorder <1 Agoraphobia without panic disorder <1 OCD <1 GAD <1	skills training 100%	
Kranzler, 2011[87]; Kranzler, 2012[88]	SERT 50-200 (63) Placebo (71)	12 (26)	Outpatient; university health center; U.S.	Primarily ads, some clinician referrals	Full sample 48 (10)	8	19	Cannabis use disorder 17 Cocaine use disorder 19 Past MDD 21	Coping skills training 100%	Med
Krystal, 2001[89] VACS 425	NTX 50 for 12 months (209) NTX 50 for 3 months then placebo (209) Placebo (209)	12 or 52	Multicenter, outpatient; U.S.	VA clinics	49 (10) 49 (1) 50 (10)	37	3	0	12-step facilitation	Med
Laaksonen, 2008[90] Laaksonen, 2013[91]	ACA 1,998 or 1,333 (81) DIS 100 to 200 (81) NTX 50 (81)	Up to 52	6 sites in 5 cities; Finland	Volunteers seeking outpatient treatment	45 (8) 43 (9) 42 (9)	0	29	NR	Manual-based CBT targeted to match medication goals	Med for 12-wk out-comes ; high for 52-wk

										out-comes
Latt, 2002[92]	NTX 50 (56) Placebo (51)	12 (26)	4 hospitals; Outpatient; Australia	NR	Full sample 58 (range 23-70)	NR	30	0	No extensive psychosocial interventions	Med
Lee, 2001[93]	NTX 50 (35) Placebo (18)	12	Mixed: initially inpatient, discharged after 1 month from SA treatment center; Singapore	Direct recruitment from inpatient facility	46 (9) 44 (10)	≥88	0	NR	Intensive inpatient rehabilitation program; postdischarge therapy encouraged 100%	High
Lhuintre, 1985[94]	ACA 1,000 to 2,250 (42) Placebo (43)	13	Outpatient; methadone mainten-ance clinics; France	Recruited as inpatients within 48 hours of admission	43 (7) 40 (7)	NR	11	NR	Meprobamate 100% for first month	High
Lhuintre, 1990[95]	ACA 1,332 (279) Placebo (290)	12	Outpatient; multicenter; France	Recruited within 48 hours of hospitaliza-tion for alcohol withdrawal	43 (9) 42 (10)	NR	18	NR	Psychotherapy allowed	Uncl
Likhitsathian, 2013[96]	TOP 100-300 (53) Placebo (53)	12	Outpatient; Thailand	Recruited during inpatient	Full sample 42 (9)	100	0	MDD 4	Individual MET sessions plus	High

				treatment at 3 sites					monthly MM	
Ling, 1983[97]	DIS 250 (41) Placebo (41)	37	Outpatient; VA; U.S.	Unclear	39 (NR)	NR	NR	Heroin use 80 Marijuana use 36 Other drug use 67 Depression 83 Moderate to high depression 50	Methadone 100%	High
Litten, 2013[98]	VAR 2 (99) Placebo (101)	13	5 outpatient academic sites; U.S.	Ads and at treatment sites	46 (11) 45 (12)	30 to 38	27-32	Marijuana use 12-14	Computerized self-help program	Low
Longabaugh, 2009[99]	NTX 50 for 24 weeks+BST (36) NTX 50 for 12 weeks then placebo for 12 weeks+BST (35) NTX 50 for 24 weeks+MET (33) NTX 50 for 12 weeks then placebo for 12 weeks+MET	12-24 (72)	Outpatient; U.S.	Newspaper ads	45 (7) 46 (8) 44 (7) 44 (8)	6-14	33-43	NR	None[g]	Med

	(38)									
Malcolm, 1992[100]	BUS target 60, mean 52 (33) Placebo (34)	26	1-2 weeks inpatient, then outpatient; VAMC alcohol depend-ence treatment unit; U.S.	Screened during inpatient stay for alcohol dependence treatment	44 (SE 2) 42 (SE 1)	15-18	0	GAD 100	None	Med
Malec, 1996[101]	BUS 40 (28) Placebo (29)	12	Hospital research center; Canada	Media ad	42 (8) 41 (8)	NR	18	NR	None prescribed but 37% received additional treatment: AA 7% Individual psychotherapy 3%	High
Mann, 2013[102] PREDICT	ACA 1,998 (172) NTX 50 (169) Placebo (86)	12	Germany; NR	Recruited from inpatient facilities of 5 academic medical centers plus 2 state-run psychiatric hospitals	45 (9) 45 (9) 47 (9)	NR	23	NR	MM	Med
Mann, 2013[103] ESENSE 1	NALM 20 as-needed (306) Placebo (298)	24	Austria, Finland, Germany, Sweden; 39 sites	Referrals and ads	51 (10) 52 (9)	<1	32-33	0	BRENDA	Med
Martinotti,	ARI 5-15 (29) NTX 50 (28)	16	Italy; out-patient;	Direct	Full sample	NR	NR	Mood disorder 19	None required	Med

2009[104]			university hospital day clinic	recruitment from local facility	40 (12)			Anxiety disorder 11[h]		
Mason, 1994[105]	NALM 10 (7) NALM 40 (7) Placebo (7)	12	NR; U.S.	Ads	Full sample 42 (9)	10	29	0	Group therapy 0 to 14% AA 0 to 29%	High
Mason, 1996[106]	DESIP 200 (37) Placebo (34)	26	Psychiatry outpatient departments at 2 urban medical centers; U.S.	Inpatient/ outpatient referral and public service announce-ments	Full sample median 40 (IQR 16)	38	17	Depression 39	AA attendance encouraged	High
Mason, 1999[107]	NALM 20 or 80 (70) Placebo (35)	12	Outpatient SA treatment; academic research center; U.S.	Ads, press releases, other non-specified sources	42 (8) 42 (10)	17-19	31-37	0	CBT 100%	Med
Mason, 2006[108]	ACA 2,000 (258) ACA 3,000 (83) Placebo (260)	24 (32)	21 outpatient clinics[i]; U.S.	Primarily by newspaper ads	45 (11) 44 (9) 45 (10)	14-15	29-36	NR	Brief abstinence-oriented protocol-specific counseling and self-help materials 100%	Low
Mason, 2014[109]	GAB 900 (54) GAB 1,800 (47) Placebo (49)	12 (36)	Outpatient clinical research site; U.S.	Print and internet ads	42 (10) 45 (11) 47 (11)	14 to 26	34 to 57	NR	Weekly manual-guided counseling	Low
McGrath, 1996[110]	IMI 50 to 300 (36) Placebo (33)	12	University-based depression	Ads and referrals	37 (7) 11 (9)[j]	17-22	49-53	MDD 71-72 Bipolar 11-12	Individual relapse prevention	Med

			research clinic; U.S.					Atypical depression 70-72 Other SA 16	counseling	
Moak, 2003[111]	SERT 50-200 (38) Placebo (44)	12	1 site; outpatient; U.S.	Newspaper, outpatient treatment	41 (11) 42 (10)	1	39	Depress-ion/ dysthymia 100	CBT	Med
Monterosso, 2001[112]	NTX 100 (121) Placebo (62)	12	Outpatient; U.S.	Ads	Full sample 46 (12)	27	27	NR	BRENDA	Med
Monti, 2001[113]; Rohsenow, 2007[114]; Rohsenow, 2000[115]	NTX 50 (64) Placebo (64)	12 (52)	2 weeks partial hospital (pre-medication); 52 weeks outpatient; U.S.	Recruited from partial hospital program in an urban private psychiatric hospital	Full sample 39 (9)	3	24	Cocaine use 23 Sedative use 8 Opiate use 4	Brief physician outpatient contacts (intensive therapy occurred prior to medication portion of trial)	Med
Morgenstern, 2012[116]	NTX 100+MBSCT (51) NTX 100 (51) Placebo+MBSCT (50) Placebo (48)	12	NR; U.S.	Ads, community outreach	38 (10) 39 (11) 42 (11) 40 (11)	26	0	HIV 15 Any drug use 67	BBCET 100%	Med
Morley, 2006[117] Morley, 2010[118]	ACA 1,998 (55) NTX 50 (53) Placebo (61)	12	3 treatment centers with "medical care typically	Patients who had attended an inpatient detox program,	45 (9) 48 (9) 42 (9)	NR	30	Severe concurrent illness (psychia-tric or other) – NOS 3	All offered 4-6 sessions of manualized compliance therapy; up-take / attendance NR	Low

			available at hospital based drug and alcohol treatment services"; Australia	outpatient treatment or followup or who responded to ads						
Morris, 2001[119]	NTX 50 (55) Placebo (56)	12	Outpatient; Australia	Outpatient, self-referral	47 (8) 48 (8)	NR	0	PTSD 23 GAD 32 Panic disorder 4 MDD 6 BPD 1	Group psychoeducation and social support	Med
Naranjo, 1995[120]	CIT 40 (53) Placebo (46)	12 (20)	Outpatient research center; Canada	Newspaper ad	44 (10) 47 (10)	NR	44	NR	Brief psychosocial intervention 100%	High
Narayana, 2008[121]	ACA 1,332 to 1,998 (28) NTX 50 (26) TOP 100 to 125 (38)	52	India; military, outpatient	Members of the Armed Forces	38 (range 30-54) 37 (range 27-51) 40 (range 29-55)	100	0	NR	Various psycho-therapies were offered	High
Nava, 2006[122]	DIS 200 (28) NTX 50 (24) GHB 150 mg/kg/day (28)	52	Italy; outpatient	Advertise-ments, word of mouth, press release	43 (5) 41 (7) 39 (8)	NR	15 %	0	CBT	High

O'Malley, 1992[123];O'Malley, 1996[124]	NTX 50+CS (29) NTX 50+ST (23) Placebo+CS (25) Placebo+ST (27)	12 (38)	Outpatient; university alcohol treatment unit; U.S.	Ads and those seeking treatment at unit	NTX (any) 43 (10) PBO (any) 39 (9)	7	26	NR	See arms	Med
O'Malley, 2007[125]	NTX 50 (57) Placebo (50) Randomization stratified by presence of eating disorder	12	University mental health center; U.S.	Newspaper ads and patients seeking SA treatment	Full sample40 (8)	11	100	Eating disorder 28	CBCST 100%, based on manualized approach used in Project MATCH	Med
O'Malley, 2008[126]	NTX 50 (34) Placebo (34) NTX 50+SERT 100 (33)	16	Outpatient; U.S.	Direct community recruitment, health clinic referral, local ads	42 (11) 39 (10) 39 (8)	70	34	NR	MM 100%	Med
Oslin, 1997[127]	NTX 100 on Monday and Wednesday, 150 on Friday (21) Placebo (23)	12	Outpatient SA clinic and VAMC; U.S.	From a VA hospital	57 (7) 59 (7)	64	NR	0	Group therapy and case manager 100%	Med
Oslin, 2008[128]	NTX 100+CBT (40) NTX 100+BRENDA (39) NTX 100+doctor only (41) Placebo+CBT (40)	24	Outpatient psychiatry clinic; U.S.	Ads in local media	45 (11) 44 (10) 42 (11) 44 (13) 44 (10) 44 (11)	27	27	NR	None	Med

	Placebo+BRENDA (40) Placebo+doctor only (40)									
Paille, 1995[129]	ACA 1.3 g (188) ACA 2 g (173) Placebo (177)	52 (78)	NR[k]; France	Referral from alcohol specialist centers	44 (9) 43 (8) 43 (9)	NR	20	NR	Supportive psychotherapy 100% Hypnotics 6 to 7% Anxiolytics 8 to 12% Antidepressants 8 to 9%	Med
Pelc, 1996[130]; Pelc, 1992[131]	ACA 1,332 to 1,998 (55) Placebo (47)	26	Outpatient; multicenter; Belgium	Post-inpatient detox	48 (8) 43 (9)	NR	31	NR	Supportive psychotherapy 100%	High
Pelc, 1997[132]	ACA 1,332 (63) ACA 1,998 (63) Placebo (62)	13	Outpatient; after inpatient detox; Belgium, France	Inpatient referral	NR	NR	NR	NR	Counseling, social support when needed 100%	Med
Petrakis, 2004[133]; Ralevski, 2006[134]	NTX 50 (16) Placebo (15)	12	At least 3 outpatient centers—MIRECC clinics; U.S.	Direct recruitment from participating centers	47 (5) 46 (6)	19	0	Schizo-phrenia or schizo-affective disorder 100	CBT+psychiatric TAU Neuroleptics 52% Benzodiazepines 16% Thymoleptics 39%	Med

Petrakis, 2005[135] Ralevski, 2007[136] Petrakis, 2007[137] Petrakis, 2006[138] VA MIRECC	DIS 250 (66) NTX 50 (59) Placebo (64) NTX 50+DIS 250 (65)	12	Outpatient; VA; U.S.	Recruited as outpatients or ad	46 (9) 48 (7) 46 (7) 48 (9)	26	3	Axis I disorder 100	Psychiatric TAU 100%	Med for NTX; high for DIS
Petrakis, 2012[139]	DESIP 200+placebo (24)[l] PAR 40+placebo (20) DESIP 200+NTX 50 (22) PAR 40+NTX 50 (22)	12	U.S.; out-patient; multiple mental illness centers, most from VAs	Ads (non-veterans); mental illness centers (veterans)	47 (10) 49 (9) 47 (10) 45 (7)	25	9	PTSD 100	Clinical management/ compliance enhancement therapy 100%	High
Pettinati, 2001[140]	SERT 200 (50) Placebo (50)	14	Outpatient; U.S.	Ads and referral	Full sample 45 (10)	80	48	Depress-ion 47	12-step facilitation	Uncl
Pettinati, 2008[141]	NTX 150 (82) Placebo (82) Participants also randomized to either CBT or BRENDA (2x2 design)[m]	12	University-affiliated outpatient SA treatment research facility; U.S.	Those seeking treatment at the facility	Full sample 39 (7)	76	29	Cocaine depend-ence 100	NR	Med
Pettinati, 2010[142]	NTX 100 (49) SERT 200 (40) Placebo (39) SERT 200+NTX	14	Outpatient; U.S.	Newspaper ads, referrals from local	43 (8) 44 (12) 43 (9) 43 (10)	35	38	Depress-ion 100	CBT 100%	Med

	100 (42)			professional or friends/ family						
Plebani, 2013[143]	VAR 2 (19) Placebo (21)	12 (13)	Outpatient; U.S.	Ads, treatment seekers	45 (12) 48 (11)	29-58	9-21	NR	Individual weekly MM	High
Poldrugo, 1997[144]	ACA 1,332 to 1,998 (122) Placebo (124)	26 (52)	Inpatient for 1-2 weeks then outpatient; multicenter community based alcohol rehabilita-tion program; Italy	From acute inpatient withdrawal treatment	43 (10) 45 (9)	NR	23-31	0	Community-based rehabilitation program with group sessions, alcohol education, community meetings 100%	Med
Ralevski, 2011[145]; Ralevski, 2011[146]	ACA 1,998 (12) Placebo (11)	12	Outpatient; university and VA health centers; U.S.	From community and through referrals from treatment facilities at a university and a VA facility	52 (9) 49 (5)	65	17	Schizo-phrenia spectrum disorders 100	Weekly skills training that incorporated CB drug relapse prevention strategies 100%	High
Rubio, 2001[147]	ACA 1,665-1,998 (80)	52	Spain;	Patients presenting to hospital	44 (12) 43 (10)	NR	0	0	Supportive group therapy weekly; weekly	High

	NTX 50 (77)		outpatient	for detox					visits with a psychiatrist for 3 months, then biweekly until end of study	
Rubio, 2009[148]	TOP 250 (31) Placebo (32)[n]	12	Outpatient; Spain	NR	43 (9) 42 (9)	NR	0	NR	Supportive group therapy offered	High
Salloum, 2005[149]	VALP 750+ (29) Placebo (30)	24	Outpatient SA service at university clinic; U.S.	Treatment seekers	37 (9) 38 (9)	25	29	Bipolar I disorder 100 Mixed bipolar subtype 58 Manic 21 Depress-ed 21 Cannabis abuse or depen-dence 29 Cocaine abuse 29	Lithium and weekly individual dual diagnosis recovery counseling 100%	Med
Sass, 1996[150]	ACA 1,332 to 1,998 (136) Placebo (136)	48 (96)	Psychiatric outpatient; Germany	Outpatient referral	42 (8) 41 (9)	NR	22	NR	Counseling / psychotherapy 100%	Med
Schmitz, 2004[151]	NTX 50+RPT (20) NTX 50+DC (20) Placebo+RPT (20) Placebo+DC (20)	12	Outpatient; U.S.	Ads	Full sample 36 (6)	71	16	Cocaine depend-ence 100	RPT or DC as randomized	High

Schmitz, 2009[152]	NTX 100+CBT (20) NTX 100+CBT and CM (25) Placebo+CBT (27) Placebo+CBT and CM (14)	12	Outpatient SA clinic; U.S.	Media ads	33 (1) 33 (1) 33 (1) 42 (7)	84-93	13	Cocaine use disorder 100	CBT 100%	High
SENSE, 2013[153]	NALM 20 as-needed (509) Placebo (166)	52 (56)	Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Russian Federation, Slovakia, Ukraine, U.K.	NR	44 (11) 44 (12)	NR	23	NR	NR	High
Stedman, 2010[154]	QUET 300-800 (175) Placebo (186)	12	Outpatient; multicenter; U.S.	NR	39 (9) 38 (10)	12	37	Bipolar 100	None	High
Tempesta, 2000[155]	ACA 1,998 (164) Placebo (166)	26 (39)	Outpatient; Italy	Recruited from outpatient internal medicine, neurology and addiction treatment programs	46 (11) 46 (11)	NR	17	0	Medical and behavioral counseling	Med

Tiihonen, 1996[156]	CIT 40 (31) Placebo (31)	13 (17)	Outpatient; community-based alcohol rehabilita-tion center; Finland	Inpatient / outpatient referral	45 (7) 47 (9)	NR	0	0	Supportive psychotherapy intervention 100%	High
Tollefson, 1991[157]; Tollefson, 1992[158]	BUS 15-60 (26) Placebo (25)	24	Outpatient; U.S.	Referred based on recent inpatient SA treatment discharges	Full sample 38 (SE 0.4)	NR	44	GAD with depress-ive features 100%	Controlled AA participation	High
Volpicelli, 1995[159] Volpicelli, 1992[160]	NTX 50 (54) Placebo (45)[o]	12	SA treatment unit of a VAMC; U.S.	Patients in the SA treatment program of a VAMC	44 (9) 43 (9)	≥78	0	NR	Outpatient treatment program and group therapy 100%	Uncl
Volpicelli, 1997[161]	NTX 50 (48) Placebo (49)	12	Outpatient SA treatment, university/V A treatment research center; U.S.	Receiving outpatient treatment	39 (9) 38 (9)	60-65	18-26	NR	Counseling 100%	Med
Whitworth, 1996[162]	ACA 1,332 or 1,998 (224) Placebo (224)	52 (104)	Outpatient specialty; Austria	Inpatient recruitment	42 (8) 42 (9)	NR	21	NR	NR	Med
Wilens, 2008[163]	ATO 25 to 100 (72)	12	Multi-institution;	NR	34 (10) 35 (10)	12	15	ADHD 100	12-step allowed; all other co-	High

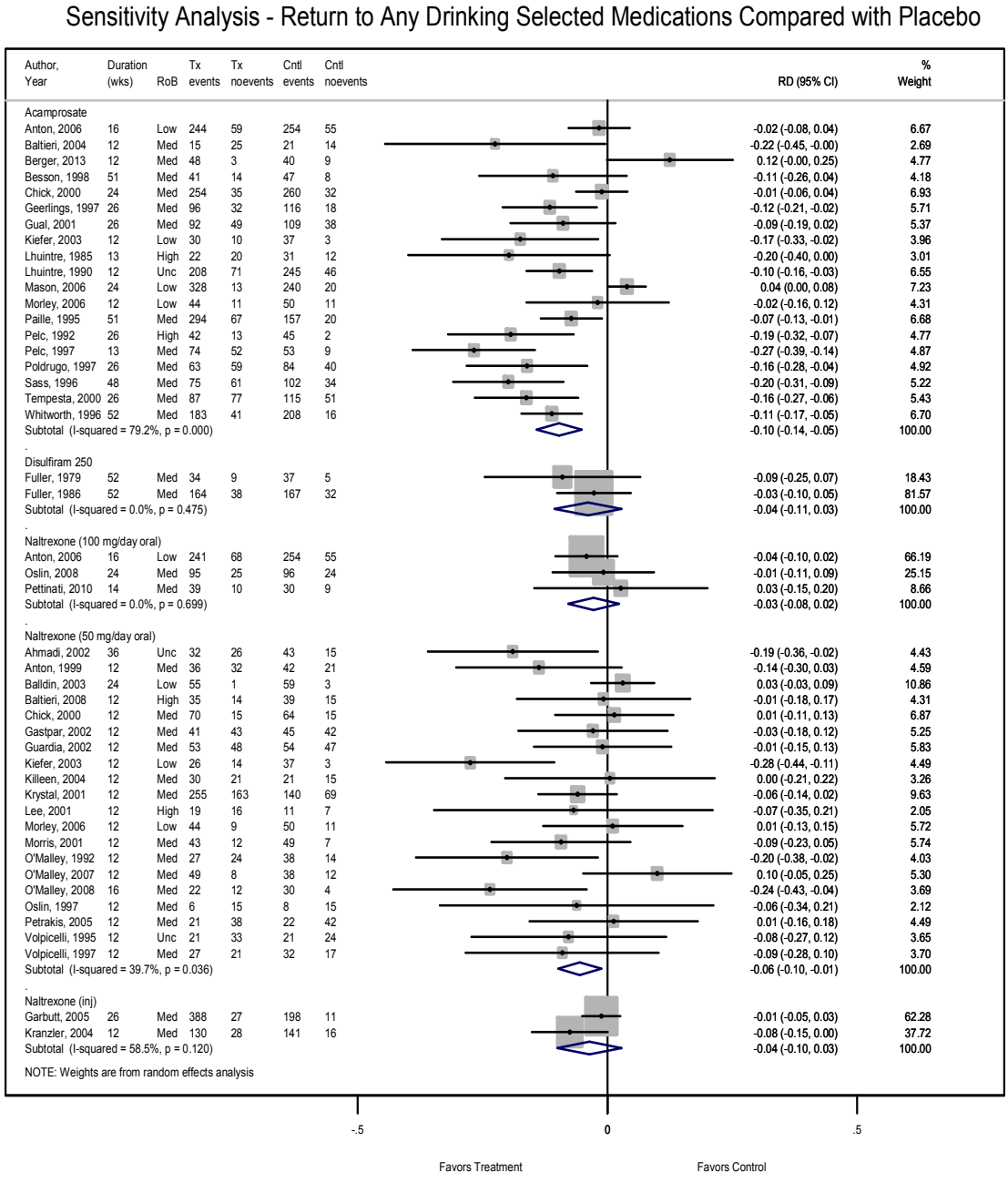
	Placebo (75)		U.S. and Canada						interventions prohibited	
Wolwer, 2011[164]	ACA 1,998+IBT (124) ACA 1,998+TAU (122)[p] Placebo+IBT (125)	24 (52)	Outpatient; 4 university hospitals 1 non-academic clinic; Germany	Recruited after inpatient detox	45 (8) 46 (8) 46 (8)	NR	29	NR	NR	Med

[a] Age is reported as mean (SD) by treatment group unless otherwise noted.
[b] Three additional treatment arms were included in COMBINE but were not relevant to our Key Questions: ACA + NTX + CBI + MM, ACA + NTX + MM, and CBI only (no pills).
[c] Dose was titrated up from 25 to 300mg/day over 8 weeks
[d] Targeted dosing; medication was taken when participants believed drinking to be imminent, rather than as a daily scheduled medication.
[e] 52 weeks total (28 weeks of initial nalmefene vs. placebo, then another randomization for nalmefene responders).
[f] Sites included 5 specialist treatment clinics, 6 private general practices, 2 occupational health care offices, and 2 outpatient clinical research facilities
[g] This study is not focused on NTX versus placebo comparison; it is a different design and has 4 arms, aiming to compare 12 versus 24 weeks of NTX and to compare MET versus BST (to determine whether the type of psychosocial treatment delivered in combination with duration of NTX may partially explain inconsistent findings regarding efficacy of NTX).
[h] Study also reported the following percentages of participants with co-occurring disorders: impulse control disorder 5%, eating disorder 1%, somatoform disorder 1%. Personality disorders: borderline 8%, antisocial 4%, avoidant 4%, histrionic 1%, paranoid 1%, dependent 1%, passive-aggressive 1%, schizoid 1%, cannabis abuse 12%, cocaine abuse 8%, benzodiazepine abuse 1%, MDMA abuse 1%.
[i] Clinics were affiliated with academic medical centers and had investigators experienced in alcoholism treatment.
[j] The study reported 11 years, but it was clearly a reporting error; likely 31 or 41 years.
[k] The article was not explicit about the setting, but patients received psychotherapy and psychiatric medication management suggesting a psychiatric outpatient setting.
[l] Because 2 of the 4 arms are combinations, they are not eligible/not comparisons of interest; only the head-to-head comparison of paroxetine+placebo and desipramine+placebo is eligible.
[m] Study stratified randomization by sex and reports the results overall and separately by sex.
[n] Numbers entered are those analyzed; 76 total were randomized, but dropouts were not reported by arm.
[o] Data are from Volpicelli 1995,[159] which reported pooled results of 99 participants. Data from a smaller subset (N=70) of this sample was reported in Volpicelli 1992.[160] For our data analyses, we used data from Volpicelli 1995 to use the larger, more complete sample and did not use data from Volpicelli 1992 to avoid double counting.
[p] Treatment as usual, seen once per week in an individual setting; MI techniques allowed.

Abbreviations: AA = Alcoholics Anonymous; ACA = acamprosate; ADHD = attention deficit hyperactivity disorder; ARI = aripiprazole; ATO = atomoxetine; BAC = baclofen; BBCET = brief behavioral compliance enhancement treatment; BPD = bipolar disorder; BRENDA = BRENDA is an acronym based on the components of the intervention: (B)iopsychosocial evaluation, (R)eport to the patient on assessment, (E)mpathic understanding of the patient's situation, (N)eeds collaboratively identified by the patient and treatment provider, (D)irect advice to the patient on how to meet those needs, (A)ssess reaction of the patient to advice and adjust as necessary for best care; BST = broad spectrum treatment; BUS = buspirone; CB = cognitive behavioral; CBCST = cognitive behavioral coping skills therapy; CBI = combined behavioral intervention; CBT = cognitive behavioral therapy; CIT = citalopram; CS = coping skills; DC = drug counseling; DESIP = desipramine; detox = detoxification; DIS = disulfiram; Dur = duration; f-u = followup; Fem = female; FLUOX = fluoxetine; FLUV = fluvoxamine; g = grams; GAB = gabapentin; GAD = generalized anxiety disorder; GHB = γ-Hydroxybuteric acid; HIV = human immunodeficiency virus; IBT = integrative behavior therapy; IMI = imipramine; inj = injectable; IQR = interquartile range; kg = kilogram; MBSCT = modified behavioral self-control therapy; MDD = major depressive disorder; Med = medium; MET = motivational enhancement therapy; mg = milligram; MIRECC = Mental Illness Research, Education and Clinical Center; MM = medical management; N = number; NALM = nalmefene; NIAAA = National Institute on Alcohol Abuse and Alcoholism; NOS = not otherwise specified; NR = not reported; NTX = naltrexone; OCD = obsessive-compulsive disorder; OLA = olanzapine; OND = ondansetron; PAR = paroxetine; PTSD = post-traumatic stress disorder; PUFA = polyunsaturated fatty acid; QUET = quetiapine; RIB = riboflavin;

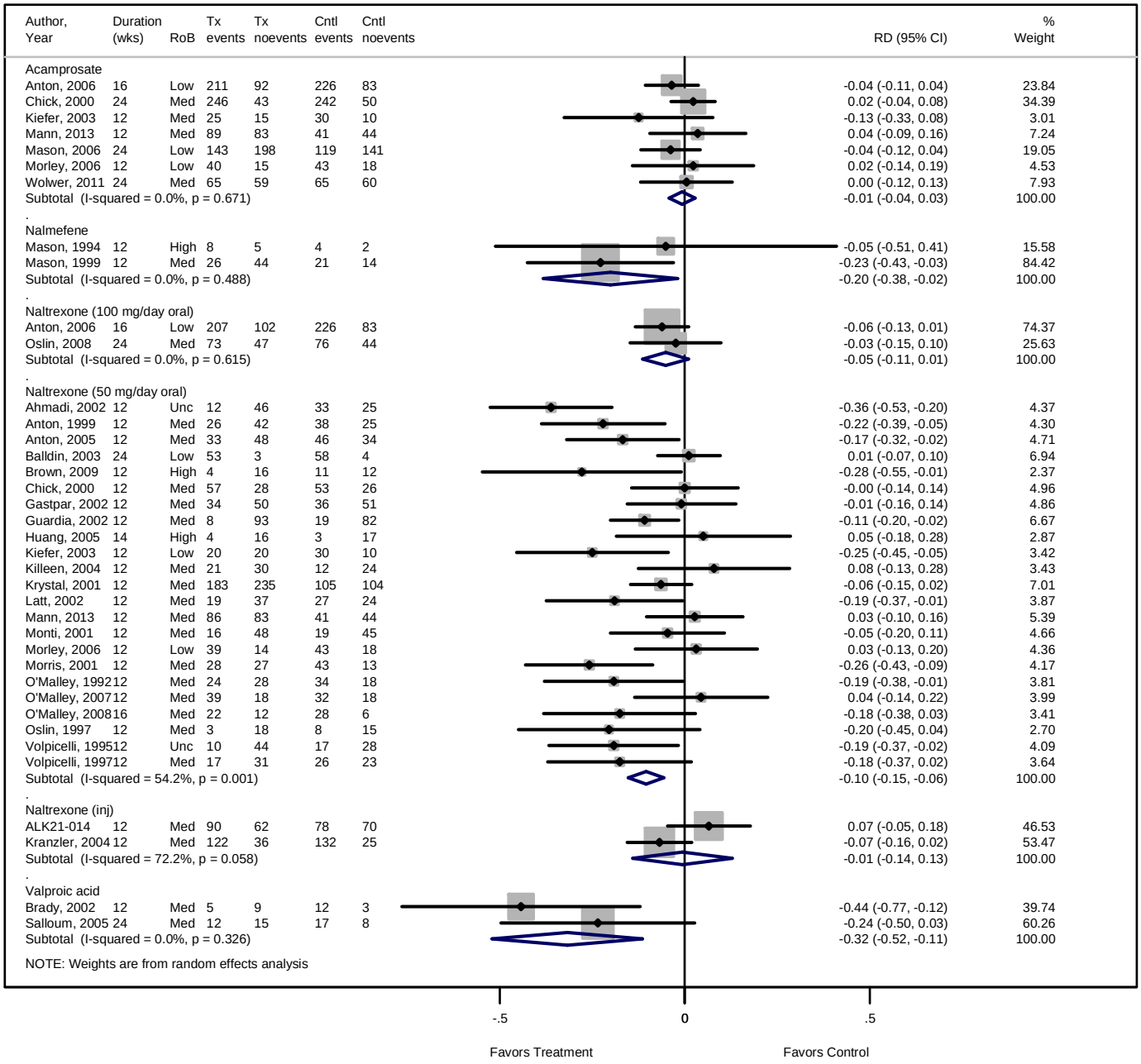
RPT = relapse prevention therapy; Rx = medication; SA = substance abuse; SE = standard error; SAD = social anxiety disorder; SERT = sertraline; ST = supportive therapy; TAU = treatment as usual; TOP = topiramate; U.K. = United Kingdom; U.S. = United States; Uncl = unclear; VA = Veterans Affairs; VACS = Veterans Affairs Cooperative Study; VALP = valproic acid; VAMC, Veterans Administration Medical Center; VAR = varenicline; Wks = weeks; Yrs = years.

eFigure 1. Return to any drinking for selected medications compared with placebo, sensitivity analysis including studies rated as high or unclear risk of bias



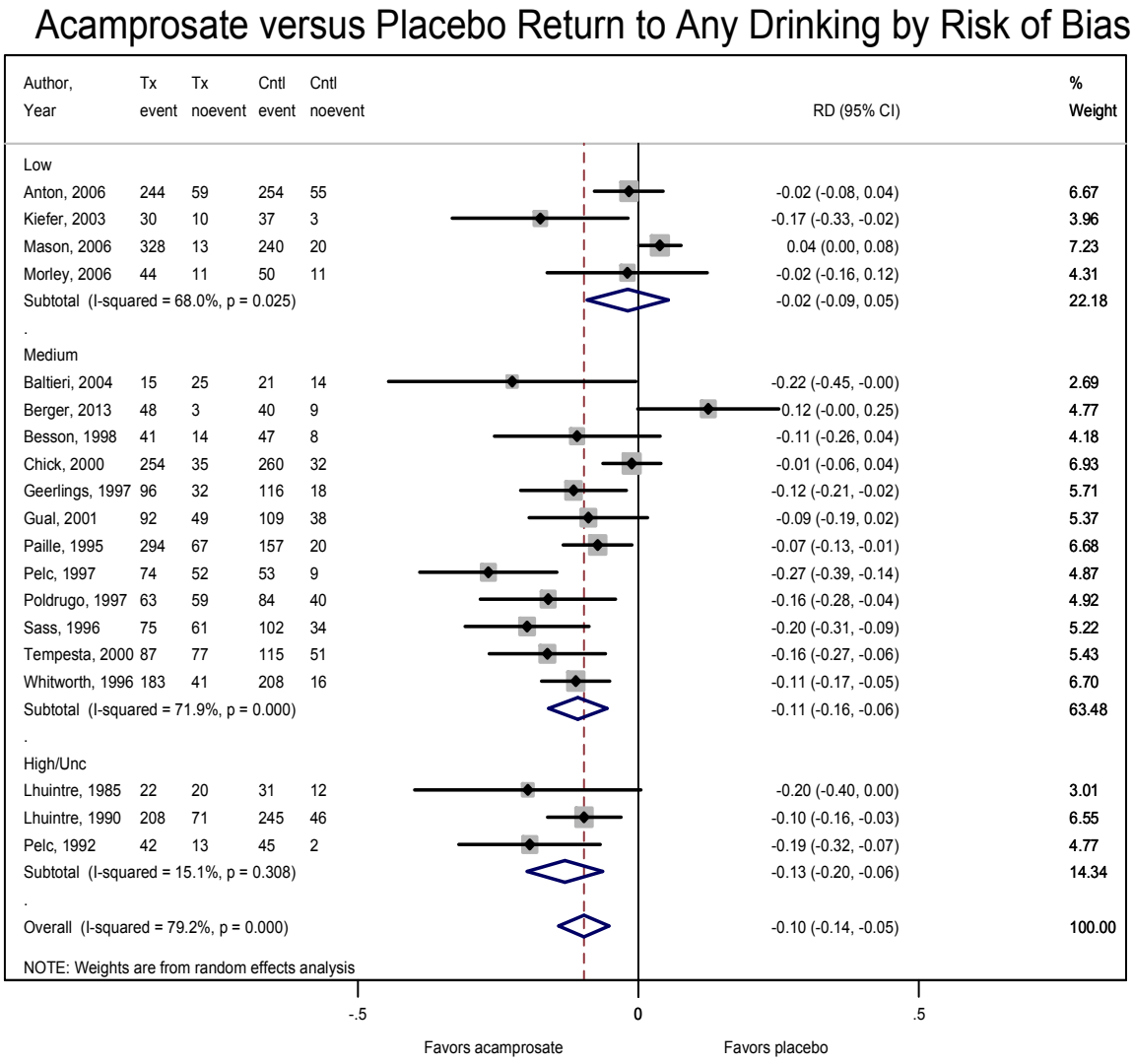
Abbreviations: CI = confidence interval; Cntl events = number of events in the control group; Cntl noevents = number of no events in the control group; Med = medium; RD = risk difference; RoB = risk of bias; Tx events = number of events in treatment group; Tx noevents = number of no events in the treatment group; wks =weeks.

eFigure 2. Return to heavy drinking for selected medications compared with placebo, sensitivity analysis including studies rated as high or unclear risk of bias

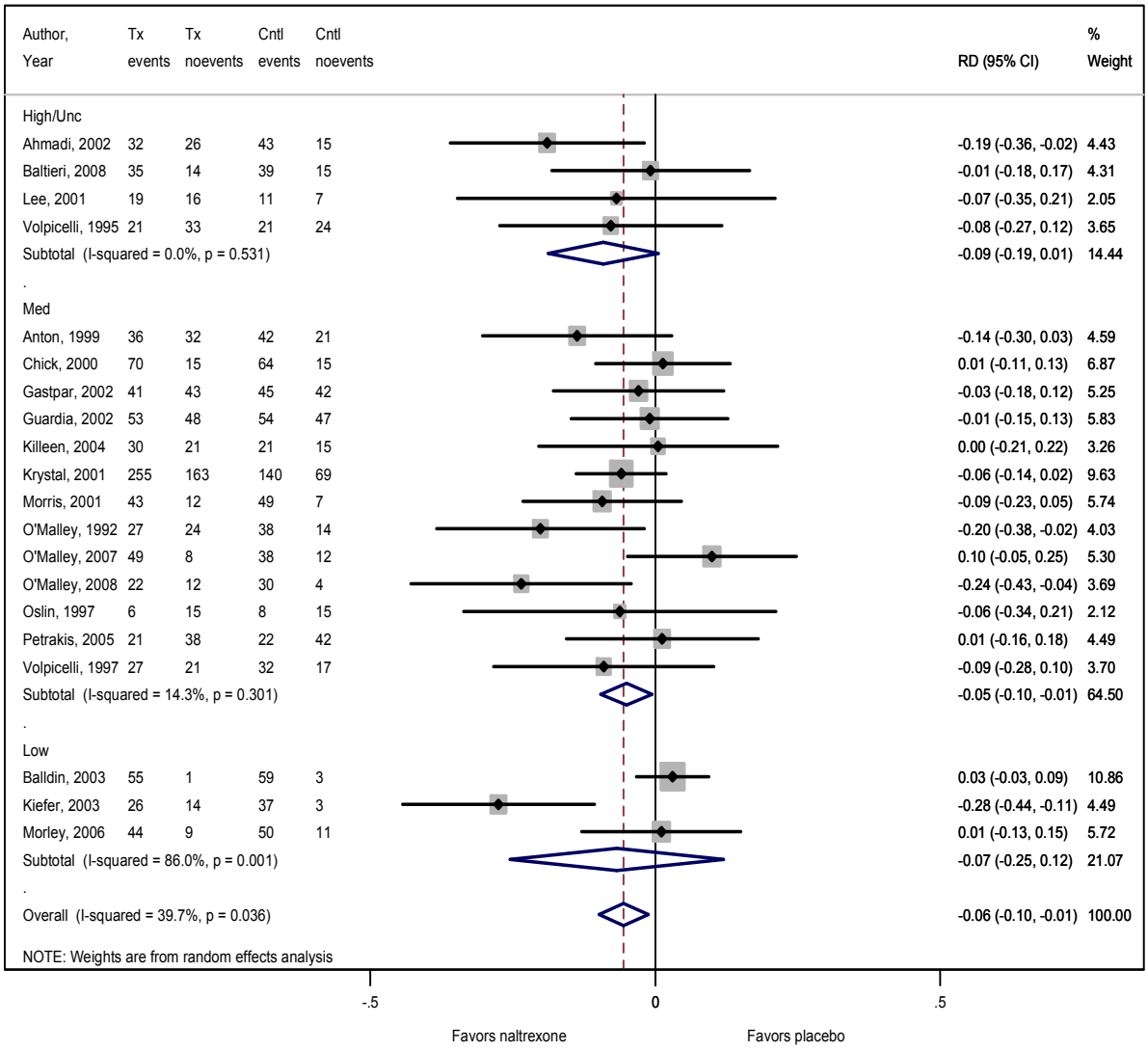


Abbreviations: CI = confidence interval; Cntl events = number of events in the control group; Cntl noevents = number of no events in the control group; Med = medium; RD = risk difference; RoB = risk of bias; Tx events = number of events in treatment group; Tx noevents = number of no events in the treatment group; wks =weeks.

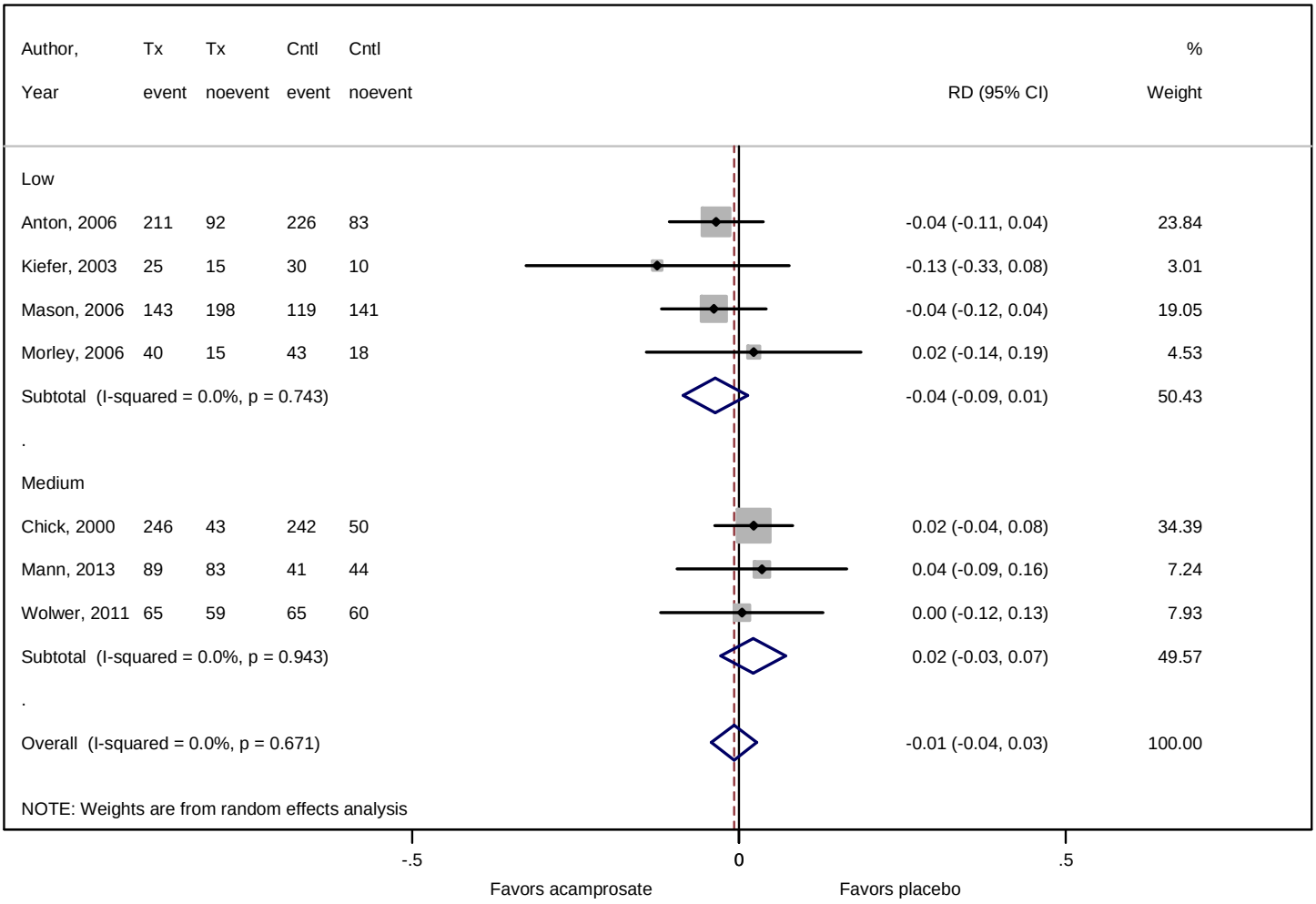
eFigure 3. Return to any drinking for acamprosate compared with placebo, subgroup analysis by risk of bias



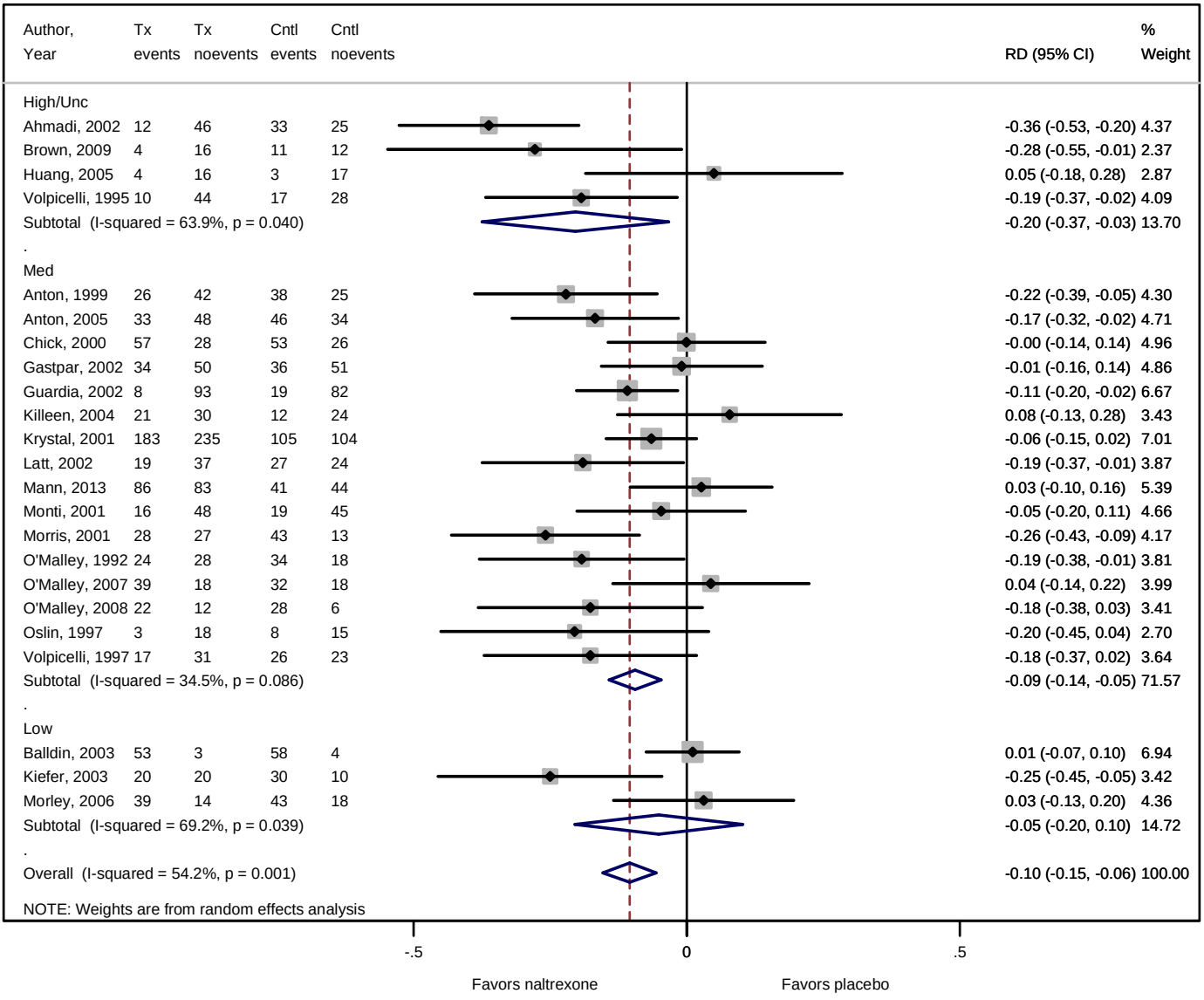
eFigure 4. Return to any drinking for oral naltrexone (50mg/day) compared with placebo, subgroup analysis by risk of bias



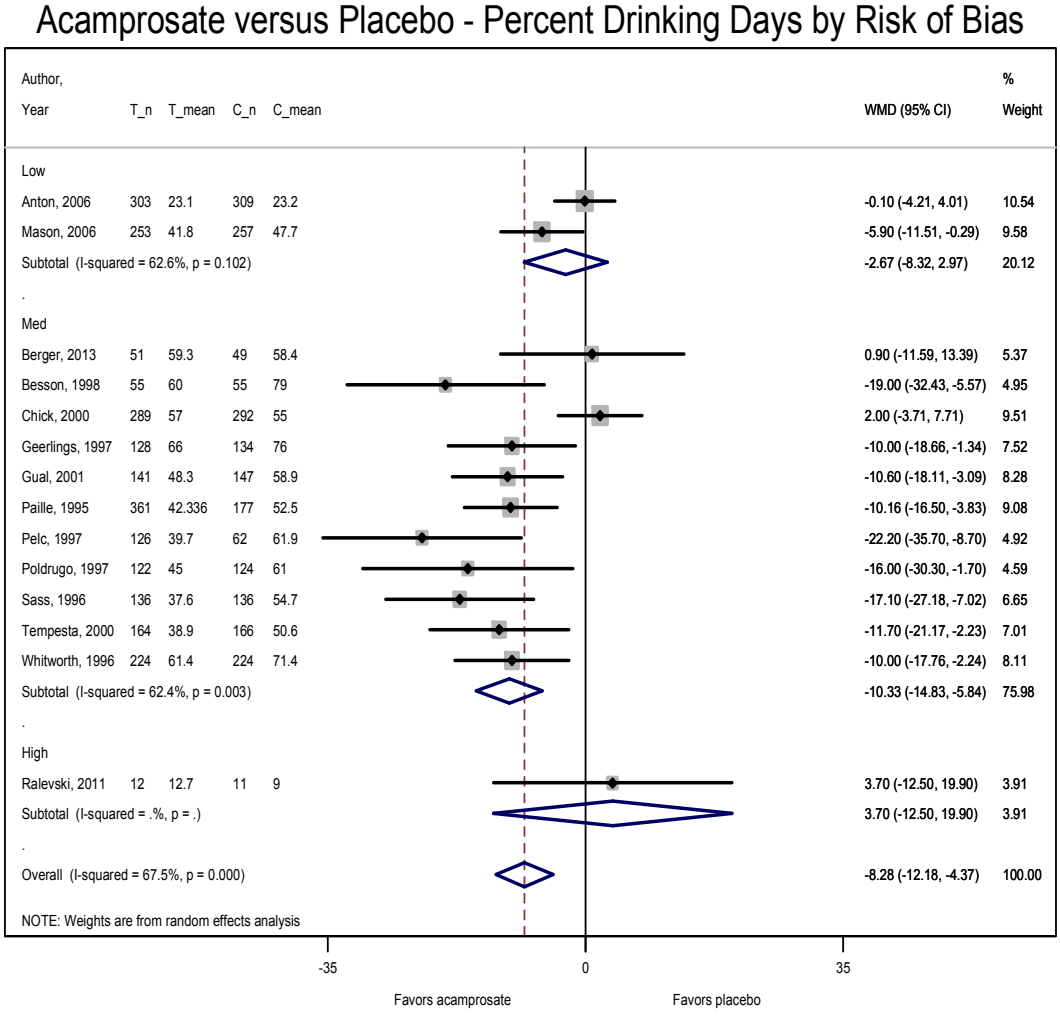
eFigure 5. Return to heavy drinking for acamprosate compared with placebo, subgroup analysis by risk of bias



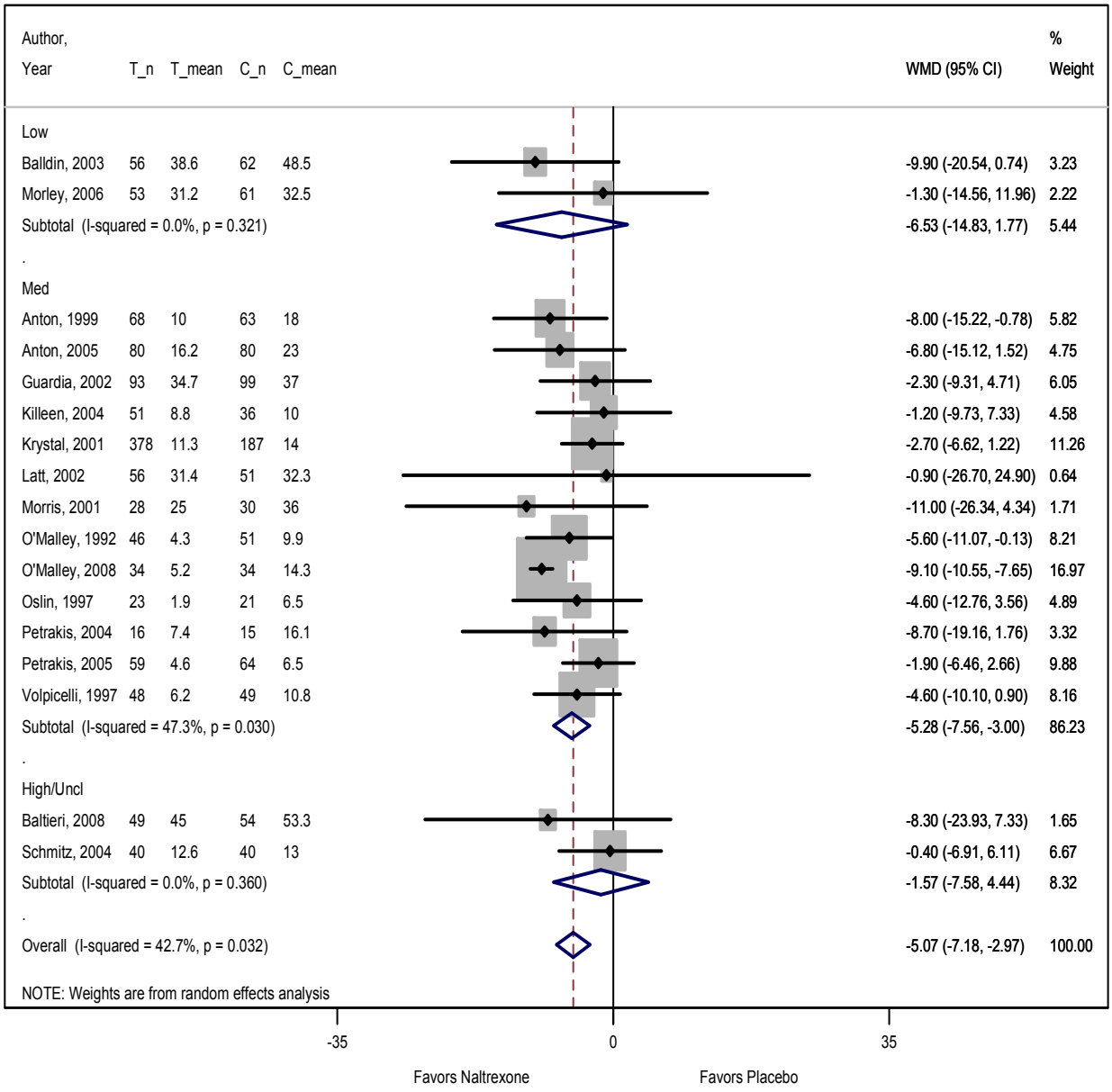
eFigure 6. Return to heavy drinking for oral naltrexone (50mg/day) compared with placebo, subgroup analysis by risk of bias



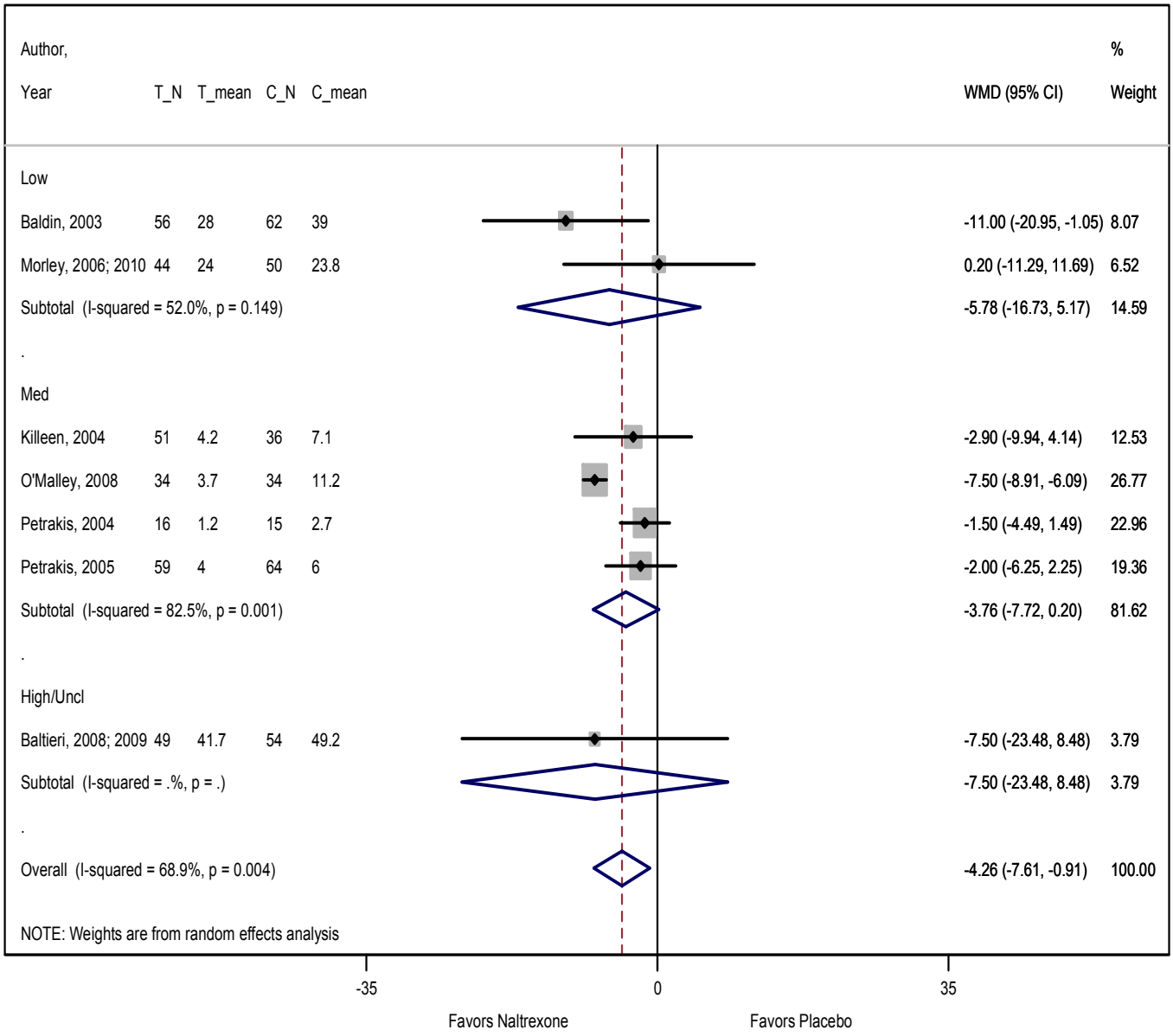
eFigure 7. Percent drinking days for acamprosate compared with placebo, subgroup analysis by risk of bias



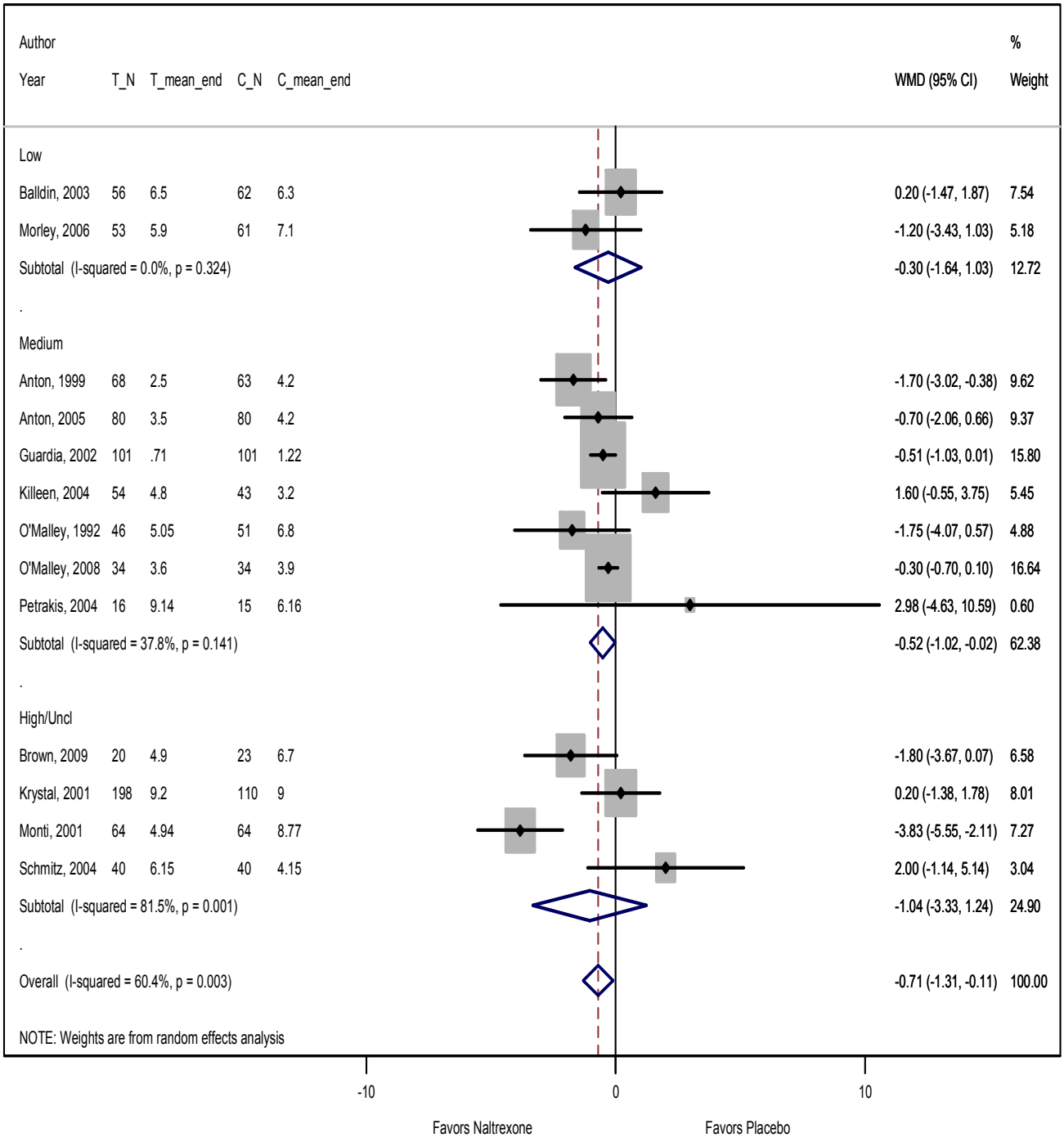
eFigure 8. Percent drinking days for oral naltrexone (50mg/day) compared with placebo, subgroup analysis by risk of bias



eFigure 9. Percent heavy drinking days for oral naltrexone (50mg/day) compared with placebo, subgroup analysis by risk of bias



eFigure 10. Drinks per drinking day for oral naltrexone (50mg/day) compared with placebo, subgroup analysis by risk of bias



eTable 5. Summary of findings and strength of evidence for alcohol consumption outcomes and health outcomes for medications used off-label or those under investigation

Intervention	Outcome	N studies[a]	N participants	Results Effect Size (95% CI)[b]	NNT (95% CI)[c]	Strength of Evidence
Amitriptyline	Return to any drinking	0	0	NA	NA	Insufficient
	Return to heavy drinking	0	0	NA	NA	Insufficient
	% DD	0	0	NA	NA	Insufficient
	% HDD	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
Aripiprazole	Return to any drinking	1[26]	288	89% (ARI) vs. 78% (PBO); P=0.02	NA	Insufficient
	Return to heavy drinking	1[26]	288	73% (ARI) vs. 73% (PBO); P=0.98	NA	Insufficient
	% DD	1[26]	288	41% (ARI) vs. 37% (PBO); P=0.23	NA	Insufficient
	% HDD	0	0	NA	NA	Insufficient
	Drinks per DD	1[26]	288	4.4 (ARI) vs. 5.5 (PBO); P<0.001	NA	Insufficient
	Accidents or injuries	0	0	NA	NA	Insufficient
	QoL or function	0	0	NA	NA	Insufficient
	Mortality	0	0	NA	NA	Insufficient
Atomoxetine	Return to any drinking	0	0	NA	NA	Insufficient

	Return to heavy drinking	0	0	NA	NA	Insufficient
	% DD	0	0	NA	NA	Insufficient
	% HDD	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
Baclofen	Return to any drinking	2[14,58]	164	Study 1: OR 6.3, 95% CI 2.4, 16.1 Study 2: NSD	NA	Insufficient
	Return to heavy drinking	2[14,58]	164	Study 1: BAC significantly lower than PBO (data in Figure, P=0.006) Study 2: HR 0.92, P=0.76	NA	Insufficient
	% DD	1[58]	80	50.1% (BAC) vs. 49.4% (PBO); P=0.50	NA	Insufficient
	% HDD	1[58]	80	25.9% (BAC) vs. 25.5% (PBO); P=0.73	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
Buspirone	Return to any drinking	1	54	RD: 0.07 (-0.19 to 0.34)	NA	Insufficient
	Return to heavy drinking	0	0	NA	NA	Insufficient
	% DD	2[49,83]	161	WMD: -3.4 (-9.2 to 2.4)	NA	Low
	% HDD	0	0	NA	NA	Insufficient

	Drinks per DD	1[83]	61	0.7 vs. 2.1; P NSD	NA	Insufficient
	Accidents or injuries	0	0	NA	NA	Insufficient
	QoL or function	0	0	NA	NA	Insufficient
	Mortality	0	0	NA	NA	Insufficient
Citalopram	Return to any drinking	0	0	NA	NA	Insufficient
	Return to heavy drinking	0	0	NA	NA	Insufficient
	% DD	0	0	NA	NA	Insufficient
	% HDD	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
Desipramine	Return to any drinking	0	0	NA	NA	Insufficient
	Return to heavy drinking	0	0	NA	NA	Insufficient
	% DD	0	0	NA	NA	Insufficient
	% HDD	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
Fluoxetine	Return to any drinking	1[43]	51	RD: -0.13 (-0.35 to 0.10)	NA	Insufficient
	Return to heavy drinking	0	0	NA	NA	Insufficient
	% DD	2[43,84]	146	WMD: -3.2 (-18.2 to 11.9)	NA	Low
	% HDD	1[43]	51	4.8 (FLUOX) vs. 16	NA	Insufficient

				(PBO); P=0.04		
	Drinks per DD	2[43,84]	146	WMD: -1.2 (-4.6 to 2.2)	NA	Low
	Accidents or injuries	0	0	NA	NA	Insufficient
	QoL or function	0	0	NA	NA	Insufficient
	Mortality	0	0	NA	NA	Insufficient
Fluvoxamine	Return to any drinking	1[42]	492	12 weeks: 58% (FLUV) vs. 54% (PBO); P=0.40 52 weeks: 71% (FLUV) vs. 71% (PBO); P=0.94	NA	Insufficient
	Return to heavy drinking	1[42]	492	12 weeks: 46% (FLUV) vs. 40% (PBO); P=0.18 52 weeks: 64% (FLUV) vs. 64% (PBO); P=0.47	NA	Insufficient
	% DD	1[42]	492	12 weeks: 31% (FLUV) vs. 23% (PBO); P=0.009 52 weeks: 44% (FLUV) vs. 38% (PBO); P=0.13	NA	Insufficient
	% HDD	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	1[42]	492	52 weeks: 1 (FLUV) vs. 1 (PBO)	NA	Insufficient
Gabapentin	Return to any drinking	1[109]	150	89% (78% to 95%) (GAB 900) vs. 83% (70% to 91%) (GAB 1800) vs. 96% (86% to 99%) (PBO)	NA	Insufficient

	Return to heavy drinking	1[109]	150	70% (57% to 81%) (GAB 900) vs. 55% (41% to 69%) (GAB 1800) vs. 78% (63% to 86%) (PBO)	NA	Insufficient
	% DD	0	0	NA	NA	Insufficient
	% HDD	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	1[109]	150	No deaths in any group	NA	Insufficient
Imipramine	Return to any drinking	1[110]	56	69% (IMI) vs. 79% (PBO); P NSD	NA	Insufficient
	Return to heavy drinking	0	0	NA	NA	Insufficient
	% DD	1[110]	56	28.3% (IMI) vs. 30.8% (PBO); P NSD	NA	Insufficient
	% HDD	1[110]	56	13.5% (IMI) vs. 9.0% (PBO); P NSD	NA	Insufficient
	Drinks per DD	1[110]	56	3.7 (IMI) vs. 4.1 (PBO); P NS	NA	Insufficient
	Accidents or injuries	0	0	NA	NA	Insufficient
	QoL or function	0	0	NA	NA	Insufficient
	Mortality	0	0	NA	NA	Insufficient
Nalmefene	Return to any drinking	0	0	NA	NA	Insufficient
	Return to heavy drinking	1[107]	105	RD: -0.23 (-0.43 to -0.03)	NA	Insufficient
	% DD	2[78,107]	508	WMD: -1.1 (-7.6 to 5.4)	NA	Low
	% HDD	1[78]	403	18.1% (NALM) vs. 29.7% (PBO); P=0.02	NA	Insufficient
	Change in HDDs per					

	month: OC analysis PMI analysis	 2[64,103] 2[64,103]	 806 1,234	 WMD: -2.0 (-3.0 to -1.0) WMD: -1.3 (-2.2 to -0.3)		Moderate
	Drinks per DD	3[21,78,107]	608	WMD: -1.02 (-1.77 to -0.28)	NA	Moderate
	Accidents or injuries	0	0	NA	NA	Insufficient
	QoL or function	0	0	NA	NA	Insufficient
	Mortality	2[64,103]	1,253	Study 1: 0 (NALM) vs. 2 (PBO) Study 2: 1 (NALM) vs. 1 (PBO)		
Olanzapine	Return to any drinking	0	0	NA	NA	Insufficient
	Return to heavy drinking	1[66]	60	37.9% (OLA) vs. 29.0% (PBO); P=0.50	NA	Insufficient
	% DD	1[66]	60	13.1% (OLA) vs. 22.7% (PBO); P=0.18	NA	Insufficient
	% HDD	0	0	NA	NA	Insufficient
	Drinks per DD	1[66]	60	1.8 (OLA) vs. 2.0 (PBO); P=0.71	NA	Insufficient
	Accidents or injuries	0	0	NA	NA	Insufficient
	QoL or function	0	0	NA	NA	Insufficient
	Mortality	0	0	NA	NA	Insufficient
Ondansetron	Return to any drinking	0	0	NA	NA	Insufficient
	Return to heavy drinking	0	0	NA	NA	Insufficient
	% DD	0	0	NA	NA	Insufficient
	% HDD	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
Paroxetine	Return to any drinking	0	0	NA	NA	Insufficient
	Return to heavy drinking	0	0	NA	NA	Insufficient
	% DD	1[34]	42	34% (PAR) vs. 35% (PBO); P=NSD	NA	Insufficient
	% HDD	1[34]	42	54% (PAR) vs. 55% (PBO); P=NSD	NA	Insufficient
	Drinks per DD	1[34]	42	5.9 (PAR) vs. 7.0 (PBO); P=NSD	NA	Insufficient
	Accidents or injuries	0	0	NA	NA	Insufficient
	QoL or function	0	0	NA	NA	Insufficient
	Mortality	0	0	NA	NA	Insufficient
Quetiapine	Return to any drinking	0	0	NA	NA	Insufficient
	Return to heavy drinking	0	0	NA	NA	Insufficient
	% DD	0	0	NA	NA	Insufficient
	% HDD	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
Sertraline	Return to any drinking	1[142]	79	72.5% (SER) vs. 76.9% (PBO); P NSD	NA	Insufficient
	Return to heavy drinking	2[46,63]	142	RD: -0.04 (-0.31 to 0.23)	NA	Low
	% DD	3[63,87,111]	299	WMD: 1.8 (-6.25 to 9.86)	NA	Low

	% HDD	2[37,87]	228	WMD: 1.9 (0.70 to 3.0)	NA	Low (favors placebo)
	Drinks per DD	2[37,111]	176	WMD: -0.86 (-2.2 to 0.48)	NA	Low
	Accidents or injuries	0	0	NA	NA	Insufficient
	QoL or function	1[63]	83	Graph only; data NR (P=0.03)	NA	Insufficient
	Mortality	1[142]	79	0 (SER) vs. 0 (PBO)	NA	Insufficient
Topiramate	Return to any drinking	0	0	NA	NA	Insufficient
	Return to heavy drinking	0	0	NA	NA	Insufficient
	% DD	2[73,77]	541	WMD: -6.5 (-12.0 to -1.0)	NA	Moderate
	% HDD	3[69,73,77]	691	WMD:-9.0 (-15.3 to -2.7)	NA	Moderate
	Drinks per DD	3[69,73,77]	691	WMD: -1.0 (-1.6 to -0.5)	NA	Moderate
	Accidents or injuries	1[73]	371	4.4% (TOP) vs. 11.7% (PBO); P=0.01	NA	Insufficient
	QoL or function	1[91]	106	SF-36 physical: 89.9 (TOP) vs. 89.4 (PBO); P=0.85 SF-36 mental: 84.0 (TOP) vs. 84.2 (PBO); P=0.92	NA	Insufficient
	Mortality	1[73]	371	0 (TOP) vs. 1 (PBO)	NA	Insufficient
Valproic acid	Return to any drinking	1[36]	29	81% (VAL) vs. 83% (PBO); P NSD	NA	Insufficient
	Return to heavy drinking	2[36,149]	81	RD: -0.32 (-0.52 to -0.11)	4 (2 to 9)	Low
	% DD	1[36]	29	15.9 (VAL) vs. 19.6 (PBO); P NSD	NA	Insufficient
	% HDD	2[36,149]	81	WMD: -8.5 (-15.9 to -	NA	Low

				1.1)		
	Drinks per DD	2[36,149]	81	WMD: -2.6 (-5.0 to -0.15)	NA	Low
	Accidents or injuries	0	0	NA	NA	Insufficient
	QoL or function	0	0	NA	NA	Insufficient
	Mortality	0	0	NA	NA	Insufficient
Varenicline	Return to any drinking	1[98]	200	98% (VAR) vs. 98% (PBO); P=0.81	NA	Insufficient
	Return to heavy drinking	1[98]	200	93% (VAR) vs. 95% (PBO); P=0.50	NA	Insufficient
	% DD	1[98]	200	60% (VAR) vs. 64% (PBO); P=0.29	NA	Insufficient
	% HDD	1[98]	200	38% (VAR) vs. 48% (PBO); P=0.03	NA	Insufficient
	Drinks per DD	1[98]	200	5.8 (VAR) vs. 6.8 (PBO); P=0.03	NA	Insufficient
	Accidents or injuries	0	0	NA	NA	Insufficient
	QoL or function	1[98]	200	SF-12 mental mean difference=0.7; P=0.55 SF-12 physical mean difference=0.4; P=0.38	NA	Insufficient
	Mortality	1[98]	200	1 (VAR) vs. 0 (PBO)	NA	Insufficient

[a] 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.
[b] Negative effect sizes favor intervention over placebo/control.
[c] NA entry for numbers needed to treat (NNT) indicates that the risk difference (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 (e.g., WMD).

Abbreviations: ARI = aripiprazole; BAC = baclofen; CI = confidence interval; DD, drinking day; FLUOX = fluoxetine; FLUV = fluvoxamine; HDD, heavy drinking day; HR = hazard ratio; IMI = imipramine; N = number; NA = not applicable; NALM = nalmefene; NNT = number needed to treat; NR = not reported; NSD = no statistically significant difference; NTX = naltrexone; OC = observed cases; OLA = olanzapine; OR = odds ratio; PAR = paroxetine; PBO = placebo; PMI = placebo bean imputation; QoL, quality of life; RD = risk difference; SER = sertraline; TOP = topiramate; VAL = valproate / valproic acid; VAR = varenicline; vs. = versus; WMD = weighted mean difference.

eTable 6. Summary of meta-analyses of adverse events from head-to-head trials comparing acamprosate with naltrexone

Outcome	N trials[a]	N participants	RD[b]	95% CI	Heterogeneity I^2
Withdrawal due to adverse events Withdrawal due to adverse events—SA	2[23,102] 3[23,102,147]	953 1,110	0.01 0.00	-0.04 to 0.07 -0.04 to 0.04	73.4% 64.5%
Diarrhea Diarrhea—SA	4[20,23,79,117] 5[20,23,79,117,147]	836 993	0.18 0.14	-0.02 to 0.37 -0.07 to 0.35	89.3% 96.0%
Dizziness Dizziness—SA	2[20,117] 3[20,90,117]	144 306	0.08 -0.03	-0.23 to 0.39 -0.19 to 0.13	81.7% 82.4%
Headache Headache—SA	3[20,117,147] 4[20,90,117,147]	301 463	-0.06 -0.09	-0.12 to 0.01 -0.16 to -0.01	0.0% 36.3%
Insomnia	2[20,117]	144	0.07	-0.20 to 0.34	65.5%
Nausea Nausea—SA	4[20,23,79,117] 6[20,23,79,90,117,147]	836 1,155	-0.08 -0.10	-0.18 to 0.02 -0.18 to -0.02	72.8% 71.6%
Vomiting	2[20,23]	648	-0.06	-0.11 to -0.01	0.0%

[a] Our main analyses for each outcome (i.e., the first row for each outcome) included studies rated as low or medium risk of bias. We did not include studies rated as high or unclear risk of bias in our main analyses, but included them in sensitivity analyses (i.e., rows labeled SA).

[b] Positive risk differences favor naltrexone. Table only includes rows for outcomes with sufficient data for meta-analyses.

Abbreviations: CI = confidence interval; N = number of trials or participants contributing data; NA, not applicable; RD = risk difference; SA = sensitivity analysis.

eTable 7. Summary of meta-analyses of adverse events from placebo-controlled trials of acamprosate, naltrexone, nalmefene, topiramate, and valproic acid[a]

Outcome	N trials[b]	N participants	RD[c]	95% CI	NNH (95% CI)	Heterogeneity I^2
Acamprosate						
Withdrawal due to adverse events	13[23,32,33,40,60,62,102,108,129,144,150,155,162]	4,653	0.01	-0.00 to 0.02	NA	8.5%
Withdrawal due to adverse events—SA	16[23,32,33,40,60,62,94,95,102,108,129,132,144,150,155,162]	5,480	0.01	0.00 to 0.01	125 (67 to 1,000	0.0%
Anxiety	1[108]	601	0.16	0.10 to 0.23	NA	NA
Anxiety—SA	2[108,145]	624	0.16	0.09 to 0.22	7 (5 to 11)	0.0%
Diarrhea	12[20,23,29,32,33,60,79,117,129,150,155,162]	2,978	0.10	0.03 to 0.17	11 (6 to 34)	88.9%
Diarrhea—SA	14[20,23,29,32,33,60,79,95,117,129,132,150,155,162]	3,797	0.09	0.04 to 0.15	11 (7 to 27)	85.8%
Dizziness	2[20,117]	151	0.08	-0.22 to 0.38	NA	80.3%
Headache	6[20,29,117,144,150,155]	1,074	0.00	-0.05 to 0.05	NA	67.0%
Headache—SA	7[20,29,95,117,144,150,155]	1,643	0.00	-0.04 to 0.04	NA	60.2%
Insomnia	3[20,32,117]	251	0.02	-0.10 to 0.14	NA	73.5%
Insomnia—SA	4[20,32,95,117]	820	0.02	-0.06 to 0.09	NA	63.8%
Nausea	7[20,23,32,79,95,117,144]	1,758	0.01	-0.01 to 0.02	NA	0.3%
Nausea—SA	8[20,23,32,79,94,95,117,144]	1,828	0.01	-0.01 to 0.03	NA	12.5%

Numbness Numbness—SA	1[60] 2[60,95]	262 831	0.01 0.01	-0.01 to 0.03 -0.01 to 0.03	NA NA	NA 0.0%
Rash Rash--SA	1[20] 2[20,94]	35 105	0.11 0.07	-0.07 to 0.29 -0.01 to 0.16	NA NA	NA 0.0%
Suicide attempts or suicidal ideation Suicide attempts or suicidal ideation—SA	1[40] 3[40,95,145]	581 1,173	0.01 0.00	-0.00 to 0.02 -0.01 to 0.01	NA NA	NA 14.6%
Vomiting Vomiting – SA	4[20,23,95,108] 5[20,23,95,108,145]	1,817 1,840	0.02 0.02	0.01 to 0.04 0.01 to 0.04	42 (24 to 143) 42 (25 to 167)	0.0% 0.0%
Naltrexone						
Withdrawal due to adverse events Withdrawal due to adverse events - SA	17[18,23,41,65,82,86,92,102,116,123,125,126,133,142,161,165] 20[18,23,41,52,65,72,82,86,92,102,116,123,125,126,133,142,152,161,165]	2,743 2,899	0.02 0.02	0.01 to 0.03 0.01 to 0.03	48 (30 to 112) 50 (32 to 125)	0.0% 0.0%
Anorexia	1[41]	175	0.08	0.01 to 0.14	NA	NA
Anxiety Anxiety—SA	7[41,55,119,125,128,166,167] 9[15,41,55,119,125,128,159,166,167]	1,461 1,676	0.01 0.01	-0.02 to 0.04 -0.02 to 0.04	NA NA	0.0% 0.0%
Cognitive dysfunction	1[135]	123	0.19	0.04 to 0.34	NA	NA
Diarrhea Diarrhea - SA	11[17,20,23,41,55,59,79,92,117,125,133] 12[17,20,23,30,41,55,59,79,92,117,125,133]	2,358 2,461	0.01	-0.01 to 0.04	NA NA	21.9% 30.2%

			0.01	-0.02 to 0.03		
Dizziness Dizziness - SA	13[17,20,41,55,59,82,86,89,117,119,123,125,126] 17[15,17,20,30,41,55,59,72,82,86,89,93,117,119,123,125,126]	2,675 2,977	0.06 0.06	0.04 to 0.09 0.04 to 0.08	16 (12 to 28) 17 (13 to 27)	37.4% 27.1%
Headache Headache - SA	17[17,20,41,55,59,65,82,85,89,92,117,119,125,127,128,133,141] 22[15,17,20,41,55,59,65,67,72,82,85,89,92,117,119,125,127,128,133,141,152,159]	3,347 3,799	0.01 0.00	-0.02 to 0.03 -0.02 to 0.03	NA NA	8.0% 20.9%
Insomnia Insomnia - SA	8[20,41,55,82,117,119,128,141] 12[15,20,30,41,55,67,82,93,117,119,128,141]	1,637 2,030	0.03 0.03	-0.00 to 0.06 0.00 to 0.05	NA 39 (20 to 1,000)	0.0% 0.0%
Nausea Nausea - SA	24[17,18,20,23,41,55,59,79,82,85,86,89,92,113,117,119,123,125-128,133,135,141] 31[15,17,18,20,23,30,41,55,59,67,72,79,82,85,86,89,92,93,113,117,119,123,125-128,133,135,141,152,159]	4,655 5,263	0.11 0.10	0.07 to 0.15 0.07 to 0.13	9 (7 to 14) 10 (8 to 15)	69.6% 65.9%
Numbness Numbness - SA	1[135] 2[30,135]	123 226	-0.01 -0.02	-0.19 to 0.17 -0.08 to 0.04	NA NA	NA 0.0%
Rash Rash - SA	4[17,20,125,133] 5[17,20,93,125,133]	469 522	-0.01 -0.02	-0.06 to 0.04 -0.06 to 0.02	NA NA	41.6% 21.5%
Taste abnormalities	1[135]	123	-0.01	-0.18 to 0.17	NA	NA
Vision changes	2[133,135]	133	0.0	-0.17 to	NA	46.3%

			8	0.33		
Vomiting Vomiting - SA	9[17,20,23,41,55,59,128,135,141] 11[17,20,23,41,55,59,72,128,135,141,159]	2,438 2,567	0.04 0.04	0.02 to 0.06 0.02 to 0.06	24 (17 to 44) 27 (19 to 56)	0.0% 1.1%
Nalmefene						
Withdrawal due to adverse events Withdrawal due to adverse events – SA	5[21,64,78,103,107] 7[21,64,78,103,105,107,153]	2,054 2,750	0.08 0.08	0.02 to 0.15 0.04 to 0.12	12 (7 to 50) 13 (9 to 28)	86.4% 79.5%
Cognitive dysfunction Cognitive dysfunction – SA	1[21] 2[21,153]	265 830	0.05 0.03	0.01 to 0.09 -0.03 to 0.08	NA NA	NA 81.9%
Diarrhea	2[78,153]	1,081	-0.03	-0.06 to -0.01	NA (more with placebo)	0.0%
Dizziness Dizziness – SA	4[21,64,78,103] 6[21,64,78,103,105,153]	1,944 2,630	0.16 0.14	0.11 to 0.21 0.10 to 0.18	7 (5 to 10) 7 (6 to 10)	58.4% 53.5%
Headache Headache – SA	3[64,103,107] 4[64,103,107,153]	1,401 2,066	0.04 0.04	0.01 to 0.07 0.01 to 0.07	26 (15 to 143) 25 (15 to 77)	0.0% 0.0%
Insomnia Insomnia – SA	5[21,64,78,103,107] 6[21,64,78,103,107,153]	2,049 2,714	0.10 0.09	0.06 to 0.14 0.06 to 0.12	10 (8 to 17) 11 (9 to 16)	47.3% 34.9%
Nausea Nausea – SA	5[21,64,78,103,107] 6[21,64,78,103,107,153]	2,049 2,714	0.16 0.16	0.10 to 0.22 0.11 to 0.21	7 (5 to 11) 7 (5 to 9)	75.8% 69.8%

Suicide attempts or suicidal ideation Suicide attempts or suicidal ideation– SA	2[64,103] 3[64,103,153]	1,253 1,918	-0.01 -0.00	-0.02 to 0.00 -0.01 to 0.01	NA NA	0.0% 39.2%
Taste abnormalities	1[78]	403	0.04	0.01 to 0.07	NA	NA
Vomiting Vomiting – SA	3[64,78,103] 4[64,78,103,153]	1,679 2,344	0.06 0.07	0.02 to 0.10 0.03 to 0.11	17 (11 to 48) 15 (10 to 30)	68.1% 76.2%
Topiramate						
Withdrawal due to adverse events Withdrawal due to adverse events - SA	3[69,73,77] 4[69,73,77,148]	691 767	0.05 0.05	-0.08 to 0.17 -0.05 to 0.14	NA NA	93.4% 86.9%
Anorexia	1[73]	371	0.13	0.06 to 0.20	NA	NA
Anxiety Anxiety – SA	1[73] 2[73,96]	371 477	-0.08 -0.04	-0.17 to 0.01 -0.14 to 0.05	NA NA	NA 69.8%
Cognitive dysfunction Cognitive dysfunction –SA	2[69,73] 3[69,73,96]	521 627	0.08 0.07	0.01 to 0.16 0.03 to 0.12	12 (7 to 84) 14 (9 to 39)	38.5% 0.0%
Diarrhea Diarrhea – SA	1[73] 2[30,73]	371 477	0.04 0.00	-0.03 to 0.10 -0.07 to 0.08	NA NA	NA 61.1%
Dizziness Dizziness – SA	2[69,73] 4[30,69,73,96]	521 733	0.10	-0.01 to 0.22	NA NA	65.0% 80.2%

			0.05	-0.03 to 0.13		
Headache Headache –SA	2[73,77] 3[73,77,96]	541 647	-0.02 0.00	-0.16 to 0.12 -0.09 to 0.09	NA NA	83.3% 78.7%
Insomnia Insomnia – SA	1[73] 2[30,73]	371 477	0.03 0.03	-0.05 to 0.11 -0.03 to 0.10	NA NA	NA 0.0%
Nausea Nausea – SA	1[73] 2[30,73]	371 477	-0.06 -0.02	-0.13 to 0.01 -0.11 to 0.06	NA NA	NA 62.0%
Numbness Numbness – SA	3[69,73,77] 5[30,69,73,77,96]	691 903	0.32 0.26	0.15 to 0.48 0.12 to 0.41	4 (3 to 7) 4 (3 to 9)	86.5% 88.0%
Taste abnormalities Taste abnormalities – SA	1[73] 2[73,96]	371 477	0.18 0.15	0.11 to 0.25 0.07 to 0.23	NA 7 (5 to 15)	NA 39.7%
Valproic acid						
Withdrawal due to adverse events	1[149]	52	0.04	-0.07 to 0.14	NA	NA
Diarrhea	1[149]	52	0.10	-0.12 to 0.32	NA	NA
Headache	1[149]	52	0.05	-0.20 to 0.30	NA	NA
Nausea	1[149]	52	0.25	0.05 to 0.46	NA	NA
Vision changes	1[149]	52	-0.02	-0.26 to 0.22	NA	NA

[a] Table includes rows for outcomes/comparisons for which there was at least one study rated low or medium risk of bias.
[b] Our main analyses for each outcome (i.e., the first row for each outcome) included studies rated as low or medium risk of bias. We did not include studies rated as high or unclear risk of bias in our main analyses, but included them in sensitivity analyses (i.e., rows labeled SA).
[c] Positive risk differences favor placebo. Sensitivity analyses include studies rated as high risk of bias.
Abbreviations: CI = confidence interval; N = number of trials or participants contributing data; NA = not applicable; NNH = number needed to harm; RD = risk difference; SA = sensitivity analysis.

eDiscussion. Applicability to Primary Care Settings

This supplement summarizes additional information about four studies that did not meet our inclusion criteria (due to study design or comparators) that have important implications for primary care settings.[168-171] While these studies found conflicting results, they demonstrate approaches to managing AUDs in primary care. 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.

First, O'Malley et al.[169] found no difference in avoiding persistent heavy drinking between those who received naltrexone plus "primary care management" (PCM) and those who received naltrexone plus cognitive behavioral therapy. Among responders enrolled in a maintenance trial, those who received naltrexone and PCM had significantly better response (no more than 2 days of heavy drinking in final 28 days) than those who received placebo and PCM (80.8% vs. 51.9%, p=0.03). Primary care management was provided by nurse practitioners, physician assistants, and one internist in an initial 45-minute visit, followed by seven 15- to 20-minute sessions in the following 10 weeks.

Second, Kiritze-Topor et al.[168] conducted a trial with 149 general practitioners in France, randomizing patients (N=422) to acamprosate plus standard care or standard care alone. The trial reported better outcomes for the acamprosate group for alcohol-related health, personal, and social problems, and for quality of life.

Third, in a U.S-based RCT (N=163), Oslin et al.[170] compared a primary-care based alcohol care management (ACM) program with a specialty outpatient addiction treatment program. The trial found that participants in the ACM program were more likely to receive naltrexone (65.9% vs. 11.5%), to be engaged in treatment (OR, 5.36; 95% CI, 2.99 to 9.59), and to have a lower percentage of heavy drinking days (OR, 2.16; 95% CI, 1.27 to 3.66) than participants in the specialty treatment program. Overall abstinence did not differ between groups.

Fourth, in the U.S.-based AHEAD trial (N=563), Saitz et al.[171] compared chronic care management (CCM) with no CCM for people with alcohol or drug dependence who were not currently engaged in primary care. Of those enrolled, 12 percent had alcohol dependence without also meeting criteria for other drug dependence. CCM involved longitudinal care coordinated by a primary care clinician, and included motivational enhancement therapy; relapse prevention counseling; on-site medical, addiction, and psychiatric treatment; social work assistance; and referrals. The no-CCM group received a primary care appointment and a list of treatment resources including a telephone number to arrange counseling. The trial found no difference between groups for the primary outcome of abstinence over 12 months.

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