

Supplementary Online Content

Jonas DE, Amick HR, Feltner C, et al. Pharmacotherapy for adults with alcohol use disorders in outpatient settings: a systematic review and meta-analysis. JAMA. doi:10.1001/jama.2014.3628.

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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	<ol style="list-style-type: none">1. Alcohol is taken in larger amounts or over a longer period than intended2. Persistent desire or unsuccessful efforts to cut down or control alcohol use3. A great deal of time is spent in activities necessary to obtain alcohol, use alcohol, or recover from its effects4. Craving, or a strong desire or urge to use alcohol5. Recurrent alcohol use resulting in a failure to fulfill major role obligations at work, school, or home6. Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol7. Important social, occupational, or recreational activities are given up or reduced because of alcohol use8. Recurrent alcohol use in situations in which it is physically hazardous9. 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 alcohol10. Tolerance, as defined by either of the following:<ol style="list-style-type: none">a) A need for markedly increased amounts of alcohol to achieve intoxication or desired effectb) A markedly diminished effect with continued use of the same amount of alcohol11. Withdrawal, as manifested by either of the following:<ol style="list-style-type: none">a) The characteristic withdrawal syndrome for alcoholb) Alcohol (or a closely related substance, such as a benzodiazepine) is taken to relieve or avoid withdrawal symptoms

<p>Alcohol abuse (DSM-IV, 2000)⁴</p>	<p>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:</p> <ul style="list-style-type: none"> (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). <p>B. The symptoms have never met the criteria for alcohol dependence.</p>
<p>Alcohol dependence (DSM-IV, 2000)⁴ (alcoholism, alcohol addiction)</p>	<p>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:</p> <ul style="list-style-type: none"> (1) tolerance, as defined by either of the following: <ul style="list-style-type: none"> (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: <ul style="list-style-type: none"> (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).

³The 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	<p>a: Which medications are efficacious for improving consumption outcomes for adults with AUDs in outpatient settings?</p> <p>b: How do medications for adults with AUDs compare for improving consumption outcomes in outpatient settings?</p>
2	<p>a: Which medications are efficacious for improving health outcomes for adults with AUDs in outpatient settings?</p> <p>b: How do medications for adults with AUDs compare for improving health outcomes in outpatient settings?</p>
3	<p>a: What adverse effects are associated with medications for adults with AUDs in outpatient settings?</p> <p>b: How do medications for adults with AUDs compare for adverse effects in outpatient settings?</p>
4	<p>Are medications for treating adults with AUDs effective in primary care settings?</p>
5	<p>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?</p>
6	<p>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])?</p>

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	% Fe m	% 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 sample ⁴ 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 Depressive 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 detoxificatio n	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 Luxembourg	centers					benzodiazepines 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 dependence treatment	46 (9) 47 (10)	NR	47	Depression/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 dependence 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 outcomes; 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 dependence 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; outpatient;	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 announcements	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	Depression/ 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 (psychiatric 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 psychotherapies were offered	High
Nava, 2006 ¹²²	DIS 200 (28) NTX 50 (24) GHB 150 mg/kg/day (28)	52	Italy; outpatient	Advertisements, 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 sample4 0 (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+BREND A (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	Schizophrenia or schizoaffective 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.; outpatient; 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 dependence 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) ^d 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.

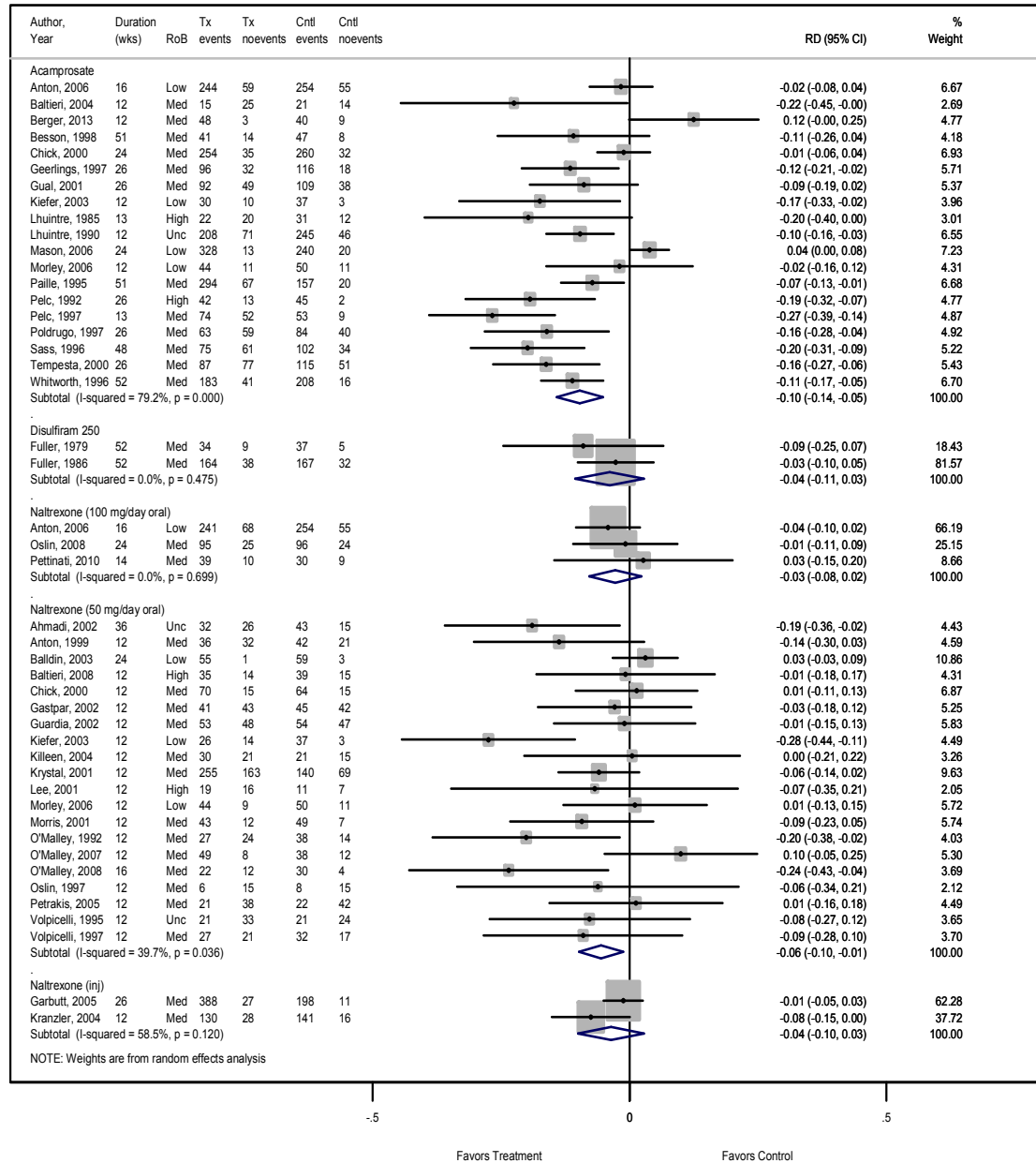
^p Treatment as usual, seen once per week in an individual setting; MI techniques allowed.

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)rief psychosocial 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 -Hydroxybutyric 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.

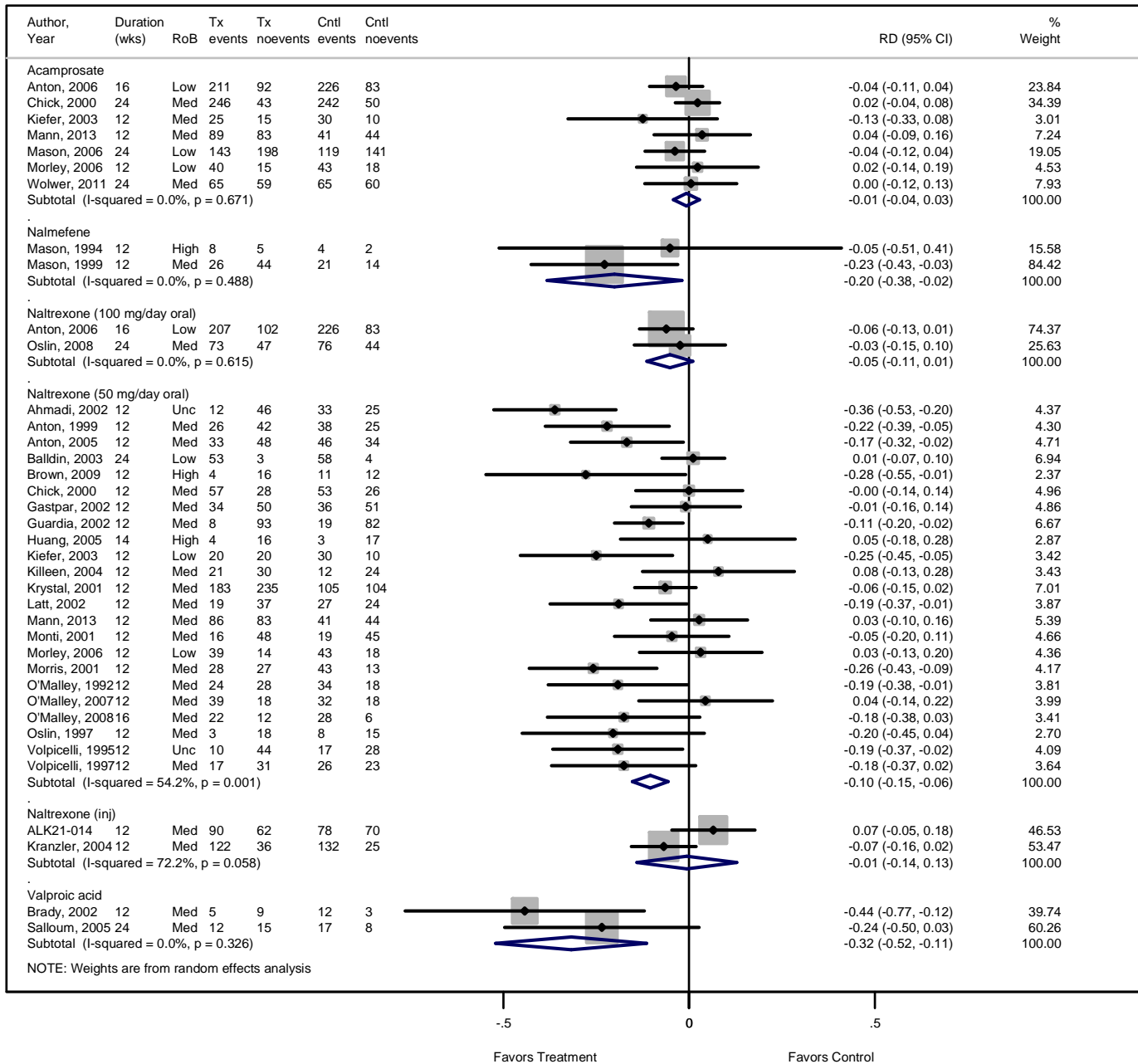
eFigure 1. Return to any drinking for selected medications compared with placebo, sensitivity analysis including studies rated as high or unclear risk of bias

Sensitivity Analysis - Return to Any Drinking Selected Medications Compared with Placebo



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.

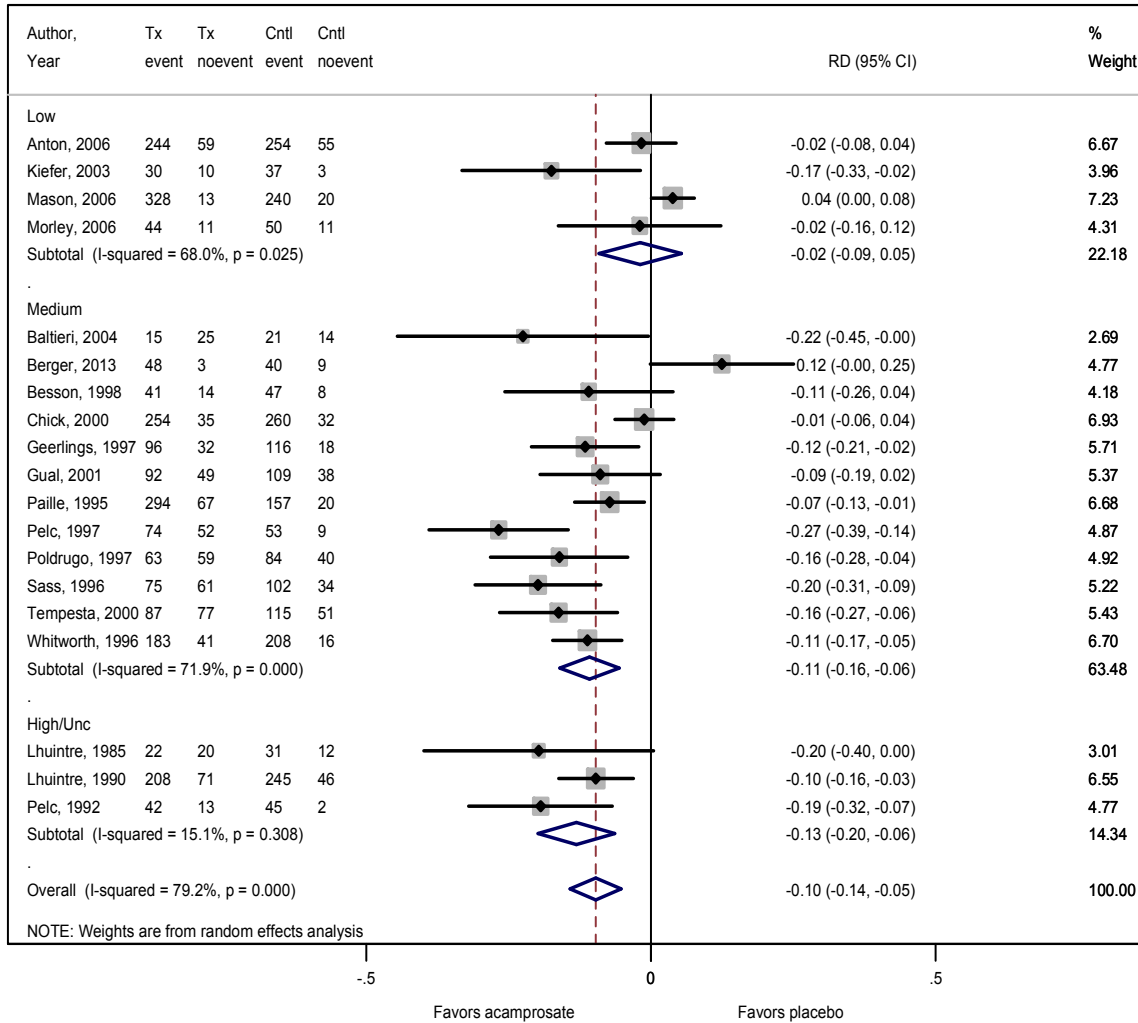
eFigure 2. Return to heavy drinking for selected medications compared with placebo, sensitivity analysis including studies rated as high or unclear risk of bias



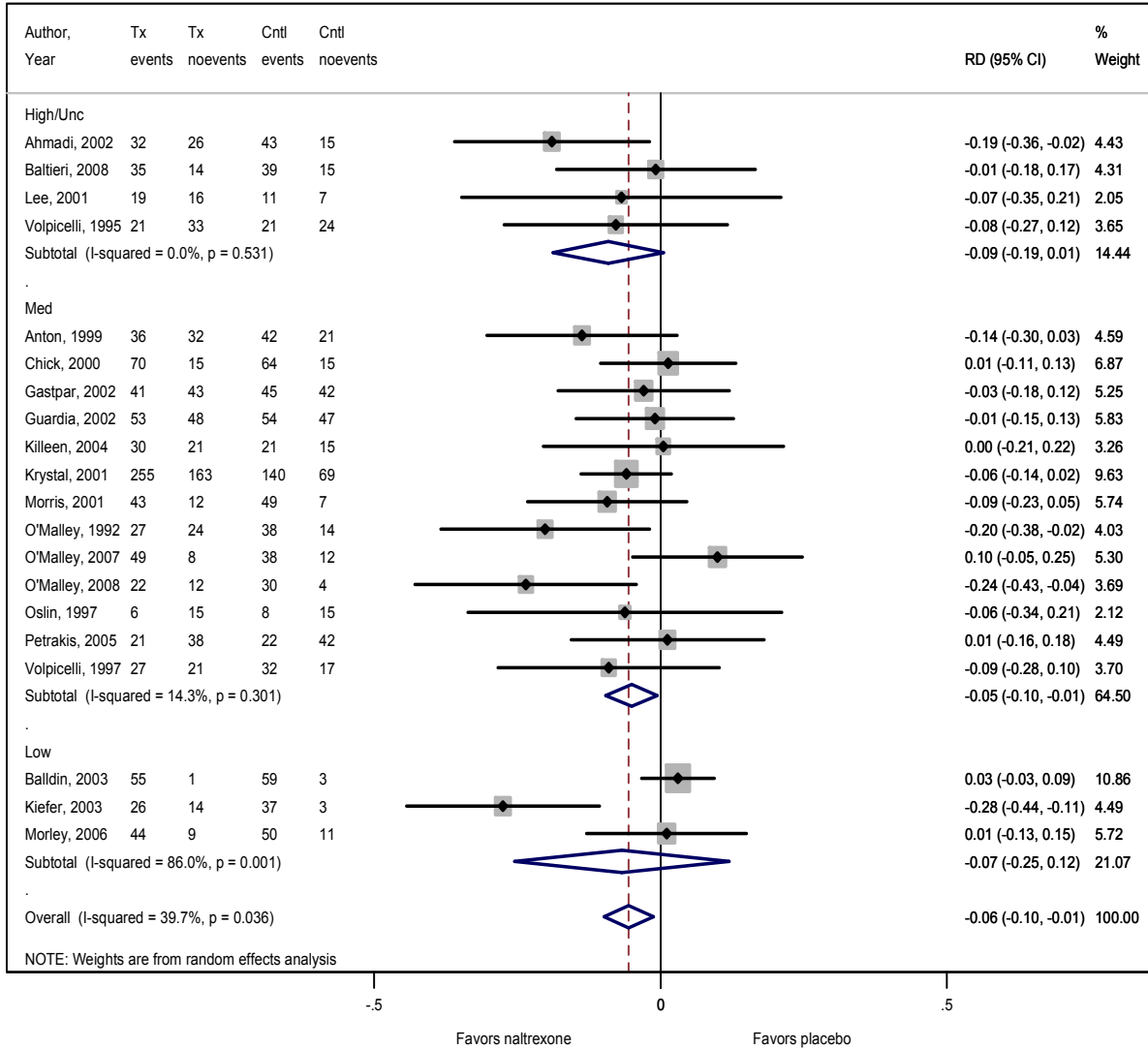
Abbreviations: CI = confidence interval; Cntl events = number of events in the control group; Cntl noevents = number of no events in the control group; Med = medium; RD = risk difference; RoB = risk of bias; Tx events = number of events in treatment group; Tx noevents = number of no events in the treatment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

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

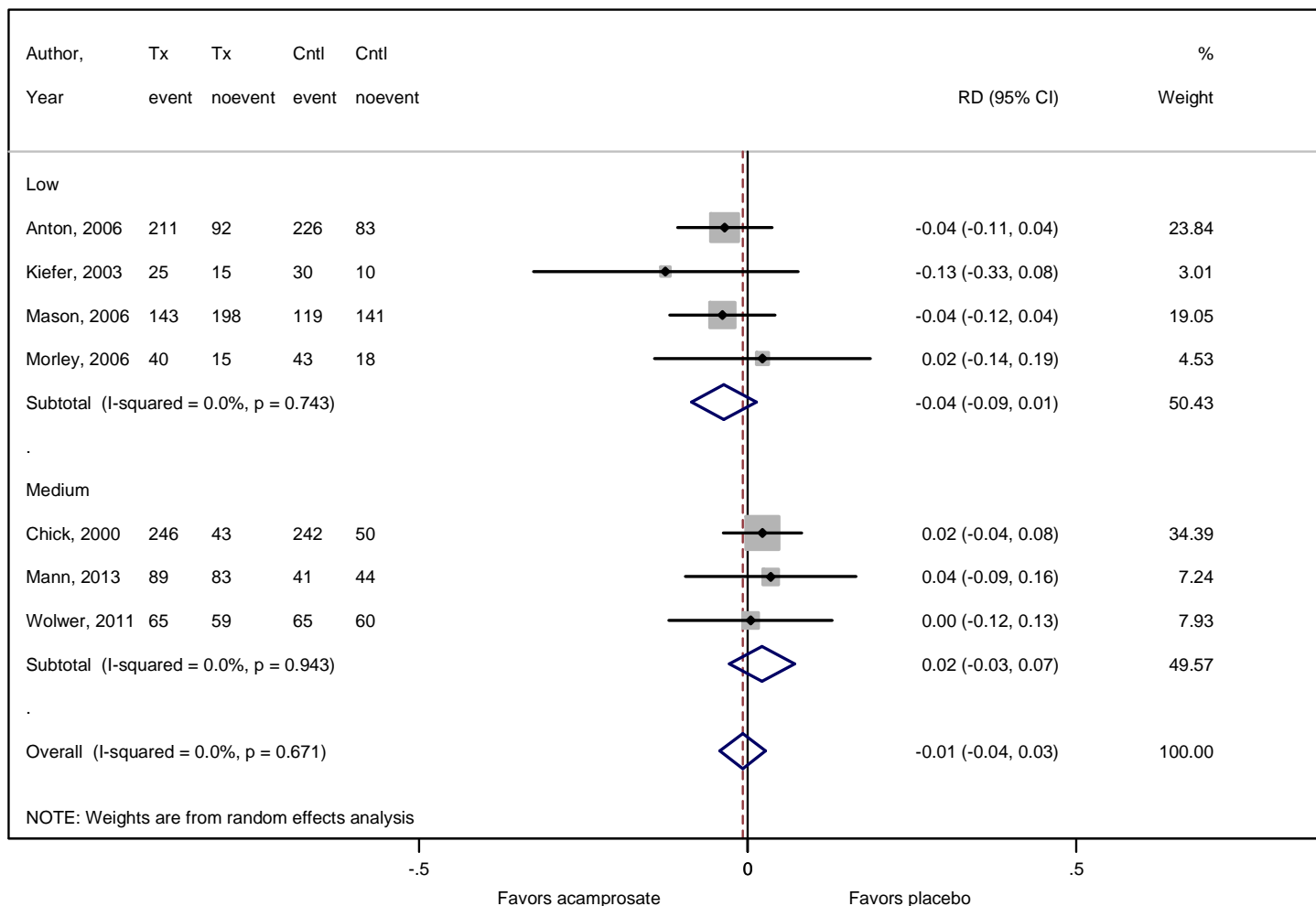
Acamprosate versus Placebo Return to Any Drinking by Risk of Bias



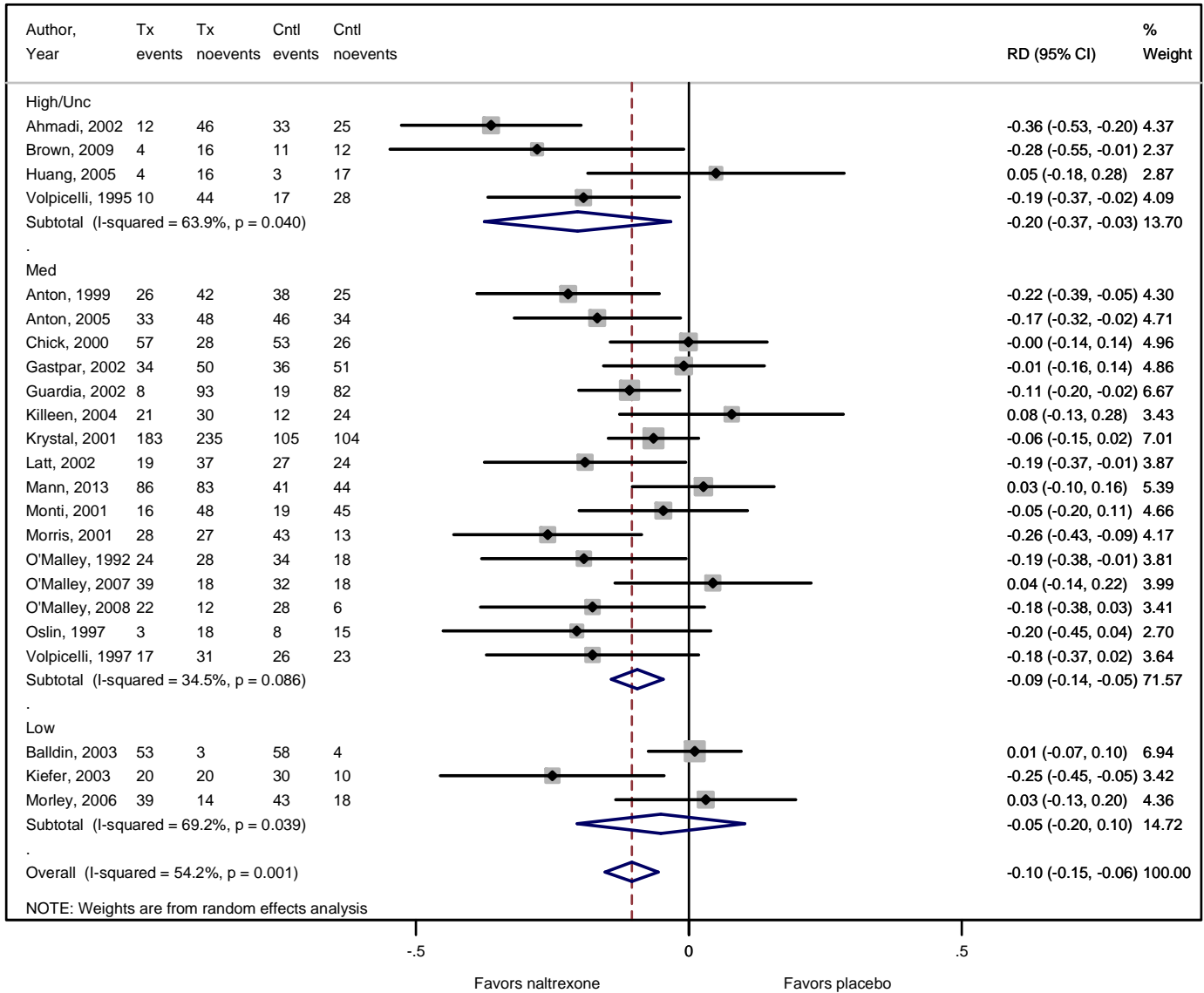
eFigure 4. Return to any drinking for oral naltrexone (50mg/day) compared with placebo, subgroup analysis by risk of bias



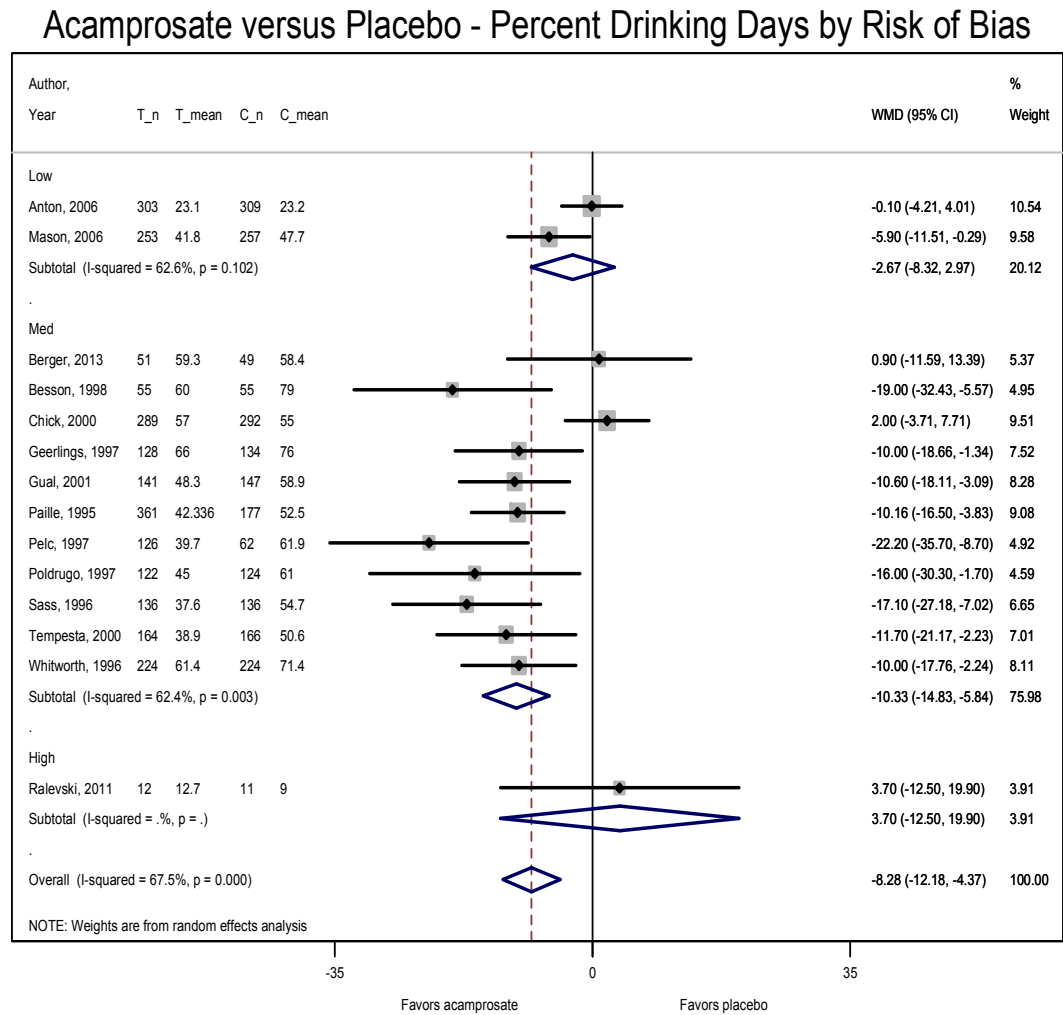
eFigure 5. Return to heavy drinking for acamprosate compared with placebo, subgroup analysis by risk of bias



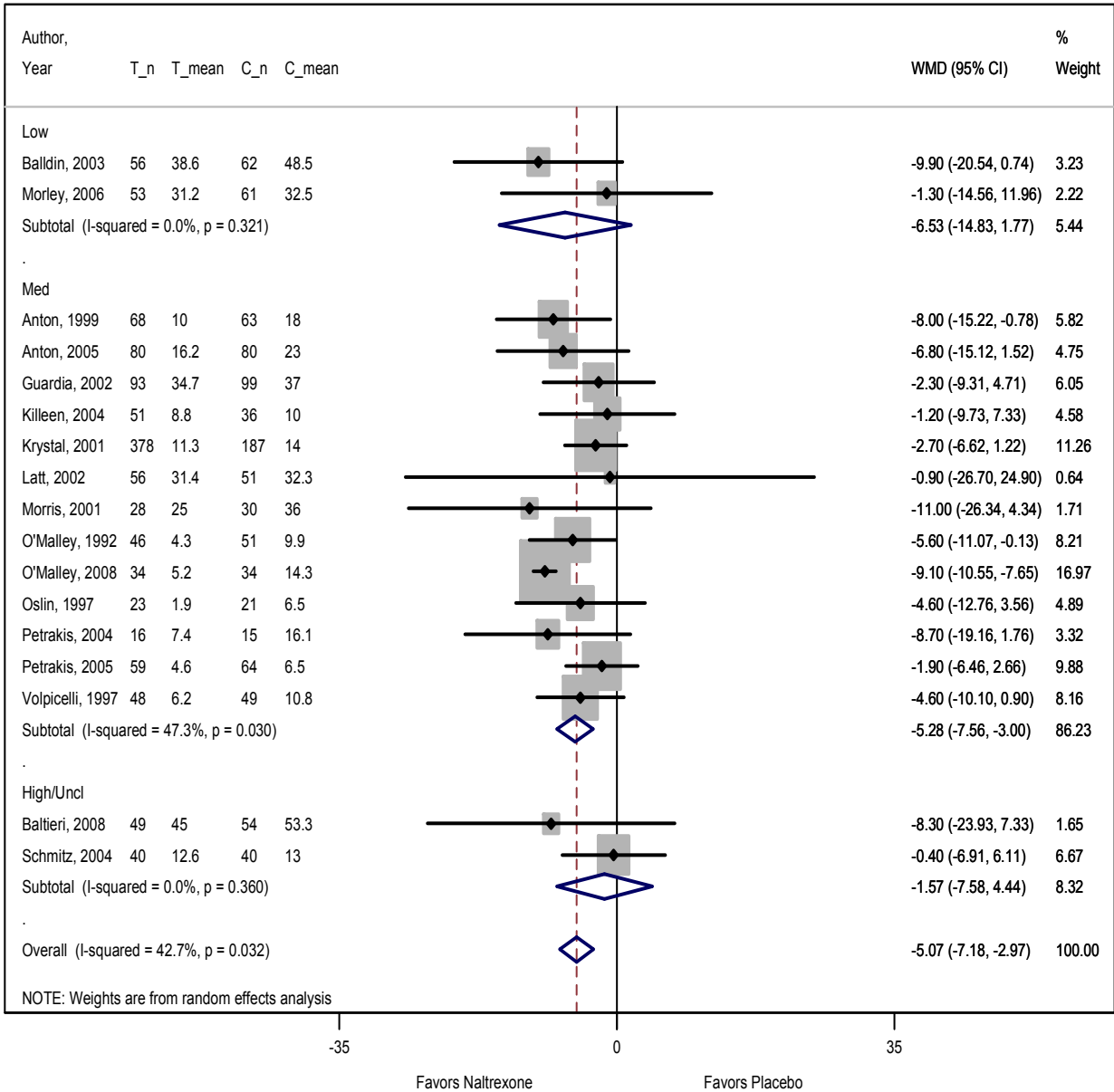
eFigure 6. Return to heavy drinking for oral naltrexone (50mg/day) compared with placebo, subgroup analysis by risk of bias



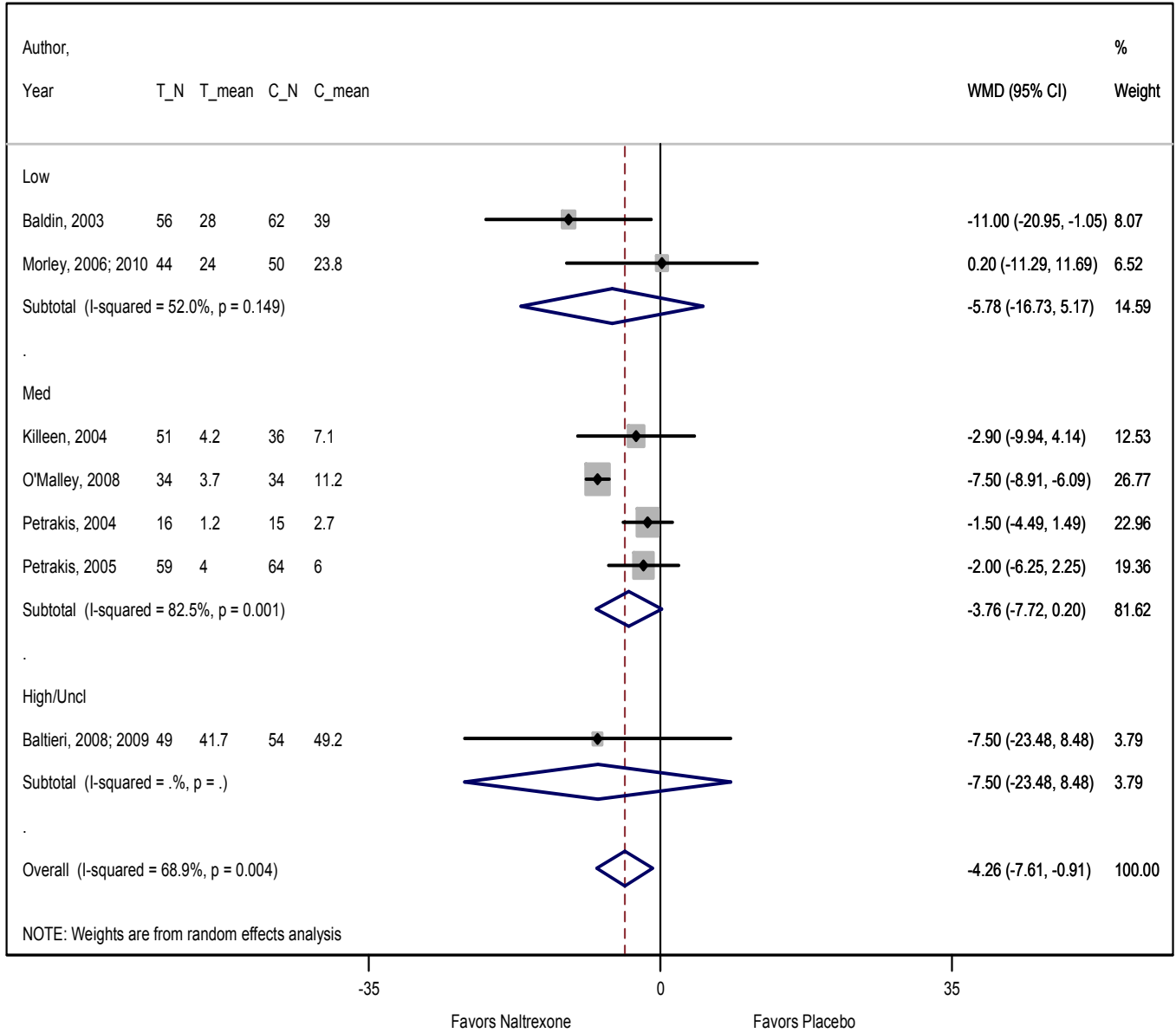
eFigure 7. Percent drinking days for acamprosate compared with placebo, subgroup analysis by risk of bias



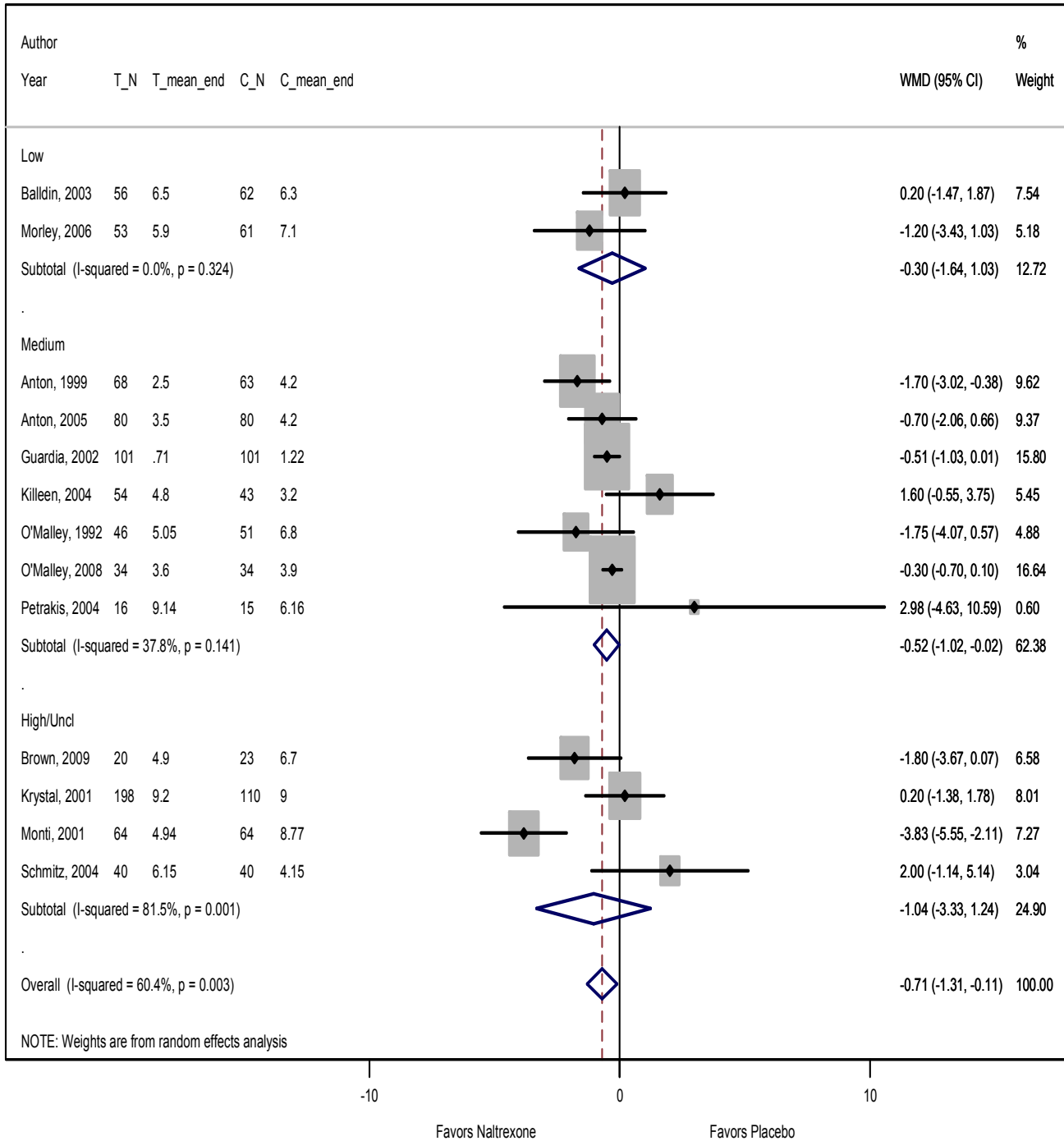
eFigure 8. Percent drinking days for oral naltrexone (50mg/day) compared with placebo, subgroup analysis by risk of bias



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	2 ^{23,102}	953	0.0	-0.04 to 0.07	73.4%
Withdrawal due to adverse events—SA	3 ^{23,102,147}	1,110	0.0	-0.04 to 0.04	64.5%
Diarrhea	4 ^{20,23,79,117}	836	0.1	-0.02 to 0.37	89.3%
Diarrhea—SA	5 ^{20,23,79,117,147}	993	0.1	-0.07 to 0.35	96.0%
Dizziness	2 ^{20,117}	144	0.0	-0.23 to 0.39	81.7%
Dizziness—SA	3 ^{20,90,117}	306	0.0	-0.19 to 0.13	82.4%
Headache	3 ^{20,117,147}	301	-	-0.12 to 0.01	0.0%
Headache—SA	4 ^{20,90,117,147}	463	0.0	-0.16 to -0.01	36.3%
Insomnia	2 ^{20,117}	144	0.0	-0.20 to 0.34	65.5%
Nausea	4 ^{20,23,79,117}	836	-	-0.18 to 0.02	72.8%
Nausea—SA	6 ^{20,23,79,90,117,147}	1,155	0.0	-0.18 to -0.02	71.6%
Vomiting	2 ^{20,23}	648	-	-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	0.0	-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	0.0	0.00 to 0.01	125 (67 to 1,000)	0.0%
Anxiety	1 ¹⁰⁸	601	0.1	0.10 to 0.23	NA	NA
Anxiety—SA	2 ^{108,145}	624	0.1	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	0.1	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	0.0	0.04 to 0.15	11 (7 to 27)	85.8%
Dizziness	2 ^{20,117}	151	0.0	-0.22 to 0.38	NA	80.3%
Headache	6 ^{20,29,117,144,150,155}	1,074	0.0	-0.05 to 0.05	NA	67.0%
Headache—SA	7 ^{20,29,95,117,144,150,155}	1,643	0.0	-0.04 to 0.04	NA	60.2%
Insomnia	3 ^{20,32,117}	251	0.0	-0.10 to 0.14	NA	73.5%
Insomnia—SA	4 ^{20,32,95,117}	820	0.0	-0.06 to 0.09	NA	63.8%
Nausea	7 ^{20,23,32,79,95,117,144}	1,758	0.0	-0.01 to 0.02	NA	0.3%
Nausea—SA	8 ^{20,23,32,79,94,95,117,144}	1,828	0.0	-0.01 to 0.03	NA	12.5%

Numbness Numbness—SA	1 ⁶⁰ 2 ^{60,95}	262 831	0.0 1 0.0 1	-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	0.1 1 0.0 7	-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	0.0 1 0.0 0	-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	0.0 2 0.0 2	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	0.0 2 0.0 2	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	0.0 8	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	0.0 1 0.0 1	-0.02 to 0.04 -0.02 to 0.04	NA NA	0.0% 0.0%
Cognitive dysfunction	1 ¹³⁵	123	0.1 9	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	0.0 1	-0.01 to 0.04	NA NA	21.9% 30.2%

			0.0 1	-0.02 to 0.03		
Dizziness	13 ^{17,20,41,55,59,82,86,89,117,119,123,125,126}	2,675	0.0	0.04 to	16 (12	37.4%
Dizziness - SA	17 ^{15,17,20,30,41,55,59,72,82,86,89,93,117,119,123,125,126}	2,977	6	0.09	to 28)	27.1%
			0.0	0.04 to	17 (13	
Headache	17 ^{17,20,41,55,59,65,82,85,89,92,117,119,125,127,128,133,141}	3,347	6	0.08	to 27)	
Headache - SA	22 ^{15,17,20,41,55,59,65,67,72,82,85,89,92,117,119,125,127,128,133,141,152,159}	3,799	1	-0.02 to 0.03	NA	8.0%
			0.0	-0.02 to 0.03	NA	20.9%
Insomnia	8 ^{20,41,55,82,117,119,128,141}	1,637	0.0	-0.00 to	NA	0.0%
Insomnia - SA	12 ^{15,20,30,41,55,67,82,93,117,119,128,141}	2,030	3	0.06	39 (20	0.0%
			0.0	0.00 to	to	
			3	0.05	1,000)	
Nausea	24 ^{17,18,20,23,41,55,59,79,82,85,86,89,92,113,117,119,123,125-128,133,135,141}	4,655	0.1	0.07 to	9 (7 to	69.6%
Nausea - SA	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}	5,263	1	0.15	14)	65.9%
			0.1	0.07 to	10 (8	
			0	0.13	to 15)	
Numbness	1 ¹³⁵	123	-	-0.19 to	NA	NA
Numbness - SA	2 ^{30,135}	226	0.0	0.17	NA	0.0%
			1	-0.08 to		
			-	0.04		
			0.0			
			2			
Rash	4 ^{17,20,125,133}	469	-	-0.06 to	NA	41.6%
Rash - SA	5 ^{17,20,93,125,133}	522	0.0	0.04	NA	21.5%
			1	-0.06 to		
			-	0.02		
			0.0			
			2			
Taste abnormalities	1 ¹³⁵	123	-	-0.18 to	NA	NA
			0.0	0.17		
			1			
Vision changes	2 ^{133,135}	133	0.0	-0.17 to	NA	46.3%

			8	0.33		
Vomiting	9 ^{17,20,23,41,55,59,128,135,141}	2,438	0.0	0.02 to	24 (17	0.0%
Vomiting - SA	11 ^{17,20,23,41,55,59,72,128,135,141,159}	2,567	4	0.06	to 44)	1.1%
			0.0	0.02 to	27 (19	
			4	0.06	to 56)	
Nalmefene						
Withdrawal due to adverse events	5 ^{21,64,78,103,107}	2,054	0.0	0.02 to	12 (7	86.4%
Withdrawal due to adverse events – SA	7 ^{21,64,78,103,105,107,153}	2,750	8	0.15	to 50)	79.5%
			0.0	0.04 to	13 (9	
			8	0.12	to 28)	
Cognitive dysfunction	1 ²¹	265	0.0	0.01 to	NA	NA
Cognitive dysfunction – SA	2 ^{21,153}	830	5	0.09	NA	81.9%
			0.0	-0.03 to		
			3	0.08		
Diarrhea	2 ^{78,153}	1,081	-	-0.06 to -	NA	0.0%
			0.0	0.01	(more	
			3		with	
					placeb	
					o)	
Dizziness	4 ^{21,64,78,103}	1,944	0.1	0.11 to	7 (5 to	58.4%
Dizziness – SA	6 ^{21,64,78,103,105,153}	2,630	6	0.21	10)	53.5%
			0.1	0.10 to	7 (6 to	
			4	0.18	10)	
Headache	3 ^{64,103,107}	1,401	0.0	0.01 to	26 (15	0.0%
Headache – SA	4 ^{64,103,107,153}	2,066	4	0.07	to	0.0%
			0.0	0.01 to	143)	
			4	0.07	25 (15	
					to 77)	
Insomnia	5 ^{21,64,78,103,107}	2,049	0.1	0.06 to	10 (8	47.3%
Insomnia – SA	6 ^{21,64,78,103,107,153}	2,714	0	0.14	to 17)	34.9%
			0.0	0.06 to	11 (9	
			9	0.12	to 16)	
Nausea	5 ^{21,64,78,103,107}	2,049	0.1	0.10 to	7 (5 to	75.8%
Nausea – SA	6 ^{21,64,78,103,107,153}	2,714	6	0.22	11)	69.8%
			0.1	0.11 to	7 (5 to	
			6	0.21	9)	

Suicide attempts or suicidal ideation	2 ^{64,103}	1,253	-	-0.02 to	NA	0.0%
Suicide attempts or suicidal ideation – SA	3 ^{64,103,153}	1,918	0.0 1	0.00 -0.01 to 0.01	NA	39.2%
Taste abnormalities	1 ⁷⁸	403	0.0 4	0.01 to 0.07	NA	NA
Vomiting	3 ^{64,78,103}	1,679	0.0	0.02 to	17 (11	68.1%
Vomiting – SA	4 ^{64,78,103,153}	2,344	6 0.0 7	0.10 0.03 to 0.11	to 48) 15 (10 to 30)	76.2%
Topiramate						
Withdrawal due to adverse events	3 ^{69,73,77}	691	0.0 5	-0.08 to 0.17	NA	93.4%
Withdrawal due to adverse events - SA	4 ^{69,73,77,148}	767	0.0 5	-0.05 to 0.14	NA	86.9%
Anorexia	1 ⁷³	371	0.1 3	0.06 to 0.20	NA	NA
Anxiety	1 ⁷³	371	-	-0.17 to	NA	NA
Anxiety – SA	2 ^{73,96}	477	0.0 8 - 0.0 4	0.01 -0.14 to 0.05	NA	69.8%
Cognitive dysfunction	2 ^{69,73}	521	0.0	0.01 to	12 (7	38.5%
Cognitive dysfunction – SA	3 ^{69,73,96}	627	8 0.0 7	0.16 0.03 to 0.12	to 84) 14 (9 to 39)	0.0%
Diarrhea	1 ⁷³	371	0.0	-0.03 to	NA	NA
Diarrhea – SA	2 ^{30,73}	477	4 0.0 0	0.10 -0.07 to 0.08	NA	61.1%
Dizziness	2 ^{69,73}	521	0.1	-0.01 to	NA	65.0%
Dizziness – SA	4 ^{30,69,73,96}	733	0	0.22	NA	80.2%

			0.0 5	-0.03 to 0.13		
Headache Headache –SA	2 ^{73,77} 3 ^{73,77,96}	541 647	- 0.0 2 0.0 0	-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	0.0 3 0.0 3	-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	- 0.0 6 - 0.0 2	-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	0.3 2 0.2 6	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	0.1 8 0.1 5	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	0.0 4	-0.07 to 0.14	NA	NA
Diarrhea	1 ¹⁴⁹	52	0.1 0	-0.12 to 0.32	NA	NA
Headache	1 ¹⁴⁹	52	0.0 5	-0.20 to 0.30	NA	NA
Nausea	1 ¹⁴⁹	52	0.2 5	0.05 to 0.46	NA	NA
Vision changes	1 ¹⁴⁹	52	- 0.0 2	-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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