Effective Health Care Program

Comparative Effectiveness Review
Number 134

Pharmacotherapy for Adults With Alcohol-Use Disorders in Outpatient Settings

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

We welcome comments on this systematic review. They may be sent by mail to Aysegul Gozu, M.D., M.P.H., at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Key Informants are the end-users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform health care decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high-priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The Task Order Officer and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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Technical Experts comprise a multidisciplinary group of clinical, content, and methodologic experts who provide input in defining populations, interventions, comparisons, or outcomes as well as identifying particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, study questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind or contribute to the writing of the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

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Peer Reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodologic expertise. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. Peer Reviewers do not participate in writing or editing the final report or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for Comparative Effectiveness Reviews and Technical Briefs, be published 3 months after the publication of the evidence report.

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Pharmacotherapy for Adults With Alcohol-Use Disorders in Outpatient Settings

Structured Abstract

Objectives. To conduct a systematic review and meta-analysis of the efficacy, comparative effectiveness, and harms of medications (both FDA approved and others) for adults with alcohol-use disorders, and to evaluate the evidence from primary care settings.

Data sources. PubMed®, Cochrane Library, PsycINFO®, CINAHL®, Embase®, U.S. Food and Drug Administration Web site, ClinicalTrials.gov, and World Health Organization International Clinical Trials Registry Platform (January 1, 1970, to October 11, 2013).

Review methods. Two investigators independently selected, extracted data from, and rated risk of bias of studies. We conducted meta-analyses using random-effects models. We graded strength of evidence (SOE) based on established guidance.

Results. We included 135 studies. Most patients met criteria for alcohol dependence; mean ages were in the 40s. Studies typically included psychosocial cointerventions; effect sizes reflect the added benefits of medications.For acamprosate and oral naltrexone (50 mg per day), numbers needed to treat (NNTs) to prevent 1 person from returning to any drinking were 12 and 20, respectively (moderate SOE); NNT to prevent 1 person from returning to heavy drinking was 12 for oral naltrexone (50 mg per day) (moderate SOE). Our meta-analyses of four head-to-head trials found no statistically significant difference between the two medications for consumption outcomes (moderate SOE). For injectable naltrexone, meta-analyses found no significant benefit for return to any or heavy drinking, but found a reduction in heavy drinking days (low SOE). Evidence from well-controlled trials does not support efficacy of disulfiram, except possibly for patients with excellent adherence. Among medications used off label, moderate evidence supports the efficacy of nalmefene and topiramate for improving some consumption outcomes, and limited evidence supports the efficacy of valproic acid. Evidence from primary care settings was scant. We found insufficient direct evidence to conclude whether medications for alcohol-use disorders are effective for improving health outcomes.

Compared with placebo, patients treated with acamprosate had a higher risk of anxiety, diarrhea, and vomiting; those treated with naltrexone had a higher risk of dizziness, nausea, and vomiting. In head-to-head studies, the risks of headache and vomiting were slightly higher for naltrexone than for acamprosate. Individual trials of topiramate reported a significantly increased risk of paresthesias, anorexia, difficulty concentrating, dizziness, psychomotor slowing, and other adverse effects.

Our meta-analyses for variation in naltrexone response related to *OPRM1* polymorphisms found no statistically significant difference between A-allele homozygotes and those with at least one G allele, but confidence intervals were wide and additional studies are needed.

Conclusions. Acamprosate and oral naltrexone have the best evidence for improving alcohol consumption outcomes for patients with alcohol-use disorders. Head-to-head trials have not consistently established the superiority of one medication. Thus, other factors may guide

medication choices, such as frequency of administration, potential adverse events, coexisting symptoms, and availability of treatments.

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Executive Summary

Background

Alcohol misuse, or unhealthful alcohol use, which includes the full spectrum from drinking above recommended limits (i.e., risky/hazardous drinking) to alcohol dependence,[1,2] is associated with numerous health and social problems, more than 85,000 deaths per year in the United States,[3,4] and an estimated annual cost to society of more than $220 billion.[5,6] Alcohol misuse is estimated to be the third leading cause of preventable mortality in the United States, following tobacco use and being overweight.[7] For this report, we use the definitions of alcohol misuse in Table A.

In the past, alcohol-use disorders (AUDs) included harmful use, alcohol abuse, and alcohol dependence.[8,9] Diagnostic criteria for AUDs have evolved. The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), published in 2013, describes a single AUD category measured on a continuum from mild to severe and no longer has separate categories for alcohol abuse and dependence. Prevalence of AUDs is higher for men than for women, with estimates indicating a lifetime risk of more than 20 percent for men.[9-12]Alcohol dependence has lifetime prevalence rates of about 17 percent for men and 8 percent for women.[13]

AUDs cause substantial morbidity and mortality—threefold to fourfold increased rates of early mortality.[14-16] They are associated with hypertension, heart disease, stroke, cancer, liver cirrhosis, amnesias, cognitive impairment, sleep problems, peripheral neuropathy, gastritis and gastric ulcers, pancreatitis, decreased bone density, anemia, depression, insomnia, anxiety, suicide, and fetal alcohol syndrome.[9,17] Excessive alcohol consumption is also a major factor in injury and violence.[18] Acute alcohol-related harm can be the result of fires, drowning, falls, homicide, suicide, motor vehicle crashes, child maltreatment, and pedestrian injuries.[19] In addition, AUDs can complicate the assessment and treatment of other medical and psychiatric problems.[9]

Treatments for Alcohol-Use Disorders

Treatments for AUDs continue to evolve as research on the effectiveness of various treatments is published, and as new treatments are introduced and used more frequently. No single best approach has yet proven superior among the variety of available treatment options. Some common treatments for AUDs include cognitive behavioral therapy, motivational enhancement therapy, 12-step programs (e.g., Alcoholics Anonymous), and pharmacotherapy. Treatment may be delivered via individual outpatient counseling, intensive outpatient programs using group or individual methods, alcoholism treatment centers, or other approaches. Most treatment is currently delivered in specialty settings rather than in primary care settings. Primary care providers are typically trained to refer patients with AUDs for specialized treatment, and primary care providers are generally unfamiliar with medications for treating AUDs.[20]

Over the past 15 to 20 years, awareness has grown that treatment may be beneficial even if complete abstinence is not achieved. As a result, research has used other outcomes to measure the effectiveness of treatment, which can be subsumed under the concept of harm reduction.[21] These measures include significant increases in abstinent days or decreases in heavy drinking episodes, improved physical health, and improvements in psychosocial functioning.

Table A. Definitions of the spectrum of alcohol misuse[a]

Term	Definition
Risky or hazardous use	Consumption of alcohol above recommended daily, weekly, or per-occasion amounts.[b] Consumption levels that increase the risk for health consequences.
Harmful use[22,23]	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).
Alcohol abuse[24] (DSM-IV, 2000)	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). (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:[24] alcoholism, alcohol addiction (DSM-IV, 2000)	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. (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. (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. (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).

Table A. Definitions of the spectrum of alcohol misuse[a] (continued)

Term	Definition
Alcohol use disorder[25] (DSM-5, 2013); levels of severity—mild: 2-3; moderate: 4-5; severe: ≥6	A. Alcohol is taken in larger amounts or over a longer period than intended. B. Persistent desire or unsuccessful efforts to cut down or control alcohol use. C. A great deal of time is spent in activities necessary to obtain alcohol, use alcohol, or recover from its effects. D. Craving, or a strong desire or urge to use alcohol. E. Recurrent alcohol use resulting in a failure to fulfill major role obligations at work, school, or home. F. Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol. G. Important social, occupational, or recreational activities are given up or reduced because of alcohol use. H. Recurrent alcohol use in situations in which it is physically hazardous. I. 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. J. Tolerance, as defined by either of the following: (1) A need for markedly increased amounts of alcohol to achieve intoxication or desired effect. (2) A markedly diminished effect with continued use of the same amount of alcohol. K. Withdrawal, as manifested by either of the following: (1) The characteristic withdrawal syndrome for alcohol. (2) Alcohol (or a closely related substance, such as a benzodiazepine) is taken to relieve or avoid withdrawal symptoms.

Note: DSM is the Diagnostic and Statistical Manual of Mental Disorders; III, IV, and 5 are editions of the DSM.
[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.[25]
[b]Maximum recommended consumption is 3 or fewer standard drinks per day (7 or fewer drinks per week) for women and for men 65 years and older, and 4 or fewer drinks per day (14 or fewer drinks per week) for men under 65.[1,26]

Pharmacological Interventions

Beginning in the 1950s, the pharmacotherapy for AUDs consisted only of disulfiram, an aversive deterrent that produces very uncomfortable symptoms when alcohol is consumed. Since the 1990s, two oral medications (naltrexone and acamprosate) and one long-acting intramuscular formulation (of naltrexone) have been approved by the U.S. Food and Drug Administration (FDA) for alcohol dependence. Table B describes the medications available in the United States that are FDA approved, their mechanism of action, and dosing. Many additional medications have been used off label or studied for treatment of AUDs. These include antidepressants, mood stabilizers, anticonvulsants, alpha-adrenergic blockers, antipsychotics, and anxiolytics.

Table B. 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

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

Despite ongoing developments and advancements in treatment approaches, AUDs are among the most undertreated disorders in the U.S. health care system; it is estimated that fewer than one in three individuals with AUDs receive treatment.[10] Furthermore, data from the Veterans Health Administration show that, of those patients who receive treatment, fewer than 1 in 10 receive medication as part of treatment.[27,28] Therefore, expanding awareness and access to this relatively new treatment modality has the potential to improve outcomes and reduce the burden of this devastating illness that affects millions.

Existing Guidance

The Department of Veterans Affairs (VA), National Institute on Alcohol Abuse and Alcoholism (NIAAA), and Substance Abuse and Mental Health Services Administration (SAMHSA) all have guidelines, manuals, or protocols addressing the use of pharmacotherapy for alcohol dependence.[29-31] The VA guidelines recommend that oral naltrexone and/or acamprosate routinely be considered for patients with alcohol dependence (although acamprosate is currently a nonformulary medication for the VA) and that medications be offered in combination with addiction-focused counseling. The NIAAA "Medical Management Treatment Manual"[30] provides direction for clinicians to provide medical management, combined behavioral intervention, and medical treatment with naltrexone or acamprosate, as provided in the COMBINE trial. The SAMHSA treatment improvement protocol provides basic information, guidelines, tools, and resources to help health care practitioners treat patients with AUDs and includes chapters on acamprosate, disulfiram, oral naltrexone, and injectable naltrexone.

The United Kingdom's National Institute for Clinical Excellence (NICE) guidelines include the following recommendations: (1) after a successful withdrawal for people with moderate or severe alcohol dependence, to consider offering acamprosate or oral naltrexone in combination with an individual psychological intervention (cognitive behavioral therapies, behavioral therapies,or social network–based and environment-based therapies) focused specifically on alcohol misuse; (2) to consider offering disulfiram in combination with a psychological intervention for people who have a goal of abstinence but for whom acamprosate and oral naltrexone are not suitable or who prefer disulfiram and understand the relative risks of taking the drug; and (3) to have specialist and competent staff administer pharmacological interventions.[8]

Scope and Key Questions

The use of medications for AUDs is associated with uncertainty and variation across providers and settings. Since the last report commissioned by the Agency for Healthcare Research and Quality (AHRQ) on medications for alcohol dependence (1999),[32,33] there has been more than a tenfold increase in the number of individuals studied in controlled clinical trials of naltrexone and acamprosate, and many trials of medications that are not FDA approved. Other reasons for conducting a new review on this topic include the following: (1) to assess the comparative effectiveness of the FDA-approved medications; (2) to determine whether any agents that are not FDA approved have evidence supporting their efficacy; (3) to evaluate the evidence on intramuscular naltrexone (Vivitrol®), a fairly recently approved medication; (4) to evaluate whether trials provide evidence of effectiveness in primary care settings; (5) to assess whether some medications are more or less effective for adults with specific genotypes; and (6) to provide a comprehensive review of medications for AUDs that is relevant for clinicians, researchers, and policymakers.

Our report focuses on clinically relevant medications—those commonly used, those with sufficient literature for systematic review, and those of greatest interest to clinicians and to the developers of guidelines. Our report is limited to people with AUDs; it does *not* address those with risky or hazardous alcohol use (for whom medications are likely not an appropriate intervention).

The main objective of this report is to conduct a systematic review and meta-analysis of the comparative effectiveness and harms of medications for adults with AUDs. In this review, we address the following Key Questions (KQs):

KQ 1a: Which medications are efficacious for improving consumption outcomes for adults with AUDs in outpatient settings?

KQ 1b: How do medications for adults with AUDs compare for improving consumption outcomes in outpatient settings?

KQ 2a: Which medications are efficacious for improving health outcomes for adults with AUDs in outpatient settings?

KQ 2b: How do medications for adults with AUDs compare for improving health outcomes in outpatient settings?

KQ3a: What adverse effects are associated with medications for adults with AUDs in outpatient settings?

KQ 3b: How do medications for adults with AUDs compare for adverse effects in outpatient settings?

KQ 4: Are medications for treating adults with AUDs effective in primary care settings?

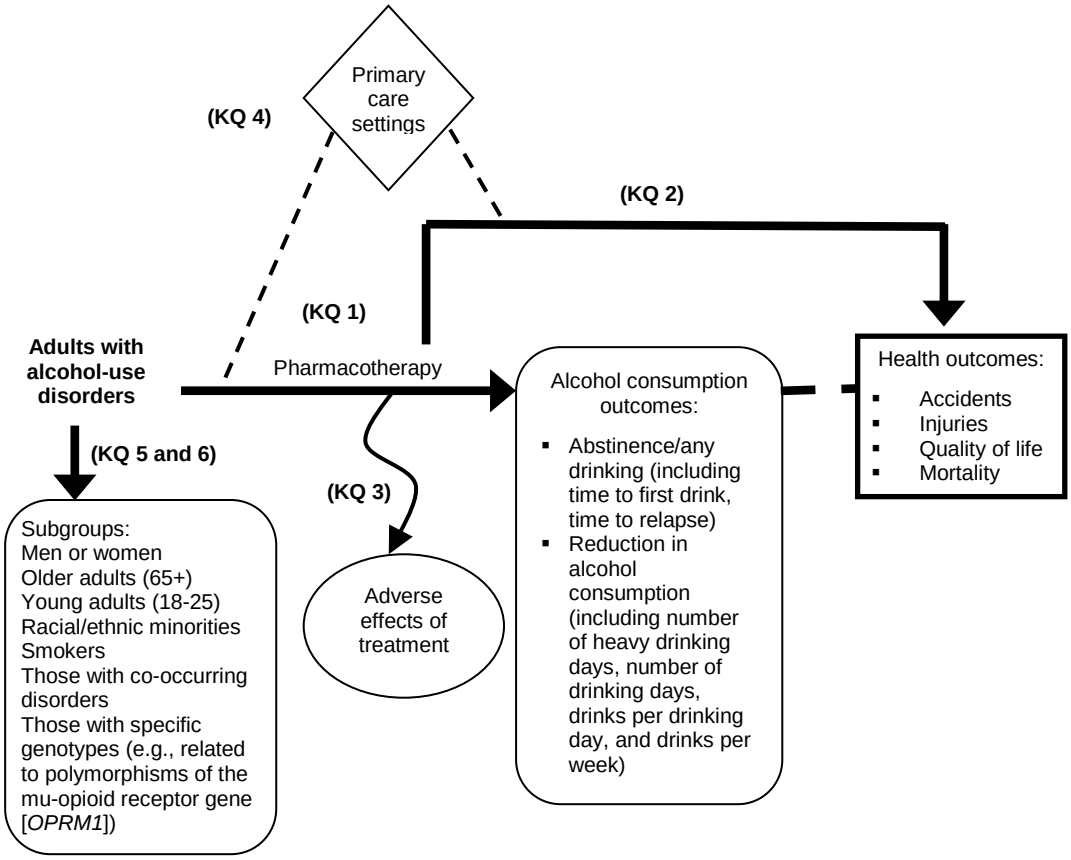
KQ 5: Are any of the medications more or less effective than other medications for men or women, older adults, young adults, racial or ethnic minorities, smokers, or those with co-occurring disorders?

KQ 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*])?

Analytic Framework

We developed an analytic framework to guide the systematic review process (Figure A).

Figure A. Analytic framework for pharmacotherapy for adults with alcohol-use disorders in outpatient settings



KQ = Key Question.

Methods

Literature Search Strategy

To identify articles relevant to each KQ, we searched PubMed®, the Cochrane Library, PsycINFO®, CINAHL®, and Embase® for English-language and human-only studies published from January 1, 1970, to October 11, 2013. Searches were run by an experienced Evidence-based Practice Center (EPC) librarian and were peer reviewed by another EPC librarian. We manually searched reference lists of pertinent reviews, trials, and background articles on this topic to look for any relevant citations that our searches might have missed.

We searched for unpublished studies relevant to this review using ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform, and the FDA Web

site. In addition, AHRQ's Scientific Resource Center requested any unpublished studies and pertinent data from relevant pharmaceutical companies. We also retrieved and assessed references suggested by our peer reviewers and the public.

Eligibility Criteria

We developed inclusion and exclusion criteria with respect to populations, interventions, comparators, outcomes, timing, and setting (PICOTS) and study designs. We included studies enrolling adults with AUDs that evaluated one or more of the following medications: acamprosate, disulfiram, naltrexone, amitriptyline, aripiprazole, atomoxetine, baclofen, buspirone, citalopram, desipramine, escitalopram, fluoxetine, fluvoxamine, gabapentin, imipramine, nalmefene, olanzapine, ondansetron, paroxetine, prazosin, quetiapine, sertraline, topiramate, valproate, varenicline, and viloxazine.

Studies were required to assess at least one of the following outcomes: return to any drinking (lapse), return to heavy drinking (relapse), drinking days, heavy drinking days, drinks per drinking day, time to lapse or relapse, accidents, injuries, quality of life (QoL), function, mortality, or adverse effects. Studies were required to treat patients with a medication for a minimum of 12 weeks in an outpatient setting.

For KQs 1, 2, and 4, double-blind randomized controlled trials (RCTs) that compared one of the medications with placebo or another medication and recent systematic reviews (searches ending no earlier than 2007) were eligible. For KQ 2b, prospective cohort studies were also eligible. For KQ 3 (harms), double-blind RCTs and recent systematic reviews that compared one of the medications with placebo or with another medication were eligible. The following designs were also eligible for KQ 3 if they compared two or more drugs of interest: nonrandomized controlled trials, open-label trials, secondary analyses or subgroup analyses from trials, prospective cohort studies, and case-control studies. For KQ 5 (subgroups), double-blind RCTs, recent systematic reviews, nonrandomized controlled trials, open-label trials, secondary analyses or subgroup analyses from trials, prospective cohort studies, and case-control studies were eligible as long as the studies compared two or more drugs. For KQ 6 (specific genotypes), double-blind RCTs, analyses of subjects enrolled in trials, and prospective cohort studies comparing people with different genotypes were eligible.

Study Selection

Two members of the research team independently reviewed each title and abstract (identified through searches) to determine eligibility. Studies marked for possible inclusion by either reviewer and those that lacked adequate information to determine eligibility underwent a full-text review. Two members of the team independently reviewed each full-text article to determine eligibility. If the reviewers disagreed, they resolved conflicts by discussion and consensus or by consulting a senior member of the team.

Data Extraction

We designed and used structured data extraction forms to gather pertinent information from each article; this included characteristics of study populations, settings, interventions, comparators, study designs, methods, and results. Trained reviewers extracted the relevant data from each included article. All data extractions were reviewed for completeness and accuracy by a second member of the team.

Risk-of-Bias Assessment of Individual Studies

To assess the risk of bias (internal validity) of studies for major outcomes of interest, we used predefined criteria based on guidance from the AHRQ "Methods Guide for Effectiveness and Comparative Effectiveness Reviews."[34] We assessed selection bias, confounding, performance bias, detection bias, and attrition bias; we included questions about adequacy of randomization, allocation concealment, similarity of groups at baseline, blinding, attrition, whether intention-to-treat analysis was used, methods of handling missing data, and fidelity. We rated the studies as low, medium, high, or unclear risk of bias.[35] Two independent reviewers assessed the risk of bias for each study. Disagreements between the two reviewers were resolved by discussion and consensus or by a third member of the team.

Data Synthesis

We conducted meta-analyses using random-effects models to estimate pooled effects.[36] For continuous outcomes, we used weighted mean differences (WMDs). For binary outcomes, we calculated risk differences (RDs) between groups. We did not include studies rated as high or unclear risk of bias in our main analyses but did include them in sensitivity analyses. We calculated the chi-squared statistic and the I^2 statistic to assess statistical heterogeneity in effects between studies.[37,38] We also examined potential sources of heterogeneity by analysis of subgroups defined by patient population (e.g., U.S. vs. non-U.S. studies) and variation in interventions (e.g., dose). When quantitative synthesis was not appropriate (e.g., because of clinical heterogeneity, insufficient numbers of similar studies, or insufficiency or variation in outcome reporting), we synthesized the data qualitatively.

Strength of the Body of Evidence

We graded the strength of evidence (SOE) as high, moderate, low, or insufficient based on established guidance.[39] Developed to grade the overall strength of a body of evidence, the approach incorporates four key domains: risk of bias (includes study design and aggregate quality), consistency, directness, and precision of the evidence. It also considers optional domains. Two reviewers assessed each domain for each key outcome and determined an overall SOE grade based on domain ratings. In the event of disagreements on the domain or overall grade, they resolved differences by discussion or by consulting an experienced investigator. We graded the SOE for the following outcomes: return to any drinking, return to heavy drinking, drinking days, heavy drinking days, drinks per drinking day, accidents, injuries, QoL or function, mortality, and adverse events.

Applicability

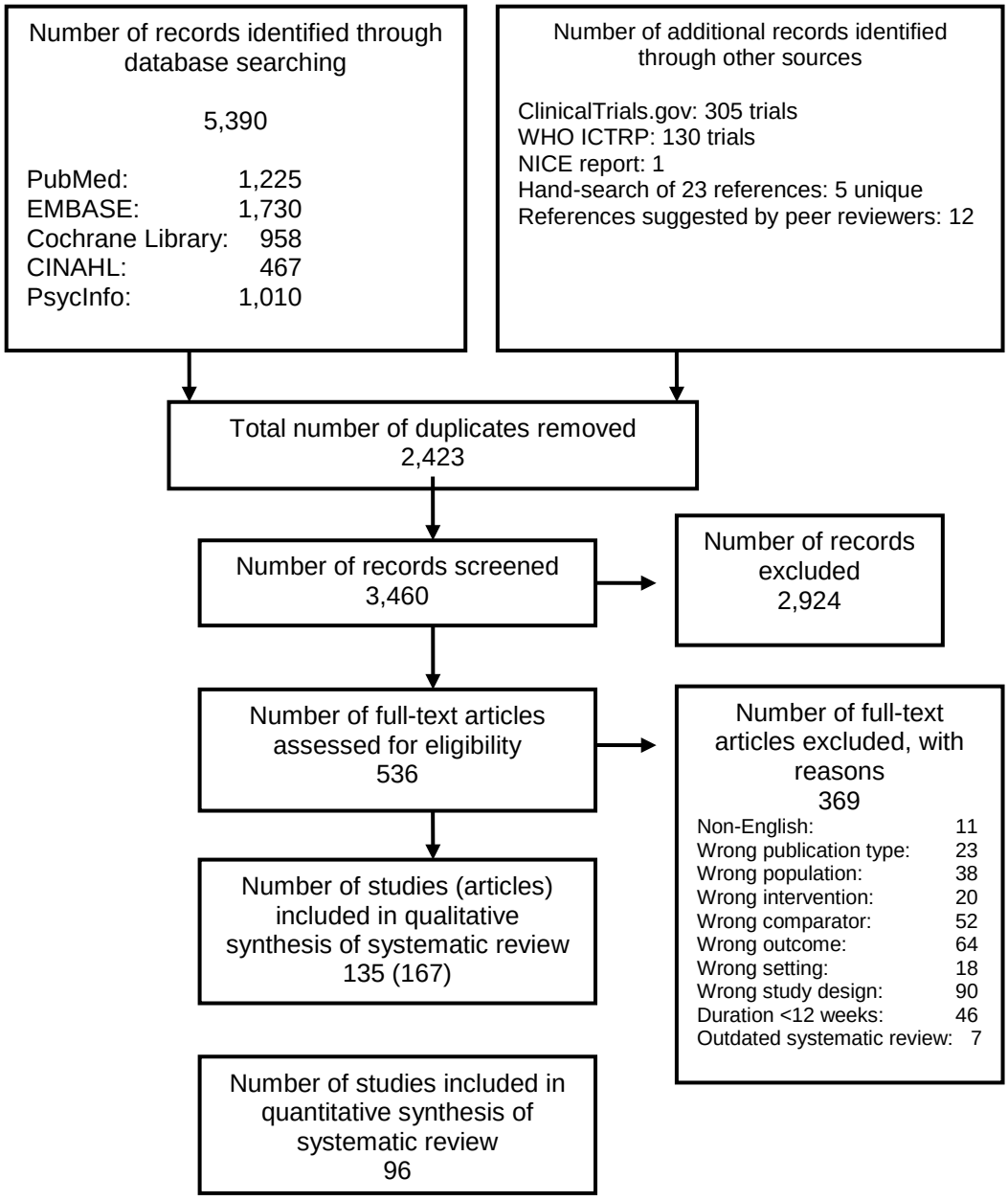
We assessed applicability of the evidence following guidance from the "Methods Guide for Effectiveness and Comparative Effectiveness Reviews."[40] We used the PICOTS framework to explore factors that affect applicability.

Results

We included 167 published articles reporting on 135 studies (Figure B): 124 were RCTs, 5 were observational studies, and 6 were systematic reviews. Studies typically included

psychosocial cointerventions; thus, effect sizes reflect the added benefits of medications beyond those of psychosocial interventions.

Figure B. Literature flow diagram



NICE = National Institute for Clinical Excellence; WHO ICTRP = World Health Organization International Clinical Trials Registry Platform.

Key Question 1. Consumption Outcomes

We found moderate SOE that both acamprosate and oral naltrexone (50 mg/day) are effective for improving alcohol consumption outcomes (Table C). Numbers needed to treat (NNTs) to

prevent 1 person from returning to any drinking were 12 and 20, respectively. For return to heavy drinking, evidence did not support the efficacy of acamprosate, whereas oral naltrexone (50 mg/day) was efficacious, with an NNT of 12. We found low SOE that injectable naltrexone is efficacious for reducing percentage of heavy drinking days. Evidence from well-controlled trials does not adequately support the efficacy of disulfiram compared with placebo for preventing return to any drinking or for other alcohol consumption outcomes. Some disulfiram trials reported fewer drinking days for subjects who returned to any drinking and who had a complete set of assessment interviews, and suggest that disulfiram may have a role in the treatment of alcohol dependence for some individuals.

Table C. Summary of findings and strength of evidence for efficacy of FDA-approved medications for alcohol dependence

Medication	Outcome	N Studies; N Subjects[a]	Results—Effect Size (95% CI)[b]	NNT[c]	Strength of Evidence
Acamprosate	Return to any drinking	16; 4,847	RD: -0.09 (-0.14 to -0.04)	12	Moderate
	Return to heavy drinking	7; 2,496	RD: -0.01 (-0.04 to 0.03)	NA	Moderate
	% DDs	13; 4,485	WMD: -8.8 (-12.8 to -4.8)	NA	Moderate
	% HDDs	1; 100	WMD: -2.6 (-11.4 to 6.2)	NA	Insufficient
	Drinks per DD	1; 116	WMD: 0.4 (-1.8 to 2.6)	NA	Insufficient
	Accidents or injuries	0;[d] 0	NA	NA	Insufficient
	QoL or function	1; 612	NSD	NA	Insufficient
	Mortality	8; 2,677	7 events (ACA) vs. 6 events (placebo)	NA	Insufficient
Disulfiram	Return to any drinking	2; 492	RD: -0.04 (-0.11 to 0.03)[e]	NA	Low
	Return to heavy drinking	0; 0	NA	NA	Insufficient
	% DDs	2; 290	NSD[f]	NA	Insufficient
	% HDDs	0; 0	NA	NA	Insufficient
	Drinks per DD	0; 0	NA	NA	Insufficient
	Accidents or injuries	0; 0	NA	NA	Insufficient
	QoL or function	0; 0	NA	NA	Insufficient
	Mortality	0; 0	NA	NA	Insufficient
Naltrexone 50 mg oral	Return to any drinking	16; 2,347	RD: -0.05 (-0.10 to -0.00)	20	Moderate
	Return to heavy drinking	19; 2,875	RD: -0.09 (-0.13 to -0.04)	12	Moderate
	% DDs	15; 1,992	WMD: -5.4 (-7.5 to -3.2)	NA	Moderate
	% HDDs	6; 521	WMD: -4.1 (-7.6 to -0.61)	NA	Moderate
	Drinks per DD	9; 1,018	WMD: -0.49 (-0.92 to -0.06)	NA	Low
Naltrexone 100 mg oral	Return to any drinking	3; 946	RD: -0.03 (-0.08 to 0.02)	NA	Low
	Return to heavy drinking	2; 858	RD: -0.05 (-0.11 to 0.01)	NA	Low
	% DDs	2; 858	WMD: -0.9 (-4.2 to 2.5)	NA	Low
	% HDDs	2; 423	WMD: -3.1 (-5.8 to -0.3)	NA	Low
	Drinks per DD	1; 240	WMD: 1.9 (-1.5 to 5.2)	NA	Insufficient
Naltrexone injection	Return to any drinking	2; 939	RD: -0.04 (-0.10 to 0.03)	NA	Low
	Return to heavy drinking	2; 615	RD: -0.01 (-0.14 to 0.13)	NA	Low
	% DDs	1; 315	WMD: -8.6 (-16.0 to -1.2)	NA	Insufficient
	% HDDs	2;[g] 926	WMD: -4.6 (-8.5 to -0.56)	NA	Low
	Drinks per DD	0; 0	NA	NA	Insufficient
Naltrexone (any dose)	Accidents or injuries	0; 0	NA	NA	Insufficient
	QoL or function	4; 1,513	Some conflicting results[h]	NA	Insufficient
	Mortality	6; 1,738	1 event (NTX) vs. 2 events (placebo)	NA	Insufficient

ACA = acamprosate; CI = confidence interval; DD = drinking day; DrInC = Drinker Inventory of Consequences; FDA = U.S. Food and Drug Administration; HDD = heavy drinking day; N = number; NA = not applicable; NNT = number needed to treat; NSD = no statistically significant difference; NTX = naltrexone; QoL = quality of life; RD = risk difference; WMD = weighted mean difference.

[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 NNT indicates that the risk difference (95% CI) was not statistically significant, so we did not calculate an NNT, or that the effect measure was not one that allows direct calculation of NNT (e.g., WMD).

[d]One study rated as unclear risk of bias reported that one patient in the placebo group died by "accident." No other details on the cause or nature of the accident were provided.[41] That study also reported 1 injury in the acamprosate group and 2 in the placebo group. Another study, rated high risk of bias, reported a traffic accident in the acamprosate group.[42]

[e]From meta-analysis of disulfiram 250 mg vs. control (disulfiram 1 mg).[43,44] Meta-analysis including studies rated as high risk of bias also found no significant difference (RD, -0.00; 95% CI, -0.10 to 0.09). Similarly, our meta-analysis found no statistically significant difference between disulfiram 250 mg per day and riboflavin (i.e., no disulfiram) (RD, -0.04; 95% CI, -0.11 to 0.03).

[f] One study (N=128) reported similar percentages and no significant difference;[44] the other reported that disulfiram was favored among the subset of subjects (N=162 of 605 subjects) who drank and had a complete set of assessment interviews, but it did not report this outcome for the full randomized sample.[43] Overall, evidence was insufficient due to imprecision, inconsistency, and indirectness.

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

[h]Unable to pool data. Two studies found no significant difference between naltrexone- and placebo-treated subjects.[45,46] One study reported that patients receiving injectable naltrexone 380 mg per month had greater improvement on the mental health summary score than those receiving placebo at 24 weeks (8.2 vs. 6.2; p=0.044).[47] One study measured alcohol-related consequences (with the DrInC) and reported that more subjects who received placebo (N=34) had at least 1 alcohol-related consequence than those who received naltrexone (N=34): 76% vs. 45%; p=0.02.[48]

Our meta-analyses of three head-to-head RCTs comparing acamprosate with naltrexone,[49-51] all rated as low risk of bias, found no statistically significant difference between the two medications for return to any drinking, and our meta-analysis of four head-to-head RCTs[49-52] similarly found no statistically significant difference between the two medications for return to heavy drinking (Table D). The COMBINE study was one of the head-to-head RCTs.[49] It found that "patients receiving medical management with naltrexone, combined behavioral intervention (CBI), or both had better drinking outcomes than those who received placebo, but acamprosate showed no evidence of efficacy, with or without CBI."

Table D. Summary of findings and strength of evidence for comparative effectiveness of acamprosate and naltrexone

Intervention	Outcome	N Studies; N Subjects[a]	Results—Effect Size (95% CI)[b]	Strength of Evidence
ACA vs. NTX	Return to any drinking	3; 800	RD: 0.02 (-0.03 to 0.08)	Moderate
	Return to heavy drinking	4; 1,141	RD: 0.01 (-0.05 to 0.06)	Moderate
	Percentage drinking days	2; 720	WMD: -2.98 (-13.4 to 7.5)	Low

ACA = acamprosate; CI = confidence interval; N = number; NTX = naltrexone; QoL = quality of life; RD = risk difference; SOE = strength of evidence; WMD = weighted mean difference.

Note: Table includes only comparisons of medications with evidence of efficacy (as determined in Key Question 1) and with sufficient data for synthesis. We did not include rows in this table for outcomes that we graded as insufficient SOE (percentage heavy drinking days, drinks per drinking day, accidents or injuries, QoL or function, and mortality).

[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 acamprosate over naltrexone

For the vast majority of medications used off label and those under investigation, either evidence was insufficient to determine whether they are efficacious for reducing alcohol consumption or evidence suggested that they are not efficacious for people with AUDs. We found some exceptions. First, for topiramate, we found moderate SOE supporting efficacy for reducing drinking days, heavy drinking days (WMD, -11.5; 95% CI [confidence interval], -18.3 to -4.8), and drinks per drinking day (WMD, -1.1; 95% CI, -1.7 to -0.4) based on the results of two RCTs rated as low or medium risk of bias (total N=521).[53,54] The included RCTs did not report data for return to any drinking or return to heavy drinking. Second, for nalmefene, we found moderate SOE supporting efficacy for reducing heavy drinking days per month (WMD, -2.0; 95% CI, -3.0 to -1.0) and drinks per drinking day (WMD, -1.0; 95% CI, -1.8 to -0.3).[55,56] Finally, limited evidence from two small RCTs (total N=88), one enrolling people with bipolar disorder, supports efficacy of valproic acid for reducing return to heavy drinking, heavy drinking days, and drinks per drinking day (low SOE).

Key Question 2. Health Outcomes

We found insufficient direct evidence from trials to conclude that treatment with acamprosate or naltrexone leads to improvement in health outcomes—i.e., accidents, injuries, QoL, function, or mortality (Table C). Very few trials reported any health outcomes, and the included trials were not designed or powered to assess impact on health outcomes; they typically focused on alcohol consumption outcomes. The largest pharmacotherapy trial, COMBINE, reported some evidence of improvement in QoL with naltrexone plus behavioral intervention (on the physical health scale from the 12-item Short Form health survey, version 2), but the difference between groups did not reach a clinically meaningful threshold.[46]

Key Question 3. Harms

Of the included studies, 114 provided information on harms. Evidence for many potential adverse events was insufficient to determine whether the risk was increased or not, often primarily because of lack of precision. For most of the specific adverse events, point estimates favored placebo (i.e., there were more adverse events with medications), but differences were not statistically significant. In head-to-head studies, the risk of withdrawal due to adverse events was not significantly different between acamprosate and naltrexone, whereas the risks of headache and vomiting were higher for those treated with naltrexone. Compared with placebo, patients treated with acamprosate had a higher risk of anxiety, diarrhea, and vomiting; those treated with naltrexone had a higher risk of dizziness, nausea, and vomiting; and those treated with nalmefene had a higher risk of dizziness, headache, insomnia, nausea, and vomiting. Individual trials of topiramate reported increased risk of many adverse events, including paresthesias, taste perversion, anorexia, difficulty with concentration/attention, nervousness, dizziness, pruritis, psychomotor slowing, and weight loss.[53,54] A single trial that reported adverse effects for valproic acid compared with placebo found a higher rate of nausea for patients treated with valproic acid.

Key Question 4. Evidence From Primary Care Settings

Evidence from primary care settings was scant. One trial (N=100) that recruited subjects primarily by advertisement in two family medicine settings in the United States found no significant treatment effect when comparing acamprosate with placebo.[57] The only other trial

meeting our inclusion criteria that was conducted partly in primary care settings compared nalmefene with placebo in 15 sites (about half were primary care settings) in Finland.[58] See the Discussion section below (under Primary Care) for more information about studies that may have applicability to primary care settings.

Key Question 5. Subgroups

We did not find any compelling evidence that naltrexone, acamprosate, topiramate, nalmefene, or valproic acid are more or less effective (compared with each other) for men or women, older adults, young adults, racial or ethnic minorities, smokers, or those with co-occurring disorders.

Key Question 6. Genetic Polymorphisms

We found no studies that assessed the clinical utility of genotype-guided dosing strategies or genotype-guided medication selection and none that randomized by genotype. All included studies were either subgroup analyses of trials or prospective cohort studies of people treated with a medication, and all assessed the association between genotype and response to medication (i.e., clinical validity). For most polymorphism-medication pairs, we found just one eligible study, and we graded the SOE as insufficient.

Seven eligible studies assessed variation in naltrexone response related to mu-opioid receptor gene (*OPRM1*) polymorphisms. Our meta-analyses for return to any drinking and return to heavy drinking found no significant difference between A-allele homozygotes and those with at least one G allele, both without inclusion of studies rated as high or unclear risk of bias (RD, -0.03; 95% CI, -0.6 to 0.5, and RD, 0.26; 95% CI, -0.01 to 0.53, respectively) and with them (RD, 0.01; 95% CI, -0.2 to 0.2, and RD, 0.14; 95% CI, -0.03 to 0.3, respectively). Point estimates for return to heavy drinking suggest it is possible that patients with at least one G allele of A118G polymorphism of *OPRM1* might be more likely to respond to naltrexone compared with patients without a G allele, but CIs were wide; additional studies are needed to improve confidence in the estimate of the effect.

Discussion

Evidence supports the efficacy of more than one pharmacological treatment for AUDs, and clinical uncertainty exists about what treatment to select for individual patients. Acamprosate and naltrexone have the best evidence supporting their efficacy, but head-to-head trials have not consistently established superiority of either medication. Thus, other factors may contribute to medication choices, such as frequency of administration, cost, potential type of benefits, potential adverse events, and availability of treatments (e.g., acamprosate and injectable naltrexone are currently nonformulary medications for the VA).

For example, acamprosate is typically dosed as two 333 mg tablets given three times daily, whereas oral naltrexone is one tablet once daily and intramuscular naltrexone is given once monthly. Acamprosate is contraindicated for people with severe renal impairment and requires dose adjustments for moderate renal impairment. Oral naltrexone is contraindicated for patients with acute hepatitis or liver failure (and has precautions for other hepatic disease) and for those currently using opioids or with anticipated need for opioids, and it can precipitate severe withdrawal for patients dependent on opioids. Larger doses may be required and respiratory depression may be deeper and more prolonged if opioid analgesia is needed. The prescribing

information for injectable naltrexone is somewhat different.[59] For example, it does not include contraindications for patients with acute hepatitis or liver failure.

Given that medications for AUDs have been underused,[28,60] entities providing health care for people with AUDs may need to develop systems to optimize dissemination and implementation of appropriate medication treatment strategies. For example, these could include campaigns to educate providers about the use of medications for AUDs; systems to screen for unhealthy alcohol use and to provide appropriate interventions for people with unhealthy alcohol use; systems to ensure that people with AUDs have access to knowledgeable providers who can prescribe medications; or systems to remind or incentivize providers to use effective medications for AUDs when appropriate.

Although we found insufficient direct evidence to conclude that treatment with medications leads to improvement in health outcomes—i.e., accidents, injuries, QoL, function, or mortality—evidence from epidemiologic literature consistently relates high average alcohol consumption and heavy per-occasion use to an increased risk of health problems, such as cancers of the oral cavity, esophagus, larynx, colon, rectum, liver, and breast; liver cirrhosis; chronic pancreatitis; coronary heart disease; stroke; depression; preterm birth complications; fetal alcohol syndrome; and injuries and violence.[1,17,61-63] Such epidemiologic evidence would suggest that improving alcohol consumption outcomes is likely to result in improved health outcomes. A recent model estimated that increasing treatment coverage to 40 percent of all people with alcohol dependence in the European Union would reduce alcohol-attributable mortality by 13 percent for men and 9 percent for women.[64] Further, a cost study based on the COMBINE trial reported that several treatment combinations that include pharmacotherapy led to reduced median social costs associated with health care, arrests, and motor vehicle accidents compared with medical management plus placebo.[65]

Primary Care

Direct evidence in primary care settings was scant. One included trial (N=100) conducted completely in primary care settings found no significant treatment effect when comparing acamprosate with placebo.[57] The only other included trial was conducted partly in primary care settings and compared nalmefene with placebo in 15 sites (about half were primary care settings) in Finland.[58]

Some included studies conducted in non–primary-care settings used interventions that may be adaptable for delivery in primary care. For example, in the COMBINE study,[49] providers delivered a medical management intervention comprised of up to nine manual-guided counseling visits. The first visit was approximately 45 minutes and followup visits were about 20 minutes each. Medical management included advice for reducing drinking, inquiries about medication side effects, and emphasis on the importance of taking medications as prescribed. Another trial (included in KQ 1 but not in KQ 4), which compared naltrexone with placebo for 12 weeks in the United States, described the use of a "primary care model."[66] Although the trial did not take place in a primary care setting (it was a treatment research center) and the investigators were from a department of psychiatry, the psychosocial cointervention was delivered by a nurse practitioner with a primary care background, and the trial may have implications for how psychosocial cointerventions could be provided in primary care settings.

In terms of implementing treatment programs for AUDs in primary care, we identified four other publications that did not meet our inclusion criteria (due to the study design or comparators) but may have important implications for primary care settings.[67-70] While these

studies found conflicting results, they demonstrated the feasibility of managing AUDs in primary care. In general, these interventions involved formal clinic structure, staffing, and protocols. They used variations of chronic care management, multidisciplinary team-based care, and care coordination between primary care providers and mental health providers (e.g., physicians coordinating with social workers to connect patients to community resources or provide counseling).

First, a nested sequence of three RCTs based in the United States compared naltrexone plus "primary care management" (PCM) with naltrexone plus cognitive behavioral therapy.[67] They found no difference in avoiding persistent heavy drinking between those who received naltrexone plus 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 than those who received placebo and PCM. Second, a pragmatic trial with 149 general practitioners in France randomized patients (N=422) to acamprosate plus standard care or standard care alone.[68] The trial reported better outcomes for the acamprosate group for alcohol-related health, personal, and social problems, and quality of life. Third, an RCT based in the United States (N=163) found that participants in a primary care–based alcohol care management program were more likely to receive naltrexone (65.9% vs. 11.5%), to be engaged in treatment (OR [odds ratio], 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 a specialty treatment program.[69] Fourth, the Alcohol Health Evaluation and Disease Management (AHEAD) study, based in the United States (N=563), compared chronic care management (CCM) that included longitudinal care coordinated by a primary care clinician with no CCM for people with alcohol or drug dependence who were not currently engaged in primary care.[70] Of those enrolled, 12 percent had alcohol dependence without also meeting criteria for other drug dependence. CCM included motivational enhancement therapy; relapse prevention counseling; onsite 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.

Barriers to prescribing medications for AUDs in primary care may include lack of familiarity with the medications, lack of confidence in their effectiveness, or inability to provide suitable psychosocial cointerventions (e.g., due to competing demands or insufficient practice resources, personnel, or training). Like behavioral counseling interventions for risky drinking delivered in primary care, implementing the use of medications and psychosocial cointerventions for AUDs in primary care might require development of support systems and additional provider and staff training.[1,3] Further, primary care providers are typically trained to refer patients with AUDs for specialized treatment. O'Malley and O'Connor recently reviewed the issues surrounding the use of medications for alcohol dependence in primary care settings.[20] They concluded that "the implementation and widespread use of medications to treat alcohol problems faces a unique set of barriers in primary care. Although primary care providers are proficient at prescribing a wide variety of medications, they generally are unfamiliar with medications for treating alcohol problems other than those used to treat alcohol withdrawal." They referenced a body of research to support basic screening methods, brief interventions, and medication therapy that has yet to have a major impact on how primary care providers care for individuals at risk for or with alcohol problems.[71]

Applicability

Most studies reported that all subjects met criteria for alcohol dependence. We did not identify any studies that evaluated medications and reported them to be efficacious for people with AUDs who did not meet criteria for alcohol dependence (i.e., people with alcohol abuse or harmful alcohol use). The included literature used definitions from DSM-III or DSM-IV. DSM-5 (2013) describes a single AUD category measured on a continuum from mild to severe and no longer has separate categories for alcohol abuse and dependence.[25] Using DSM-5 terminology, most participants in the included studies likely had moderate to severe AUD. Thus, applicability of our findings to people with mild AUDs is uncertain.The mean age of subjects was generally in the 40s, with very few studies enrolling slightly younger or older populations. Thus, it is uncertain whether the medications have similar efficacy for older (e.g., 65 and older) or younger (e.g., in the 20s) subgroups. We did not find evidence to confirm or refute whether treatments are more or less efficacious for gender groups, racial or ethnic minorities, smokers or nonsmokers, and those with certain coexisting conditions.

Although the majority of included trials assessing the efficacy of acamprosate were conducted in Europe (16 of 22) and a minority were conducted in the United States (4 of 22), the opposite was true for naltrexone (27 of 44 in the United States and 8 of 44 in Europe). Further, the few studies of acamprosate conducted in the United States did not find it to be efficacious. It is unclear whether the different results were due to population differences or other factors. The European trials of acamprosate typically identified patients from inpatient settings or treatment programs, whereas the trials of acamprosate based in the United States relied on advertisements and referrals. It is possible that this resulted in populations with differing AUDs severity and differing potential for benefit. For example, studies of subjects recruited via advertisements may enroll people who have less severe disorders.

Most studies required patients to abstain for at least a few days prior to initiating medication, and the medications are generally recommended for maintenance of abstinence. Acamprosate and injectable naltrexone are approved only for use in patients who have established abstinence, although the duration of required abstinence is not set. However, some studies enrolling patients who were not yet abstinent reported reduction in heavy drinking with naltrexone[72,73] or acamprosate.[74]

Limitations of the Comparative Effectiveness Review Process

The scope of this review was focused on medications. We did not evaluate the effectiveness or comparative effectiveness of other interventions for AUDs (e.g., 12-step programs). We required that trials have at least 12 weeks of followup from the time of medication initiation, excluding trials of shorter duration. Some might consider this approach to omit potentially important information. However, longitudinal studies have found that shorter treatment periods may yield misleading conclusions about treatment efficacy due to fluctuations in drinking behavior that are typical of the course of AUDs,[75,76] suggesting that longer durations of followup might more accurately reflect the outcomes of greatest interest and importance.

Our review focused on benefits and harms of medications and how they compare with other medications, and our findings generally reflect the added benefits of medications beyond those of psychosocial cointerventions. However, studies used a variety of different psychosocial cointerventions, and this heterogeneity limits our certainty about the effect of medications when used alone (with no psychosocial cointervention) or when added to a particular psychosocial

intervention. Reporting of previous and ongoing psychosocial interventions was variable across the included studies, and we were unable to determine whether subjects actually received some cointerventions; for example, Alcoholics Anonymous was recommended, but no information was reported about how many subjects adhered to the recommendation.

Finally, publication bias and selective reporting are potential limitations. Although we searched for unpublished studies and unpublished outcomes, and did not find direct evidence of either of these biases, many of the included trials were published prior to the availability of trial registries (e.g., clinicaltrials.gov) that would allow for greater certainty in determining the potential for either type of bias.

Limitations of the Evidence Base

The evidence base was inadequate to draw conclusions for some of our questions or subquestions of interest. In particular, as described above, we found insufficient direct evidence on health outcomes, limited and varying reporting on harms, few trials conducted in primary care settings, and scant head-to-head evidence on differences for population subgroups.

We found insufficient direct evidence to determine whether medications are efficacious for improving health outcomes. Although evidence from epidemiologic literature consistently relates high average and heavy per-occasion alcohol use to an increased risk of health problems, it is challenging to estimate the magnitude of reduction in the risk of health problems that is derived from a reduction in consumption. For example, it is unclear how much benefit for health outcomes is derived from 10 percent fewer patients returning to any drinking.

Many included trials had methodological limitations introducing some risk of bias. Some had high proportions of subjects lost to followup. High attrition rates are not uncommon in studies of psychiatric conditions, but methods of handling missing data varied, and some trials did nothing to address missing data (i.e., analyzing only completers). However, many trials conducted true intention-to-treat analyses and used appropriate methods of handling missing data, such as imputing return to heavy drinking for subjects lost to followup or using multiple imputations.

Future Research

We identified numerous gaps in the evidence that future research could address. Many of these gaps are highlighted in the previous sections of this Discussion. Of note, these gaps relate only to the KQs addressed by this report, and they should not eliminate a wide range of potentially important research that falls outside of our scope. Table E summarizes the key gaps and potential future research that could address the gaps.

Table E. Evidence gaps for future research by Key Question

KQ	Evidence Gap	Potential Future Research
1	Evidence was insufficient to determine efficacy of some medications, either because of inconsistency and imprecision or because we found 0 or just 1 small trial with low to medium risk of bias (e.g., amitriptyline, aripiprazole, atomoxetine, baclofen, buspirone, citalopram, desipramine, fluoxetine, fluvoxamine, imipramine, olanzapine, paroxetine, quetiapine).	Future studies could evaluate medications that have some evidence (often from 1 or 2 small trials) suggesting possible efficacy (e.g., baclofen) or medications that have not yet been studied with some theoretical basis to support their potential efficacy.
1	We found no head-to-head studies of oral naltrexone and injectable naltrexone.	Future studies could compare the benefits or harms of oral and injectable naltrexone.
1	Whether patients need to stop drinking before starting medications in order to benefit is somewhat unclear. Most studies required patients to abstain for at least a few days prior to initiating medication, but some studies enrolling patients who were not yet abstinent reported reduction in heavy drinking with naltrexone[72,73] or acamprosate.[74]	Future studies could assess the efficacy of medications for patients who are not ready to abstain.
2	We found insufficient[a] direct evidence to conclude that treatment with acamprosate or naltrexone leads to improvement in health outcomes.	Future studies could focus on health outcomes, such as accidents, injuries, QoL, function, or mortality. These could include large prospective studies to evaluate harm and health consequences with various levels of drinking.
3	Relatively few studies reported information about suicide, suicidal ideation, or self-harmful behaviors.	Additional studies could be conducted to determine whether precautions about suicide, suicidal thoughts, or self-harmful behaviors are warranted.
3	Little evidence was available to determine whether naltrexone can be used for people with various liver conditions.[b]	Future studies could evaluate the use of naltrexone for people with various chronic liver conditions.
4	No eligible trials assessed the use of FDA-approved medications in primary care settings.	Future studies could evaluate the use of acamprosate and naltrexone in primary care settings.
5	Evidence on whether any medications are more or less effective than other medications for population subgroups was scant.	Future studies could compare the use of acamprosate and naltrexone for subgroups of patients (e.g., enrolling subjects who all have depression or other psychiatric conditions; comparing effectiveness for men or women or among older or younger patients).
6	Relatively few subjects contributed data to our analyses of variation in naltrexone response and *OPRM1* polymorphisms. Patients with at least 1 G allele may be more likely to respond to naltrexone compared with patients without a G allele, but confidence intervals were wide and the effect was not statistically significant.	Additional studies are likely to change our confidence in the estimate of the effect and to change the estimate.
6	No studies assessed the clinical utility of genotype-guided dosing strategies or genotype-guided medication selection, and none randomized by genotype.	If variation in naltrexone response by *OPRM1* polymorphisms becomes established, then future studies could assess the clinical utility of using genotype-guided dosing strategies. For example, studies might compare the use of genotype-guided dosing strategies (e.g., use naltrexone for patients with at least 1 G allele but use acamprosate for A-allele homozygotes) with using naltrexone or acamprosate for all subjects.
6	Only 1 study was available for most polymorphism-medication response associations.	Future studies could explore other genotypic associations (i.e., not limiting future studies to *OPRM1* polymorphisms).

FDA = U.S. Food and Drug Administration; KQ = Key Question; *OPRM1* = mu-opioid receptor gene; QoL = quality of life.

[a]Evidence was insufficient for health outcomes because we found no trials meeting inclusion/exclusion criteria rated as low or medium risk of bias (i.e., for accidents and injuries) or because of inconsistency and imprecision (i.e., for QoL and mortality).

Very few trials reported any health outcomes, and the included trials were not designed or powered to assess impact on health outcomes; they typically focused on alcohol consumption outcomes.

[b]The FDA removed the black box warning for hepatotoxicity for injectable naltrexone, but it is unclear whether naltrexone should be used in people with various chronic liver conditions.

Conclusions

Acamprosate and oral naltrexone (50 mg/day) are effective for improving alcohol consumption outcomes for patients with AUDs (moderate SOE). NNTs to prevent 1 person from returning to any drinking were 12 and 20, respectively; NNT to prevent 1 person from returning to heavy drinking was 12 for oral naltrexone (50 mg/day). Our meta-analyses of head-to-head trials found no statistically significant difference between the two medications for improvement in alcohol consumption outcomes (moderate SOE). Among medications used off label, moderate evidence supports the efficacy of nalmefene and topiramate for improving some consumption outcomes, and limited evidence supports the efficacy of valproic acid. We found insufficient direct evidence to conclude whether medications for AUDs are effective for improving health outcomes. Evidence from primary care settings was scant. Evidence was generally insufficient to determine comparative effectiveness of acamprosate and naltrexone for subgroups.

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Introduction

Background

Alcohol misuse, which includes the full spectrum from drinking above recommended limits (i.e., risky or hazardous drinking) to alcohol dependence,[1-3] is associated with numerous health and social problems, more than 85,000 deaths per year in the United States,[4,5] and an estimated annual cost to society of more than $220 billion.[6,7] Alcohol misuse is estimated to be the third leading cause of preventable mortality in the United States, following tobacco use and being overweight.[8] Definitions of the spectrum of alcohol misuse (i.e., unhealthy alcohol use[1]) continue to evolve. For the purposes of this report, we use the definitions described in Table 1.

Table 1. Definitions of the spectrum of alcohol misuse[a]

Term	Definition
Risky or hazardous use	Consumption of alcohol above recommended daily, weekly, or per-occasion amounts.[b] Consumption levels that increase the risk for health consequences.
Harmful use[9,10]	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).
Alcohol abuse[11] DSM-IV, 2000	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). (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[11] (alcoholism, alcohol addiction) DSM-IV, 2000	A. 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. (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. (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. (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).

Table 1. Definitions of the spectrum of alcohol misuse (continued)

Term	Definition
Alcohol use disorder[12] DSM-5, 2013 Levels of severity Mild: 2-3 Moderate: 4-5 Severe: ≥6	A. Alcohol is taken in larger amounts or over a longer period than intended. B. Persistent desire or unsuccessful efforts to cut down or control alcohol use. C. A great deal of time is spent in activities necessary to obtain alcohol, use alcohol, or recover from its effects. D Craving, or a strong desire or urge to use alcohol. E. Recurrent alcohol use resulting in a failure to fulfill major role obligations at work, school, or home. F. Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol. G. Important social, occupational, or recreational activities are given up or reduced because of alcohol use. H. Recurrent alcohol use in situations in which it is physically hazardous. I. 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. J. Tolerance, as defined by either of the following: (1) A need for markedly increased amounts of alcohol to achieve intoxication or desired effect. (2) A markedly diminished effect with continued use of the same amount of alcohol. K. Withdrawal, as manifested by either of the following: (1) The characteristic withdrawal syndrome for alcohol. L. Alcohol (or a closely related substance, such as a benzodiazepine) is taken to relieve or avoid withdrawal symptoms.

Note: DSM is the Diagnostic and Statistical Manual of Mental Disorders; III, IV, and 5 are editions of the DSM.

[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.[12]

[b] Maximum recommended consumption is 3 or fewer standard drinks per day (7 or fewer drinks per week) for women and those older than 65 years, and 4 or fewer drinks per day (14 or fewer drinks per week) for men.[13,14]

Alcohol-use disorders (AUDs) include harmful use, alcohol abuse, and alcohol dependence;[15,16] they are relatively common in developed countries.[15] Prevalence of AUDs is higher for men than for women, with estimates indicating a lifetime risk of more than 20 percent for men.[15,17-19] Alcohol dependence has lifetime prevalence rates of about 17 percent for men and 8 percent for women.[20]

Alcohol use disorders cause substantial morbidity and mortality—that is, threefold to fourfold increased rates of early mortality.[21-23] They are associated with hypertension, heart disease, stroke, cancer (e.g., mouth, throat, espophagus, colon, liver, and breast), liver cirrhosis, amnesias, cognitive impairment, sleep problems, peripheral neuropathy, gastritis and gastric ulcers, pancreatitis, decreased bone density, anemia, depression, insomnia, anxiety, suicide, and fetal alcohol syndrome.[15,24] In 2009, the number of alcoholic liver disease deaths was 15,183 and the number of alcohol-induced deaths, excluding accidents and homicides, was 24,518.[8] Excessive alcohol consumption is also a major factor in injury and violence.[25] Acute alcohol-related harm can be the result of fires, drowning, falls, homicide, suicide, motor vehicle crashes, child maltreatment, and pedestrian injuries.[26] In addition, AUDs can complicate the assessment and treatment of other medical and psychiatric problems.[15]

Alcohol use disorders often begin in the teens and 20s and fluctuate over time, with periods of abstinence (perhaps following a crisis), subsequent periods of sobriety followed by temporary controlled drinking, and then enhanced likelihood of increasing intake and problems.[15] Twenty to

30 percent of people with alcohol use disorders achieve long-term remission without any formal treatment.[15,27,28]

Some studies indicate that less than 10 percent of those with AUDs are able to achieve long periods of nonproblematic drinking.[29-33] Thus, the goal of treatment in the United States has traditionally been complete abstinence, because of the belief that it is unlikely that those with alcohol use disorders can return to controlled, healthy alcohol use. However, controlled drinking and harm reduction are often goals of treatment in parts of Europe.[15,32]

Treatments for Alcohol-Use Disorders

Treatments for AUDs continue to evolve as research on the effectiveness of various treatments is published, and new treatments, including pharmacotherapy, are introduced and used more frequently. No single best approach has yet proven superior among the variety of available treatment options. Some common treatments for AUDs include cognitive behavioral therapy, motivational enhancement therapy, 12-step programs (e.g., Alcoholics Anonymous), and pharmacotherapy. Treatment may be delivered via individual outpatient counseling, intensive outpatient programs using group or individual methods, alcoholism treatment centers, or other approaches. Most treatment is currently delivered in specialty settings rather than in primary care settings. Primary care providers are typically trained to refer patients with AUDs for specialized treatment, and primary care providers are generally unfamiliar with medications for treating AUDs.[34]

Using complete abstinence as an outcome, from 15 to 35 percent of patients have been reported to achieve 1 year of sobriety following a variety of treatment approaches.[35] Treatment approaches reviewed have included clinical trials of disulfiram, motivational enhancement therapy, cognitive behavioral therapy, and 12-step facilitation, as well as treatment as usual within alcoholism-treatment centers. Sobriety outcomes at 3 to 5 years or longer have been reported to be in a similar range.[15]

Over the past 15 to 20 years, awareness has grown that treatment may still be beneficial even if complete abstinence is not achieved. As a result, research has used other outcomes to measure the effectiveness of treatment, which can be subsumed under the concept of harm reduction.[36] These measures include significant increases in abstinent days or decreases in heavy drinking episodes, improved physical health, and improvements in psychosocial functioning. Research using these outcomes can provide additional evidence for the effectiveness of treatment for alcohol dependence.

Variation in response to the medications has been described,[37-39] some of which may be related to genetic polymorphisms. For example, some previous studies have reported associations between mu-opioid receptor gene (*OPRM1*) polymorphisms and clinical response to the opiate antagonist naltrexone.[40,41] In theory, it makes sense that *OPRM1* polymorphisms could alter the response to naltrexone because its mechanism of action is to competitively bind to opioid receptors and block the effects of endogenous opioids. Further, it has the highest affinity for the mu-opioid receptor. However, some studies of *OPRM1* polymorphisms did not find an association with response to naltrexone.[42,43]

Pharmacological Interventions for Alcohol-Use Disorders

From the 1950s until the early 1990s, the pharmacotherapy for alcohol dependence consisted only of disulfiram, an aversive deterrent that produces significant physical symptoms, such as nausea or tachycardia, when alcohol is consumed. Since the 1990s, two oral medications

(naltrexone and acamprosate) and one long-acting intramuscular formulation (of naltrexone) have been approved by the U.S. Food and Drug Administration (FDA) for alcohol dependence. These medications are recommended for people with alcohol dependence, generally after a successful withdrawal from alcohol, and together with psychological intervention.[16] Table 2 describes the medications available in the United States that are FDA approved for treatment of AUDs, their mechanism of action, and dosing. The medications are usually prescribed for 3 to 12 months, though much longer courses of treatment are not uncommon in clinical practice. In clinical trials, the FDA-approved medications have shown evidence for efficacy in enhancing abstinence, reducing relapse to heavy drinking, and reducing overall drinking behavior.[39] Many additional medications have been used off-label or studied for treatment of AUDs. These include antidepressants, mood stabilizers, anticonvulsants, alpha-adrenergic blockers, antipsychotics, and anxiolytics.

Table 2. Medications that are FDA approved for treating adults with alcohol-use disorders

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

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

Despite ongoing developments and advancements in treatment approaches, alcohol dependence represents one of the most undertreated disorders in the U.S. health care system; it is estimated that fewer than 1 in 3 individuals with AUDs receives treatment.[17] Furthermore, of those patients who receive treatment, data from the Veterans Health Administration show that less than 1 in 10 receives medication as part of his or her treatment.[44,45] Therefore, expanding awareness and access to this relatively new treatment modality has the potential to improve health outcomes and reduce the burden of this devastating illness that affects an estimated 8 million to 9 million U.S. citizens.

Existing Guidance

The Veterans Administration (VA), National Institute on Alcohol Abuse and Alcoholism (NIAAA), and Substance Abuse and Mental Health Services Administration (SAMHSA) all have guidelines, manuals, or protocols addressing the use of pharmacotherapy for alcohol dependence.[46-48] The VA guidelines recommend that oral naltrexone and/or acamprosate routinely be considered for patients with alcohol dependence (although acamprosate is currently a nonformulary medication for the VA), and that medications be offered in combination with addiction-focused counseling. The NIAAA *Medical Management Treatment Manual* provides direction for clinicians to provide medical management, combined behavioral intervention (CBI), and medical treatment with naltrexone or acamprosate as provided in the COMBINE trial.[47] The SAMHSA treatment improvement protocol provides basic information, guidelines, tools, and

resources to help health care practitioners treat patients with AUDs and includes chapters on acamprosate, disulfiram, oral naltrexone, and injectable naltrexone.

In 2011, the United Kingdom's National Institute for Clinical Excellence (NICE) released a set of clinical guidelines on the identification and treatment of people with alcohol dependence and harmful alcohol use.[16] The guidelines include the following recommendations: (1) after a successful withdrawal for people with moderate or severe alcohol dependence, to consider offering acamprosate or oral naltrexone (extended release naltrexone injection is not available in the United Kingdom) in combination with an individual psychological intervention (cognitive behavioral therapies, behavioral therapies, or social network and environment-based therapies) focused specifically on alcohol misuse; (2) to consider offering disulfiram in combination with a psychological intervention for people who have a goal of abstinence but for whom acamprosate and oral naltrexone are not suitable, or who prefer disulfiram and understand the relative risks of taking the drug; and (3) to have specialist and competent staff administer pharmacological interventions.

Scope and Key Questions

The use of medications for alcohol-use disorders is associated with uncertainty and variation across providers and settings. In recent years, many new trials of medications for alcohol-use disorders have been published. Since the 1999 Agency for Healthcare Research and Quality (AHRQ) report on medications for alcohol dependence,[49,50] there has been more than a 10-fold increase in the number of individuals studied in controlled clinical trials of naltrexone and acamprosate, and a series of well-conducted trials have been completed with other pharmacotherapeutic agents that are not FDA-approved for treating alcohol dependence. Other reasons for conducting a new review on this topic include the following: (1) to assess the comparative effectiveness of the FDA approved medications; (2) to determine whether any agents that are not FDA approved have evidence supporting their efficacy; (3) to evaluate the evidence on intramuscular naltrexone (Vivitrol®), a fairly recently approved medication; (4) to evaluate whether or not trials provide evidence of effectiveness in primary care settings; (5) to assess whether some medications are more or less effective for adults with specific genotypes; and (6) to provide a comprehensive review on medications for AUDs that is relevant for clinicians, researchers, and policymakers.

We approach each Key Question (KQ) by considering the relevant Populations, Interventions, Comparators, Outcomes, Timing, and Settings (PICOTS). Our report focuses on clinically relevant medications (those that are commonly used, those with sufficient literature for systematic review, and those of greatest interest to clinicians and to the developers of guidelines). Our report is limited to people with AUDs; it does *not* address people with risky or hazardous alcohol use (for whom medications are likely not an appropriate intervention).

The main objective of this report is to conduct a systematic review and meta-analysis of the comparative effectiveness and harms of medications for adults with alcohol-use disorders. In this review, we address the following KQs:

KQ 1a: Which medications are efficacious for improving consumption outcomes for adults with alcohol-use disorders in outpatient settings?

KQ 1b: How do medications for adults with alcohol-use disorders compare for improving consumption outcomes in outpatient settings?

KQ 2a: Which medications are efficacious for improving health outcomes for adults with alcohol-use disorders in outpatient settings?

KQ 2b: How do medications for adults with alcohol-use disorders compare for improving health outcomes in outpatient settings?

KQ 3a: What adverse effects are associated with medications for adults with alcohol-use disorders in outpatient settings?

KQ 3b: How do medications for adults with alcohol-use disorders compare for adverse effects in outpatient settings?

KQ 4: Are medications for treating adults with alcohol-use disorders effective in primary care settings?

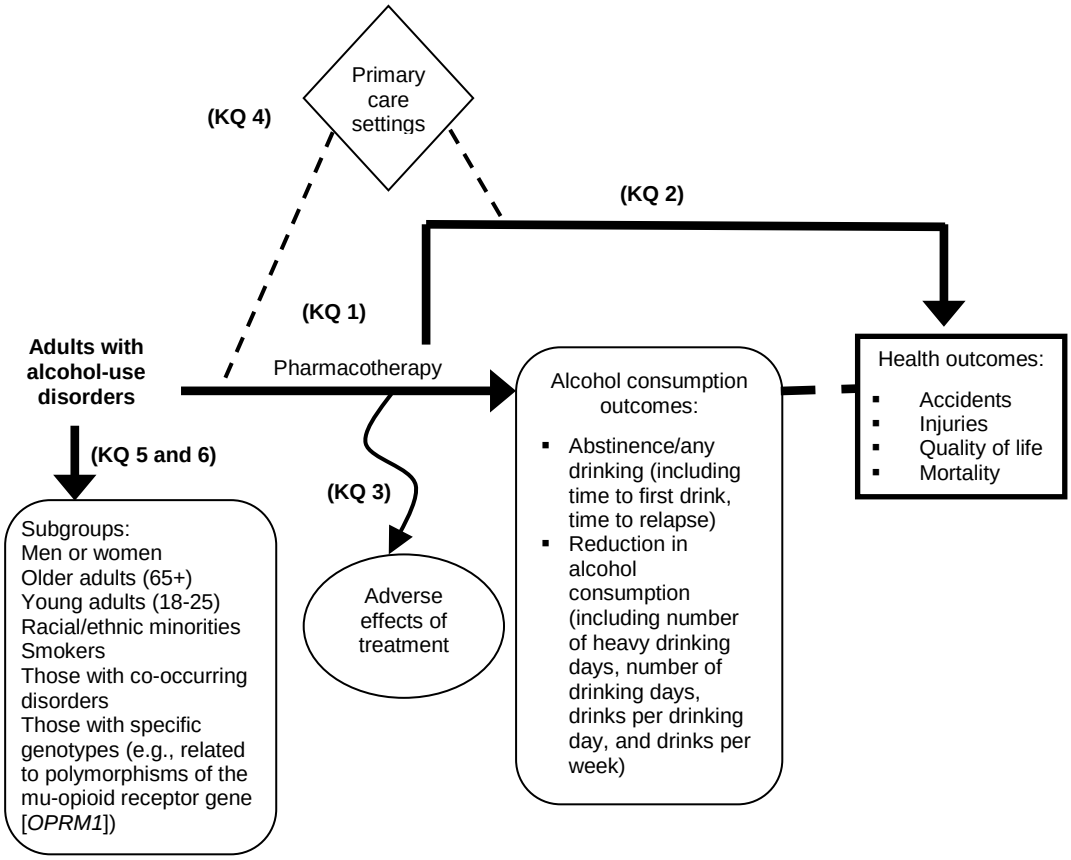
KQ 5: Are any of the medications more or less effective than other medications for men or women, older adults, young adults, racial or ethnic minorities, smokers, or those with co-occurring disorders?

KQ 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*])?

Analytic Framework

We developed an analytic framework to guide the systematic review process (Figure 1).

Figure 1. Analytic framework for pharmacotherapy for adults with alcohol-use disorders in outpatient settings



KQ 1 assesses which medications are efficacious and how they compare with one another for improving alcohol consumption outcomes. KQ 2 examines which medications are efficacious and how they compare with one another for improving health outcomes. KQ 3 examines harms. KQ 4 focuses on evidence for primary care settings. KQ 5 assesses whether the medications are more or less effective compared with each other for a variety of subgroups. KQ 6 assesses whether any of the medications are more or less effective for adults with specific genotypes than for adults with different genotypes.

Methods

The methods for this comparative effectiveness review (CER) follow the methods suggested in the Agency for Healthcare Research and Quality (AHRQ) "Methods Guide for Effectiveness and Comparative Effectiveness Reviews" (http://www.effectivehealthcare.ahrq.gov/methodsguide.cfm).

Topic Refinement and Review Protocol

This topic was nominated by a physician affiliated with the Substance Abuse and Mental Health Services Administration (SAMHSA), which works to improve the quality and availability of substance abuse prevention, alcohol and drug use disorder treatment, and mental health services. During the topic development and refinement processes, we engaged in a public process to develop a draft and final protocol for the CER process. We generated an analytic framework, preliminary Key Questions (KQs), and preliminary inclusion/exclusion criteria in the form of PICOTS (populations, interventions, comparators, outcomes, timing, settings). The processes were guided by the information provided by the topic nominator, a scan of the literature, methods and content experts, and Key Informants. We worked with six Key Informants during the topic refinement, all of whom subsequently served on the Technical Expert Panel (TEP) for this report. The TEP consisted of a distinguished group of eight scientists and clinicians, including individuals with expertise in addiction medicine, psychiatry, pharmacotherapy, regulatory and medical education, and policy. Key Informants and TEP members participated in conference calls and discussions through email to review the scope, analytic framework, KQs, and PICOTS; provided input on the information and categories included in evidence tables; and provided input on the data analysis plan. A list of the Key Informants and TEP members is included in the front matter of this report.

The KQs were posted for public comment on AHRQ's Effective Health Care Web site from September 20 to October 18, 2012; we put them into final form after review of the comments and discussion with the TEP. The only comments we received were attempts to provide answers to the questions rather than to provide input about the draft scope, KQs, PICOTS, or analytic framework. Therefore, no changes were made based on public review. We then drafted a protocol for this CER and refined the protocol in consultation with AHRQ and the TEP before it was posted on the Effective Health Care Web site on April 29, 2013.

Literature Search Strategy

Search Strategy

To identify articles relevant to each KQ, we searched PubMed®, the Cochrane Library, PsycINFO®, CINAHL®, and Embase®. The full search strategy is presented in Appendix A. We used either Medical Subject Headings (MeSH) or major headings as search terms when available or key words when appropriate, focusing on terms to describe the relevant populations and interventions of interest. We reviewed our search strategy with the TEP and incorporated their input. Searches were run by an experienced information scientist serving as the Evidence-based Practice Center (EPC) librarian and were peer-reviewed by another information scientist/EPC librarian.

We limited the electronic searches to English-language, adult (18 and older), and human-only studies. Sources were searched from January 1, 1970, to October 11, 2013. This search date was

selected based on the earliest publications found during the topic refinement process, the earliest study found in previous systematic reviews (which was from 1974), and expert opinion.

We manually searched reference lists of pertinent reviews, trials, and background articles on this topic to look for any relevant citations that our searches might have missed. We also reviewed references suggested by peer and public reviewers. We imported all citations into an EndNote® X4 (Thomson Reuters, New York, NY) electronic database.

We also searched for unpublished studies relevant to this review using ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform, and the Web site for the U.S. Food and Drug Administration (FDA). In addition, AHRQ's Scientific Resource Center requested scientific information packets from relevant pharmaceutical companies, asking for any unpublished studies or data relevant to this CER. Scientific information packets allow pharmaceutical companies to provide the EPC with published or unpublished data that they believe should be considered for the review. Any additional studies identified from the packets will be included in the post-peer/public review report.

In cases in which relevant information was unclear or not reported, we contacted authors to get additional or unpublished information. When successful, this information was included in the findings.

Inclusion and Exclusion Criteria

We developed eligibility (inclusion and exclusion) criteria with respect to PICOTS and study designs and durations for each KQ (Table 3).

Table 3. Eligibility criteria

Category	Inclusion	Exclusion
Population	Adults (age 18 years or older) with alcohol-use disorders (as defined in the Introduction). For KQ 5, co-occurring disorders include other mental health or substance use disorders (e.g., depression, cocaine use disorder) and acute or chronic medical conditions (e.g., cirrhosis).	Children and adolescents under 18
Interventions	Medications approved by FDA for treating alcohol dependence (acamprosate, disulfiram, naltrexone) and the following medications, which have been used off-label or are under investigation: amitriptyline, aripiprazole, atomoxetine, baclofen, buspirone, citalopram, desipramine, escitalopram, fluoxetine, fluvoxamine, gabapentin, imipramine, nalmefene, olanzapine, ondansetron, paroxetine, prazosin, quetiapine, sertraline, topiramate, valproate, varenicline, viloxazine.	Pharmacotherapy for alcohol withdrawal; any drugs not listed; combinations of medications (e.g., studies randomizing subjects to naltrexone plus ondansetron vs. placebo)
Comparators	For KQs 1 through 5, studies must compare one of the medications listed above with placebo or another medication. For KQ 6, studies must compare people who have a specific genotype or allele with people who have different genotypes or alleles.	No comparison; nonconcordant historical controls

Table 3. Eligibility criteria (continued)

Category	Inclusion	Exclusion
Outcomes	Consumption outcomes: return to any drinking, return to heavy drinking, drinking days, heavy drinking days[a], drinks per drinking day, time to lapse or relapse. Health outcomes: accidents, injuries[b], quality of life, function, mortality. Adverse effects of intervention(s): withdrawals due to adverse events, nausea/vomiting, diarrhea, anorexia, palpitations, headache, dizziness, cognitive dysfunction, taste abnormalities, paresthesias (numbness, tingling), metabolic acidosis, glaucoma, vision changes, suicidal ideation, insomnia, anxiety, rash.	Craving; cue reactivity
Timing/length of followup	At least 12 weeks of followup from the time of medication initiation.	Less than 12 weeks
Settings	Outpatient health care (i.e., nonlaboratory) settings, including studies that begin in or recruit subjects from inpatient settings but then follow and assess subjects receiving pharmacotherapy as outpatients. KQ 4 applies to primary care settings only (i.e., internal medicine, family medicine, pediatrics, obstetrics/gynecology, or college and university health clinics).	All other settings; laboratory settings; inpatient settings (if most or all of the study followed inpatients)
Publication language	English	All other languages
Admissible evidence (study design and other criteria)	Original research; eligible study designs include the following: • For KQs 1, 2, and 4, double-blind RCTs and recent systematic reviews were eligible. • For KQ 2b (head-to-head studies reporting health outcomes), prospective cohort studies were also eligible. • For KQ 3 (harms), double-blind RCTs and recent systematic reviews that compare medication with placebo or with another medication were eligible. The following designs were also eligible if they compared 2 or more drugs of interest: nonrandomized controlled trials, open-label trials, secondary analyses or subgroup analyses from trials, prospective cohort studies, and case-control studies. • For KQ 5 (subgroups), double-blind RCTs, recent systematic reviews, nonrandomized controlled trials, open-label trials, secondary analyses or subgroup analyses from trials, prospective cohort studies, and case-control studies were eligible, as long as the studies compared 2 or more drugs. • For KQ 6, double-blind RCTs, analyses of subjects from trials, and prospective cohort studies were eligible.	Case series Case reports Nonsystematic reviews Systematic reviews with searches that ended prior to 2007 Systematic reviews that had been updated Editorials Letters to the editor Studies with historical, rather than concurrent, control groups

FDA = U.S. Food and Drug Administration; KQ = Key Question; RCT = randomized controlled trial.

[a] Heavy drinking days were defined as 4 or more drinks per day for women and 5 or more drinks per day for men.

[b] Accidents typically refer to motor vehicle accidents. Injuries may be from a wide variety of alcohol-related problems (e.g., violence, falls). We did not use strict definitions for accidents and injuries. Knowing a priori that we would find very little evidence for these outcomes, we used definitions provided by studies and we included studies that did not provide definitions (but that only gave a number of injuries, for example).

Study Selection

Two trained members of the research team independently reviewed each title and abstract (identified through searches) against our eligibility criteria. Studies marked for possible inclusion by either reviewer underwent a full-text review. For titles or abstracts that lacked adequate information to determine eligibility, we retrieved and reviewed the full text. Two trained members of the research team independently reviewed each full-text article and determined eligibility based on the criteria described above. If the reviewers disagreed, they resolved conflicts by discussion and consensus or by consulting a third, senior member of the team. We recorded the principal reason that each excluded full-text publication did not satisfy the eligibility criteria (Appendix B). All results in both review stages were tracked in an EndNote® database.

Data Extraction

For studies that met our inclusion criteria, we extracted important information into evidence tables. We designed, pilot-tested, and used structured data extraction forms to gather pertinent information from each article; this included characteristics of study populations, settings, interventions, comparators, study designs, methods, and results. Trained reviewers extracted the relevant data from each included article. All data abstractions were reviewed for completeness and accuracy by a second member of the team. We recorded intention-to-treat (ITT) results if available. All data abstraction was performed using Microsoft Word® or Excel® software.

Risk-of-Bias Assessment of Individual Studies

To assess the risk of bias (internal validity) of studies for major outcomes of interest, we used predefined criteria based on guidance from the AHRQ "Methods Guide for Effectiveness and Comparative Effectiveness Reviews." We assessed selection bias, confounding, performance bias, detection bias, and attrition bias; we included questions about adequacy of randomization, allocation concealment, similarity of groups at baseline, blinding, attrition, whether ITT analysis was used, methods of handling missing data, and fidelity. We rated the studies as low, medium, high, or unclear risk of bias.[52]

In general terms, studies categorized as low risk of bias imply high confidence that the results represent the true treatment effects. Studies with medium risk of bias are susceptible to some risk of bias but probably not enough to invalidate the results. Studies with a medium risk of bias did not meet all criteria required for low risk of bias. These studies had some flaws in design or execution (e.g., inadequate description of methods of randomization and allocation concealment) but they provided enough information to allow readers to determine that the flaws did not likely cause major bias. Missing information often led to ratings of medium as opposed to low risk of bias. Studies assessed as high risk of bias have significant flaws stemming from serious errors in design, conduct, or analysis that may invalidate the results (e.g., high overall or differential attrition without appropriate handling of missing data).

For systematic reviews, we assessed the review questions, the literature search strategy, the eligibility criteria, whether dual review was used, whether the internal validity of included studies was assessed, whether publication bias was assessed, whether heterogeneity was assessed and addressed, the data synthesis approach, and whether conclusions were supported by the data presented.

Two independent reviewers assessed the risk of bias for each study; one of the two reviewers was always an experienced EPC investigator. Disagreements between the two reviewers were resolved by discussion and consensus or by a third member of the team. We omitted studies deemed high risk of bias by two reviewers from our main data synthesis and main analyses; we included them only in sensitivity analyses. Appendix C details the criteria used for evaluating the risk of bias of all included studies and explains the rationale for high risk of bias ratings.

Data Synthesis

We conducted quantitative synthesis using meta-analyses of outcomes reported by multiple studies that were sufficiently homogeneous to justify combining their results. To determine whether meta-analyses were appropriate, we assessed the clinical and methodological heterogeneity of the studies under consideration following established guidance.[53] We did this by qualitatively assessing the PICOTS of the included studies and looking for similarities and differences. When quantitative synthesis was not appropriate (e.g., because of clinical heterogeneity, insufficient numbers of similar studies, or insufficiency or variation in outcome reporting), we synthesized the data qualitatively.

We used random-effects models to estimate pooled effects.[54] For continuous outcomes (e.g., scales for symptom reduction), we used weighted mean differences (WMDs). For binary outcomes we calculated risk differences (RDs) between groups. We did not include studies rated as high or unclear risk of bias in our main analyses, but did include them in sensitivity analyses. For alcohol consumption outcomes, if studies reported consumption in grams, we used a conversion factor of 13.7 grams as equivalent to a standard drink.[55] All quantitative analyses were conducted using Stata® version 11.1 (StataCorp LP, College Station, TX).

We calculated the chi-squared statistic and the I^2 statistic to assess statistical heterogeneity in effects between studies.[56,57] An I^2 from 0 to 40 percent might not be important, 30 percent to 60 percent may represent moderate heterogeneity, 50 percent to 90 percent may represent substantial heterogeneity, and ≥75 percent represents considerable heterogeneity.[58] The importance of the observed value of I^2 depends on the magnitude and direction of effects and on the strength of evidence (SOE) for heterogeneity (e.g., p value from the chi-squared test, or a confidence interval for I^2). Whenever we include a meta-analysis with considerable statistical heterogeneity in this report, we attempt to provide an explanation for the heterogeneity, considering the magnitude and direction of effects.[58] We examined potential sources of heterogeneity by stratifying analyses by patient population or setting (i.e., U.S.-based trials compared with others; studies that enrolled a dual diagnosis population compared with those that did not), variation in interventions (i.e., dose and route of delivery), and duration of treatment.

For systematic reviews meeting our inclusion criteria, we describe their main findings qualitatively to allow a comparison of our findings with those of recent systematic reviews.

Strength of the Body of Evidence

We graded SOE based on the guidance established for the Evidence-based Practice Center program.[59] Developed to grade the overall strength of a body of evidence, this approach incorporates four key domains: risk of bias (includes study design and aggregate quality), consistency, directness, and precision of the evidence. It also considers optional domains, such as a dose-response association, plausible confounding that would decrease the observed effect, strength of association (magnitude of effect), and publication bias. Table 4 defines the grades of evidence that we assigned.

Table 4. Definitions of the grades of overall strength of evidence

Grade	Definition
High	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit estimation of an effect.

Source: Owens et al., 2010[59]

Two reviewers assessed each domain for each key outcome and determined an overall SOE grade based on domain ratings. We generally required consistent, direct, precise evidence from studies with aggregate low risk of bias to give high SOE grades. An unfavorable assessment for any one of the four key domains (i.e., inconsistency, indirectness, imprecision, or medium aggregate risk of bias) typically resulted in downgrading to moderate SOE. Two unfavorable assessments typically resulted in downgrading to low SOE. We allowed reviewers to include the optional domains listed above (e.g., dose-response association, publication bias) if relevant, and to upgrade or downgrade the SOE for those domains if appropriate. In the event of disagreements on the domain or overall grade, they resolved differences by consensus discussion or by consulting with a third, experienced EPC investigator.

We graded the SOE for the following outcomes: return to any drinking, return to heavy drinking, drinking days, heavy drinking days, drinks per drinking day, accidents, injuries, quality of life or function, mortality, and adverse events. Appendix D includes tables showing our assessments for each domain and the resulting SOE grades for each outcome, organized by KQ and intervention/comparison pair.

Applicability

We assessed applicability of the evidence following guidance from the "Methods Guide for Comparative Effectiveness Reviews."[60] We used the PICOTS framework to explore factors that affect applicability. Some factors identified a priori that may limit the applicability of evidence include the age, sex, and race or ethnicity of enrolled populations; smoking status of enrolled populations; co-occurring disorders of enrolled populations; setting; type of provider prescribing the treatment; and source of subject recruitment. Regarding the source of subject recruitment, studies of subjects recruited via advertisements may enroll people that have less severe disorders, and may be less applicable to patients with more severe forms of alcohol-use disorders.

Peer Review and Public Commentary

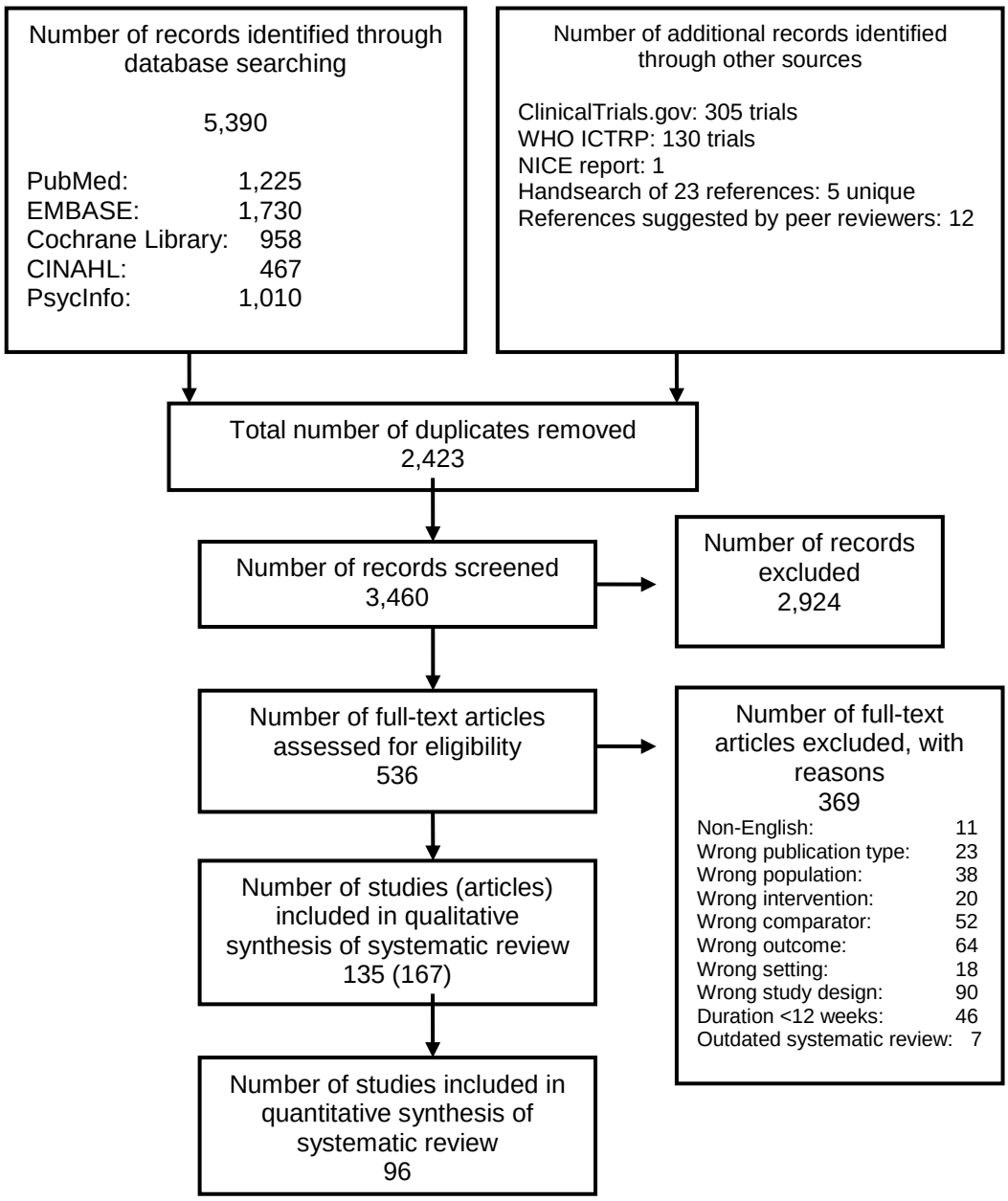
An external peer review was performed on this report. We compiled all comments and addressed each one individually, revising the text as appropriate. AHRQ also provided review from its own staff. In addition, AHRQ's Scientific Resource Center placed the draft report on the AHRQ Web site (www.effectivehealthcare.ahrq.gov/) for public review.

Results

Results of Literature Searches

Results of our searches appear in Figure 2. We included 167 published articles reporting on 135 studies. Of the included studies, 124 were randomized controlled trials, 5 were observational studies, and 6 were systematic reviews. Additional details describing the included studies are provided in the relevant sections of this results chapter.

Figure 2. Literature flow diagram



Key Question 1. Efficacy and Comparative Effectiveness for Improving Consumption Outcomes

For this Key Question (KQ), we describe the characteristics of included trials and then results for alcohol consumption outcomes (return to any drinking, return to heavy drinking, drinking days, heavy drinking days, drinks per drinking day) for medications for which we included multiple trials. For medications with just 1 eligible trial, we graded the strength of evidence (SOE) as insufficient (because evidence was imprecise, unknown consistency, and medium or high risk of bias); information on the characteristics and results for medications with just 1 eligible trial is provided in Appendix E.

Throughout this KQ, we include headers and sections only for consumption outcomes with sufficient data for synthesis. Negative effect sizes favor medication over placebo. Positive effect sizes favor placebo. Studies typically included psychosocial co-interventions; thus, effect sizes reflect the added benefits of medications beyond those of psychosocial interventions. We describe the results of sensitivity analyses that included studies rated as high or unclear risk of bias only if they changed the effect size significantly. Results of all such sensitivity analyses are provided in Appendix F.

Detailed Synthesis: Placebo-Controlled Trials of FDA-Approved Medications for Treating Alcohol Dependence

Acamprosate

Characteristics of Trials

Table 5 summarizes characteristics of the 22 trials meeting our inclusion criteria. The majority were parallel two-arm trials comparing acamprosate with placebo. Doses ranged from 1,000 to 3,000 mg per day; 1,998 mg per day (divided into 3 doses) was the most frequently used dose. Duration of treatment ranged from 12 to 52 weeks; most (18 trials) treated subjects for 12 to 26 weeks; 4 trials treated subjects for longer periods, 48 to 52 weeks. Followup to 1 year or longer was available for 8 trials.

The majority were conducted in Europe (16 trials); 4 were conducted in the United States, 1 in Brazil, and 1 in Australia. Recruitment methods varied, with trials typically identifying patients through treatment programs (e.g., inpatient detoxification, outpatient treatment), advertisements, referrals, or some combination of those.

Mean age was very similar across trials, usually in the early to mid-40s. All subjects met criteria for alcohol dependence in 21 trials; 1 trial did not report the proportion with alcohol dependence, but most subjects likely had alcohol dependence.[61] Most studies did not report information on race; 1 trial reported enrolling a majority (65 percent) of nonwhite subjects.[62] Most trials enrolled between 11 and 36 percent females; 1 trial enrolled all males,[63] and 1 did not report information on sex.[64] Just 4 trials reported information on smoking history at baseline; those trials had 46 to 81 percent smokers enrolled.[61,65-67]

The majority of trials either did not report information about how many subjects had co-occurring psychiatric conditions or excluded subjects with other psychiatric disorders; 1 trial enrolled subjects with alcohol dependence and schizophrenia spectrum disorders.[62] Trials often included or encouraged psychological or psychosocial co-interventions.

Table 5. Characteristics of included double-blind randomized placebo-controlled trials of acamprosate

Author, Year Trial Name	Arm Dose, mg/Day (N)	Rx Duration, Weeks (Followup)	Country	Setting	Recruitment Method	Age, Years	% Non-White	% Female	% With Co-occurring Condition	Cointervention	Risk of Bias
Anton, 2006[65] Donovan, 2008[68] 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)[a]	16 (68)	U.S.	11 U.S. academic sites	Ads, community resources, clinical referrals at 11 academic sites	44	23	31	NR	As randomized; Community support group participation (like AA) encouraged	Low
Baltieri, 2004[63]	ACA 1,998 (40) Placebo (35)	12 (24)	Brazil	Outpatient	Patients seeking treatment at an outpatient clinic for treatment of drug dependence	18-60	NR	0	0	AA encouraged	Medium
Berger, 2013[69]	ACA 1,998 (51) Placebo (49)	12	U.S.	2 outpatient primary care clinics	Provider referral and ads	48	9	38	NR	Brief structured behavioral intervention from primary care physician	Medium
Besson, 1998[70]	ACA 1,300 to 1,998 (55) Placebo (55)	52 (108)	Switzerland	Outpatient; 3 psychiatric treatment centers	From inpatient treatment unit	42	NR	20	0	Routine counseling 100% Voluntary disulfiram 22-24%	Medium
Chick, 2000[71]	ACA 1,998 (289) Placebo (292)	24	U.K.	Outpatient	Recruited from treatment programs	43	NR	16	0	Usual psychosocial outpatient treatment program	Medium
Geerlings, 1997[72]	ACA 1,332 to 1,998 (128) Placebo (134)	26 (52)	Belgium, the Netherlands, and Luxembourg	Outpatient substance abuse treatment centers	Recruited from detoxification patients in same centers	40-42	NR	24	NR	ACA: benzodiazepines 5% Placebo: benzodiazepines 6%	Medium

Table 5. Characteristics of included double-blind randomized placebo-controlled trials of acamprosate (continued)

Author, Year Trial Name	Arm Dose, mg/Day (N)	Rx Duration, Weeks (Followup)	Country	Setting	Recruitment Method	Age, Years	% Non-White	% Female	% With Co-occurring Condition	Cointervention	Risk of Bias
Gual, 2001[73]	ACA 1,998 (148) Placebo (148)	26	Spain	Outpatient; multicenter; hospitals	NR	41	NR	20 to 21	NR	NR	Medium
Kiefer, 2003[74] Kiefer, 2004[75] Kiefer, 2005[76]	ACA 1,998 (40) NTX 50 (40) Placebo (40) ACA 1,998 + NTX 50 (40)	12	Germany	1 site, Hamburg outpatient	Inpatient withdrawal treatment	46	NR	26	0	Group therapy	Low
Lhuintre, 1985[77]	ACA 1,000 to 2,250 (42) Placebo (43)	13	France	Outpatient; methadone maintenance clinics	Recruited as inpatients within 48 hours of admission	40 to 43	NR	11	NR	Meprobamate 100% for first month	High
Lhuintre, 1990[78]	ACA 1,332 (279) Placebo (290)	12	France	Outpatient; multicenter	Recruited within 48 hours of hospitalization for alcohol withdrawal	42 to 43	NR	18	NR	Psychotherapy allowed	Unclear
Mann, 2012[79] 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	NR	23	NR	Medical management	Medium
Mason, 2006[66]	ACA 2,000 (258) ACA 3,000 (83) Placebo (260)	24 (32)	U.S.	21 outpatient clinics[b]	Primarily by newspaper ads	44 to 45	14 to 15	29 to 36	NR	Brief abstinence-oriented protocol-specific counseling and self-help materials 100%	Low

Table 5. Characteristics of included double-blind randomized placebo-controlled trials of acamprosate (continued)

Author, Year Trial Name	Arm Dose, mg/Day (N)	Rx Dura-tion, Weeks (Fol-lowup)	Country	Setting	Recruitment Method	Age, Years	% Non-White	% Fe-male	% With Co-occurring Condition	Cointervention	Risk of Bias
Morley, 2006[61] Morley, 2010[80]	ACA 1,998 (55) NTX 50 (53) Placebo (61)	12	Australia	3 treatment centers with "medical care typically available at hospital based drug and alcohol treatment services"	Patients who had attended an inpatient detoxification program, outpatient treatment or followup or who responded to live or print ads	45	NR	30	Severe concurrent illness (psychiatric or other) –NOS 3	All offered 4-6 sessions of manualized compliance therapy Up-take / attendance NR	Low
Paille, 1995[81]	ACA 1.3 g (188) ACA 2 g (173) Placebo (177)	52 (78)	France	NR[c]	Referral from alcohol specialist centers	43	NR	20	NR	Supportive psychotherapy 100% Hypnotics 6 to 7% Anxiolytics 8 to 12% Antidepressants 8 to 9%	Medium
Pelc, 1996[82]; Pelc, 1992[83]	ACA 1,332 to 1,998 (55) Placebo (47)	26	Belgium	Outpatient; multicenter	Post-inpatient detoxification	43	NR	31	NR	Supportive psychotherapy 100%	High
Pelc, 1997[64]	ACA 1,332 (63) ACA 1,998 (63) Placebo (62)	13	Belgium, France	Outpatient; after inpatient detoxification	Inpatient referral	NR	NR	NR	NR	Counseling, social support when needed 100%	Medium
Poldrugo, 1997[84]	ACA 1,332 to 1,998 (122) Placebo (124)	26 (52)	Italy	Inpatient for 1-2 weeks then outpatient; multicenter community based alcohol rehabilitation program	From acute inpatient withdrawal treatment	43 to 45	NR	23 to 31	0	Community-based rehabilitation program with group sessions, alcohol education, community meetings 100%	Medium

Table 5. Characteristics of included double-blind randomized placebo-controlled trials of acamprosate (continued)

Author, Year Trial Name	Arm Dose, mg/Day (N)	Rx Dura-tion, Weeks (Fol-lowup)	Country	Setting	Recruitment Method	Age, Years	% Non-White	% Fe-male	% With Co-occurring Condition	Cointervention	Risk of Bias
Ralevski, 2011[62]; Ralevski, 2011[85]	ACA 1,998 (12) Placebo (11)	12	U.S.	Outpatient; university and VA health centers	From community and through referrals from treatment facilities at a university and a VA facility	51	65	17	Schizophrenia spectrum disorders 100	Weekly skills training that incorporated CB drug relapse prevention strategies 100%	High
Sass, 1996[86]	ACA 1,332 to 1,998 (136) Placebo (136)	48 (96)	Germany	Psychiatric outpatient	Outpatient referral	41 to 42	NR	22	NR	Counseling / psychotherapy 100%	Medium
Tempesta, 2000[87]	ACA 1,998 (164) Placebo (166)	26 (39)	Italy	Outpatient	Recruited from outpatient internal medicine, neurology and addiction treatment programs	46	NR	17	0	Medical and behavioral counseling	Medium
Whitworth, 1996[88]	ACA 1,332 or 1,998 (224) Placebo (224)	52 (104)	Austria	Outpatient specialty	Inpatient recruitment	42	NR	21	NR	NR	Medium
Wolwer, 2011[89]	ACA 1,998 + IBT (124) ACA 1,998 + TAU (122)[d] Placebo + IBT (125)	24 (52)	Germany	Outpatient; 4 university hospitals 1 non-academic clinic	Recruited after inpatient detoxification	46	NR	29	NR	NR	Medium

AA = Alcoholics Anonymous; ACA = acamprosate; CB = cognitive behavioral; CBI = combined behavioral intervention; COMBINE = Combined Pharmacotherapies and Behavioral Intervention; IBT = integrative behavior therapy; mg = milligram; MM = medical management; N = number; NOS = not otherwise specified; NR = not reported; NTX = naltrexone; TAU = treatment as usual; U.K. = United Kingdom; U.S. = United States; VA = Veterans Affairs

Note: Age, Years is the mean age in years, unless otherwise stated.

[a] 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).

[b] Clinics were affiliated with academic medical centers and had investigators experienced in alcoholism treatment.

[c] The article was not explicit about the setting, but patients received psychotherapy and psychiatric medication management suggesting a psychiatric outpatient setting.

[d] Treatment as usual, seen once per week in an individual setting; MI techniques allowed.

Return to Any Drinking

Nineteen of the 22 trials reported sufficient data for meta-analysis. All but 1 study[66] had point estimates trending in favor of acamprosate. Our meta-analysis of low and medium risk of bias trials found that 9 percent fewer subjects treated with acamprosate returned to any drinking than with placebo (risk difference [RD], -0.09; 95% CI, -0.14 to -0.04). Statistical heterogeneity was considerable (I^2 80.8 percent).

Differences in country and duration of treatment seem to explain much of the heterogeneity. The only 3 U.S.-based trials contributing data found no difference between acamprosate and placebo.[65,66,69] Stratifying our meta-analysis by U.S. and non-U.S. studies found no difference for the 3 U.S.-based trials (RD, 0.03; 95% CI, -0.03 to 0.09), but found 12 percent fewer subjects treated with acamprosate returned to any drinking than with placebo for trials conducted in other countries (RD, -0.12; 95% CI, -0.16 to -0.08), and statistical heterogeneity decreased to the moderate range. Stratifying by duration of treatment (which corresponds to timing of outcome assessment used in analyses) found low heterogeneity among studies treating patients for 48 to 52 weeks, with an 11 percent absolute reduction in return to any drinking (RD, -0.11; 95% CI, -0.16 to -0.06; 4 trials).

Return to Heavy Drinking

Our meta-analysis found no significant difference between acamprosate and placebo (RD, -0.01; 95% CI, -0.04 to 0.03; I^2 0 percent; 7 trials).

Drinking Days

Patients treated with acamprosate had 8.8 percent fewer drinking days than those treated with placebo (weighted mean difference [WMD], -8.8; 95% CI, -12.8 to -4.8; 13 trials).

Three U.S.-based trials contributed data.[65,66,69] Stratifying our meta-analysis by U.S. and non-U.S. studies found no difference for the 3 U.S.-based trials (WMD, -2.1; 95% CI, -6.4 to 2.1), but found that patients treated with acamprosate had 11.2 percent fewer drinking days than those treated with placebo for trials conducted in other countries (WMD, -11.2; 95% CI, -15.8 to -6.6). Stratifying by duration of treatment (which corresponds to timing of outcome assessment used in our analyses) found that patients treated with acamprosate had 12.2 percent fewer drinking days than those treated with placebo over 48 to 52 weeks (WMD, -12.2; 95% CI, -16.4 to -8.0; I^2 0 percent).

Heavy Drinking Days

Only 1 trial rated as low or medium risk of bias[69] reported data for heavy drinking days. The trial found no significant difference between acamprosate and placebo (WMD, -2.6; 95% CI, -11.4 to 6.2)

Drinks per Drinking Day

Just 1 trial rated as low or medium risk of bias reported data. It found no statistically significant difference between acamprosate and placebo (WMD, 0.4; 95% CI, -1.8 to 2.6).[61]

Disulfiram

Characteristics of Trials

Table 6 summarizes characteristics of the four trials meeting our inclusion criteria. All four were conducted in Veterans Administration Medical Centers. Three compared disulfiram with placebo or riboflavin (which was intended as placebo); one compared disulfiram with naltrexone, placebo, and the combination of naltrexone and disulfiram.[90] Doses for the intended active disulfiram arms were the same (250 mg per day) in all four trials. Two of the four trials were rated as high risk of bias, either primarily for high risk of attrition bias and inadequate handling of missing data,[91] or primarily for high risk of ascertainment bias[90]; see Appendix C for details.

Duration of treatment ranged from 12 to 52 weeks. Three of the four trials followed subjects for 9 to 12 months. All four were conducted in the United States. Mean age was very similar across trials, ranging from 39 to 47 years. All subjects likely met criteria for alcohol dependence. Very few female subjects were enrolled (0 to 3 percent in the 3 trials reporting). None of the trials reported information on smoking history at baseline. One trial enrolled subjects with alcoholism who were also in methadone maintenance programs.[91] Another enrolled subjects with co-occurring psychiatric disorders.[90] Neither of the trials rated as medium risk of bias reported information on how many subjects had co-occurring psychiatric conditions.

Return to Any Drinking

Three of the four trials reported data. Our meta-analysis found no statistically significant difference between disulfiram 250 mg per day and disulfiram 1 mg per day or placebo, both without (RD, 0.04; 95% CI, -0.03 to 0.11) and with inclusion of the studies rated as high risk of bias (RD, -0.00; 95% CI, -0.10 to 0.09). Both medium risk of bias studies found point estimates favoring placebo/disulfiram 1 mg, but differences between groups were not statistically significant.

Our meta-analysis found no statistically significant difference between disulfiram 250 mg per day and riboflavin (i.e., no disulfiram) (RD, -0.04; 95% CI, -0.11 to 0.03). Both medium risk of bias studies found point estimates favoring disulfiram 250 mg per day, but differences between groups were not statistically significant.

The largest trial (N=605)[92] reported a significant relationship between adherence and complete abstinence in all groups (disulfiram 250 mg, disulfiram 1 mg, and no disulfiram/riboflavin). The other trial assessed as medium risk of bias similarly reported that complete abstinence correlated significantly with adherence.[93]

Drinking Days

Both medium risk of bias trials reported some information about the percentage of drinking days. The smaller trial (N=128) reported no statistically significant differences among the three groups in percentage of drinking days (31 percent versus 32 percent versus 37 percent, for disulfiram 500/250, disulfiram 1, and riboflavin, respectively, p NR). The larger trial (N=605) reported this outcome only for the subset of subjects who drank and had a complete set of assessment interviews (N=162). It found that patients among this subset treated with disulfiram reported fewer drinking days than those given disulfiram 1 mg or those given riboflavin (49 percent versus 75.4 percent versus 86.5 percent, respectively, p=0.05).

Table 6. Characteristics of included double-blind randomized placebo-controlled trials of disulfiram

Author, Year Trial Name	Arm Dose, mg/Day (N)	Rx Dura-tion, Weeks	Country	Setting	Recruitment Method	Age, Years	% Non-White	% Female	% With Additional Condition	Co-intervention	Risk of Bias
Fuller, 1979[93]	DIS 250 (43) DIS 1 (43) RIB 50 (42)	52	U.S.	Outpatient; VA hospital	Patients presenting to VA hospital requesting treatment for alcoholism or patients admitted for alcohol-related illness	43	61	0	NR	Counseling (unspecified) 100%	Medium
Fuller, 1986[92]	DIS 250 (202) DIS 1 (204) RIB 50 (199)	52	U.S.	Outpatient; 9 VAMCs	Screened as inpatients in 7 centers and outpatients at 2	41 to 42	47	0	NR	Counseling (loosely defined) % NR	Medium
Ling, 1983[91]	DIS 250 (41) Placebo (41)	37	U.S.	Outpatient; VA	Unclear	39	NR	NR	Heroin use 80 Marijuana use 36 Other drug use 67 Depression 83 Moderate to high depression 50	Methadone 100%	High
Petrakis, 2005[90] Ralevski, 2007[94] Petrakis, 2007[95] Petrakis, 2006[96] VA MIRECC	DIS 250 (66) NTX 50 (59) Placebo (64) NTX 50 + DIS 250 (65)	12	U.S.	Outpatient; VA	Recruited as outpatients or ad	47	26	3	Axis I disorder 100	Psychiatric treatment as usual 100%	High for DIS vs. placebo

DIS = disulfiram; mg = milligram; MIRECC = Mental Illness Research, Education and Clinical Center; N = number; NR = not reported; NTX = naltrexone; RIB = riboflavin; U.S. = United States; VA = Veterans Affairs; VAMC = Veterans Administration Medical Center.

Note: Age, Years is the mean age in years, unless otherwise stated.

Naltrexone

Characteristics of Trials

Table 7 summarizes characteristics of the 44 trials meeting our inclusion criteria. Less than half were parallel two-arm trials comparing naltrexone with placebo; most had three or more study arms. Four trials evaluated long-acting, injectable naltrexone, at doses from 150 to 400 mg per month.[97-100] The rest administered oral naltrexone—32 trials used a dose of 50 mg per day, 6 used 100 mg per day,[65,101-105] 1 used 150 mg per day,[106] and 1 used 100 mg on Mondays and Wednesdays and 150 mg on Fridays (weekly average of 50 mg per day).[107] Duration of treatment ranged from 12 to 52 weeks; most (38 trials) treated subjects for 12 to 17 weeks; 6 trials included treatment with naltrexone for longer periods—24 to 52 weeks.[97,103,108-111] Two of the latter groups included comparisons of different treatment durations for 50 mg per day, either comparing 12 versus 24 weeks[111] or comparing 12 versus 52 weeks.[110]

The majority were conducted in the United States only (27 trials); 8 were conducted in Europe, 3 in Australia, 2 in Brazil, 1 multinational (United States, France, and the Netherlands), and 1 each in Singapore, Iran, and Taiwan. Recruitment methods varied, with trials typically identifying patients through treatment programs (e.g., inpatient detoxification, outpatient treatment), advertisements, referrals, or some combination of those.

Mean age was very similar across trials, usually in the 40s (34 trials) or 30s (6 trials); 3 trials did not report mean age, and 1 trial enrolled older subjects (mean age 58).[107] All subjects met criteria for alcohol dependence in the vast majority of trials. Nine trials enrolled a majority of nonwhite subjects (60 to 100 percent).[42,105-107,112-116] Most trials enrolled a third or fewer females; 1 trial enrolled all women.[117] Just 9 trials reported information on smoking history at baseline, with most of those reporting a majority of smokers (55 to 77 percent) enrolled in those trials[42,61,65,110,118-120] and 2 reporting a minority (17 and 47 percent).[97,104]

Eight trials reported enrolling all or a majority of subjects with co-occurring psychiatric disorders, including bipolar disorder,[120] schizophrenia or schizoaffective disorder,[121] cocaine use disorders,[105,106,114] depression,[104] another Axis I disorder,[90] or any comorbid psychiatric disorder.[122] Trials generally included or encouraged psychological or psychosocial co-interventions.

Table 7. Characteristics of included double-blind randomized placebo-controlled trials of naltrexone

Author, Year Trial Name	Arm Dose, mg/Day (N)	Rx Duration, Weeks (Followup)	Country	Setting	Recruitment Method	Age, Years	% Non-White	% Female	% With Additional Condition	Cointervention	Risk of Bias
Ahmadi, 2002[123]; Ahmadi, 2004[124]	NTX 50 (58) Placebo (58)	12	Iran	Outpatient treatment	Self-referral	43	NR	0	NR	Individual counseling 100%	Unclear
Anton, 1999[125]; Anton, 2001[126]	NTX 50 (68) Placebo (63)	12	U.S.	Outpatient academic research center	Ads, referrals for treatment-seekers	41 to 44	11 to 18	27 to 31	0	CBT 100%	Medium
Anton, 2005[127]	NTX 50 + CBT (39) NTX 50 + MET (41) Placebo + CBT (41) Placebo + MET (39)	12	U.S.	Outpatient	Ads, referred to clinical service	43 to 45	8 to 23	21 to 27	NR	CBT and MET as randomized	Medium
Anton, 2006[65] Donovan, 2008[68] COMBINE	ACA[a] 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)	16 (68)	U.S.	11 U.S. academic sites	Ads, community resources, clinical referrals at 11 academic sites	44	23	31	NR	As randomized; community support group participation (like AA) encouraged	Low
Anton, 2011[118]	NTX 50 (50) Placebo (50) NTX 50 + 6 weeks gabapentin, with 1,200 maximum dose (50)	16	U.S.	Outpatient	NR	43 to 47	13	18	NR	Used COMBINE's manual (CBT + MM + 12-step techniques) 100%	Medium

Table 7. Characteristics of included double-blind randomized placebo-controlled trials of naltrexone (continued)

Author, Year Trial Name	Arm Dose, mg/Day (N)	Rx Dura-tion, Weeks (Fol-lowup)	Country	Setting	Recruitment Method	Age, Years	% Non-White	% Fe-male	% With Additional Condition	Cointervention	Risk of Bias
Balldin, 2003[108]	NTX 50 + CBT (25) NTX 50 +ST (31) Placebo + CBT (30) Placebo + ST (32)	26	Sweden	10 sites outpatient	Newspaper, outpatient treatment	48 to 51	NR	9 to 23	0	None	Low
Baltieri, 2008[119]; Baltieri, 2009[128]	TOP target 200, maximum 400 (52) NTX 50 (49) Placebo (54)	12	Brazil	Outpatient	NR	44 to 45	29	0	NR	Psychosocial 100%	High
Brown, 2009[120]	NTX 50 (20) Placebo (23)	12	U.S.	Outpatient; university health center	Newspaper ads, physician referral, flyers and brochures at clinics	41	26	49	Bipolar (current depressed or mixed mood) 100 Cannabis abuse 21 Cocaine abuse 12 Amphetamine abuse 7	CBT 100%	High
Chick, 2000[129]	NTX 50 (90) Placebo (85)	12	U.K.	Outpatient	From patients starting outpatient alcohol rehabilitation program	43	NR	25	0	"Usual psychosocial treatment program"	Med-ium
Fogaca, 2011[130]	NTX 50 (20) Placebo (20) NTX 50 + PUFA (20) PUFA (20)	12	Brazil	Outpatient	Newspaper and radio ads	NR	NR	0	NR	None	High
Garbutt, 2005[97]; Pettinati, 2009[131]; Lucey, 2008[132]	NTX inj 380 every 4 weeks (208) NTX inj 190 every 4 weeks (210) Placebo (209)	26	U.S.	Inpatient and outpatient, private and VA	NR	45	17	32	NR	BRENDA[b] standardized ST 100%	Med-ium

Table 7. Characteristics of included double-blind randomized placebo-controlled trials of naltrexone (continued)

Author, Year Trial Name	Arm Dose, mg/Day (N)	Rx Duration, Weeks (Followup)	Country	Setting	Recruitment Method	Age, Years	% Non-White	% Female	% With Additional Condition	Cointervention	Risk of Bias
Gastpar, 2002[133]	NTX 50 (84) Placebo (87)	12	Germany	7 centers; outpatient	Outpatient and inpatient recruitment	43	0	28	0	Psychosocial treatment	Medium
Guardia, 2002[134]	NTX 50 (101) Placebo (101)	12	Spain	7 centers, outpatient	Recruited treatment-seeking patients	NR	NR	25	NR	Psychosocial	Medium
Heinala, 2001[109]	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	Finland	Outpatient	Ads	46	NR	29	0	None	High
Huang, 2005[112]	NTX 50 (20) Placebo (20)	14	Taiwan	Alcoholism treatment unit of an inpatient psychiatric hospital; 1 week inpatient, remainder outpatient	Recruited as inpatients after admission for detoxification	38 to 43	100	0	NR	Weekly individual psychotherapy sessions 100%	High
Johnson, 2004[98]	NTX inj 400 every 28 days (25) Placebo inj (5)	17	U.S., France, the Netherlands	4 centers; outpatient	NR	43	37	27	NR	Psychosocial support 100%	High
Kiefer, 2003[74] Kiefer, 2004[75] Kiefer, 2005[76]	ACA 1,998 (40) NTX 50 (40) Placebo (40) ACA 1,998 + NTX 50 (40)	12	Germany	1 site; outpatient	Inpatient withdrawal treatment	46	NR	26	0	Group therapy	Low
Killeen, 2004[122]	NTX 50 + TAU (54) Placebo + TAU(43) TAU alone (48)	12	U.S.	Outpatient community substance abuse treatment center	Clinic treatment seekers	37	24	37	Comorbid psychiatric disorder 51 Additional substance use disorder 35	Several types and intensities	Medium

Table 7. Characteristics of included double-blind randomized placebo-controlled trials of naltrexone (continued)

Author, Year Trial Name	Arm Dose, mg/Day (N)	Rx Dura-tion, Weeks (Fol-lowup)	Country	Setting	Recruitment Method	Age, Years	% Non-White	% Fe-male	% With Additional Condition	Cointervention	Risk of Bias
Kranzler, 2004[99]	NTX inj once a month 150 (185) Placebo inj (157)	12	U.S.	Outpatient	Ads, recruited as outpatients	44	17 to 18	33 to 37	NR	MET 100%	Med-ium
Kranzler, 2009[135]	NTX 50 targeted (38) NTX 50 once daily (45) Placebo targeted (39) Placebo once daily (41)	12	U.S.	Outpatient	Media ads, local provider referral	49	3	42	Drug use disorder <1 Social phobia 3 Antisocial personality disorder 3 Dysthymic disorder <1 Agoraphobia without panic disorder <1 OCD <1 GAD <1	Brief coping skills training 100%	Med-ium
Krystal, 2001[110] VACS 425	NTX 50 for 12 months (209) NTX 50 for 3 months then placebo (209) Placebo (209)	12 or 52	U.S.	Multicenter, outpatient	VA clinics	49	37	3	0	12-step facilitation	Med-ium
Latt, 2002[136]	NTX 50 (56) Placebo (51)	12 (26)	Australia	4 hospitals ; outpatient	NR	45	NR	30	0	No extensive psychosocial interventions	Med-ium
Lee, 2001[113]	NTX 50 (35) Placebo (18)	12	Singapore	Mixed: initially inpatient, discharged after 1 month from substance abuse treatment center	Direct recruitment from inpatient facility	45	≥88	0	NR	Intensive inpatient rehabilitation program; postdischarge therapy encouraged 100%	High

Table 7. Characteristics of included double-blind randomized placebo-controlled trials of naltrexone (continued)

Author, Year Trial Name	Arm Dose, mg/Day (N)	Rx Duration, Weeks (Followup)	Country	Setting	Recruitment Method	Age, Years	% Non-White	% Female	% With Additional Condition	Cointervention	Risk of Bias
Longabaugh, 2009[111]	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 (38)[c]	12-24 (72)	U.S.	Outpatient	Newspaper ads	44 to 46	6 to 14	33 to 43	NR	None[d]	Medium
Mann, 2012[79] 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	NR	23	NR	Medical Management	Medium
Monterosso, 2001[101]	NTX 100 (121) Placebo (62)	12	U.S.	Outpatient	Ads	46	27	27	NR	BRENDA[b]	Medium
Monti, 2001[137]; Rohsenow, 2007[138]; Rohsenow, 2000[139]	NTX 50 (64) Placebo (64)	12 (52)	U.S.	2 weeks partial hospital (pre-medication); 52 weeks outpatient	Recruited from partial hospital program in an urban private psychiatric hospital	39	3	24	Cocaine use 23 Sedative use 8 Opiate use 4	Brief physician outpatient contacts (intensive therapy occurred prior to medication portion of trial)	Medium
Morgenstern, 2012[102]	NTX 100 + MBSCT (51) NTX 100 (51) Placebo + MBSCT (50) Placebo (48)	12	U.S.	NR	Ads, community outreach	40	26	0	HIV 15 Any drug use 67	BBCET 100%	Medium

Table 7. Characteristics of included double-blind randomized placebo-controlled trials of naltrexone (continued)

Author, Year Trial Name	Arm Dose, mg/Day (N)	Rx Duration, Weeks (Followup)	Country	Setting	Recruitment Method	Age, Years	% Non-White	% Female	% With Additional Condition	Cointervention	Risk of Bias
Morley, 2006[61] Morley, 2010[80]	ACA 1,998 (55) NTX 50 (53) Placebo (61)	12	Australia	3 treatment centers with "medical care typically available at hospital based drug and alcohol treatment services"	Patients who had attended an inpatient detoxification program, outpatient treatment, or followup or who responded to live or print ads	45	NR	30	Severe concurrent illness (psychiatric or other) –NOS 3	All offered 4 to 6 sessions of manualized compliance therapy Up-take / attendance NR	Low
Morris, 2001[140]	NTX 50 (55) Placebo (56)	12	Australia	Outpatient	Outpatient, self-referral	47	NR	0	PTSD 23 GAD 32 Panic disorder 4 MDD 6 BPD 1	Group psychoeducation and social support	Medium
O'Malley, 1992[141];O'Malley, 1996[142]	NTX 50 + CS (29) NTX 50 + ST (23) Placebo + CS (25) Placebo + ST (27)	12 (38)	U.S.	Outpatient; university alcohol treatment unit	Ads and those seeking treatment at unit	41	7	26	NR	See arms	Medium
O'Malley, 2007[117]	NTX 50 (57) Placebo (50) Randomization stratified by presence of eating disorder	12	U.S.	University mental health center	Newspaper ads and patients seeking substance abuse treatment	40	11	100	Eating disorder 28	CBCST 100%, based on manualized approach used in Project MATCH	Medium
O'Malley, 2008[42]	NTX 50 (34) Placebo (34) NTX 50 + SERT 100 (33)	16	U.S.	Outpatient	Direct community recruitment, health clinic referral, local ads	40	70	34	NR	MM 100%	Medium
Oslin, 1997[107]	NTX 100 on Monday and Wednesday, 150 on Friday (21) Placebo (23)	12	U.S.	Outpatient substance abuse clinic and VAMC	From a VA hospital	58	64	NR	0	Group therapy and case manager 100%	Medium

Table 7. Characteristics of included double-blind randomized placebo-controlled trials of naltrexone (continued)

Author, Year Trial Name	Arm Dose, mg/Day (N)	Rx Duration, Weeks (Followup)	Country	Setting	Recruitment Method	Age, Years	% Non-White	% Female	% With Additional Condition	Cointervention	Risk of Bias
Oslin, 2008[103]	NTX 100 + CBT (40) NTX 100 + BRENDA[b] (39) NTX 100 + doctor only (41) Placebo + CBT (40) Placebo + BRENDA[b] (40) Placebo + doctor only (40)	24	U.S.	Outpatient psychiatry clinic	Ads in local media	41	27	27	NR	None	Medium
Petrakis, 2004[121]; Ralevski, 2006[143]	NTX 50 (16) Placebo (15)	12	U.S.	At least 3 outpatient centers—MIRECC clinics	Direct recruitment from participating centers	46	19	0	Schizophrenia or schizoaffective disorder 100	CBT + psychiatric TAU Neuroleptics 52% Benzodiazepines 16% Thymoleptics 39%	Medium
Petrakis, 2005[90] Ralevski, 2007[94] Petrakis, 2007[95] Petrakis, 2006[96] VA MIRECC DBRCT	DIS 250 (66) NTX 50 (59) Placebo (64) NTX 50 + DIS 250 (65)	12	U.S.	Outpatient VA	Recruited as outpatient or ads	47	26	3	Axis I disorder 100	Psychiatric TAU 100%	Medium for NTX vs. placebo
Pettinati, 2008[106]	NTX 150 (82) Placebo (82) Subjects also randomized to either CBT or BRENDA[b] (2x2 design)[e]	12	U.S.	University-affiliated outpatient substance abuse treatment research facility	Those seeking treatment at the facility	39	76	29	Cocaine dependence 100	NR	Medium

Table 7. Characteristics of included double-blind randomized placebo-controlled trials of naltrexone (continued)

Author, Year Trial Name	Arm Dose, mg/Day (N)	Rx Duration, Weeks (Followup)	Country	Setting	Recruitment Method	Age, Years	% Non-White	% Female	% With Additional Condition	Cointervention	Risk of Bias
Pettinati, 2010[104]	SERT 200 (40) NTX 100 (49) Placebo (39) SERT 200 + NTX 100 (42)	14	U.S.	Outpatient	Newspaper ads, referrals from local professional or friends/family	43	35	38	Depression 100	CBT 100%	Medium
Schmitz, 2004[114]	NTX 50 + RPT (20) NTX 50 + DC (20) Placebo + RPT (20) Placebo + DC (20)	12	U.S.	Outpatient	Ads	36	71	16	Cocaine dependence 100	RPT or DC as randomized	High
Schmitz, 2009[105]	NTX 100 + CBT (20) NTX 100 + CBT and CM (25) Placebo + CBT (27) Placebo + CBT and CM (14)	12	U.S.	Outpatient substance abuse clinic	Media ads	34	84 to 93	13	Cocaine use disorder 100	CBT 100%	High
Volpicelli, 1995[115] Volpicelli, 1992[144]	NTX 50 (54) Placebo (45)[f]	12	U.S.	Substance abuse treatment unit of a VAMC	Patients in the substance abuse treatment program of a VAMC	NR	≥78	0	NR	Outpatient treatment program and group therapy 100%	Unclear
Volpicelli, 1997[116]	NTX 50 (48) Placebo (49)	12	U.S.	Outpatient substance abuse treatment, university/VA treatment research center	Receiving outpatient treatment	38 to 39	60 to 65	18 to 26	NR	Counseling 100%	Medium
ALK21-014, 2011[100]	NTX inj 380 every 4 weeks (152) Placebo (148)	12	Germany, Austria	Outpatient	NR	46	NR	20	NR	NR	Medium

AA = Alcoholics Anonymous; ACA = acamprosate; 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; CB = cognitive behavioral; CBCST = cognitive behavioral coping skills therapy; CBI = combined behavioral intervention; CBT = cognitive behavioral therapy; CS = coping skills; COMBINE = Combined Pharmacotherapies and Behavioral Intervention; DC = drug counseling; GAD = generalized anxiety disorder; HIV = human immunodeficiency virus; inj = injectable; MATCH = Matching Alcoholism Treatments to Client Heterogeneity; MBSCT = modified

behavioral self-control therapy; MDD = major depressive disorder; MET = motivational enhancement therapy; mg = milligram; MIRECC = Mental Illness Research, Education and Clinical Center; MM = medical management; N = number; NOS = not otherwise specified; NR = not reported; NTX = naltrexone; OCD = obsessive-compulsive disorder; PTSD = post-traumatic stress disorder; PUFA = polyunsaturated fatty acid; RPT = relapse prevention therapy; SERT = sertraline; ST = supportive therapy; TAU = treatment as usual; TOP = topiramate; U.K. = United Kingdom; U.S. = United States; VA = Veterans Affairs; VACS = Veterans Affairs Cooperative Study; VAMC = Veterans Administration Medical Center.

Note: Age, Years is the mean age in years, unless otherwise stated.

[a] 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).

[b] BRENDA is a psychosocial program designed to enhance medication and treatment compliance. The approach has six components: biopsychosocial evaluation, giving the patient a report of findings from the evaluation, empathy, addressing patient needs, providing direct advice, and assessing patient reaction to advice and adjusting the treatment plan as needed.

[c] Ns are numbers analyzed, numbers randomized to each group NR. Total number randomized was 174.

[d] 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).

[e] Study stratified randomization by sex and reports the results overall and separately by sex.

[f] Data are from Volpicelli 1995,[115] which reported pooled results of 99 subjects. Data from a smaller subset (N=70) of this sample was reported in Volpicelli 1992.[144] 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.

Return to Any Drinking

Our meta-analysis of low and medium risk of bias trials found that 4 percent fewer subjects treated with naltrexone returned to any drinking than with placebo (RD, -0.04; 95% CI, -0.07 to -0.01; 21 trials). Separating U.S.- and non-U.S.-based trials found no difference in point estimates by country (both found RD, -0.04), but the effect did not reach statistical significance for the non-U.S. trials (95% CI, -0.11 to 0.03; 7 trials). Stratifying by dose and delivery method found similar effect sizes for 50 mg per day orally (RD, -0.05), 100 mg per day orally (RD, -0.03), and injectable naltrexone (RD, -0.04), although the effect did not reach statistical significance for 100 mg per day or for injectable naltrexone.

Return to Heavy Drinking

Our meta-analysis of low and medium risk of bias trials found that 7 percent fewer subjects treated with naltrexone returned to heavy drinking than with placebo (RD, -0.07; 95% CI, -0.11 to -0.03; 23 trials). Including studies rated as high risk of bias resulted in a slightly larger effect size (RD, -0.09; 95% CI, -0.13 to -0.05; 27 trials). Separating U.S.- and non-U.S.-based trials found a small difference in point estimates by country (U.S. RD, -0.08; non-U.S. RD, -0.05), and the effect did not reach statistical significance for the non-U.S. trials (95% CI, -0.12 to 0.01; 10 trials). Stratifying by dose and delivery method found a trend toward greater effect sizes for 50 mg per day (RD, -0.09) than for 100 mg per day (RD, -0.05) or injectable naltrexone (RD, -0.01). The effect did not reach statistical significance for 100 mg per day or for injectable naltrexone, but those analyses had many fewer studies and subjects (and thus less precision) and confidence intervals overlapped for all three dose categories.

Drinking Days

Subjects treated with naltrexone had 4.6 percent fewer drinking days than those treated with placebo (WMD, -4.6; 95% CI, -6.6 to -2.5; 19 trials). All point estimates (of the individual studies) favored naltrexone over placebo. Stratifying our meta-analysis by U.S. and non-U.S. studies found similar effect sizes for U.S-based (WMD, -4.5) and non-U.S.-based trials (WMD, -4.7). The effect did not reach statistical significance for non-U.S.-based trials, but the analysis had fewer studies and subjects (and thus less precision) and confidence intervals overlapped.

Stratifying by dose and delivery method found a trend toward greater effect sizes for 50 mg per day (WMD, -5.4) than for 100 mg per day (WMD, -0.86); the single study of injectable naltrexone found a larger effect size (WMD, -8.6). The effect did not reach statistical significance for 100 mg per day (95% CI, -4.2 to 2.5).

Heavy Drinking Days

Subjects treated with naltrexone had 3.8 percent fewer heavy drinking days than those treated with placebo (WMD, -3.8; 95% CI, -5.8 to -1.8; 11 trials). Separating by U.S.- and non-U.S.-based trials found that the effect remained statistically significant for U.S.-based trials (WMD, -3.7; 95% CI, -5.8 to -1.6; 9 trials) but the pooled effect size did not reach statistical significance for the 2 non-U.S.-based studies (WMD, -5.8; 95% CI, -16.7 to 5.2).

Drinks per Drinking Day

Subjects treated with naltrexone had 0.5 percent fewer drinks per drinking day than those treated with placebo (WMD, -0.54; 95% CI, -1.01 to -0.07; 11 trials). Stratifying our meta-

analysis by U.S. and non-U.S. studies found similar effect sizes for U.S.- and non-U.S.-based trials.

Detailed Synthesis: Placebo-Controlled Trials of Medications Used Off-Label or Those Under Investigation

We found no studies meeting inclusion criteria for amitriptyline. We found 1 placebo-controlled trial for each of the following medications: aripiprazole, atomoxetine, desipramine, fluvoxamine, imipramine, olanzapine, ondansetron, paroxetine, and varenicline. We found insufficient evidence to support the efficacy of these medications. We provide additional details about the individual trials evaluating each of these medications in Appendix E.

We found multiple placebo-controlled trials for baclofen (2), buspirone (5), citalopram (2), fluoxetine (3), nalmefene (7), quetiapine (3), sertraline (7), topiramate (4), and valproic acid (2).

Baclofen

Characteristics of Baclofen Trials

Two trials met our inclusion criteria (Table 8). Both were parallel two-arm trials comparing baclofen with placebo for 12 weeks. Mean age was 49 years in both trials. All subjects met criteria for alcohol dependence. The trials enrolled 27 percent[145] and 45 percent females.[146] Neither trial reported information on smoking history at baseline. All patients included in 1 trial had liver cirrhosis.[145] Both trials included psychological co-interventions.

Table 8. Characteristics of included double-blind randomized placebo-controlled trials of baclofen

Author, Year	Arm Dose, mg/Day (N)	Rx Duration, Weeks	Setting	Recruitment Method	Age, Years	% Non-White	% Female	% With Additional Condition	Cointervention	Risk of Bias
Addolorato, 2007[145]	BAC 30 (42) Placebo (42)	12	Italy; university treatment and research center	People contacting alcohol treatment unit	49	NR	24 to 31	Liver cirrhosis 100 Hepatitis B 15 Hepatitis C 29	Routine psychological support 100%	Medium
Garbutt, 2010[146]	BAC 30 (40) Placebo (40)	12	U.S.; outpatient, details NR	Newspaper and radio ads	49	4	45	NR	BRENDA 100%	Medium

BAC = baclofen; 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; mg = milligram; N = number; NR = not reported; U.S. = United States.

Note: Age, Years is the mean age in years, unless otherwise stated.

Return to Any Drinking

The trial conducted in Italy reported that a lower percentage of patients treated with baclofen returned to any drinking than with placebo (29 percent [12 of 42 patients] versus 71 percent [30 of 42]; odds ratio [OR], 6.3; 95% CI, 2.4 to 16.1).[145] The trial conducted in the United States did not report numbers for rates of return to any drinking, but reported no difference between groups

for time to first usage (p=0.13), and included a figure for percentage abstinent that shows over 90 percent of subjects returned to any drinking over the course of the trial.[146]

Return to Heavy Drinking

The trial conducted in Italy reported a greater proportion of patients in the placebo group relapsing to heavy drinking than in the baclofen group (data not reported, shown in figure only, p=0.0062). Relapse was defined as a daily alcohol intake of more than 4 drinks or an overall consumption of 14 drinks or more per week during at least 4 weeks.[145]

The trial conducted in the United States found no significant difference between groups for the proportion of patients returning to heavy drinking (hazard ratio [HR], 0.924; p=0.76).[146]

Drinking Days

Only the U.S.-based trial reported data for percentage of drinking days. The trial found no significant difference between groups (baclofen versus placebo: 50.1 versus 49.4, p=0.50).[146]

Heavy Drinking Days

Only the U.S.-based trial reported data for percentage of heavy drinking days. The trial found no significant difference between groups (baclofen versus placebo: 25.9 versus 25.5, p=0.73).[146]

Buspirone

Characteristics of Buspirone Trials

We included 5 trials comparing buspirone with placebo (Table 9). Doses ranged from 40 to 60 mg per day. Duration of treatment ranged from 12 to 52 weeks. Four trials were conducted in the United States and 1 was conducted in Canada. Mean age was very similar across trials, in the early 40s. All subjects met criteria for alcohol dependence. Two studies did not report information on race; 3 reported enrolling between 0 and 18 percent nonwhite subjects across study arms. Three trials included no women; 2 included a minority of women (18 to 26 percent across study arms). None of the trials reported information on smoking history at baseline.

Two trials enrolled a majority of subjects[147] or all subjects[148] with anxiety disorders; 1 included almost half with depression.[149] Most trials included or encouraged psychological or psychosocial co-interventions.

Return to Any Drinking

Just 2 of the 5 trials reported data for return to any drinking;[148,150] 1 of them was rated as high risk of bias.[150] Neither trial found a statistically significant difference between groups, and point estimates favored placebo in both trials.

Drinking Days

Two trials rated as medium risk of bias reported data.[147,149] One trial (N=61) enrolling anxious alcoholics reported fewer drinking days for subjects treated with buspirone than for those who received placebo (at 12 weeks: 3.6 versus 13.3, p<0.10; at posttreatment follow up 26 weeks later: 9.5 versus 24.8, p<0.01).[147] One trial comparing buspirone, lithium, and placebo found no significant difference between groups (over months 1 to 3: 7 percent versus 10 percent versus 8 percent, respectively).[149] Our meta-analysis found no difference between buspirone and placebo (WMD, -3.4; 95% CI, -9.2 to 2.4; 2 trials).

Drinks per Drinking Day

Just 1 trial (N=61) enrolling anxious alcoholics reported drinks per day.[147] It found no statistically significant difference between subjects treated with buspirone and those who received placebo over 12 weeks (0.7 versus 2.1, p NS), or at posttreatment follow up 26 weeks later (0.9 versus 4.8, p<0.10).

Table 9. Characteristics of included double-blind randomized placebo-controlled trials of buspirone

Author, Year	Arm Dose, mg/Day (N)	Rx Duration, Weeks (Followup)	Setting	Recruitment Method	Age, Years	% Non-White	% Female	% With Co-occurring Condition	Cointervention	Risk of Bias
Fawcett, 2000[149]	Buspirone 40 (48) Placebo (52) Lithium 1,200 (56)	26	U.S.; Outpatient	Ad, referral, inpatient/outpatient programs	40	16	0	Depression 48	Supportive therapy	Medium
George, 1999[151]	Buspirone 60 (25) Placebo (24)	52	U.S.; Outpatient	Recruited from inpatient research unit at NIAAA	42	NR	0	0	Care of psychiatrist and nurse at posthospital clinic 100%	High
Kranzler, 1994[147]	Buspirone 15-60, mean 52.5 (31) Placebo (30)	12 (38)	U.S.; Outpatient; university health center	Ads	39 to 40	0 to 10	20 to 26	GAD 37 to 46 Anxiety disorder 50 to 52 MDD 25 to 27	CBT 100%	Medium
Malcolm, 1992[148]	Buspirone target 60, mean 52 (33) Placebo (34)	26	U.S.; 1-2 weeks inpatient, then outpatient; VAMC alcohol dependence treatment unit	Screened during inpatient stay for alcohol dependence treatment	42 to 44	15 to 18	0	GAD 100	None	Medium
Malec, 1996[150]	Buspirone 40 (28) Placebo (29)	12	Canada; hospital research center	Media ad	42	NR	18	NR	None prescribed but 37% received additional treatment: AA 7% Individual psychotherapy 3%	High

AA = Alcoholics Anonymous; CBT = cognitive behavioral therapy; GAD = generalized anxiety disorder; MDD = major depressive disorder; mg = milligram; N = number; NIAAA = National Institute on Alcohol Abuse and Alcoholism; NR = not reported; U.S. = United States; VAMC = Veterans Administration Medical Center.

Note: Age, Years is the mean age in years, unless otherwise stated.

Citalopram

Characteristics of Citalopram Trials

We included 2 trials comparing citalopram 40 mg per day with placebo for 12 to 13 weeks (Table 10). Mean age was in the mid-40s for both trials. All subjects met criteria for alcohol dependence. Neither trial reported information on race. One trial enrolled all males[152] and 1 enrolled 44 percent females.[153] One did not report information on smoking history;[152] 1 included 34 percent smokers.[153] Both trials included psychological or psychosocial co-interventions. We rated both trials as high risk of bias, primarily for high risk of attrition bias and inadequate handling of missing data (see Appendix C for details).

Table 10. Characteristics of included double-blind randomized placebo-controlled trials of citalopram

Author, Year	Arm Dose, mg/Day (N)	Rx Duration, Weeks (Followup)	Setting	Recruitment Method	Age, Years	% Female	% With Co-occurring Condition	Cointervention	Risk of Bias
Naranjo, 1995[153]	Citalopram 40 (53) Placebo (46)	12 (20)	Canada; outpatient research center	Newspaper ad	45	44	NR	Brief psychosocial intervention 100%	High
Tiihonen, 1996[152]	Citalopram 40 (31) Placebo (31)	13 (17)	Finland; outpatient; community-based alcohol rehabilitation center	Inpatient / outpatient referral	45 to 47	0	0	Supportive psychotherapy intervention 100%	High

mg = milligram; N = number; NR = not reported.

Note: Age, Years is the mean age in years, unless otherwise stated.

Return to Any Drinking

The trial conducted in Finland reported 25 of 31 citalopram-treated patients and 28 of 31 placebo-treated patients returned to any drinking (p=0.10).[152]

Drinking Days

The trial conducted in Canada found similar proportions of drinking days for those who received citalopram and those who received placebo over the 12 weeks of treatment (72.7 percent versus 76.5 percent, p NS).[153]

Drinks per Drinking Day

The trial conducted in Canada found similar reductions in drinks per drinking day for those who received citalopram and those who received placebo over the 12 weeks of treatment (26.1 percent versus 26.4 percent, p NS).[153]

Fluoxetine

Characteristics of Fluoxetine Trials

We included 3 trials comparing fluoxetine with placebo (Table 11). Doses ranged from 20 to 60 mg per day. Duration of treatment ranged from 12 to 15 weeks. All 3 trials were conducted in the United States. Mean age ranged from 35 to 47. All subjects met criteria for alcohol dependence. For 2 trials, about half of enrolled subjects were nonwhite;[154,155] 1 enrolled 5 percent nonwhite subjects.[156] One trial enrolled all males;[155] the other 2 enrolled 20 percent[156] or 49 percent[154] females. None of the trials reported information on smoking history at baseline. One trial only enrolled subjects with major depressive disorder and alcohol dependence.[154] Two trials included or encouraged psychological or psychosocial co-interventions.

Table 11. Characteristics of included double-blind randomized placebo-controlled trials of fluoxetine

Author, Year	Arm Dose, mg/Day (N)	Rx Duration, Weeks (Followup)	Setting	Recruitment Method	Age, Years	% Non-White	% Female	% With Co-occurring Condition	Cointervention	Risk of Bias
Cornelius, 1997[154]; Cornelius, 1995[157]	Fluoxetine 20-40 (25) Placebo (26)	12	U.S.; inpatient psychiatric institute	Recruited as inpatient	35	53	49	MDD 100%	Usual care: psychotherapy 100%	Medium
Kabel, 1996[155]	Fluoxetine 20-60 (15) Placebo (13)	15	U.S.; inpatient substance abuse treatment	Inpatient recruitment	47	46	0	Cocaine use 14%	NR	High
Kranzler, 1995[156]	Fluoxetine 20-60, mean 47 (51) Placebo (50)	12 (38)	U.S.; outpatient clinic	Ads	40	5	20	Major depression 14%	Group psychotherapy 79% Individual psychotherapy 21%	Medium

MDD = major depressive disorder; mg = milligram; N = number; NR = not reported; U.S. = United States.

Note: Age, Years is the mean age in years, unless otherwise stated.

Return to Any Drinking

Two small trials, 1 rated as medium risk of bias (N=51) and 1 rated as high risk of bias (N=28), reporting return to any drinking found no statistically significant difference between fluoxetine and placebo.[154,155]

Drinking Days

Both medium risk of bias trials reported drinking days. Our meta-analysis of these 2 trials found no statistically significant difference between fluoxetine and placebo (WMD, -3.2; 95% CI, -18.2 to 11.9), but statistical heterogeneity was considerable (I^2 82.7 percent). The trial enrolling subjects who all had major depressive disorder (N=51) found that subjects treated with fluoxetine had fewer drinking days than those who received placebo (WMD, -11.6; 95% CI, -

22.7 to -0.5). The trial enrolling a population with 14 percent of subjects with major depression found no difference between groups, and a point estimate trending in favor of placebo (WMD, 3.8; 95% CI, -2.1 to 9.7).

Heavy Drinking Days

The trial enrolling subjects who all had major depressive disorder (N=51) reported fewer heavy drinking days for subjects treated with fluoxetine than for those who received placebo (cumulative number of days of heavy drinking: 4.8 versus 16, p=0.04).

Drinks per Drinking Day

Both medium risk of bias trials reported this outcome. Similar to the analysis for drinking days, our meta-analysis of these 2 trials found no statistically significant difference between fluoxetine and placebo (WMD, -1.2; 95% CI, -4.6 to 2.2), but statistical heterogeneity was considerable (I^2 78.3 percent). The trial enrolling subjects who all had major depressive disorder (N=51) found that subjects treated with fluoxetine had fewer drinks per drinking day than those who received placebo (WMD, -3.0; 95% CI, -5.4 to -0.6). The trial enrolling a population with 14 percent of subjects with major depression found no difference between groups, and a point estimate trending in favor of placebo (WMD, 0.5; 95% CI, -1.6 to 2.6).

Nalmefene

Characteristics of Nalmefene Trials

We included 7 trials comparing nalmefene with placebo (Table 12). Doses ranged from 5 to 80 mg per day. Four trials assessed targeted dosing, instructing patients to take the medication when they believed drinking to be imminent, rather than as a daily scheduled medication.[158-161] Duration of treatment ranged from 12 to 52 weeks. Three trials were conducted in the United States, 1 in Finland, and 3 were multi-national. Mean age was in the 40s in all but 1 trial. All subjects met criteria for alcohol dependence in 6 trials; 1 trial reported that 93 percent met criteria for alcohol dependence.[158] The trials enrolled 0 to 19 percent nonwhite subjects and from 19 to 37 percent females across study arms. None of the trials reported information on smoking history at baseline. The proportion of subjects with co-occurring psychiatric conditions was either zero or was not reported.

Return to Heavy Drinking

Two trials, 1 rated as medium risk of bias (N=105)[162] and 1 pilot study rated as high risk of bias (N=21),[163] reported return to heavy drinking. The former found that 23 percent fewer patients treated with nalmefene returned to heavy drinking than with placebo (RD, -0.23; 95% CI, -0.43 to -0.03). The pilot study found no difference between groups (RD, -0.05; 95% CI, -0.51 to 0.41).

Drinking Days

Our meta-analysis of 2 trials,[158,162] both rated as medium risk of bias, that reported data for this outcome found no significant difference between nalmefene and placebo (WMD, -1.1; 95% CI, -7.6 to 5.4).

Heavy Drinking Days

The trial conducted in Finland (N=403)[158] that assessed targeted dosing reported a lower percentage of heavy drinking days for patients treated with targeted nalmefene than for those who received placebo (18.1 percent versus 29.7 percent, p=0.024). The ESENSE1 trial (N analyzed=365)[159] reported a greater reduction from baseline to month 6 in number of monthly heavy drinking days in patients treated with as-needed nalmefene than for those who received placebo (mean difference, -2.3; 95% CI, -3.8 to -0.8). Similarly, the ESENSE2 trial (N analyzed =441)[160] reported a difference favoring nalmefene at month 6 (mean difference, -1.7; 95% CI, -3.1 to -0.3). The SENSE trial (N analyzed=430) did not find a difference in monthly heavy drinking days between the 2 treatments at month 6, but did report a difference at month 13 (mean difference, -1.6; 95% CI, -2.9 to -0.2). Our meta-analysis of the 2 medium risk of bias studies[159,160] found a statistically significant difference between nalmefene and placebo for change in heavy drinking days over the past month (WMD, -1.98; 95% CI, -3.0 to -0.96).

Drinks per Drinking Day

Three of the trials rated as medium risk of bias reported data.[158,162,164] Our meta-analysis found that subjects treated with nalmefene had 1 fewer drink per drinking day than those who received placebo (WMD, -1.0; 95% CI, -1.8 to -0.3).

Table 12. Characteristics of included double-blind randomized placebo-controlled trials of nalmefene

Author, Year	Arm Dose, mg/Day (N)	Rx Duration, Weeks	Setting	Recruitment Method	Age, Years	% Non-White	% Female	% With Co-occurring Condition	Counter-vention	Risk of Bias
Anton, 2004[164]	NALM 5 (68) NALM 20 (66) NALM 40 (68) Placebo (68)	12	U.S.; outpatient	Ads, recruited as outpatients	44 to 46	6 to 15	22 to 33	NR	MET 100%	Medium
Gual, 2013[160] ESENSE 2	NALM 20 as-needed (358) Placebo (360)	24	Belgium, Czech Republic, France, Italy, Poland, Portugal, Spain; 57 sites	Referrals and ads	44 to 45	1	26 to 29	0	BRENDA	Medium
Karhuvaara, 2007[158]	NALM 10 to 40 Targeted dose[a] (242) Placebo (161)	28[b]	Finland; 15 sites[c]	Mainly by newspaper ads	49	0	19	NR	Some elements of BRENDA	Medium
Mann, 2013[159] ESENSE 1	NALM 20 as-needed (306) Placebo (298)	24	Austria, Finland, Germany, Sweden; 39 sites	Referrals and ads	52	<1	32 to 33	0	BRENDA	Medium
Mason, 1994[163]	NALM 10 (7) NALM 40 (7) Placebo (7)	12	U.S.; NR	Ads	42	10	29	0	Group therapy 0 to 14% AA 0 to 29%	High

Table 12. Characteristics of included double-blind randomized placebo-controlled trials of nalmefene (continued)

Author, Year	Arm Dose, mg/Day (N)	Rx Duration, Weeks	Setting	Recruitment Method	Age, Years	% Non-White	% Female	% With Co-occurring Condition	Cointervention	Risk of Bias
Mason, 1999[162]	NALM 20 or 80 (70) Placebo (35)	12	U.S.; outpatient substance abuse treatment; academic research center	Ads, press releases, other non-specified sources	42	17 to 19	31 to 37	0	CBT (used in MATCH) 100%	Medium
SENSE, 2013[161]	NALM 20 as-needed (509) Placebo (166)	52 (56)	Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Russian Federation, Slovakia, Ukraine, U.K.	NR	44	NR	23	NR	NR	High

AA = Alcoholics Anonymous; 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; CBT = cognitive behavioral therapy; ESENSE/SENSE = Safety and Efficacy of Nalmefene in Patients With Alcohol Dependence; MATCH = Matching Alcoholism Treatments to Clinical Heterogeneity; MET = motivational enhancement therapy; mg = milligram; N = number; NALM = nalmefene; NR = not reported; U.K. = United Kingdom; U.S. = United States.

Note: Age, Years is the mean age in years, unless otherwise stated.

[a] Targeted dosing; medication was taken when subjects believed drinking to be imminent, rather than as a daily scheduled medication.

[b] 52 weeks total (28 weeks of initial nalmefene vs. placebo, then another randomization for nalmefene responders).

[c] Sites included 5 specialist treatment clinics, 6 private general practices, 2 occupational health care offices, and 2 outpatient clinical research facilities.

Quetiapine

Characteristics of Quetiapine Trials

We included 3 trials comparing quetiapine with placebo for 12 weeks (Table 13). All 3 trials were conducted in the United States. Mean age ranged from late 30s to late 40s. All subjects met criteria for alcohol dependence in 2 trials; 1 reported that 97 percent of subjects met criteria.[165] Just 1 trial reported information on smoking history at baseline, with 56 percent smokers enrolled.[166] For 2 trials, all subjects had co-occurring bipolar disorder.[165,166] We rated all 3 trials as high risk of bias, primarily for high risk of attrition bias, high risk of selection bias, and inadequate handling of missing data (see Appendix C for details).

Table 13. Characteristics of included double-blind randomized placebo-controlled trials of quetiapine

Author, Year	Arm Dose, mg/Day (N)	Rx Duration, Weeks	Setting	Recruitment Method	Age, Years	% Non-White	% Female	% With Co-occurring Condition	Cointervention	Risk of Bias
Brown, 2008[165]	QUET titrated from 25 to 600 over 6 weeks (52) Placebo (50)	12	U.S.; NR	From community	38	39	37	Bipolar 100	NR	High
Kampman, 2007[167]	QUET 400 (29) Placebo (32)	12	U.S.; outpatient	Community referrals, media ads	47	46	23	MDD 15 Antisocial personality disorder 11 PTSD 8 Panic disorder 5 Social phobia 5 GAD 3 OCD 2	BRENDA 100%	High
Stedman, 2010[166]	QUET 300-800 (175) Placebo (186)	12	U.S.; outpatient; multicenter	NR	39	12	37	Bipolar 100	None	High

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; GAD = generalized anxiety disorder; MDD = major depressive disorder; mg = milligram; N = number; NR = not reported; OCD = obsessive-compulsive disorder; PTSD = post-traumatic stress disorder; QUET = quetiapine; U.S. = United States.

Note: Age, Years is the mean age in years, unless otherwise stated.

Return to Any Drinking

The trial that did not enroll subjects with co-occurring bipolar disorder reported that more subjects treated with quetiapine achieved complete abstinence (9 of 29 patients versus 2 of 32, p=0.012)—that is, fewer subjects treated with quetiapine returned to any drinking (20 of 29 versus 30 of 32).

Drinking Days

All 3 trials reported this outcome. Our meta-analysis of the 3 trials found no difference between patients treated with quetiapine and those who received placebo (WMD, -2.7; 95% CI, -12.8 to 7.5).

Heavy Drinking Days

All 3 trials reported this outcome. Our meta-analysis of the 3 trials found no difference between patients treated with quetiapine and those who received placebo (WMD, -3.1; 95% CI, -10.1 to 4.0).

Sertraline

Characteristics of Sertraline Trials

We included 7 trials comparing sertraline with placebo (Table 14). Doses ranged from 50 to 200 mg per day. Duration of treatment ranged from 12 to 26 weeks. The majority were conducted in the United States (5 trials); 1 was conducted in Turkey and 1 in Spain. Mean age was very similar across trials, usually in the 40s. All subjects met criteria for alcohol dependence in 6 trials; 1 trial reported that 99 percent of subjects met criteria for alcohol dependence.[168] The percentage of nonwhite subjects enrolled was not reported by 3 trials, was a small minority (1 to 8 percent) in 2 trials, was about a third in 1 trial, and was the majority (80 percent) in 1 trial. Six trials enrolled between 19 and 48 percent females; 1 enrolled all men.[169] Just 1 trial reported information on smoking history at baseline, with 17 percent smokers enrolled.[104] Most trials enrolled subjects with comorbidities—3 only included patients with depressive disorders;[104,168,170] 1 only included those with post-traumatic stress disorder (PTSD);[171] and 1 reported that about half of subjects had depression.[172] Trials typically included or encouraged psychological or psychosocial co-interventions.

Table 14. Characteristics of included double-blind randomized placebo-controlled trials of sertraline

Author, Year	Arm Dose, mg/Day (N)	Rx Duration, Weeks (Followup)	Setting	Recruitment Method	Age, Years	% Non-White	% Female	% With Co-occurring Condition	Cointervention	Risk of Bias
Brady, 2005[171]	SERT 150 (49) Placebo (45)	12	U.S.; outpatient	Ads, outpatient substance abuse treatment programs	37	NR	43 to 49	PTSD 100 Depressive disorder 51 Anxiety disorder 38	CBT 100%	Medium
Coskunol, 2002[169]	SERT 100 (30) Placebo (29)	26	Turkey; inpatient (mean 1 month) followed by 6 months outpatient; substance abuse treatment unit	NR	44	NR	0	For eligibility, required no concurrent Axis I disorders	Thiamine 500 mg per day 100% Pyridoxone 500 mg per day 100% AA during inpatient 100%	Medium
Gual, 2003[170]	SERT 50-150 (44) Placebo (39)	24	Spain; 1 center; outpatient	Outpatient alcohol dependence treatment	47	NR	47	Depression/ dysthymia 100	NR	Medium
Kranzler, 2011[173]; Kranzler, 2012[174]	SERT 50-200 (63) Placebo (71)	12 (26)	U.S.; outpatient; university health center	Primarily ads, some clinician referrals	48	8	19	Cannabis use disorder 17.2 Cocaine use disorder 19.4 Past MDD 20.9	Coping skills training 100%	Medium

Table 14. Characteristics of included double-blind randomized placebo-controlled trials of sertraline (continued)

Author, Year	Arm Dose, mg/day (N)	Rx Duration, Weeks (Followup)	Setting	Recruitment Method	Age, Years	% Non-white	% Female	% With Co-occurring Condition	Co-intervention	Risk of Bias
Moak, 2003[168]	SERT 50-200 (38) Placebo (44)	12	U.S.; 1 site; outpatient	Newspaper, outpatient treatment	41	1	39	Depression/ dysthymia 100	CBT	Medium
Pettinati, 2001[172]	SERT 200 (50) Placebo (50)	14	U.S.; outpatient	Ads and referral	44	80	48	Depression 47	12-step facilitation	Unclear
Pettinati, 2010[104]	SERT 200 (40) NTX 100 (49) Placebo (39) SERT 200 + NTX 100 (42)	14	U.S.; outpatient	Newspaper ads and referrals	43	35	38	Depression 100	CBT 100%	Medium

CBT = cognitive behavioral therapy; MDD = major depressive disorder; mg = milligram; N = number; NR = not reported; NTX = naltrexone; PTSD = post-traumatic stress disorder; SERT = sertraline; U.S. = United States.

Note: Age, Years is the mean age in years, unless otherwise stated.

Return to Any Drinking

Just 1 trial reported this outcome—the trial that compared sertraline, naltrexone, sertraline plus naltrexone, and placebo.[104] It found similar proportions of patients treated with sertraline returning to any drinking as with placebo (29 of 40 patients versus 30 of 39, p NS).

Return to Heavy Drinking

Two of the trials reported this outcome—the trials conducted in Turkey and Spain.[169,170] Our meta-analysis found no difference between patients treated with sertraline and those who received placebo (RD, -0.04; 95% CI, -0.31 to 0.23).

Drinking Days

Four of the trials reported this outcome—the trial conducted in Spain,[170] the 2 trials conducted in the United States rated as medium risk of bias,[168,173] and the U.S.-based trial rated as unclear risk of bias.[172] Our meta-analysis found no significant difference between patients treated with sertraline and those who received placebo, both without (WMD, 1.8; 95% CI, -6.3 to 9.9) and with inclusion of the trial rated as unclear risk of bias (WMD, 0.6; 95% CI, -5.7 to 7.0).

Heavy Drinking Days

Two trials reported this outcome.[171,173] One trial enrolled patients with PTSD and alcohol dependence (N=94),[171] and the other did not require a co-occurring condition for study entry (N=134). Both trials reported numerically more heavy drinking days for patients treated with sertraline than for those who received placebo.[171]Our meta-analysis found a statistically significant difference in favor of placebo (WMD, 1.9; 95% CI, 0.7 to 3.0)—i.e., more heavy drinking days for those who received sertraline.

Drinks per Drinking Day

Two of the trials reported this outcome—the trial conducted in South Carolina (N=82)[168] and the U.S.-based trial that enrolled patients with PTSD and alcohol dependence (N=94).[171] Our meta-analysis found no significant difference between patients treated with sertraline and those who received placebo (WMD, -0.9; 95% CI, -2.2 to 0.5).

Topiramate

Characteristics of Topiramate Trials

We included 4 trials comparing topiramate with placebo for 12 to 14 weeks (Table 15). Two trials were conducted in the United States, 1 in Brazil, and 1 in Spain. Mean age was in the 40s in all 4 trials. All subjects met criteria for alcohol dependence in 3 trials; 1 trial did not report the proportion with alcohol dependence, but most subjects likely had alcohol dependence.[175] Two trials enrolled all males;[119,176] the other 2 included from 26 to 40 percent females across study arms. The 2 non-U.S.-based trials reported information on smoking history at baseline, with 66 to 80 percent smokers enrolled in those trials.[119,176] Three of the 4 trials offered or included psychological or psychosocial co-interventions.

Table 15. Characteristics of included double-blind randomized placebo-controlled trials of topiramate

Author, Year	Arm Dose, mg/Day (N)	Rx Duration, Weeks	Setting	Recruitment Method	Age, Years	% Non-White	% Female	% With Co-occurring Condition	Cointervention	Risk of Bias
Baltieri, 2008[119]; Baltieri, 2009[128]	TOP target 200, maximum 400 (52) NTX 50 (49) Placebo (54)	12	Brazil; outpatient	NR	44 to 45	29	0	NR	Psychosocial 100%	High
Johnson, 2003[175] Ma, 2006[177]; Johnson, 2004[178]	TOP 25-300 (75) Placebo (75)	12	U.S.; 1 site; outpatient	Newspaper	41	NR	28 to 40	0	None	Medium
Johnson, 2007[179] Johnson, 2008[180]	TOP 50-300, mean 171 (183) Placebo (188)	14	U.S.; 17 academic sites	From academic sites; by newspaper, radio, television ads	47 to 48	15	26 to 28	NR	BBCET 100%	Low
Rubio, 2009[176]	TOP 250 (31) Placebo (32)[a]	12	Spain; outpatient	NR	42	NR	0	NR	Supportive group therapy offered	High

BBCET = brief behavioral compliance enhancement treatment; mg = milligram; N = number; NR = not reported; NTX = naltrexone; TOP = topiramate; U.S. = United States.

Note: Age, Years is the mean age in years, unless otherwise stated.

[a] Numbers entered are those analyzed; 76 total were randomized, but dropouts were not reported by arm.

Return to Any Drinking

Just 1 trial reported this outcome—the trial conducted in Brazil that was rated as high risk of bias.[119] It reported that more patients treated with topiramate returned to any drinking than with placebo (24 of 52 patients versus 15 of 54).

Drinking Days

Three of the trials reported this outcome—2 U.S.-based trials rated as low (N=371)[179] or medium risk of bias (N=150)[175] and the trial conducted in Spain (N=63) that was rated as high risk of bias.[176] The trial rated as low risk of bias found a lower percentage of drinking days for patients treated with topiramate than for those who received placebo (WMD, -8.5; 95% CI, -15.9 to -1.1); meta-analysis combining this trial with the trial rated as high risk of bias found a lower percentage of drinking days for patients treated with topiramate than for those who received placebo (WMD, -9.7; 95% CI, -16.4 to -3.1). We were unable to include the smaller U.S.-based trial (N=150) in the meta-analysis due to differences in the type of data reported—it reported that subjects treated with topiramate had a greater percentage of days abstinent than those who received placebo (mean difference -11.6, 95% CI, -3.98 to -19.3).

Heavy Drinking Days

Three of the trials reported this outcome—2 U.S.-based trials rated as low (N=371)[179] or medium risk of bias (N=150)[175] and the trial conducted in Spain (N=63) that was rated as high risk of bias.[176] Our meta-analysis found a lower percentage of heavy drinking days for patients treated with topiramate than for those who received placebo both without (WMD, -11.5; 95% CI, -18.3 to -4.8) and with inclusion of the trial rated as high risk of bias (WMD, -12.5; 95% CI, -17.9 to -7.2).

Drinks per Drinking Day

Three of the trials reported this outcome—2 U.S.-based trials rated as low (N=371)[179] or medium risk of bias (N=150)[175] and the trial conducted in Spain (N=63) that was rated as high risk of bias.[176] Our meta-analysis found that patients treated with topiramate had fewer drinks per drinking day than those treated with placebo both without (WMD, -1.1; 95% CI, -1.7 to -0.4) and with inclusion of the trial rated as high risk of bias (WMD, -1.2; 95% CI, -1.8 to -0.6).

Valproic Acid

Characteristics of Valproic Acid Trials

We included 2 trials comparing valproic acid with placebo (Table 16). Duration of treatment ranged from 12 to 24 weeks. Both trials were conducted in the United States. Mean age was very similar across trials, 38 to 40. All subjects met criteria for alcohol dependence. The trials enrolled from 25 percent[181] to 54 percent[182] nonwhite subjects, and from 29 percent[181] to 62 percent[182] women. Just 1 of the trials reported information on smoking history at baseline, reporting that 71 percent of subjects were smokers.[181] One trial only enrolled subjects with bipolar disorder.[181] Both trials included co-interventions—1 with lithium and weekly dual diagnosis (alcohol dependence and bipolar disorder) recovery counseling,[181] and 1 with cognitive behavioral therapy.[182]

Table 16. Characteristics of included double-blind randomized placebo-controlled trials of valproic acid

Author, Year	Arm Dose, mg/Day (N)	Rx Dura-tion, Weeks	Setting	Recruitment Method	Age, Years	% Non-White	% Fe-male	% With Co-occurring Condition	Cointer-vention	Risk of Bias
Brady, 2002[182]	Valproic acid 1,500 (14) Placebo (15)	12	U.S.; outpatient	Newspaper; several treatment settings	40	54	62	0	CBT	Med-ium
Salloum, 2005[181]	Valproate 750+ (29) Placebo (30)	24	U.S.; outpatient substance abuse service at university clinic	Treatment seekers	38	25	29	Bipolar I disorder 100 Mixed bipolar subtype 58 Manic 21 Depressed 21 Cannabis abuse or dependence 29 Cocaine abuse 29	Lithium and weekly individual dual diagnosis recovery counseling 100%	Med-ium

CBT = cognitive behavioral therapy; mg = milligram; N = number; U.S. = United States.

Note: Age, Years is the mean age in years, unless otherwise stated.

Return to Any Drinking

One trial (N=29) reported no significant difference in the percentage of subjects who returned to any drinking over 12 weeks (valproic acid versus placebo: 81 versus 83, p NS).[182]

Return to Heavy Drinking

Our meta-analysis found that 32 percent fewer subjects treated with valproic acid returned to heavy drinking than with placebo (RD, -0.32; 95% CI, -0.52 to -0.11; 2 trials).

Drinking Days

One trial (N=29) reported no significant difference in the percentage of drinking days over 12 weeks between subjects treated with valproic acid and those who received placebo (15.9 versus 19.6, p NS).[182]

Heavy Drinking Days

Our meta-analysis found a lower percentage of heavy drinking days for patients treated with valproic acid than for those who received placebo (WMD, -8.5; 95% CI, -15.9 to -1.1; 2 trials).

Drinks per Drinking Day

Our meta-analysis found that subjects treated with valproic acid had 2.6 fewer drinks per drinking day than those who received placebo (WMD, -2.6; 95% CI, -5.0 to -0.2; 2 trials).

Detailed Synthesis: Head-to-Head Trials

Acamprosate Versus Disulfiram

Characteristics of Trials

We found no studies meeting our inclusion criteria. Our searches did identify some studies comparing acamprosate with disulfiram that did not meet our inclusion criteria for this section because they were open-label studies.[183,184]

Acamprosate Versus Naltrexone

Characteristics of Trials

We included 4 trials comparing acamprosate with naltrexone (Table 17). Three used 50 mg per day doses for naltrexone;[61,74,79] 1 used 100 mg per day.[65] Three used 1,998 mg per day doses for acamprosate;[61,74,79] 1 used 3,000 mg per day.[65] Duration of treatment ranged from 12 to 16 weeks. One trial was conducted in the United States, 2 in Germany, and 1 in Australia. Mean age was in the mid-40s for all 4 trials. All subjects met criteria for alcohol dependence in 3 trials; 1 trial did not report the proportion with alcohol dependence, but most subjects likely had alcohol dependence.[61] Three studies did not report information on race; 1 trial reported enrolling 23 percent nonwhite subjects.[65] The trials enrolled a similar proportion of women (23 to 31 percent). Two trials reported information on smoking history at baseline—1 reported that 55 percent of pill-taking subjects were smokers;[65] 1 reported that 72 to 81 percent of subjects were smokers across study arms.[61] Trials included or encouraged psychological or psychosocial co-interventions.

Table 17. Characteristics of double-blind head-to-head randomized controlled trials of acamprosate versus naltrexone

Author, Year Trial Name	Arm Dose, mg/Day (N)	Rx Duration, Weeks (Followup)	Setting	Recruitment Method	Age, Years	% Non-White	% Female	% With Co-occurring Condition	Cointervention	Risk of Bias
Anton, 2006[65] Donovan, 2008[68] 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)[a]	16 (68)	U.S.; 11 academic sites	Ads, community resources, clinical referrals	44	23	31	NR	Community support group participation (like AA) encouraged	Low
Kiefer, 2003[74] Kiefer, 2004[75] Kiefer, 2005[76]	ACA 1,998 (40) NTX 50 (40) Placebo (40) ACA 1.998 + NTX 50 (40)	12	Germany; 1 site in Hamburg; outpatient	From inpatient withdrawal treatment	46	NR	26	0	Group therapy	Low

Table 17. Characteristics of double-blind head-to-head randomized controlled trials of acamprosate versus naltrexone (continued)

Author, Year Trial Name	Arm Dose, mg/Day (N)	Rx Duration, Weeks (Followup)	Setting	Recruitment Method	Age, Years	% Non-White	% Female	% With Co-occurring Condition	Cointervention	Risk of Bias
Mann, 2012[79] 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	NR	23	NR	Medical Management	Medium
Morley, 2006[61] Morley, 2010[80]	ACA 1,998 (55) NTX 50 (53) Placebo (61)	12	Australia; 3 treatment centers in Sydney	Patients who had attended an inpatient detoxification program, outpatient treatment, or followup, or who responded to live or print ads	45	NR	30	Severe concurrent illness (psychiatric or other) – NOS 3	All offered 4-6 sessions of manualized compliance therapy	Low

AA = Alcoholics Anonymous; ACA = acamprosate; CBI = combined behavioral intervention; COMBINE = Combined Pharmacotherapies and Behavioral Intervention; mg = milligram; MM = medical management; N = number; NA = not applicable; NOS = not otherwise specified; NTX = naltrexone; U.S. = United States.

Note: Age, Years is the mean age in years, unless otherwise stated.

[a] 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).

Return to Any Drinking

Our meta-analysis found no statistically significant difference between naltrexone and acamprosate (RD, 0.02; 95% CI, -0.03 to 0.08; 3 trials).

Return to Heavy Drinking

Our meta-analysis found no statistically significant difference between naltrexone and acamprosate (RD, 0.01; 95% CI, -0.05 to 0.06; 4 trials).

Drinking Days

Two of the 4 trials reported sufficient data for meta-analysis for drinking days; neither found a statistically significant difference between treatments.[61,65] Our meta-analysis found no statistically significant difference between naltrexone and acamprosate (WMD, -2.98; 95% CI, -13.4 to 7.5).

Heavy Drinking Days

The COMBINE study reported that analyses of alternative summary measures of drinking, including heavy drinking days per month (p=0.006) were consistent with those for the coprimary end points (percentage of days abstinent from alcohol and time to first heavy drinking day), all showing a significant naltrexone by combined behavioral intervention (CBI) interaction.

Drinks per Drinking Day

Two of the trials reported some information about drinks per drinking day, but not enough data for us to conduct quantitative synthesis. The trial conducted in Australia reported no statistically significant difference between acamprosate and naltrexone (mean [SD], 7.5 [6.1] versus 5.9 [6.1]; p not reported). The COMBINE study reported that analyses of alternative summary measures of drinking, including drinks per drinking day (p=0.03), were consistent with those for the coprimary end points (percentage of days abstinent from alcohol and time to first heavy drinking day), all showing a significant naltrexone by CBI interaction.

Disulfiram Versus Naltrexone

Characteristics of Trials

We included 1 trial comparing disulfiram with naltrexone (Table 18). It compared disulfiram, naltrexone, placebo, and the combination of disulfiram plus naltrexone for 12 weeks in Veterans Administration outpatient settings. All subjects met criteria for alcohol dependence and had co-occurring Axis I psychiatric disorders. Almost all subjects were male. The trial did not report information on smoking history at baseline.

Table 18. Characteristics of double-blind head-to-head randomized controlled trials of disulfiram versus naltrexone

Author, Year Trial Name	Arm Dose, mg/Day (N)	Rx Duration, Weeks	Setting	Recruitment Method	Age, Years	% Non-White	% Female	% With Co-occurring Condition	Cointervention	Risk of Bias
Petrakis, 2005[90] Ralevski, 2007[94] Petrakis, 2007[95] Petrakis, 2006[96] VA MIRECC	DIS 250 (66) NTX 50 (59) Placebo (64) NTX 50 + DIS 250 (65)	12	U.S.; outpatient VA	Recruited as outpatients or by ads	47	26	3	Axis I disorder 100	Psychiatric treatment as usual 100%	High[a]

DIS = disulfiram; mg = milligram; MIRECC = Mental Illness Research, Education and Clinical Center; N = number; NTX = naltrexone; U.S. = United States; VA = Veterans Administration.

Note: Age, Years is the mean age in years, unless otherwise stated.

[a] High risk of bias for disulfiram versus naltrexone; medium for naltrexone versus placebo.

The study used a double-blind design for the comparison between naltrexone and placebo, but not for disulfiram (which was given open label). We rated the trial as high risk of bias for the comparison between disulfiram and naltrexone, primarily for high risk of ascertainment bias (see Appendix C for details; we rated it as medium risk of bias for naltrexone versus placebo).

Other studies that did not meet our inclusion criteria for this section comparing disulfiram with naltrexone were either open-label studies[184-186] or were conducted in adolescents.[187]

Return to Any Drinking

The trial reported no statistically significant difference between disulfiram and naltrexone for number of subjects achieving total abstinence (51 versus 38, p=0.11).

Drinking Days

The trial reported no statistically significant difference between disulfiram and naltrexone for the percentage of days abstinent (96.6 versus 95.4, p=0.55).

Heavy Drinking Days

The trial reported no statistically significant difference between disulfiram and naltrexone for the percentage of heavy drinking days (3.2 versus 4, p=0.65).

Head-to-Head Trials Including Medications Used Off-Label or Those Under Investigation

Characteristics of Trials

We found 4 eligible trials (Table 19). All 4 utilized naltrexone; none treated subjects with acamprosate or disulfiram. Off-label medications evaluated included aripiprazole, desipramine, paroxetine, sertraline, and topiramate. No 2 trials assessed the same head-to-head comparison. Duration of treatment ranged from 12 to 16 weeks. Two were conducted in the United States, 1 in Brazil, and 1 in Italy. Mean age of subjects was similar across trials (in the 40s). All subjects met criteria for alcohol dependence. One trial enrolled all males,[119] and 1 did not report information on sex.[188] The other 2 included 9 to 38 percent women.[104,189] One trial only included subjects with both PTSD and alcohol dependence;[189] 1 only included those with depression and alcohol dependence.[104] Trials typically included or encouraged psychological or psychosocial co-interventions.

Aripiprazole Compared With Naltrexone

The only included trial reported no significant differences between groups for number of subjects who remained abstinent, number of subjects who relapsed, mean number of abstinent days, and heavy drinking days.[188]

Desipramine Compared With Paroxetine

One included trial, rated as high risk of bias, randomized patients with PTSD and alcohol dependence to desipramine, paroxetine, desipramine plus naltrexone, or paroxetine plus naltrexone.[189] The trial found that patients treated with desipramine had fewer heavy drinking days (p=0.009) and drinks per drinking day (p=0.027) than those who received paroxetine.

Table 19. Characteristics of double-blind head-to-head randomized controlled trials including medications used off-label, or those under investigation

Author, Year	Arm Dose, mg/Day (N)	Rx Duration, Weeks	Setting	Recruitment method	Age, Years	% Non-White	% Female	% With Co-occurring Condition	Cointervention	Risk of Bias
Baltieri, 2008[119]; Baltieri, 2009[128]	Topiramate target 200, maximum 400 (52) NTX 50 (49) Placebo (54)	12	Brazil; outpatient	NR	44 to 45	29	0	NR	Psychosocial 100%	High
Martinotti, 2009[188]	Aripiprazole 5-15 (29) NTX 50 (28)	16	Italy; outpatient; university hospital day clinic	Direct recruitment from local facility	40	NR	NR	Mood disorder 19 Anxiety disorder 11[a]	None required	Medium
Petrakis, 2012[189]	Desipramine 200 + placebo (24)[b] Paroxetine 40 + placebo (20) Desipramine 200 + NTX 50 (22) Paroxetine 40 + NTX 50 (22)	12	U.S.; outpatient; multiple mental illness centers, most from VAs	Local advertising (nonveterans); mental illness centers (veterans)	47	25	9	PTSD 100	Clinical management/ compliance enhancement therapy 100%	High
Pettinati, 2010[104]	Sertraline 200 (40) NTX 100 (49) Placebo (39) Sertraline 200 + NTX 100 (42)	14	U.S.; outpatient	Newspaper ads, referrals	43	35	38	Depression 100	CBT 100%	Medium

CBT = cognitive behavioral therapy; mg = milligram; N = number; NR = not reported; NTX = naltrexone; PTSD = post-traumatic stress disorder; U.S. = United States; VA = Veterans Affairs.

Note: Age, Years is the mean age in years, unless otherwise stated.

[a] Study also reported the following percentages of subjects 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%.

[b] 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.

Sertraline Compared With Naltrexone

The only included trial reported a higher abstinence rate for patients (all had alcohol dependence and co-occurring depression) who received the combination of sertraline and naltrexone than for those who received either naltrexone, sertraline, or placebo only (53.7 percent versus 21.3 percent versus 27.5 percent versus 23.1 percent; p=0.001).[104] The difference between naltrexone and sertraline given alone was not significant.

Topiramate Compared With Naltrexone

The only included trial, rated as high risk of bias, reported no significant differences between topiramate and naltrexone for proportion of abstinent subjects, cumulative abstinence duration,

time to first relapse, or heavy drinking weeks.[119] Significantly more subjects in the topiramate group participated in AA than in the naltrexone group (19.2 percent versus 4.1 percent, p=0.04).

Systematic Reviews

We included 5 systematic reviews for this KQ.[37,38,190-192] Two were reviews from the Cochrane Collaboration assessing acamprosate[37] or opioid antagonists (naltrexone and nalmefene).[38] One assessed the efficacy of disulfiram,[190] 1 was a sex-specific individual patient data meta-analysis of response to acamprosate,[191] and 1 was for the United Kingdom's National Institute for Clinical Excellence (NICE) guidelines on alcohol-use disorders.[192] All 5 were rated as low or medium risk of bias. In general, the 5 systematic reviews did not report findings that conflict with our results, so we describe them only briefly in this report. None of the reviews included publications from the past few years, as literature searches were typically completed 3 or more years ago.

The Cochrane Collaboration review of acamprosate for people with alcohol dependence (literature searches through January 2009) found acamprosate to be effective.[37] It reported a 14 percent reduction in return to any drinking compared with placebo (relative risk [RR], 0.86; 95% CI, 0.81 to 0.91; number needed to treat [NNT], 9.1; 95% CI, 6.7 to 14.3). The Cochrane Collaboration review of opioid antagonists (literature searches through January 2010) reported that naltrexone reduced the risk of heavy drinking (RR, 0.83; 95% CI, 0.76 to 0.90; NNT, 9.1), decreased drinking days (WMD, -3.89; 95% CI, -5.75 to -2.04), and decreased heavy drinking days (WMD, -3.25; 95% CI, -5.51 to -0.99) compared with placebo.[38] Effects of naltrexone on return to any drinking were not statistically significant (RR, 0.96; 95% CI, 0.92 to 1.00).

The sex-specific individual patient data meta-analysis (N=6,111) of response to acamprosate found a significant effect of acamprosate compared with placebo for improving rates of abstinence and no heavy drinking in both women and men.[191] Men and women did not differ on any measure of acamprosate efficacy.

The review for the NICE guidelines found that the evidence for both acamprosate and naltrexone supports their efficacy for improving alcohol consumption outcomes.[192] It reported a significant effect of acamprosate in promoting abstinence when compared with placebo (RR, 0.83; 95% CI, 0.77 to 0.88) and for the number of individuals relapsing to heavy drinking (RR, 0.90; 95% CI, 0.81 to 0.99). It found that oral naltrexone reduced rates of relapse to heavy drinking (RR, 0.83; 95% CI, 0.75 to 0.91), reduced mean drinks per drinking day (standardized mean difference [SMD], -0.28; 95% CI, -0.44 to -0.11), and reduced days of heavy drinking (SMD -0.43; 95% CI, -0.82 to -0.03) compared with placebo. Oral disulfiram was not significantly different from placebo in preventing participants from lapsing to alcohol consumption (RR, 1.05; 95% CI, 0.96 to 1.15).

Key Question 2. Health Outcomes

For this Key Question (KQ), we describe the characteristics of included studies and then results for the included health outcomes (accidents, injuries, quality of life [QoL], function, and mortality). Throughout this KQ, we include headers and sections only for outcomes reported by the included studies.

Detailed Synthesis: Placebo-Controlled Trials of FDA-Approved Medications for Treating Alcohol Dependence

We found no placebo-controlled trials of disulfiram that reported a health outcome of interest. Below we describe 10 placebo-controlled trials of acamprosate and 9 placebo-controlled trials of naltrexone that reported a health outcome of interest (including the COMBINE study, which has comparisons between placebo and both medications). These represent a subset of the trials included in KQ 1.

Acamprosate

Characteristics of Trials

Ten placebo-controlled RCTs reported a health outcome (Table 20). Sample sizes ranged from 100 to 612 participants in acamprosate plus placebo arms. Duration of treatment ranged from 12 to 52 weeks. Followup to 1 year or longer was available for 6 trials. No studies identified a health outcome as their primary outcome.

The mean age of patients ranged from 40 to 48. All patients enrolled in the trials had alcohol dependence. Two trials reported on race: 9 to 15 percent of patients were nonwhite.[66,69] Females made up 18 to 38 percent of the patients across studies. Three trials[65,66,69] reported smoking status at baseline, from 44 percent to 55 percent.[65] No trials specified the percentage of patients who had a co-existing medical or psychiatric condition.

There was minor variation in the dosing of acamprosate across trials. Most studies used doses from 1,332 to 1,998 mg per day and determined dosing based on weight. Two studies included an arm who received 3 g per day.[65,66] Three studies commented on the use of other pharmacotherapy to address alcohol or comorbid psychiatric disorders. One trial allowed the use of disulfiram on a voluntary basis.[70] Two other trials reported that 5 to 6 percent of patients in either treatment group were prescribed benzodiazepines.[72], and 1 trial allowed the use of "hypnotics, anxiolytics or antidepressants" in either group.[81]

Three studies were conducted in the United States;[65,66,69] all others were conducted in European countries. One study was conducted in a primary care setting;[69] most of the others were conducted in outpatient substance abuse or psychiatric treatment centers. The majority of trials recruited patients during or shortly after discharge from an inpatient substance abuse treatment center. Two U.S. trials recruited patients via newspaper advertisement[66] or a combination of advertisements and provider referrals.[69] One German trial recruited patients from outpatient substance abuse treatment centers.[86] The COMBINE study recruited patients by advertisement and referral from 11 academic centers.[65]

Table 20. Characteristics of included double-blind randomized placebo-controlled trials of acamprosate that report a health outcome

Author, Year Trial Name Design	Arm Dose, mg/Day (N)	Rx Duration, Weeks (Followup)	Setting	Recruitment Method	Age, Years	% Non-White	% Female	Cointervention	Risk of Bias
Anton, 2006[65] Donovan, 2008[68] LoCastro, 2009[193] 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)[a]	16 (68)	U.S.; 11 academic sites	Ads, community resources, clinical referrals	44	23	31	As randomized; community support group participation (like AA) encouraged	Low
Berger, 2013[69]	ACA 1,998 (51) Placebo (49)	12	U.S.; 2 outpatient primary care clinics	Provider referral and ads	48	9	38	Brief structured behavioral intervention from primary care physician	Medium
Besson, 1998[70]	ACA 1,300 to 1,998 (55) Placebo (55)	52 (108)	Switzerland; Outpatient; 3 psychiatric treatment centers	From inpatient treatment unit	42	NR	20	Routine counseling 100% Voluntary disulfiram 22% to 24%	Medium
Geerlings, 1997[72]	ACA 1,332 to 1,998 (128) Placebo (134)	26 (52)	Belgium, the Netherlands, and Luxembourg; Outpatient substance abuse treatment centers	Recruited from detoxification patients in same centers	40 to 42	NR	24	ACA: benzodiazepines 5% Placebo: benzodiazepines 6%	Medium
Lhuintre, 1990[78]	ACA 1,332 (279) Placebo (290)	12 (12)	France; Outpatient substance abuse treatment centers	Inpatient treatment centers (30 centers across France)	42 to 43	NR	18	None	Unclear
Mason, 2006[66]	ACA 2,000 (258) ACA 3,000 (83) Placebo (260)	24 (32)	U.S.; 21 outpatient clinics[b]	Primarily by newspaper ads	44 to 45	14 to 15	29 to 36	Brief abstinence-oriented protocol-specific counseling and self-help materials 100%	Low
Paille, 1995[81]	ACA 1.3 g (188) ACA 2 g (173) Placebo (177)	52 (78)	France; NR[c]	Referral from alcohol specialist centers	43	NR	20	Supportive psychotherapy 100% Hypnotics 6 to 7% Anxiolytics 8 to 12% Antidepressants 8 to 9%	Medium

Table 20. Characteristics of included double-blind randomized placebo-controlled trials of acamprosate that report a health outcome (continued)

Author, Year Trial Name Design	Arm Dose, mg/day (N)	Rx Duration, Weeks (Followup)	Setting	Recruitment Method	Age, Years	% Non-white	% Female	Co-intervention	Risk of Bias
Poldrugo, 1997[84]	ACA 1,332 to 1,998 (122) Placebo (124)	26 (52)	Italy; Inpatient for 1-2 weeks then outpatient; multicenter community-based alcohol rehabilitation program	From acute inpatient withdrawal treatment	43 to 45	NR	23 to 31	Community-based rehabilitation program with group sessions, alcohol education, community meetings 100%	Medium
Sass, 1996[86]	ACA 1,332 to 1,998 (136) Placebo (136)	48 (96)	Germany; Psychiatric outpatient	Outpatient referral	41 to 42	NR	22	Counseling / psychotherapy 100%	Medium
Whitworth, 1996[88]	ACA 1,332 or 1,998 (224) Placebo (224)	52 (52)	Austria; Outpatient specialty	Recruited after inpatient detoxification	42	NR	21	NR	Medium

AA = Alcoholics Anonymous; ACA = acamprosate; CBI = combined behavioral intervention; COMBINE = Combined Pharmacotherapies and Behavioral Intervention; mg = milligram; MM = medical management; N = number; NR = not reported; NTX = naltrexone; U.S. = United States.

Note: Age, Years is the mean age in years, unless otherwise stated.

[a] 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).

[b] Clinics were affiliated with academic medical centers and had investigators experienced in alcoholism treatment.

[c] The article was not explicit about the setting, but patients received psychotherapy and psychiatric medication management suggesting a psychiatric outpatient setting.

Eight trials were rated as low or medium risk of bias. One trial was rated as unclear risk of bias, primarily due to unclear handling of missing data and unclear masking of outcome assessors (see Appendix C for details).[78]

Accidents or Injuries

We identified 1 study, rated as unclear risk of bias, reporting that one patient in the placebo group died by "accident." No other details on the cause or nature of the accident were provided.[78]

Quality of Life or Function

The COMBINE study assessed QoL using the World Health Organization Quality of Life (WHOQOL) and 12-item Short-Form Health Survey (SF-12v2) physical and mental health scores. Results were not presented for each treatment group separately.[193] These results are discussed in detail in the acamprosate versus naltrexone section (below). Briefly, no clinically significant differences were found across the eight combinations of pharmacological and behavioral treatments for QoL for acamprosate compared with placebo.[193]

Mortality

Nine trials of acamprosate reported on mortality. Few deaths were reported; no study reported more than two deaths in any group. Table 21 shows the number of deaths in studies which report deaths per study arm. In the COMBINE trial, the authors reported that one fatal serious adverse event was reported during the 16-week treatment phase. Investigators classified this death as being unrelated to the study medication. No details were provided on which group the death occurred in, the nature of the adverse event, or the cause of death.[65]

Table 21. Mortality reported in placebo-controlled trials of acamprosate[a]

Author, Year	Study Duration, Weeks	N (Cause) Deaths, Placebo Arm	N (Cause) Deaths, Acamprosate Arm
Berger, 2013[69]	12	0	0
Besson, 1998[70]	52	1 (cardiac arrest)	0
Geerlings, 1997[72]	26	0	0
Mason, 2006[66]	26	0	0
Paille, 1995[81]	51	2 (NR)	4 (NR)[b]
Poldrugo, 1997[84]	26	1 (NR)	0
Sass, 1996[86]	52	1 (suicide, by hanging)	1 (suicide, by hanging)
Whitworth, 1996[88]	26	1 (NR)	2 (NR)

N = number; NR = not reported.

[a] The table includes 8 of the 9 trials that reported on mortality. The other trial was the COMBINE trial (as described in the text, it did not report which group the death occurred in).

[b] The study reported 2 deaths in the arm receiving 1.3 grams daily and 2 deaths in the arm receiving 2 grams daily.

Naltrexone

Characteristics of Trials

Nine RCTs comparing naltrexone with placebo reported at least one health outcome of interest (Table 22). All 9 trials were rated as low or medium risk of bias. Sample sizes ranged from 31 to 618 participants in the naltrexone plus placebo arms. Duration of treatment ranged from 12 to 26 weeks.

Mean age was similar across trials, ranging from 39 to 50. Two trials included only male patients;[102,121] females made up 3 to 38 percent of patients in the other trials. One study did not report on the race of study participants[108]; most of the other trials enrolled a minority of nonwhite subjects (17 to 35 percent) and 2 enrolled a majority (70 to 76 percent).[42,106] Three studies provided information on smoking status; approximately half of participants in those trials were smokers.[42,65,97] All trials enrolled a vast majority (93 percent or more) of patients with alcohol dependence. Three trails did not specifically include (or describe) whether study participants had any co-existing medical or psychiatric disorders.[97,106,108] One trial was conducted among men who have sex with men; 67 percent reported any other drug use and 15 percent had HIV.[102] Four trials were conducted among populations who all had a specific psychiatric comorbidity: 1 among patients with either schizophrenia or schizoaffective disorder,[121] 1 among patients with cocaine dependence,[106] 1 among patients with at least one other psychiatric (Axis I) disorder,[90] and 1 among patients with depression.[104]

Table 22. Characteristics of included double-blind randomized placebo-controlled trials of naltrexone that report a health outcome

Author, Year Trial Name	Arm Dose, mg/Day (N)	Rx Duration, Weeks (Follow-up)	Setting	Recruitment Method	Age, Years	% Non-White	% Female	% With Co-occurring Condition	Cointervention	Risk of Bias
Anton, 2006[65] Donovan, 2008[68] LoCastro, 2009[193] 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)[a]	16 (68)	U.S.; 11 academic sites	Ads, community resources, clinical referrals at 11 academic sites	44	23	31	NR	As randomized; community support group participation (like AA) encouraged	Low
Balldin, 2003[108]	NTX 50 (56) Placebo (62)	26	Sweden; 10 sites outpatient	Ads, outpatient treatment center	48 to 51	NR	9 to 23	0	None	Low
Garbutt, 2005[97]; Pettinati, 2009[131]	NTX inj 380 every 4 weeks (208) NTX inj 190 every 4 weeks (210) Placebo (209)	26	U.S.; Inpatient and outpatient, private and VA	NR	45	17	32	NR	BRENDA standardized supportive therapy 100%	Medium
Morgenstern, 2012[102]	NTX 100 + MBSCT (51) NTX 100 (51) Placebo + MBSCT (50) Placebo (48)	12	U.S.; NR	Ads, community outreach	40	26	0	HIV 15 Any drug use 67	BBCET 100%	Medium
O'Malley, 2008[42]	NTX 50 (34) Placebo (34) NTX 50 + SER 100 (33)	16	U.S.; Outpatient	Direct community recruitment, health clinic referral, local ads	40	70	34	NR	MM 100%	Medium
Petrakis, 2004[121]; Ralevski, 2006[143]	NTX 50 (16) Placebo (15)	12	U.S.; At least 3 outpatient centers—MIRECC clinics	Direct recruitment from participating centers	46	19	0	Schizophrenia or schizoaffective disorder 100	CBT + psychiatric treatment as usual Neuroleptics 52% Benzodiazepines 16% Thymoleptics 39%	Medium
Pettinati, 2008[106]	NTX 150 (82) Placebo (82) Subjects also randomized to either CBT or BRENDA (2x2 design)	12	U.S.; University-affiliated outpatient substance abuse treatment research facility	Those seeking treatment at the facility	39	76	29	Cocaine dependence 100	NR	Medium

Table 22. Characteristics of included double-blind randomized placebo-controlled trials of naltrexone that report a health outcome (continued)

Author, Year Trial Name	Arm Dose, mg/day (N)	Rx Duration, Weeks (Follow-up)	Setting	Recruitment Method	Age, Years	% Non-white	% Female	% With Co-occurring Condition	Co-intervention	Risk of Bias
Pettinati, 2010[104]	SER 200 (40) NTX 100 (49) Placebo (39) SER 200 + NTX 100 (42)	14	U.S.; Outpatient	Newspaper ads, referrals from local professional or friends / family	43	35	38	Depression 100	CBT 100%	Medium
Petrakis, 2005[90] Ralevski, 2007[94] Petrakis, 2007[95] Petrakis, 2006[96] VA MIRECC	DIS 250 (66) NTX 50 (59) Placebo (64) NTX 50 + DIS 250 (65)	12	U.S.; Outpatient VA	Recruited as outpatients or ads	47	26	3	Axis I disorder 100	Psychiatric treatment as usual 100%	Medium

AA = Alcoholics Anonymous; ACA = acamprosate; 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; CBI = combined behavioral intervention; CBT = cognitive behavioral therapy; COMBINE = Combined Pharmacotherapies and Behavioral Intervention; DIS = disulfiram; inj = injection; mg = milligram; MBSCT = modified behavioral self-control therapy; MIRECC = Mental Illness Research, Education and Clinical Center; MM = medical management; N = number; NR = not reported; NTX = naltrexone; SER = sertraline; U.S. = United States; VA = Veterans Affairs.

Note: Age, Years is the mean age in years, unless otherwise stated.

[a] 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).

One trial evaluated the efficacy of two doses of injectable naltrexone[97] and the remainder randomized patients to oral naltrexone either at 50, 100,[102,104,193] or 150 mg per day.[106] Four trials described a specific behavioral or psychological co-intervention.[97,102,108,131] Two trials conducted among those with a psychiatric comorbidity specified that patients continued medical management and usual psychiatric care[90,121] and 1 included cognitive behavioral therapy for depressed patients.[104] No specific co-intervention was described in the trial comparing naltrexone with placebo in patients with cocaine dependence.[106]

One trial was conducted in Sweden;[108] all others were conducted in the United States. Most were conducted at an outpatient substance abuse or mental health center; none were conducted in primary care settings.

Mortality

Six placebo-controlled trials of naltrexone reported mortality rates; no study found more than one death in each treatment group. Three studies reported that there were no deaths in either group,[104,106,131] 1 reported one death in each study arm without providing additional details,[90] and 1 study reported a death due to alcohol intoxication in the placebo group.[108] In the COMBINE trial, the authors reported that one fatal serious adverse event was reported during the 16-week treatment phase. Investigators classified this death as being unrelated to the study medication. No details were provided on which group the death occurred in, the nature of the adverse event, or the cause of death.[65]

Quality of Life or Function

Four placebo-controlled trials of naltrexone measured QoL or some aspect of function, each trial using a different measure. One trial conducted among men who have sex with men[102] measured QoL at 13 weeks using the Short Inventory of Problems,[194] an alcohol-specific QoL measure used to assess negative consequences of drinking. No differences between naltrexone and placebo in end-of-treatment scores were found when using a last observation carried forward (LOCF) method to impute missing data (mean difference between groups at 13 weeks was -1.7, $p<0.09$).[102]

One study comparing injectable naltrexone with placebo measured QoL using the Medical Outcomes Study 36-item short-form health survey (SF-36).[131,195] Data were reported separately for the overall physical and overall mental health summary scores of the SF-36. The study found no significant difference on either scale at 24 weeks between the placebo group and the injectable naltrexone 190 mg per month group. Patients receiving naltrexone 380 mg per month had greater improvement on the mental health summary score than those receiving placebo at 24 weeks (8.2 versus 6.2, $p=0.044$), but there was no difference in improvement found on the physical health summary score (0.2 versus -0.1, $p=0.51$).[131]

The COMBINE study assessed QoL using the WHOQOL and SF-12v2 physical and mental health scores. Results were not presented for each treatment group separately.[193] See the section below on acamprosate versus naltrexone for details on these results. Briefly, the results indicate that the eight combinations of pharmacological and behavioral treatments did not show clinically significant differential effects on QoL for either scale.[193]

One placebo-controlled study of naltrexone 50 mg measured the Drinker Inventory of Consequences (DrInC) at 16 weeks.[42] The DrInC is a 50-item questionnaire designed to measure adverse consequences of alcohol abuse in five areas: interpersonal, physical, social, impulsive,

and intrapersonal.[194] More patients in the placebo group reported one or more alcohol-related consequence than in the naltrexone group, as measured by the DrInC (76 versus 45%, p=0.02).[42]

Detailed Synthesis: Placebo-Controlled Trials of Medications Used Off-Label or Those Under Investigation

As described in KQ 1, we found just 1 placebo-controlled trial meeting our inclusion criteria for each of the following medications: aripiprazole, atomoxetine, desipramine, fluvoxamine, imipramine, olanzapine, ondansetron, paroxetine, and varenicline. We found insufficient evidence to support the efficacy of these medications. Among these studies, just 2 reported a health outcome (number of deaths for fluvoxamine and placebo[196] and varenicline and placebo, and QoL for varenicline and placebo).[197] We provide additional details about these trials in Appendix E.

For the medications with multiple placebo-controlled trials (baclofen, buspirone, citalopram, fluoxetine, nalmefene, quetiapine, sertraline, topiramate, and valproic acid), 6 trials reported outcomes relevant to KQ 2 (Table 23): 2 placebo-controlled trials of as-needed nalmefene,[159,160] 1 trial of quetiapine in bipolar patients with alcohol dependence,[166] 2 placebo-controlled trials of sertraline in patients with co-existing depression or dysthymia,[104,170] and 1 placebo-controlled trial of topiramate.[179,180] Sample size ranged from 83 to 718. Duration of treatment ranged from 12 to 24 weeks.

Table 23. Characteristics of included double-blind randomized placebo-controlled trials of medications used off-label or those under investigation

Author, Year	Arm Dose, mg/Day (N)	Rx Duration, Weeks	Setting	Recruitment Method	Age, Years	% Non-White	% Female	% With Co-occurring Condition	Cointervention	Risk of Bias
Gual, 2003[170]	SER 50-150 (44) Placebo (39)	24	Spain; Outpatient	Outpatient alcohol dependence treatment	47	NR	47	Depression/ dysthymia 100	NR	Medium
Gual,, 2013[160]	NALM 20 as-needed (358) Placebo (360)	24	Belgium, Czech Republic, France, Italy, Poland, Portugal, Spain; 57 sites	Referrals and ads	44 to 45	1	26 to 29	0	BRENDA	Medium
Johnson, 2007[179] Johnson, 2008[180]	TOP 50-300[a] (183) Placebo (188)	14	U.S.; 17 academic sites; outpatient	Academic sites and by newspaper, radio, television ads	47 to 48	15	26 to 28	NR	BBCET 100%	Low
Mann, 2013[159]	NALM 20 as-needed (306) Placebo (298)	24	Austria, Finland, Germany, Sweden; 39 sites	Referrals and ads	52	<1	32 to 33	0	BRENDA	Medium

Table 23. Characteristics of included double-blind randomized placebo-controlled trials of medications used off-label, or those under investigation (continued)

Author, Year	Arm Dose, mg/day (N)	Rx Duration, Weeks	Setting	Recruitment Method	Age, Years	% Non-white	% Female	% With Co-occurring Condition	Co-intervention	Risk of Bias
Pettinati, 2010[104]	SER 200 (40) NTX 100 (49) Placebo (39) SER 200 + NTX 100 (42)	14	U.S.; Outpatient	Newspaper ads, referrals	43	35	38	Depression 100	CBT 100%	Medium
Stedman, 2010[166]	Quetiapine 300-800 (175) Placebo (186)	12	U.S.; Outpatient; 43 centers	NR	39	12	37	Bipolar 100	None	High

BBCET, brief behavioral compliance enhancement treatment; 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; CBT, cognitive behavioral therapy; mg = milligram; N = number; NR, not reported; NTX = naltrexone; SER, sertraline; TOP, topiramate; U.S., United States.

Note: Age, Years is the mean age in years, unless otherwise stated.

[a] Dose titrated over a 5-week period from 25 to a maximum of 300 mg; mean 171.

The mean age of participants was similar across trials—39 to 52 years. Twenty-six to 47 percent of patients were female, and from less than 1 to 35 percent of patients were nonwhite in the 5 trials reporting information on race; 1 did not report information on race.[159,160,170] Two trials reported smoking status: 1 placebo-controlled trial of sertraline enrolled 14 to 20 percent smokers,[104] and the trial of quetiapine enrolled 56 percent smokers.[166] Five of the trials were conducted in those with alcohol dependence; the trial of topiramate did not specify the percentage who met criteria for alcohol dependence.[179] Three trials were conducted in the United States, 1 in Spain,[170] and 2 were multinational European.[159,160]

The placebo-controlled trial of quetiapine was rated as high risk of bias, primarily for high risk of attrition bias and methods of handling of missing data (see Appendix C for details).[166]

Nalmefene

Mortality

Two placebo-controlled trials of as-needed nalmefene reported deaths in at least one treatment group over 24 weeks. In one (N=598),[159] no patients in the nalmefene group died, but two patients in the placebo group died. Both deaths were due to suicide. In the other trial (N=655),[160] one patient randomized to placebo died of hepatocellular carcinoma and one patient randomized to nalmefene experienced sudden death of unknown cause (assessed by the investigator as not being related to the study medication).

Quetiapine

Mortality

Two deaths (one in each treatment group) were reported in the placebo-controlled trial of quetiapine rated as high risk of bias; one after a skull fracture caused by blunt trauma in the quetiapine group and one attributed to myocardial ischemia more than 30 days after treatment in the placebo group.[166] Both deaths were judged to be unrelated to the study medications by the study investigators.

Quality of Life or Function

No difference was found between the quetiapine and placebo groups in health-related QoL assessed by the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q)[198] at 12 weeks (mean score 46.9 versus 47.7, p=0.63). Functional impairment was assessed using the Sheehan Disability Score (SDS),[199] a questionnaire that aims to assess the relationship between symptoms and impairment in work, social, and family life. No statistically significant differences between quetiapine and placebo groups were found for mean total SDS score (11.03 versus 9.17), mean SDS number of lost work days per week (1.1 versus 0.7), and SDS number of underproductive days per week over 12 weeks (1.8 versus 1.3).[166]

Sertraline

Mortality

One placebo-controlled trial of sertraline in patients with co-existing alcohol dependence and depression reported no deaths in either treatment group at 13 weeks.[104]

Quality of Life or Function

One study of patients with co-existing depression measured QoL using the SF-36 at 24 weeks. Scores were presented in a figure only (bar graph, data not reported). QoL improved during treatment for both the placebo and sertraline groups; the authors noted that the sertraline group improved more than placebo in only the mental health summary score of the SF-36 (p=0.031).[170]

Topiramate

Accident or Injury

One placebo-controlled trial of topiramate reported injury in a list of adverse events occurring during treatment (over 12 weeks).[179] Eight patients (4.4 percent) in the topiramate group and 22 patients in the placebo group (11.7 percent) had an injury (p=0.01). The authors note that three separate individuals in the placebo group experienced a tibial plateau fracture. No other information is provided on the cause or nature of the injuries.[179]

Mortality

The placebo-controlled trial of topiramate reported one death in the placebo group following a cardiac arrest associated with gastrointestinal tract bleeding and seizures.[179] According to the investigators, the precipitating incident could not be determined. There was no mention of deaths in the topiramate group.[179]

Detailed Synthesis: Head-to-Head Trials Including FDA-Approved Medications

We identified 3 RCTs (Table 24) that reported at least one health outcome of interest. Two of these were rated as high risk of bias for the head-to-head comparison—one three-arm study comparing naltrexone with disulfiram or placebo,[90] and one four-arm open-label trial comparing acamprosate, disulfiram, and naltrexone.[184] Both trials had high risk of ascertainment bias; one did not adequately handle missing data for QoL outcomes (see Appendix C for additional details about risk of bias ratings).

Table 24. Characteristics of head-to-head randomized controlled trials reporting a health outcome

Author, Year Trial Name Design	Arm Dose, mg/Day (N)	Rx Duration, Weeks (Followup)	Setting	Recruitment Method	Age, Years	% Non-White	% Female	Cointervention	Risk of Bias
Anton, 2006[65] LoCastro, 2009[193] COMBINE DBRCT	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)[a]	68	U.S.; 11 sites	Ads, community resources, clinical referrals at 11 academic sites	44	23	31	Community support group participation encouraged (e.g., AA)	Low
Laaksonen, 2008[184] OLRCT	ACA 1,998 or 1,333 (81) DIS 100 to 200 (81) NTX 50 (81)	Up to 52 (119)	Finland; 6 sites in 5 cities	Volunteers seeking outpatient treatment for alcohol problems	43	0	29	Manual-based CBT[b]	High for quality of life / KQ 2
Petrakis, 2005[90] Ralevski, 2007[94] Petrakis, 2007[95] Petrakis, 2006[96] VA MIRECC DBRCT	DIS 250 (66) NTX 50 (59) Placebo (64) NTX 50 + DIS 250 (65)	12	U.S.; Outpatient VA	Recruited as outpatients or via ads	47	26	3	Psychiatric treatment as usual 100%	High for DIS vs. NTX

AA = Alcoholics Anonymous; ACA = acamprosate; CBI = combined behavioral intervention; COMBINE = Combined Pharmacotherapies and Behavioral Intervention; DBRCT = double-blind randomized controlled trial; DIS = disulfiram; mg =

milligram; MIRECC = Mental Illness Research, Education and Clinical Center; MM = medical management; N = number; NR = not reported; NTX = naltrexone; OLRCT = open-label randomized controlled trial; U.S. = United States; VA = Veterans Affairs.

Note: Age, Years is the mean age in years, unless otherwise stated.

[a] 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).

[b] Co-intervention included a "Winning at last--defeating the drinking problem" booklet targeted to match medication goals (i.e., reduction in drinking or abstinence for ACA and NTX; abstinence for DIS).

One study (COMBINE), rated as low risk of bias, reported mortality and QoL. COMBINE is a multicenter nine-arm trial that compared eight groups of patients receiving medical management with 16 weeks of naltrexone (100 mg per day) or acamprosate (3 g per day), both, and/or both placebos, with or without a combined behavioral intervention (CBI). The ninth group received CBI only and no drug or placebo. Mean age was 44 years; all patients met criteria for alcohol dependence.

Acamprosate Versus Naltrexone

Mortality

In the COMBINE trial, the authors reported that one fatal serious adverse event was reported during the 16-week treatment phase. This was classified by investigators as not related to the study medication. No details were provided on which group the death occurred in, the nature of the adverse event, or the cause of death.

One study, rated as high risk of bias, reported that one person committed suicide and two persons drowned in the acamprosate group but reported no events in the naltrexone group.[184]

Quality of Life or Functional Status

The COMBINE study assessed QoL using the WHOQOL and SF-12v2 physical and mental health scores. Results were not presented for each treatment group separately.[193] To analyze the treatment effects of specific pharmacological and behavior treatment combinations on QoL, a mixed-effects general linear model was used to examine the main and interaction effects of three treatments (acamprosate, naltrexone, and CBIs) from baseline to 26 weeks and from baseline to 52 weeks (20 ANOVAs were conducted unadjusted and 20 were adjusted for percentage heavy drinking days). The results indicate that the eight combinations of pharmacological and behavioral treatments did not show differential effects on QoL for either scale. The only two significant effects reaching a p value of <0.001 (to account for multiple tests) were the two-way interaction of naltrexone by CBI for the SF-12v2 physical health score at 52 weeks for both the adjusted and unadjusted analyses. The authors conclude that this suggests CBI and naltrexone combined have a greater impact than either alone for the SF-12v2 physical health scale; however, the difference between groups was no larger than 2.1, and unlikely to suggest a clinically meaningful difference (the 95% confidence interval for the SF-12v2 physical health scale is 6.6).[193]

One study rated as high risk of bias measured QoL with the European Quality of Life Scale (EQ-5),[200] Koskenvuo Quality of Life Scale (KQL),[201] and Visual Analogue Scale (VAS).[202]

QoL improved for both groups over the 52-week followup compared with baseline with no difference between the acamprosate or naltrexone groups.[184]

Acamprosate Versus Disulfiram

Accident or Injury

One study, rated as high risk of bias, reported one traffic accident in the disulfiram group and none in the acamprosate group over 52 weeks.[184] No details of the event were described; the study coordinator determined that the event was not related to the study treatment.

Mortality

One study, rated as high risk of bias, reported that one person committed suicide and two persons drowned in the acamprosate group and reported no events in the disulfiram group.[184]

Quality of Life

QoL was measured in one study rated high risk of bias with the EQ-5, KQL, and VAS. QoL improved for both groups over the 52-week followup compared with baseline with no difference between the acamprosate or disulfiram groups.[184]

Disulfiram Versus Naltrexone

Accident or Injury

One study, rated as high risk of bias, reported one traffic accident in the disulfiram group and no accident or injuries in the naltrexone group.[184] No details of the event were described; the study coordinator determined that the event was not related to the study treatment.

Mortality

In 1 study rated high risk of bias that compared disulfiram and naltrexone among patients with co-existing depression, one person died in the naltrexone group and no deaths were reported in the disulfiram group.[90]

Quality of Life

QoL was measured in 1 study rated high risk of bias with the EQ-5, KQL, and VAS. QoL improved for both groups over the 52-week followup compared with baseline with no difference between the disulfiram or naltrexone groups.[184]

Detailed Synthesis: Head-to-Head Trials Including Medications Used Off-Label or Those Under Investigation

We identified 3 head-to-head trials of off-label medications that measured an eligible health outcome (Table 25). One compared sertraline with naltrexone; 2 compared topiramate with naltrexone. Sample size ranged from 89 to 182 within the relevant head-to-head arms. All subjects met criteria for alcohol dependence, the average age of participants was similar across trials (43 to 48), and females made up 15 to 38 percent of participants. The trial comparing sertraline with naltrexone was conducted among patients with co-occurring depression.[104] The trials comparing topiramate with naltrexone enrolled about a quarter of subjects with personality

disorders.[203,204] Only the study comparing sertraline with naltrexone reported on smoking rates: 14 to 20 percent of participants were smokers. All studies included a psychological co-intervention.

One double-blind RCT compared sertraline 200 mg per day with naltrexone 100 mg per day[104] and 2 open-label RCTs compared topiramate 200 mg per day to naltrexone 50 mg per day.[203,204] One study was conducted within the United States[104] and 2 were conducted in Spain.[203,204] The trial comparing sertraline to naltrexone was rated as medium risk of bias and the 2 studies comparing topiramate to naltrexone were rated as high risk of bias.[203,204] One study allowed titration of topiramate from 200 mg per day up to 300 to 400 mg per day based on continued alcohol consumption or craving.[203]

Table 25. Characteristics of head-to-head randomized controlled trials including medications used off-label or those under investigation

Author, Year Design	Arm Dose, mg/Day (N)	Rx Duration, Weeks	Setting	Recruitment Method	Age, Years	% Non-White	% Female	% With Co-occurring Condition	Cointervention	Risk of Bias
Florez, 2008[205] OLRCT	TOP intended 200[a] (51) NTX 50 (51)	26	Spain; Outpatient substance abuse clinic, referrals	Recruited when presenting for treatment	47	0	15	Personality disorders 27	Therapy based on Relapse Prevention Model 100%	High
Florez, 2011[204] OLRCT	TOP 200 (91) NTX 50 (91)	26	Spain; Outpatient substance abuse clinic, referrals	Recruited and screened when presenting for treatment	47 to 48	NR	15	Personality disorders 23	BRENDA 100% At least monthly meeting with psychiatrist 100%	High
Pettinati, 2010[104] DBRCT	SER 200 (40) NTX 100 (49) Placebo (39) SER 200 + NTX 100 (42)	14	U.S.; Outpatient	Newspaper ads, referrals	43	35	38	Depression 100	CBT 100%	Medium

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; CBT = cognitive behavioral therapy; DBRCT = double-blind randomized controlled trial; mg = milligram; N = number; OLRCT = open-label randomized controlled trial; TOP = topiramate; U.S., United States.

Note: Age, Years is the mean age in years, unless otherwise stated.

[a]Actual dosing: increased by 50 mg per day up to 300 or 400 mg based on consumption control or cravings.

Sertraline Versus Naltrexone

Mortality

One trial comparing sertraline with naltrexone among patients with co-occurring depression and alcohol dependence reported no deaths in either group.[104]

Topiramate Versus Naltrexone

Quality of Life or Function

One unblinded study rated as high risk of bias used the World Health Organization Psychiatric Disability Assessment Schedule (WHO/DAS) to assess alcohol dependence-related disability at 3 and 6 months.[204] No significant changes were found in most domains of the WHO/DAS at 3 months (personal, family, social), with one exception: patients taking topiramate had a lower disability score on the employment domain (1.64 versus 2.2, p=0.047). At 6 months, the topiramate group had lower disability scores for the family (0.58 versus 1.05, p=0.035) and social domains (0.46 versus 0.83, p=0.154); there was no difference between the two groups in the employment or personal domains at 6 months.[204] A similar study (by the same author), which dosed topiramate based on continued alcohol intake or craving, found no difference between the topiramate and naltrexone groups on any of the WHO/DAS domains at 3 or 6 months.[203]

This same study measured QoL using the EQ-5D at 3 and 6 months.[204] At 3 months, the topiramate group had a small, but statistically significant, greater improvement in QoL compared

with the naltrexone group (96.10 versus 94.16, p=0.014); there was no difference between the two groups at 6 months.[204] A similar study (by the same author), which dosed topiramate based on continued alcohol intake or craving, found that patients treated with topiramate had better QoL at 3 months compared with naltrexone (96.88 versus 95.21, p=0.014) but no statistically significant difference was found between the two groups at 6 months.[203]

Key Question 3. Adverse Effects of Medications

For this question, we evaluated trials included in Key Questions (KQs) 1 and 2. In addition, we searched for nonrandomized controlled trials (non-RCTs), open-label trials, single-blind trials, prospective cohort studies, and case-control studies otherwise meeting the eligibility criteria. We ultimately included 105 double-blind RCTs, eight open-label or single-blind RCTs, and one prospective cohort study. Throughout this KQ, we often describe risks of various adverse events—risks reported are absolute risk differences (RDs) between intervention and control. Because the studies were not primarily focused on harms, the reporting of harms varied across studies significantly. Limited information was reported for most of the off-label medications—insufficient for synthesis of specific adverse events or for making definitive conclusions. We therefore focus here on the Food and Drug Administration (FDA)-approved medications and those with moderate or better evidence supporting efficacy. We do not include information on medications with insufficient evidence to support their efficacy (i.e., efficacy as determined in KQ 1).

Key Points

- Adverse events were often not collected using standardized measures, and methods for systematically capturing adverse events were often not reported.
- Selective outcome reporting could impact our results. Reporting varied across studies, with some studies only reporting adverse effects that were significantly different from placebo (or control) group, some reporting effects observed in more than some percentage of patients (e.g., 5 percent or more), and others listing effects that were considered in the study.
- While major harms were rarely reported in the studies, some minor harms (e.g., diarrhea) were reported more consistently.
- For many serious harms, the evidence was insufficient to determine comparative rates of adverse events — very little data were available.
- **Suicidality, or self-harmful behaviors**: evidence was insufficient to determine whether risk was increased with any of the medications. Evidence from studies of FDA-approved drugs was limited to 3 cases of suicide attempts or suicidal ideation reported in acamprosate arms and 3 in placebo arms. In studies that compared nalmefene with placebo, there were 4 cases of suicide attempts or suicidal ideation in nalmefene arms and 9 in placebo arms.
- **Withdrawals due to adverse events**: In head-to-head studies, the risk of withdrawals due to adverse events was not significantly different between acamprosate and naltrexone.
- **Specific adverse events:** Compared with placebo, patients treated with acamprosate had a higher risk of anxiety, diarrhea, and vomiting; those treated with naltrexone had a higher risk of dizziness, nausea, and vomiting; those treated with nalmefene had a higher

risk of dizziness, headache, insomnia, nausea, and vomiting. Trials of topiramate reported increased risks of many adverse events, including paresthesias, taste perversion, anorexia, difficulty with concentration/attention, nervousness, dizziness, pruritis, psychomotor slowing, and weight loss. In head-to-head studies, patients treated with acamprosate had a slightly lower risk of headache and vomiting than those treated with naltrexone.

Detailed Synthesis

In this section, we have considered harms associated with acamprosate, disulfiram, naltrexone, nalmefene, topiramate, and valproic acid. Our main meta-analyses included studies of low and medium risk of bias reporting results for the specific adverse event. We conducted sensitivity analyses that also included studies rated as high or unclear risk of bias. Insufficient data were available to conduct meta-analyses of results from studies that compared disulfiram with placebo, acamprosate, naltrexone, or other controls. Therefore, we described and summarized these qualitatively when possible.

Characteristics of Included Studies

The vast majority of the included RCTs are described in KQs 1 and 2, and we do not describe them again in this KQ. Ten studies not described in KQs 1 or 2 were eligible for inclusion in this KQ. These included 7 open-label[183,185,186,203,204,206] or single-blind RCTs,[207] 2 double-blind RCTs,[208-210] and 1 prospective cohort study.[211] Of those 10, 6 focused on comparisons addressed in this KQ (Table 26); the other 4 focused on comparisons with medications used off-label—either topiramate[203,204,206] or buspirone.[208,209] All but 1 of the studies[210] listed in Table 26 were rated as high risk of bias, primarily due to concerns with selection bias, attrition bias, measurement bias, confounding, or selective outcome reporting bias (see Appendix C for details).

For the 6 studies not described elsewhere that focused on comparisons addressed in this KQ, 2 compared acamprosate with naltrexone,[207,211] 1 was the multiarm COMBINE pilot study,[210] 2 compared naltrexone with disulfiram,[185,186] and 1 compared acamprosate with disulfiram.[183] Study duration ranged from 35 to 52 weeks. Three of the studies were conducted in India, 1 in the United States, 1 in Spain, and 1 in Italy. For 3 trials, study participants were recruited as inpatients. For the other trials, recruitment methods included advertisements, word of mouth, clinical referrals, and a press release.[186] The prospective cohort study[211] followed members of the armed forces. Mean age ranged from 38 to 47 years. Two of the studies included women.[186,210] In 2 studies,[183,211] all participants were nonwhite; 1 study enrolled 17 to 22 percent nonwhite subjects;[210] race and ethnicity was not reported in the other 3 studies.

Table 26. Characteristics of studies included for Key Question 3 that were not in Key Question 1 or 2

Author, Year Design	Arm Dose, mg/Day (N)	Rx Dura-tion, Weeks	Country Setting	Recruitment Method	Age, Years	% Non-White	% Fe-male	% With Additional Condition	Cointer-vention	Risk of Bias
Anton, 2003[210] COMBINE pilot DBRCT	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	38 to 42	17 to 22	22 to 33	NR	As randomized	Med
De Sousa, 2005[183] OLRCT	ACA 1,998 (50) DIS 250 (50)	35	India; outpatient, private psychiatric hospital	Patients undergoing detoxification	42 to 43	100	0	NR	Weekly supportive group psychotherapy offered	High
De Sousa, 2004[185] OLRCT	DIS 250 (50) NTX 50 (50)	52	India; outpatient	Recruited as inpatients	43 to 47	NR	0	NR	Supportive group psychotherapy	High
Narayama, 2008 [211] Prospective cohort	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	100	0	NR	Various psycho-therapies were offered	High
Nava, 2006[186] OLRCT	GHB 50 [a] (28) NTX 50 (24) DIS 200 (28)	52	Italy; outpatient	Advertisements, word of mouth, press release	38.5 to 42.7	NR	15%	0	Cognitive behavioral therapy	High
Rubio, 2001[207] SBRCT	ACA 1,665-1,998 (80) NTX 50 (77)	52	Spain; outpatient	Patients presenting to hospital for detoxification	44	NR	0	0	Supportive group therapy weekly; weekly visits with a psychiatrist for 3 months, then biweekly until end of study	High

ACA = acamprosate; CBI = combined behavioral intervention; COMBINE = Combined Pharmacotherapies and Behavioral Intervention; DIS = disulfiram; DBRCT = double-blind randomized controlled trial; FDA = U.S. Food and Drug Administration; GHB = γ-Hydroxybuteric acid; med = medium; mg = milligrams; MM = medical management; N = number; NR = not reported; NTX = naltrexone; OLRCT = open-label randomized controlled trial; SBRCT = single-blind randomized controlled trial; TOP = topiramate; U.S. = United States.

Notes: Age, Years is the mean age in years, unless otherwise stated.

The following studies also met the inclusion criteria, but assessed harms of an off-label medication (compared with placebo) without evidence of efficacy, or compared an off-label medication without evidence of efficacy with an FDA-approved medication, and are therefore not described further in this Key Question: Florez, 2011,[204], Florez, 2008[203], De Sousa, 2008,[206] and Tollefson, 1991.[208,209]

[a] Dose is 50 mg per kg of body weight 3 times a day.

[b] Three additional treatment arms were included in COMBINE pilot study but were not relevant to our Key Questions: ACA + NTX + CBI + MM, ACA + NTX + MM, and CBI only (no pills).

Acamprosate Compared With Placebo

Table 27 summarizes the main results of our meta-analyses. The only statistically significant findings for harms from our main analyses were for anxiety, diarrhea, and vomiting. Statistical heterogeneity was considerable for the diarrhea analysis (I^2 88.9 percent), with some studies finding much higher rates of diarrhea than with placebo (with absolute risks increased as much as 33 percent). Sensitivity analyses for withdrawals due to adverse events, anxiety, diarrhea, and vomiting were also statistically significant (finding higher risk with acamprosate).

Table 27. Results of meta-analyses and risk difference calculations for adverse events: acamprosate compared with placebo

Outcome	N Trials	N Subjects	RD	95% CI	Heterogeneity I^2
Withdrawal due to adverse events	13	4,653	0.01	-0.00 to 0.02	8.5%
Withdrawal due to adverse events—SA	16	5,480	0.01	0.00 to 0.01	0.0%
Anxiety	1	601	0.16	0.10 to 0.23	NA
Anxiety—SA	2	624	0.16	0.09 to 0.22	0.0%
Diarrhea	12	3,299	0.10	0.03 to 0.17	88.9%
Diarrhea—SA	14	4,118	0.09	0.04 to 0.15	85.8%
Dizziness	2	151	0.08	-0.22 to 0.38	80.3%
Headache	6	1,074	0.001	-0.05 to 0.05	67.0%
Headache—SA	7	1,643	0.002	-0.04 to 0.04	60.2%
Insomnia	3	251	0.02	-0.10 to 0.14	73.5%
Insomnia—SA	4	820	0.02	-0.06 to 0.09	63.8%
Nausea	7	1,758	0.01	-0.01 to 0.02	0.3%
Nausea—SA	8	1,828	0.01	-0.01 to 0.03	12.5%
Numbness	1	262	0.01	-0.01 to 0.03	NA
Numbness—SA	2	831	0.01	-0.01 to 0.03	0.0%
Rash	1	35	0.11	-0.07 to 0.29	NA
Rash—SA	2	105	0.07	-0.01 to 0.16	0.0%
Suicide attempts or suicidal ideation	1	581	0.007	-0.005 to 0.019	NA
Suicide attempts or suicidal ideation—SA	3	1,173	0.002	-0.008 to 0.011	14.6%
Vomiting	4	1,817	0.02	0.01 to 0.04	0.0%
Vomiting – SA	5	1,840	0.02	0.01 to 0.04	0.0%

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

Note: Positive risk differences favor placebo. Sensitivity analyses include studies rated as high risk of bias.

Disulfiram Compared With Placebo or Control

Four included studies compared disulfiram with placebo or control.[90-93] One of these did not report results for adverse events.[93] The other 3 did not yield sufficient quantitative data to conduct meta-analyses.

One study of disulfiram compared with placebo in patients who were all taking methadone reported that "there were no deaths, serious adverse reactions, or illnesses that could be attributed to the combined use of the drugs [disulfiram and methadone]" but did not provide details about the incidence of specific adverse events in the study population.[91]

In another study, patients who received 250 mg per day of disulfiram reported "moderate or severe" drowsiness more often than those not given disulfiram (8 versus 2 percent, p=0.03). There was no significant difference in the incidence of drowsiness between the 250 and 1 mg per day disulfiram groups.[92] In this same study, disulfiram was discontinued by 3 patients in the 250

mg per day group and 1 patient in the 1 mg per day group because of increased serum alkaline phosphatase or aspartate aminotransferase. Psychiatric problems were observed in 11 patients with no statistically significant difference between the three groups.[92]

Results from a four-arm study comparing disulfiram combined with naltrexone, disulfiram combined with placebo, naltrexone alone, and placebo alone showed that patients on any study medication experienced aftertaste, blurred vision, confusion, constipation, drowsiness, dry mouth, loss of appetite, nausea, or tremors more often than patients who received placebo. There were no statistically significant between-group differences for other adverse events.[90] Six of the 14 serious adverse events reported in this study occurred in the disulfiram with placebo group (4 psychiatric hospitalizations—2 for a change in mental status and 2 for suicidal ideation, 1 cardiac event, and 1 hospitalization for acute axonal neuropathy) and 3 occurred in the placebo group (1 death, 1 drug and alcohol overdose, and 1 hospitalization for pneumonia).[90]

Naltrexone Compared With Placebo

Table 28 summarizes the main results of our meta-analyses. We found statistically significant increased risk of withdrawal due to adverse events, dizziness, nausea, and vomiting.

Acamprosate Compared With Disulfiram

Both studies reporting results for adverse events for this comparison were rated as high risk of bias; both reported no statistically significant differences between the acamprosate and disulfiram groups.[183,184]

One of the studies reported that six patients who received disulfiram experienced elevated alanine transaminase (ALAT) levels. Subsequently, three of the patients discontinued the medication, and three continued to receive a half dose; ALAT levels normalized within 2 to 3 weeks.[184] The most common adverse events reported in the study for patients treated with acamprosate were diarrhea and dermatological problems; for patients treated with disulfiram—tiredness and headache.

Table 28. Results of meta-analyses and risk difference calculations for adverse events: naltrexone compared with placebo

Outcome	N Trials	N Subjects	RD	95% CI	Heterogeneity I^2
Withdrawal due to adverse events	17	2,743	0.02	0.01 to 0.03	0.0%
Withdrawal due to adverse events - SA	20	2,899	0.02	0.01 to 0.03	0.0%
Anxiety	7	1,461	0.01	-0.02 to 0.04	0.0%
Anxiety—SA	9	1,676	0.01	-0.02 to 0.04	0.0%
Diarrhea	11	2,358	0.01	-0.01 to 0.04	21.9%
Diarrhea – SA	12	2,461	0.01	-0.02 to 0.03	30.2%
Dizziness	13	2,675	0.06	0.04 to 0.09	37.4%
Dizziness - SA	17	2,977	0.06	0.04 to 0.08	27.1%
Headache	17	3,347	0.01	-0.02 to 0.03	8.0%
Headache - SA	22	3,799	0.00	-0.02 to 0.03	20.9%
Insomnia	8	1,637	0.03	-0.003 to 0.06	0.0%
Insomnia - SA	12	2,030	0.03	0.001 to 0.05	0.0%
Nausea	24	4,655	0.11	0.07 to 0.15	69.6%
Nausea - SA	31	5,263	0.10	0.07 to 0.13	65.9%
Numbness	1	123	-0.01	-0.19 to 0.17	NA
Numbness - SA	2	226	-0.02	-0.08 to 0.04	0.0%
Rash	4	469	-0.01	-0.06 to 0.04	41.6%
Rash – SA	5	522	-0.02	-0.06 to 0.02	21.5%
Blurred vision	2	133	0.08	-0.17 to 0.33	46.3%
Vomiting	9	2,438	0.04	0.02 to 0.06	0.0%
Vomiting - SA	11	2,567	0.04	0.02 to 0.06	1.1%

Note: Positive risk differences favor placebo. Sensitivity analyses include studies rated as high risk of bias.
Abbreviations: CI = confidence interval; N = number of trials or subjects contributing data; NA = not applicable; RD = risk difference; SA = sensitivity analysis.

Acamprosate Compared With Naltrexone

Table 29 summarizes the main results of our meta-analyses. The risks of headache, nausea, and vomiting were slightly higher for those treated with naltrexone in either the main analyses or in sensitivity analyses that included studies rated as high or unclear risk of bias.

Table 29. Results of meta-analyses for adverse events: acamprosate compared with naltrexone

Outcome	N Trials	N Subjects	RD	95% CI	Heterogeneity I^2
Withdrawal due to adverse events	2	953	0.01	-0.04 to 0.07	73.4%
Withdrawal due to adverse events—SA	3	1,110	0.00	-0.04 to 0.04	64.5%
Diarrhea	4	836	0.18	-0.02 to 0.37	89.3%
Diarrhea—SA	5	993	0.14	-0.07 to 0.35	96.0%
Dizziness	2	144	0.08	-0.23 to 0.39	81.7%
Dizziness—SA	3	306	-0.03	-0.19 to 0.13	82.4%
Headache	3	301	-0.06	-0.12 to 0.01	0.0%
Headache—SA	4	463	-0.09	-0.16 to -0.01	36.3%
Insomnia	2	144	0.07	-0.20 to 0.34	65.5%
Nausea	4	836	-0.08	-0.18 to 0.02	72.8%
Nausea—SA	6	1,155	-0.10	-018 to -0.02	71.6%
Vomiting	2	648	-0.06	-0.11 to -0.01	0.0%

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

Note: Positive risk differences favor naltrexone. Table only includes rows for outcomes with sufficient data for meta-analyses.

A prospective cohort study rated as high risk of bias comparing acamprosate with naltrexone reported that adverse events were uncommon, mild, and temporary in both groups. The most common adverse events in the naltrexone group (N=26) were anxiety (23.07 percent), nervousness (23.07 percent), and insomnia (15.4 percent); these were not reported in the acamprosate group. The most common adverse events in the acamprosate group (N=28) were nausea (25.0 percent) and diarrhea (21.42 percent); 11 percent of those in the naltrexone group experienced nausea, but none reported diarrhea.[211]

Disulfiram Compared With Naltrexone

We found 4 studies comparing disulfiram with naltrexone and reporting on adverse events; all 4 were rated as high risk of bias.[90,184-186] One of these reported no statistically significant difference in the incidence of adverse events between groups;[184] another stated that no serious adverse events occurred during the study and reported the incidence of adverse events only among those who withdrew because of adverse events.[186]

In 1 of the studies, nausea, drowsiness, abdominal pain, and diarrhea were more common among patients receiving naltrexone than among those receiving disulfiram, but statistical significance was not reported.[185]

A four-arm study comparing disulfiram combined with naltrexone, disulfiram combined with placebo, naltrexone alone, and placebo alone found that fever was more common in the disulfiram group than in the naltrexone group (p=0.03); nervousness (p=0.005) and restlessness (p=0.03) were more common in the naltrexone group than in the disulfiram group.[90]

Nalmefene Compared With Placebo

Table 30 summarizes the main results of our meta-analyses. Considering outcomes with multiple low or medium risk of bias studies, our main meta-analyses found that patients treated with nalmefene had a higher risk of withdrawal due to adverse events, dizziness, headache, insomnia, nausea, and vomiting, compared with patients who received placebo. Sensitivity analyses including studies rated as high or unclear risk of bias found similar results. Nalmefene was associated with a lower risk of diarrhea than placebo.

Table 30. Results of meta-analyses and risk difference calculations for adverse events: nalmefene compared with placebo

Outcome	N Trials	N Subjects	RD	95% CI	Heterogeneity I^2
Withdrawal due to adverse events	5	2,054	0.08	0.02 to 0.15	86.4%
Withdrawal due to adverse events—SA	7	2,750	0.08	0.04 to 0.12	79.5%
Cognitive dysfunction	1	265	0.05	0.01 to 0.09	NA
Cognitive dysfunction—SA	2	830	0.03	-0.03 to 0.08	81.9%
Diarrhea	2	1,081	-0.03	-0.06 to -0.01	0.0%
Dizziness	4	1,944	0.16	0.11 to 0.21	58.4%
Dizziness—SA	6	2,630	0.14	0.10 to 0.18	53.5%
Headache	3	1,401	0.04	0.01 to 0.07	0.0%
Headache—SA	4	2,066	0.04	0.01 to 0.07	0.0%
Insomnia	5	2,049	0.10	0.06 to 0.14	47.3%
Insomnia—SA	6	2,714	0.09	0.06 to 0.12	34.9%
Nausea	5	2,049	0.16	0.10 to 0.22	75.8%
Nausea—SA	6	2,714	0.16	0.11 to 0.21	69.8%
Suicide attempts or suicidal ideation	2	1,253	-0.01	-0.02 to 0.00	0.0%
Suicide attempts or suicidal ideation—SA	3	1,918	-0.00	-0.01 to 0.01	39.2%
Vomiting	3	1,679	0.06	0.02 to 0.10	68.1%
Vomiting—SA	4	2,344	0.07	0.03 to 0.11	76.2%

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

Note: Positive risk differences favor placebo. Sensitivity analyses include studies rated as high risk of bias.

Topiramate Compared With Placebo

Trials of topiramate reported increased risk of many adverse events, including paresthesias, taste perversion, anorexia, difficulty with concentration/attention, nervousness, dizziness, pruritis, psychomotor slowing, and weight loss.[175,179] Table 31 summarizes the main results of our meta-analyses; few studies of topiramate contributed adverse events data.

Table 31. Results of meta-analyses and risk difference calculations for adverse events: topiramate compared with placebo

Outcome	N Trials	N Subjects	RD	95% CI	Heterogeneity I^2
Withdrawal due to adverse events	2	521	0.06	-0.12 to 0.25	93.4%
Withdrawal due to adverse events—SA	3	599	0.06	-0.06 to 0.18	86.9%
Anorexia	1	371	0.13	0.06 to 0.20	NA
Cognitive dysfunction	2	521	0.08	0.01 to 0.16	38.5%
Diarrhea	1	371	0.04	-0.03 to 0.10	NA
Diarrhea—SA	2	477	0.00	-0.07 to 0.08	61.1%
Dizziness	2	521	0.10	-0.01 to 0.22	65.0%
Dizziness—SA	3	627	0.08	0.01 to 0.14	51.5%
Headache	1	371	-0.08	-0.17 to 0.01	NA
Insomnia	1	371	0.03	-0.05 to 0.11	NA
Insomnia—SA	2	477	0.03	-0.03 to 0.10	0.0%
Nausea	1	371	-0.06	-0.13 to 0.01	NA
Nausea—SA	2	477	-0.02	-0.11 to 0.06	62.0%
Numbness/tingling/paresthesias	2	521	0.40	0.32 to 0.47	0.0%
Numbness/tingling/paresthesias—SA	3	627	0.29	0.05 to 0.52	93.1%
Taste abnormalities	1	371	0.18	0.11 to 0.25	NA

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

Note: Positive risk differences favor placebo. Sensitivity analyses include studies rated as high risk of bias.

Valproic Acid Compared With Naltrexone

A single trial that reported adverse effects for valproic acid compared with placebo found a higher rate of nausea for patients treated with valproic acid (Table 32).

Table 32. Results of risk difference calculations for adverse events: valproic acid compared with placebo

Outcome	N Trials	N Subjects	RD	95% CI	Heterogeneity I^2
Withdrawal due to adverse events	1	52	0.04	-0.07 to 0.14	NA
Diarrhea	1	52	0.10	-0.12 to 0.32	NA
Headache	1	52	0.05	-0.20 to 0.30	NA
Nausea	1	52	0.25	0.05 to 0.46	NA
Vision changes	1	52	-0.02	-0.26 to 0.22	NA

CI = confidence interval; N = number of trials or subjects contributing data; NA = not applicable; RD = risk difference.

Note: Positive risk differences favor placebo. Sensitivity analyses include studies rated as high risk of bias.

Key Question 4. Evidence From Primary Care Settings

Characteristics of Included Trials

We identified 1 eligible trial conducted completely in primary care settings.[69] It compared acamprosate 1,998 milligrams per day with placebo for 12 weeks and was based in two U.S. primary care clinics. Primary care providers also delivered a brief structured behavioral intervention. Mean age of patients was 48, 9 percent of patients were non-White, and almost 40 percent were female.

One additional included trial compared targeted nalmefene with placebo for 28 weeks in 15 sites in Finland—5 of the sites were specialist treatment clinics, 6 were private general practice offices, 2 were offices for occupational health, and 2 were specialized in conducting outpatient clinical research (Table 33).[158] For targeted nalmefene dosing, patients were instructed to take the medication when they believed drinking to be imminent, rather than as a daily scheduled medication. The trial reported that 93 percent of subjects met criteria for alcohol dependence. It did not report information on smoking history at baseline. The study did not include any formal manualized psychosocial treatment, but did include some elements of BRENDA,[212] including biopsychosocial assessment, feedback to subjects about assessments, simple advice to reduce drinking, and monitoring of treatment progress—with the emphasis on correct use of the study medication.

Table 33. Characteristics of included randomized controlled trials of FDA-approved medications for treating alcohol dependence in primary care settings

Author, Year	Arm Dose, mg/Day (N)	Rx Duration, Weeks (Followup)	Setting	Recruitment Method	Age, Years	% Non-White	% Female	% With Co-occurring Condition	Counter-vention	Risk of Bias
Berger, 2013[69]	ACA 1,998 (51) Placebo (49)	12	U.S.; 2 primary care sites	Provider referral and ads	48	9	38	NR	Brief structured behavioral intervention from primary care physician	Medium
Karhuvaara, 2007[158]	Nalmefene 10 to 40 targeted dose (242) Placebo (161)	28 (52)[a]	Finland; 15 sites	Mainly by newspaper ads	49	0	19	NR	Some elements of BRENDA	Medium

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; FDA = U.S. Food and Drug Administration; mg = milligram; N = number; NR = not reported; U.S. = United States.

Note: Age, Years is the mean age in years, unless otherwise stated.

[a]After 28 weeks, nalmefene responders were invited to continue in a double-blind randomized controlled trial for an additional 24 weeks.

Several other published studies, including some in other sections of this report, may have implications for or some applicability to primary care settings, an issue addressed in the report Discussion.

Results for Consumption Outcomes

The trial conducted completely in primary care settings (N=100)[69] found no significant treatment effect of acamprosate on drinking days (effect size, 0.14; 95% CI, -0.26 to 0.53) or heavy drinking days (effect size, 0.27; 95% CI, -0.12 to 0.67).

The Finnish trial (N=403) found no significant difference in percentage of drinking days between nalmefene and placebo (WMD, -3.8; 95% CI, -9.3 to 1.7), but reported a lower percentage of heavy drinking days for patients treated with targeted nalmefene (18.1 percent versus 29.7 percent, p=0.024) and 1 fewer drink per drinking day for patients treated with nalmefene (WMD, -1.0; 95% CI, -2.0 to -0.02) than for those who received placebo.

Key Question 5. Subgroups

We evaluated evidence on whether any of the medications were more or less effective than other medications for the following subgroups: men or women, older adults, young adults, racial

or ethnic minorities, smokers, or those with co-occurring disorders. Only studies that compared at least two medications with each other were eligible for this Key Question (KQ). Throughout this KQ, we include headers and sections only for subgroups reported by the included studies.

Detailed Synthesis

Characteristics of Included Studies

Eleven RCTs and 1 observational study addressed this KQ (Table 34). Studies included FDA-approved (acamprosate, disulfiram, naltrexone, topiramate) and non-FDA-approved (desipramine, paroxetine, sertraline, topiramate) medications. Treatment durations ranged from 12 weeks (7 studies) to 68 weeks. All but 1 of the studies reported concurrent psychiatric care, psychotherapy, or other psychosocial support. Studies were conducted in Australia, Brazil, Germany, and India in addition to the United States.

Mean age ranged from 32 to 47, the reported proportion nonwhite ranged from 23 to 100 percent, and the reported proportion female ranged from 0 to 72 percent. In 11 of the studies, all participants had alcohol dependence; in 1 it was not reported. Smoking rates were high (55 to 81 percent of participants) in 3 studies;[61,67,80,119,128] all patients in 1 study[213] had cocaine dependence. Three studies included only participants with psychiatric comorbidities (Axis I disorders, depression, or PTSD).[90,94-96,104,189] Participants were recruited from the community as well as from outpatient and inpatient contacts. Three of these studies were rated low risk of bias, 3 were rated medium, and the rest were rated high risk of bias, primarily due to concerns with attrition bias, inadequate handling of missing data, or measurement bias (see Appendix C for details).

Table 34. Characteristics of head-to-head medication studies that evaluated subgroups

Author, Year Trial Name Design	Arm Dose, mg/Day (N)	Subgroup(s)	Rx Duration, Weeks	Setting	Age, Years	% Non-White	% Female	Cointervention	Risk of Bias
Baltieri, 2008[119]; Baltieri, 2009[128] NA DBRCT	TOP target 200, maximum 400 (52) NTX 50 (49) Placebo (54)	Smokers	12	Brazil; outpatient	44 to 45	29	0	Psychosocial 100%	High
Carroll, 1993[213] NA OLRCT	DIS 250 (9) NTX 50 (9)	Cocaine dependence	12	U.S.; outpatient substance abuse	32	39	72	Weekly individual psychotherapy 100%	High
De Sousa, 2004[185] NA OLRCT	DIS 250 (50) NTX 50 (50)	Men	52	India; outpatient	43 to 47	NR	0	Supportive group psychotherapy 100%	High
De Sousa, 2005[183] NA OLRCT	ACA 1,998 (50) DIS 250 (50)	Men	35	India; outpatient; private psychiatric hospital	42 to 43	100	0	Weekly supportive group psychotherapy offered	High

Table 34. Characteristics of head-to-head medication studies that evaluated subgroups (continued)

Author, Year Trial Name Design	Arm Dose, mg/Day (N)	Subgroup(s)	Rx Dura-tion, Weeks	Setting	Age, Years	% Non-White	% Fe-male	Cointervention	Risk of Bias
De Sousa, 2008[206] NA OLRCT	TOP 150 (50) DIS 250 (50)	Men	39	India; center with facilities for both in- and outpatient treatment of alcohol dependence and substance abuse	43	100	0	Offered weekly supporting group psychotherapy – % NR	High
Greenfield, 2010[214] Fucito, 2012[67] COMBINE DBRCT	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)	Men/women; smokers	68	11 U.S. academic sites	44	23	31	As randomized; community support group participation (like AA) encouraged	Low
Kiefer, 2005[76] NA DBRCT	ACA 1,998 (40) NTX 50 (40) Placebo (40) ACA 1,998 + NTX 50 (40)	Somatic distress, depression, anxiety	12	Germany; 1 site, outpatient	46	NR	26	Group therapy	Low
Morley, 2006[61] Morley, 2010[80] NA DBRCT	ACA 1,998 (55) NTX 50 (53) Placebo (61)	Depression	12	Australia; 3 treatment centers with "medical care typically available at hospital based drug and alcohol treatment services"	45	NR	30	All offered 4-6 sessions of manualized compliance therapy Up-take / attendance NR	Low
Narayana, 2008[211] Prospective cohort	ACA 1,332 to 1,998 (28) NTX 50 (26) TOP 100 to 125 (38)	Men	52	Indian military, outpatient	38	100	0	NR	High
Petrakis, 2005[90] Ralevski, 2007[94] Petrakis, 2007[95] Petrakis, 2006[96] VA MIRECC DBRCT	DIS 250 (66) NTX 50 (59) Placebo (64) NTX 50 + DIS 250 (65)	Axis I disorders	12	U.S.; outpatient VA	47	26	3	Psychiatric treatment as usual 100%	High for DIS vs. NTX

Table 34. Characteristics of head-to-head medication studies that evaluated subgroups (continued)

Author, Year Trial Name Design	Arm Dose, mg/Day (N)	Subgroup(s)	Rx Duration, Weeks	Setting	Age, Years	% Non-White	% Female	Cointervention	Risk of Bias
Petrakis, 2012[189] NA DBRCT	DES 200 + placebo (24) PAR 40 + placebo (20) PAR 40 + NTX 50 (22) DES 200 + NTX 50 (22)	PTSD, depression	12	U.S.; outpatient; multiple mental illness centers, most subjects from VAs	47	25	9	Clinical management/ compliance enhancement therapy 100%	High
Pettinati, 2010[104] NA DBRCT	SER 200 (40) NTX 100 (49) Placebo (39) SER 200 + NTX 100 (42)	Depression	14	U.S.; outpatient	43	35	38	CBT 100%	Medium

AA = Alcoholics Anonymous; ACA = acamprosate; CBI = combined behavioral intervention; CBT = cognitive behavioral therapy; COMBINE = Combined Pharmacotherapies and Behavioral Intervention; DBRCT = double-blind randomized controlled trial; DES = desipramine; DIS = disulfiram; mg = milligram; MIRECC = Mental Illness Research, Education and Clinical Center; MM = medical management; N = number; NR = not reported; NTX = naltrexone; OLRCT = open-label randomized controlled trial; PAR = paroxetine; PTSD = post-traumatic stress disorder; SER = sertraline; TOP = topiramate; U.S. = United States; VA = Veterans Affairs.

Note: Age, Years is the mean age in years, unless otherwise stated.

Sex

Five studies—4 trials and 1 prospective cohort—provided evidence about the effectiveness of medications by sex.[183,185,206,211,214]

Subgroup analyses from the COMBINE study,[214] the only study among this group rated as low risk of bias, found no significant association between sex and the impact of acamprosate or naltrexone treatment on percentage of days abstinent, time to heavy drinking, or percentage of heavy drinking days.

Three trials, all open-label and from the same group of investigators, and all rated as high risk of bias, found that naltrexone and topiramate have a greater impact than disulfiram and disulfiram has a greater impact than acamprosate on reducing drinking for men.[183,185,206]

The prospective cohort study, rated as high risk of bias, found that treatment with topiramate had a greater impact than acamprosate or naltrexone on any drinking for men.[211]

Smokers

Two studies provided evidence about the effectiveness of medications by smoking status. Subgroup analyses from the COMBINE study[67] found that smokers who received naltrexone had more days abstinent (78 percent versus 72 percent, p=0.004) and fewer heavy drinking days (14 percent versus 20 percent, p=0.003) than smokers who received placebo. No data were reported on the effectiveness of acamprosate among smokers—only that smokers did not benefit differentially from acamprosate. Subgroup analyses from a trial comparing naltrexone, topiramate, and placebo found no association between the number of cigarettes smoked per day at the start of the trial and the effect of naltrexone or topiramate on any drinking outcomes.[119,128]

People With Co-Occurring Disorders

Six studies provided evidence about the effectiveness of medications on individuals with co-occurring psychiatric disorders or other substance use disorders. Five studies addressed co-occurring psychiatric disorders, including depression or anxiety,[61,80,104] Axis I disorders,[90,94-96] PTSD and depression,[189] and somatic distress/depression/anxiety;[76] 1 addressed co-occurring cocaine dependence.[213] Two were rated low risk of bias, 1 as medium risk of bias, and 3 as high risk of bias. Four were conducted in the United States, 1 in Germany,[76] and 1 in Australia.[61,80]

The German study addressing patients with co-occurring somatic distress/depression/anxiety[76] evaluated the effects of naltrexone and acamprosate in patients with scores above and below the median on the Symptom Checklist-90 (SCL-90) and its subscales.[215] In patients with total SCL-90 scores above the median, naltrexone was associated with a longer time to lapse compared with acamprosate (51.3 versus 30.1 days, p NR). Similar differences between naltrexone and acamprosate were found for the above-median scores for somatic distress (45.5 versus 20.3), depression (53.4 versus 28.1), and anxiety (47.3 versus 24.4), though none reached statistical significance. Results for time to relapse were similar, and were not statistically significantly different.

In 1 U.S.-based study of patients with co-occurring alcohol dependence and depression,[104] patients treated with naltrexone reported numerically longer time to relapse than patients treated with sertraline (45.2 versus 39.9 days, p NR). A slightly higher percent of patients treated with sertraline (27.5 percent) remained abstinent during treatment compared with naltrexone (21.3 percent, p NR).

Another U.S.-based study compared disulfiram (plus placebo) with naltrexone in a population of veterans with comorbid Axis I disorders.[90] There were no significant differences between disulfiram and naltrexone in percentage of days abstinent (97 percent versus 95 percent, respectively, p=0.55), percentage of heavy drinking days (3.2 percent versus 4.0 percent, p=0.65), or percentage remaining abstinent (77.3 percent versus 64.4 percent, p=0.11). This study was rated high risk of bias. When subgroups of the Axis I disorders were examined, results were similar, with no significant differences in alcohol use outcomes by treatment for patients diagnosed with depression,[95] borderline personality disorder,[94] antisocial personality disorder,[94] or post-traumatic stress disorder.[96]

The Australian study examined acamprosate and naltrexone in patients with and without depression or anxiety.[61,80] It did not find a naltrexone or acamprosate by depression interaction when assessing predictors of abstinence (no lapse)—odds ratios (ORs) were 0.78 (95% CI, 0.60 to 1.01) and 0.95 (95% CI, 0.81 to 1.12), respectively. It also reported no anxiety by naltrexone or acamprosate interaction when assessing predictors of abstinence (OR for acamprosate by anxiety interaction, 0.92; 95% CI, 0.74 to 1.15; OR for naltrexone by anxiety, 1.06; 95% CI, 0.83 to 1.35). When assessing predictors of no relapse (at least 4 drinks for females and at least 6 drinks for males), the study found a significant naltrexone by depression interaction—OR, 0.77 (95% CI, 0.63 to 0.95) but no significant interactions for acamprosate by depression, naltrexone by anxiety, or acamprosate by anxiety.

In the U.S.-based study of patients with PTSD and alcohol dependence,[189] desipramine was associated with a lower percentage of heavy drinking days (p=0.009) and fewer drinks per drinking day (p=0.027) compared with paroxetine, but specific alcohol use data were not reported and the study was rated high risk of bias.

In the U.S.-based study of patients with both alcohol and cocaine dependence,[213] disulfiram was associated with a significantly lower percentage of drinking days compared with naltrexone (4.0 percent versus 26.3 percent, respectively, $p<0.01$).This study was rated high risk of bias.

Key Question 6. Genetic Polymorphisms

For this KQ, we describe the characteristics of included studies and then evidence on whether any of the medications are more or less effective for adults with specific genotypescompared with adults with different genotypes. The most commonly evaluated polymorphisms were those of the mu-opioid receptor gene. For most polymorphism-medication pairs, we found just 1 eligible study, and we graded the SOE as insufficient (because evidence was imprecise, had unknown consistency, and had medium or high risk of bias)—information on the study characteristics and results for polymorphism-medication pairs with just 1 eligible study is provided in Appendix G. These included 1 study each for the following: nalmefene and opioid receptor gene polymorphisms; topiramate or naltrexone and *DRD2*, *DRD3*, *HTR2A*, or *SLC6A* gene polymorphisms; olanzapine and *DRD4* gene polymorphisms; acamprosate or naltrexone and *GATA4* polymorphisms; sertraline and *5-HTTLPR* polymorphisms; and disulfiram and *DBH* polymorphisms.

Characteristics of Included Studies

We found no studies that assessed the clinical utility of genotype-guided dosing strategies or genotype-guided medication selection, and none randomized by genotype; all included studies assessed the association between genotype and response to medication. We found 7 eligible studies assessing variation in naltrexone response related to polymorphisms of the opioid receptor gene (Table 35). Four studies were analyses of subjects from U.S.-based randomized controlled trials; 3 were prospective cohort studies conducted in Australia,[216] South Korea,[217] or Spain.[43] All 7 studies assessed mu-opioid receptor gene (*OPRM1*) polymorphisms; 1 also assessed polymorphisms of the genes that encode the delta- and kappa-opioid receptors (*OPRD1* and *OPRK1*, respectively). The main polymorphism tested is in exon 1 of the *OPRM1* gene (118A>G), resulting in an asparagine to aspartate substitution at position 40 of the amino acid sequence (Asn40Asp) of the mu-opioid receptor.

Most of the studies used naltrexone 50 mg; 1 used 100 mg.[40] Duration of treatment ranged from 12 to 16 weeks. Mean age was very similar across studies, from 40 to 50 years. All subjects met criteria for alcohol dependence in 6 of the studies; 1 study reported that 95 percent of subjects met criteria for alcohol dependence.[41] Three studies enrolled all males[43,217,218]; the others enrolled between 30 and 43 percent females. Information on race was not reported in 2 studies;[43,216] 2 reported including a majority of non-white subjects;[42,217] and 3 reported including zero[40] or a small percentage[41,218] of nonwhite subjects. The study that reported including zero non-white subjects[40] restricted analyses to Caucasians because the main polymorphism tested for (118A>G) is rare in African Americans. Three studies reported consistency of genotype frequencies with Hardy-Weinberg equilibrium; the others did not report checking for it.

One additional study (Oslin et al., 2003) was identified that did not meet inclusion criteria.[219] It pooled data for a subset of subjects from 3 separate trials, 1 of which was less than 12 weeks in treatment duration. Because this study may include useful information, and has been included in previous reviews, we conducted sensitivity analyses that include this study (see below in the Overview of Results section).

Table 35. Characteristics of included studies that assessed the association between opioid receptor gene polymorphisms and naltrexone response

Author, Year	Arm Dose, mg/Day (N)	Genotypes Assessed	Rx Duration, Weeks	Setting	Age, Years	% Non-White	% Female	Cointer-vention	Risk of Bias
Anton, 2008[40]	Naltrexone 100 (301) Placebo (303)	*OPRM1*	16	U.S.; Outpatient 11 sites	45 to 46	0	30	MM 100% CBI 49% ACA % NR	Medium
Coller, 2011[216]	Naltrexone 50 (100)	*OPRM1*	12	Australia; substance abuse treatment, outpatient	43	NR	43	CBI 100%	Medium
Gelernter, 2007[218]	Naltrexone 50 (149) Placebo (64)	*OPRM1* *OPRD1* *OPRK1*	13	U.S.; Multisite VAMCs	50	26	0	NR	High
Kim, 2009[217]	Naltrexone 50 (32)	*OPRM1*	12	South Korea; Multiple hospitals	46 to 49	100	0	CBT 100%	High
Kranzler, 2013[41]	Naltrexone 50—daily or targeted (81) Placebo (77)	*OPRM1*	12	U.S.; Outpatient; university health center	49	3	42	Coping skills therapy 100%	Medium
O'Malley, 2008[42]	Naltrexone 50 (34) Placebo (34) Naltrexone 50 + Sertraline 100 (33)[a]	*OPRM1*	16	U.S.; Native and non-native Alaskans, outpatient	40	70	34	MM 100%	Medium
Rubio, 2002[43]	Naltrexone 50 (45)	*OPRM1*	12	Spain; outpatient	NR	NR	0	NR	Unclear

mg = milligram; MM = medical management; N = number; NR = not reported; *OPRM1* = the mu-opioid receptor gene; U.S. = United States; VAMC = Veterans Administration Medical Center.

Note: Age, Years is the mean age in years, unless otherwise stated.

[a] Usable DNA was available for 92 of the 101 participants in the randomized controlled trial. Of those, 17 had one or more copies of the Asp40 allele (9 placebo, 3 NTX only, and 5 NTX + sertraline), so the authors restricted statistical analyses to the participants who were homozygous for the Asn40 allele.

Overview of Results

Three of the studies reported some positive associations between polymorphisms and response to naltrexone (Table 36).[40,41,217]

Our meta-analyses for return to any drinking found no significant difference between A-allele homozygotes and those with at least one G allele among patients treated with naltrexone, both without (RD, -0.03; 95% CI, -0.6 to 0.5) and with inclusion of the studies rated as high or unclear risk of bias (RD, 0.01; 95% CI, -0.2 to 0.2). Sensitivity analyses including the Oslin 2003 study also found no difference for return to any drinking.[219]

Table 36. Results of included studies that assessed the association between mu-opioid receptor gene polymorphisms and naltrexone response

Author, year	Reported a Significant Positive Association?	AA, N	AA, Return to Any Drinking	AA, Return to Heavy Drinking—Relapse	AG/GG, N	AG/GG, Return to Any Drinking	AG/GG, Return to Heavy Drinking—Relapse
Anton, 2008[40]	Yes[a]	115[b]	NR	52	31[b]	NR	4
Coller, 2011[216]	No	NR	NR	NR	NR	NR	NR
Gelernter, 2007[218]	No	98	NR	35	33	NR	12
Kim, 2009[217]	Mixed[c]	16	8	6	16	9	3
Kranzler, 2013[41]	Yes	59	NR	NR	22	NR	NR
O'Malley, 2008[42]	No[d]	25	16	16	3	2	2
Rubio, 2002[43]	No	29	9	9	16	4	4

CBI = combined behavioral intervention; N = number; NR = not reported.

Note: Table only includes data for subjects who received naltrexone; it does not include data for those who received placebo or who received naltrexone plus sertraline.

[a] Statistically significant difference between groups for return to heavy drinking.

[b] Data are for those who received naltrexone and medical management, and do not include those who received naltrexone + medical management + CBI. The study found no gene by medication by time interactions for the latter group for percentage of days abstinent or heavy drinking days, and did not report specific numbers by genotype for the outcomes.

[c] Yes for time to first relapse (p=0.014); no for abstinent rate (p=0.656) and relapse rate (p=0.072).

[d] Study authors restricted analyses to A-allele homozygotes because they had only 17 of 92 genotyped participants with at least one G allele. The results for the 75 A-allele homozygotes were similar to the results for the total sample, indicating that treatment efficacy was not dependent on the presence of the G allele.

Similarly, our meta-analyses for return to heavy drinking found no statistically significant difference between A-allele homozygotes and those with at least one G allele among patients treated with naltrexone, both without (RD, 0.26; 95% CI, -0.01 to 0.53) and with inclusion of the studies rated as high or unclear risk of bias (RD, 0.14; 95% CI, -0.03 to 0.3). Sensitivity analyses including the Oslin 2003 study,[219] along with all other studies regardless of risk of bias rating, found that a lower percentage of patients with a G allele returned to heavy drinking than A-allele homozygotes (RD, 0.16; 95% CI, 0.02 to 0.29).

Detailed Results of Individual Studies

Subgroup analysis from the COMBINE study found no gene by medication by time interactions for patients treated with medical management plus CBI, but reported an interaction between treatment and genotype for the time trend of percentage of days abstinent and for percentage of heavy drinking days for patients who received medical management (with no CBI).[40] Among those who received medical management, patients with at least one Asp40 allele and treated with naltrexone had a higher proportion of good clinical outcomes (87.1 percent) than patients homozygous for Asn40 treated with naltrexone (54.8 percent) and those who received placebo who did and did not have an Asp40 allele (48.6 percent and 54 percent, respectively).

The study conducted in Australia reported a significant decrease in alcohol use over time, but no genotype by time interaction and no difference between the two genotypic groups (median grams per week: AA, 48.0 versus AG or GG, 37.5, p=0.78).[216] It also reported no difference between genotypic groups (AA versus AG or GG) for time to first relapse (11 versus 10 days, p=0.40) and for mean number of drinking days (17.6 versus 21.9, p=0.56).

One U.S.-based study, a subgroup analysis of data from a trial conducted in Veteran's Affairs Medical Centers, reported no association between the *OPRM1* genotype and naltrexone response.[218] Patients who were A-allele homozygotes had about the same rate of relapse as those who carried a G allele (35.7 versus 36.0). The larger trial (N=627) that the study sample (N=220) was drawn from did not show a positive effect of naltrexone. The authors explained that the lack of an overall treatment effect of naltrexone in the larger trial might suggest that this was a sub-optimal sample in which to evaluate pharmacogenomic predictors of treatment. However, the subsample for which genotype information was available did show a positive naltrexone treatment effect, which would seem to diminish this problem.

The cohort study conducted in South Korea provided outcome information only for the subjects who were adherent to naltrexone for 12 weeks (32 of 63 subjects who initiated treatment).[217] Among those, it reported longer time to relapse for patients with a G allele than for A-allele homozygotes (73.3 versus 59.9 days, p=0.014), but no statistically significant difference between groups for abstinent rate (43.8 percent versus 50 percent, p=0.656) or for relapse rate (18.8 percent versus 37.5 percent, p=0.072).

Another U.S.-based study, an analysis of data from a trial conducted in a university-based center, reported that neither genotype nor medication significantly predicted mean daily drinking levels.[41] However, it found a positive desire by genotype by medication condition interaction, with a significant desire by genotype interaction for the placebo group (p=0.001) but not for the naltrexone group (p=0.74). In other words, when the evening desire to drink was high, G allele carriers were at greater risk to drink than A-allele homozygotes, except when treated with naltrexone.[41]

One U.S.-based study, an analysis of data from a trial conducted with Alaskans, restricted its analyses to A-allele homozygotes.[42] The authors reported that this was because they had only 17 of 92 genotyped participants with at least one G allele. They found that the results for the 75 A-allele homozygotes were similar to the results for the total sample (for percentage abstinent and percentage relapsed to a heavy drinking day), indicating that treatment efficacy was not dependent on the presence of the G allele.

The cohort study conducted in Spain (N=45) was reported as an abstract only, with very little details about the methods.[43] We assessed the risk of bias of this study as unclear due to very limited reporting of information. The study did not find a significant difference in consumption outcomes (abstinence/return to any drinking, or relapse) between patients who were A-allele homozygotes and those with a G allele.

Discussion

Below, we summarize the main findings and strength of evidence (SOE). We then discuss the findings in relation to what is already known, applicability of the findings, implications for decisionmaking, limitations, research gaps, and conclusions. When we have graded evidence as insufficient, it indicates that evidence is either unavailable, does not permit estimation of an effect, or does not permit us to draw a conclusion with at least a low level of confidence. It does not indicate that a treatment has been proven to lack efficacy.

Key Findings and Strength of Evidence

Efficacy and Comparative Effectiveness

We found moderate SOE that both acamprosate and oral naltrexone (50 mg per day) are effective for improving alcohol consumption outcomes (Table 37). Numbers needed to treat (NNT) to prevent 1 person from returning to any drinking were 12 and 20, respectively. For return to heavy drinking, evidence did not support the efficacy of acamprosate, whereas oral naltrexone (50 mg per day) was efficacious with an NNT of 12. Relatively limited evidence from well-controlled trials does not adequately support the efficacy of disulfiram compared with placebo for preventing return to any drinking or for other alcohol consumption outcomes. Some disulfiram trials reported fewer drinking days for subjects who returned to any drinking and who had a complete set of assessment interviews, and suggest that disulfiram may have a role in the treatment of AUDs for some individuals.

We found insufficient direct evidence to conclude that treatment with acamprosate or naltrexone leads to improvement in health outcomes—i.e., accidents, injuries, quality of life (QoL), function, or mortality. Very few trials reported any health outcomes, and the included trials were not designed or powered to assess impact on health outcomes—they typically focused on alcohol consumption outcomes. It is noteworthy that the largest pharmacotherapy trial in alcohol dependence, COMBINE, did report some evidence of improvement in QoL with naltrexone plus behavioral intervention (on the 12-item Short-Form Health Survey [SF-12v2] physical health scale), but the difference between groups did not reach a clinically meaningful threshold.[193] Evidence from epidemiologic literature consistently relates high average alcohol consumption and heavy per-occasion use to an increased risk of health problems, such as cancers of the oral cavity, esophagus, larynx, colon, rectum, liver, and breast; liver cirrhosis; chronic pancreatitis; coronary heart disease; stroke; depression; preterm birth complications; fetal alcohol syndrome; and injuries and violence.[13,24,220-222] Such epidemiologic evidence would suggest that improving alcohol consumption outcomes is likely to result in improved health outcomes. A recent model estimated that increasing treatment coverage to 40 percent of all people with alcohol dependence in the European Union would reduce alcohol-attributable mortality by 13 percent for men and 9 percent for women.[223] Further, a cost study based on the COMBINE trial reported that several treatment combinations that include pharmacotherapy led to reduced median social costs associated with health care, arrests, and motor vehicle accidents compared with medical management plus placebo.[224]

Table 37. Summary of findings and strength of evidence for efficacy of FDA-approved medications for alcohol dependence

Medication	Outcome	N Studies; N Subjects[a]	Results Effect Size (95% CI)[b]	NNT[c]	Strength of Evidence
ACA	Return to any drinking	16; 4,847	RD: -0.09 (-0.14 to -0.04)	12	Moderate
	Return to heavy drinking	7; 2,496	RD: -0.01 (-0.04 to 0.03)	NA	Moderate
	% DDs	13; 4,485	WMD: -8.8 (-12.8 to -4.8)	NA	Moderate
	% HDDs	1; 100	WMD: -2.6 (-11.4 to 6.2)	NA	Insufficient
	Drinks per DD	1; 116	WMD: 0.4 (-1.8 to 2.6)	NA	Insufficient
	Accidents or injuries	0;[d] 0	NA	NA	Insufficient
	QoL or function	1; 612	NSD	NA	Insufficient
	Mortality	8; 2,677	7 events (ACA) vs. 6 events (placebo)	NA	Insufficient
DIS	Return to any drinking	2; 492	RD: -0.04 (-0.11 to 0.03)[e]	NA	Low
	Return to heavy drinking	0; 0	NA	NA	Insufficient
	% DDs	2; 290	NSD[f]	NA	Insufficient
	% HDDs	0; 0	NA	NA	Insufficient
	Drinks per DD	0; 0	NA	NA	Insufficient
	Accidents or injuries	0; 0	NA	NA	Insufficient
	QoL or function	0; 0	NA	NA	Insufficient
	Mortality	0; 0	NA	NA	Insufficient
NTX 50 mg oral	Return to any drinking	16; 2,347	RD: -0.05 (-0.10 to -0.00)	20	Moderate
	Return to heavy drinking	19; 2,875	RD: -0.09 (-0.13 to -0.04)	12	Moderate
	% DDs	15; 1,992	WMD: -5.4 (-7.5 to -3.2)	NA	Moderate
	% HDDs	6; 521	WMD: -4.1 (-7.6 to -0.61)	NA	Moderate
	Drinks per DD	9; 1,018	WMD: -0.49 (-0.92 to -0.06)	NA	Low
NTX 100 mg oral	Return to any drinking	3; 946	RD: -0.03 (-0.08 to 0.02)	NA	Low
	Return to heavy drinking	2; 858	RD: -0.05 (-0.11 to 0.01)	NA	Low
	% DDs	2; 858	WMD: -0.9 (-4.2 to 2.5)	NA	Low
	% HDDs	2; 423	WMD: -3.1 (-5.8 to -0.3)	NA	Low
	Drinks per DD	1; 240	WMD: 1.9 (-1.5 to 5.2)	NA	Insufficient
NTX injection	Return to any drinking	2; 939	RD: -0.04 (-0.10 to 0.03)	NA	Low
	Return to heavy drinking	2; 615	RD: -0.01 (-0.14 to 0.13)	NA	Low
	% DDs	1; 315	WMD: -8.6 (-16.0 to -1.2)	NA	Insufficient
	% HDDs	2[g]; 926	WMD: -4.6 (-8.5 to -0.56)	NA	Low
	Drinks per DD	0; 0	NA	NA	Insufficient
NTX (any dose)	Accidents or injuries	0; 0	NA	NA	Insufficient
	QoL or function	4; 1,513	Some conflicting results[h]	NA	Insufficient
	Mortality	6; 1,738	1 event (NTX) vs. 2 events (placebo)	NA	Insufficient

ACA = acamprosate; CI = confidence interval; DD, drinking day; DIS = disulfiram; FDA = U.S. Food and Drug Administration; HDD, heavy drinking day; N = number; NA = not applicable; NNT = number needed to treat; NSD = no statistically significant difference; NTX = naltrexone; QoL, quality of life; RD = risk difference; vs. = versus; WMD = weighted mean difference.

[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).

[d] One study rated as unclear risk of bias reported that one patient in the placebo group died by "accident." No other details on the cause or nature of the accident were provided.[78] That study also reported 1 injury in the acamprosate group and 2 in the placebo group. Another study, rated high risk of bias, reported a traffic accident in the acamprosate group.[184]

[e] From meta-analysis of disulfiram 250 mg versus control (disulfiram 1 mg).[92,93] Meta-analysis including studies rated as high risk of bias also found no significant difference (RD, -0.00; 95% CI, -0.10 to 0.09). Similarly, our meta-analysis found no statistically significant difference between disulfiram 250 mg per day and riboflavin (i.e., no disulfiram) (RD, -0.04; 95% CI, -0.11 to 0.03).

[f] One study (N=128) reported similar percentages and no significant difference;[93] the other reported that disulfiram was favored among the subset of subjects (N=162 of 605 subjects) who drank and had a complete set of assessment interviews, but it did not report this outcome for the full randomized sample.[92] Overall, evidence was insufficient due to imprecision, inconsistency, and indirectness.

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

[h] Unable to pool data. Two studies found no significant difference between naltrexone- and placebo-treated subjects.[102,193] One study reported that patients receiving injectable naltrexone 380 mg per month had greater improvement on the mental health summary score than those receiving placebo at 24 weeks (8.2 versus 6.2, p=0.044).[131] One study measured alcohol-related consequences (with the DrInC) and reported that more subjects who received placebo (N=34) had at least 1 alcohol-related consequence than those who received naltrexone (N=34): 76 percent versus 45 percent, p=0.02.[42]

Our meta-analyses of 4 head-to-head randomized controlled trials (RCTs) comparing acamprosate with naltrexone,[61,65,74,79] all rated as low risk of bias, found no statistically significant difference between the two medications for improvement in alcohol consumption outcomes (Table 38). The COMBINE study was one of the 4 RCTs.[65] It found that "patients receiving medical management with naltrexone, combined behavioral intervention (CBI), or both fared better on drinking outcomes than those who received placebo, but acamprosate showed no evidence of efficacy, with or without CBI."

Table 38. Summary of findings and strength of evidence for comparative effectiveness of acamprosate and naltrexone

Intervention	Outcome	N studies; N subjects[a]	Results Effect Size (95% CI)[b]	Strength of Evidence
ACA vs. NTX	Return to any drinking	3; 800	RD: 0.02 (-0.03 to 0.08)	Moderate
	Return to heavy drinking	4; 1,141	RD: 0.01 (-0.05 to 0.06)	Moderate
	Percentage drinking days	2; 720	WMD: -2.98 (-13.4 to 7.5)	Low

ACA = acamprosate; CI = confidence interval; N = number; NTX = naltrexone; RD = risk difference; WMD = weighted mean difference.

Note: Table only includes comparisons of medications with evidence of efficacy (as determined in KQ 1) and with sufficient data for synthesis. We did not include rows in this table for outcomes that we graded as having insufficient SOE (percentage heavy drinking days, drinks per drinking day, accidents or injuries, quality of life or function, and mortality).

[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 acamprosate over naltrexone.

For the vast majority of medications used off-label, and those under investigation, the evidence either was insufficient to determine whether they are efficacious for reducing alcohol consumption or the evidence suggested that they are not efficacious for people with AUDs. We found some exceptions. First, for topiramate, we found moderate SOE supporting efficacy for reducing drinking days, heavy drinking days, and drinks per drinking day—based on the results of 2 RCTs rated as low or medium risk of bias (total N=521).[175,179] The included RCTs did not report data for return to any drinking or return to heavy drinking. Second, for nalmefene, we found moderate SOE supporting efficacy for reducing heavy drinking days per month (WMD -2.0; 95% CI, -3.0 to -1.0) and drinks per drinking day (WMD, -1.0; 95% CI, -1.8 to -0.3).[159,160] We found insufficient evidence of efficacy for nalmefene for other consumption outcomes (return to any drinking and return to heavy drinking) and low SOE that nalmefene is not efficacious for reducing drinking days (WMD, -1.1; 95% CI, -7.6 to 5.4). Finally, limited evidence from 2 small RCTs (total N=88) supports efficacy of valproic acid for reducing return to heavy drinking, heavy drinking days, and drinks per drinking day (low SOE for all).

Harms

Adverse events were often not collected using standardized measures, and methods for systematically capturing adverse events were often not reported. Studies were generally not designed primarily to assess adverse events; the vast majority focused on alcohol consumption outcomes. Evidence for many potential adverse events was insufficient to determine whether the risk was increased or not, often primarily because of lack of precision. For most of the specific adverse events, point estimates favored placebo (i.e., there were more adverse events with medications), but the differences were not statistically significant.

In head-to-head studies, the risk of withdrawal due to adverse events was not significantly different between acamprosate and naltrexone, whereas the risks of headache and vomiting were higher for those treated with naltrexone. Compared with placebo, patients treated with acamprosate had a higher risk of anxiety, diarrhea, and vomiting; those treated with naltrexone had a higher risk of dizziness, nausea, and vomiting; and those treated with nalmefene had a higher risk of dizziness, headache, insomnia, nausea, and vomiting. Trials of topiramate reported increased risk of many adverse events, including paresthesias, taste perversion, anorexia, difficulty with concentration/attention, nervousness, dizziness, pruritis, psychomotor slowing, and weight loss.[175,179] A single trial that reported adverse effects for valproic acid compared with placebo found a higher rate of nausea for patients treated with valproic acid.

According to the package insert,[225] acamprosate is contraindicated for people with severe renal impairment (creatinine clearance 30 mL per minute or less) and requires dose adjustments for moderate renal impairment (creatinine clearance between 30 and 50 mL per minute). Precautions are listed to monitor for depression and suicidal ideation. Common side effects include diarrhea and somnolence.

Oral naltrexone is contraindicated for patients with acute hepatitis or liver failure, and for those currently using opioids or with anticipated need for opioids.[226,227] It can precipitate severe withdrawal for patients dependent on opioids.[226,227] Precautions are listed in the package insert for other hepatic disease, renal impairment, and history of suicide attempts or depression. Patients should be advised to carry a wallet card to alert medical personnel because larger doses may be required and respiratory depression may be deeper and more prolonged if opioid analgesia is needed. Serious adverse events include precipitation of severe withdrawal if the patient is dependent on opioids, and hepatotoxicity (although it is not believed to be a hepatotoxin at the recommended doses). Common side effects include nausea, vomiting, decreased appetite, headache, dizziness, fatigue, somnolence, and anxiety. Injectable naltrexone can also cause injection site reactions. The prescribing information for injectable naltrexone is somewhat different.[227] For example, contraindications for injectable naltrexone include patients receiving opioid analgesics, with current physiologic opioid dependence, with acute opioid withdrawal, or who have failed a naloxone challenge test. It is not contraindicated for patients with acute hepatitis or liver failure, or for those with anticipated need for opioids.

Primary Care Settings

Evidence from primary care settings was scant. One trial (N=100) that recruited subjects primarily by advertisement in two family medicine settings in the United States found no significant treatment effect when comparing acamprosate with placebo.[69] The only other trial meeting our inclusion criteria that was conducted partly in primary care settings compared nalmefene with placebo in 15 sites (about half were primary care settings) in Finland.[158]

Some included studies conducted in non-primary care settings used interventions that may be adaptable for delivery in primary care. For example, in the COMBINE study,[65] providers delivered a medical management intervention of up to 9 manual-guided counseling visits. The first visit was approximately 45 minutes and followup visits were about 20 minutes each. Medical management included advice for reducing drinking, inquiries about medication side-effects, and emphasis on the importance of taking medications as prescribed. Another trial (included in Key Question [KQ] 1 but not in KQ 4) that compared naltrexone with placebo for 12 weeks in the United States described the use of a "primary care model."[101] Although the trial did not take place in a primary care setting (it was a treatment research center), and the investigators were from a department of psychiatry, the psychosocial co-intervention was delivered by a nurse practitioner with a primary care background, and the trial may have implications for how psychosocial co-interventions could be provided in primary care settings.

In terms of implementing treatment programs for AUDs in primary care, we identified four other publications that did not meet our inclusion criteria (due to the study design or comparators) that may have important implications for primary care settings.[228-231] While these studies found conflicting results, they demonstrated the feasibility of managing AUDs in primary care. In general, these 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 providers and mental health providers (e.g., physicians coordinating with social workers to connect patients to community resources or provide counseling).

First, a nested sequence of three U.S.-based RCTs compared naltrexone plus "primary care management" (PCM) with naltrexone plus cognitive behavioral therapy.[228] PCM was provided by nurse practitioners, physician assistants, and one internist in an initial 45-minute visit, followed by 15- to 20-minute sessions in weeks 1, 2, 3, 4, 6, 8, and 10. The study found no difference in response to treatment, as measured by avoiding persistent heavy drinking, between those who received PCM and those who received cognitive behavioral therapy (84.1 percent versus 86.5 percent). Among responders enrolled in a maintenance trial, it found higher response for those who received naltrexone and PCM than for those who received placebo and PCM (80.8 percent versus 51.9 percent, p=0.03). Second, a pragmatic trial with 149 general practitioners in France who were "used to managing alcohol-dependent patients in their daily practice" randomized patients (N=422) to acamprosate plus standard care or standard care alone.[229] Standard care in France was described as typically consisting of outpatient detoxification followed by a rehabilitation program (involving some type of psychotherapy). The trial reported better outcomes for the acamprosate group for the Alcohol-Related Problems Questionnaire score, the number of subjects with no alcohol-related problems, and for all secondary outcome measures, including QoL. Third, another U.S-based RCT (N=163) compared a primary-care based alcohol care management (ACM) program with a specialty outpatient addiction treatment program.[230] A greater proportion of the ACM group received naltrexone than the specialty treatment group (65.9 percent versus 11.5 percent), the ACM group had a higher proportion of participants engaged in treatment over the 26 weeks (OR, 5.36; 95 % CI, 2.99 to 9.59), and the percentage of heavy drinking days was lower in the ACM group (OR, 2.16; 95 % CI, 1.27 to 3.66). Overall abstinence did not differ between groups. Fourth, the U.S.-based AHEAD trial (N=563) compared chronic care management (CCM) that included longitudinal care coordinated by a primary care clinician with no CCM for people with alcohol or drug dependence who were not currently engaged in primary care.[231] Of those enrolled, 12 percent had alcohol dependence

without also meeting criteria for other drug dependence. CCM 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.

Barriers to prescribing medications for AUDs in primary care may include lack of familiarity with the medications, lack of confidence in their effectiveness, or inability to provide suitable psychosocial co-interventions (e.g., due to competing demands or insufficient practice resources, personnel, or training). Like behavioral counseling interventions for risky drinking delivered in primary care, implementing the use of medications and psychosocial co-interventions for AUDs in primary care might require development of support systems and additional provider and staff training.[13,232] Further, primary care providers are typically trained to refer patients with AUDs for specialized treatment. O'Malley and O'Connor recently reviewed the issues surrounding the use of medications for alcohol dependence in primary care settings.[34] They concluded that "the implementation and widespread use of medications to treat alcohol problems faces a unique set of barriers in primary care. Although primary care providers are proficient at prescribing a wide variety of medications, they generally are unfamiliar with medications for treating alcohol problems other than those used to treat alcohol withdrawal." They referenced a growing body of research to support basic screening methods, brief interventions, and especially medication therapy that has yet to have a major impact on how primary care providers care for individuals at risk for or with alcohol problems.[233]

Subgroups and Genetic Polymorphisms

We did not find any convincing evidence that either naltrexone or acamprosate are more or less effective (compared with each other) for men or women, older adults, young adults, racial or ethnic minorities, smokers, or those with co-occurring disorders. We found no studies that assessed the clinical utility of genotype-guided dosing strategies or genotype-guided medication selection, and none that randomized by genotype. All included studies were either subgroup analyses of trials or prospective cohort studies of people treated with a medication, and all assessed the association between genotype and response to medication (i.e., clinical validity). For most polymorphism-medication pairs, we found just 1 eligible study, and we graded the SOE as insufficient.

We found 7 eligible studies assessing variation in naltrexone response related to mu-opioid receptor gene (*OPRM1*) polymorphisms. Our meta-analyses for return to any drinking and return to heavy drinking found no significant difference between A-allele homozygotes and those with at least one G allele, both without and with inclusion of studies rated as high or unclear risk of bias. Of note, the total number of subjects contributing data to the analyses was relatively low, and firm conclusions are limited by the imprecision of the results. Point estimates for return to heavy drinking suggest it is possible that patients with at least one G allele of A118G polymorphism of *OPRM1* might be more likely to respond to naltrexone, but confidence intervals were wide; additional studies are needed to improve confidence in the estimate of the effect.

Findings in Relation to What Is Already Known

Existing guidelines and systematic reviews support our main findings.[16,37,38,46-48] As described in the introduction, the U.S. Department of Veterans Affairs (VA), National Institute on Alcohol Abuse and Alcoholism (NIAAA), and Substance Abuse and Mental Health Services Administration (SAMHSA) all have guidelines addressing the use of pharmacotherapy for alcohol dependence.[46-48] The various guidelines recommend that naltrexone and/or acamprosate routinely be considered for patients with alcohol dependence in combination with addiction-focused counseling.

Whereas we did not find statistically significant effects on alcohol consumption outcomes for injectable naltrexone,fewer studies and subjects were available for injectable naltrexone; thus, analyses have less precision.

Applicability

Most studies reported that all subjects met criteria for alcohol dependence. We did not identify any studies that evaluated medications and reported them to be efficacious for people with alcohol use disorders who did not meet criteria for alcohol dependence (i.e., people with alcohol abuse or harmful alcohol use). 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.[12] Using DSM-5 terminology, most participants in the included studies likely had moderate to severe AUDs. Thus, applicability of our findings to people with mild AUDs is uncertain. The mean age of subjects was generally in the 40s, with very few studies enrolling slightly younger or older populations. Thus, it is uncertain whether the medications have similar efficacy for older (e.g., those 65 and older) or younger (e.g., in the 20s) subgroups as they have for patients enrolled in the trials. We did not find evidence to confirm or refute whether treatments are more or less efficacious for many other subgroups, including gender groups, racial or ethnic minorities, smokers or nonsmokers, and those with certain coexisting conditions.

Although the majority of included trials assessing the efficacy of acamprosate were conducted in Europe (16 of 22) and a minority were conducted in the United States (4 of 22), the opposite was true for naltrexone (27 of 44 in the United States and 8 of 44 in Europe). Further, the few studies of acamprosate conducted in the United States did not find it to be efficacious. It is unclear whether the different results were due to population differences or other factors. The European trials of acamprosate typically identified patients from inpatient settings or treatment programs, whereas the U.S.-based trials of acamprosate relied on advertisements and referrals. It is possible that this resulted in populations with differing AUD severity and differing potential for benefit. For example, studies of subjects recruited via advertisements may enroll people who have less severe disorders, and may be less applicable to patients with more severe forms of alcohol-use disorders.

Most studies required patients to abstain for at least a few days prior to initiating medication, and the medications are generally recommended for maintenance of abstinence. Acamprosate and injectable naltrexone are only approved for use in patients who have established abstinence, though the duration of required abstinence is not set. However, some studies enrolling patients who were not yet abstinent have reported reduction in heavy drinking with naltrexone[97,234] or acamprosate.[73]

Implications for Clinical and Policy Decisionmaking

Evidence supports the efficacy of more than one pharmacological treatment for AUDs, and clinical uncertainty exists about what treatment to select for individual patients. Acamprosate and naltrexone have the best evidence supporting their efficacy, but head-to-head trials have not consistently established superiority of either medication. Thus, other factors may contribute to medication choices, such as frequency of administration, cost, potential type of benefits, potential adverse events, and availability of treatments (e.g., acamprosate and injectable naltrexone[227] are currently nonformulary medications for the VA).

For example, acamprosate is typically dosed as two 333 mg tablets given three times daily, whereas oral naltrexone is one tablet once daily, and injectable naltrexone is given once monthly. Acamprosate is contraindicated for people with severe renal impairment and requires dose adjustments for moderate renal impairment. Oral naltrexone is contraindicated for patients with acute hepatitis or liver failure, and for those currently using opioids or with anticipated need for opioids, and it can precipitate severe withdrawal for patients dependent on opioids (see Harms section above for injectable naltrexone contraindications). Trials of topiramate have reported a significantly increased risk of many adverse events, including paresthesias, taste perversion, anorexia, difficulty with concentration/attention, nervousness, dizziness, pruritis, psychomotor slowing, and weight loss.[175,179]

Given that medications for AUDs have been underutilized,[45,235] entities providing health care for people with AUDs may need to develop systems to optimize dissemination and implementation. For example, these could include campaigns to educate providers about the use of medications for AUDs; systems to screen for unhealthy alcohol use and to provide appropriate interventions for people with unhealthy alcohol use; systems to ensure that people with AUDs have access to knowledgeable providers who can prescribe medications for AUDs; or systems to remind or incentivize providers to use effective medications for AUDs when appropriate.

Although we did not evaluate the effectiveness or comparative effectiveness of psychosocial interventions for alcohol use disorders (e.g., cognitive behavioral therapy, 12-step programs, combined behavioral intervention), such interventions have been evaluated within some of the included pharmacotherapy studies and in studies that were not included in our review. It may be important for decisionmakers to have information about the efficacy of psychosocial interventions from other sources. Further, decisionmakers may want information about the efficacy of medications when used independently of psychosocial interventions (which is limited) and when used together with them.

Limitations of the Comparative Effectiveness Review Process

The scope of this review was focused on medications. We did not evaluate the effectiveness or comparative effectiveness of other interventions for alcohol use disorders (e.g., cognitive behavioral therapy, motivational enhancement therapy, 12-step programs). We required that trials have at least 12 weeks of followup from the time of medication initiation, excluding trials of shorter duration. Some might consider this approach to omit potentially important information from shorter trials. However, longitudinal studies have found that shorter treatment periods may yield misleading conclusions about treatment efficacy, due to fluctuations in drinking behavior that are typical of the course of AUDs[236,237]—suggesting that longer durations of followup might more accurately reflect the outcomes of greatest interest and importance.

Our review focused on benefits and harms of medications and how they compare with other medications, and our findings generally reflect the added benefits of medications beyond those of psychosocial co-interventions. However, studies used a variety of different psychosocial co-interventions, and this heterogeneity limits our certainty about the effect of medications when used alone (with no psychosocial co-intervention) or when added to a particular psychosocial intervention. Reporting of previous and ongoing psychosocial interventions was variable across the included studies and we were unable to determine whether subjects actually received some co-interventions (e.g., Alcoholics Anonymous was recommended, but no information was reported about how many subjects adhered to the recommendation).

We combined studies that described including populations with a dual diagnosis (e.g., alcohol dependence and depression) and those that did not in our meta-analyses. To determine whether this potential population heterogeneity would have a significant impact on our conclusions, we conducted sensitivity analyses for acamprosate and naltrexone (the medications with enough studies to conduct a stratified analysis by presence of dual diagnosis). Ultimately, the analyses were not very revealing and do not significantly impact our findings because there are so few studies that specify enrolling a population with dual diagnoses (just 1 trial for acamprosate and 6 for naltrexone that contributed data to any of our meta-analyses; see Appendix F). Effect sizes did not change significantly and were sometimes identical. The one possible exception, that might be considered a significant change in the effect size, was for heavy drinking days and naltrexone. When including all studies, subjects treated with naltrexone had 3.8 percent fewer heavy drinking days than those treated with placebo (WMD, -3.8; 95% CI, -5.8 to -1.8; 11 trials); when excluding 3 studies that enrolled patients with dual diagnoses, the effect size was slightly larger (WMD -4.9; 95% CI, -7.1 to -2.7; 8 trials). It might be somewhat artificial to separate studies that describe a dual diagnosis population from those that do not because many people with AUDs have additional psychiatric diagnoses and many studies don't report information on co-occurring diagnoses.

For KQ 5 (on subgroups), we did not review subgroup analyses from placebo-controlled trials. The question we aimed to answer was a comparative question. We were looking for direct evidence for whether any of the medications are more or less effective than other medications for certain subgroups. To be eligible, studies had to compare at least 2 medications.

Finally, publication bias and selective reporting are potential limitations. Although we searched for unpublished studies and unpublished outcomes, and did not find direct evidence of either of these biases, many of the included trials were published prior to the availability of trial registries (e.g., clinicaltrials.gov) that would allow for greater certainty in determining the potential for either type of bias.

Limitations of the Evidence Base

The evidence base was inadequate to draw conclusions for some of our questions or subquestions of interest. In particular, as described above, we found insufficient direct evidence on health outcomes, limited and varying reporting on harms, few trials conducted in primary care settings, and scant head-to-head evidence on differences for population subgroups.

We found insufficient direct evidence to determine whether medications are efficacious for improving health outcomes. Although evidence from epidemiologic literature consistently relates high average and heavy per-occasion alcohol use to an increased risk of health problems, it is challenging to estimate the magnitude of reduction in the risk of health problems that is derived from a reduction in consumption. For example, it is unclear how much benefit (for health

outcomes) is derived from 10 percent fewer patients returning to any drinking, or from 8 percent fewer patients returning to heavy drinking.

Many of the included trials had methodological limitations introducing some risk of bias. Some trials had high proportions of subjects lost to follow up. High attrition rates are not uncommon in studies of psychiatric conditions. Methods of handling missing data varied, and some trials did nothing to address missing data (i.e., only analyzing completers). However, many trials conducted true intention-to-treat analyses and used appropriate methods of handling missing data, such as imputing return to heavy drinking for subjects lost to followup or multiple imputation.

Reporting of previous treatments and ongoing treatments (i.e., co-interventions) was variable across the included studies. We were often unable to determine whether subjects had received any previous treatments for AUDs.

Research Gaps

We identified numerous gaps in the evidence that future research could address. Many of these gaps are highlighted in the previous sections of this Discussion. Of note, these gaps relate only to the KQs addressed by this report, and they should not eliminate a wide range of potentially important research that falls outside of our scope. Table 39 summarizes the key gaps and potential future research that could address the gaps.

Conclusions

Acamprosate and oral naltrexone (50 mg per day) are effective for improving alcohol consumption outcomes for patients with AUDs (moderate SOE). Numbers needed to treat (NNT) to prevent one person from returning to any drinking were 12 and 20, respectively; NNT to prevent one person from returning to heavy drinking was 12 for oral naltrexone (50 mg per day). Our meta-analyses of head-to-head trials found no statistically significant difference between the two medications for improvement in alcohol consumption outcomes (moderate SOE). Among medications used off-label, moderate evidence supports the efficacy of nalmefene and topiramate for improving some consumption outcomes, and limited evidence supports the efficacy of valproic acid. We found insufficient direct evidence to conclude whether medications for AUDs are effective for improving health outcomes. Evidence from primary care was scant. Evidence was generally insufficient to determine comparative effectiveness of acamprosate and naltrexone for subgroups.

Table 39. Evidence gaps for future research by key question

KQ	Evidence Gap	Potential Future Research
1	Evidence was insufficient to determine efficacy of some medications either because of inconsistency and imprecision or because we found 0 or just 1 small trial with low to medium risk of bias (e.g., amitryptiline, aripiprazole, atomoxetine, baclofen, buspirone, citalopram, desipramine, fluoxetine, fluvoxamine, imipramine, olanzapine, paroxetine, quetiapine).	Future studies could evaluate medications that have some evidence (often from 1 or 2 small trials) suggesting possible efficacy (e.g., baclofen) or medications that have not yet been studied with some theoretical basis to support their potential efficacy.

Table 39. Evidence gaps for future research by key question (continued)

KQ	Evidence Gap	Potential Future Research
1	We found no head-to-head studies of oral naltrexone and injectable naltrexone.	Future studies could compare the benefits of harms of oral and injectable naltrexone.
1	Whether patients need to stop drinking before starting medications in order to benefit is somewhat unclear. Most studies required patients to abstain for at least a few days prior to initiating medication, but some studies enrolling patients who were not yet abstinent have reported reduction in heavy drinking with naltrexone[97,234] or acamprosate.[73]	Future studies could assess the efficacy of medications for patients who are not ready to abstain.
2	We found insufficient[a] direct evidence to conclude that treatment with acamprosate or naltrexone leads to improvement in health outcomes.	Future studies could focus on health outcomes, such as accidents, injuries, QoL, function, or mortality. These could include large prospective studies to evaluate harm and health consequences with various levels of drinking.
3	Relatively few studies reported information about suicide, suicidal ideation, or self-harmful behaviors.	Additional studies could be conducted to determine whether precautions about suicide, suicidal thoughts, or self-harmful behaviors are warranted.
3	Little evidence was available to determine whether naltrexone can be used for people with various liver conditions.[b]	Future studies could evaluate the use of naltrexone for people with various chronic liver conditions.
4	No eligible trials assessed the use of FDA-approved medications in primary care settings.	Future studies could evaluate the use of acamprosate and naltrexone in primary care settings.
5	Evidence on whether any medications are more or less effective than other medications for population subgroups was scant.	Future studies could compare the use of acamprosate and naltrexone for subgroups of patients (e.g., enrolling subjects who all have depression or other psychiatric conditions; comparing effectiveness for men or women or among older or younger patients)
6	Relatively few subjects contributed data to our analyses of variation in naltrexone response and *OPRM1* polymorphisms. Patients with at least one G allele may be more likely to respond to naltrexone, but confidence intervals were wide and the effect was not statistically significant.	Additional studies are likely to change our confidence in the estimate of the effect and to change the estimate.
6	No studies assessed the clinical utility of genotype-guided dosing strategies or genotype-guided medication selection, and none randomized by genotype.	If variation in naltrexone response by *OPRM1* polymorphisms becomes established, then future studies could assess the clinical utility of using genotype-guided dosing strategies. For example, studies might compare the use of genotype-guided dosing strategies (e.g., use naltrexone for patients with at least one G allele, but use acamprosate for A-allele homozygotes) with using naltrexone or acamprosate for all subjects.
6	Only 1 study was available for most polymorphism-medication response associations.	Future studies could explore other genotypic associations (i.e., not limiting future studies to *OPRM1* polymorphisms).

FDA = U.S. Food and Drug Administration; *OPRM1* = mu-opioid receptor gene; QoL = quality of life.

[a]Evidence was insufficient for health outcomes because we found no trials meeting inclusion/exclusion criteria rated as low or medium risk of bias (i.e., accidents and injuries) or mainly because of inconsistency and imprecision (i.e., quality of life and mortality). Very few trials reported any health outcomes, and the included trials were not designed or powered to assess impact on health outcomes—they typically focused on alcohol consumption outcomes.

[b] The FDA removed the black box warning for hepatotoxicity for injectable naltrexone, but it is unclear whether naltrexone should be used in people with various chronic liver conditions.

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Appendix A. Search Strategy

PubMed, Original Search, 2-6-13

Search	Query	Items found
#1	Search “Alcohol-Related Disorders” [MeSH]	92008
#2	Search “Alcoholism” [MeSH]	64059
#3	Search “Alcohol Drinking” [MeSH]	46842
#4	Search alcohol depend*	8221
#5	Search "alcohol misuse"	1331
#6	Search alcohol addiction*	724
#7	Search "alcohol abuse"	12291
#8	Search problem drink*	2220
#9	Search alcohol problem*	2955
#10	Search “alcohol consumption”	25255
#11	Search harmful alcohol*	223
#12	Search harmful drink*	244
#13	Search ((drinking[tiab] OR drinker[tiab] OR drinkers[tiab]) AND alcohol[tiab])	24901
#14	Search (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13)	146095
#15	Search "Alcohol Deterrents”[MeSH]	1053
#16	Search ("Naltrexone"[Mesh] OR naltrexone)	7566
#17	Search ReVia	7567
#18	Search Vivitrol	12
#19	Search ("acamprosate" [Supplementary Concept] OR acamprosate)	603
#20	Search Campral	605
#21	Search ("Disulfiram"[Mesh] OR Disulfiram)	3661
#22	Search Antabuse	3730
#23	Search ("Amitriptyline"[Mesh] OR Amitriptyline)	7828
#24	Search ("aripiprazole" [Supplementary Concept] OR aripiprazole)	2079
#25	Search ("atomoxetine" [Supplementary Concept] OR atomoxetine)	964
#26	Search ("Baclofen"[Mesh] OR Baclofen)	6326
#27	Search ("Buspirone"[Mesh] OR Buspirone)	2546
#28	Search ("Citalopram"[Mesh] OR citalopram)	4661
#29	Search ("Desipramine"[Mesh] OR Desipramine)	7383
#30	Search escitalopram	4916
#31	Search ("Fluoxetine"[Mesh] OR Fluoxetine)	10276
#32	Search ("Fluvoxamine"[Mesh] OR Fluvoxamine)	2470
#33	Search ("gabapentin" [Supplementary Concept] OR gabapentin)	4127
#34	Search ("Imipramine"[Mesh] OR Imipramine)	12137
#35	Search ("nalmefene" [Supplementary Concept] OR nalmefene)	245
#36	Search ("olanzapine" [Supplementary Concept] OR olanzapine)	6265
#37	Search ("Ondansetron"[Mesh] OR Ondansetron)	3576
#38	Search ("Paroxetine"[Mesh] OR paroxetine)	4965
#39	Search ("Prazosin"[Mesh] OR Prazosin)	12613
#40	Search ("quetiapine" [Supplementary Concept] OR quetiapine)	3081
#41	Search ("Sertraline"[Mesh] OR Sertraline)	3462
#42	Search ("topiramate"[Supplementary Concept] OR topiramate)	3130
#43	Search ("Valproic Acid"[Mesh] OR Valproate)	13895
#44	Search ("varenicline"[Supplementary Concept] OR varenicline)	820
#45	Search ("Viloxazine"[Mesh] OR Viloxazine)	318
#46	Search (#15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45)	105016

#47	**Search (#14 and #46)**	**3828**
#48	Search (#14 and #46) Filters: Humans	2856
#49	Search (#14 and #46) Filters: Humans; English	2406
#50	Search (#14 and #46) Filters: Humans; English; Adult: 19+ years	1296
#51	Search (#14 and #46) Filters: Publication date from 1970/01/01; Humans; English; Adult: 19+ years	1270
#52	Search (comment[pt] OR editorial[pt] OR letter[pt] OR news[pt])	1353911
#53	Search (#51 not #52)	**1165**

PubMed, Update Search, 10-11-13

Search	Query	Items found
#1	Search “Alcohol-Related Disorders” [MeSH]	93541
#2	Search “Alcoholism” [MeSH]	64878
#3	Search “Alcohol Drinking” [MeSH]	48394
#4	Search alcohol depend*	8688
#5	Search "alcohol misuse"	1428
#6	Search alcohol addiction*	797
#7	Search "alcohol abuse"	12796
#8	Search problem drink*	2299
#9	Search alcohol problem*	3053
#10	Search “alcohol consumption”	26558
#11	Search harmful alcohol*	259
#12	Search harmful drink*	282
#13	Search ((drinking[tiab] OR drinker[tiab] OR drinkers[tiab]) AND alcohol[tiab])	26208
#14	Search (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13)	150350
#15	Search "Alcohol Deterrents”[MeSH]	1080
#16	Search ("Naltrexone"[Mesh] OR naltrexone)	7792
#17	Search ReVia	7793
#18	Search Vivitrol	17
#19	Search ("acamprosate" [Supplementary Concept] OR acamprosate)	634
#20	Search Campral	636
#21	Search ("Disulfiram"[Mesh] OR Disulfiram)	3719
#22	Search Antabuse	3791
#23	Search ("Amitriptyline"[Mesh] OR Amitriptyline)	7964
#24	Search ("aripiprazole" [Supplementary Concept] OR aripiprazole)	2278
#25	Search ("atomoxetine" [Supplementary Concept] OR atomoxetine)	1054
#26	Search ("Baclofen"[Mesh] OR Baclofen)	6471
#27	Search ("Buspirone"[Mesh] OR Buspirone)	2583
#28	Search ("Citalopram"[Mesh] OR citalopram)	4889
#29	Search ("Desipramine"[Mesh] OR Desipramine)	7431
#30	Search escitalopram	5185
#31	Search ("Fluoxetine"[Mesh] OR Fluoxetine)	10600
#32	Search ("Fluvoxamine"[Mesh] OR Fluvoxamine)	2516
#33	Search ("gabapentin" [Supplementary Concept] OR gabapentin)	4349
#34	Search ("Imipramine"[Mesh] OR Imipramine)	12228
#35	Search ("nalmefene" [Supplementary Concept] OR nalmefene)	251
#36	Search ("olanzapine" [Supplementary Concept] OR olanzapine)	6590
#37	Search ("Ondansetron"[Mesh] OR Ondansetron)	3695
#38	Search ("Paroxetine"[Mesh] OR paroxetine)	5103
#39	Search ("Prazosin"[Mesh] OR Prazosin)	12737
#40	Search ("quetiapine" [Supplementary Concept] OR quetiapine)	3297
#41	Search ("Sertraline"[Mesh] OR Sertraline)	3608
#42	Search ("topiramate"[Supplementary Concept] OR topiramate)	3339
#43	Search ("Valproic Acid"[Mesh] OR Valproate)	14447

#44	Search ("varenicline"[Supplementary Concept] OR varenicline)	923
#45	Search ("Viloxazine"[Mesh] OR Viloxazine)	319
#46	Search (#15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45)	108190
#47	Search (#14 and #46)	3952
#48	Search (#14 and #46) Filters: Humans	2926
#49	Search (#14 and #46) Filters: Humans; English	2462
#50	Search (#14 and #46) Filters: Humans; English; Adult: 19+ years	1328
#51	Search (#14 and #46) Filters: Publication date from 1970/01/01; Humans; English; Adult: 19+ years	1302
#52	Search (comment[pt] OR editorial[pt] OR letter[pt] OR news[pt]))	1409249
#53	Search (#51 NOT #52)	1197
#54	Search (#51 NOT #52) Filters: Publication date from 2012/02/11 to 2013/12/31	**60**
#55	Search (#47 AND (“retraction”[All Fields] OR “Retracted Publication”[pt]))	**4**

PSYCINFO, Original Search, 2-11-13

Search ID#	Search Terms	Search Options	Actions
S49	S48	Limiters - Publication Year from: 1970-2013; English; Language: English; Age Groups: Adulthood (18 yrs & older); Population Group: Human Search modes - Boolean/Phrase	View Results (957) View Details Edit
S48	S14 AND S46	Narrow by SubjectAge: - adulthood (18 yrs & older) Search modes - Boolean/Phrase	View Results (997) View Details Edit
S47	S14 AND S46	Search modes - Boolean/Phrase	View Results (1,938) View Details Edit
S46	S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45	Search modes - Boolean/Phrase	View Results (33,948) View Details Edit
S45	Viloxazine	Search modes - Boolean/Phrase	View Results (108) View Details Edit
S44	varenicline	Search modes - Boolean/Phrase	View Results (314) View Details Edit
S43	"Valproic Acid" OR Valproate	Search modes - Boolean/Phrase	View Results (3,170) View Details Edit
S42	topiramate	Search modes - Boolean/Phrase	View Results (1,147) View Details Edit
S41	Sertraline	Search modes - Boolean/Phrase	View Results (2,064) View Details Edit
S40	quetiapine	Search modes - Boolean/Phrase	View Results (2,387) View Details Edit

Search ID#	Search Terms	Search Options	Actions
S39	Prazosin	Search modes - Boolean/Phrase	View Results (486) View Details Edit
S38	Paroxetine	Search modes - Boolean/Phrase	View Results (2,731) View Details Edit
S37	Ondansetron	Search modes - Boolean/Phrase	View Results (367) View Details Edit
S36	olanzapine	Search modes - Boolean/Phrase	View Results (4,620) View Details Edit
S35	nalmefene	Search modes - Boolean/Phrase	View Results (68) View Details Edit
S34	Imipramine	Search modes - Boolean/Phrase	View Results (3,866) View Details Edit
S33	gabapentin	Search modes - Boolean/Phrase	View Results (954) View Details Edit
S32	Fluvoxamine	Search modes - Boolean/Phrase	View Results (1,413) View Details Edit
S31	Fluoxetine	Search modes - Boolean/Phrase	View Results (5,313) View Details Edit
S30	escitalopram	Search modes - Boolean/Phrase	View Results (759) View Details Edit
S29	Desipramine	Search modes - Boolean/Phrase	View Results (1,996) View Details Edit
S28	Citalopram	Search modes - Boolean/Phrase	View Results (1,977) View Details Edit
S27	Buspirone	Search modes - Boolean/Phrase	View Results (1,303) View Details Edit
S26	Baclofen	Search modes - Boolean/Phrase	View Results (936) View Details Edit
S25	atomoxetine	Search modes - Boolean/Phrase	View Results (495) View Details Edit
S24	aripiprazole	Search modes - Boolean/Phrase	View Results (1,410) View Details Edit
S23	Amitriptyline	Search modes - Boolean/Phrase	View Results (2,183) View Details Edit
S22	Antabuse	Search modes - Boolean/Phrase	View Results (154) View Details Edit
S21	Disulfiram	Search modes - Boolean/Phrase	View Results (573) View Details Edit

Search ID#	Search Terms	Search Options	Actions
S20	Campral	Search modes - Boolean/Phrase	View Results (13) View Details Edit
S19	acamprosate	Search modes - Boolean/Phrase	View Results (329) View Details Edit
S18	Vivitrol	Search modes - Boolean/Phrase	View Results (12) View Details Edit
S17	ReVia	Search modes - Boolean/Phrase	View Results (18) View Details Edit
S16	naltrexone	Search modes - Boolean/Phrase	View Results (2,556) View Details Edit
S15	"Alcohol Deterrents"	Search modes - Boolean/Phrase	View Results (1) View Details Edit
S14	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13	Search modes - Boolean/Phrase	View Results (69,149) View Details Edit
S13	TI ((drinking OR drinker OR drinkers) AND alcohol) OR AB ((drinking OR drinker OR drinkers) AND alcohol)	Search modes - Boolean/Phrase	View Results (19,034) View Details Edit
S12	harmful drink*	Search modes - Boolean/Phrase	View Results (355) View Details Edit
S11	harmful alcohol*	Search modes - Boolean/Phrase	View Results (479) View Details Edit
S10	“alcohol consumption”	Search modes - Boolean/Phrase	View Results (11,811) View Details Edit
S9	alcohol problem*	Search modes - Boolean/Phrase	View Results (10,184) View Details Edit
S8	problem drink*	Search modes - Boolean/Phrase	View Results (4,978) View Details Edit
S7	"alcohol abuse"	Search modes - Boolean/Phrase	View Results (20,553) View Details Edit
S6	alcohol addiction*	Search modes - Boolean/Phrase	View Results (2,985) View Details Edit
S5	"alcohol misuse"	Search modes - Boolean/Phrase	View Results (1,159) View Details Edit
S4	alcohol depend*	Search modes - Boolean/Phrase	View Results (14,899) View Details Edit
S3	(DE "Alcohol Drinking Attitudes" OR DE "Alcohol Drinking Patterns") OR (DE "Alcohol Intoxication")	Search modes - Boolean/Phrase	View Results (19,320) View Details Edit

Search ID#	Search Terms	Search Options	Actions
S2	DE "Alcoholism"	Search modes - Boolean/Phrase	View Results (23,596) View Details Edit
S1	"Alcohol-Related Disorders"	Search modes - Boolean/Phrase	View Results (203) View Details Edit

PSYCINFO, Update Search, 10-11-13

#	Query	Limiters/Expanders	Last Run Via	Results
S50	S49	Limiters - Published Date: 20120801-20131231 Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	53
S49	S48	Limiters - Publication Year: 1970-2013; English; Language: English; Age Groups: Adulthood (18 yrs & older); Population Group: Human Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	1,002
S48	S14 AND S46	Limiters - Age Groups: Adulthood (18 yrs & older) Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	1,042
S47	S14 AND S46	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	2,035
S46	S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	35,405
S45	Viloxazine	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	109
S44	varenicline	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	372
S43	"Valproic Acid" OR Valproate	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	3,339

#	Query	Limiters/Expanders	Last Run Via	Results
S42	topiramate	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	1,227
S41	Sertraline	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	2,159
S40	quetiapine	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	2,551
S39	Prazosin	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	512
S38	Paroxetine	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	2,810
S37	Ondansetron	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	383
S36	olanzapine	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	4,873
S35	nalmefene	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	72
S34	Imipramine	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	3,909
S33	gabapentin	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	1,010
S32	Fluvoxamine	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	1,444
S31	Fluoxetine	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	5,497

#	Query	Limiters/Expanders	Last Run Via	Results
S30	escitalopram	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	849
S29	Desipramine	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	2,015
S28	Citalopram	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	2,076
S27	Buspirone	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	1,326
S26	Baclofen	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	998
S25	atomoxetine	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	555
S24	aripiprazole	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	1,550
S23	Amitriptyline	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	2,216
S22	Antabuse	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	157
S21	Disulfiram	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	592
S20	Campral	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	13
S19	acamprosate	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	352

#	Query	Limiters/Expanders	Last Run Via	Results
S18	Vivitrol	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	14
S17	ReVia	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	19
S16	naltrexone	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	2,649
S15	"Alcohol Deterrents"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	1
S14	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	71,938
S13	TI ((drinking OR drinker OR drinkers) AND alcohol) OR AB ((drinking OR drinker OR drinkers) AND alcohol)	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	20,047
S12	harmful drink*	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	385
S11	harmful alcohol*	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	524
S10	“alcohol consumption”	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	12,456
S9	alcohol problem*	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	10,591
S8	problem drink*	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	5,157
S7	"alcohol abuse"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	21,291

#	Query	Limiters/Expanders	Last Run Via	Results
S6	alcohol addiction*	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	3,141
S5	"alcohol misuse"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	1,245
S4	alcohol depend*	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	15,716
S3	(DE "Alcohol Drinking Attitudes" OR DE "Alcohol Drinking Patterns") OR (DE "Alcohol Intoxication")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	19,962
S2	DE "Alcoholism"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	24,275
S1	"Alcohol-Related Disorders"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - PsycINFO	213

CINAHL, Original Search, 2-11-13

#	Query	Limiters/Expanders	Last Run Via	Results
S50	S48 NOT S49	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	6
S49	PT comment OR editorial OR letter OR news	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	65,069
S48	S47	Limiters - Published Date from: 19700101-20131231; English Language; Exclude MEDLINE records; Human; Language: English; Age Groups: All Adult Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	6
S47	S14 AND S46	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	676

#	Query	Limiters/Expanders	Last Run Via	Results
S46	S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	9,728
S45	Viloxazine	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	4
S44	varenicline	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	233
S43	"Valproic Acid" OR Valproate	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	1,159
S42	topiramate	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	676
S41	Sertraline	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	602
S40	quetiapine	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	555
S39	Prazosin	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	0
S38	Paroxetine	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	695
S37	Ondansetron	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	491
S36	olanzapine	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	1,060
S35	nalmefene	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	20
S34	Imipramine	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	211
S33	gabapentin	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	909
S32	Fluvoxamine	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	139

#	Query	Limiters/Expanders	Last Run Via	Results
S31	Fluoxetine	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	1,095
S30	escitalopram	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	173
S29	Desipramine	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	111
S28	Citalopram	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	566
S27	Buspirone	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	147
S26	Baclofen	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	608
S25	atomoxetine	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	245
S24	aripiprazole	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	391
S23	Amitriptyline	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	512
S22	Antabuse	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	16
S21	Disulfiram	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	153
S20	Campral	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	5
S19	acamprosate	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	115
S18	Vivitrol	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	35
S17	ReVia	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	11
S16	Naltrexone	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	800
S15	(MH "Alcohol Deterrents")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	150
S14	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	25,084

#	Query	Limiters/Expanders	Last Run Via	Results
S13	TI ((drinking OR drinker OR drinkers) AND alcohol) OR AB ((drinking OR drinker OR drinkers) AND alcohol)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	5,120
S12	harmful drink*	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	145
S11	harmful alcohol*	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	199
S10	“alcohol consumption”	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	4,342
S9	alcohol problem*	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	2,512
S8	problem drink*	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	744
S7	"alcohol abuse"	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	6,285
S6	alcohol addiction*	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	291
S5	"alcohol misuse"	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	490
S4	alcohol depend*	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	2,448
S3	(MH "Alcohol Drinking")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	10,939
S2	(MH "Alcoholism")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	7,614
S1	(MH "Alcohol-Related Disorders")	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL with Full Text	297

CINAHL, Update Search, 10-11-13

#	Query	Limiters/Expanders	Last Run Via	Results
S51	S50	Limiters - Published Date: 20120801-20131231 Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	0
S50	S48 NOT S49	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	6

#	Query	Limiters/Expanders	Last Run Via	Results
S49	PT comment OR editorial OR letter OR news	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	67,134
S48	S47	Limiters - Published Date: 19700101-20131231; English Language; Exclude MEDLINE records; Human; Language: English; Age Groups: All Adult Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	6
S47	S14 AND S46	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	707
S46	S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	10,125
S45	Viloxazine	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	4
S44	varenicline	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	254
S43	"Valproic Acid" OR Valproate	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	1,218
S42	topiramate	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	701
S41	Sertraline	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	624
S40	quetiapine	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	575

#	Query	Limiters/Expanders	Last Run Via	Results
S39	Prazosin	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	168
S38	Paroxetine	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	714
S37	Ondansetron	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	515
S36	olanzapine	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	1,088
S35	nalmefene	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	22
S34	Imipramine	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	214
S33	gabapentin	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	947
S32	Fluvoxamine	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	142
S31	Fluoxetine	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	1,121
S30	escitalopram	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	188
S29	Desipramine	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	111
S28	Citalopram	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	610
S27	Buspirone	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	151

#	Query	Limiters/Expanders	Last Run Via	Results
S26	Baclofen	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	625
S25	atomoxetine	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	257
S24	aripiprazole	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	416
S23	Amitriptyline	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	535
S22	Antabuse	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	16
S21	Disulfiram	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	156
S20	Campral	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	4
S19	acamprosate	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	119
S18	Vivitrol	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	27
S17	ReVia	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	11
S16	Naltrexone	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	855
S15	MH "Alcohol Deterrents"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	156

#	Query	Limiters/Expanders	Last Run Via	Results
S14	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	26,288
S13	TI ((drinking OR drinker OR drinkers) AND alcohol) OR AB ((drinking OR drinker OR drinkers) AND alcohol)	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	5,369
S12	harmful drink*	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	152
S11	harmful alcohol*	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	211
S10	“alcohol consumption”	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	4,535
S9	alcohol problem*	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	2,609
S8	problem drink*	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	772
S7	"alcohol abuse"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	6,574
S6	alcohol addiction*	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	304
S5	"alcohol misuse"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	529
S4	alcohol depend*	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	2,554

#	Query	Limiters/Expanders	Last Run Via	Results
S3	MH "Alcohol Drinking"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	11,535
S2	MH "Alcoholism"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	7,875
S1	MH "Alcohol-Related Disorders"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL with Full Text	355

EMBASE Minus PubMed, Original Search, 2-6-13

ID	Search	Hits
#50	#48 NOT #49 AND [1970-2013]/py	1,730
#49	editorial:it OR letter:it OR note:it AND [1970-2013]/py	1,757,884
#48	#47 AND ([adult]/lim OR [aged]/lim) AND [humans]/lim AND [english]/lim AND [embase]/lim AND [1970-2013]/py	1,929
#47	#14 AND #46	10,860
#46	#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45	249,162
#45	'viloxazine'/exp OR viloxazine	1,500
#44	'varenicline'/exp OR varenicline	2,131
#43	'valproic acid'/exp OR 'valproic acid' OR 'valproate'/exp OR valproate	47,334
#42	'topiramate'/exp OR topiramate	13,558
#41	'sertraline'/exp OR sertraline	18,228
#40	'quetiapine'/exp OR quetiapine	14,084
#39	'prazosin'/exp OR prazosin	23,503
#38	'paroxetine'/exp OR paroxetine	21,767
#37	'ondansetron'/exp OR ondansetron	12,066
#36	'olanzapine'/exp OR olanzapine	22,547
#35	'nalmefene'/exp OR nalmefene	851
#34	'imipramine'/exp OR imipramine	33,844
#33	'gabapentin'/exp OR gabapentin	18,926
#32	'fluvoxamine'/exp OR fluvoxamine	11,524
#31	'fluoxetine'/exp OR fluoxetine	35,680
#30	'escitalopram'/exp OR escitalopram	5,709
#29	'desipramine'/exp OR desipramine	20,984
#28	'citalopram'/exp OR citalopram	16,194
#27	'buspirone'/exp OR buspirone	7,963
#26	'baclofen'/exp OR baclofen	14,053
#25	'atomoxetine'/exp OR atomoxetine	2,961
#24	'aripiprazole'/exp OR aripiprazole	7,609
#23	'amitriptyline'/exp OR amitriptyline	32,939
#22	'antabuse'/exp OR antabuse	7,397
#21	'disulfiram'/exp OR disulfiram	7,707
#20	'campral'/exp OR campral	1,631
#19	'acamprosate'/exp OR acamprosate	1,672
#18	'vivitrol'/exp OR vivitrol	10,702
#17	'revia'/exp OR revia	10,713
#16	'naltrexone'/exp OR naltrexone	11,537
#15	'alcohol deterrents'	14
#14	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13	218,034
#13	drinking:ti OR drinker:ti OR drinkers:ti AND alcohol:ti OR (drinking:ab OR drinker:ab OR drinkers:ab AND alcohol:ab)	31,024
#12	harmful AND drink*	1,545
#11	harmful AND alcohol*	2,907
#10	'alcohol consumption'/exp	64,311
#9	'alcohol'/exp AND problem*	50,149
#8	problem AND drink*	41,548
#7	'alcohol abuse'/exp	20,002
#6	'alcohol'/exp AND addiction*	36,999
#5	'alcohol misuse'	1,697
#4	'alcohol'/exp AND depend*	30,931
#3	'drinking behavior'/exp	32,528
#2	'alcoholism'/exp	95,795
#1	'alcohol-related disorders'/exp	95.795

Cochrane Library, Original Search, 2-8-13

Cochrane Reviews – 209
Other reviews – 12
Trials – 587

Technology Assessments (1) ● Economic Evaluations (9) ● Cochrane Groups (3)

ID	Search	Hits
#1	[mh "Alcohol-Related Disorders"]	3159
#2	[mh Alcoholism]	2169
#3	[mh "Alcohol Drinking"]	2082
#4	alcohol depend*	3909
#5	"alcohol misuse"	170
#6	alcohol addiction*	1223
#7	"alcohol abuse"	1013
#8	problem drink*	1172
#9	alcohol problem*	2315
#10	“alcohol consumption”	2443
#11	harmful alcohol*	426
#12	harmful drink*	195
#13	(drinking:ti or drinking:ab or drinker:ti or drinker:ab or drinkers:ti or drinkers:ab) and (alcohol:ti or alcohol:ab)	2424
#14	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13	9573
#15	[mh "Alcohol Deterrents"]	146
#16	[mh Naltrexone] or naltrexone	1073
#17	ReVia	8
#18	Vivitrol	3
#19	acamprosate	182
#20	Campral	8
#21	[mh Disulfiram] or Disulfiram	224
#22	Antabuse	24
#23	[mh Amitriptyline] or Amitriptyline	2241
#24	aripiprazole	431
#25	atomoxetine	217
#26	[mh Baclofen] or Baclofen	346
#27	[mh Buspirone] or Buspirone	488
#28	[mh Citalopram] or Citalopram	1232
#29	[mh Desipramine] or Desipramine	797
#30	escitalopram	507
#31	[mh Fluoxetine] or Fluoxetine	2595
#32	[mh Fluvoxamine] or Fluvoxamine	846
#33	gabapentin	770
#34	[mh Imipramine] or Imipramine	2152
#35	nalmefene	79
#36	olanzapine	1881
#37	[mh Ondansetron] or Ondansetron	1664
#38	[mh Paroxetine] or Paroxetine	1915
#39	[mh Prazosin] or Prazosin	1010
#40	quetiapine	773
#41	[mh Sertraline] or Sertraline	1450
#42	topiramate	604
#43	[mh "Valproic Acid"] or Valproate	1172
#44	varenicline	215
#45	[mh Viloxazine] or Viloxazine	142
#46	#15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or	19565

ID	Search	Hits
	#28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45	
#47	#14 and #46	1238
#48	comment:pt or editorial:pt or letter:pt or news:pt	6337
#49	#47 not #48 from 1970 to 2013	1223
#50	adult or adults or [mh adult]	292412
#51	#49 and #50	821

Cochrane Library, Update Search, 10-11-13

Cochrane reviews = 116
Other reviews = 2
Trials = 31

ID	Search	Hits
#1	[mh "Alcohol-Related Disorders"]	3280
#2	[mh Alcoholism]	2249
#3	[mh "Alcohol Drinking"]	2172
#4	alcohol depend*	4188
#5	"alcohol misuse"	189
#6	alcohol addiction*	1266
#7	"alcohol abuse"	1065
#8	problem drink*	1248
#9	alcohol problem*	2476
#10	"alcohol consumption"	1849
#11	harmful alcohol*	486
#12	harmful drink*	227
#13	(drinking:ti or drinking:ab or drinker:ti or drinker:ab or drinkers:ti or drinkers:ab) and (alcohol:ti or alcohol:ab)	2514
#14	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13	9883
#15	[mh "Alcohol Deterrents"]	155
#16	[mh Naltrexone] or naltrexone	1146
#17	ReVia	10
#18	Vivitrol	4
#19	acamprosate	202
#20	Campral	8
#21	[mh Disulfiram] or Disulfiram	234
#22	Antabuse	25
#23	[mh Amitriptyline] or Amitriptyline	2278
#24	aripiprazole	506
#25	atomoxetine	235
#26	[mh Baclofen] or Baclofen	363
#27	[mh Buspirone] or Buspirone	497
#28	[mh Citalopram] or Citalopram	1307
#29	[mh Desipramine] or Desipramine	809
#30	escitalopram	596
#31	[mh Fluoxetine] or Fluoxetine	2668
#32	[mh Fluvoxamine] or Fluvoxamine	863
#33	gabapentin	860
#34	[mh Imipramine] or Imipramine	2170
#35	nalmefene	86
#36	olanzapine	1967
#37	[mh Ondansetron] or Ondansetron	1694
#38	[mh Paroxetine] or Paroxetine	1994

ID	Search	Hits
#39	[mh Prazosin] or Prazosin	1037
#40	quetiapine	849
#41	[mh Sertraline] or Sertraline	1532
#42	topiramate	680
#43	[mh "Valproic Acid"] or Valproate	1233
#44	varenicline	240
#45	[mh Viloxazine] or Viloxazine	145
#46	#15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45	20437
#47	#14 and #46	1333
#48	comment:pt or editorial:pt or letter:pt or news:pt	6440
#49	#47 not #48	1326
#50	#49 from 1970 to 2013	1318
#51	adult or adults or [mh adult]	300762
#52	#50 and #51	883
#53	#52 from 2012 to 2013	150

ClinicalTrials.gov, Original Search, 2-8-13

((“Alcohol-Related Disorders” OR “Alcoholism” OR “Alcohol Drinking” OR alcohol depend* OR "alcohol misuse" OR alcohol addiction* OR "alcohol abuse" OR problem drink* OR alcohol problem* OR “alcohol consumption” OR harmful alcohol* OR harmful drink* OR (drinking OR drinkerOR drinkers) AND alcohol) AND (“Alcohol Deterrents” OR naltrexone OR Revia OR Vivitrol OR acamprosate OR Campral OR disulfiram OR Antabuse OR amitriptyline OR aripiprazole OR atomoxetine OR baclofen OR buspirone OR citalopram OR desipramine OR escitalopram OR fluoxetine OR fluvoxamine OR gabapentin OR imipramine OR nalmefene OR olanzapine OR ondansetron OR paroxetine OR prazosin OR quetiapine OR sertraline OR topiramate OR valproate OR "Valproic Acid" OR varenicline OR vilozaxine)) [ALL-FIELDS] AND ("Adult" OR "Senior") [AGE-GROUP] AND ("01/01/1970" : "02/08/2013") [FIRST-RECEIVED-DATE]

Limited to:
Age Groups: Adult, Senior
First Received: 1/1/1970 - 2/8/2013

ClinicalTrials.gov Update, Update Search, 11-13-13

((“Alcohol-Related Disorders” OR “Alcoholism” OR “Alcohol Drinking” OR alcohol depend* OR "alcohol misuse" OR alcohol addiction* OR "alcohol abuse" OR problem drink* OR alcohol problem* OR “alcohol consumption” OR harmful alcohol* OR harmful drink* OR (drinking OR drinkerOR drinkers) AND alcohol) AND (“Alcohol Deterrents” OR naltrexone OR Revia OR Vivitrol OR acamprosate OR Campral OR disulfiram OR Antabuse OR amitriptyline OR aripiprazole OR atomoxetine OR baclofen OR buspirone OR citalopram OR desipramine OR escitalopram OR fluoxetine OR fluvoxamine OR gabapentin OR imipramine OR nalmefene OR olanzapine OR ondansetron OR paroxetine OR prazosin OR quetiapine OR sertraline OR

topiramate OR valproate OR "Valproic Acid" OR varenicline OR vilozaxine)) [ALL-FIELDS] AND ("Adult" OR "Senior") [AGE-GROUP] AND ("02/08/2013" : "11/13/2013") [LAST-RELEASE-DATE]

WHO ICTRP (World Health Organization International Clinical Trials Registry Platform), Original Search, 2-8-2013

Condition:
Alcohol-Related Disorders OR Alcoholism OR Alcohol

Intervention:
alcohol deterrents OR naltrexone OR Revia OR Vivitrol OR acamprosate OR Campral OR disulfiram OR Antabuse OR amitriptyline OR aripiprazole OR atomoxetine OR baclofen OR buspirone OR citalopram OR desipramine OR escitalopram OR fluoxetine OR fluvoxamine OR gabapentin OR imipramine OR nalmefene OR olanzapine OR ondansetron OR paroxetine OR prazosin OR quetiapine OR sertraline OR topiramate OR valproate OR Valproic Acid OR varenicline OR vilozaxine

Limited to:
Did not check box to look for trials in children.
First Received: 1/1/1970 – 2/8/2013

WHO ICTRP (World Health Organization International Clinical Trials Registry Platform), Update Search, 10-11-2013

Condition:
Alcohol-Related Disorders OR Alcoholism OR Alcohol

Intervention:
alcohol deterrents OR naltrexone OR Revia OR Vivitrol OR acamprosate OR Campral OR disulfiram OR Antabuse OR amitriptyline OR aripiprazole OR atomoxetine OR baclofen OR buspirone OR citalopram OR desipramine OR escitalopram OR fluoxetine OR fluvoxamine OR gabapentin OR imipramine OR nalmefene OR olanzapine OR ondansetron OR paroxetine OR prazosin OR quetiapine OR sertraline OR topiramate OR valproate OR Valproic Acid OR varenicline OR vilozaxine

Limited to:
Did not check box to look for trials in children.
First Received: 1/8/2013 - 10/11/2013

Appendix B. Excluded Studies

Exclusion Codes:

- X1: Not published in English
- X2: Not original research
- X3: Ineligible population
- X4: Ineligible intervention
- X5: Ineligible comparator
- X6: Ineligible outcome
- X7: Ineligible setting
- X8: Ineligible study design
- X9: Treatment duration less than 12 weeks
- X10: Systematic review with search that ended prior to 2007

1. Preventing Alcohol Withdrawal With Oral Baclofen. Exclusion Code: X7
2. Testing combined pharmacotherapies and behavioral interventions in alcohol dependence: Rationale and methods. Alcohol. 2003;27(7):1107-22. Exclusion Code: X6
3. The Effects of Quetiapine (Seroquel XR) on Sleep During Alcohol Abstinence. 2013. Exclusion Code: X9
4. Oral vs. Injectable Naltrexone for Hospitalized Veterans With Alcohol Dependence. 2014. Exclusion Code: X7
5. Extended-Release vs. Oral Naltrexone Alcohol Treatment in Primary Care. 2018. Exclusion Code: X5
6. Harm Reduction With Pharmacotherapy (HaRP). 2018. Exclusion Code: X8
7. Abtahi MA, Abtahi SH, Fazel F, et al. Topiramate and the vision: A systematic review. Clin Opthalmol. 2012;6(1):117-31. Exclusion Code: X3
8. Addolorato G, Caputo F, Capristo E, et al. Baclofen efficacy in reducing alcohol craving and intake: a preliminary double-blind randomized controlled study. Alcohol Alcohol. 2002 Sep-Oct;37(5):504-8. PMID: 12217947. Exclusion Code: X9
9. Addolorato G, Leggio L, Ferrulli A, et al. Dose-response effect of baclofen in reducing daily alcohol intake in alcohol dependence: secondary analysis of a randomized, double-blind, placebo-controlled trial. Alcohol Alcohol. 2011 May-Jun;46(3):312-7. PMID: 21414953. Exclusion Code: X8
10. Adler L, Wilens T, Zhang S, et al. Retrospective safety analysis of atomoxetine in adult ADHD patients with or without comorbid alcohol abuse and dependence. Am J Addict. 2009 Sep-Oct;18(5):393-401. PMID: 19874159. Exclusion Code: X8
11. Agosti V, Nunes EV, O'Shea D. Do manualized psychosocial interventions help reduce relapse among alcohol-dependent adults treated with naltrexone or placebo? A meta-analysis. Am J Addict. 2012;21(6):501-7. Exclusion Code: X5
12. Aguiar P, Neto D, Lambaz R, et al. Prognostic factors during outpatient treatment for alcohol dependence: Cohort study with 6 months of treatment follow-up. Alcohol Alcohol. 2012;47(6):702-10. Exclusion Code: X5
13. Ait-Daoud N, Johnson BA, Javors M, et al. Combining ondansetron and naltrexone treats biological alcoholics: corroboration of self-reported drinking by serum carbohydrate deficient transferrin, a biomarker. Alcohol Clin Exp Res. 2001 Jun;25(6):847-9. PMID: 11410720. Exclusion Code: X4
14. Ait-Daoud N, Johnson BA, Prihoda TJ, et al. Combining ondansetron and naltrexone reduces craving among biologically predisposed alcoholics: preliminary clinical evidence. Psychopharmacology (Berl). 2001 Feb;154(1):23-7. PMID: 11292002. Exclusion Code: X4
15. Aliyev NN. Trial of interferon in chronic alcoholism. Psychiatry Res. 1994;54(3):307-8. PMID: 7792335. Exclusion Code: X5

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Appendix C. Risk of Bias Assessments for Included Studies

Table C-1. Risk of bias assessment for RCTs and related secondary/subgroup analyses

Author, Year Trial Name Design	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	What was the overall attrition?	What was the differential attrition?	Did the study have overall high attrition or differential attrition raising concern for bias?	Did the study have cross-overs or contamination raising concern for bias?	Was intervention fidelity adequate?
Petrakis, 2012[1] NA DBRCT	NR/CND	NR/CND	Yes	44.3	24[a]	Yes	No	Yes
Kranzler, 2012[2] NA SSGA	Yes	NR/CND	Yes	38	12 (14 at 6 month follow up)	Yes	No	Yes
Fogaca, 2011[3] NA DBRCT	NR/CND	NR/CND	NR/CND	46	15% (between PUFAs group and NTX+PUFAs); 0% (between NTX and placebo groups as both were 45% attrition)	Yes	No	NR/CND
Ralevski, 2011[4]; Ralevski, 2011[5] NA DBRCT	NR/CND	NR/CND	Yes, except all 4 women were randomized to the placebo group	35	NR/CND	Yes	No	NR/CND
Wolwer, 2011[6] NA DBRCT	NR/CND	Yes	Yes, except for fewer women in IBT+placebo group	~20 lost to follow-up; 55% did not complete (most due to relapse)	4	No	No	NR/CND
Anton, 2011[7] NA DBRCT	NR/CND	NR/CND	Yes	3% had no drinking data; 35% did not complete treatment;12 to 18% provided drinking data for all 16 weeks	1% for no drinking data; 10% for not completing treatment; 6% for providing drinking data for all 16 weeks	No	No	NR/CND

Table C-1. Risk of bias assessment for RCTs and related secondary/subgroup analyses (continued)

Author, Year Trial Name Design	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	What was the overall attrition?	What was the differential attrition?	Did the study have overall high attrition or differential attrition raising concern for bias?	Did the study have cross-overs or contamination raising concern for bias?	Was intervention fidelity adequate?
Kranzler, 2011[7] DBRCT	Yes	NR/CND	Yes	38% did not complete 12		Yes	No	Yes
Florez, 2011[8] NA OLRCT	NR/CND	NR/CND	Yes	9	5	No	No	Yes
Garbutt, 2010[9] NA DBRCT	Yes	NR/CND	Yes	24	8	No	No	NR/CND
Stedman, 2010[10] NA DBRCT	NR/CND	NR/CND	Yes	57	1	Yes	NR/CND	NR/CND
Kiefer, 2011[11] NA SSGA	Yes (for the PREDICT study)	NR/CND	NR/CND	NR/CND	NR/CND	NR/CND	NR/CND	NR/CND
Pettinati, 2010[12] NA DBRCT	Yes	NR/CND	Yes	43 (did not complete study, but just 3/170 subjects had no data for drinking outcomes)	6.5	Yes	No	Yes
Rubio, 2009[13] NA DBRCT	NR/CND	NR/CND	Yes	17	2	No	No	NR/CND
Schmitz, 2009[14] NA DBRCT	Yes	Yes	No	76% completed 12 weeks; 60% completed 6 weeks; lost to follow-up/missing data NR	NR (but median survival times before dropout were similar)	Yes	NR/CND	NR/CND

Table C-1. Risk of bias assessment for RCTs and related secondary/subgroup analyses (continued)

Author, Year Trial Name Design	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	What was the overall attrition?	What was the differential attrition?	Did the study have overall high attrition or differential attrition raising concern for bias?	Did the study have cross-overs or contamination raising concern for bias?	Was intervention fidelity adequate?
Brown, 2009[15] NA DBRCT	NR/CND	NR/CND	Mixed	48	17	Yes	Yes	NR/CND
Longabaugh, 2009[16] NA DBRCT	Yes	NR/CND	No	18	NR/CND for the 4 groups; 0% for those receiving BST vs. MET	No	NR/CND	NR/CND
Kranzler, 2009[17] NA DBRCT	NR/CND	NR/CND	NR/CND	15	NR/CND	No	NR/CND	Yes
Baltieri, 2008[18]; Baltieri, 2009[19] NA DBRCT	Yes	Yes	Yes	45	4.3, 16.6, and 20.9 differences between each pair of groups	Yes	Yes	NR/CND
Florez, 2008[20] NA SSGA	NA (NR/CND for the parent study)	NR/CND	NR/CND	NR/CND	NR/CND	NR/CND	NR/CND	NR/CND
Oslin, 2008[21] NA DBRCT	NR/CND	NR/CND	No	23	5 (for all NTX vs. all placebo)	No	No	Yes
Arias, 2008[22] NA SSGA	NA (yes for the parent study)	Yes for the parent study	No	33	NR/CND	Yes	NR/CND	NR/CND
Martinotti, 2009[23] NA DBRCT	Yes	Yes	NR/CND	25	1	No	No	NR/CND

Table C-1. Risk of bias assessment for RCTs and related secondary/subgroup analyses (continued)

Author, Year Trial Name Design	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	What was the overall attrition?	What was the differential attrition?	Did the study have overall high attrition or differential attrition raising concern for bias?	Did the study have cross-overs or contamination raising concern for bias?	Was intervention fidelity adequate?
Florez, 2008[24] NA OLRCT	NR/CND	NR/CND	No	10	4	No	No	Yes
O'Malley, 2008[25] NA DBRCT	NR/CND	NR/CND	Yes	33% did not complete; 25% unable to contact or declined further contact or moved	15	Yes	No	Yes
Wilens, 2008[26] NA DBRCT	NRCND	NR/CND	Yes	54	20	Yes	No	Yes
Brown, 2008[27] NA DBRCT	NR/CND	NR/CND	Yes, for most characteristics; No, for race/ethnicity, and concomitant medications	NR/CND	NR/CND	NR/CND	Yes	NR/CND

Table C-1. Risk of bias assessment for RCTs and related secondary/subgroup analyses (continued)

Author, Year Trial Name Design	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	What was the overall attrition?	What was the differential attrition?	Did the study have overall high attrition or differential attrition raising concern for bias?	Did the study have cross-overs or contamination raising concern for bias?	Was intervention fidelity adequate?
Anton, 2008[28] COMBINE SSGA	NA (Yes for parent trial)	Yes for parent trial	Yes	Overall NR/CND 14% of white subjects in the parent trial who received NTX or placebo were not included in this study (604/706 were included); 56% of subjects randomized in COMBINE were not included in this study (604/1383 were included); Overall attrition in COMBINE was 6%	NR/CND (but was very low in overall COMBINE, and unlikely to be much different)	No	No	Yes
Anton, 2008[29] NA DBRCT	NR/CND	NR/CND	Yes for most characteristics; more males in aripiprazole group (75% vs. 62%)	*Aripiprazole vs. Placebo* Loss to follow-up: 7.4% vs. 9.6% Did not complete treatment phase: 41% vs. 26.7%	Loss to follow up: 2.2% Did not complete: 14%	Yes	No	Yes
Addolorato, 2007[30] NA DBRCT	Yes	Yes	Yes	Loss to follow-up: 14% Total dropouts: 23%	Loss to follow-up: 9% Total dropouts: 17%	Yes, differential	No	NR/CND

Table C-1. Risk of bias assessment for RCTs and related secondary/subgroup analyses (continued)

Author, Year Trial Name Design	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	What was the overall attrition?	What was the differential attrition?	Did the study have overall high attrition or differential attrition raising concern for bias?	Did the study have cross-overs or contamination raising concern for bias?	Was intervention fidelity adequate?
Laaksonen, 2008[31] NA OLRCT	Yes	NR/CND	Yes for most variables; no for smoking	25% at 12 weeks (continuous med phase); 52% at 52 weeks (after targeted med phase)	7% at 12 weeks; 5% at 52 weeks	No at 12 weeks; Yes at 52 weeks	Np	Yes
Johnson, 2007[32] Johnson, 2008[33] NA DBRCT	Yes	Yes	Yes	Loss to follow-up: 6% Non-completers: 31%	Loss to follow-up: 4% Non-completers: 15%	Yes	No	Yes
Pettinati, 2008[34] NA DBRCT	NR/CND	NR/CND	Yes	36% did not complete	10	Yes	No	Yes
Kampman, 2007[35] NA DBRCT	NR/CND	NR/CND	No	23	2	No	No	Yes (considering that dose reductions were allowed)
De Sousa, 2008[36] NA OLRCT	NR/CND	NR/CND	Yes	8	0	No	No	Yes
Karhuvaara, 2007[37] NA DBRCT	Yes	Yes	Yes	37 noncompleters; 9% lost to follow-up	8; 1	Yes	CND	Yes
Book, 2008[38]; Thomas, 2008[39] NA DBRCT	Yes	Yes	Yes	About 37% (from Figure) did not provide data at weeks 12 and 16; % lost to followup/missing data NR	CND (appears <2% from Figure)	Yes	No	Yes
O'Malley, 2007[40] NA DBRCT	NR/CND	NR/CND	Yes	23	1.2	No	No	NR/CND

Table C-1. Risk of bias assessment for RCTs and related secondary/subgroup analyses (continued)

Author, Year Trial Name Design	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	What was the overall attrition?	What was the differential attrition?	Did the study have overall high attrition or differential attrition raising concern for bias?	Did the study have cross-overs or contamination raising concern for bias?	Was intervention fidelity adequate?
Gelernter, 2007[41] VACS 425 SSGA	NA	NA	NR/CND	65 (just 220/627 subjects in the main trial were included in this sample)	NR/CND	Yes	No	Yes
Nava, 2006[42] NA OLRCT	Yes	NR/CND	Yes	31	17	Yes	NR/CND	CND
Morley, 2006[43] Morley, 2010[44] NA DBRCT	Yes	NR/CND	Yes	Loss to follow-up or unwilling to continue: 12% Non-completers: 31%	Loss to follow-up or unwilling to continue: 5% Non-completers: 9%	No	NR/CND	Yes
Anton, 2006[45] Donovan, 2008[46] LoCastro, 2009[47] Greenfield, 2010[48] Fucito, 2012[49] COMBINE DBRCT	Yes	Yes	Yes	6 (16 wks) 18 (1 year)	7 (1 year)	No	No	Yes
Mason, 2006[50] NA DBRCT	Yes	Yes	Yes	Loss to follow-up: 13% Non-completers: 51%	Loss to follow-up: 6% Non-completers: 14%	No	No	Yes
Hutchison, 2006[51] NA SBRCT	NR/CND	NR/CND	No	20	5	No	NR/CND	Yes
Huang, 2005[52] NA DBRCT	NR/CND	NR/CND	Yes	No data for primary outcome: 20 Non-completers: 40	No data for primary outcome: 10% Non-completers: 10%	No	NR/CND	NR/CND
De Sousa, 2005[53] NA OLRCT	NR/CND	No	Yes	7	2	No	No	Yes

Table C-1. Risk of bias assessment for RCTs and related secondary/subgroup analyses (continued)

Author, Year Trial Name Design	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	What was the overall attrition?	What was the differential attrition?	Did the study have overall high attrition or differential attrition raising concern for bias?	Did the study have cross-overs or contamination raising concern for bias?	Was intervention fidelity adequate?
Anton, 2005[54] NA DBRCT	NR/CND	NR/CND	Yes	19% did not complete 9 to 11 trial; 15% did not have complete 12 week drinking data		No	No	Yes
Petrakis, 2005[55] Ralevski, 2007[56] Petrakis, 2007[57] Petrakis, 2006[58] VA MIRECC DBRCT	NR/CND	NR/CND	Yes for most characteristic; No for number of other psych meds	11% without 12-week outcome data	2 to 7	No	Yes: some concern for contamination from additional psychiatric medications	NR/CND
Garbutt, 2005[59] NA DBRCT	Yes	Yes	Yes	39% did not complete; 13% lost to follow-up	1%; 3%	Yes	NR/CND	NR/CND
Brady, 2005[60] NA DBRCT	Yes	NR/CND	Yes	34 % (from consent to randomization); NR/CND for loss to follow-up	6	NR/CND	NR/CND	NR/CND
Salloum, 2005[61] NA DBRCT	Yes	NR/CND	Yes	62% non-completers; on average, 86% underwent assessment at each point; 100% underwent assessment at week 24	12; CND	Yes, but not high concern	No	NR/CND
Killeen, 2004[62] NA DBRCT	Yes	NR/CND	No	28	9	No	NR/CND	NR/CND
De Sousa, 2004[63] NA OLRCT	Yes	No	Yes	3	2	No	NR/CND	NR/CND

Table C-1. Risk of bias assessment for RCTs and related secondary/subgroup analyses (continued)

Author, Year Trial Name Design	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	What was the overall attrition?	What was the differential attrition?	Did the study have overall high attrition or differential attrition raising concern for bias?	Did the study have cross-overs or contamination raising concern for bias?	Was intervention fidelity adequate?
Schmitz, 2004[64] NA DBRCT	NR/CND	NR/CND	No	69% did not complete 12 weeks of treatment; lost to follow-up/missing data NR; mean sessions attended: 10.3	NR/CND	Yes	NR/CND	NR/CND
Johnson, 2004[65] NA DBRCT	NR/CND	NR/CND	No	30	12	Yes	NR/CND	NR/CND
Johnson, 2004[66] NA DBRCT	NR/CND	NR/CND	NR/CND	35	11	Yes	NR/CND	NR/CND
Kranzler, 2004[67] NA DBRCT	NR/CND	Yes	Yes	22	5	No	NR/CND	Yes
Anton, 2004[68] NA DBRCT	NR/CND	NR/CND	Yes	26 did not complete 12 weeks; smaller number for lost-to follow up (6 to 16%) and missing data	1 to 9	No	NR/CND	NR/CND
Guardia, 2004[69] NA DBRCT	Yes	NR/CND	Yes	32% non-completers; % missing data NR	19	Yes	NR/CND	NR/CND
Chick, 2004[70] NA DBRCT	Yes	Yes	Yes	64% non-completers; 5.6% post-randomization exclusions (nont in ITT sample); 21% of the ITT sample lost to follow-up	17; 1; 1	Yes	No	NR/CND
Baltieri, 2004[71] NA DBRCT	NR/CND	NR/CND	Yes	23	5	No	NR/CND	NR/CND

Table C-1. Risk of bias assessment for RCTs and related secondary/subgroup analyses (continued)

Author, Year Trial Name Design	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	What was the overall attrition?	What was the differential attrition?	Did the study have overall high attrition or differential attrition raising concern for bias?	Did the study have cross-overs or contamination raising concern for bias?	Was intervention fidelity adequate?
Petrakis, 2004[72]; Ralevski, 2006[73] NA DBRCT	NR/CND	NR/CND	Yes	19	12	No	No	NR/CND
Gual, 2003[74] NA DBRCT	NR/CND	NR/CND	Yes	45% did not complete; 13% lost to follow-up	2	Yes	No	NR/CND
Moak, 2003[75] NA DBRCT	Yes	NR/CND	Yes	28% did not complete; missing data NR	18	No	No	Yes
Balldin, 2003[76] NA DBRCT	Yes	Yes	Yes	22% terminated the study early; 9% had missing drinking data	NR/CND	No	No	Yes
Johnson, 2003[77] Ma, 2006[78]; Johnson, 2004[66] NA DBRCT	Yes	NR/CND	Yes	35% did not complete; 5% not assessed for outcomes at all; unclear amount of missing data	9; 2; unclear for missing data	CND	No	NR/CND
Kiefer, 2003[79] Kiefer, 2005[80] NA DBRCT	Yes	Yes	Yes, for most characteristics; Drug arms had slightly more severe problems on some alcohol measures	0 lost to follow-up; 11% dropout; 53% did not complete trial (most because of relapse)	0 for lost to follow-up; 40% for completion of trial (because 75% of the placebo group relapsed and did not complete)	No	No	NR/CND
Gastpar, 2002[81] NA DBRCT	NR/CND	NR/CND	Yes	36% did not complete (19% failed to return/lost to follow-up, 8% withdrew consent, 4% AEs, 1% protocol violations, 4% other reasons)	5	Yes	No	NR/CND

Table C-1. Risk of bias assessment for RCTs and related secondary/subgroup analyses (continued)

Author, Year Trial Name Design	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	What was the overall attrition?	What was the differential attrition?	Did the study have overall high attrition or differential attrition raising concern for bias?	Did the study have cross-overs or contamination raising concern for bias?	Was intervention fidelity adequate?
Guardia, 2002[82] NA DBRCT	NR/CND	NR/CND	Yes	5% did not have assessable data; 26% dropout, treatment refusal, or other reasons for not completing; 41% total did not complete the study for any reason	0%; 7%; 2	Yes	Possible contamination due to allowed SSRIs	NR/CND
Brady, 2002[83] NA DBRCT	NR/CND	NR/CND	Yes	26% non-completers; 6.5% not included in analyses	NR/CND	No	NR/CND	Yes
Latt, 2002[84] NA DBRCT	Yes	NR/CND	Yes	31% lost to follow-up; 0% excluded from analyses	3%; 0%	Yes	No	NR/CND
Morris, 2001[85] NA DBRCT	NR/CND	NR/CND	No	36% did not complete; 20% dropout for reasons other than relapse	10%; 3%	No	No	NR/CND
Krystal, 2001[86] VACS 425 DBRCT	NR/CND	NR/CND	Yes	27% did not complete; 22% did not have complete data and 10% did not have complete or partially complete data for drinking at week 13	NR/CND; 2%; 1%	No	No	NR/CND
Monti, 2001[87]; Rohsenow, 2007[88]; Rohsenow, 2000[89] NA DBRCT	NR/	NR/CND	NR/CND	9 to 13	NR/CND	No	No	Yes
Monterosso, 2001[90] NA DBRCT	NR/CND	NR/CND	NR/CND	17	NR/CND	No	No	Yes

Table C-1. Risk of bias assessment for RCTs and related secondary/subgroup analyses (continued)

Author, Year Trial Name Design	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	What was the overall attrition?	What was the differential attrition?	Did the study have overall high attrition or differential attrition raising concern for bias?	Did the study have cross-overs or contamination raising concern for bias?	Was intervention fidelity adequate?
Rubio, 2001[91] NA SBRCT	Yes	NA (open-label trial)	Yes	17	13	No	Yes	Yes
Heinala, 2001[92] NA DBRCT	NR/CND	NR/CND	NR/CND	32% did not complete study	NR/CND	Yes	NR/CND	NR/CND
Pettinati, 2001[93] NA DBRCT	NR/CND	NR/CND	Yes	42% did not complete the study; NR/CND for loss to follow-up; unclear how much missing data for alcohol outcomes among those	12%; NR/CND	Yes	No	NR/CND
Chick, 2000[94] NA DBRCT	NR/CND	NR/CND	Yes	19% lost to follow-up; 59% did not complete 12 weeks36	1% for lost to follow up and for completing 12 weeks	Yes	No	Yes
Fawcett, 2000[95] NA DBRCT	NR/CND	NR/CND	Yes	53% (93/175 did not complete 3 months); 11% post-randomization exclusions; missing data/lost to follow-up NR, but Table 2 suggests very low among the 156/175 used for their ITT sample	19; 2 (for missing data first 3 mths for alcohol consumption outcomes)	Yes	No	Yes
Tempesta, 2000[96] NA DBRCT	NR/CND	NR/CND	Yes, for most characteristic; not for previous treatment for alcoholism No (see comment)	26% did not complete; 9% for lost to follow-up	2%; 0% for lost to follow-up	No	No	Yes

Table C-1. Risk of bias assessment for RCTs and related secondary/subgroup analyses (continued)

Author, Year Trial Name Design	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	What was the overall attrition?	What was the differential attrition?	Did the study have overall high attrition or differential attrition raising concern for bias?	Did the study have cross-overs or contamination raising concern for bias?	Was intervention fidelity adequate?
Chick, 2000[97] NA DBRCT	NR/CND	NR/CND	Yes	16% not interviewed at end of medication phase; 32% lost to follow up or missed many appointments; 65% did not complete 6-month study	5% for lost to follow up or missed many appointments	No	No	Yes
Anton, 1999[98]; Anton, 2001[99] NA DBRCT	NR/CND	NR/CND	Yes	17 (but all but 2 subjects, 1.5%, had week 12 drinking data)	9	No	No	Yes
George, 1999[100] NA DBRCT	NR/CND	Yes	NR/CND	42% completed 1 year; 34% lost to follow up	NR/CND	Yes	No	Yes
Besson, 1998[101] NA DBRCT	NR/CND	NR/CND	Yes	30 at 90 days; 65 at 360 days	6 at 90 days; 0 at 360 days	No at 90 days; Yes by 360 days	Yes	NR/CND
Poldrugo, 1997[102] NA DBRCT	NR/CND	NR/CND	Yes	4% lost to follow-up; 55% did not complete 6 months (top reasons were severe relapse, non-compliance, and refusal to continue	0 for lost to follow-up; 15% for completing 6 months (most of difference accounted for by higher severe relapse rate in placebo group)	No	No	NR/CND
Oslin, 1997[103] NA DBRCT	NR/CND	NR/CND	Yes	39% did not complete; 20% with some missing data (lost to follow-up or dropped out)	10%; 7%	No	No	Yes
Volpicelli, 1997[104] NR DBRCT	Yes	NR/CND	Yes	27% did not comlpete	0	No	No	NR/CND (for therapy co-intervention); Yes for medication

Table C-1. Risk of bias assessment for RCTs and related secondary/subgroup analyses (continued)

Author, Year Trial Name Design	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	What was the overall attrition?	What was the differential attrition?	Did the study have overall high attrition or differential attrition raising concern for bias?	Did the study have cross-overs or contamination raising concern for bias?	Was intervention fidelity adequate?
Cornelius, 1997[105]; Cornelius, 1995[106] NA DBRCT	NR/CND	NR/CND	No	10	NR/CND	No	No	Yes
Pelc, 1997[107] NA DBRCT	NR/CND	NR/CND	NR/CND ("no statistical differences" was reported, but data not provided)	37% did not completethe study; 14% lost to follow-up	18% for not completing; 14.7% forlost to follow-up	No	No	Yes
Sass, 1996[108] NA DBRCT	NR/CND	Yes	Yes	20% lost to follow-up; 51% did not complete 48 weeks50	1.5% for lost to follow-up; 18% for completing	No	No	Yes
Kabel, 1996[109] NA DBRCT	NR/CND	NR/CND	NR/CND	42% did not complete 12 weeks (including those who dropped out before discharge); loss to follow-up NR	10	Yes	No	Yes
Whitworth, 1996[110] NA DBRCT	Yes	Yes	Yes	15% for loss to follow-up; 60% did not complete double-blind treatment	1.4% for lost to follow-up	No	No	Yes
Malec, 1996[111] NA DBRCT	NR/CND	NR/CND	Yes	37	13	Yes	No	Yes
Mason, 1996[112] NA DBRCT	NR/CND	NR/CND	Yes	28% (20/71) post-randomization exclusions for dropping out in the first 14 days; among the 51analyzed, 33% refused to continue in the study, were non-compliant, or moved	NR; 0-16	Yes	No	Yes

Table C-1. Risk of bias assessment for RCTs and related secondary/subgroup analyses (continued)

Author, Year Trial Name Design	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	What was the overall attrition?	What was the differential attrition?	Did the study have overall high attrition or differential attrition raising concern for bias?	Did the study have cross-overs or contamination raising concern for bias?	Was intervention fidelity adequate?
McGrath, 1996[113] NA DBRCT	NR/CND	NR/CND	No	19	NR/CND	No	No	Yes
Tiihonen, 1996[114] NA DBRCT	NR/CND	NR/CND	Yes	45% (“drop-outs”)	26	Yes	No	Yes
Kranzler, 1995[115] NA DBRCT	NR/CND	NR/CND	Yes	6	8	No	No	Yes
Paille, 1995[116] NA DBRCT	NR/CND	NR/CND	Yes	13.9% lost to follow-up; 56% did not complete 12 months (top reason was relapse)	2% for loss to follow-up	No	No	Yes
Naranjo, 1995[117] NA DBRCT	NR/CND	NR/CND	NR/CND	37	9	Yes, overall	No	Yes
Volpicelli, 1995[118] NA DBRCT	NR/CND	NR/CND	NR/CND	NR/CND	NR/CND	NR/CND	No	Yes
Kranzler, 1994[119] NA DBRCT	NR/CND	NR/CND	No	31% did not complete 12 weeks; loss to follow-up not totally clear, but was 13% or less (based on review of reasons for not completing	30.6% for not completing; NR for loss to follow-up	Yes	No	Yes
Malcolm, 1992[120] NA DBRCT	NR/CND	NR/CND	Yes	10% lost to follow-up	3	No	No	Yes

Table C-1. Risk of bias assessment for RCTs and related secondary/subgroup analyses (continued)

Author, Year Trial Name Design	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	What was the overall attrition?	What was the differential attrition?	Did the study have overall high attrition or differential attrition raising concern for bias?	Did the study have cross-overs or contamination raising concern for bias?	Was intervention fidelity adequate?
O'Malley, 1992[121]; O'Malley, 1996[122] NA DBRCT	NR/CND	NR/CND	No	35% did not complete; 7% were not included in analyses	8% for did not complete (NTX vs. placebo); 9.6% for inclusion in analyses (NTX vs. placbo)	No	No	Yes
Lhuintre, 1990[123] NA DBRCT	NR/CND	NR/CND	Yes	37% drop-outs	<1% drop-outs	Yes	No	NR/CND
Fuller, 1986[124] NA DBRCT	Yes	Yes	Yes	5	<5% across three groups	No	No	Yes
Lhuintre, 1985[125] NA DBRCT	NR/CND	NR/CND	NR/CND; only age, ggt and MCV level reported	11% lost to follow-up; 18% did not complete	2% for lost to follow-up; 7% for did not complete	No	Yes	NR/CND
Ling, 1983[126] NA DBRCT	NR/CND	NR/CND	NR/CND	57% did not complete 12 week study; 55% lost to follow-up	3% for completion of study; 22% for lost to follow-up	Yes	No	NR/CND
Fuller, 1979[127] NA DBRCT	Yes	NR/CND	NR/CND (no data provided; per authors, groups were similar at baseline)	2% for final assessment after 1 year; 18% for regular bimonthly and final assessments	NR/CND	No	No	Yes
Gual, 2001[128] NA DBRCT	NR/CND	NR/CND	Yes	16% lost to follow-up; 35% non-completers	4% lost to follow-up; 7% non-completers	No	No	Yes
Coskunol, 2002[129] NA DBRCT	Yes	NR/CND	Yes	0% lost to follow-up (3 left study because they developed depression; appears they were included in the analysis)	0	No	No	Yes

Table C-1. Risk of bias assessment for RCTs and related secondary/subgroup analyses (continued)

Author, Year Trial Name Design	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	What was the overall attrition?	What was the differential attrition?	Did the study have overall high attrition or differential attrition raising concern for bias?	Did the study have cross-overs or contamination raising concern for bias?	Was intervention fidelity adequate?
Kranzler, 2013[130] NA SSGA	NR/CND	NR/CND	NR/CND (data provided for sample as a whole, and authors report that there was no differences between groups but data not given)	15% of initial sample did not complete trial, but outcomes were available on entire sample. For this analysis, 74.6% of possible person days of drinking were included. Incomplete drinking data was not included.	NR/CND	No	No	Yes
Ahmadi, 2002[131]; Ahmadi, 2004[132] NA DBRCT	NR/CND	NR/CND	NR/CND (no data provided; per authors, groups were similar at baseline)	NR/CND	NR/CND	NR/CND	NR/CND	NR/CND
Mason, 1999[133] NA DBRCT	NR/CND	NR/CND	Yes	35% noncompleters; about 10% lost to follow-up	1	No	No	Yes
Geerlings, 1997[134] NA DBRCT	NR/CND	NR/CND	Yes	15% lost to follow up; 64% did not complete the study (most common reason was relapse leading to hospitalization)	1% lost to follow up; 10% for completing the study	No	No	Yes
Mason, 1994[135] NA DBRCT	NR/CND	NR/CND	NR/CND; study gives means for demographic and lab values for sample as a whole and reports none were statistically significant, but does not provide data.	62% did not complete; missing data and lost to follow up NR	14%	Yes	No	Yes

Table C-1. Risk of bias assessment for RCTs and related secondary/subgroup analyses (continued)

Author, Year Trial Name Design	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	What was the overall attrition?	What was the differential attrition?	Did the study have overall high attrition or differential attrition raising concern for bias?	Did the study have cross-overs or contamination raising concern for bias?	Was intervention fidelity adequate?
Tollefson, 1991[136]; Tollefson, 1992[137] NA DBRCT	NR/CND	NR/CND	Yes, in regards to alcohol related items. Those randomized to the active drug was reported to be more likely to have used prior benzodiazepines but rates of prior usage were not provided.	73% "dropped out"; 1% were lost to follow-up; 16% were excluded from the analysis because they did not complete at least 4 weeks of treatment	Twenty two % "dropped out" (more in placebo group); there was no differential loss to follow-up or number of participants completing 4 weeks.	No	No	Yes
Lee, 2001[138] NA DBRCT	NR/CND	NR/CND	Yes	66% did not complete 12 weeks; 26% did not have any drinking data	18%; 15%	Yes	No	Yes
Carroll, 1993[139] NA OLRCT	NR/CND	NR/CND	NR/CND- study says groups were comparable, but data not presented.	67	22	Yes	No	Yes
Morgenstern, 2012[140] NA DBRCT	Yes	NR/CND	No, but relatively small differences	16% discontinued treatment; 7% were unavailable for follow-up.	4	No	No	Yes
Pelc, 1996[141]; Pelc, 1992[142] DBRCT	NR/CND	NR/CND	Yes	45% lost to follow-up by day 90; 65% by day 180	17%; 21%	Yes	No	NR/CND
Berger, 2013[143] DBRCT	Yes	Yes	Yes, for most characterstics	19%	5%	No	No	Yes
Corrêa Filho, 2013[144] DBRCT	Yes	NR/CND	Yes	50%	16%	Yes	No	NR/CND
Mann, 2013[145] ESENSE 1 DBRCT	Yes	Yes	Yes	6% not included in analysis; 42% dropped out	NR for not included in analysis; 22% for dropout	Yes	No	NR/CND

Table C-1. Risk of bias assessment for RCTs and related secondary/subgroup analyses (continued)

Author, Year Trial Name Design	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	What was the overall attrition?	What was the differential attrition?	Did the study have overall high attrition or differential attrition raising concern for bias?	Did the study have cross-overs or contamination raising concern for bias?	Was intervention fidelity adequate?
Gual, 2013[146] ESENSE 2 DBRCT	Yes	Yes	Yes	43% non-completers; 9% lost to follow-up or never took study medication; 9% not included in efficacy analysis	3% for non-completers; 1% for lost to follow-up or never took study medication	Yes	No	NR/CND
ALK21-014[147] DBRCT	NR/CND	NR/CND	Yes	37% did not complete; all patients included in analysis	8%	Yes	No	NR/CND
SENSE, 2013[148] DBRCT	NR/CND	NR/CND	Yes	36% did not complete study (no final visit); 36% not included in efficacy analyses for consumption outcomes; 1% not included in harms analyses	6%; 3%	Yes	No	NR/CND
Litten, 2013[149] DBRCT	Yes	NR/CND	Yes	10% discontinued completely; additional 5% discontinued medication but remained in study; 1% not included in analyses	8% overall	No	No	NR/CND
Mann, 2012[150] PREDICT DBRCT	Yes	NR/CND	Yes	34% discontinued; <1% not included in analyses	0% to 2%	Yes	No, since cross-overs were considered to have discontinued	Yes

Table C-1. Risk of bias assessment for RCTs and related secondary/subgroup analyses (continued)

Author, Year Trial Name Design	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	What was the overall attrition?	What was the differential attrition?	Did the study have overall high attrition or differential attrition raising concern for bias?	Did the study have cross-overs or contamination raising concern for bias?	Was intervention fidelity adequate?
Anton, 2003[151] COMBINE pilot DBRCT	Yes	NR/CND	Yes	31% discontinued	11% to 20%	Yes	No	Yes

[a] Unable to determine exact differential attrition because they don't report number by group for all 4 groups for how many completed the trial; the flowchart provides number that completed all visits and number that completed week 12 assessments or were on meds for at least 10 weeks (but does not separate the latter group). 24 percent differential attrition is based on 14/22 versus 16/20 versus 16/22 versus 21/24 (who completed all visits/assessments or were on meds for at least 10 weeks). Article reports data in another place suggesting differential attrition of 20% between all those on desipramine (65 percent completed the trial) and those on paroxetine (45 percent completed the trial).

Abbreviations: CND = cannot determine; COMBINE = Combined Pharmacotherapies and Behavioral Intervention; DBRCT = double-blind randomized controlled trial; ESENSE/SENSE = Safety and Efficacy of Nalmefene in Patients With Alcohol Dependence; NA = not applicable; NR = not reported; OLRCT = open-label randomized controlled trial; SBRCT = single-blind randomized controlled trial; SSGA = secondary or subgroup analysis

Table C-2. Continued risk of bias assessment for RCTs and related secondary/subgroup analyses

Author, Year Trial name Design	Was adherence to the intervention adequate?	Were outcome assessors masked?	Were care providers masked?	Were patients masked?	Were outcome measures equal, valid, and reliable?	Did the study use acceptable statistical methods?	Was an appropriate method used to handle missing data?	Risk of bias	Comments
Petrakis, 2012[1] NA DBRCT	NR/CND	NR/CND	Yes	Yes	Yes	Yes	NR[a]/CND	High	High risk of attrition bias with almost 45% attrition and over 20% differential attrition, along with method of handling missing data; method of randomization and allocation concealment NR
Kranzler, 2012[152] NA SSGA	Yes	NR/CND	Yes	Yes	Yes	Yes	Yes	Medium	Some information in companion Kranzler[2]
Fogaca, 2011[3] NA DBRCT	NR/CND	NR/CND	Yes	Yes	NR/CND	No	No	High	High risk of attrition bias, completer's analysis (excluded 37/80 patients after randomization); methods of randomization and allocation concealment NR; unclear method of measurement for consumption outcomes
Ralevski, 2011[4]; Ralevski, 2011[5] NA DBRCT	No	NR/CND	Yes	Yes	Yes	NR/CND	NR/CND	High	High risk of attrition bias; some baseline differences in sex (all females in the placebo group) and very small sample size of 23; methods of randomization and allocation concealment NR; unclear how missing data was handled; no reporting of masking outcome assessors
Wolwer, 2011[6] NA DBRCT	No	NR/CND	Yes	Yes	Yes	Yes	Yes	Medium	
Anton, 2011[7] NA DBRCT	Yes	NR/CND	Yes	Yes	Yes	No	No	Medium	Note on statistical methods and missing data: 4 post-randomizations excluded; missing data due to dropout censored, but very low percentage of subjects

Table C-2. Continued risk of bias assessment for RCTs and related secondary/subgroup analyses (continued)

Author, Year Trial name Design	Was adherence to the intervention adequate?	Were outcome assessors masked?	Were care providers masked?	Were patients masked?	Were outcome measures equal, valid, and reliable?	Did the study use acceptable statistical methods?	Was an appropriate method used to handle missing data?	Risk of bias	Comments
Kranzler, 2011[2] DBRCT	Yes	NR/CND	Yes	Yes	Yes	Yes	Yes	Medium	
Florez, 2011[8] NA OLRCT	Yes	NR/CND	No	No	Yes	Yes	NR/CND	High	Open-label trial of topiramate and naltrexone; no masking of patients, providers or outcome assessors; unclear method of randomization and allocation concealment; For missing data, they report assuming that subjects resumed heavy drinking, but not what was done for the quality of life outcomes that we would be interested in from this article (it's not eligible for our KQ 1b because it's open label)
Garbutt, 2010[9] NA DBRCT	NR/CND	NR/CND	Yes	Yes	Yes	Yes	Yes	Medium	
Stedman, 2010[10] NA DBRCT	Yes	NR/CND	Yes	Yes	Yes	Yes	No	High	Very high attrition (57% in this 12 week study); over half of the subjects did not complete the study; no reporting of methods of randomization or allocation concealment or masking of outcome assessors; some concern for contamination and methods of handling missing data (used LOCF for some outcomes and used available data for some others)

Table C-2. Continued risk of bias assessment for RCTs and related secondary/subgroup analyses (continued)

Author, Year Trial name Design	Was adherence to the intervention adequate?	Were outcome assessors masked?	Were care providers masked?	Were patients masked?	Were outcome measures equal, valid, and reliable?	Did the study use acceptable statistical methods?	Was an appropriate method used to handle missing data?	Risk of bias	Comments
Kiefer, 2011[11] NA SSGA	NR/CND	NR/CND	Yes	Yes	Yes	NR/CND	NR/CND	High	Exploratory, hypothesis-generating study; secondary analysis of data from PREDICT (N=430), a German RCT of ACA, NTX, and placebo designed similar to COMBINE; this study used data from 374/430 (87%) of the subjects; those for whom genotype data was available, but unclear how many of those also provided outcome data; study provides unadjusted association between GATA4 genotype (SNP rs13273672) and relapse over 90 days, and associatd the finding with response to ACA; high risk of selection bias and confounding; no reporting of baseline characteristics of the groups being compared (across the genotypes or the medications) other than saying they were not different for sex, age, and age of dependence onset and giving p values for those.
Pettinati, 2010[12] NA DBRCT	Yes	NR/CND	Yes	Yes	Yes	Yes	No	Medium	Methods of allocation concealment and masking of outcome assessors NR; some risk of attrition bias; Did not impute anything for missing data, but 84.1% of patients provided drinking reports that were 100% complete, and analyses are time to event analyses

Table C-2. Continued risk of bias assessment for RCTs and related secondary/subgroup analyses (continued)

Author, Year Trial name Design	Was adherence to the intervention adequate?	Were outcome assessors masked?	Were care providers masked?	Were patients masked?	Were outcome measures equal, valid, and reliable?	Did the study use acceptable statistical methods?	Was an appropriate method used to handle missing data?	Risk of bias	Comments
Rubio, 2009[13] NA DBRCT	Yes	NR/CND	Yes	Yes	Yes	No	No	High	Completer's analysis (N=63 analyzed), not ITT; no approach to handling missing data; methods of randomization and allocation concealment and masking of outcome assessors NR
Schmitz, 2009[14] NA DBRCT	No	Yes	Yes	Yes	Yes	Yes	No	High	High risk of selection bias, primarily due to attrition; only 40.5% of subjects completed at least 6 weeks of treatment and just 24% completed all 12 weeks; median follow up prior to dropout was around 30 days; some baseline differences between groups for sex (lower percentage of males in the naltrexone+CBT+CM group); adherence ranged from 50 to 80%; missing data due to dropout were handled as missing (indicating that nothing was done for missing data due to dropout)
Brown, 2009[15] NA DBRCT	Yes	NR/CND	Yes	Yes	Yes	No	No	High	High risk of selection bias and confounding; 7 out of 50 post-randomization exclusions; 48% of subjects did not complete the study; inadequate handling of missing data; Groups similar at baseline for demographics, but higher proportion of anticonvulsant, antidepressant, and sedative/hypnotic use in the naltrexone group; methods of randomization and allocation concealment NR; allowed adjustment of medications or addition of new medications raising some concern for contamination

Table C-2. Continued risk of bias assessment for RCTs and related secondary/subgroup analyses (continued)

Author, Year Trial name Design	Was adherence to the intervention adequate?	Were outcome assessors masked?	Were care providers masked?	Were patients masked?	Were outcome measures equal, valid, and reliable?	Did the study use acceptable statistical methods?	Was an appropriate method used to handle missing data?	Risk of bias	Comments
Longabaugh, 2009[16] NA DBRCT	No	NR/CND	Yes	Yes	Yes	Yes	No	Medium	Moderate risk of selection bias and confounding; inadequate handling of missing data; Excluded 32/174 (18.4%) randomized subjects from analyses, although non-differential; some baseline differences between the four groups for marital status, education, abstinent days and heavy drinking days in previous 90 days (possibly a result of not using the sample that was randomized, which may have undermined the randomization); methods of allocation concealment NR
Kranzler, 2009[17] NA DBRCT	Yes	NR/CND	Yes	Yes	Yes	Yes	Yes	Medium	Methods of randomization and allocation concealment NR; unclear if outcome assessors were masked; very little baseline information reported to allow comparing the two groups at baseline
Baltieri, 2008[18]; Baltieri, 2009[19] NA DBRCT	NR/CND	Yes	Yes	Yes	NR/CND	Yes	Yes	High	High risk of selection bias and confounding; high overall attrition (45% did not complete the 12-week study) and differential attrition; Concern for contamination as the groups had differences in rates of AA participation (the authors provide some adjusted analyses to attempt to address this); Those with insufficient adherence were dropped from the study; Some concern for measurement bias as the study did not report using TLFB method to ascertain drinking outcomes (used self-report to ascertain quantity and frequency, but further details of method NR)

Table C-2. Continued risk of bias assessment for RCTs and related secondary/subgroup analyses (continued)

Author, Year Trial name Design	Was adherence to the intervention adequate?	Were outcome assessors masked?	Were care providers masked?	Were patients masked?	Were outcome measures equal, valid, and reliable?	Did the study use acceptable statistical methods?	Was an appropriate method used to handle missing data?	Risk of bias	Comments
Florez, 2008[20] NA SSGA	NR/CND	NR/CND	NR/CND	NR/CND	Yes	Yes	Yes	High	Exploratory, hypothesis-generating study; secondary analysis of data from a trial; the analyses really focus on whether the outcomes differ by genotype, combining subjects receiving different treatments for main analyses (so not that directly relevant to our questions); evaluates 6 polymorphisms; relatively small sample to attempt this many exploratory genotype analyses (N=90); high risk of selection bias and confounding; no reporting of baseline characteristics of the groups being compared (across the genotypes); study provides unadjusted associations; no adjustment for potential confounders
Oslin, 2008[21] NA DBRCT	No	Yes	Yes	Yes	Yes	Yes	Yes	Medium	Methods of randomization and allocation concealment NR; some baseline differences between groups (race), but analyses adjusted for age, race, gender, pretreatment percent of HDDs; only 50% adhered to medication across conditions

Table C-2. Continued risk of bias assessment for RCTs and related secondary/subgroup analyses (continued)

Author, Year Trial name Design	Was adherence to the intervention adequate?	Were outcome assessors masked?	Were care providers masked?	Were patients masked?	Were outcome measures equal, valid, and reliable?	Did the study use acceptable statistical methods?	Was an appropriate method used to handle missing data?	Risk of bias	Comments
Arias, 2008[22] NA SSGA	Yes	NR/CND	Yes	Yes	Yes	Yes	Yes (from parent article)	High	Secondary analysis of data from a trial; evaluates 5 polymorphisms; high risk of selection bias and confounding; used 67% of the subjects from the parent trial (those with complete data and genotype information available); does not report baseline characteristics for the comparisons of interest to this article (the different genotypes); some baseline differences in alcohol consumption for those receiving nalmefene compared with those receiving placebo in this sample (statistical methods did make adjustment for these); inadequate consideration of potential confounding
Martinotti, 2009[23] NA DBRCT	NR/CND	NR/CND	Yes	Yes	CND	Yes	No	Medium	Data not provided to allow assessment of comparison of groups at baseline (text reports no differences for demographics, etc.); used self-report, but not TLFB to gather consumption data; this head-to-head study used LOCF for missing data, but attrition was not too high and was non-differential

Table C-2. Continued risk of bias assessment for RCTs and related secondary/subgroup analyses (continued)

Author, Year Trial name Design	Was adherence to the intervention adequate?	Were outcome assessors masked?	Were care providers masked?	Were patients masked?	Were outcome measures equal, valid, and reliable?	Did the study use acceptable statistical methods?	Was an appropriate method used to handle missing data?	Risk of bias	Comments
Florez, 2008[24] NA OLRCT	Yes	No	No	No	Yes	Yes	Yes, for consumption and composite measure (assumed relapse); No, for quality of life measures and other outcomes (nothing done to handle missing data)	High	Open label; no masking; some baseline differences between groups that may bias results in favor of topiramate—including more nicotine addiction in the naltrexone group, higher proportions of family history of alcoholism, personality disorders, and higher alcohol intake; baseline means on some scales show trends toward worse scores for naltrexone (Fagerstrom, OCDS, most EuropASI subscales, EQ-5D); methods of randomization and allocation concealment NR
O'Malley, 2008[25] NA DBRCT	No	Yes	Yes	Yes	Yes	Yes	Yes	Medium	Methods of randomization and allocation concealment NR; 33% did not complete study; adherence was 59 to 67% across groups
Wilens, 2008[26] NA DBRCT	NR/CND	NR/CND	Yes	Yes	Yes	Yes	No	High	High risk of attrition bias; 54% did not complete the study; high differential attrition of 20%; inadequate handling of missing data; results for drinking outcomes reported with censoring of missing data (authors report that they also ran analyses counting lost to follow up as relapsed, but data is not shown); methods of randomization and allocation concealment NR

Table C-2. Continued risk of bias assessment for RCTs and related secondary/subgroup analyses (continued)

Author, Year Trial name Design	Was adherence to the intervention adequate?	Were outcome assessors masked?	Were care providers masked?	Were patients masked?	Were outcome measures equal, valid, and reliable?	Did the study use acceptable statistical methods?	Was an appropriate method used to handle missing data?	Risk of bias	Comments
Brown, 2008[27] NA DBRCT	NR/CND	NR/CND	Yes	Yes	Yes	Yes	No	High	High risk of selection bias, attrition bias; inadequate handling of missing data (used LOCF for early withdrawals); poor reporting of methods; 13/115 randomized subjects (11%) excluded after randomization, and information about attrition not reported for the remaining 102 analyzed; methods of randomization and allocation concealment NR; some baseline differences between groups
Anton, 2008[28] COMBINE SSGA	Yes	Yes for meds; no for psychosocial treatment	Yes	Yes	Yes	Yes	Yes	Medium	Subgroup analysis of data from COMBINE, by genotype; some risk of selection bias and confounding; subjects not randomized by genotype; missing genotype data for some; nevertheless, key variables seem to be distributed similarly across genotype groups; several strengths in design, conduct, and analyses
Anton, 2008[29] NA DBRCT	NR/CND	NR/CND	Yes	Yes	Yes	Yes	Yes	Medium	
Addolorato, 2007[30] NA DBRCT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Medium	Some concern for attrition bias due to differential attrition, and because most subjects counted as relapses in the placebo group were those who dropped out or didn't follow up (accounted for 10/21 relapses) rather than those with actual outcome data confirming relapse

Table C-2. Continued risk of bias assessment for RCTs and related secondary/subgroup analyses (continued)

Author, Year Trial name Design	Was adherence to the intervention adequate?	Were outcome assessors masked?	Were care providers masked?	Were patients masked?	Were outcome measures equal, valid, and reliable?	Did the study use acceptable statistical methods?	Was an appropriate method used to handle missing data?	Risk of bias	Comments
Laaksonen, 2008[31] NA OLRCT	Yes for NTX and ACA during continuous phase; No for DIS (67.5%)	NR/CND	No	No	Yes	Yes for some outcomes; no for others (see comments)	No	High for quality of life/KQ 2 outcomes	Open label trial; no masking; Quality of life outcomes were reported for the 52 week timepoint (with less than 50% of subjects reaching that timepoint); inadequate handling of missing data for AUDIT, SADD, QL measures (per-protocol analysis including patients that completed the study); used ITT for primary outcomes (consumption outcomes) but study is not eligible for KQ 1 because it is open label.
Johnson, 2007[32] Johnson, 2008[33] NA DBRCT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low	High differential attrition, with 61.2% completing the trial in the topiramate group compared with 76.6% in the placebo group, but not concerned that introduces significant risk of bias because they have outcome information for most of the non-completers and imputed missing data with baseline values (which were all heavy drinking), so the analysis would be likely to underestimate the benefit of topiramate, if anything; also, few subjects were actually lost to follow up; statistical analysis methods and approach to handling missing data were good.
Pettinati, 2008[34] NA DBRCT	No	NR/CND	Yes	Yes	Yes	Yes	Yes	Medium	Methods of randomization and allocation concealment NR; moderate risk of selection bias due to attrition; <50% had adequate adherence (over 80%) to medication; unclear if outcome assessors were masked

Table C-2. Continued risk of bias assessment for RCTs and related secondary/subgroup analyses (continued)

Author, Year Trial name Design	Was adherence to the intervention adequate?	Were outcome assessors masked?	Were care providers masked?	Were patients masked?	Were outcome measures equal, valid, and reliable?	Did the study use acceptable statistical methods?	Was an appropriate method used to handle missing data?	Risk of bias	Comments
Kampman, 2007[35] NA DBRCT	No	NR/CND	Yes	Yes	Yes	NR/CND	NR/CND	High	Methods of randomization, allocation concealment, and handling of missing data NR; some baseline differences between groups for race, sex, drinks/drinking day, HAM-D and HAM-A scores; inadequate adherence to medication 70 to 77%;small pilot study
De Sousa, 2008[36] NA OLRCT	CND	No	No	No	No	Yes	Yes	High	Methods of randomization (by the "qualified statistician") and allocation concealment NR; High risk of ascertainment bias; no masking; Open label trial comparing disulfiram and topiramate; potentially had more effort to ensure adherence in the disulfiram group
Karhuvaara, 2007[37] NA DBRCT	CND	Yes	Yes	Yes	Yes	Yes	Yes	Medium	
Book, 2008[38]; Thomas, 2008[39] NA DBRCT	Yes	Yes	Yes	Yes	Yes	Yes	CND	Medium	Some concern for attrition bias and missing data in this small (N=42) trial, but attrition was non-differential, and study used mixed model analysis considered robust to non-informative missing data
O'Malley, 2007[40] NA DBRCT	Yes, when calculation based on number of days in treatment	Yes	Yes	Yes	Yes	Yes	Yes	Medium	Methods of randomization and allocation concealment NR; our attrition calculations based on having complete timeline data

Table C-2. Continued risk of bias assessment for RCTs and related secondary/subgroup analyses (continued)

Author, Year Trial name Design	Was adherence to the intervention adequate?	Were outcome assessors masked?	Were care providers masked?	Were patients masked?	Were outcome measures equal, valid, and reliable?	Did the study use acceptable statistical methods?	Was an appropriate method used to handle missing data?	Risk of bias	Comments
Gelernter, 2007[41] VACS 425 SSGA	CND	Yes	Yes	Yes	Yes	Yes	NR/CND	High	Secondary analysis of data from a trial; evaluates opioid receptor gene variants; high risk of selection bias and confounding; used 35% of subjects from the parent trial; does not report baseline characteristics for the comparisons of interest to this article (the different genotypes); and not randomized by genotype; concern for significant differences between this sample and that of the main trial (as the parent trial found no effect of NTX and this study sample providing DNA had an overall reduction in relapse).
Nava, 2006[42] NA OLRCT	CND	No	No	No	Yes	No	No	High	Completers analysis; inadequate handling of missing data; all patients who relapsed were excluded from the analyses; high overall and differential attrition; open label trial with no masking
Morley, 2006[43] Morley, 2010[44] NA DBRCT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low	
Anton, 2006[45] Donovan, 2008[46] LoCastro, 2009[47] Greenfield, 2010[48] Fucito, 2012[49] COMBINE DBRCT	Yes	Yes to meds, no to psychosocial treatment	Yes	Yes	Yes	Yes	Yes	Low	

Table C-2. Continued risk of bias assessment for RCTs and related secondary/subgroup analyses (continued)

Author, Year Trial name Design	Was adherence to the intervention adequate?	Were outcome assessors masked?	Were care providers masked?	Were patients masked?	Were outcome measures equal, valid, and reliable?	Did the study use acceptable statistical methods?	Was an appropriate method used to handle missing data?	Risk of bias	Comments
Mason, 2006[50] NA DBRCT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low	
Hutchison, 2006[51] NA SBRCT	Yes	NR/CND	No	Yes	Yes	NR/CND	NR/CND	High	No masking of providers; unclear whether outcome assessors were masked; unclear whether used ITT analysis for the drinking outcomes and how missing data were handled (used ITT for craving outcomes and LOCF for missing data); methods or randomization and allocation concealment NR; baseline differences between the groups being compared (i.e., since the analyses were by genotype subgroups and not by the full groups that subjects were ransomized to; e.g. those with DRD4 genotype randomized to olanzapine vs. placebo); no adjustment for baseline differences in the comparison by genotype; would consider the genotype findings to be hypothesis generating exploratory analyses

Table C-2. Continued risk of bias assessment for RCTs and related secondary/subgroup analyses (continued)

Author, Year Trial name Design	Was adherence to the intervention adequate?	Were outcome assessors masked?	Were care providers masked?	Were patients masked?	Were outcome measures equal, valid, and reliable?	Did the study use acceptable statistical methods?	Was an appropriate method used to handle missing data?	Risk of bias	Comments
Huang, 2005[52] NA DBRCT	NR/CND	NR/CND	Yes	Yes	NR/CND	CND	CND	High	High risk of measurement bias and confounding; statistical methods don't report whether they used an ITT or completer's analysis; no description of approach to handling missing data; methods of randomization and allocation concealment NR; no description of ascertainment methods for drinking quantity and frequency; relatively few subjects with missing data because they interviewed those who did not complete the study visits and were able to determine that many of them relapsed, they ultimately had outcome data for 80% of subjects
De Sousa, 2005[53] NA OLRCT	NR/CND	No	No	No	NR/CND	Yes	Yes	High	Methods of randomization (by the "qualified statistician") NR; no allocation concealment; High risk of ascertainment bias; no masking; Open label trial comparing disulfiram and acamprosate; potentially had more effort to ensure adherence in the disulfiram group
Anton, 2005[54] NA DBRCT	Yes	NR/CND	Yes	Yes	Yes	Yes	NR/CND	Medium	Therapists were blind to drug assignment but not therapy type, and since the drug is our treatment of interest, we considered the care providers masked.

Table C-2. Continued risk of bias assessment for RCTs and related secondary/subgroup analyses (continued)

Author, Year Trial name Design	Was adherence to the intervention adequate?	Were outcome assessors masked?	Were care providers masked?	Were patients masked?	Were outcome measures equal, valid, and reliable?	Did the study use acceptable statistical methods?	Was an appropriate method used to handle missing data?	Risk of bias	Comments
Petrakis, 2005[55] Ralevski, 2007[56] Petrakis, 2007[57] Petrakis, 2006[58] VA MIRECC DBRCT	Yes	NR/CND	Mixed (yes for NTX, no for DIS)	Mixed (yes for NTX, no for DIS)	Yes	Yes	NR/CND	Medium for NTX vs. pbo High for DIS vs. NTX or pbo	For the DIS comparisons, high risk of ascertainment bias, with no masking; DIS was open-label.
Garbutt, 2005[59] NA DBRCT	See comment	Yes	Yes	Yes	Yes	Yes	No	Medium	64% received all 6 injections; 74% received at least 4 injections. Moderate risk of attrition bias due to dropoupts, but non-differential.
Brady, 2005[60] NA DBRCT	CND	NR/CND	Yes	Yes	Yes	Yes	Yes	Medium	
Salloum, 2005[61] NA DBRCT	Yes	NR/CND	Yes	Yes	Yes	Yes	Yes	Medium	Medium to low risk of bias
Killeen, 2004[62] NA DBRCT	No	NR/CND	Yes	Yes	Yes	Yes	NR/CND	Medium	
De Sousa, 2004[63] NA OLRCT	Yes	No	No	No	Yes	Yes	Drop-out considered relapse	High	

Table C-2. Continued risk of bias assessment for RCTs and related secondary/subgroup analyses (continued)

Author, Year Trial name Design	Was adherence to the intervention adequate?	Were outcome assessors masked?	Were care providers masked?	Were patients masked?	Were outcome measures equal, valid, and reliable?	Did the study use acceptable statistical methods?	Was an appropriate method used to handle missing data?	Risk of bias	Comments
Schmitz, 2004[64] NA DBRCT	Yes	NR/CND	Yes	Yes	Yes	Yes	Restricted Maximum Likelihood Estimation, repeated ANCOVA & survival analyses	High	High risk of selection bias and confounding; high overall attrition, unclear differential attrition and missing data, methods of randomization, allocation concealment, and masking of outcome assessors NR; unclear why patients dropped out and if they were included in the analysis
Johnson, 2004[65] NA DBRCT	Yes	NR/CND	Yes	Yes	Yes	NR/CND	NR/CND	High	High risk of selection bias and confounding. Groups were not similar at baseline, with differences for sex and higher baseline heavy drinking days for the placebo group. Not surprising that groups were different at baseline in this small, pilot study with 25 NTX subjects and 5 placebo subjects. High attrition. Methods of statistical analyses and handling of missing data NR.
Johnson, 2004[66] NA DBRCT	NR/CND	NR/CND	Yes	Yes	Yes	Yes	generalized estimating equations	Medium	
Kranzler, 2004[67] NA DBRCT	Yes	NR/CND	Yes	Yes	Yes	Yes	Yes	Medium	
Anton, 2004[68] NA DBRCT	Yes	Yes	Yes	Yes	Yes	Yes	No	Medium	
Guardia, 2004[69] NA DBRCT	No	Yes	Yes	Yes	Yes	Yes	No	Medium	Moderate risk of attrition bias and inadequate handling of missing data. Missing data were not replaced, but amount of missing data may be very low.

Table C-2. Continued risk of bias assessment for RCTs and related secondary/subgroup analyses (continued)

Author, Year Trial name Design	Was adherence to the intervention adequate?	Were outcome assessors masked?	Were care providers masked?	Were patients masked?	Were outcome measures equal, valid, and reliable?	Did the study use acceptable statistical methods?	Was an appropriate method used to handle missing data?	Risk of bias	Comments
Chick, 2004[70] NA DBRCT	NR/CND	Yes	Yes	Yes	Yes	Yes	Mixed	Medium	Moderate risk of attrition bias; some LOCF used for missing data that might introduce bias, but study found trend for fluvoxamine group to do worse than placebo.
Baltieri, 2004[71] NA DBRCT	NR/CND	NR/CND	Yes	Yes	Yes	Yes	Yes	Medium	All missing data entered as nonabstinent; the ASI includes a field for "Alcohol-any use at all" allowing a reasonably valid and reliable ascertainment
Petrakis, 2004[72]; Ralevski, 2006[73] NA DBRCT	No	NR/CND	Yes	Yes	Yes	Yes	Yes	Medium	Methods of randomization and allocation concealment NR; some baseline differences between groups for drinking; low adherence; masking of outcome assessors NR
Gual, 2003[74] NA DBRCT	NR/CND	NR/CND	Yes	Yes	Yes	Yes	Yes	Medium	
Moak, 2003[75] NA DBRCT	No	NR/CND	Yes	Yes	Yes	Yes	Yes	Medium	
Balldin, 2003[76] NA DBRCT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low	
Johnson, 2003[77] Ma, 2006[78]; Johnson, 2004[66] NA DBRCT	Yes	Yes	Yes	Yes	Yes	Yes	CND	Medium	No completely clear how much missing data for consumption outcomes there was; methods of handling missing data—used data reduction technique taking mean of weeks 1 through 12, weighted by number of study weeks completed with non-missing data; unclear how this would compare with imputing heavy drinking for missing data

Table C-2. Continued risk of bias assessment for RCTs and related secondary/subgroup analyses (continued)

Author, Year Trial name Design	Was adherence to the intervention adequate?	Were outcome assessors masked?	Were care providers masked?	Were patients masked?	Were outcome measures equal, valid, and reliable?	Did the study use acceptable statistical methods?	Was an appropriate method used to handle missing data?	Risk of bias	Comments
Kiefer, 2003[79] Kiefer, 2005[80] NA DBRCT	NR/CND	Yes	Yes	Yes	Yes	Yes	Yes	Low	
Gastpar, 2002[81] NA DBRCT	Yes	NR/CND	Yes	Yes	Yes	Yes	No	Medium	
Guardia, 2002[82] NA DBRCT	No	NR/CND	Yes	Yes	Yes	Yes	No	Medium	Risk of attrition bias, but non-differential; some were excluded post-randomization and not evaluated; apparently censored dropouts in the survival analysis.
Brady, 2002[83] NA DBRCT	Yes	NR/CND	Yes	Yes	Yes	Yes	No	Medium	Some concern with approach to handling missing data; some LOCF using previous week's drinking data was used for some missing data; for other missing data (collected monthly), they used monthly group means
Latt, 2002[84] NA DBRCT	NR/CND	NR/CND	Yes	Yes	Yes	Yes	NR/CND	Medium	Moderate risk of attrition bias; unclear how missing values were imputed for some analyses
Morris, 2001[85] NA DBRCT	Yes	Yes	Yes	Yes	Yes	Yes	No	Medium	Some baseline differences, with NTX patients drinking 15 more drinks/wk than placebo; inadequate handling of missing data
Krystal, 2001[86] VACS 425 DBRCT	Yes	NR/CND	Yes	Yes	Yes	Yes	No	Medium	Inadequate handling of missing data, but relatively low % without complete or partial data (10%) that were not included in the analyses, and non-differential missing data.

Table C-2. Continued risk of bias assessment for RCTs and related secondary/subgroup analyses (continued)

Author, Year Trial name Design	Was adherence to the intervention adequate?	Were outcome assessors masked?	Were care providers masked?	Were patients masked?	Were outcome measures equal, valid, and reliable?	Did the study use acceptable statistical methods?	Was an appropriate method used to handle missing data?	Risk of bias	Comments
Monti, 2001[87]; Rohsenow, 2007[88]; Rohsenow, 2000[153] NA DBRCT	No	Yes	Yes	Yes	Yes	Yes	Yes	Medium	Rated on basis of medication part of the study (not the preceding psychological treatment part)
Monterosso, 2001[90] NA DBRCT	No	NR/CND	Yes	Yes	Yes	Yes	Yes	Medium	
Rubio, 2001[91] NA SBRCT	Yes	Yes	No	No	Yes	Yes	Yes	High	Significantly more patients in the acamprosate group were prescribed disulfiram during the course of the study.
Heinala, 2001[92] NA DBRCT	NR/CND	NR/CND	NR/CND	Yes	Yes	NR/CND	NR/CND	High	High risk of selection bias, attrition bias, and confounding. No description of randomization, allocation concealment, outcome assessor masking, or details of statistical methods. Methods section does not include any information on statistical analyses. Patient characteristics according to treatment group NR. High rate of overall attrition with no reporting of differential attrition and inadequate description of how missing data was handled.
Pettinati, 2001[93] NA DBRCT	No	NR/CND	Yes	Yes	Yes	Yes	NR/CND	Unclear	High overall attrition (42%) and 12% differential attrition for study completion; and degree of missing data/loss to follow-up NR for alcohol consumption outcomes; unclear methods of handling missing data for alcohol consumption outcomes.

Table C-2. Continued risk of bias assessment for RCTs and related secondary/subgroup analyses (continued)

Author, Year Trial name Design	Was adherence to the intervention adequate?	Were outcome assessors masked?	Were care providers masked?	Were patients masked?	Were outcome measures equal, valid, and reliable?	Did the study use acceptable statistical methods?	Was an appropriate method used to handle missing data?	Risk of bias	Comments
Chick, 2000[94] NA DBRCT	No	NR/CND	Yes	Yes	Yes	Yes	Yes	Medium	
Fawcett, 2000[95] NA DBRCT	Yes	No	Yes	Yes	Yes	Yes	Yes	Medium	
Tempesta, 2000[96] NA DBRCT	Yes	NR/CND	Yes	Yes	Yes	Yes	Yes	Medium	
Chick, 2000[97] NA DBRCT	No	NR/CND	Yes	Yes	Yes	Yes	Yes	Medium	
Anton, 1999[98]; Anton, 2001[99] NA DBRCT	Yes	NR/CND	Yes	Yes	Yes	Yes	Yes	Medium	
George, 1999[100] NA DBRCT	NR/CND	NR/CND	Yes	Yes	Yes	Yes	No	High	High risk of selection bias; inadequate handling of missing data; censored those lost to follow up (34% of subjects); differential loss to follow-up NR
Besson, 1998[101] NA DBRCT	NR/CND	NR/CND	Yes	Yes	Yes	Yes	Yes	Medium	Use of disulfiram (voluntary, not randomized) was allowed; randomization was stratified by disulfiram use. Missing data was assumed to be relapse.
Poldrugo, 1997[102] NA DBRCT	NR/CND	NR/CND	Yes	Yes	Yes	Yes	Yes	Medium	

Table C-2. Continued risk of bias assessment for RCTs and related secondary/subgroup analyses (continued)

Author, Year Trial name Design	Was adherence to the intervention adequate?	Were outcome assessors masked?	Were care providers masked?	Were patients masked?	Were outcome measures equal, valid, and reliable?	Did the study use acceptable statistical methods?	Was an appropriate method used to handle missing data?	Risk of bias	Comments
Oslin, 1997[103] NA DBRCT	Yes	NR/CND	Yes	Yes	Yes	Yes	NR/CND	Medium	Unclear handling of missing data, but non-differential missing data; methods of randomization and allocation concealment NR
Volpicelli, 1997[104] NR DBRCT	Yes	NR/CND	Yes	Yes	Yes	Yes	CND	Medium	
Cornelius, 1997[105]; Cornelius, 1995[154] NA DBRCT	Yes	NR/CND	Yes	Yes	Yes	Yes	No	Medium	LOCF used for missing data, but just 5 subjects
Pelc, 1997[107] NA DBRCT	Yes	NR/CND	Yes	Yes	Yes	Yes	Yes	Medium	Slightly high differential loss to follow-up, but overall loss to follow-up was low and the higher loss to follow-up was in the placebo group, who also had higher rate of severe relapse
Sass, 1996[108] NA DBRCT	Yes	NR/CND	Yes	Yes	Yes	Yes	Yes	Medium	
Kabel, 1996[109] NA DBRCT	NR/CND	NR/CND	Yes	Yes	Yes	Yes	Yes	High	High overall attrition (but unclear how many of those were lost to follow-up and had missing data) and high risk of confounding; 15% post-enrollment exclusions (of an already very small sample); Unable to determine comparability of groups at baseline--along with small sample size raises concern for selection bias/confounding.
Whitworth, 1996[110] NA DBRCT	NR/CND	NR/CND	Yes	Yes	Yes	Yes	Yes	Medium	

Table C-2. Continued risk of bias assessment for RCTs and related secondary/subgroup analyses (continued)

Author, Year Trial name Design	Was adherence to the intervention adequate?	Were outcome assessors masked?	Were care providers masked?	Were patients masked?	Were outcome measures equal, valid, and reliable?	Did the study use acceptable statistical methods?	Was an appropriate method used to handle missing data?	Risk of bias	Comments
Malec, 1996[111] NA DBRCT	Yes	NR/CND	Yes	Yes	Yes	Yes	No	High	High overall attrition; 13% differential attrition; and inadequate handling of missing data; completer's analysis.
Mason, 1996[112] NA DBRCT	Yes	NR/CND	Yes	Yes	Yes	Yes	No	High	High risk of attrition bias, inadequate handling of missing data; 28% of subjects that dropped out in the first 2 weeks were not included in analyses. Methods of randomization and allocation concealment NR.
McGrath, 1996[113] NA DBRCT	Yes	NR/CND	Yes	Yes	Yes	Yes	Yes	Medium	Some baseline differences for % married and days of drinking heavily and drinks per drinking day. Missing data was handled with LOCF; but participants were not required to be abstinent before study entry. Abstinence of > 2 weeks before randomization was an exclusion criteria.
Tiihonen, 1996[114] NA DBRCT	Yes	NR/CND	Yes	Yes	Yes	Yes	No	High	High overall and differential attrition; inadequate handling of missing data; unclear methodology for randomization, allocation concealment
Kranzler, 1995[115] NA DBRCT	No	NR/CND	Yes	Yes	Yes	Yes	Yes	Medium	
Paille, 1995[116] NA DBRCT	Yes	NR/CND	Yes	Yes	Yes	Yes	Yes	Medium	Study counted those lost to follow-up as not abstinent.
Naranjo, 1995[117] NA DBRCT	Yes	NR/CND	Yes	Yes	Yes	Yes	No	High	Completer's analysis (62/99); high attrition; inadequate handling of missing data

Table C-2. Continued risk of bias assessment for RCTs and related secondary/subgroup analyses (continued)

Author, Year Trial name Design	Was adherence to the intervention adequate?	Were outcome assessors masked?	Were care providers masked?	Were patients masked?	Were outcome measures equal, valid, and reliable?	Did the study use acceptable statistical methods?	Was an appropriate method used to handle missing data?	Risk of bias	Comments
Volpicelli, 1995[118] NA DBRCT	Yes	NR/CND	Yes	Yes	Yes	Yes	NR/CND	Unclear	Unclear risk of selection bias, confounding, and attrition bias. Baseline characteristics are not reported by treatment group. Inadequate description of handling of missing data. No information is provided regarding attrition or differential attrition. Methods of randomization, allocation concealment, and masking outcome assessors NR.
Kranzler, 1994[119] NA DBRCT	Yes	Yes	Yes	Yes	Yes	Yes	NR/CND	Medium	.95% of subjects were interviewed at study completion to obtain information on consumption outcomes.
Malcolm, 1992[120] NA DBRCT	Yes	NR/CND	Yes	Yes	Yes	Yes	Yes	Medium	
O'Malley, 1992[121];O'Malley, 1996[122] NA DBRCT	Yes	Yes	Yes (to medication, not therapy)	Yes	Yes	Yes	Mixed	Medium	Subjects randomized to supportive therapy had more severe alcohol problems and drank more alcohol per occasion during baseline compared to those randomized to supportive psychotherapy; inadequate handling of missing data for some analyses; methods of randomization and allocation concealment NR.
Lhuintre, 1990[123] NA DBRCT	NR/CND	NR/CND	Yes	Yes	Yes	NR/CND	NR/CND	Unclear	Unclear analytic methods and methods of handling missing data; some indications that this is a completers analysis, but unclear; 37% of study participants dropped-out; althoughnon-differential attrition. Methods of randomization, allocation concealment, and masking of outcome assessors NR.

Table C-2. Continued risk of bias assessment for RCTs and related secondary/subgroup analyses (continued)

Author, Year Trial name Design	Was adherence to the intervention adequate?	Were outcome assessors masked?	Were care providers masked?	Were patients masked?	Were outcome measures equal, valid, and reliable?	Did the study use acceptable statistical methods?	Was an appropriate method used to handle missing data?	Risk of bias	Comments
Fuller, 1986[124] NA DBRCT	No	Yes	Yes	Partially	Yes	Yes	No	Medium	Subjects receiving 250 or 1 mg doses of disulfiram were masked to the dose they received, but told they were receiving disulfiram (aim was to control for implied threat of the disulfiram-ethanol reaction); subjects receiving riboflavin were told they were being given a vitamin; missing data censored (if no interview obtained, they were considered to be abstinent until censored) and did not impute assumed lapse/relapse, but relatively little missing data.
Lhuintre, 1985[125] NA DBRCT	NR/CND	NR/CND	Yes	Yes	NR/CND	No	No	High	High risk of selection bias and confounding; medium to high risk of ascertainment bias; completers-only analysis (70/85 randomized subjects in the analysis); methods of randomization, allocation concealment, and consumption outcome assessment NR; inadequate handling of missing data; some concern for contamination because of the use of meprobamate; unable to assess similarity of groups at baseline

Table C-2. Continued risk of bias assessment for RCTs and related secondary/subgroup analyses (continued)

Author, Year Trial name Design	Was adherence to the intervention adequate?	Were outcome assessors masked?	Were care providers masked?	Were patients masked?	Were outcome measures equal, valid, and reliable?	Did the study use acceptable statistical methods?	Was an appropriate method used to handle missing data?	Risk of bias	Comments
Ling, 1983[126] NA DBRCT	NR/CND	NR/CND	Yes	Yes	NR/CND	Yes	No for most outcomes; Yesfor return to heavy drinking	High	High risk of selection bias and confounding, primarily due to attrition; very high overall and differential loss to follow-up; inadequate handling of missing data for most outcomes (e.g., completers analysis for everything in the Table); methods of randomization, allocation concealment, and masking outcome assessors NR; unclear whether consumption outcomes used valid and reliable measures (just reports that it was self-report, but no description of timeline follow back or other details).
Fuller, 1979[127] NA DBRCT	No	Yes	Yes	Partially	Yes	Yes	NR/CND	Medium	Subjects receiving 250 or 1 mg doses of disulfiram were masked to the dose they received, but told they were receiving disulfiram (aim was to control for implied threat of the disulfiram-ethanol reaction); subjects receiving riboflavin were told they were not receiving disulfiram
Gual, 2001[128] NA DBRCT	Yes	NR/CND	Yes	Yes	Yes	Yes	Yes	Medium	
Coskunol, 2002[129] NA DBRCT	Yes	Yes	Yes	Yes	Yes	Yes	NR/CND	Medium	

Table C-2. Continued risk of bias assessment for RCTs and related secondary/subgroup analyses (continued)

Author, Year Trial name Design	Was adherence to the intervention adequate?	Were outcome assessors masked?	Were care providers masked?	Were patients masked?	Were outcome measures equal, valid, and reliable?	Did the study use acceptable statistical methods?	Was an appropriate method used to handle missing data?	Risk of bias	Comments
Kranzler, 2013[130] NA SSGA	Yes	NR/CND; daily drinking data was recorded electronical-ly by participants.	Yes	Yes	Yes	Yes	No	Medium	This analysis looks at genetic variation and the effect on craving and subsequent drinking. Data that was incomplete was not included for some outcomes.
Ahmadi, 2002[131]; Ahmadi, 2004[132] NA DBRCT	NR/CND	NR/CND	Yes	Yes	Yes	Yes	NR/CND	Unclear	Unclear risk of bias due to limited reporting of methods; methods of randomization, allocation concealment, and handling of missing data NR; baseline characteristics of groups and loss-to-follow up data NR. Primary outcome was abstinence (completers); those who relapsed were non-completers. It is not clearly stated whether outcome data is available for all participants, or whether those who were not available for follow-up were considered to be relapsed.
Mason, 1999[133] NA DBRCT	Yes	NR/CND	Yes	Yes	Yes	Yes	Yes	Medium	
Geerlings, 1997[134] NA DBRCT	Yes	NR/CND	Yes	Yes	Yes	Yes	Yes	Medium	Although his study had a high rate of non-completers, they have follow-up information for most of those subjects, and all subjects were considered to be non-abstinent for the period during which there was missing data.

Table C-2. Continued risk of bias assessment for RCTs and related secondary/subgroup analyses (continued)

Author, Year Trial name Design	Was adherence to the intervention adequate?	Were outcome assessors masked?	Were care providers masked?	Were patients masked?	Were outcome measures equal, valid, and reliable?	Did the study use acceptable statistical methods?	Was an appropriate method used to handle missing data?	Risk of bias	Comments
Mason, 1994[135] NA DBRCT	NR/CND; patients were discontinued from the study if they were not adherent	NR/CND	Yes	Yes	Yes	Yes	No	High	Overall attrition very high, and may have substantially affected the findings given the small sample size (N=21). inadequate handling of missing data, and unclear how much missing data for consumption outcomes
Tollefson, 1991[136]; Tollefson, 1992[137] NA DBRCT	Yes	NR/CND	Yes	Yes	Yes	No	No	High	For participants who did not complete 4 weeks of study duration, a LOCF analysis was used for drinking outcomes. It is unclear whether there was an attempt to determine drinking outcomes after participants dropped out of the study.
Lee, 2001[138] NA DBRCT	NR/CND	NR/CND	Yes, but NTX and placebo pills not identical	Yes	Yes	No	No	High	High risk of selection bias and confounding; high rate of overall and differential attrition; inadequate handling of missing data; methods of randomization and allocation concealment NR; LOCF analysis used which included some, but not all non-completers
Carroll, 1993[139] NA OLRCT	NR/CND	Yes	No	No	Yes	Yes	No	High	Very high rate of attrition; inadequate description of how missing data was handled.
Morgenstern, 2012[140] NA DBRCT	Yes	NR/CND	Yes	Yes	Yes	Yes	No	Medium	
Pelc, 1996[141]; Pelc, 1992[142]	NR/CND	NR/CND	Yes	Yes	Yes	Yes	Yes	High	High risk of selection bias and confounding, primarily due to potential attrition bias due to high overall (65% loss to follow-up) and high differential attrition; methods of randomization and allocation concealment NR

Table C-2. Continued risk of bias assessment for RCTs and related secondary/subgroup analyses (continued)

Author, Year Trial name Design	Was adherence to the intervention adequate?	Were outcome assessors masked?	Were care providers masked?	Were patients masked?	Were outcome measures equal, valid, and reliable?	Did the study use acceptable statistical methods?	Was an appropriate method used to handle missing data?	Risk of bias	Comments
Berger, 2013[143] DBRCT	Yes	Yes	Yes	Yes	Yes	Yes	No	Medium	Some baseline differences between groups for current tobacco use and previous alcohol treatment (although not statistically significant); nothing done to handle missing data; no data imputation was performed, but they had relatively little missing data (19% lost to follow-up) and it was non-differential.
Corrêa Filho, 2013[144] DBRCT	NR/CND	Yes	Yes	Yes	Yes	Yes	Yes	High	Very high overall attrition (50%) and high differential attrition; methods of allocation concealment not reported
Mann, 2013[145] ESENSE1 DBRCT	No	Yes	Yes	Yes	Yes	Yes	Yes	Medium	
Gual, 2013[146] ESENSE 2 DBRCT	No	Yes	Yes	Yes	Yes	Yes	Yes	Medium	
ALK21-014, 2011[147] DBRCT	NR/CND	Yes	Yes	Yes	Yes	Yes	NR/CND	Medium	All information came from clinicaltrials.gov; study not yet published
SENSE, 2013[148] DBRCT	NR/CND	NR/CND	Yes	Yes	Yes	NR/CND	No	High	Inadequate handling of missing data; analysis for consumption outcomes excluded 36% of randomized participants; high risk of attrition bias; all information came from clinicaltrials.gov; study not yet published
Litten, 2013[149] DBRCT	Yes	NR/CND	Yes	Yes	Yes	Yes	Yes	Low	
Mann, 2012[150] PREDICT DBRCT	Yes	NR/CND	Yes	Yes	Yes	Yes	Yes	Medium	High attrition and marginal adherence, but use of worst-case imputation

Table C-2. Continued risk of bias assessment for RCTs and related secondary/subgroup analyses (continued)

Author, Year Trial name Design	Was adherence to the intervention adequate?	Were outcome assessors masked?	Were care providers masked?	Were patients masked?	Were outcome measures equal, valid, and reliable?	Did the study use acceptable statistical methods?	Was an appropriate method used to handle missing data?	Risk of bias	Comments
Anton, 2003[151] COMBINE pilot DBRCT	No	Yes	Yes	Yes	Yes	Yes	NR/CND	Medium	

[a] Used mixed effects model, assuming that missing data were missing at random, but unable to determine if that is true from the article, and the study had high differential attrition

Abbreviations: CND = cannot determine; COMBINE = Combined Pharmacotherapies and Behavioral Intervention; DBRCT = double-blind randomized controlled trial; ESENSE/SENSE = Safety and Efficacy of Nalmefene in Patients With Alcohol Dependence; NA = not applicable; NR = not reported; OLRCT = open-label randomized controlled trial; SBRCT = single-blind randomized controlled trial; SSGA = secondary or subgroup analysis

Table C-3. Additional risk of bias questions for RCTs and related secondary/subgroup analyses that report harms

Author, Year Trial Name Design	Were harms prespecified and defined?	Were ascertainment techniques for harms adequately described?	Were ascertainment techniques for harms equal, valid and reliable?	Was the duration of follow-up adequate for harms assessment?	Risk of bias	Comments
Petrakis, 2012[1] NA DBRCT	No	No	Yes	Yes	High	Used a modified version of the Systematic Assessment for Treatment Emergent Events, but don't describe details or what was modified; Some of the same reasons for high risk of bias as for benefits questions, primarily related to attrition bias
Fogaca, 2011[3] NA DBRCT	No	No	NR/CND	Yes	High	
Ralevski, 2011[4]; Ralevski, 2011[5] NA DBRCT	No	No	Yes	Yes	High	
Anton, 2011[7] NA DBRCT	No	No	NR/CND	Yes	Medium	
Kranzler, 2011[2] DBRCT	No	No	NR/CND	Yes	Medium	Assessed AEs at every visit with self-reported questionnaire; no further details reported
Florez, 2011[8] NA OLRCT	No	Yes	Yes	Yes	High	See comments for effectiveness risk of bias assessment
Garbutt, 2010[9] NA DBRCT	No	Yes	NR/CND	Yes	Medium	
Stedman, 2010[10] NA DBRCT	Mixed	No	Yes	Yes	High	Unclear how most AEs were identified (implication is voluntary self-report); used specific instruments for EPS and to classify AEs that were reported; same concerns as with efficacy assessment regarding attrition, contamination, etc.
Pettinati, 2010[12] NA DBRCT	No	No	Yes	Yes	Medium	Used Systematic Assessment for Treatment Emergent Effects, no other details reported

Table C-3. Additional risk of bias questions for RCTs and related secondary/subgroup analyses that report harms (continued)

Author, Year Trial Name Design	Were harms prespecified and defined?	Were ascertainment techniques for harms adequately described?	Were ascertainment techniques for harms equal, valid and reliable?	Was the duration of follow-up adequate for harms assessment?	Risk of bias	Comments
Rubio, 2009[13] NA DBRCT	Yes	Yes	Yes	Yes	Medium	Describe using an interview that assessed 38 specific AEs and open-ended questions to assess unexpected AEs; in the results, only withdrawals due to AEs are reported (no specific AEs); unlike the benefits analyses for alcohol consumption (which were only of completers), the AEs reported do include the full sample
Schmitz, 2009[14] NA DBRCT	No	No	NR/CND	Yes	High	See comments for efficacy assessment. AEs were evaluated by study nurse and physician; article reports that it included a "standardized reporting system when appropriate", but no further details
Brown, 2009[15] NA DBRCT	No	No	NR/CND	Yes	High	Only information reported is that side effect assessments were repeated at each weekly appointment
Longabaugh, 2009[16] NA DBRCT	No	Yes	NR/CND	Yes	Medium	
Kranzler, 2009[17] NA DBRCT	Yes	Yes	Yes	Yes	Medium	Self report screening questionnaire was followed by a nurse's inquiry concerning the presence of 11 AEs commonly associated with naltrexone
Baltieri, 2008[18]; Baltieri, 2009[19] NA DBRCT	No	No	NR/CND	Yes	High	See comments for efficacy/effectiveness risk of bias also
Oslin, 2008[21] NA DBRCT	No	NR/CND	NR/CND	Yes	Medium	Minimal description; AEs were monitored by the research physician's probing for side effects commonly associated with NTX
Martinotti, 2009[23] NA DBRCT	No	Yes, for EKG, UA, blood tests; No, for symptoms	NR/CND	Yes	Medium	

Table C-3. Additional risk of bias questions for RCTs and related secondary/subgroup analyses that report harms (continued)

Author, Year Trial Name Design	Were harms prespecified and defined?	Were ascertainment techniques for harms adequately described?	Were ascertainment techniques for harms equal, valid and reliable?	Was the duration of follow-up adequate for harms assessment?	Risk of bias	Comments
Florez, 2008[24] NA OLRCT	Yes	No	NR/CND	Yes	High	Used UKU Side Effect Rating Scale (which prespecifies a list of potential harms), but unclear how it was used (who assessed the side effects or completed the scale; whether it was a structured interview or just relied on medical records, whether the person completing this was blinded [likely not, in this open label trial], how involved the patients were in the process, etc.)
O'Malley, 2008[25] NA DBRCT	NR/CND	No	NR/CND	Yes	Medium	
Wilens, 2008[26] NA DBRCT	No	No	NR/CND	Yes	High	
Brown, 2008[27] NA DBRCT	No	No	NR/CND	Yes	High	
Anton, 2008[29] NA DBRCT	Yes for EPS; No for others	Yes for EPS; No for others	NR/CND	Yes	Medium	
Addolorato, 2007[30] NA DBRCT	NR/CND	No	NR/CND	Yes	Medium	
Laaksonen, 2008[31] NA OLRCT	No	No	NR/CND	Yes	High	No masking; open label trial; only reports that harms were elicited at each visit and recorded in the drinking diary; labs were drawn at wk 0, 6, and 52, but very high attrition by week 52
Johnson, 2007[32] Johnson, 2008[33] NA DBRCT	Yes for vital signs and lab tests; No for symptoms	No	Yes for vital signs and lab tests; NR/CND for symptoms	Yes	Medium	
Pettinati, 2008[34] NA DBRCT	NR/CND	Yes	Yes	Yes	Medium	Harms were prespecified; not clear if they were defined; see comments for effectiveness assessment of risk of bias

Table C-3. Additional risk of bias questions for RCTs and related secondary/subgroup analyses that report harms (continued)

Author, Year Trial Name Design	Were harms prespecified and defined?	Were ascertainment techniques for harms adequately described?	Were ascertainment techniques for harms equal, valid and reliable?	Was the duration of follow-up adequate for harms assessment?	Risk of bias	Comments
Kampman, 2007[35] NA DBRCT	No	No	No	Yes	High	Results describe that adverse events were assessed at each visit as NPs asked if there were any changes in their health since the last visit
De Sousa, 2008[36] NA OLRCT	No	No	No	Yes	High	
Karhuvaara, 2007[37] NA DBRCT	NR/CND	No	NR/CND	Yes	Medium	
Book, 2008[38]; Thomas, 2008[39] NA DBRCT	NR/CND	No	NR/CND	Yes	Medium	
O'Malley, 2007[40] NA DBRCT	No	Yes for some (depression, liver enzymes); No for self-reported adverse effects	NR/CND	Yes	Medium	
Nava, 2006[42] NA OLRCT	No	No	NR/CND	Yes	High	
Morley, 2006[43] Morley, 2010[44] NA DBRCT	No	Yes	NR/CND	Yes	Medium	
Anton, 2006[45] Donovan, 2008[46] LoCastro, 2009[47] Greenfield, 2010[48] Fucito, 2012[49] COMBINE DBRCT	Yes	Yes	Yes	Yes	Low	

Table C-3. Additional risk of bias questions for RCTs and related secondary/subgroup analyses that report harms (continued)

Author, Year Trial Name Design	Were harms prespecified and defined?	Were ascertainment techniques for harms adequately described?	Were ascertainment techniques for harms equal, valid and reliable?	Was the duration of follow-up adequate for harms assessment?	Risk of bias	Comments
Mason, 2006[50] NA DBRCT	NR/CND	No	NR/CND	Yes	Medium	Only report that adverse drug events were assessed at every study visit by an open-ended question and coded with the Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART)
De Sousa, 2005[53] NA OLRCT	No	No	NR/CND	Yes	High	
Petrakis, 2005[55] Ralevski, 2007[56] Petrakis, 2007[57] Petrakis, 2006[58] VA MIRECC DBRCT	Yes	Yes	Yes	Yes	Medium for NTX vs. pbo; High for DIS vs. NTX or vs. pbo	
Garbutt, 2005[59] NA DBRCT	NR/CND	Yes	Yes	Yes	Medium	
Salloum, 2005[61] NA DBRCT	Yes	Yes	Yes	Yes	Low	Somatic symptoms checklist, weekly
Killeen, 2004[62] NA DBRCT	NR/CND	Yes	Yes	Yes	Medium	
De Sousa, 2004[63] NA OLRCT	No	No	NR/CND	Yes	High	
Schmitz, 2004[64] NA DBRCT	NR/CND	Yes	NR/CND	Yes	High	Used preset list of harms, but not clear if those were defined. See comments for efficacy assessment; no usable harms data reported in results
Johnson, 2004[65] NA DBRCT	No	No	NR/CND	Yes	High	Also see comments for efficacy risk of bias
Johnson, 2004[66] NA DBRCT	No	No	NR/CND	Yes	High	

Table C-3. Additional risk of bias questions for RCTs and related secondary/subgroup analyses that report harms (continued)

Author, Year Trial Name Design	Were harms prespecified and defined?	Were ascertainment techniques for harms adequately described?	Were ascertainment techniques for harms equal, valid and reliable?	Was the duration of follow-up adequate for harms assessment?	Risk of bias	Comments
Kranzler, 2004[67] NA DBRCT	No	No	NR/CND	Yes	Medium	Very few details about harms data collection; specific harms were only reported if overall frequency >=10% or significant group difference
Anton, 2004[68] NA DBRCT	No	No	NR/CND	Yes	Medium	
Guardia, 2004[69] NA DBRCT	Yes	Yes	Yes	Yes	Medium	See comments for efficacy
Chick, 2004[70] NA DBRCT	No	No	NR/CND	Yes	Medium	
Baltieri, 2004[71] NA DBRCT	Yes	Yes	Yes	Yes	Medium	
Petrakis, 2004[72]; Ralevski, 2006[73] NA DBRCT	Yes	Yes	Yes	Yes	Medium	See comments for efficacy assessment
Gual, 2003[74] NA DBRCT	No	Yes	No	Yes	High	AEs were spontaneously reported or observed by investigator, then classified.
Moak, 2003[75] NA DBRCT	No	No	NR/CND	Yes	Medium	
Balldin, 2003[76] NA DBRCT	No	Yes	Equal but not valid/reliable	Yes	Medium	
Johnson, 2003[77] Ma, 2006[78]; Johnson, 2004[66] NA DBRCT	Yes	Yes	Yes	Yes	Medium	See comments for efficacy assessment

Table C-3. Additional risk of bias questions for RCTs and related secondary/subgroup analyses that report harms (continued)

Author, Year Trial Name Design	Were harms prespecified and defined?	Were ascertainment techniques for harms adequately described?	Were ascertainment techniques for harms equal, valid and reliable?	Was the duration of follow-up adequate for harms assessment?	Risk of bias	Comments
Kiefer, 2003[79] Kiefer, 2005[80] NA DBRCT	No	No	NR/CND	Yes	Medium	Ascertainment techniques for lab measures adequately described, but nothing reported for subjective AEs (e.g., fatigue, diarrhea, etc.)
Gastpar, 2002[81] NA DBRCT	No	No	NR/CND	Yes	Medium	
Guardia, 2002[82] NA DBRCT	No	No	NR/CND	Yes	Medium	
Latt, 2002[84] NA DBRCT	No	Yes	NR/CND	Yes	Medium	
Morris, 2001[85] NA DBRCT	No	No	NR/CND	Yes	Medium	
Krystal, 2001[86] VACS 425 DBRCT	NR/CND	No	NR/CND	Yes	Medium	
Monti, 2001[87]; Rohsenow, 2007[88]; Rohsenow, 2000[153] NA DBRCT	NR/CND	Yes	NR/CND	Yes	Medium	open-ended description of specific symptoms
Rubio, 2001[91] NA SBRCT	No	No	No	Yes	High	
Heinala, 2001[92] NA DBRCT	No	No	NR/CND	Yes	High	
Pettinati, 2001[93] NA DBRCT	No	No	NR/CND	Yes	Unclear	

Table C-3. Additional risk of bias questions for RCTs and related secondary/subgroup analyses that report harms (continued)

Author, Year Trial Name Design	Were harms prespecified and defined?	Were ascertainment techniques for harms adequately described?	Were ascertainment techniques for harms equal, valid and reliable?	Was the duration of follow-up adequate for harms assessment?	Risk of bias	Comments
Chick, 2000[94] NA DBRCT	No	No	NR/CND	Yes	Medium	
Fawcett, 2000[95] NA DBRCT	No (aside from monitoring for lithium toxicity)	Yes – labs only, not for other harms	Yes- labs only, not for other harms	Yes	Medium	Monitoring for lithium toxicity was prespecified and described. Other harms are reported but no information is given on ascertainment techniques.
Tempesta, 2000[96] NA DBRCT	No	No	Yes	Yes	Medium	Harms were not defined; recorded by spontaneous reporting and by a questionnaire, but it is unclear what the questionnaire asks.
Chick, 2000[97] NA DBRCT	No	No	NR/CND	Yes	Medium	
Anton, 1999[98]; Anton, 2001[991] NA DBRCT	No	Yes	Yes	Yes	Medium	
Besson, 1998[101] NA DBRCT	No	No	NR/CND	Yes	Medium	
Poldrugo, 1997[102] NA DBRCT	NR/CND	No	NR/CND	Yes	Medium	Reports using a systematic questionnaire for evaluation of adverse events; details NR
Oslin, 1997[103] NA DBRCT	NR/CND	Yes	NR/CND	Yes	Medium	Harms prespecified, used checklist, but not clear if defined
Volpicelli, 1997[104] NR DBRCT	NR/CND	Yes	NR/CND	Yes	Medium	Used a side effects checklist, so harms were prespecified, but unclear if they were defined and how they were defined
Cornelius, 1997[105]; Cornelius, 1995[106] NA DBRCT	No	No	NR/CND	Yes	Medium	

Table C-3. Additional risk of bias questions for RCTs and related secondary/subgroup analyses that report harms (continued)

Author, Year Trial Name Design	Were harms prespecified and defined?	Were ascertainment techniques for harms adequately described?	Were ascertainment techniques for harms equal, valid and reliable?	Was the duration of follow-up adequate for harms assessment?	Risk of bias	Comments
Pelc, 1997[107] NA DBRCT	No	Yes	Yes	Yes	Medium	
Sass, 1996[108] NA DBRCT	No	No	NR/CND	Yes	Medium	
Whitworth, 1996[110] NA DBRCT	Yes	Yes	NR/CND	Yes	Medium	Asked about 44 AEs (details of the list of 44 and their definitions NR) and rated for severity, and classified into one of seven categories
Malec, 1996[111] NA DBRCT	No	No	NR/CND	Yes	High	
Mason, 1996[112] NA DBRCT	No	No	NR/CND	Yes	High	
McGrath, 1996[113] NA DBRCT	No	No	NR/CND	Yes	Medium	Harms are reported, but no information is given on ascertainment techniques.
Tiihonen, 1996[114] NA DBRCT	No	No	NR/CND	Yes	High	
Kranzler, 1995[115] NA DBRCT	NR/CND	Yes	Yes	Yes	Medium	This study did not prespecify harms, but described using a standardized questionnaire to assess harms.
Paille, 1995[116] NA DBRCT	No	Yes	Yes	Yes	Medium	
Naranjo, 1995[117] NA DBRCT	No	No	NR/CND	Yes	High	
Volpicelli, 1995[118] NA DBRCT	No	No	NR/CND	Yes	Unclear	See comments on efficacy assessment

Table C-3. Additional risk of bias questions for RCTs and related secondary/subgroup analyses that report harms (continued)

Author, Year Trial Name Design	Were harms prespecified and defined?	Were ascertainment techniques for harms adequately described?	Were ascertainment techniques for harms equal, valid and reliable?	Was the duration of follow-up adequate for harms assessment?	Risk of bias	Comments
Kranzler, 1994[119] NA DBRCT	No	No	NR/CND	Yes	Medium	
Malcolm, 1992[120] NA DBRCT	No	Yes	Yes	Yes	Medium	
O'Malley, 1992[121];O'Malley, 1996[122] NA DBRCT	No	No	NR/CND	Yes	Medium	
Lhuintre, 1990[123] NA DBRCT	Yes	Yes	Yes	Yes	Medium	Used a 44-item questionnaire of somatic complaints; AEs assessment includes those who dropped out due to AEs (whereas it was unclear whether efficacy outcomes only included completers)
Fuller, 1986[124] NA DBRCT	No	Yes	Yes	Yes	Medium	
Lhuintre, 1985[125] NA DBRCT	No	No	NR/CND	Yes	High	
Ling, 1983[126] NA DBRCT	No	No	NR/CND	Yes	High	
Gual, 2001[128] NA DBRCT	No	No	NR/CND	Yes	Medium	
Ahmadi, 2002[131]; Ahmadi, 2004[132] NA DBRCT	No	No	NR/CND	Yes	Unclear	See comments for efficacy risk of bias assessment
Mason, 1999[133] NA DBRCT	No	No	NR/CND	Yes	Medium	

Table C-3. Additional risk of bias questions for RCTs and related secondary/subgroup analyses that report harms (continued)

Author, Year Trial Name Design	Were harms prespecified and defined?	Were ascertainment techniques for harms adequately described?	Were ascertainment techniques for harms equal, valid and reliable?	Was the duration of follow-up adequate for harms assessment?	Risk of bias	Comments
Geerlings, 1997[134] NA DBRCT	No	No	NR/CND	Yes	Medium	
Mason, 1994[135] NA DBRCT	Only weight loss. No other harms prespecified.	No	NR/CND	Yes	High	Harms were not prespecified and ascertainment techniques were not described.
Tollefson, 1991[136]; Tollefson, 1992[137] NA DBRCT	No	No	NR/CND	Yes	High	
Lee, 2001[138] NA DBRCT	No	No (a questionnaire was used, but not described)	NR/CND	Yes	High	
Morgenstern, 2012[140] NA DBRCT	NR/CND	NR/CND	NR/CND	Yes	High	
Pelc, 1996[141]; Pelc, 1992[142]	No	Yes	NR/CND	Yes	High	High risk of selection bias and confounding due to attrition bias. AEs prespecified (checklist used) but not defined. Harms rates only reported for AEs with >5% occurrence. With relatively small Ns, this could be an issue.
Berger, 2013[143] DBRCT	No	No	NR/CND	Yes	Medium	Adverse events were coded using the Medical Dictionary for Regulatory Activities Version 14 (MedDRA, 2011); although harms were not prespecified, the outcome assessors were masked and any problems with ascertainment are likely nondifferential.
Corrêa Filho, 2013[144] DBRCT	No	Yes	Yes	Yes	High	See comments for assessment of efficacy; high risk of attrition bias; UKU Side Effect Rating Scale used at each visit for harms, but significant overall and differential attrition introduces high risk of bias.

Table C-3. Additional risk of bias questions for RCTs and related secondary/subgroup analyses that report harms (continued)

Author, Year Trial Name Design	Were harms prespecified and defined?	Were ascertainment techniques for harms adequately described?	Were ascertainment techniques for harms equal, valid and reliable?	Was the duration of follow-up adequate for harms assessment?	Risk of bias	Comments
Mann, 2013[145] ESENSE1 DBRCT	Mixed	Yes	Mixed	Yes	Medium	Psychiatric harms were prespecified and defined; other harms were not. Adverse events were coded using the Medical Dictionary for Regulatory Activities Version 13.
Gual, 2013[146] ESENSE 2 DBRCT	Mixed	Yes	Mixed	Yes	Medium	Psychiatric harms were prespecified and defined; other harms were not.
ALK21-014[147]	NR/CND	Yes	NR/CND	Yes	Medium	
SENSE, 2013[148]	NR/CND	No	NR/CND	Yes	High	
Litten, 2013[149] DBRCT	Mixed	Yes	Mixed	Yes	Medium	Psychiatric harms were prespecified and defined; other harms were assessed with an open-ended question.
Mann, 2012[150] PREDICT DBRCT	Yes	No	Yes	Yes	Medium	Side effects assessed with SAFTEE per methods paper
Anton, 2003[151] COMBINE pilot DBRCT	Yes	Yes	Yes	Yes	Medium	SAFTEE assessments (method for systematic assessment of side effects in clinical trials) and lab tests (some of harms description is in other publications)

Abbreviations: AE = adverse effect; CND = cannot determine; COMBINE = Combined Pharmacotherapies and Behavioral Intervention; DBRCT = double-blind randomized controlled trial; ESENSE/SENSE = Safety and Efficacy of Nalmefene in Patients With Alcohol Dependence; NA = not applicable; NR = not reported; OLRCT = open-label randomized controlled trial; SBRCT = single-blind randomized controlled trial; SSGA = secondary or subgroup analysis

Table C-4. Risk of bias assessment for observational studies

Author, Year Trial Name Design	Was the sample size adequate?	Were groups recruited from the same source population?	Were groups recruited over the same time period?	Were inc/exc criteria applied equally for all groups?	Were groups similar at baseline?	What was the overall attrition?	What was the differential attrition?	Did the study have overall high attrition or differential attrition raising concern for bias?	Was intervention fidelity adequate?
Coller, 2011[155] Prospective cohort	Yes	NR/CND	NR/CND	Yes	Yes	32	<1	Yes	NR/CND
Kim, 2009[156] Prospective cohort	No	Yes	NR/CND	Yes	No	49	22	Yes	NR/CND
Narayana, 2008[157] Prospective cohort	Yes	Yes	Yes	Yes	Yes, for the few characteristics reported	29	CND exact number, but appears to be about 20% higher in the NTX and ACA groups than the TOP group	Yes	NR/CND
Mutschler, 2012[158] Prospective cohort	Yes	Yes	NR/CND	NR/CND	Yes	NR/CND	NR/CND	NR/CND	NR/CND
Rubio, 2002[159] Prospective cohort	No	NR/CND	NR/CND	NR/CND	NR/CND	NR/CND	NR/CND	NR/CND	NR/CND

Abbreviations: ACA = acamprosate; CND = cannot determine; NR = not reported; NTX = naltrexone; TOP = topiramate

Table C-5. Continued risk of bias assessment for observational studies

Author, Year Trial Name Design	Was adherence to the intervention adequate?	Were outcome assessors masked?	Were outcome measures equal, valid, and reliable?	Were differences between groups taken into account in statistical analysis?	Was confounding adequately accounted for either through study design or statistical analysis?	Was an appropriate method used to handle missing data? Which?	Was time of follow-up equal in both groups?	RISK OF BIAS	Notes; explain "high" ratings
Coller, 2011[155] Prospective cohort	Yes	NR/CND	NR/CND	Yes	NR/CND	NR/CND	Yes	Medium	Moderate risk of attrition bias and confounding
Kim, 2009[156] Prospective cohort	No	NR/CND	Yes	Yes	Yes	No	Yes	High	High risk of selection bias and confounding; analysis of 32/63 patients in the original cohort who finished the trial and were at least 80% adherent to NTX. The 6 excluded for non-adherence all came from one group.
Narayana, 2008[157] Prospective cohort	NR/CND	No	No	NR/CND	NR/CND	NR/CND	Yes	High	Very high differential attrition, completers-only analysis. Inadequate handling of missing data; high risk of selection bias and confounding.
Mutschler, 2012[158] Prospective cohort	NR/CND	NR/CND	NR/CND	NR/CND	No	NR/CND	NR/CND	High	High risk of selection bias and confounding
Rubio, 2002[159]	NR/CND	NR/CND	NR/CND	NR/CND	NR/CND	NR/CND	NR/CND	Unclear	Reported as abstract only, with very limited information about the population and the methods

Abbreviations: CND = cannot determine; NR = not reported; NTX = naltrexone

Table C-6. Additional risk of bias questions for observational studies that report harms

Author, Year Trial Name Design	Were harms prespecified and defined?	Were ascertainment techniques for harms adequately described?	Were ascertainment techniques for harms equal, valid and reliable?	Was the duration of follow-up adequate for harms assessment?	Risk of bias
Narayana, 2008[157] Prospective cohort	No	No	NR/CND	Yes	High

Abbreviations: CND = cannot determine; NR = not reported

Table C-7. Risk of bias assessment for systematic reviews and meta-analyses

Author, year	Was the review based on a focused question of interest?	Was the literature search strategy clearly described?	Was there evidence of a substantial effort to search for all relevant research?	Were there explicit inclusion/ exclusion criteria for the selection of studies?	Did at least 2 people independently review studies?	Was the validity of included studies adequately assessed?	Was publication bias assessed?	Was heterogeneity assessed and addressed?
Mason, 2012[160]	Yes	Yes	Yes	Yes	NR	Yes	No	Mixed
Jorgensen, 2011[161]	Yes	Yes	No	Yes	NR	Yes	No	Yes
Rosner, 2010[162]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Rosner, 2010[163]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Lobmaier, 2008[164]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
NICE, 2011[165]	Yes	Yes	Yes	Yes	No	Yes	No	Yes

Abbreviations: NR = not reported

Table C-8. Continued risk of bias assessment for systematic reviews and meta-analyses

Author, Year	Was the approach used to synthesize the information adequate and appropriate?	Were the author's conclusions supported by the evidence they presented?	Risk of Bias	Notes; explain "high" ratings
Mason, 2012[160]	Yes	Yes	Medium	Unclear whether they had dual independent review for study selection.
Jorgensen, 2011[161]	Yes	Yes	Medium	Did not search for unpublished studies; did not assess publication bias; unsure about dual review.
Rosner, 2010[162]	Yes	Yes	Medium	Did not have dual independent review of abstracts and full texts
Rosner, 2010[163]	Yes	Yes	Medium	Did not have dual independent review of abstracts and full texts
Lobmaier, 2008[164]	Yes	Yes	Low	The ROB is low, but only harms data for the subset of alcohol-dependent studies are useful for the purposes of our report (the rest is beyond our scope).
NICE, 2011[165]	Yes	Yes	Medium	Did not have dual independent review of abstracts and full texts

Additional Risk of Bias Assessment Information for Included Studies Assessing Naltrexone Response and Polymorphisms of the Opioid Receptor Gene

In general terms, studies categorized as low risk of bias imply high confidence that the results represent the true treatment effects. We considered that studies would be rated as low risk of bias that had favorable responses to all of the questions included in our risk of bias assessment (Table C-9), including randomization by genotype. Studies with medium risk of bias are susceptible to some risk of bias but probably not enough to invalidate the results. Studies with a medium risk of bias did not meet all criteria required for low risk of bias. These studies had some flaws in design or execution (e.g., inadequate description of methods) but they provided enough information to allow readers to determine that the flaws did not likely cause major bias. Missing information often leads to ratings of medium as opposed to low risk of bias. Studies assessed as high risk of bias have significant flaws stemming from serious errors in design, conduct, or analysis that may invalidate the results (e.g., high overall or differential attrition without appropriate handling of missing data). Table C-9 shows our risk of bias assessments for each study. Whenever we rated a study as high or unclear risk of bias, we provide some additional comments and explanation below the table.

Table C-9. Risk of bias assessments for studies assessing naltrexone response and polymorphisms of the opioid receptor gene

Author, Year Trial Name	Did the study randomize by genotype?	Did the study report consistency of genotype frequencies with HWE?	What was the genotyping error rate and completion rate?	Were groups similar at base-line?	What were the overall and differential attrition?	Did the study have overall high attrition or differential attrition raising concern for bias?	Was adherence adequate?	Were outcome assessors masked?	Were outcome measures equal, valid, and reliable? [a]	Adequate attempts to control for baseline differences between groups and potential confounders?	Was an appropriate method used to handle missing data?	Risk of bias
Anton, 2008[40] COMBINE	No	Yes	0% and 99.6%	Yes	NR[b] and NR	No	Yes	Yes	Yes	Yes	Yes	Med-ium
Coller, 2011[216]	No	No, NR	NR	Yes	32% and <1%	Yes	Yes	NR	NR	NR	NR	Med-ium
Gelernter, 2007[218] VACS 425	No	Yes	0% (of the 8% retested for quality control) and NR[e]	Data NR	65%[c] and NR	Yes	NR	Yes	Yes	CND[d]	NR	High
Kim, 2009[217]	No	No, NR	0% and 0%	No	49% and 22%	Yes	No	NR	Yes	Yes	No	High
Kranzler, 2013[41]	No	No, NR	0% and 2.5% (4/163)	Yes	75% of possible person days were included and NR	No	Yes	NR	Yes	Unclear[f]	No	Med-ium
O'Malley, 2008[42]	No	Yes	0% and 99% (95/96)	Yes	33% did not complete; 25% unable to contact and 15%	Yes	No	Yes	Yes	Yes	Yes	Med-ium
Rubio, 2002[43]	No	No, NR	NR and NR[g]	Data NR	NR and NR	NR	NR	NR	NR	NR	NR	Un-clear

[a] For example, the timeline follow-back (TLFB) method for self-report of alcohol consumption.

[b] Overall attrition in the parent trial was 6%; 14% of white subjects in the parent trial who received NTX or placebo were not included in this study (604/706 were included); 56% of subjects randomized in the parent trial (COMBINE) were not included in this study (604/1383 were included).

[c] 220/627 subjects in the main trial were included in this sample.

[d] Baseline data not reported to allow comparison between groups by genotype and to help determine what variables should be considered in the model. Covariates in the analysis included race, age, marital status, years of education, some drinking history variables, and Brief Symptom Inventory score.

[e] 240/251 who gave consent had both genotype and phenotype data available

[f] The authors included sex, years of education, and pre-treatment proportion of drinking days in the first step of the multiple regression model. No other variables were included, but the groups were similar at baseline.

[g] But a completion rate of 100% is implied by the Ns consented and Ns with results.

Additional comments about high or unclear risk of bias ratings

Gelernter, 2007: Analysis of data from a trial; evaluates opioid receptor gene variants; high risk of selection bias and confounding; used 35% of subjects from the parent trial; does not report baseline characteristics for the comparisons of interest to this article (the different genotypes); and not randomized by genotype; significant differences between this sample and that of the main trial, but unclear how the different genotype groups compared at baseline.

Kim, 2009: High risk of selection bias and confounding; analysis of 32/63 patients in the original cohort who finished the trial and were at least 80% adherent to naltrexone. The 6 excluded for non-adherence all came from one group.

Rubio, 2002: Reported as abstract only, with very limited information about the population and the methods

Abbreviations: CND, cannot determine; COMBINE = Combined Pharmacotherapies and Behavioral Intervention; HWE, Hardy-Weinberg equilibrium; NR, not reported;

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Appendix D. Strength of Evidence Assessments

KQ 1 and KQ 2

Table D-1. Acamprosate compared with placebo

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength of Evidence Grade
Return to any drinking	16[a]; 4,847	Medium; RCTs	Consistent[b]	Direct	Precise	RD: -0.09 (-0.14 to -0.04)	Moderate
Return to heavy drinking	7; 2,496	Low; RCTs	Consistent	Direct	Precise	RD: -0.01 (-0.04 to 0.03)	Moderate[c]
Drinking days	13[d]; 4,485	Medium; RCTs	Consistent	Direct	Precise	WMD: -8.8 (-12.8 to -4.8)	Moderate
Heavy drinking days	1; 100	Medium; RCT	Unknown	Direct	Imprecise	WMD: -2.6 (-11.4 to 6.2)	Insufficient
Drinks per drinking day	1[d]; 116	Low; RCT	Unknown	Direct	Imprecise	WMD: 0.40 (-1.81 to 2.61)	Insufficient
Accidents	0[e]; 0	NA	NA	NA	NA	NA	Insufficient
Injuries	0; 0	NA	NA	NA	NA	NA	Insufficient
Quality of life or function	1; 612	Low; RCT	Unknown	Direct	Unknown	NSD[f]	Insufficient
Mortality	8[g]; 2,677	Medium; RCTs	Unknown	Direct	Imprecise	7 (ACA) vs. 6 (PBO)	Insufficient

[a] 2 additional studies were rated high risk of bias; 1 additional study was rated as unclear risk of bias

[b] Although there was considerable statistical heterogeneity, fourteen of fifteen studies reported point estimates that favored acamprosate; differences were in magnitude of benefit

[c] The relatively small number of studies reporting this outcome raises concern for potential reporting bias, hence the rating of moderate rather than high rating

[d] 1 additional study was rated high risk of bias

[e] The single study that reported this outcome was rated as unclear risk of bias. It reported that one patient in the placebo group died by "accident." No other details on the cause or nature of the accident were provided.[1]

[f] Results were not reported for each treatment group separately, but there were no clinically significant differences across treatment groups

[g] One additional study reported a death but did not specify in which treatment group it occurred.[2]

Abbreviations: ACA = acamprosate; CI = confidence interval; NA = not applicable; NSD = no statistically significant difference; PBO = placebo; RCT = randomized controlled trial; RD = risk difference; WMD = weighted mean difference

Table D-2. Disulfiram compared with control

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength of Evidence Grade
Return to any drinking	2[a]; 492	Medium; RCTs	Consistent[b]	Direct	Imprecise	RD: 0.04 (-0.11 to 0.03)	Low
Return to heavy drinking	0; 0	NA	NA	NA	NA	NA	Insufficient
Drinking days	2; 290	Medium; RCTs	Inconsistent	Indirect[c]	Imprecise	1 study reported similar percentages and no significant difference; the other reported that DIS was favored among the subset of subjects who drank and had a complete set of assessment interviews (N=162/605 subjects), p=0.05	Insufficient
Heavy drinking days	0; 0	NA	NA	NA	NA	NA	Insufficient
Drinks per drinking day	0; 0	NA	NA	NA	NA	NA	Insufficient
Accidents	0; 0	NA	NA	NA	NA	NA	Insufficient
Injuries	0; 0	NA	NA	NA	NA	NA	Insufficient
Quality of life or function	0; 0	NA	NA	NA	NA	NA	Insufficient
Mortality	0; 0	NA	NA	NA	NA	NA	Insufficient

[a] 1 additional study was rated high risk of bias.[3]

[b] Inclusion of the study rated high risk of bias would have made this inconsistent, though it would not have changed the conclusion (the meta-analysis still found no statistically significant difference between groups).

[c] We considered this indirect because the larger study did not report the outcome for the randomized sample; it only reported this outcome for the subset (162/605) who drank and who had a complete set of assessment interviews.

Abbreviations: CI = confidence interval; NA = not applicable; RCT = randomized controlled trial; RD = risk difference

Table D-3. Naltrexone (any dose and delivery) compared with placebo

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength of Evidence Grade
Return to any drinking	21[a]; 4,233	Medium; RCTs	Consistent	Direct	Precise	RD: -0.04 (-0.07 to -0.01)	Moderate
Return to heavy drinking	23[a]; 4,347	Medium; RCTs	Consistent	Direct	Precise	RD: -0.07 (-0.11 to -0.03)	Moderate
Drinking days	19[b]; 3,329	Medium; RCTs	Consistent	Direct	Precise	WMD: -4.57 (-6.61 to -2.53)	Moderate
Heavy drinking days	11[c]; 2034	Medium; RCTs	Consistent	Direct	Precise	WMD: -3.81 (-5.85 to -1.78)	Moderate
Drinks per drinking day	11[d]; 1,422	Medium; RCTs	Consistent	Direct	Imprecise	WMD: -0.54 (-1.01 to -0.07)	Low
Accidents	0; 0	NA	NA	NA	NA	NA	Insufficient
Injuries	0; 0	NA	NA	NA	NA	NA	Insufficient
Quality of life	4; 1,513	Medium; RCTs	Inconsistent	Direct	Imprecise	Unable to pool data, some conflicting results[e]	Insufficient
Mortality	6[f]; 1,738	Medium; RCTs	Unknown	Direct	Imprecise	1 (NTX) vs. 2 (PBO)	Insufficient

[a] 2 additional studies were rated high risk of bias; 2 additional studies were rated as unclear risk of bias

[b] 3 additional studies were rated high risk of bias

[c] 2 additional studies were rated high risk of bias

[d] 5 additional studies were rated high risk of bias

[e] Two studies found no significant difference between naltrexone- and placebo-treated subjects.[4,5] One study reported that patients receiving injectable naltrexone 380mg/month had greater improvement on the mental health summary score than those receiving placebo at 24 weeks (8.2 vs. 6.2, p=0.044).[6] One study measured alcohol-related consequences (with the DrInC) and reported that more subjects who received placebo (N=34) had ≥1 alcohol-related consequence than those who received naltrexone (N=34): 76% vs. 45%, P=0.02.[7]

[f] One additional study reported a death but did not specify in which treatment group it occurred.[2]

Abbreviations: CI, confidence interval; NA, not applicable; NSD, no significant difference; NTX, naltrexone; PBO, placebo; RCT, randomized controlled trial; RD, risk difference; WMD, weighted mean difference

Table D-4. Oral naltrexone (50mg) compared with placebo

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength of Evidence Grade
Return to any drinking	16; 2,347	Medium; RCTs	Consistent	Direct	Precise	RD: -0.05 (-0.10 to -0.00)	Moderate
Return to heavy drinking	19; 2,875	Medium; RCTs	Consistent	Direct	Precise	RD: -0.09 (-0.13 to -0.04)	Moderate
Drinking days	15; 1,992	Medium; RCTs	Consistent	Direct	Precise	WMD: -5.4 (-7.5 to -3.2)	Moderate
Heavy drinking days	6; 521	Medium; RCTs	Consistent	Direct	Precise	WMD: -4.1 (-7.6 to -0.61)	Moderate
Drinks per drinking day	9; 1,018	Medium; RCTs	Consistent	Direct	Imprecise	WMD: -0.49 (-0.92 to -0.06)	Low

Abbreviations: CI, confidence interval; NA, not applicable; NSD, no significant difference; NTX, naltrexone; PBO, placebo; RCT, randomized controlled trial; RD, risk difference; WMD, weighted mean difference

Table D-5. Oral naltrexone (100mg) compared with placebo

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength of Evidence Grade
Return to any drinking	3; 946	Medium; RCTs	Consistent	Direct	Imprecise	RD: -0.03 (-0.08 to 0.02)	Low
Return to heavy drinking	2; 858	Medium; RCTs	Consistent	Direct	Imprecise	RD: -0.05 (-0.11 to 0.01)	Low
Drinking days	2; 858	Medium; RCTs	Consistent	Direct	Imprecise	WMD: -0.9 (-4.2 to 2.5)	Low
Heavy drinking days	2; 423	Medium; RCTs	Consistent	Direct	Imprecise	WMD: -3.1 (-5.8 to -0.3)	Low
Drinks per drinking day	1; 240	Medium; RCTs	Unknown	Direct	Imprecise	WMD: 1.9 (-1.5 to 5.2)	Insufficient

Abbreviations: CI, confidence interval; NA, not applicable; NSD, no significant difference; NTX, naltrexone; PBO, placebo; RCT, randomized controlled trial; RD, risk difference; WMD, weighted mean difference

Table D-6. Injectable naltrexone compared with placebo

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength of Evidence Grade
Return to any drinking	2; 939	Medium; RCTs	Consistent	Direct	Imprecise	RD: -0.04 (-0.10 to 0.03)	Low
Return to heavy drinking	2; 615	Medium; RCTs	Inconsistent	Direct	Imprecise	RD: -0.01 (-0.14 to 0.13)	Low
Drinking days	1; 315	Medium; RCTs	Unknown	Direct	Imprecise	WMD: -8.6 (-16.0 to -1.2)	Insufficient
Heavy drinking days	2[a]; 926	Medium; RCTs	Consistent	Direct	Imprecise	WMD: -4.6 (-8.5 to -0.56)	Low
Drinks per drinking day	0; 0	NA	NA	NA	NA	NA	Insufficient

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

Abbreviations: CI, confidence interval; NA, not applicable; NSD, no significant difference; NTX, naltrexone; PBO, placebo; RCT, randomized controlled trial; RD, risk difference; WMD, weighted mean difference

Table D-7. Acamprosate compared with disulfir77am

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength of Evidence Grade
Return to any drinking	0; 0	NA	NA	NA	NA	NA	Insufficient
Return to heavy drinking	0; 0	NA	NA	NA	NA	NA	Insufficient
Drinking days	0; 0	NA	NA	NA	NA	NA	Insufficient
Heavy drinking days	0; 0	NA	NA	NA	NA	NA	Insufficient
Drinks per drinking day	0; 0	NA	NA	NA	NA	NA	Insufficient
Accidents	0[a]; 0	NA	NA	NA	NA	NA	Insufficient
Injuries	0; 0	NA	NA	NA	NA	NA	Insufficient
Quality of life or function	0[a]; 0	NA	NA	NA	NA	NA	Insufficient
Mortality	0[a]; 0	NA	NA	NA	NA	NA	Insufficient

[a] The one study reporting this outcome was rated high risk of bias.[8] It reported one traffic accident in the disulfiram group and none in the acamprosate group over 52 weeks. No details of the event were described, it was noted that the study coordinator determined that the event was not related to the study treatment. One person committed suicide and two persons drowned in the acamprosate group but there were no events in the disulfiram group. Quality of life improved for both groups over the 52 week follow-up compared with baseline with no difference between the acamprosate and disulfiram groups.

Abbreviations: CI, confidence interval; NA, not applicable

Table D-8. Acamprosate compared with naltrexone

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength of Evidence Grade
Return to any drinking	3; 800	Low; RCTs	Consistent	Direct	Imprecise	RD: 0.02 (-0.03 to 0.08)[a]	Moderate
Return to heavy drinking	4; 1,141	Low; RCTs	Consistent	Direct	Imprecise	RD: 0.01 (-0.05 to 0.06)[a]	Moderate
Drinking days	2; 720	Low; RCTs	Inconsistent	Direct	Imprecise	WMD: -2.98 (-13.42 to 7.45)[a]	Low
Heavy drinking days	1; 612	Low; RCT	Unknown	Direct	Unknown	Significant NTX by CBI interaction, P=0.006	Insufficient
Drinks per drinking day	2; 720	Low; RCTs	Inconsistent	Direct	Unknown	Unable to pool data[b]	Insufficient
Accidents	0; 0	NA	NA	NA	NA	NA	Insufficient
Injuries	0; 0	NA	NA	NA	NA	NA	Insufficient
Quality of life or function	1[c]; 612	Low; RCT	Unknown	Direct	Imprecise	NSD for all measures except SF-12v2 physical health, which favored NTX+CBI	Insufficient
Mortality	0[d]; 0	NA	NA	NA	NA	NA	Insufficient

[a] Positive value indicates that naltrexone is favored

[b] Two trials reported some information about drinks per drinking day, but not enough data for us to conduct quantitative synthesis. One trial conducted in Australia reported no statistically significant difference between acamprosate and naltrexone (mean, SD: 7.5, 6.1 vs. 5.9, 6.1; P not reported).[9,10] The COMBINE study reported that analyses of alternative summary measures of drinking, including drinks per drinking day (P=0.03), were consistent with those for the co-primary end points (percent days abstinent from alcohol and time to first heavy drinking day), all showing a significant naltrexone by CBI interaction.[2]

[c] One additional study was rated high risk of bias.[8] It found that quality of life improved for both groups over the 52 week follow-up compared with baseline, but found no difference between the acamprosate and naltrexone groups.

[d] One study that reported this outcome was rated high risk of bias; another reported one death but did not specify in which treatment group it occurred

Abbreviations: ACA = acamprosate; CBI = combined behavioral intervention; CI = confidence interval; NA = not applicable; NTX = naltrexone; RCT = randomized controlled trial; RD = risk difference; WMD = weighted mean difference

Table D-9. Disulfiram compared with naltrexone

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength of Evidence Grade
Return to any drinking	0[a]; 0	NA	NA	NA	NA	NA	Insufficient
Return to heavy drinking	0; 0	NA	NA	NA	NA	NA	Insufficient
Drinking days	0[a]; 0	NA	NA	NA	NA	NA	Insufficient
Heavy drinking days	0[a]; 0	NA	NA	NA	NA	NA	Insufficient
Drinks per drinking day	0; 0	NA	NA	NA	NA	NA	Insufficient
Accidents	0[b]; 0	NA	NA	NA	NA	NA	Insufficient
Injuries	0; 0	NA	NA	NA	NA	NA	Insufficient
Quality of life or function	0[b]; 0	NA	NA	NA	NA	NA	Insufficient
Mortality	0[c]; 0	NA	NA	NA	NA	NA	Insufficient

[a] The single study that reported this outcome was rated high risk of bias.[3] The trial reported no statistically significant difference between disulfiram and naltrexone for number of subjects achieving total abstinence (51 vs. 38, P=0.11), the percentage of days abstinent (96.6 vs. 95.4, P=0.55), or the percentage of heavy drinking days (3.2 vs. 4, P=0.65).

[b] The only study that reported this outcome was rated high risk of bias.[8] It reported one traffic accident in the disulfiram group and no accident or injuries in the naltrexone group. No details of the event were described, it was noted that the study coordinator determined that the event was not related to the study treatment. Quality of life improved for both groups over the 52 week follow-up compared with baseline with no difference between the disulfiram and naltrexone groups.

[c] The only study that reported this outcome was rated high risk of bias.[3] One person died in the naltrexone group and no deaths were reported in the disulfiram group.

Abbreviations: CI = confidence interval; NA = not applicable; RCT = randomized controlled trial

Table D-10. Amitriptyline compared with placebo

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength of Evidence Grade
Return to any drinking	0; 0	NA	NA	NA	NA	NA	Insufficient
Return to heavy drinking	0; 0	NA	NA	NA	NA	NA	Insufficient
Drinking days	0; 0	NA	NA	NA	NA	NA	Insufficient
Heavy drinking days	0; 0	NA	NA	NA	NA	NA	Insufficient
Drinks per drinking day	0; 0	NA	NA	NA	NA	NA	Insufficient
Accidents	0; 0	NA	NA	NA	NA	NA	Insufficient
Injuries	0; 0	NA	NA	NA	NA	NA	Insufficient
Quality of life or function	0; 0	NA	NA	NA	NA	NA	Insufficient
Mortality	0; 0	NA	NA	NA	NA	NA	Insufficient

Abbreviations: CI, confidence interval; NA, not applicable

Table D-11. Aripiprazole compared with placebo

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size	Strength of Evidence Grade
Return to any drinking	1; 288	Medium; RCT	Unknown	Direct	Imprecise	89% (ARI) vs. 78% (PBO); p=0.02	Insufficient
Return to heavy drinking	1; 288	Medium; RCT	Unknown	Direct	Imprecise	73% (ARI) vs. 73% (PBO); p=0.98	Insufficient
Drinking days	1; 288	Medium; RCT	Unknown	Direct	Imprecise	41% (ARI) vs. 37% (PBO); p=0.23	Insufficient
Heavy drinking days	0; 0	NA	NA	NA	NA	NA	Insufficient
Drinks per drinking day	1; 288	Medium; RCT	Unknown	Direct	Imprecise	4.4 (ARI) vs. 5.5 (PBO); p<0.001	Insufficient
Accidents	0; 0	NA	NA	NA	NA	NA	Insufficient
Injuries	0; 0	NA	NA	NA	NA	NA	Insufficient
Quality of life or function	0; 0	NA	NA	NA	NA	NA	Insufficient
Mortality	0; 0	NA	NA	NA	NA	NA	Insufficient

Abbreviations: ARI, aripiprazole; NA, not applicable; PBO, placebo; RCT, randomized controlled trial

Table D-12. Atomoxetine compared with placebo

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength of Evidence Grade
Return to any drinking	0; 0	NA	NA	NA	NA	NA	Insufficient
Return to heavy drinking	0[a]; 0	NA	NA	NA	NA	NA	Insufficient
Drinking days	0[a]; 0	NA	NA	NA	NA	NA	Insufficient
Heavy drinking days	0[a]; 0	NA	NA	NA	NA	NA	Insufficient
Drinks per drinking day	0[a]; 0	NA	NA	NA	NA	NA	Insufficient
Accidents	0; 0	NA	NA	NA	NA	NA	Insufficient
Injuries	0; 0	NA	NA	NA	NA	NA	Insufficient
Quality of life or function	0; 0	NA	NA	NA	NA	NA	Insufficient
Mortality	0; 0	NA	NA	NA	NA	NA	Insufficient

[a]The single study reporting this outcome was rated high risk of bias.[11] The trial found no significant difference between groups for return to heavy drinking (94% for atomoxetine vs. 96% for placebo), drinking days, or reduction in drinks per drinking day. It did report a 26% lower rate of cumulative heavy drinking days for atomoxetine compared with placebo (P=0.02).

Abbreviations: ATO = atomoxetine; CI = confidence interval; HDD = heavy drinking days; NA = not applicable; PBO = placebo; RCT = randomized controlled trial

Table D-13. Baclofen compared with placebo

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size	Strength of Evidence Grade
Return to any drinking	2; 164	Medium; RCTs	Inconsistent	Direct	Imprecise	Study 1: OR 6.3, 95% CI, 2.4 to 16.1 Study 2: No difference[a]	Insufficient
Return to heavy drinking	2; 164	Medium; RCTs	Inconsistent	Direct	Imprecise	Study 1: BAC significantly lower than PBO (data in Figure, p=0.0062) Study 2: HR 0.924, p=0.76	Insufficient
Drinking days	1; 80	Medium; RCT	Unknown	Direct	Imprecise	50.1% (BAC) vs. 49.4% (PBO); p=0.50	Insufficient
Heavy drinking days	1; 80	Medium; RCT	Unknown	Direct	Imprecise	25.9% (BAC) vs. 25.5% (PBO); p=0.73	Insufficient
Drinks per drinking day	0; 0	NA	NA	NA	NA	NA	Insufficient
Accidents	0; 0	NA	NA	NA	NA	NA	Insufficient
Injuries	0; 0	NA	NA	NA	NA	NA	Insufficient
Quality of life or function	0; 0	NA	NA	NA	NA	NA	Insufficient
Mortality	0; 0	NA	NA	NA	NA	NA	Insufficient

[a] One trial conducted in Italy (N=84) reported that a lower percentage of patients treated with baclofen returned to any drinking than with placebo (29 percent [12/42] versus 71 percent [30/42]; OR, 6.3; 95% CI, 2.4 to 16.1).[12] One trial conducted in the U.S. (N=80) did not report numbers for rates of return to any drinking, but reported no difference between groups for time to first usage (p=0.13), and included a figure for percentage abstinent that shows over 90 percent of subjects returned to any drinking over the course of the trial.[13]

Abbreviations: BAC = baclofen; CI = confidence interval; NA = not applicable; PBO = placebo; RCT = randomized controlled trial

Table D-14. Buspirone compared with placebo

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength of Evidence Grade
Return to any drinking	1[a]; 54	Medium; RCT	Unknown	Direct	Imprecise	RD: 0.07 (-0.19 to 0.34)	Insufficient
Return to heavy drinking	0; 0	NA	NA	NA	NA	NA	Insufficient
Drinking days	2; 161	Medium; RCTs	Consistent	Direct	Imprecise	WMD: -3.39 (-9.23 to 2.44)	Low
Heavy drinking days	0; 0	NA	NA	NA	NA	NA	Insufficient
Drinks per drinking day	1; 61	Medium; RCT	Unknown	Direct	Imprecise	0.7 vs. 2.1; p NS	Insufficient
Accidents	0; 0	NA	NA	NA	NA	NA	Insufficient
Injuries	0; 0	NA	NA	NA	NA	NA	Insufficient
Quality of life or function	0; 0	NA	NA	NA	NA	NA	Insufficient
Mortality	0; 0	NA	NA	NA	NA	NA	Insufficient

[a]1 additional study was rated high risk of bias.[14] Neither trial found a statistically significant difference between groups, and point estimates favored placebo in both trials.[14,15]

Abbreviations: CI, confidence interval; NA, not applicable; RCT, randomized controlled trial; RD, risk difference; weighted mean difference

Table D-15. Citalopram compared with placebo

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength of Evidence Grade
Return to any drinking	0[a]; 0	NA	NA	NA	NA	NA	Insufficient
Return to heavy drinking	0; 0	NA	NA	NA	NA	NA	Insufficient
Drinking days	0[b]; 0	NA	NA	NA	NA	NA	Insufficient
Heavy drinking days	0; 0	NA	NA	NA	NA	NA	Insufficient
Drinks per drinking day	0[b]; 0	NA	NA	NA	NA	NA	Insufficient
Accidents	0; 0	NA	NA	NA	NA	NA	Insufficient
Injuries	0; 0	NA	NA	NA	NA	NA	Insufficient
Quality of life or function	0; 0	NA	NA	NA	NA	NA	Insufficient
Mortality	0; 0	NA	NA	NA	NA	NA	Insufficient

[a] One trial conducted in Finland, rated as high risk of bias, reported 25 of 31 citalopram-treated patients and 28 of 31 placebo-treated patients returned to any drinking (p=0.10).[16]

[b] One trial rated as high risk of bias conducted in Canada found similar proportions of drinking days for those who received citalopram and those who received placebo (72.7 percent versus 76.5 percent, p NS) and similar reductions in drinks per drinking day for those who received citalopram and those who received placebo (26.1 percent versus 26.4 percent, p NS) over the 12 weeks of treatment.[17]

Abbreviations: CI, confidence interval; NA, not applicable; RCT, randomized controlled trial

Table D-16. Desipramine compared with placebo

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength of Evidence Grade
Return to any drinking	0; 0	NA	NA	NA	NA	NA	Insufficient
Return to heavy drinking	0[a]; 0	NA	NA	NA	NA	NA	Insufficient
Drinking days	0[a]; 0	NA	NA	NA	NA	NA	Insufficient
Heavy drinking days	0; 0	NA	NA	NA	NA	NA	Insufficient
Drinks per drinking day	0; 0	NA	NA	NA	NA	NA	Insufficient
Accidents	0; 0	NA	NA	NA	NA	NA	Insufficient
Injuries	0; 0	NA	NA	NA	NA	NA	Insufficient
Quality of life or function	0; 0	NA	NA	NA	NA	NA	Insufficient
Mortality	0; 0	NA	NA	NA	NA	NA	Insufficient

[a] One study rated as high risk of bias, reported that 12 percent of patients in the desipramine arm returned to heavy drinking, compared with 32 percent of patients taking placebo (p=NS).[18] It also reported that non-depressed patients treated with desipramine (N=14) drank on a median of 68 percent of days; non-depressed patients treated with placebo (N=15) drank on 72 percent of days (p NS).

Abbreviations: CI = confidence interval; NA = not applicable

Table D-17. Fluoxetine compared with placebo

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength of Evidence Grade
Return to any drinking	1[a]; 51	Medium; RCT	Unknown	Direct	Imprecise	RD: -0.13 (-0.35 to 0.10)	Insufficient
Return to heavy drinking	0; 0	NA	NA	NA	NA	NA	Insufficient
Drinking days	2; 146	Medium; RCTs	Inconsistent	Direct	Imprecise	WMD: -3.15 (-18.2 to 11.9)	Low
Heavy drinking days	1; 51	Medium; RCT	Unknown	Direct	Imprecise	4.8 (FLUOX) vs. 16 (PBO); P=0.04	Insufficient
Drinks per drinking day	2; 146	Medium; RCTs	Inconsistent	Direct	Imprecise	WMD: -1.20 (-4.63 to 2.23)	Low
Accidents	0; 0	NA	NA	NA	NA	NA	Insufficient
Injuries	0; 0	NA	NA	NA	NA	NA	Insufficient
Quality of life or function	0; 0	NA	NA	NA	NA	NA	Insufficient
Mortality	0; 0	NA	NA	NA	NA	NA	Insufficient

[a] 1 additional study (N=28) reporting this outcome was rated high risk of bias.[19] Both trials found no statistically significant difference between fluoxetine and placebo.[19,20]

Abbreviations: CI = confidence interval; FLUOX = fluoxetine; NA = not applicable; PBO = placebo; RCT = randomized controlled trial; RD = risk difference; WMD = weighted mean difference

Table D-18. Fluvoxamine compared with placebo

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength of Evidence Grade
Return to any drinking[a]	1; 492	Medium; RCT	Unknown	Direct	Imprecise	12 weeks: 58% (FLUV) vs. 54% (PBO); P=0.40 52 weeks: 71% (FLUV) vs. 71% (PBO); P=0.94	Insufficient
Return to heavy drinking	1; 492	Medium; RCT	Unknown	Direct	Imprecise	12 weeks: 46% (FLUV) vs. 40% (PBO); P=0.18 52 weeks: 64% (FLUV) vs. 64% (PBO); P=0.47	Insufficient
Drinking days[a]	1; 492	Medium; RCT	Unknown	Direct	Imprecise	12 weeks: 31% (FLUV) vs. 23% (PBO); P=0.009 52 weeks: 44% (FLUV) vs. 38% (PBO); P=0.13	Insufficient
Heavy drinking days	0; 0	NA	NA	NA	NA	NA	Insufficient
Drinks per drinking day	0; 0	NA	NA	NA	NA	NA	Insufficient
Accidents	0; 0	NA	NA	NA	NA	NA	Insufficient
Injuries	0; 0	NA	NA	NA	NA	NA	Insufficient
Quality of life or function	0; 0	NA	NA	NA	NA	NA	Insufficient
Mortality	1; 492	Medium; RCT	Unknown	Direct	Imprecise	52 weeks: 1 (FLUV) vs. 1 (PBO)	Insufficient

[a] The study reported return to drinking and percent drinking days since the previous assessment. At 12 weeks, the previous assessment was at week 8; at 52 weeks, the previous assessment was at week 40.[21]

Abbreviations: CI = confidence interval; FLUV = fluvoxamine; NA = not applicable; PBO = placebo; RCT = randomized controlled trial

Table D-19. Imipramine compared with placebo

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength of Evidence Grade
Return to any drinking[a]	1; 56	Medium; RCT	Unknown	Direct	Imprecise	69% (IMI) vs. 79% (PBO); P NS	Insufficient
Return to heavy drinking	0; 0	NA	NA	NA	NA	NA	Insufficient
Drinking days	1; 56	Medium; RCT	Unknown	Direct	Imprecise	28.3% (IMI) vs. 30.8% (PBO); P NS	Insufficient
Heavy drinking days	1; 56	Medium; RCT	Unknown	Direct	Imprecise	13.5% (IMI) vs.9.0% (PBO); P NS	Insufficient
Drinks per drinking day	1; 56	Medium; RCT	Unknown	Direct	Imprecise	3.7 (IMI) vs. 4.1 (PBO); P NS	Insufficient
Accidents	0; 0	NA	NA	NA	NA	NA	Insufficient
Injuries	0; 0	NA	NA	NA	NA	NA	Insufficient
Quality of life or function	0; 0	NA	NA	NA	NA	NA	Insufficient
Mortality	0; 0	NA	NA	NA	NA	NA	Insufficient

[a]The study reported return to drinking within the previous 4 weeks.[22]

Abbreviations: CI = confidence interval; IMI = imipramine; NA = not applicable; NS = not significant; PBO = placebo; RCT = randomized controlled trial

Table D-20. Nalmefene compared with placebo

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength of Evidence Grade
Return to any drinking	0; 0	NA	NA	NA	NA	NA	Insufficient
Return to heavy drinking	1[a]; 105	Medium; RCT	Unknown	Direct	Imprecise	RD: -0.23 (-0.43 to -0.03)[a]	Insufficient
Drinking days	2; 508	Medium; RCTs	Inconsistent	Direct	Imprecise	WMD: -1.1 (-7.6 to 5.4)	Low
Heavy drinking days	1; 403	Medium; RCT	Unknown	Direct	Imprecise	18.1% (NALM) vs. 29.7% (PBO); P=0.024	Insufficient
Change in HDDs per month: OC analysis PMI analysis	2[b]; 806 2; 1,234	Medium; RCTs	Consistent	Direct	Precise	WMD: -2.0 (-3.0 to -1.0) WMD: -1.3 (-2.2 to -0.3)	Moderate
Drinks per drinking day	3; 608	Medium; RCTs	Consistent	Direct	Precise	WMD: -1.02 (-1.77 to -0.28)	Moderate
Accidents	0; 0	NA	NA	NA	NA	NA	Insufficient
Injuries	0; 0	NA	NA	NA	NA	NA	Insufficient
Quality of life or function	0; 0	NA	NA	NA	NA	NA	Insufficient
Mortality	2; 1,253	Medium; RCTs	Inconsistent	Direct	Imprecise	Study 1: 0 (NALM) vs. 2 (PBO)[23] Study 2: 1 (NALM) vs. 1 (PBO)[24]	Insufficient

[a] 1 additional study reported return to heavy drinking—a pilot study rated as high risk of bias (N=21).[25] It found no difference between groups (RD, -0.05; 95% CI, -0.51 to 0.41). Pooling both studies found a 19% reduction in return to heavy drinking with nalmefene (RD, -0.19; 95% CI, -0.37 to, -0.01).

[b] 1 additional trial (the SENSE trial) rated as high risk of bias reported change in HDDs per month using an OC analysis.[26] The trial (N analyzed=430) did not find a difference in monthly heavy drinking days between the 2 treatments at month 6, but did report a difference at month 13 (mean difference, -1.6; 95% CI, -2.9 to -0.2).

Abbreviations: CI = confidence interval; NA = not applicable; NALM = nalmefene; OC = observed cases; PBO = placebo; PMI = placebo mean imputation; RCT = randomized controlled trial; RD = risk difference; WMD = weighted mean difference

Table D-21. Olanzapine compared with placebo

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength of Evidence Grade
Return to any drinking	0; 0	NA	NA	NA	NA	NA	Insufficient
Return to heavy drinking	1; 60	Medium; RCT	Unknown	Direct	Imprecise	37.9% (OLA) vs. 29.0% (PBO); p=0.50[24]	Insufficient
Drinking days	1; 60	Medium; RCT	Unknown	Direct	Imprecise	13.1% (OLA) vs. 22.7% (PBO); p=0.18[24]	Insufficient
Heavy drinking days	0; 0	NA	NA	NA	NA	NA	Insufficient
Drinks per drinking day	1; 60	Medium; RCT	Unknown	Direct	Imprecise	1.79 (OLA) vs. 2.02 (PBO); p=0.71[24]	Insufficient
Accidents	0; 0	NA	NA	NA	NA	NA	Insufficient
Injuries	0; 0	NA	NA	NA	NA	NA	Insufficient
Quality of life or function	0; 0	NA	NA	NA	NA	NA	Insufficient
Mortality	0; 0	NA	NA	NA	NA	NA	Insufficient

Abbreviations: CI = confidence interval; NA = not applicable; OLA = olanzapine; PBO = placebo; RCT = randomized controlled trial

Table D-22. Ondansetron compared with placebo

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength of Evidence Grade
Return to any drinking	0; 0	NA	NA	NA	NA	NA	Insufficient
Return to heavy drinking	0; 0	NA	NA	NA	NA	NA	Insufficient
Drinking days	0[a]; 0	NA	NA	NA	NA	NA	Insufficient
Heavy drinking days	0[a]; 0	NA	NA	NA	NA	NA	Insufficient
Drinks per drinking day	0; 0	NA	NA	NA	NA	NA	Insufficient
Accidents	0; 0	NA	NA	NA	NA	NA	Insufficient
Injuries	0; 0	NA	NA	NA	NA	NA	Insufficient
Quality of life or function	0; 0	NA	NA	NA	NA	NA	Insufficient
Mortality	0; 0	NA	NA	NA	NA	NA	Insufficient

[a] The only study that met our inclusion criteria was rated as high risk of bias.[27] It reported drinking days and heavy drinking days. Patients treated with ondansetron drank on a mean of 22 percent of days; patients treated with placebo drank on 33 percent of days. The difference was not statistically significant. Patients treated with ondansetron drank heavily (>5 drinks) on a mean of 8 percent of days; patients treated with placebo drank heavily on 12 percent of days. The difference was statistically significant (p=0.02).

Abbreviations: CI = confidence interval; NA = not applicable; PBO = placebo; RCT = randomized controlled trial; RD = risk difference; VAL = valproic acid; WMD = weighted mean difference

Table D-23. Paroxetine compared with placebo

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength of Evidence Grade
Return to any drinking	0; 0	NA	NA	NA	NA	NA	Insufficient
Return to heavy drinking	0; 0	NA	NA	NA	NA	NA	Insufficient
Drinking days	1; 42	Medium; RCT	Unknown	Direct	Imprecise	34% (PAR) vs. 35% (PBO); p=NS[25,26]	Insufficient
Heavy drinking days[a]	1; 42	Medium; RCT	Unknown	Direct	Imprecise	54% (PAR) vs. 55% (PBO); p=NS[25,26]	Insufficient
Drinks per drinking day	1; 42	Medium; RCT	Unknown	Direct	Imprecise	5.9 (PAR) vs. 7.0 (PBO); p=NS[25,26]	Insufficient
Accidents	0; 0	NA	NA	NA	NA	NA	Insufficient
Injuries	0; 0	NA	NA	NA	NA	NA	Insufficient
Quality of life or function	0; 0	NA	NA	NA	NA	NA	Insufficient
Mortality	0; 0	NA	NA	NA	NA	NA	Insufficient

[a] These results indicate the percent of heavy drinking days within the number of any drinking days.

Abbreviations: CI = confidence interval; NA = not applicable; PAR = paroxetine; PBO = placebo; RCT = randomized controlled trial

Table D-24. Quetiapine compared with placebo

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength of Evidence Grade
Return to any drinking	0[a]; 0	NA	NA	NA	NA	NA	Insufficient
Return to heavy drinking	0; 0	NA	NA	NA	NA	NA	Insufficient
Drinking days	0[b]; 0	NA	NA	NA	NA	NA	Insufficient
Heavy drinking days	0[b]; 0	NA	NA	NA	NA	NA	Insufficient
Drinks per drinking day	0; 0	NA	NA	NA	NA	NA	Insufficient
Accidents	0; 0	NA	NA	NA	NA	NA	Insufficient
Injuries	0; 0	NA	NA	NA	NA	NA	Insufficient
Quality of life or function	0[c]; 0	NA	NA	NA	NA	NA	Insufficient
Mortality	0[c]; 0	NA	NA	NA	NA	NA	Insufficient

[a] The one study that reported this outcome was rated as high risk of bias.[28] It did not enroll subjects with co-occurring bipolar disorder and it reported that more subjects treated with quetiapine achieved complete abstinence (9/29 versus 2/32, p=0.012)—i.e., fewer subjects treated with quetiapine returned to any drinking (20/29 versus 30/32).

[b] Three studies reported this outcome; all three were rated as high risk of bias.[28-30] Our meta-analysis of the three trials found no difference in drinking days between patients treated with quetiapine and those who received placebo (WMD, -2.7; 95% CI, -12.8 to 7.5). Our meta-analysis of the three trials found no difference in heavy drinking days between patients treated with quetiapine and those who received placebo (WMD, -3.1; 95% CI, -10.1 to 4.0).

[c] One placebo-controlled trial of quetiapine rated as high risk of bias reported two deaths (one in each treatment group); one after a skull fracture caused by blunt trauma in the quetiapine group and one attributed to myocardial ischemia more than 30 days after treatment in the placebo group.[30] Both deaths were judged to be unrelated to the study medications by the study investigators. The trial also reported no difference between groups for quality of life and function.

Abbreviations: CI = confidence interval; NA = not applicable

Table D-25. Sertraline compared with placebo

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength of Evidence Grade
Return to any drinking	1; 79	Medium; RCT	Unknown	Direct	Imprecise	29/40 (SER) vs. 30/39 (PBO), p NS.	Insufficient
Return to heavy drinking	2; 142	Medium; RCTs	Inconsistent	Direct	Imprecise	RD: -0.04 (-0.31 to 0.23)	Low
Drinking days	3[a]; 299	Medium; RCTs	Consistent	Direct	Imprecise	WMD: 1.8 (-6.25 to 9.86)[a]	Low
Heavy drinking days	2; 228	Medium; RCT	Consistent	Direct	Imprecise	WMD: 1.85 (0.70 to 3.0)	Low (favors placebo)
Drinks per drinking day	2; 176	Medium; RCTs	Consistent	Direct	Imprecise	WMD: -0.9 (-2.2 to 0.5)	Low
Accidents	0; 0	NA	NA	NA	NA	NA	Insufficient
Injuries	0; 0	NA	NA	NA	NA	NA	Insufficient
Quality of life or function	1; 83	Medium; RCT	Unknown	Direct	Imprecise	Graph only, data NR (p=0.031)[b]	Insufficient
Mortality	1; 79	Medium; RCT	Unknown	Direct	Imprecise	0 (SER) vs. 0 (PBO)[31]	Insufficient

[a] One additional study reporting this outcome was rated as unclear risk of bias.[31] Our meta-analysis found no significant difference between patients treated with sertraline and those who received placebo, both without and with including the trial rated as unclear risk of bias (when including that trial: WMD, -0.64; 95% CI, -5.71 to 6.99).

[b] The single study that reported this outcome enrolled patients with co-existing depression and measured QoL using the SF-36 at 24 weeks. Scores were presented in a figure only (bar graph, data not reported). QoL improved during treatment for both the placebo and sertraline groups; the authors noted that the sertraline group improved more than placebo in only the mental health summary score of the SF-36 (p=0.031).[32]

Abbreviations: CI = confidence interval; NA = not applicable; PBO = placebo; RCT = randomized controlled trial; RD = risk difference; SER = sertraline; WMD = weighted mean difference

Table D-26. Topiramate compared with placebo

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength of Evidence Grade
Return to any drinking	0[a]; 0	NA	NA	NA	NA	NA	Insufficient
Return to heavy drinking	0; 0	NA	NA	NA	NA	NA	Insufficient
Drinking days	2[b]; 521	Low; RCTs	Consistent	Direct	Imprecise	Trial 1[34]: WMD: -8.5 (-15.9 to -1.1)[b] Trial 2[35]: mean difference -11.6 (-3.98 to -19.3)	Moderate[b]
Heavy drinking days	2[b]; 521	Low; RCTs	Consistent	Direct	Imprecise	WMD: -11.53 (-18.29 to -4.77)	Moderate[b]
Drinks per drinking day	2[b]; 521	Low; RCT	Consistent	Direct	Imprecise	WMD: -1.10 (-1.75 to -0.45)	Moderate[b]
Accidents	0; 0	NA	NA	NA	NA	NA	Insufficient
Injuries	1; 371	Low; RCT	Unknown	Direct	Imprecise	4.4% (TOP) vs. 11.7% (PBO); p=0.01[34]	Insufficient
Quality of life or function	0; 0	NA	NA	NA	NA	NA	Insufficient
Mortality	1; 371	Low; RCT	Unknown	Direct	Imprecise	0 (TOP) vs. 1 (PBO)[34]	Insufficient

[a] One study conducted in Brazil, rated as high risk of bias, reported this outcome.[33] It reported that more patients treated with topiramate returned to any drinking than with placebo (24/52 versus 15/54).

[b] One additional study reporting this outcome was rated as high risk of bias.[34] Our meta-analysis found a lower percentage of drinking days for patients treated with topiramate than for those who received placebo both without and with including the trial rated as high risk of bias (WMD, -9.7; 95% CI, -16.4 to -3.1). Our meta-analysis found a lower percentage of heavy drinking days for patients treated with topiramate than for those who received placebo both without and with including the trial rated as high risk of bias (WMD, -11.4; 95% CI, -20.4 to -2.4). Our meta-analysis found no statistically significant difference between topiramate and placebo when only including the trial rated as low risk of bias, but found a statistically significant reduction of 1.2 drinks per drinking day when including the trial rated as high risk of bias (WMD, -1.2; 95% CI, -2.2 to -0.2). We were unable to include "trial 2" (N=150),[35] rated as medium risk of bias, in our meta-analyses due to differences in the type of data reported, but its findings are shown in the SOE table, and were generally consistent with those of the low risk of bias trial ("trial 1", N=371).[35]

Abbreviations: CI = confidence interval; NA = not applicable; PBO = placebo; RCT = randomized controlled trial; TOP = topiramate; WMD = weighted mean difference

Table D-27. Valproic acid compared with placebo

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength of Evidence Grade
Return to any drinking	1; 29	Medium; RCT	Unknown	Direct	Imprecise	81% (VAL) vs. 83% (PBO); P NS	Insufficient
Return to heavy drinking	2; 81	Medium; RCTs	Consistent	Direct	Imprecise	RD: -0.32 (-0.52 to -0.11)	Low
Drinking days	1; 29	Medium; RCT	Unknown	Direct	Imprecise	15.9 (VAL) vs. 19.6 (PBO); P NS	Insufficient
Heavy drinking days	2; 81	Medium; RCTs	Consistent	Direct	Imprecise	WMD: -8.5 (-15.9 to -1.1)	Low
Drinks per drinking day	2; 81	Medium; RCTs	Consistent	Direct	Imprecise	WMD: -2.6 (-5.0 to -0.2)	Low
Accidents	0; 0	NA	NA	NA	NA	NA	Insufficient
Injuries	0; 0	NA	NA	NA	NA	NA	Insufficient
Quality of life or function	0; 0	NA	NA	NA	NA	NA	Insufficient
Mortality	0; 0	NA	NA	NA	NA	NA	Insufficient

Abbreviations: CI = confidence interval; NA = not applicable; PBO = placebo; RCT = randomized controlled trial; RD = risk difference; VAL = valproic acid; WMD = weighted mean difference

Table D-28. Varenicline compared with placebo

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength of Evidence Grade
Return to any drinking	1; 200	Low; RCT	Unknown	Direct	Imprecise	97.9% (VAR) vs. 98% (PBO); p 0.81	Insufficient
Return to heavy drinking	1; 200	Low; RCT	Unknown	Direct	Imprecise	92.7% (VAR) vs. 95% (PBO); p 0.50	Insufficient
Drinking days	1; 200	Low; RCT	Unknown	Direct	Imprecise	60.0% (VAR) vs. 64.4% (PBO); p 0.29	Insufficient
Heavy drinking days	1; 200	Low; RCT	Unknown	Direct	Imprecise	37.9% (VAR) vs. 48.4% (PBO); p 0.03	Insufficient
Drinks per drinking day	1; 200	Low; RCT	Unknown	Direct	Imprecise	5.8 (VAR) vs. 6.8 (PBO); p 0.03	Insufficient
Accidents	0; 0	NA	NA	NA	NA	NA	Insufficient
Injuries	0; 0	NA	NA	NA	NA	NA	Insufficient
Quality of life or function	1; 200	Low; RCT	Unknown	Direct	Imprecise	The study found no difference in SF-12 mental (mean difference 0.7; p 0.55) or physical (mean difference 0.4; p 0.38) scores between varenicline-treated and placebo-treated patients.	Insufficient
Mortality	1; 200	Low; RCT	Unknown	Direct	Imprecise	During the 13-week treatment period, there was 1 shooting death in the varenicline arm and no deaths in the placebo arm.	Insufficient

Abbreviations: CI = confidence interval; NA = not applicable; PBO = placebo; RCT = randomized controlled trial; RD = risk difference; VAL = valproic acid; WMD = weighted mean difference

Table D-29. Aripiprazole compared with naltrexone

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength of Evidence Grade
Return to any drinking	1; 57	Medium; RCT	Unknown	Direct	Imprecise	NSD[38]	Insufficient
Return to heavy drinking	1; 57	Medium; RCT	Unknown	Direct	Imprecise	NSD[38]	Insufficient
Drinking days	1; 57	Medium; RCT	Unknown	Direct	Imprecise	NSD[38]	Insufficient
Heavy drinking days	1; 57	Medium; RCT	Unknown	Direct	Imprecise	NSD[38]	Insufficient
Drinks per drinking day	0; 0	NA	NA	NA	NA	NA	Insufficient
Accidents	0; 0	NA	NA	NA	NA	NA	Insufficient
Injuries	0; 0	NA	NA	NA	NA	NA	Insufficient
Quality of life or function	0; 0	NA	NA	NA	NA	NA	Insufficient
Mortality	0; 0	NA	NA	NA	NA	NA	Insufficient

Abbreviations: CI = confidence interval; NA = not applicable; NSD = no significant difference; RCT = randomized controlled trial

Table D-30. Desipramine compared with paroxetine

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength of Evidence Grade
Return to any drinking	0; 0	NA	NA	NA	NA	NA	Insufficient
Return to heavy drinking	0; 0	NA	NA	NA	NA	NA	Insufficient
Drinking days	0; 0	NA	NA	NA	NA	NA	Insufficient
Heavy drinking days	0[a]; 0	NA	NA	NA	NA	NA	Insufficient
Drinks per drinking day	0[a]; 0	NA	NA	NA	NA	NA	Insufficient
Accidents	0; 0	NA	NA	NA	NA	NA	Insufficient
Injuries	0; 0	NA	NA	NA	NA	NA	Insufficient
Quality of life or function	0; 0	NA	NA	NA	NA	NA	Insufficient
Mortality	0; 0	NA	NA	NA	NA	NA	Insufficient

[a] One included trial, rated as high risk of bias, randomized patients with PTSD and alcohol dependence to desipramine, paroxetine, desipramine plus naltrexone, or paroxetine plus naltrexone.[36] The trial found that patients treated with desipramine had fewer heavy drinking days (p=0.009) and drinks per drinking day (p=0.027) than those who received paroxetine.

Abbreviations: CI = confidence interval; NA = not applicable

Table D31. Sertraline compared with naltrexone

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength of Evidence Grade
Return to any drinking	1; 89	Medium; RCT	Unknown	Direct	Imprecise	72.5% (SER) vs. 78.7 (NTX); p NS[31]	Insufficient
Return to heavy drinking	0; 0	NA	NA	NA	NA	NA	Insufficient
Drinking days	0; 0	NA	NA	NA	NA	NA	Insufficient
Heavy drinking days	0; 0	NA	NA	NA	NA	NA	Insufficient
Drinks per drinking day	0; 0	NA	NA	NA	NA	NA	Insufficient
Accidents	0; 0	NA	NA	NA	NA	NA	Insufficient
Injuries	0; 0	NA	NA	NA	NA	NA	Insufficient
Quality of life or function	0; 0	NA	NA	NA	NA	NA	Insufficient
Mortality	1; 89	Medium; RCT	Unknown	Direct	Imprecise	0 (SER) vs. 0 (NTX)[31]	Insufficient

Abbreviations: CI = confidence interval; NA = not applicable; NTX = naltrexone; RCT = randomized controlled trial; SER = sertraline

Table D-32. Topiramate compared with naltrexone

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength of Evidence Grade
Return to any drinking	0[a]; 0	NA	NA	NA	NA	NA	Insufficient
Return to heavy drinking	0; 0	NA	NA	NA	NA	NA	Insufficient
Drinking days	0[a]; 0	NA	NA	NA	NA	NA	Insufficient
Heavy drinking days	0[a]; 0	NA	NA	NA	NA	NA	Insufficient
Drinks per drinking day	0; 0	NA	NA	NA	NA	NA	Insufficient
Accidents	0; 0	NA	NA	NA	NA	NA	Insufficient
Injuries	0; 0	NA	NA	NA	NA	NA	Insufficient
Quality of life or function	0[b]; 0	NA	NA	NA	NA	NA	Insufficient
Mortality	0; 0	NA	NA	NA	NA	NA	Insufficient

[a] The only included trial that was eligible for KQ 1 and that reported these outcomes, rated as high risk of bias, reported no significant differences between topiramate and naltrexone for proportion of abstinent subjects, cumulative abstinence duration, time to first relapse, or heavy drinking weeks.[33] Significantly more subjects in the topiramate group participated in AA than in the naltrexone group (19.2 percent versus 4.1 percent, p=0.04).

[b] The two studies that reported this outcome were rated as high risk of bias.

Abbreviations: CI = confidence interval; NA = not applicable

KQ 3

Table D-33. Acamprosate compared with placebo

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength of Evidence Grade
Withdrawals due to AEs	13[a]; 4,653	Medium; RCTs	Consistent	Direct	Imprecise	RD 0.006 (-0.003 to 0.015)	Low
Anorexia	0; 0	NA	NA	NA	NA	NA	Insufficient
Anxiety	1[b]; 601	Medium; RCT	Unknown	Direct	Imprecise	RD 0.164 (0.095 to 0.234)	Insufficient
Cognitive dysfunction	0; 0	NA	NA	NA	NA	NA	Insufficient
Diarrhea	12[c]; 3,299	Medium; RCTs	Consistent	Direct	Precise	RD 0.099 (0.030 to 0.168)	Moderate
Dizziness	2; 151	Low to medium; RCTs	Inconsistent	Direct	Imprecise	RD 0.08 (-0.22 to 0.38)	Low
Headache	6[b]; 1,074	Medium; RCTs	Inconsistent	Direct	Imprecise	RD 0.001 (-0.052 to 0.05)	Low
Insomnia	3[b]; 251	Medium; RCT	Inconsistent	Direct	Imprecise	RD 0.019 (-0.10 to 0.138)	Low
Nausea	7[b]; 1,758	Low to medium; RCTs	Consistent	Direct	Imprecise	RD 0.006 (-0.012 to 0.023)	Moderate
Numbness / tingling / paresthesias	1[b]; 262	Medium; RCT	Unknown	Direct	Imprecise	RD 0.008 (-0.013 to 0.029)	Insufficient
Rash	1[b]; 35	Low; RCT	Unknown	Direct	Imprecise	RD 0.111 (-0.069 to 0.291)	Insufficient
Suicide attempts or suicidal ideation	1[c]; 581	Medium; RCT	Unknown	Direct	Imprecise	RD 0.007 (-0.005, 0.019)	Insufficient
Taste abnormalities	0; 0	NA	NA	NA	NA	NA	Insufficient
Vision changes	0; 0	NA	NA	NA	NA	NA	Insufficient
Vomiting	4[b]; 1,817	Medium; RCTs	Consistent	Direct	Precise	RD 0.024 (0.007 to 0.042)	Moderate

[a] Three additional studies were rated high or unclear risk of bias

[b] One additional study was rated high or unclear risk of bias

[c] Two additional studies were rated high or unclear risk of bias

Abbreviations: AE = adverse effect; CI = confidence interval; RCT = randomized controlled trial; RD risk difference

Table D-34. Naltrexone compared with placebo

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength of Evidence Grade
Withdrawals due to AEs	17[a]; 2,743	Medium; RCTs	Consistent	Direct	Precise	RD 0.021 (0.009 to 0.034)	Moderate
Anorexia	1; 175	Medium; RCT	Unknown	Direct	Imprecise	RD 0.077 (0.014 to 0.140)	Insufficient
Anxiety	7[b]; 1,461	Medium; RCTs	Consistent	Direct	Imprecise	RD 0.007 (-0.022 to 0.036)	Low
Cognitive dysfunction	1; 123	Medium; RCT	Unknown	Direct	Imprecise	RD 0.190 (0.038 to 0.341)	Insufficient
Diarrhea	11[c]; 2,358	Medium; RCTs	Consistent	Direct	Imprecise	RD 0.013 (-0.011 to 0.038)	Moderate
Dizziness	13[d]; 2,675	Medium; RCTs	Consistent	Direct	Precise	RD 0.063 (0.036 to 0.089)	Moderate
Headache	17[e]; 3,347	Medium; RCTs	Inconsistent	Direct	Imprecise	RD 0.008 (-0.019 to 0.034)	Low
Insomnia	8[d]; 1,637	Medium; RCTs	Consistent	Direct	Imprecise	RD 0.027 (-0.002 to 0.057)	Low
Nausea	24[f]; 4,655	Medium; RCTs	Consistent	Direct	Precise	RD 0.112 (0.075 to 0.149)	Moderate
Numbness / tingling / paresthesias	1[b]; 123	Medium; RCT	Unknown	Direct	Imprecise	RD -0.008 (-0.185 to 0.168)	Insufficient
Rash	4[c]; 469	Medium; RCTs	Consistent	Direct	Imprecise	RD -0.010 (-0.060 to 0.040)	Low
Suicide	0; 0	NA	NA	NA	NA	NA	Insufficient
Taste abnormalities	1; 123	Medium; RCT	Unknown	Direct	Imprecise	RD -0.006 (-0.182 to 0.171)	Insufficient
Vision changes (blurred vision)	2; 133	Medium; RCTs	Inconsistent	Direct	Imprecise	RD 0.079 (-0.172 to 0.331)	Low
Vomiting	9[b]; 2,438	Medium; RCTs	Consistent	Direct	Precise	RD 0.043 (0.023 to 0.062)	Moderate

[a] Three additional studies were rated high or unclear risk of bias

[b] Two additional studies were rated high or unclear risk of bias

[c] One additional study was rated high or unclear risk of bias

[d] Four additional studies were rated high or unclear risk of bias

[e] Five additional studies were rated high or unclear risk of bias

[f] Seven additional studies were rated as high or unclear risk of bias

Abbreviations: AE = adverse effect; CI = confidence interval; RD = risk difference

Table D-35. Acamprosate compared with Naltrexone

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)[a]	Strength of Evidence Grade
Withdrawals due to AEs	2[b]; 953	Medium; RCT	Consistent	Direct	Imprecise	RD 0.015 (-0.04 to 0.07)	Low
Anorexia	0; 0	NA	NA	NA	NA	NA	Insufficient
Anxiety	0; 0	NA	NA	NA	NA	NA	Insufficient
Cognitive dysfunction	0; 0	NA	NA	NA	NA	NA	Insufficient
Diarrhea	4[b]; 836	Low to medium; RCTs	Consistent	Direct	Imprecise	RD 0.18 (-0.02 to 0.37)	Moderate
Dizziness	2[b]; 144	Low to medium; RCT	Inconsistent	Direct	Imprecise	RD 0.08 (-0.23 to 0.39)	Low
Headache	3[b]; 301	Medium; RCT	Inconsistent	Direct	Imprecise	RD -0.056 (-0.120 to 0.008)	Low[d]
Insomnia	2; 144	Low to medium; RCTs	Inconsistent	Direct	Imprecise	RD 0.07 (-0.20 to 0.34)	Low
Nausea	4[c]; 836	Low to medium; RCTs	Consistent	Direct	Imprecise	RD -0.08 (-0.18 to 0.02)	Low[e]
Numbness / tingling / paresthesias	0; 0	NA	NA	NA	NA	NA	Insufficient
Rash	0; 0	NA	NA	NA	NA	NA	Insufficient
Suicide	0; 0	NA	NA	NA	NA	NA	Insufficient
Taste abnormalities	0; 0	NA	NA	NA	NA	NA	Insufficient
Vision changes	0; 0	NA	NA	NA	NA	NA	Insufficient
Vomiting	2; 648	Low; RCTs	Consistent	Direct	Precise	RD -0.06 (-0.11 to -0.01)	Moderate

[a] In this column, a positive value favors naltrexone

[b] One additional study was rated high or unclear risk of bias

[c] Two additional studies were rated high risk of bias

[d] The additional study rated as high risk of bias found similar results as the medium risk of bias studies. Meta-analysis including all three found a higher risk of headache with naltrexone than with acamprosate: RD -0.087 (-0.159 to -0.015)

[e] Meta-analysis including the two additional studies rated as high or unclear risk of bias found a higher risk of nausea with naltrexone than with acamprosate: RD -0.096 (-0.178 to -0.015)

Abbreviations: ACA = acamprosate; AE = adverse effect; CI = confidence interval; NTX = naltrexone; RCT = randomized controlled trial; RD = risk difference

Table D-36. Nalmefene compared with placebo

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength of Evidence Grade
Withdrawals due to AEs	5[a]; 2,054	Medium; RCTs	Consistent	Direct	Precise	RD 0.083 (0.020 to 0.145)	Moderate
Anorexia	0; 0	NA	NA	NA	NA	NA	Insufficient
Anxiety	0; 0	NA	NA	NA	NA	NA	Insufficient
Cognitive dysfunction	1[b]; 265	Medium; RCT	Unknown	Direct	Imprecise	RD 0.051 (0.013 to 0.088)	Insufficient
Diarrhea	2; 1,081	Medium; RCTs	Consistent	Direct	Precise	RD -0.031 (-0.056 to -0.006)	Moderate
Dizziness	4[a]; 1,944	Medium; RCTs	Consistent	Direct	Precise	RD 0.158 (0.108 to 0.207)	Moderate
Headache	3[b]; 1,401	Medium; RCTs	Consistent	Direct	Precise	RD 0.039 (0.007 to 0.071)	Moderate
Insomnia	5[b]; 2,049	Medium; RCTs	Consistent	Direct	Precise	RD 0.101 (0.061 to 0.141)	Moderate
Nausea	5[b]; 2,049	Medium; RCTs	Consistent	Direct	Precise	RD 0.158 (0.095 to 0.220)	Moderate
Numbness / tingling / paresthesias	0; 0	NA	NA	NA	NA	NA	Insufficient
Rash	0; 0	NA	NA	NA	NA	NA	Insufficient
Suicide attempts or suicidal ideation	2[b]; 1,253	Medium; RCTs	Consistent	Direct	Imprecise	RD -0.01 (-0.021 to 0.001)	Low
Taste abnormalities	1; 403	Medium; RCT	Unknown	Direct	Imprecise	RD 0.041 (0.008 to 0.074)	Insufficient
Vision changes	0; 0	NA	NA	NA	NA	NA	Insufficient
Vomiting	3[b]; 1,679	Medium; RCTs	Consistent	Direct	Precise	RD 0.059 (0.021 to 0.096)	Moderate

[a] Two additional studies were rated high or unclear risk of bias

[b] One additional study was rated high or unclear risk of bias

Abbreviations: AE = adverse effect; CI = confidence interval; RCT = randomized controlled trial; RD risk difference

Table D-37. Topiramate compared with placebo

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength of Evidence Grade
Withdrawals due to AEs	2[a]; 521	Medium; RCTs	Inconsistent	Direct	Imprecise	RD 0.065 (-0.119 to 0.248)	Low
Anorexia	1; 371	Medium; RCT	Unknown	Direct	Imprecise	RD 0.128 (0.060 to 0.196)	Insufficient
Anxiety	0; 0	NA	NA	NA	NA	NA	Insufficient
Cognitive dysfunction	2; 521	Medium; RCTs	Consistent	Direct	Precise	RD 0.084 (0.012 to 0.156)	Moderate
Diarrhea	1[a]; 371	Medium; RCT	Unknown	Direct	Imprecise	RD 0.035 (-0.027 to 0.097)	Insufficient
Dizziness	2[a]; 521	Medium; RCTs	Consistent	Direct	Imprecise	RD 0.105 (-0.007 to 0.216)	Low
Headache	1; 371	Medium; RCT	Unknown	Direct	Imprecise	RD -0.079 (-0.170 to 0.012)	Insufficient
Insomnia	1[a]; 371	Medium; RCT	Unknown	Direct	Imprecise	RD 0.032 (-0.046 to 0.109)	Insufficient
Nausea	1[a]; 371	Medium; RCT	Unknown	Direct	Imprecise	RD -0.061 (-0.130 to 0.008)	Insufficient
Numbness / tingling / paresthesias	2[a]; 521	Medium; RCTs	Consistent	Direct	Precise	RD 0.398 (0.325 to 0.471)	Moderate
Rash	0; 0	NA	NA	NA	NA	NA	Insufficient
Suicide attempts or suicidal ideation	0; 0	NA	NA	NA	NA	NA	Insufficient
Taste abnormalities	1; 371	Medium; RCT	Unknown	Direct	Imprecise	RD 0.182 (0.113 to 0.250)	Insufficient
Vision changes	0; 0	NA	NA	NA	NA	NA	Insufficient
Vomiting	0; 0	NA	NA	NA	NA	NA	Insufficient

[a] One additional study was rated high or unclear risk of bias

Abbreviations: AE = adverse effect; CI = confidence interval; RCT = randomized controlled trial; RD risk difference

Table D-38. Valproic acid compared with placebo

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength of Evidence Grade
Withdrawals due to AEs	1; 52	Low; RCT	Unknown	Direct	Imprecise	RD 0.037 (-0.065 to 0.140)	Insufficient
Anorexia	0; 0	NA	NA	NA	NA	NA	Insufficient
Anxiety	0; 0	NA	NA	NA	NA	NA	Insufficient
Cognitive dysfunction	0; 0	NA	NA	NA	NA	NA	Insufficient
Diarrhea	1; 52	Low; RCT	Unknown	Direct	Imprecise	RD 0.099 (-0.120 to 0.318)	Insufficient
Dizziness	0; 0	NA	NA	NA	NA	NA	Insufficient
Headache	1; 52	Low; RCT	Unknown	Direct	Imprecise	RD 0.053 (-0.197 to 0.304)	Insufficient
Insomnia	0; 0	NA	NA	NA	NA	NA	Insufficient
Nausea	1; 52	Low; RCT	Unknown	Direct	Imprecise	RD 0.253 (0.046 to 0.461)	Insufficient
Numbness / tingling / paresthesias	0; 0	NA	NA	NA	NA	NA	Insufficient
Rash	0; 0	NA	NA	NA	NA	NA	Insufficient
Suicide attempts or suicidal ideation	0; 0	NA	NA	NA	NA	NA	Insufficient
Taste abnormalities	0; 0	NA	NA	NA	NA	NA	Insufficient
Vision changes	1; 52	Low; RCT	Unknown	Direct	Imprecise	RD -0.021 (-0.262 to 0.221)	Insufficient
Vomiting	0; 0	NA	NA	NA	NA	NA	Insufficient

Abbreviations: AE = adverse effect; CI = confidence interval; RCT = randomized controlled trial; RD risk difference

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Appendix E. Placebo-Controlled Trials of Medications Used Off-Label or Those Under Investigation for Which We Found Only One Trial Meeting Inclusion Criteria

Aripiprazole

Characteristics of Trials

Table E-1 summarizes characteristics of the one trial meeting our inclusion criteria.[1] It was conducted across 16 academic centers in the U.S. and compared aripiprazole, titrated from 2 mg/day to 30 mg/day over the initial four weeks, with placebo. All participants (N=295) received an enhanced form of cognitive behavioral therapy. The recruitment method was not reported. All patients were alcohol-dependent, and the proportions of smokers and of patients with co-occurring conditions were not reported.

Table E-1. Characteristics of included double-blind randomized placebo-controlled trials of aripiprazole

Author, Year	Arm Dose, mg/day (N)	Medication Duration (Followup)	Country	Setting	Age Years	Per-cent-age Non-White	Percent-age Female	Co-intervention(s)	Risk of Bias
Anton, 2008[1]	Aripiprazole titrated from 2 to 30 over 4 wks (149) Placebo (146)	12	U.S.	16 academic centers	47	15 to 16	25 to 38	Enhanced CBT 100%	Med

Notes: Age (y) is the mean age in years, unless otherwise stated

Abbreviations: CBT = cognitive behavioral therapy; mg = milligrams; U.S. = United States; wks = weeks

Return to Any Drinking

More patients treated with aripiprazole returned to any drinking than with placebo (89 percent versus 78 percent, p=0.02).

Return to Heavy Drinking

The proportion returning to heavy drinking did not differ between groups (73 percent versus 73 percent).

Drinking Days

Patients treated with aripiprazole drank on a mean of 41 percent of days; patients treated with placebo drank on 37 percent of days. The difference was not statistically significant.

Drinks per Drinking Day

Patients treated with aripiprazole reported fewer drinks per drinking day than patients treated with placebo (4.4 versus 5.5, p<0.001).

Atomoxetine

Characteristics of Trials

Table E-2 summarizes characteristics of the one trial meeting our inclusion criteria.[2] It was a multi-institutional study conducted in the U.S. and Canada. Investigators compared atomoxetine, titrated from 25 mg/day to 100 mg/day, with placebo. The mean final dose for atomoxetine was 89.9mg. Twelve-step program attendance was allowed, but all other types of co-intervention were prohibited. The recruitment method was not reported. Slightly more than half of the patients met criteria for alcohol dependence, and all patients were diagnosed with attention deficit hyperactivity disorder (ADHD). The proportion of smokers was not reported. The study was rated as high risk of bias, primarily for high risk of attrition bias and inadequate handling of missing data (see Appendix C for details).

Table E-2. Characteristics of included double-blind randomized placebo-controlled trials of atomoxetine

Author, Year	Arm Dose, mg/day (N)	Medication Duration (Follow-up)	Country	Setting	Age Years	Per-cent-age Non-White	Per-cent-age F	Percentage With Co-Occurring Condition(s)	Risk of Bias
Wilens, 2008[2]	Atomoxetine titrated from 25 to 100 (72) Placebo (75)	12	U.S. and Canada	Multi-institution	35	12	15	100 (ADHD)	High

Notes: Age (y) is the mean age in years, unless otherwise stated

Abbreviations: ADHD, attention deficit hyperactivity disorder; mg, milligrams; Rx = prescription; U.S., United States

Return to Heavy Drinking

The trial found no significant difference between groups. (94 percent for patients treated with atomoxetine versus 96 percent for patients taking placebo).

Drinking Days

Patients treated with atomoxetine drank on roughly 50 percent of days; patients treated with placebo drank on roughly 60 percent of days. The difference between groups was not statistically significant.

Heavy Drinking Days

Atomoxetine-treated patients had a 26 percent lower rate of heavy drinking days compared with placebo (event ratio=0.74, p=0.02).

Drinks per Drinking Day

The reduction in drinks per drinking day from baseline was not significantly different between groups (1.1 for the atomoxetine group versus 0.6 for the placebo group, p NS).

Desipramine

Characteristics of Trials

Table E-3 summarizes characteristics of the one trial meeting our inclusion criteria.[3] It was conducted in the outpatient psychiatry departments at two urban medical centers in the U.S. Investigators compared desipramine (median dose=200 mg/day) with placebo. No co-interventions were required, though Alcoholics Anonymous attendance was encouraged. Patients were recruited through inpatient and outpatient psychiatric referrals and via public service announcements. All patients met criteria for alcohol dependence, and 39 percent were also diagnosed with depression. The proportion of smokers was not reported. The study was rated as high risk of bias, primarily for high risk of attrition bias and inadequate handling of missing data (see Appendix C for details).

Table E-3. Characteristics of included double-blind randomized placebo-controlled trials of desipramine

Author, Year	Arm Dose, mg/day (N)	Medication Duration (follow-up)	Country	Setting	Age Years	Percentage Non-White	Percentage Female	Percentage With Co-Occurring Condition(s)	Risk of Bias
Mason, 1996[3]	Desipramine median 200 (37) Placebo (34)	26	U.S.	Psychiatry outpatient departments at 2 urban medical centers	Median= 40	38	17	Depression 39%	High

Notes: Age (y) is the mean age in years, unless otherwise stated

Abbreviations: U.S. = United States; wks = weeks

Return to Heavy Drinking

In this study, a return to heavy drinking was defined as two heavy drinking days per week for two consecutive weeks. Twelve percent of patients in the desipramine arm returned to heavy drinking, compared with 32 percent of patients taking placebo. The difference between groups was not statistically significant.

Drinking Days

Non-depressed patients treated with desipramine (N=14) drank on a median of 68 percent of days; non-depressed patients treated with placebo (N=15) drank on 72 percent of days (p NS). Depressed patients treated with desipramine (N=12) drank on a median of 40 percent of days; depressed patients treated with placebo (N=10) drank on 64 percent of days (p NS).

Fluvoxamine

Characteristics of Trials

Table E-4 summarizes characteristics of the one trial meeting our inclusion criteria.[4] It was conducted in ten outpatient sites in four European countries. Investigators compared fluvoxamine 100-300 mg/day with placebo. In addition, patients received each site's usual psychosocial treatment. Recruitment method was not reported. All patients met criteria for alcohol dependence; the study did not report the proportion of patients with co-occurring conditions. The proportions of smokers and non-white participants were not reported.

Table E-4. Characteristics of Included double-blind randomized placebo-controlled trials of fluvoxamine

Author, Year	Arm Dose, mg/day (N)	Medication Duration (Follow-up)	Country	Setting	Age Years	Percentage Female	Risk of Bias
Chick, 2004[4]	Fluvoxamine 100-300 (261) Placebo (260)	52	U.K., Eire, Austria, Switzerland	10 outpatient sites	42 (19-72)	35	Med

Notes: Age (y) is the mean age in years, unless otherwise stated

Abbreviations: mg = milligram; N = number; U.K. = United Kingdom

Return to Any Drinking

At 12 weeks, the trial found no significant different between groups (58 percent of fluvoxamine-treated patients versus 54 percent of placebo-treated patients returned to drinking since the assessment at week 8, P NS). Similarly, at 52 weeks, there was no difference between groups in percentage of patients who returned to drinking since the previous assessment at week 40 (71 percent versus 71 percent).

Return to Heavy Drinking

At 12 weeks, the study did not find a difference between those treated with fluvoxamine and those who received placebo (46 percent versus 40 percent, P NS). Similarly, at 52 weeks, the study reported no difference between groups (64 percent versus 64 percent).

Drinking Days

At 12 weeks, fluvoxamine-treated patients had more drinking days since the previous (at week 8) assessment than placebo-treated patients (31 percent versus 23 percent, p=0.009). At 52 weeks, the study did not find a significant difference between groups for dinking days since the previous assessment (44 percent versus 38 percent, p NS).

Mortality

During the 52-week study, there was no difference between those treated with fluvoxamine and those who received placebo: one patient in each arm died.

Imipramine

Characteristics of Trials

Table E-5 summarizes characteristics of the one trial meeting our inclusion criteria.[5] It was conducted in a university-based depression research clinic in the U.S. Investigators compared imipramine 50-300 mg/day (mean dose=262 mg/day) with placebo. In addition, all patients received individual relapse prevention counseling. Patients were recruited using advertisements and via referrals. Almost all patients met criteria for alcohol dependence (96 percent), and all had some form of depression. The proportion of smokers was not reported. Roughly 20 percent of enrollees were non-white, and about half were female.

Table E-5. Characteristics of included double-blind randomized placebo-controlled trials of imipramine

Author, Year	Arm Dose, mg/day (N)	Medication Duration (Follow-up)	Country	Setting	Age Years	Per-cent-age Non-White	Per-cent-age Female	Percentage With Co-Occurring Condition(s)	Risk of Bias
McGrath, 1996[5]	Imipramine 50-300; mean 262 (36) Placebo (33)	12	U.S.	University-based depression research clinic	37 imipramine, 11 placebo[a]	17 to 22	49 to 53	MDD 71 to 72 Bipolar 11 to 12 Atypical depression 70 to 72 Other substance abuse 16	Med

[a]The study reported 11 years, but it was clearly a reporting error; likely 31 or 41 years.

Notes: Age (y) is the mean age in years, unless otherwise stated

Abbreviations: MDD = major depressive disorder; mg = milligrams; U.S. = United States

Return to Any Drinking

The study found no significant difference between groups (69 percent of those receiving imipramine versus 79 percent of those receiving placebo, p NS).

Drinking Days

The study found no significant difference between groups (Imipramine-treated patients drank on 28 percent of days versus 31 percent for those who received placebo, p NS).

Heavy Drinking Days

The study found no significant difference between groups (Imipramine-treated patients drank heavily on 13.5 percent of days versus 9 percent for those who received placebo, p NS).

Drinks per Drinking Day

The mean number of drinks per drinking day was 3.7 for imipramine-treated patients and 4.1 for placebo-treated patients. The difference between groups was not statistically significant.

Olanzapine

Characteristics of Trials

Table E-6 summarizes characteristics of the one trial meeting our inclusion criteria.[6] Patients were treatment-seekers in a psychiatry department-based addictive behavior unit in a hospital in Spain. Investigators compared olanzapine 5 to 15 mg/day with placebo. In addition, all patients received cognitive behavioral therapy. All patients met criteria for alcohol dependence. The proportions of smokers and non-white patients were not reported.

Table E-6. Characteristics of included double-blind randomized placebo-controlled trials of olanzapine

Author, Year	Arm Dose, mg/day (N)	Medication Duration (Follow-up)	Country	Setting	Age Years	Percentage Female	Risk of Bias
Guardia, 2004[6]	Olanzapine 5-15 (29) Placebo (31)	12 (16)	Spain	Addictive behavior unit of a hospital psychiatry department	43	23 to 27	Med

Notes: Age (y) is the mean age in years, unless otherwise stated

Abbreviations: mg = milligrams; N = number; Rx = prescription

Return to Heavy Drinking

Thirty-eight percent of olanzapine patients returned to heavy drinking by the end of the study compared with 29 percent of placebo-treated patients. The difference between groups was not statistically significant.

Drinking Days

Olanzapine-treated patients drank on 13 percent of days; those who received placebo drank on 23 percent of days. The difference between groups was not statistically significant.

Drinks per Drinking Day

The mean number of drinks per drinking day was 1.8 for olanzapine-treated patients and 2.0 for placebo-treated patients. This difference was not statistically significant.

Ondansetron

Characteristics of Trials

Table E-7 summarizes characteristics of the one trial meeting our inclusion criteria.[7] It was conducted at a single university in Brazil and compared ondansetron 16 mg/day with placebo. All participants (N=102) received a standardized brief cognitive behavioral intervention. Patients were enrolled as outpatients in a substance abuse treatment program at the university. All patients were alcohol-dependent, and 64% were smokers.

Table E-7. Characteristics of included double-blind randomized placebo-controlled trials of ondansetron

Author, Year	Arm Dose, mg/day (N)	Medication Duration (Followup)	Country	Setting	Age Years	Per-cent-age Non-White	Percent-age Female	Co-intervention(s)	Risk of Bias
Corrêa Filho, 2013[7]	Ondansetron 16 (50) Placebo (52)	12	Brazil	University-based outpatient substance abuse treatment center	42 to 44	60 to 73	0	Standardized brief cognitive behavioral intervention	High

Notes: Age (y) is the mean age in years, unless otherwise stated

Abbreviations: mg = milligrams

Drinking Days

Patients treated with ondansetron drank on a mean of 22 percent of days; patients treated with placebo drank on 33 percent of days. The difference was not statistically significant.

Heavy Drinking Days

Patients treated with ondansetron drank heavily (>5 drinks) on a mean of 8 percent of days; patients treated with placebo drank heavily on 12 percent of days. The difference was statistically significant (p=0.02).

Paroxetine

Characteristics of Trials

Table E-8 summarizes characteristics of the one trial meeting our inclusion criteria.[8,9] It was conducted in the U.S., but the specific setting was not reported. Investigators compared paroxetine, titrated from 10 to 60 mg/day over four weeks (mean dose=45 mg/day) with placebo; no psychosocial or psychological therapy was provided. Patients were recruited using media advertisements. Most of the patients met criteria for alcohol dependence (79 percent), and all had social anxiety disorder. Roughly ten percent were also diagnosed with major depression. The proportion of smokers was not reported.

Table E-8. Characteristics of included double-blind randomized placebo-controlled trials of paroxetine

Author, Year	Arm Dose, mg/day (N)	Medication Duration (Follow-up)	Country	Age Years	Per-cen-tage Non-White	Per-cent-age Female	Percentage With Co-Occurring Condition(s)	Risk of Bias
Book, 2008[8]; Thomas, 2008[9]	Paroxetine titration over 4 weeks 10-60; avg. 45 (20) Placebo (22)	16	U.S.	28 to 30	0 to 18	45 to 50	Social anxiety disorder 100%; MDD ~10	Med

Notes: Age (y) is the mean age in years, unless otherwise stated

Abbreviations: MDD = major depressive disorder; mg = milligrams; U.S. = United States

Drinking Days

The study found no significant difference between groups (paroxetine-treated patients versus placebo-treated: 34 percent versus 35 percent, p NS).

Heavy Drinking Days

The study found no significant difference between groups (paroxetine-treated patients versus placebo-treated: 54 percent versus 55 percent, p NS).

Drinks per Drinking Day

At week 16, the mean number of drinks per drinking day was 5.9 for paroxetine-treated patients and 7.0 for placebo-treated patients. The difference between groups was not statistically significant.

Varenicline

Characteristics of Trials

Table E-9 summarizes characteristics of the one trial meeting our inclusion criteria.[10] It was conducted at 5 outpatient academic sites in the U.S. Investigators compared varenicline, titrated from 0.5mg/day to 2 mg/day during the first week and at 2 mg/day through week 13, with placebo. Patients were also required to participate in a computerized self-help program. Patients were recruited via advertisements at each study site. All patients were alcohol dependent, 39 percent were smokers, and 13% used marijuana.

Table E-9. Characteristics of included double-blind randomized placebo-controlled trials of varenicline

Author, Year	Arm Dose, mg/day (N)	Medication Duration (Follow-up)	Country	Age Years	Per-cen-tage Non-White	Per-cent-age Female	Percentage With Co-Occurring Condition(s)	Risk of Bias
Litten, 2013[10]	Varenicline 2 (99) Placebo (101)	13	U.S.	45 to 46	30 to 38	27 to 32	12 to 14% marijuana users	Low

Notes: Age (y) is the mean age in years, unless otherwise stated

Abbreviations: MDD = major depressive disorder; mg = milligrams; U.S. = United States

Return to Any Drinking

The study found no difference between varenicline-treated patients and placebo-treated (97.9 percent versus 98 percent, respectively; p=0.81)

Return to Heavy Drinking

The study found no difference between varenicline-treated patients and placebo-treated (92.7 percent versus 95 percent, respectively; p=0.50)

Drinking Days

The study found no difference between varenicline-treated patients and placebo-treated (60.0 percent versus 64.4 percent, respectively; p=0.29).

Heavy Drinking Days

The study found that varenicline-treated patients reported fewer heavy drinking days compared with placebo-treated (37.9 percent versus 48.4 percent, respectively; p=0.03).

Drinks per Drinking Day

The study found that varenicline-treated patients reported fewer drinks per drinking day compared with placebo-treated (5.8 versus 6.8; p=0.03).

Quality of Life

The study found no difference in SF-12 mental (mean difference 0.7; p=0.55) or physical (mean difference 0.4; p=0.38) scores between varenicline-treated and placebo-treated patients.

Mortality

During the 13-week treatment period, there was a shooting death in the varenicline arm and no deaths in the placebo arm.

References for Appendix E

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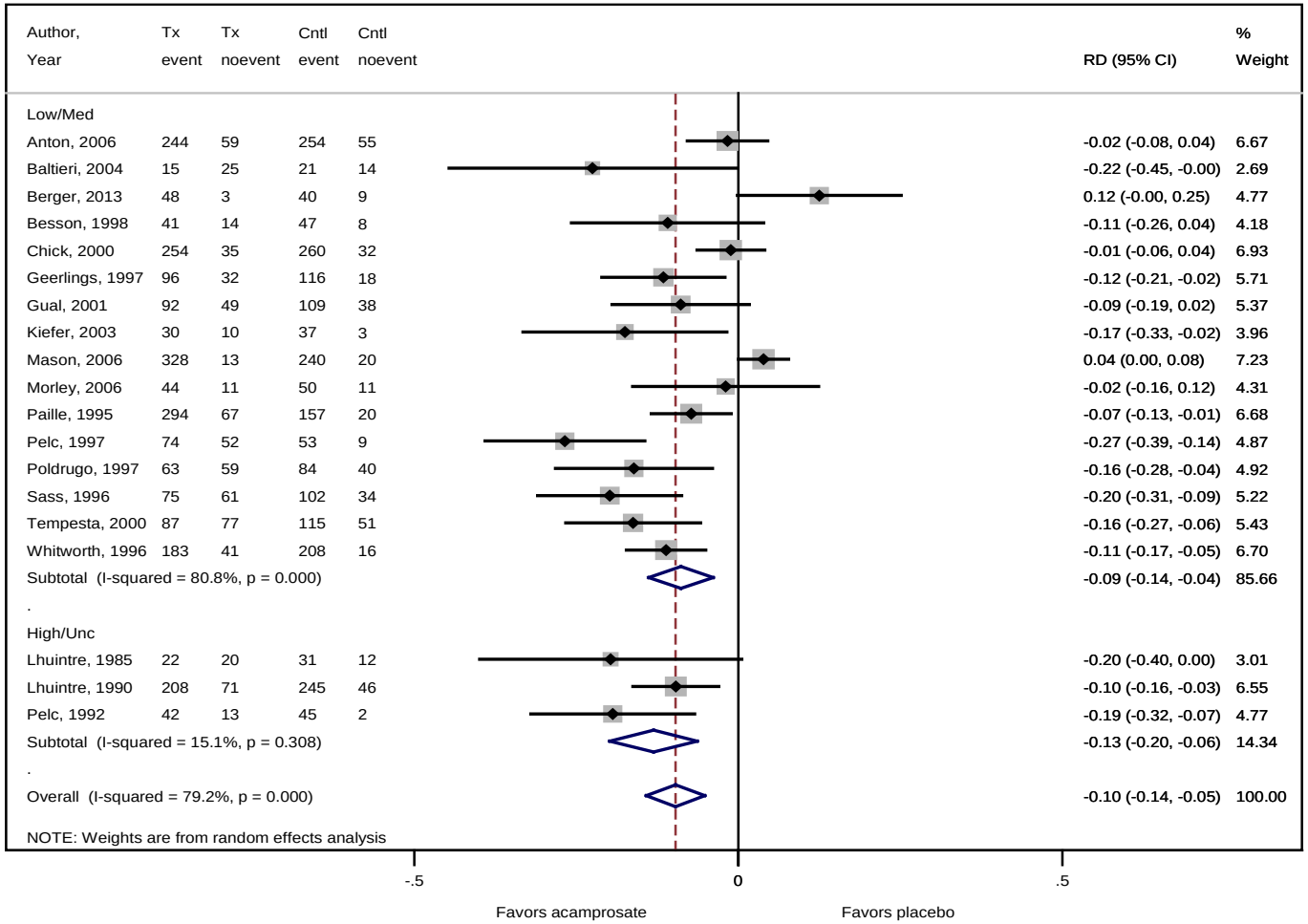
Appendix F. Meta-Analyses

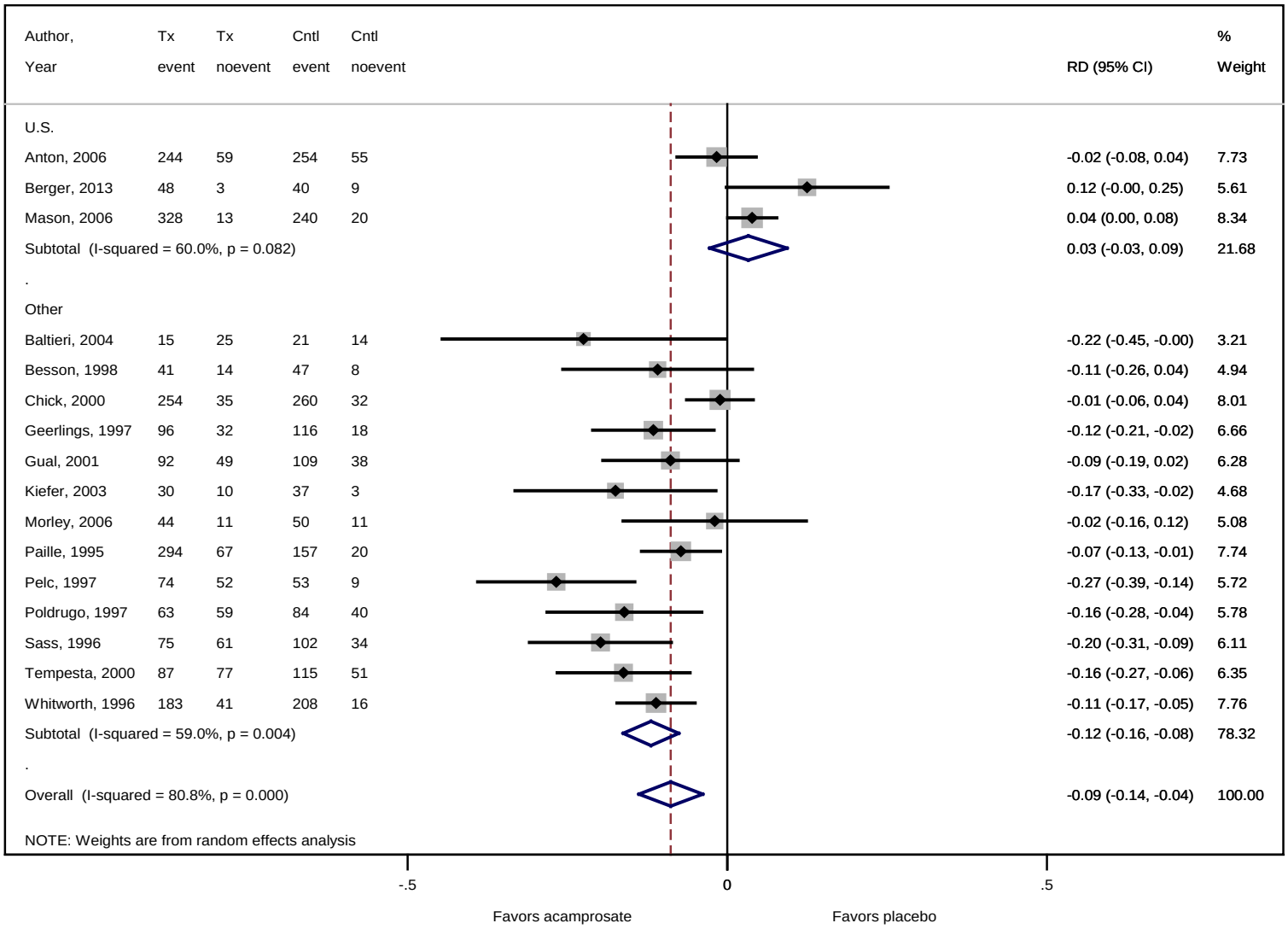
Key Question 1 Meta-Analysis Results

Figure F-1. Acamprosate versus placebo: Return to any drinking by risk of bias rating



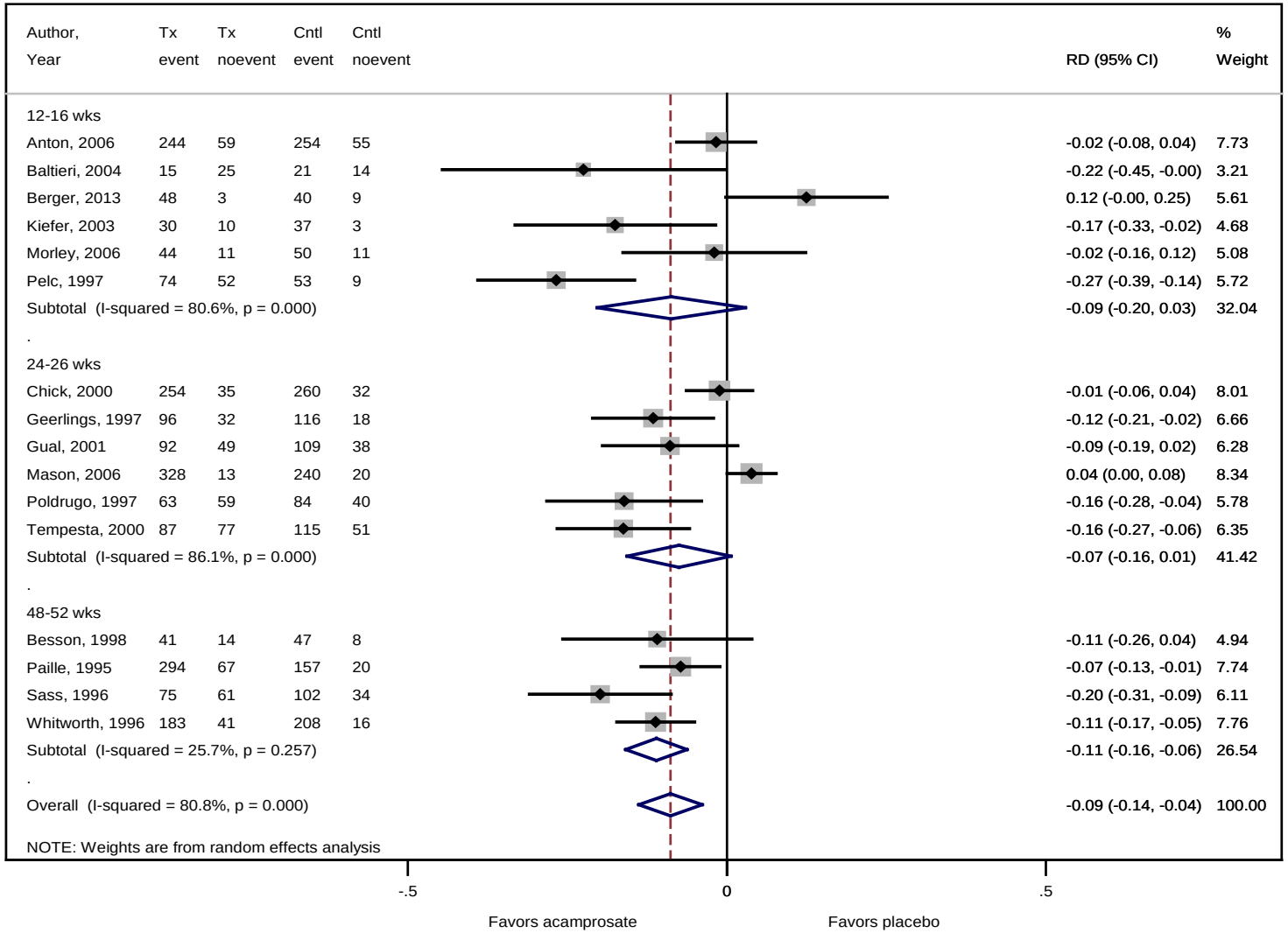
Note: doses combined for Mason, 2006, Paille, 1995, and Pelc, 1997.

Figure F-2. Acamprosate versus placebo: Return to any drinking by country



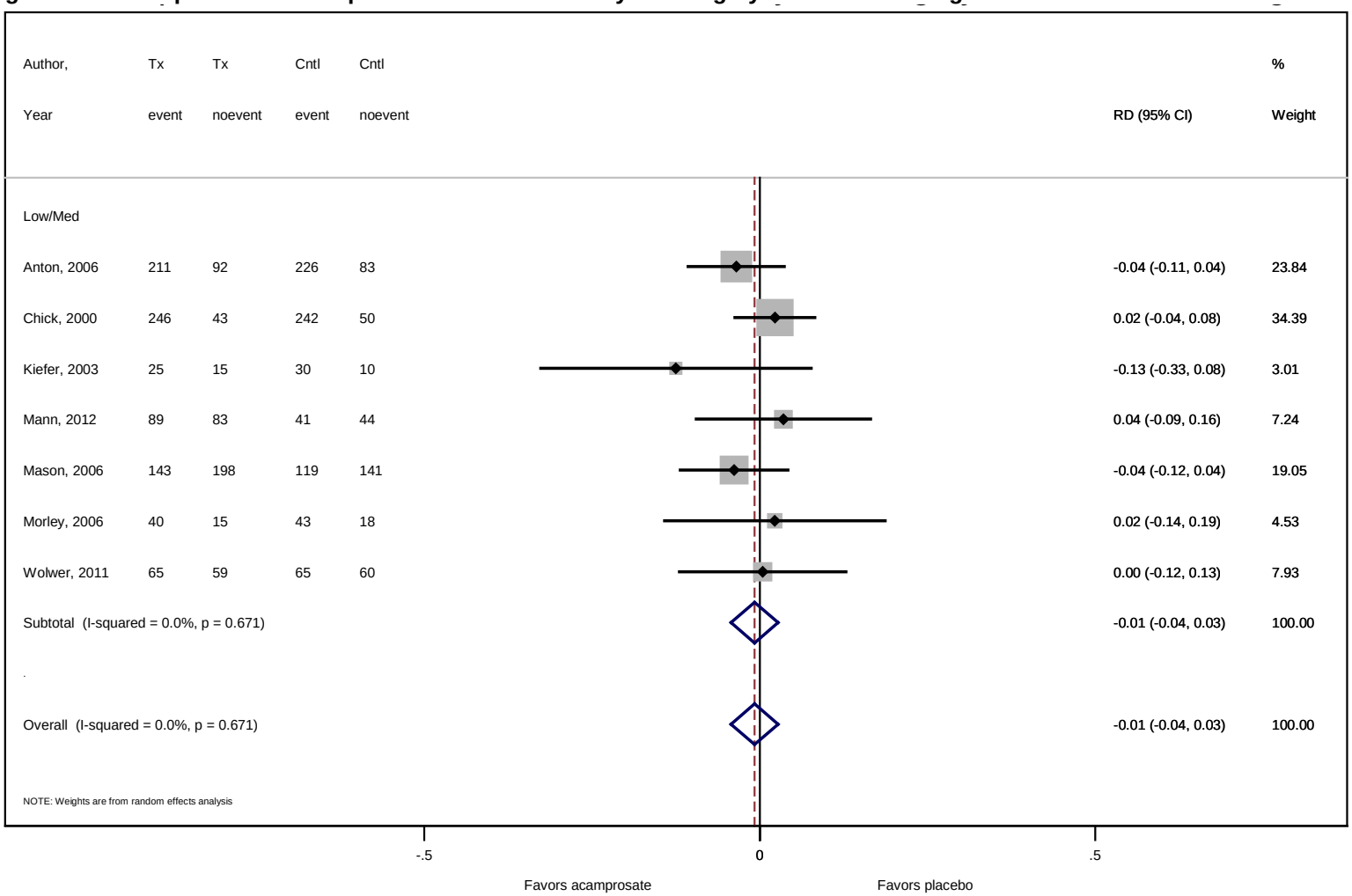
Note: doses combined for Mason, 2006, Paille, 1995, and Pelc, 1997.

Figure F-3. Acamprosate versus placebo: Return to any drinking by duration of treatment



Note: doses combined for Mason, 2006, Paille, 1995, and Pelc, 1997.

Figure F-4. Acamprosate versus placebo: Return to heavy drinking by risk of bias rating



Note: doses combined for Mason, 2006

Figure F-5. Acamprosate versus placebo: Percent drinking days by risk of bias rating

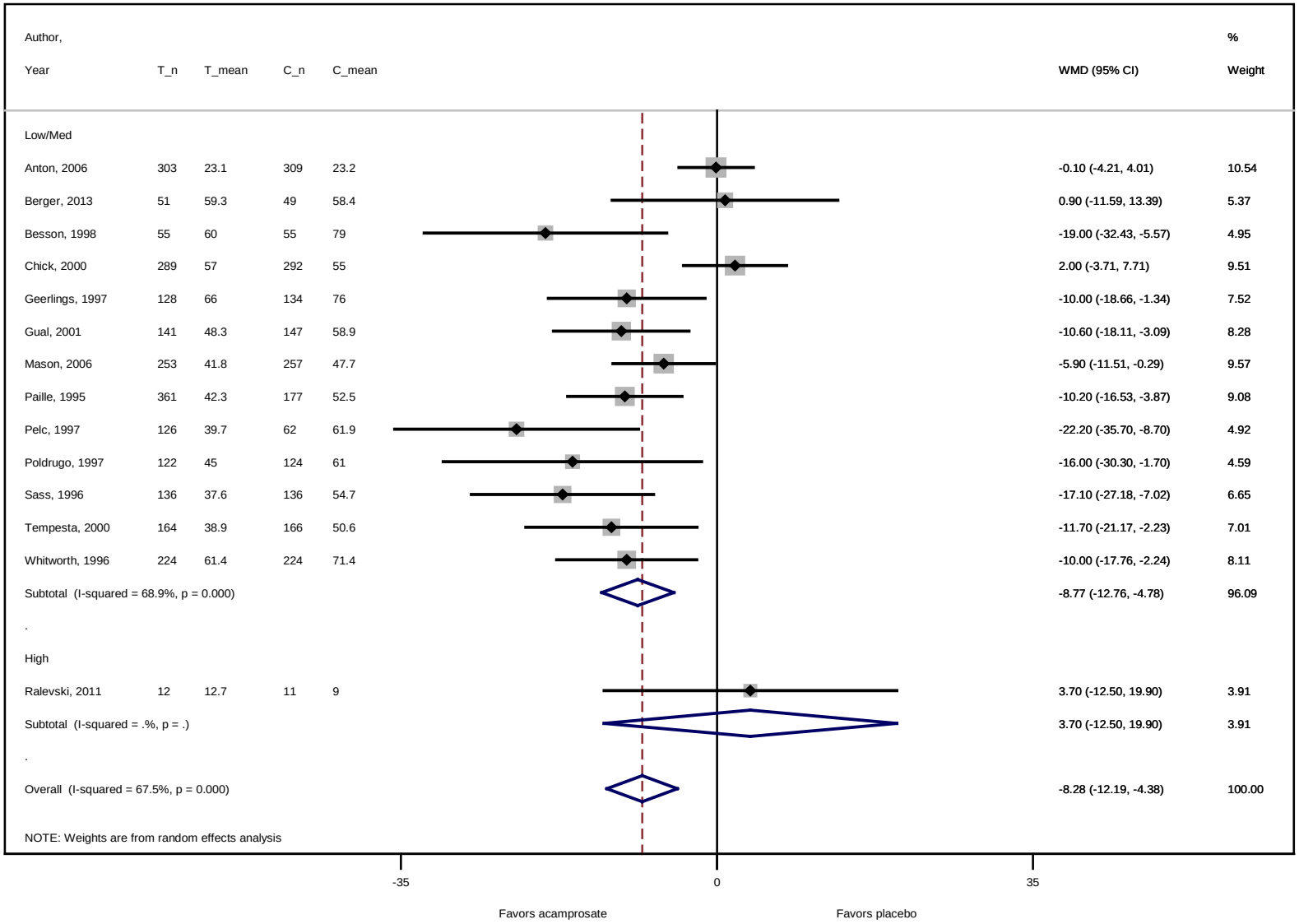


Figure F-6. Acamprosate versus placebo: Percent drinking days by country

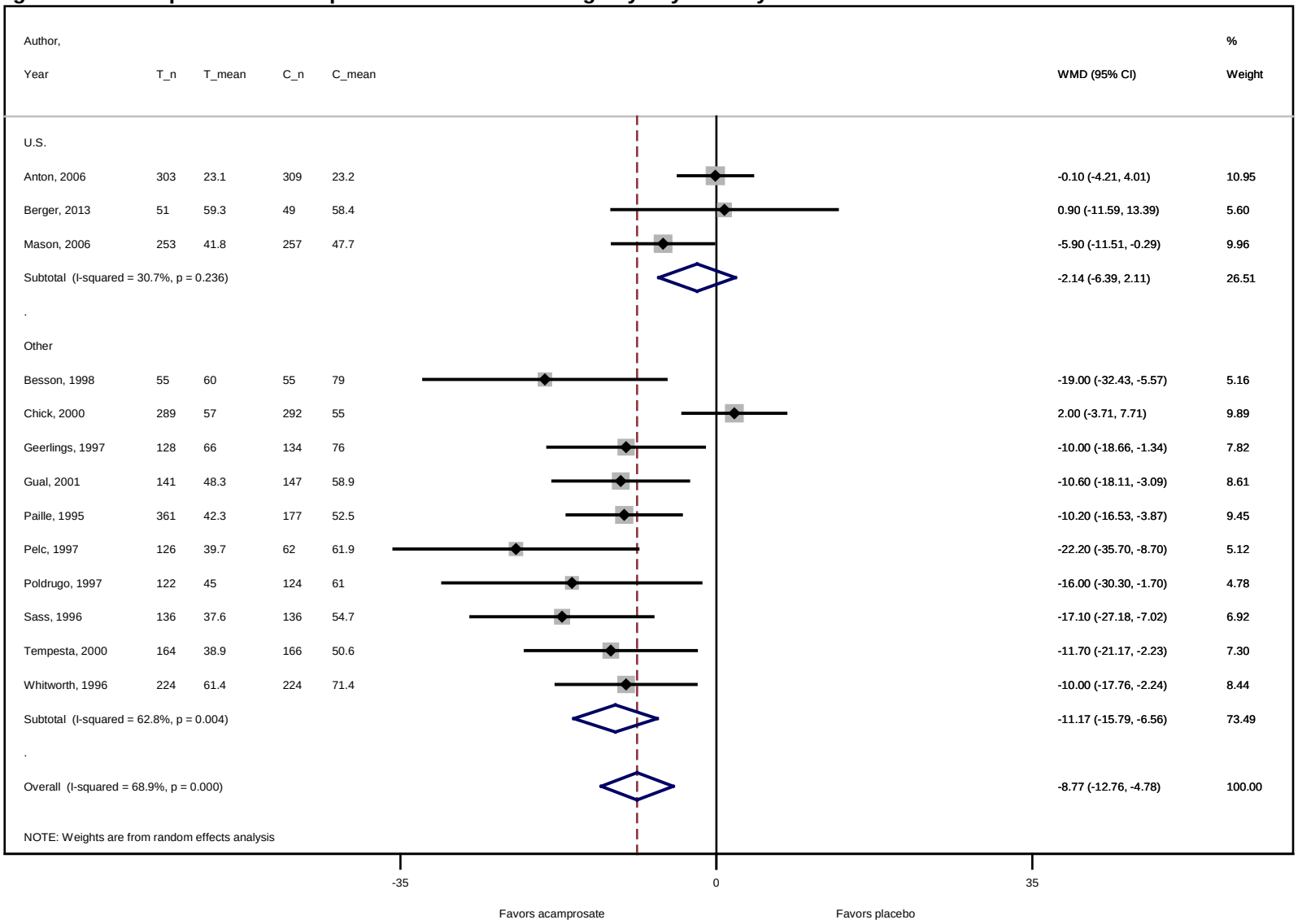


Figure F-7. Acamprosate versus placebo: Percent drinking days by duration of treatment

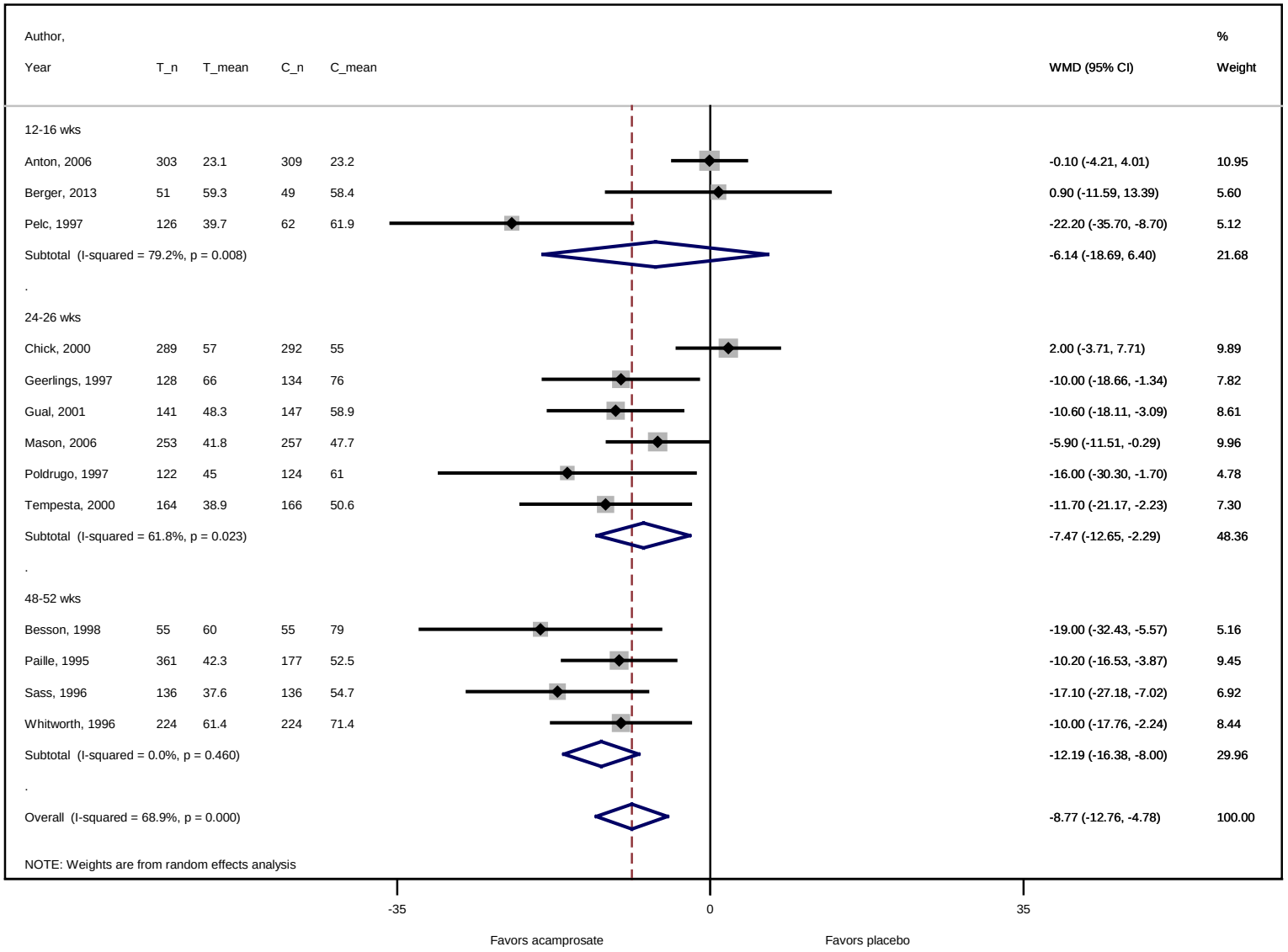


Figure F-8. Acamprosate versus placebo: Percent drinking days by dual diagnosis (low/medium risk of bias only)

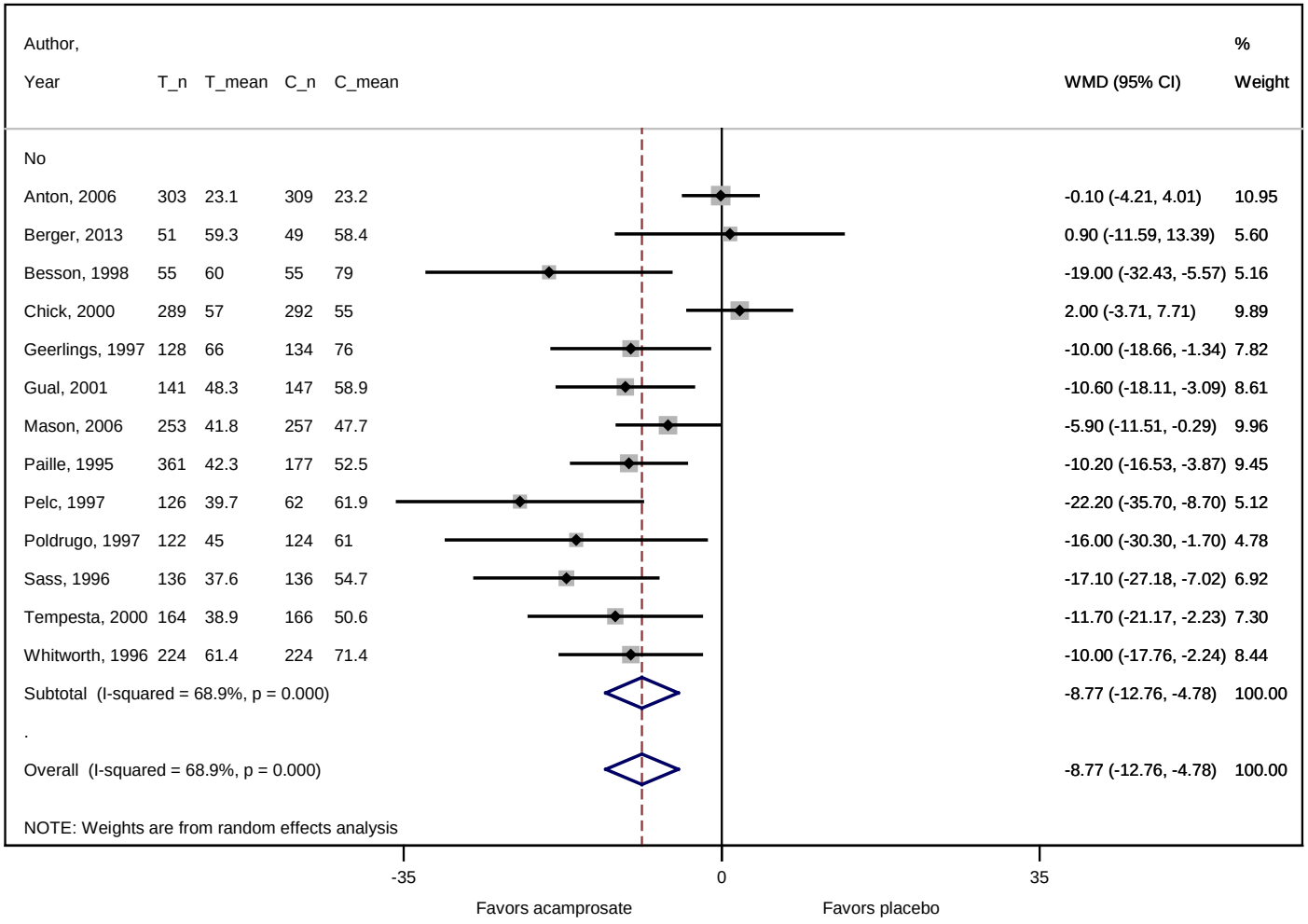


Figure F-9. Acamprosate versus placebo: Percent drinking days by dual diagnosis (all risk of bias)

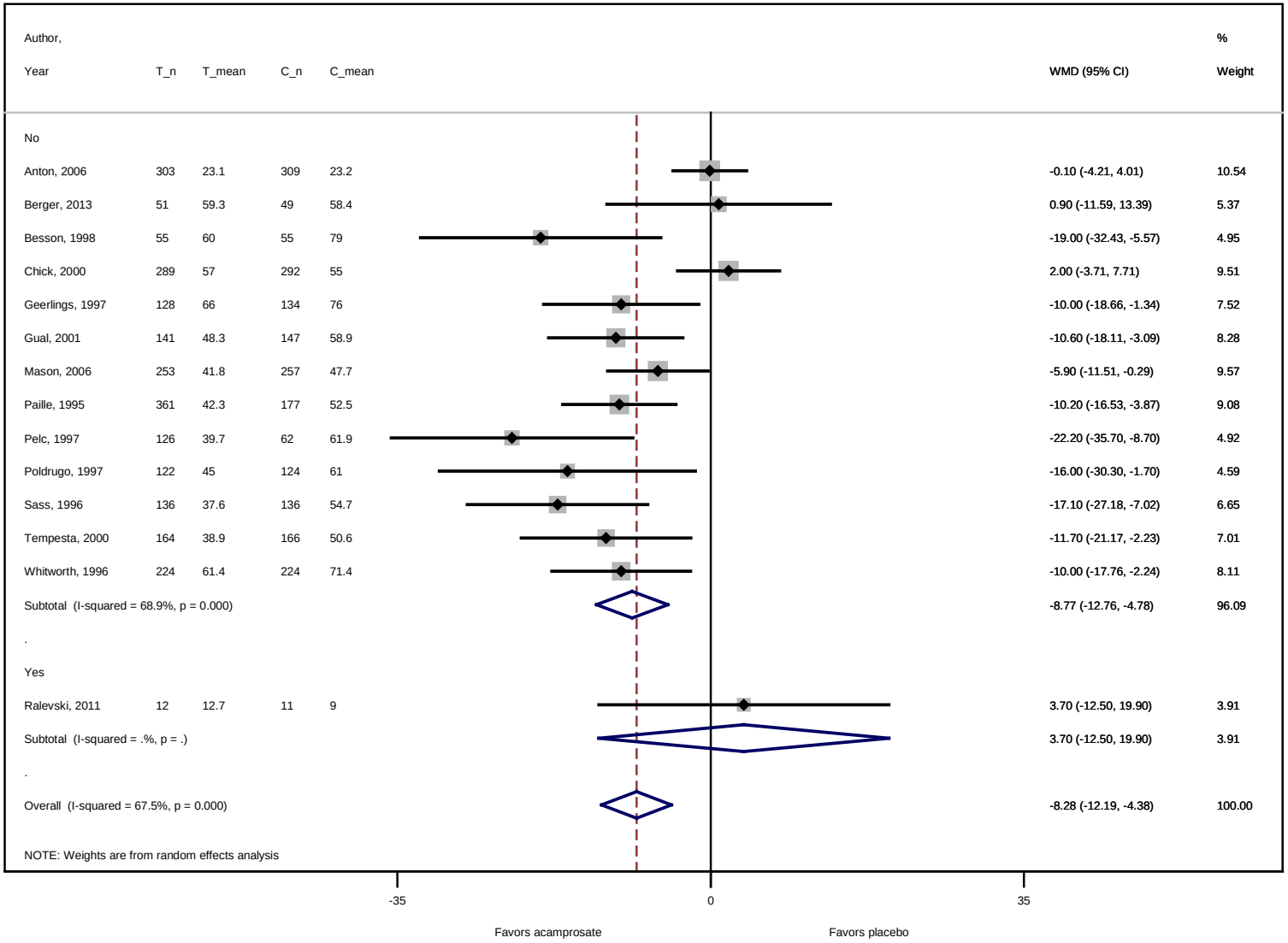


Figure F-10. Acamprosate versus placebo: Percent heavy drinking days by risk of bias

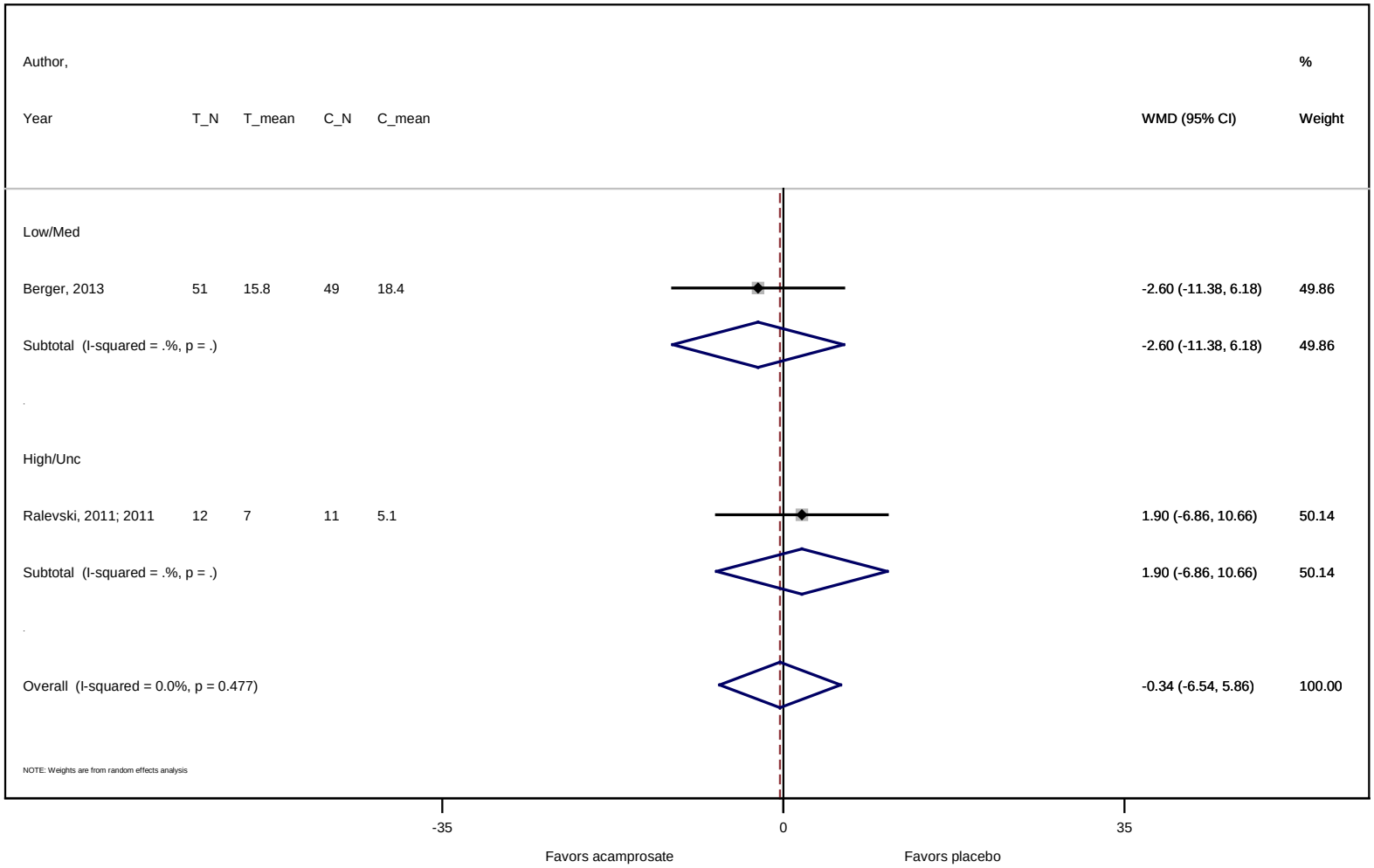
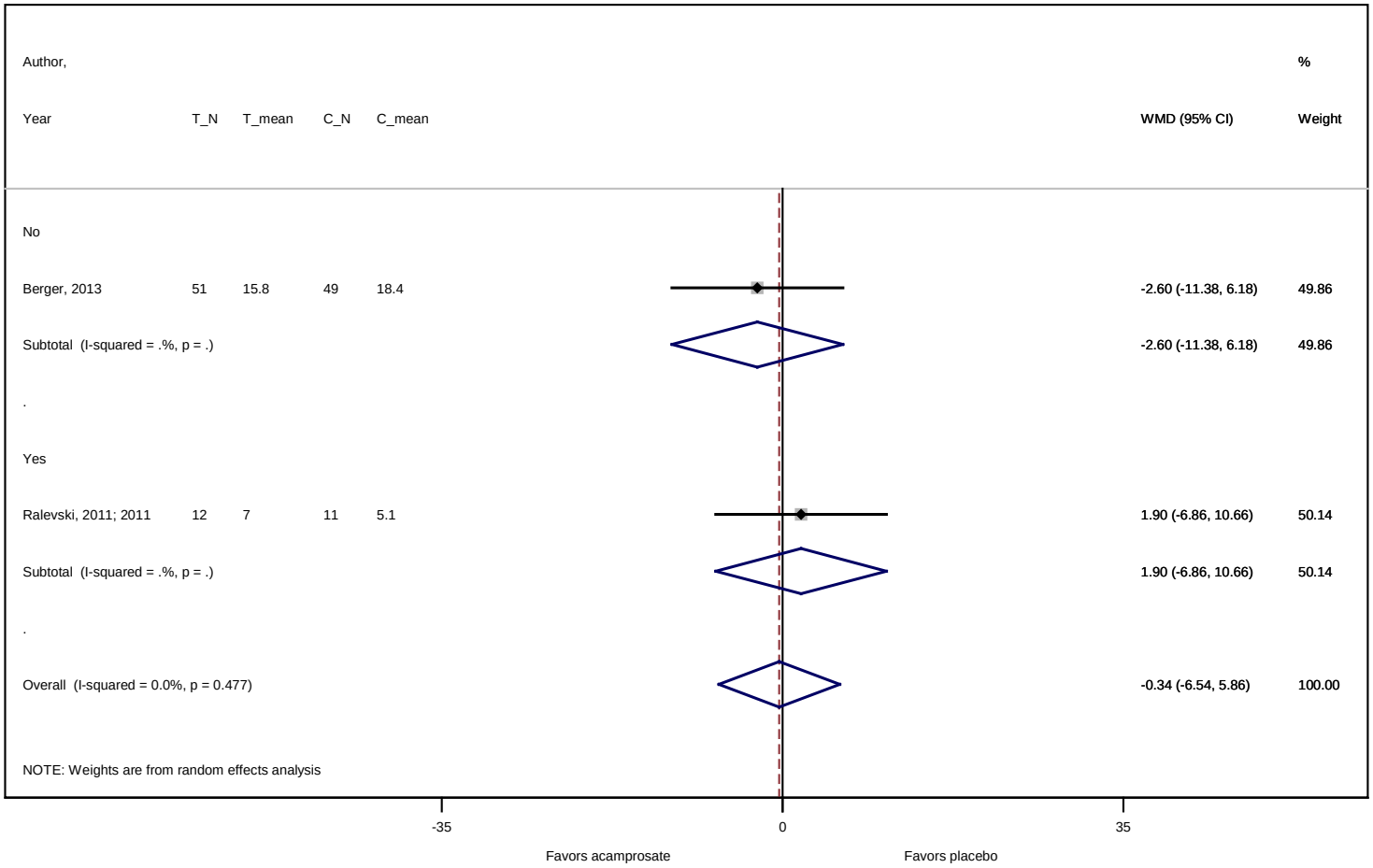


Figure F-11. Acamprosate versus placebo: Percent heavy drinking days by dual diagnosis



Note: Berger is low/medium risk of bias; Ralevski is high risk of bias

Figure F-12. Acamprosate versus placebo: Drinks per drinking day by risk of bias

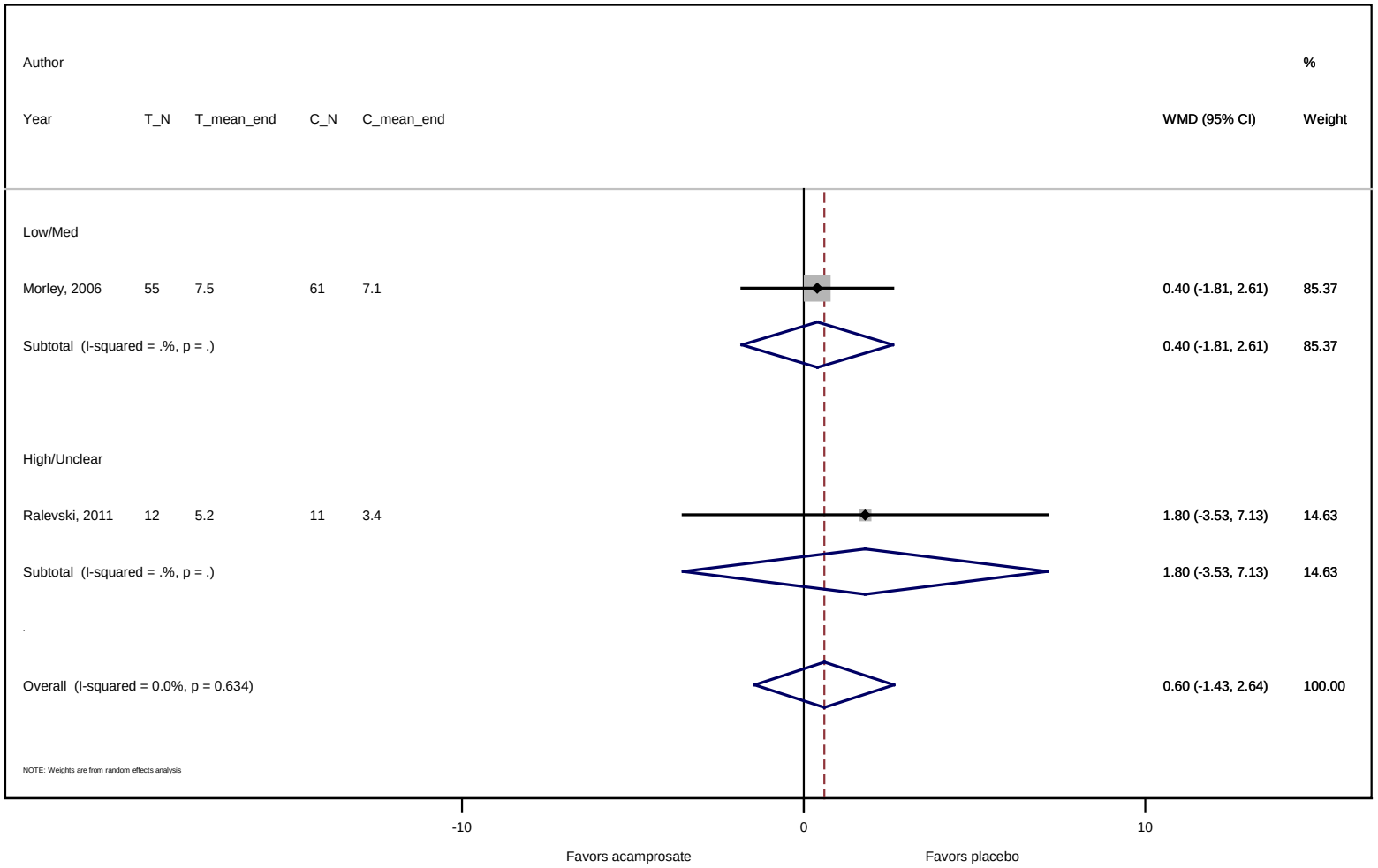
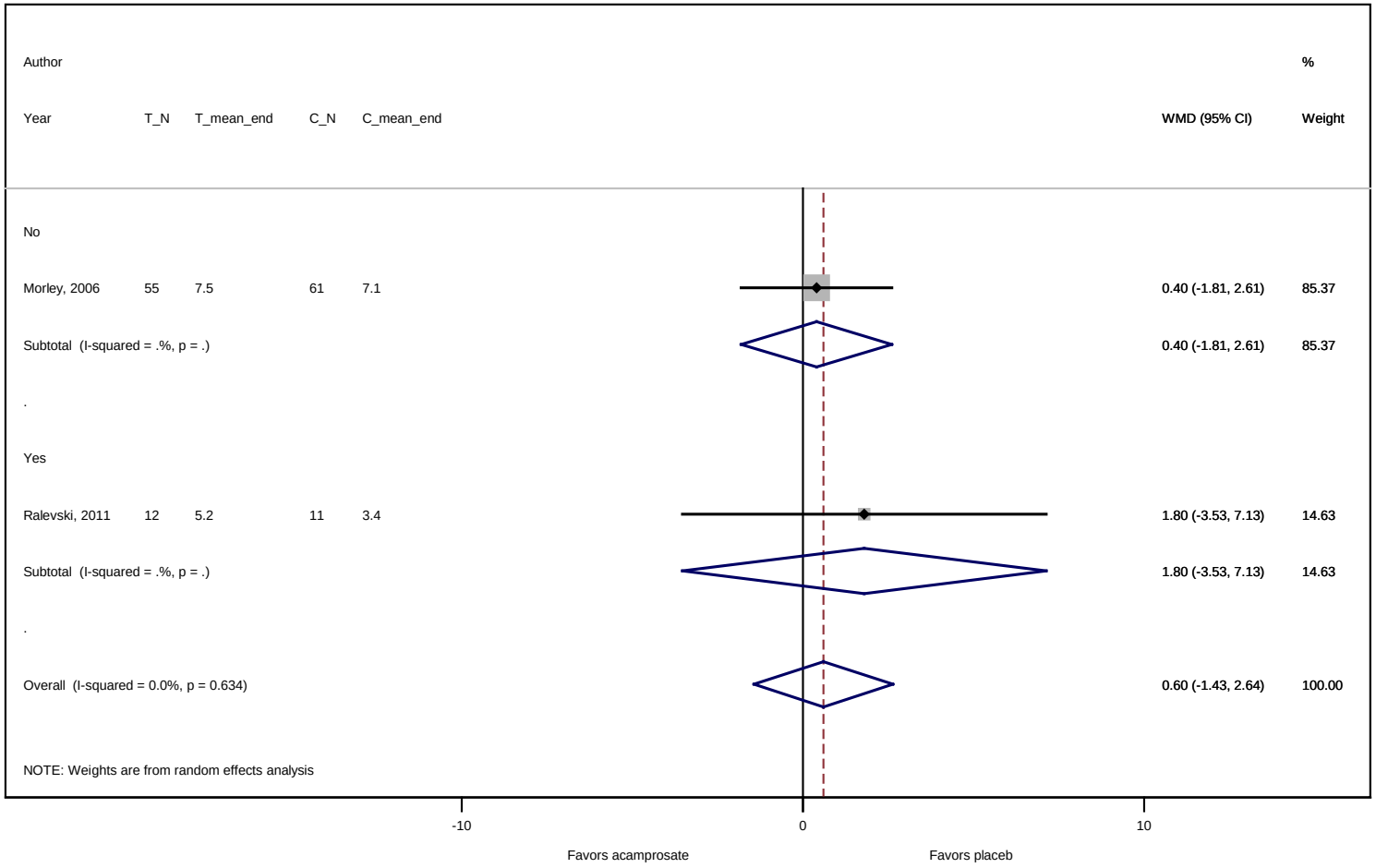
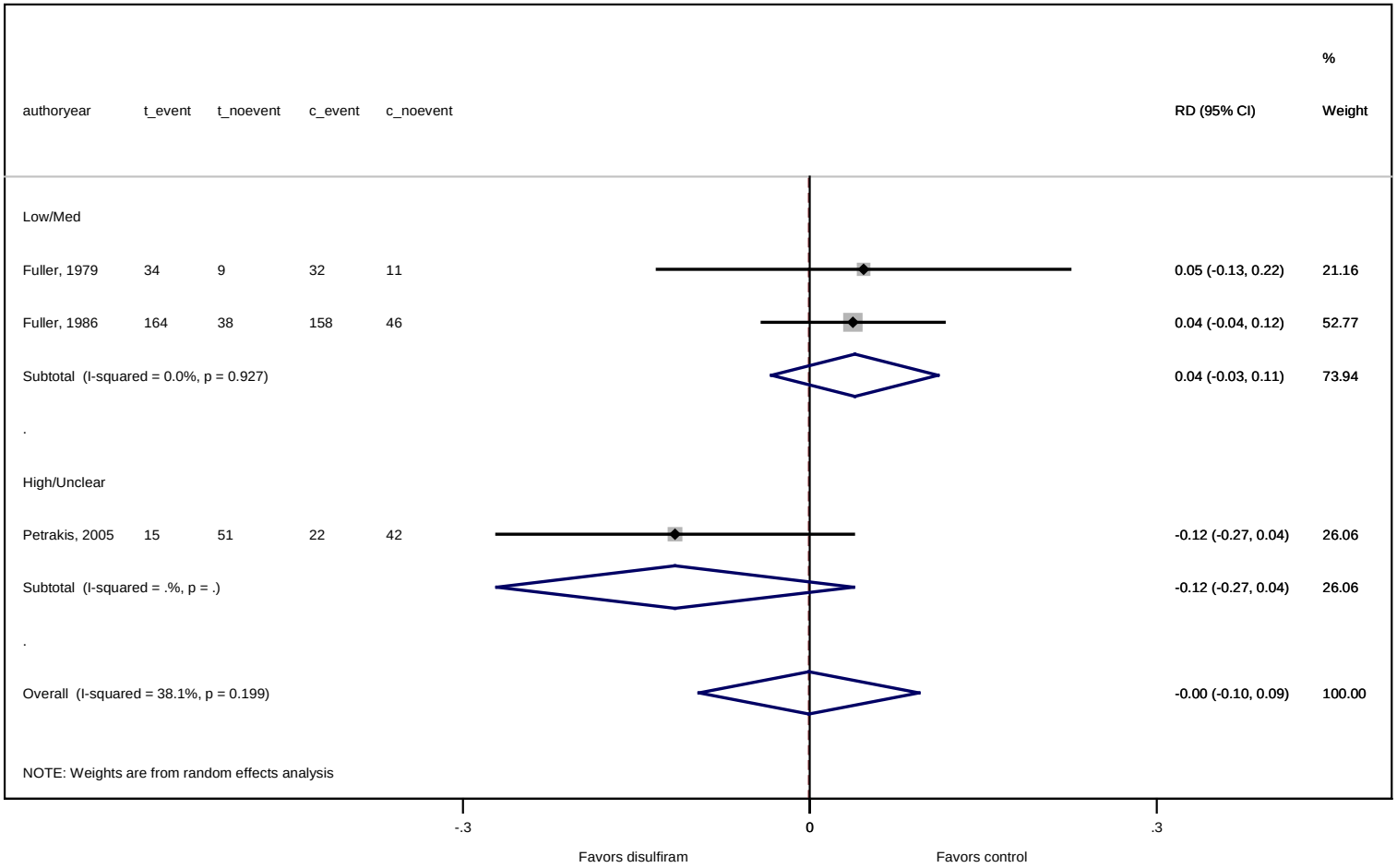


Figure F-13. Acamprosate versus placebo: Drinks per drinking day by dual diagnosis



Note: Morley is low/medium risk of bias; Ralevski is high risk of bias

Figure F-14. Disulfiram versus control: Return to any drinking by risk of bias



Note: Control - Fuller, 1979 and Fuller, 1986 control = Disulfiram 1 mg; Petrakis, 2005 control = placebo

Figure F-15. Disulfiram versus no disulfiram: Return to any drinking by risk of bias

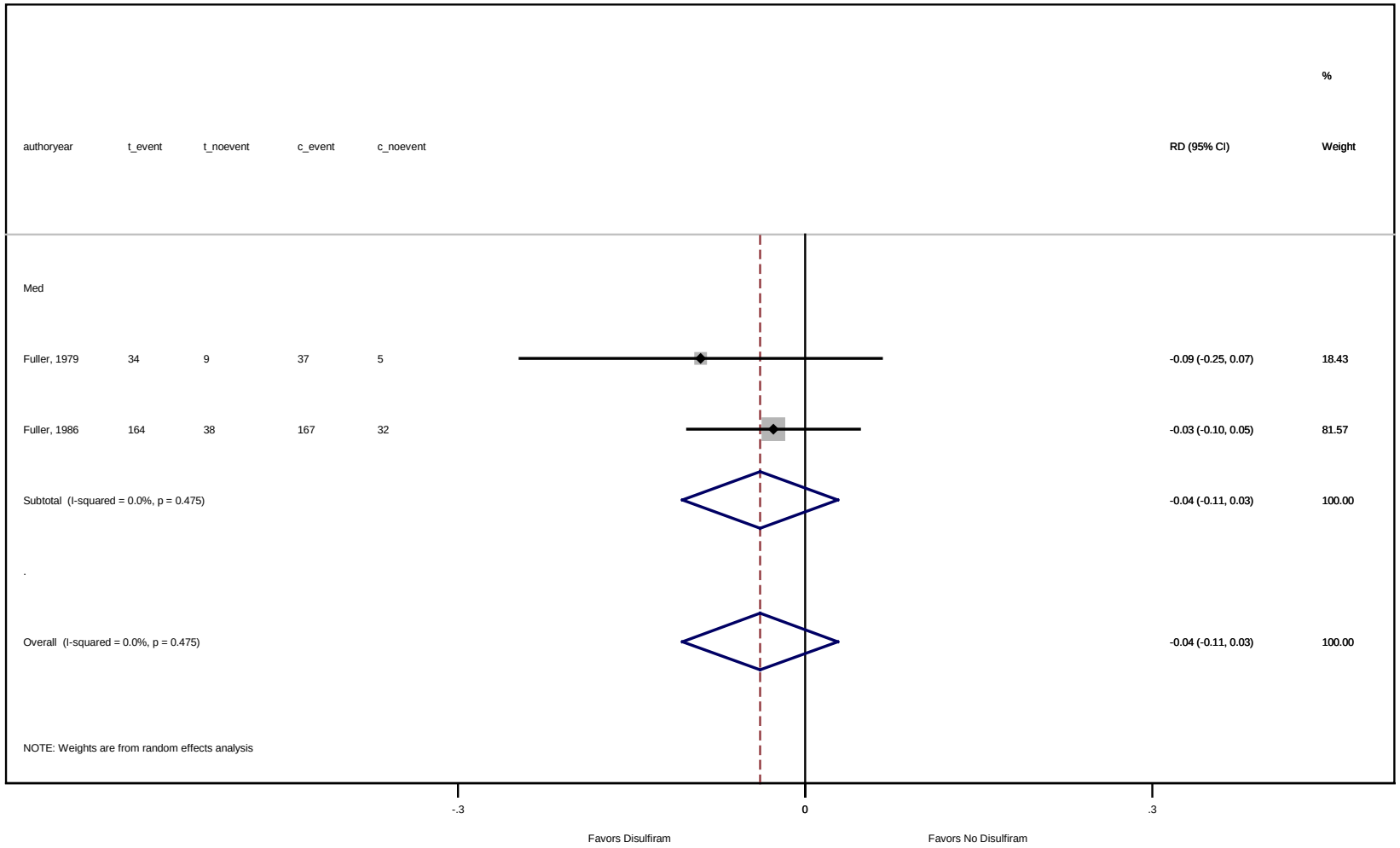
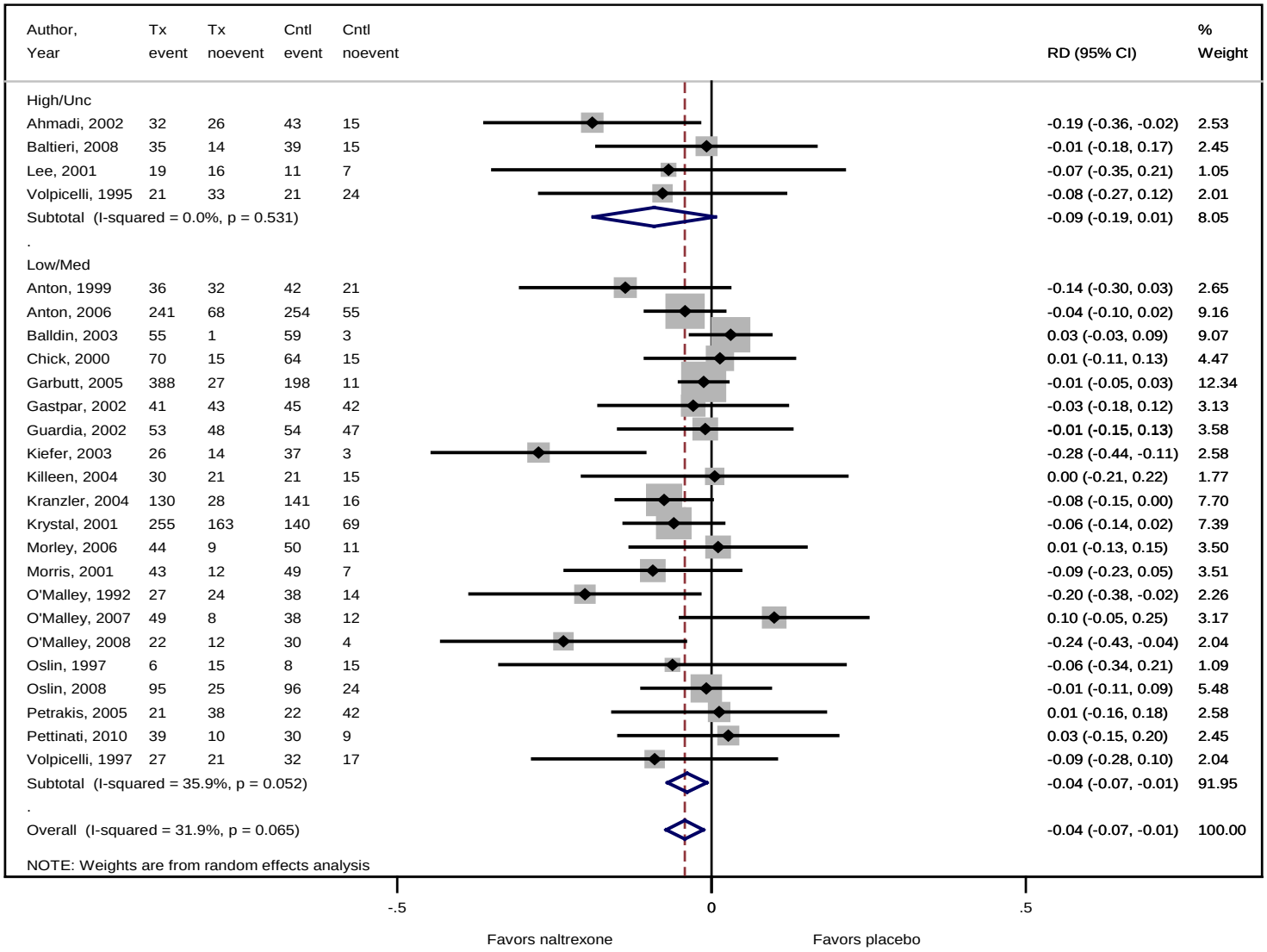


Figure F-16. Naltrexone versus placebo: Return to any drinking by risk of bias



Note: does not include Brown, 2009; doses combined for Garbutt, 2005; used data from Volpicelli 1995 (N=99) rather than the smaller subset (N=70) in Volpicelli 1992 to avoid double counting.

Figure F-17. Naltrexone versus placebo: Return to any drinking by country

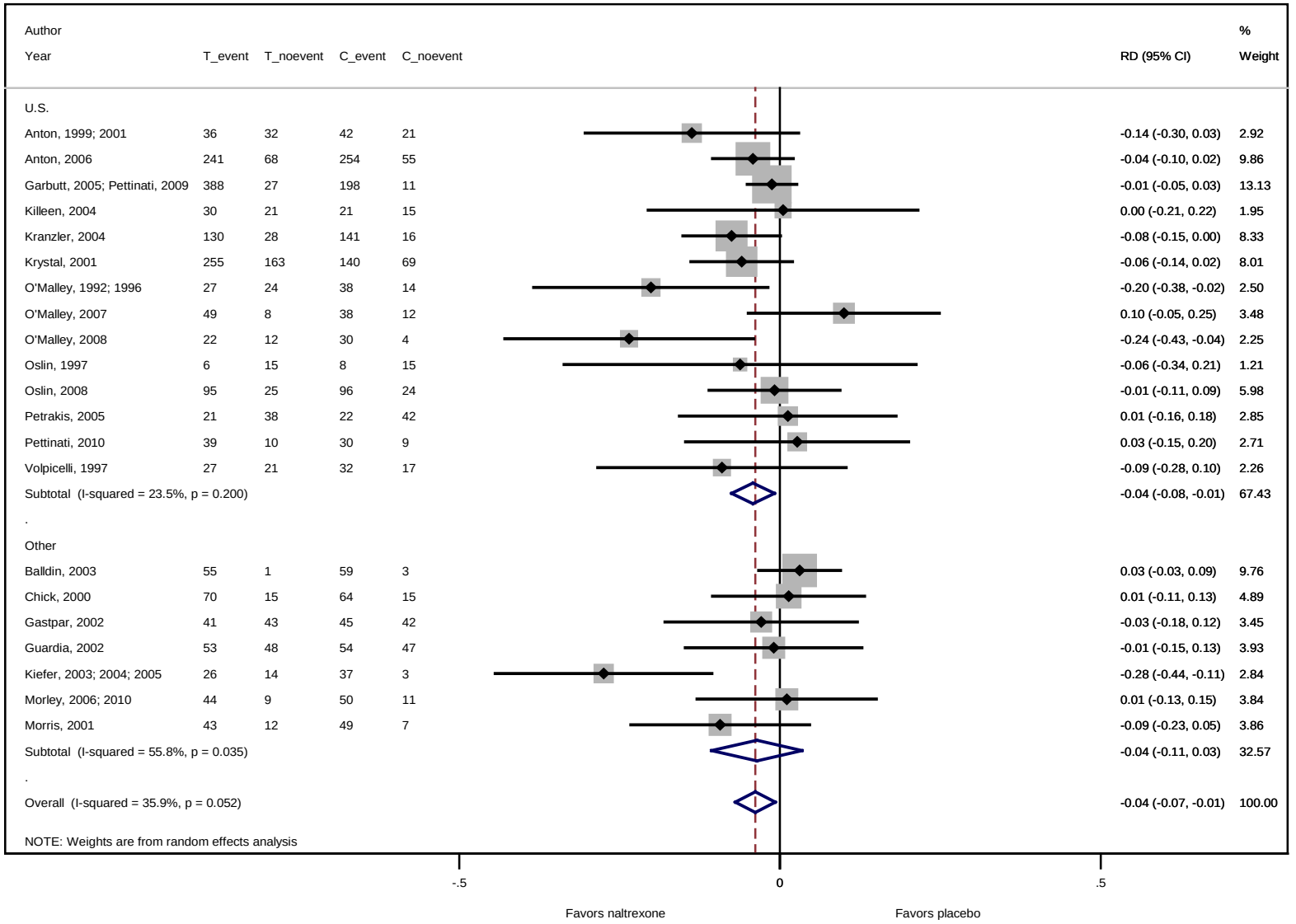


Figure F-18. Naltrexone versus placebo: Return to any drinking by duration of treatment

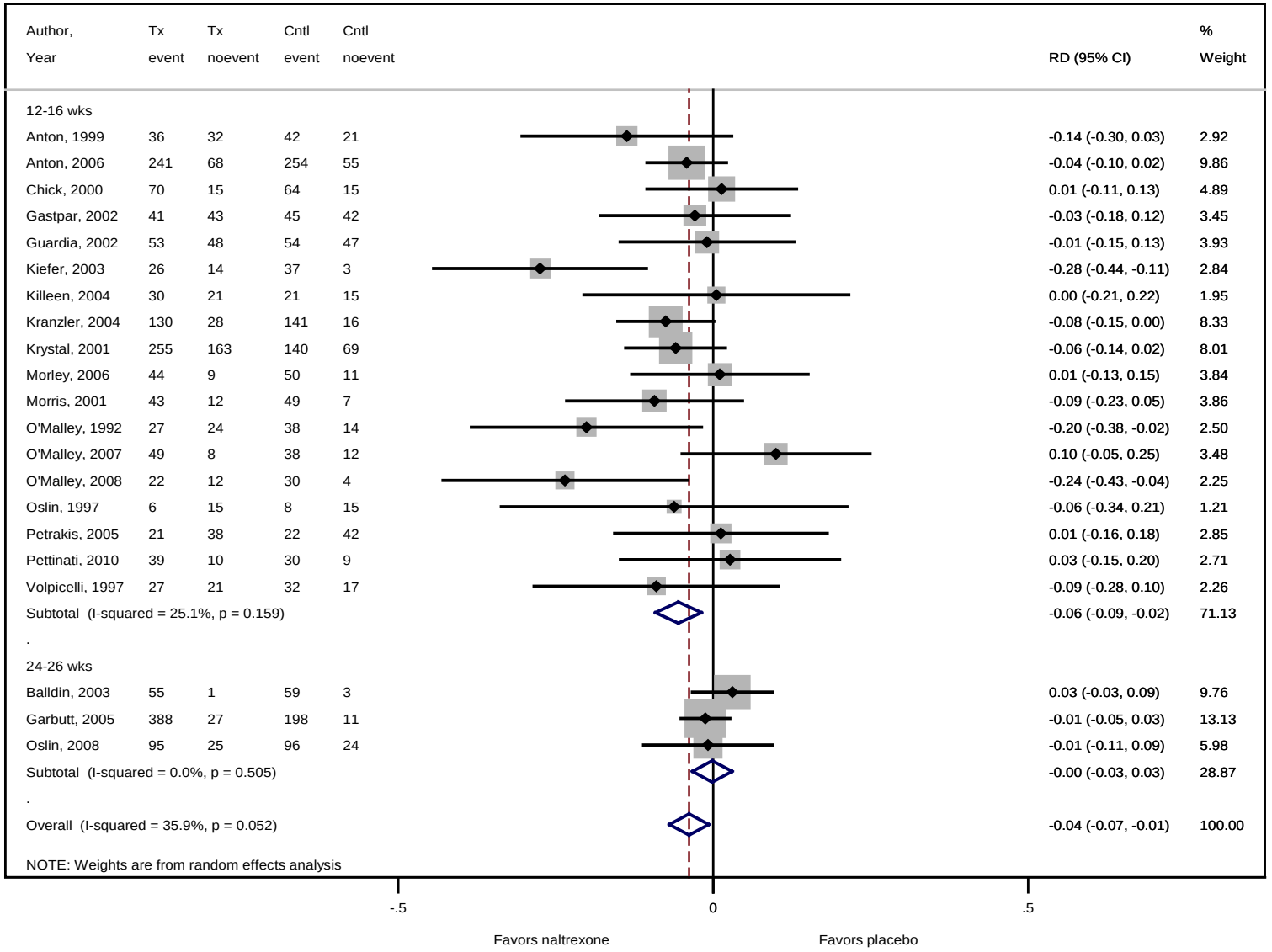
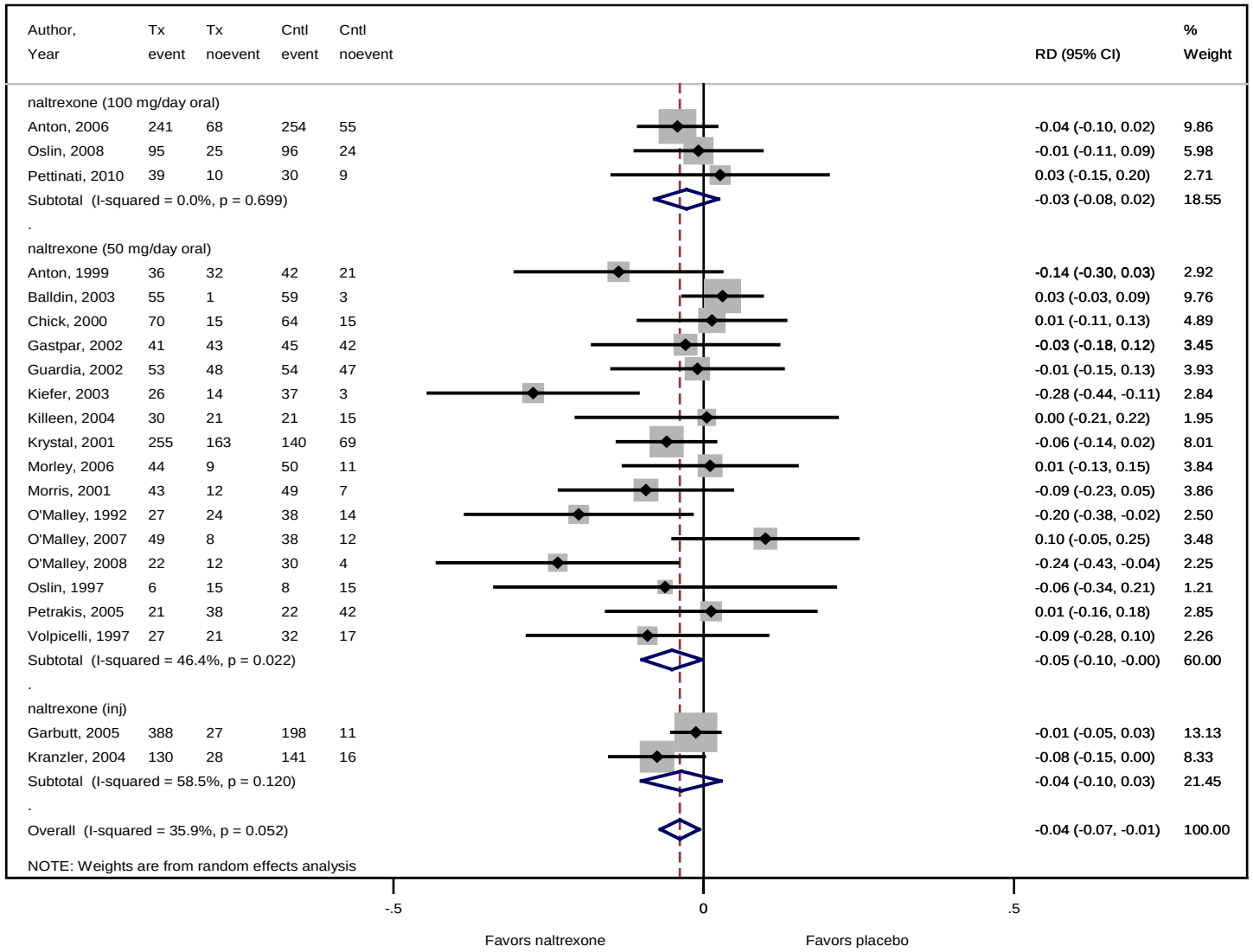


Figure F-19. Naltrexone versus placebo: Return to any drinking by naltrexone dose



Note: Dose for Oslin, 1997 represents an average of 50 mg.day; study participants received 100 mg two times per week and 150 mg one time per week.

Figure F-20. Naltrexone versus placebo: Return to any drinking by dual diagnosis (low/medium risk of bias only)

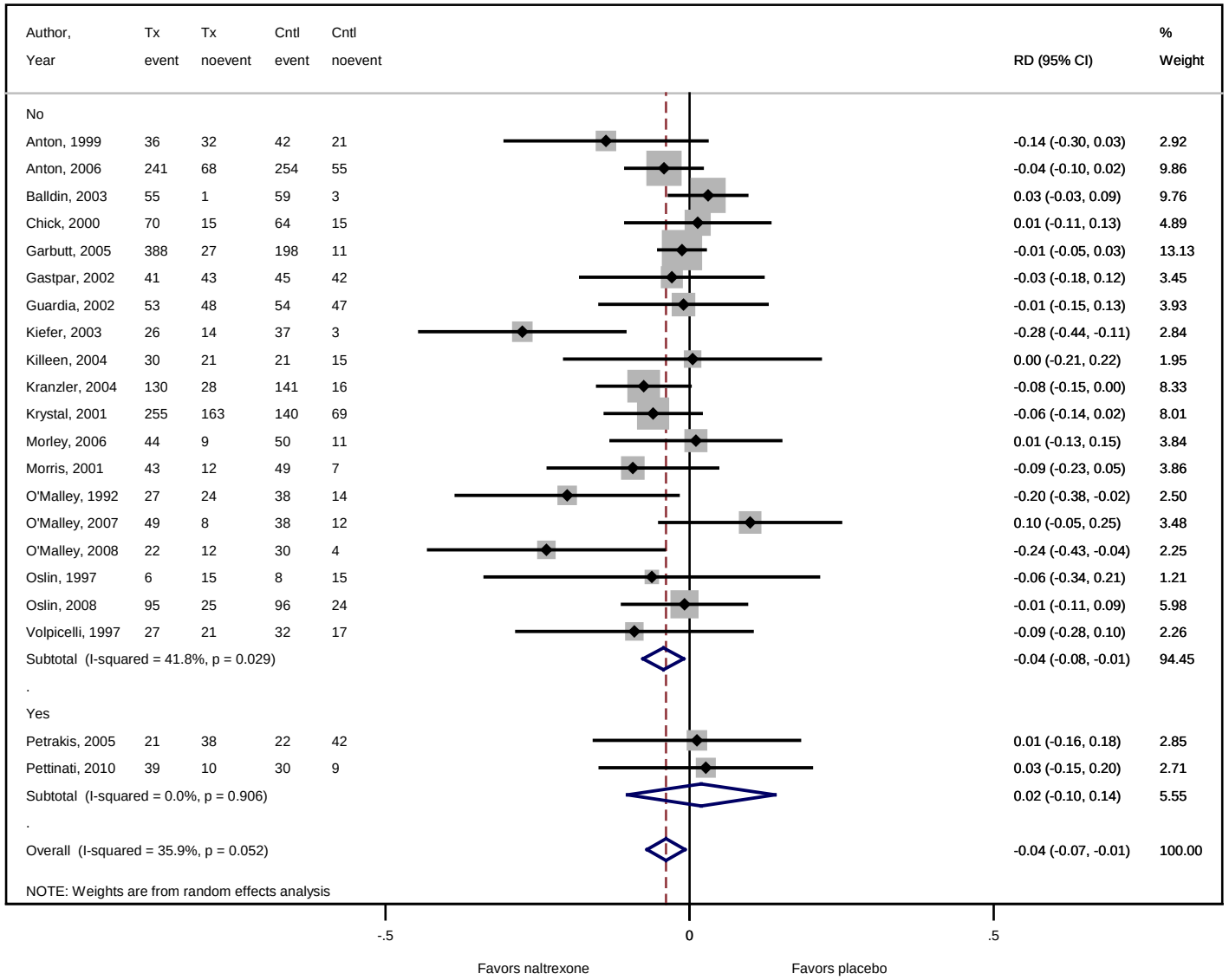


Figure F-21. Naltrexone versus placebo: Return to any drinking by dual diagnosis (all risk of bias)

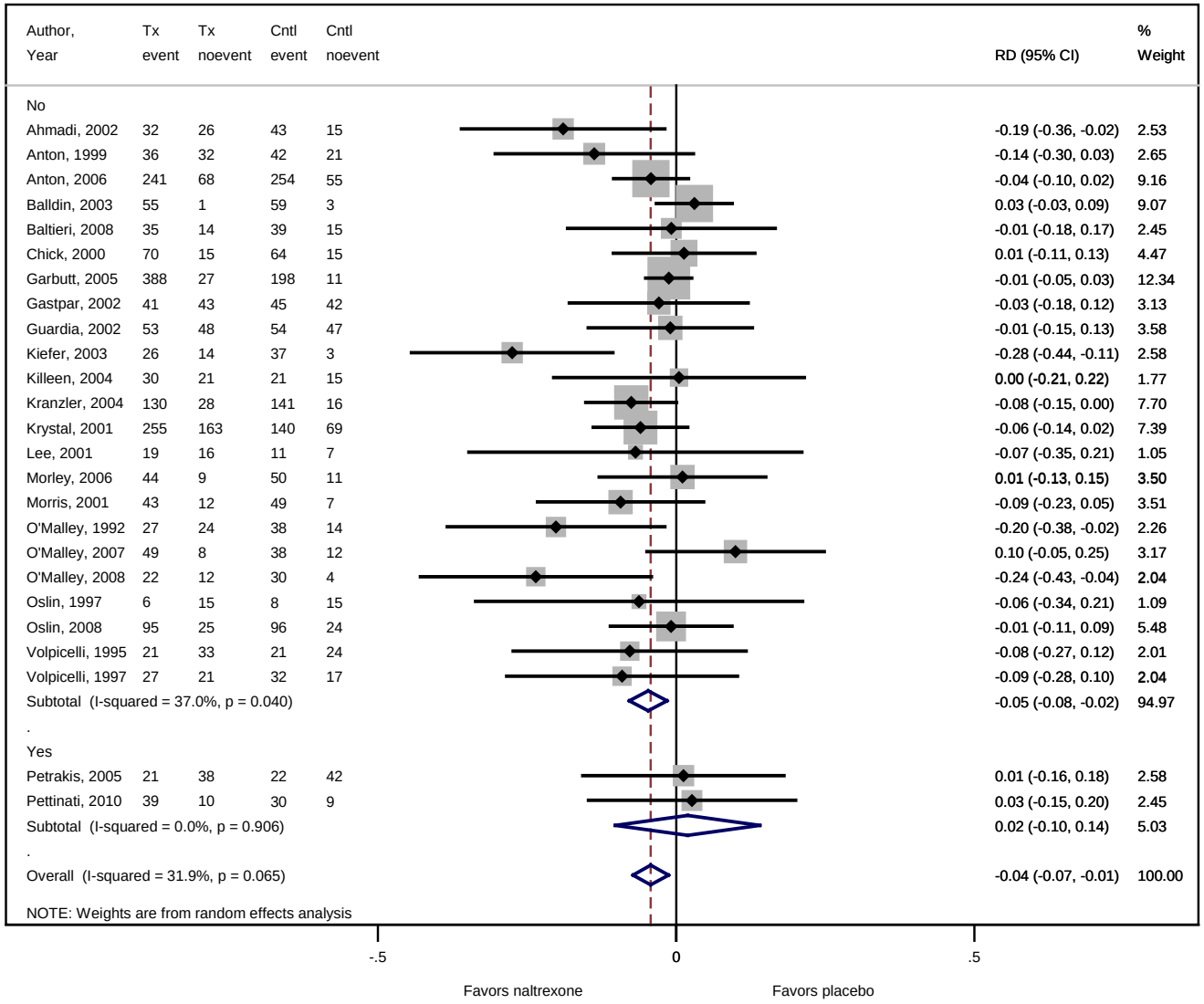
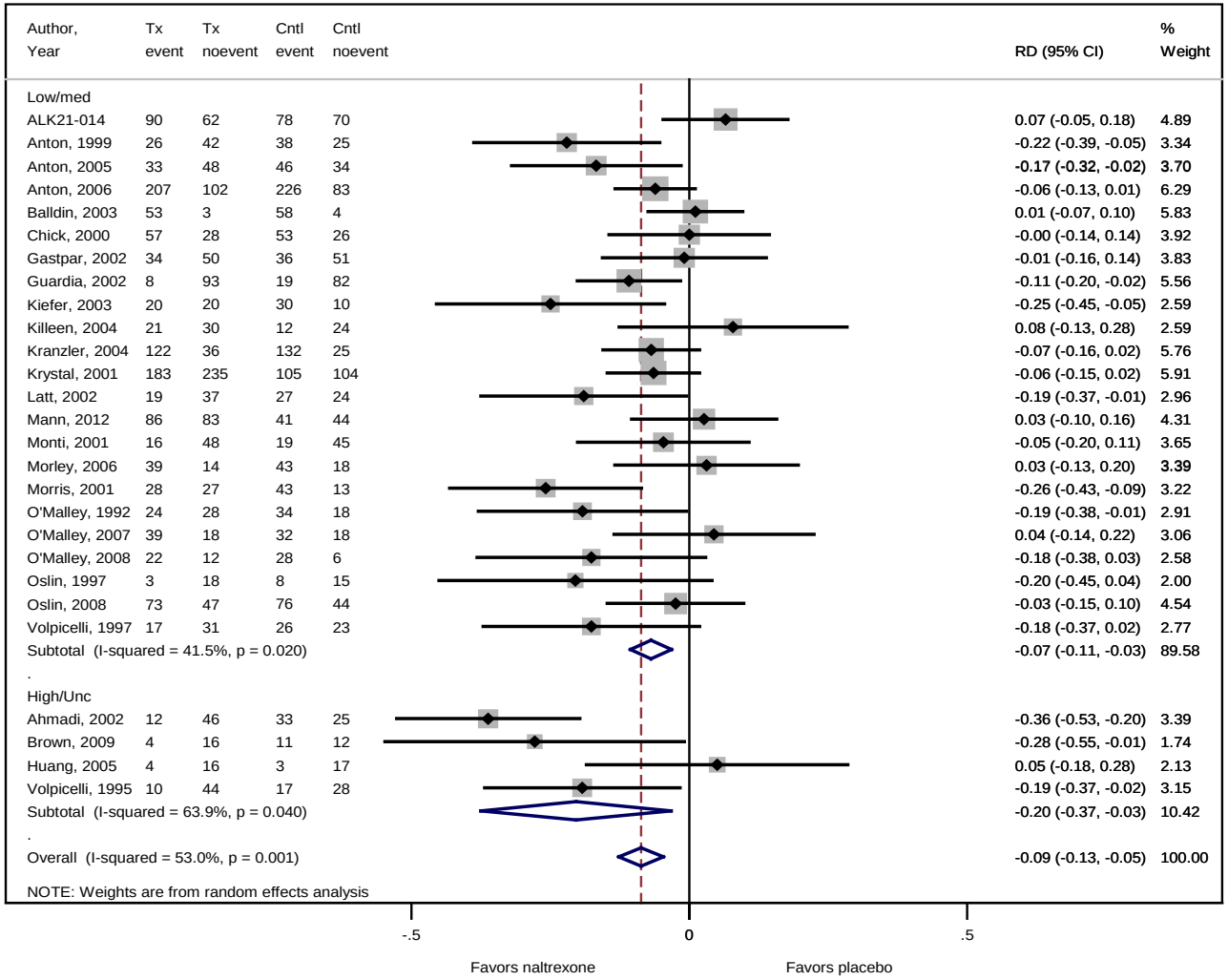


Figure F-22. Naltrexone versus placebo: Return to heavy drinking by risk of bias



Note: Used data from Volpicelli 1995 (N=99) rather than the smaller subset (N=70) in Volpicelli 1992 to avoid double counting

Figure F-23. Naltrexone versus placebo: Return to heavy drinking by country

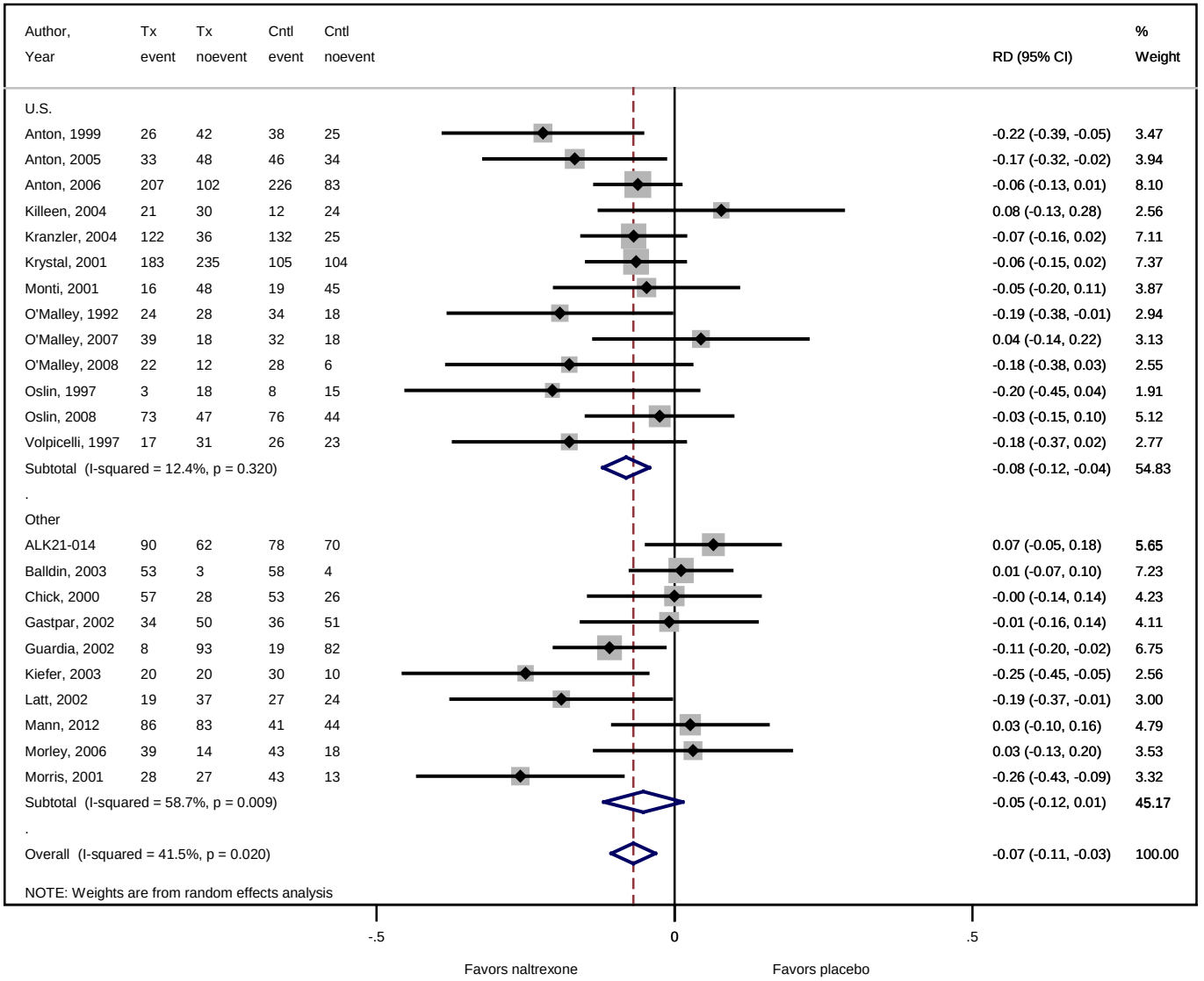


Figure F-24. Naltrexone versus placebo: Return to heavy drinking by duration of treatment

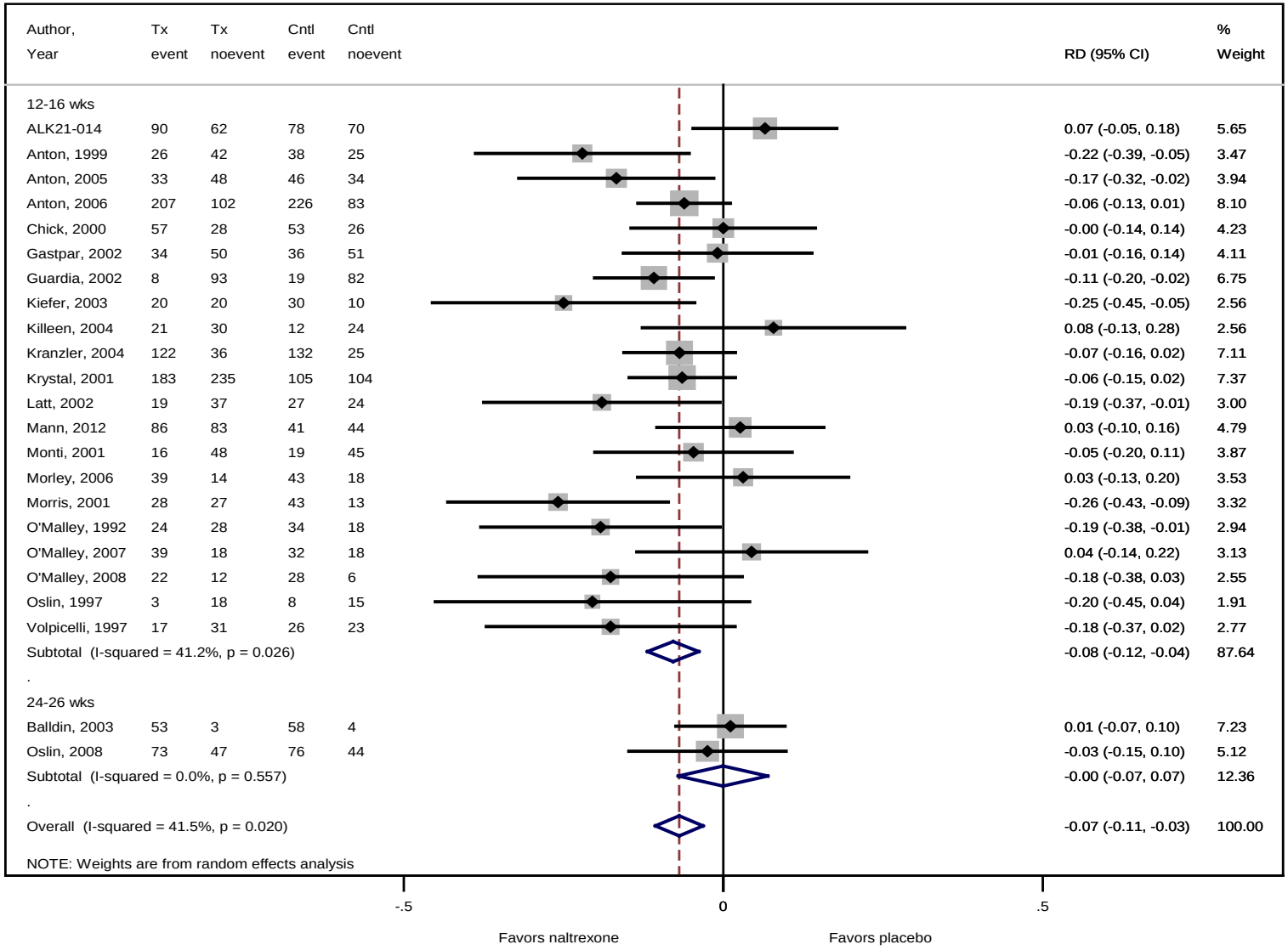
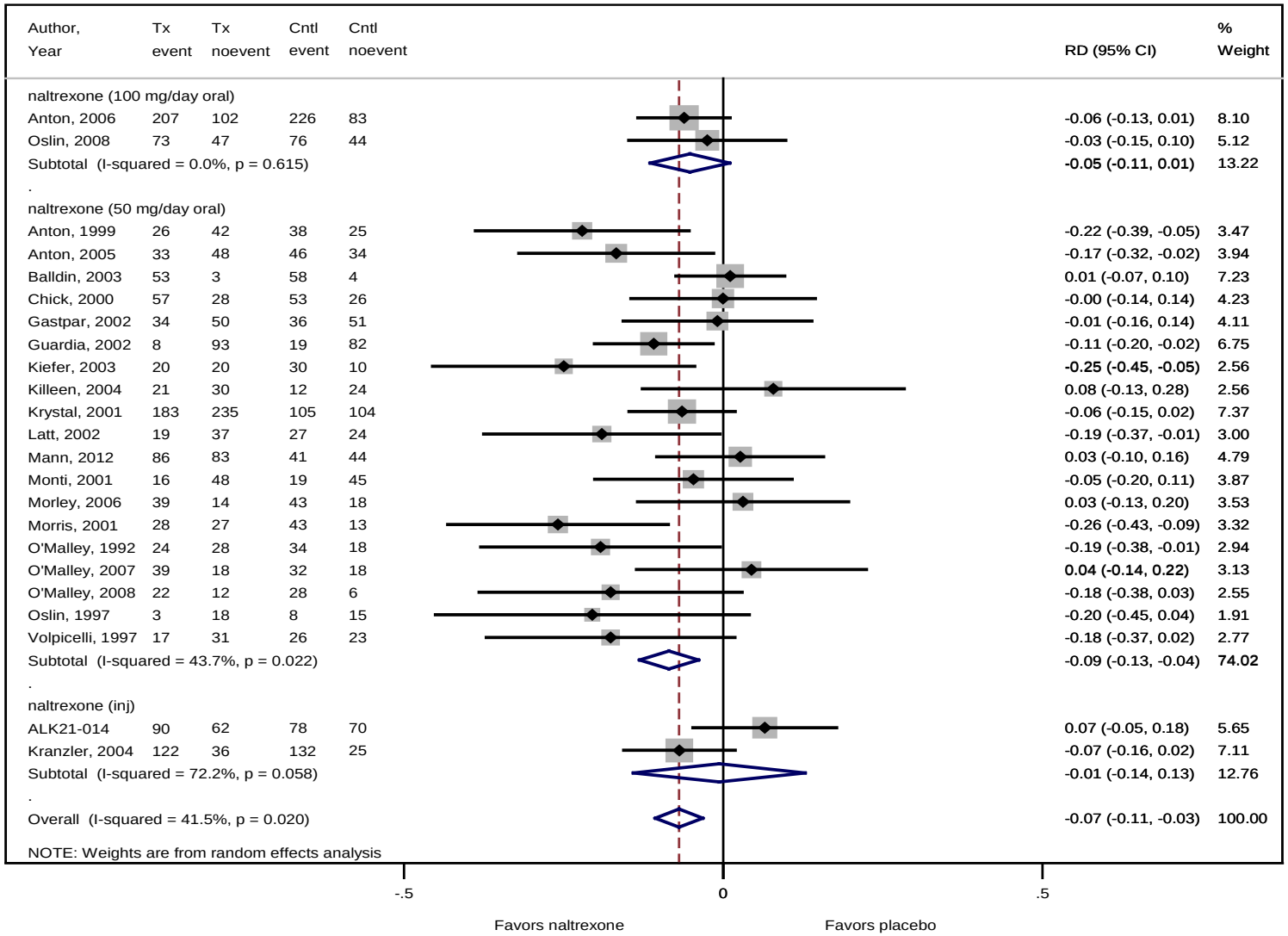


Figure F-25. Naltrexone versus placebo: Return to heavy drinking by naltrexone dose



Note: Dose for Oslin, 1997 represents an average of 50 mg.day; study participants received 100 mg two times per week and 150 mg one time per week.

Figure F-26. Naltrexone versus placebo: Return to heavy drinking by dual diagnosis (low/medium risk of bias only)

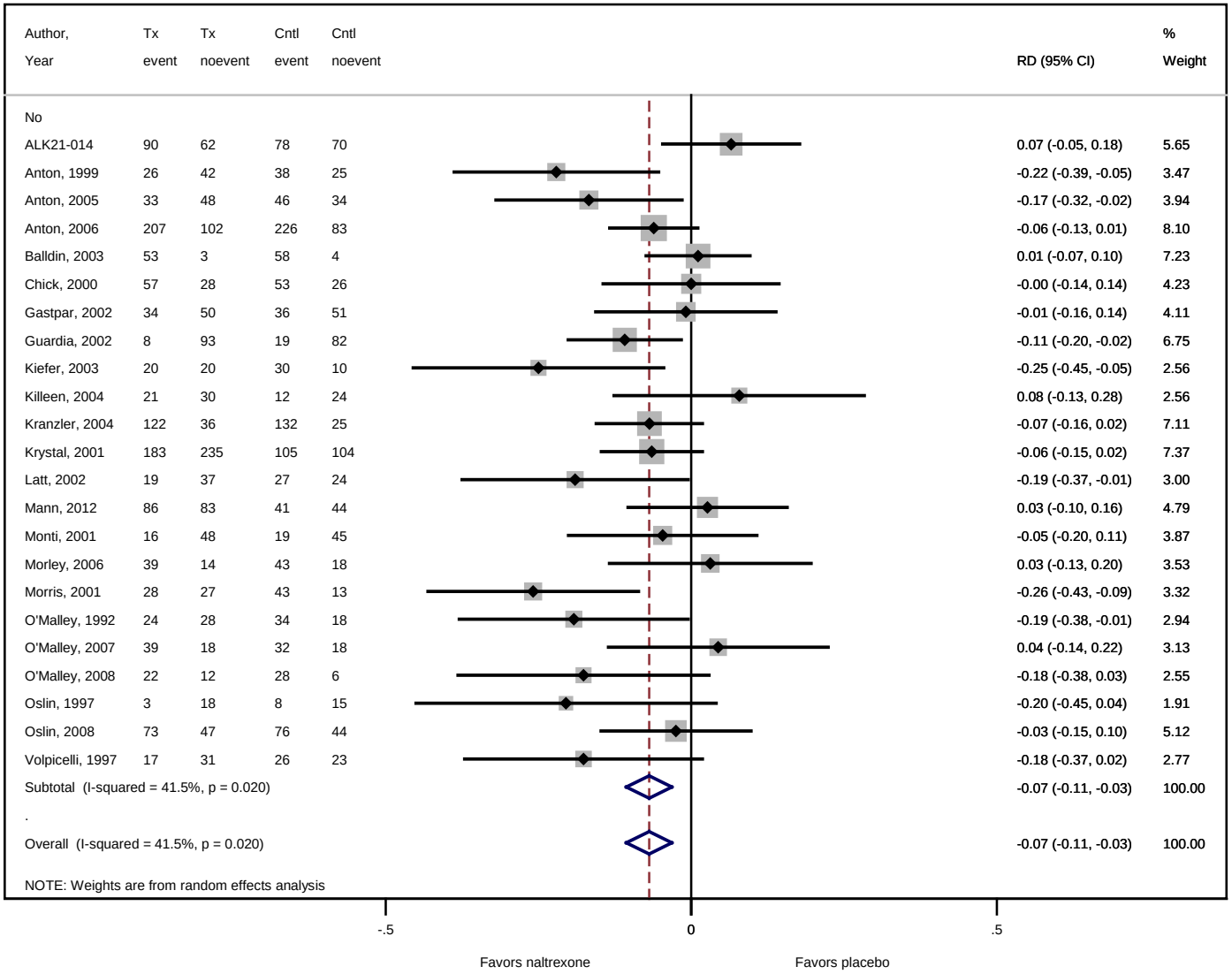


Figure F-27. Naltrexone versus placebo: Return to heavy drinking by dual diagnosis (all risk of bias)

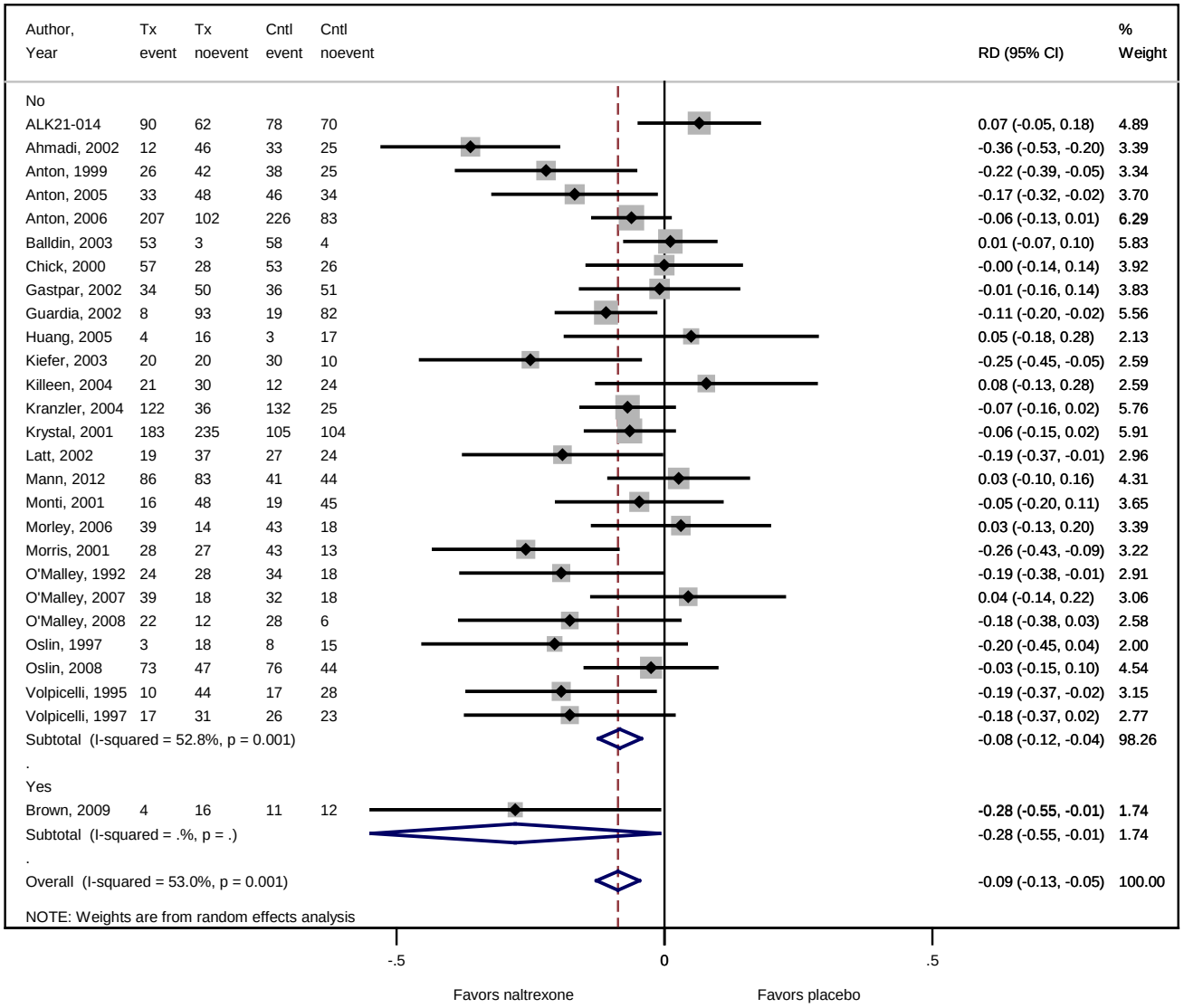
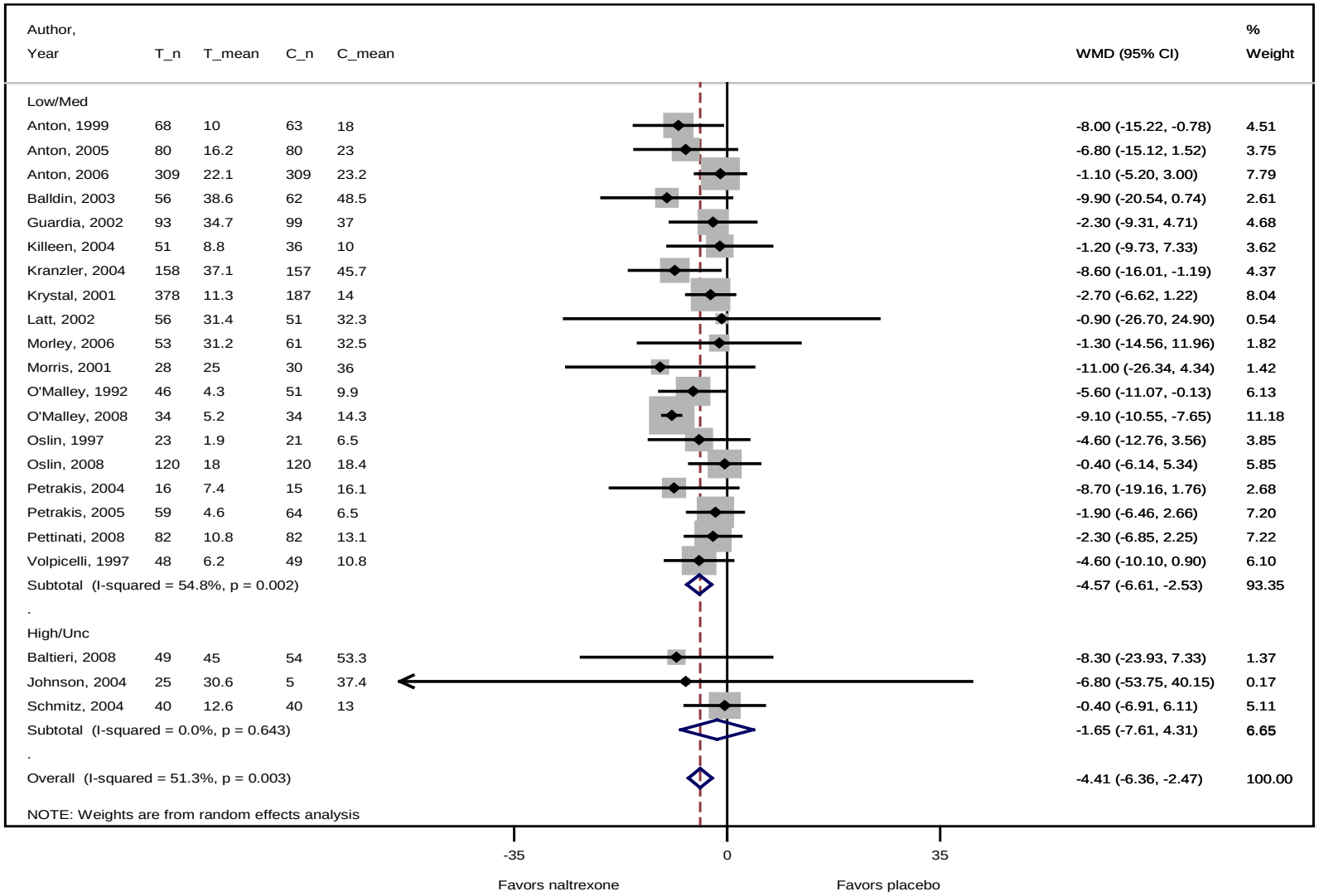


Figure F-28. Naltrexone versus placebo: Percent drinking days by risk of bias



Note: Brown, 2009 not included

Figure F-29. Naltrexone versus placebo: Percent drinking days by country

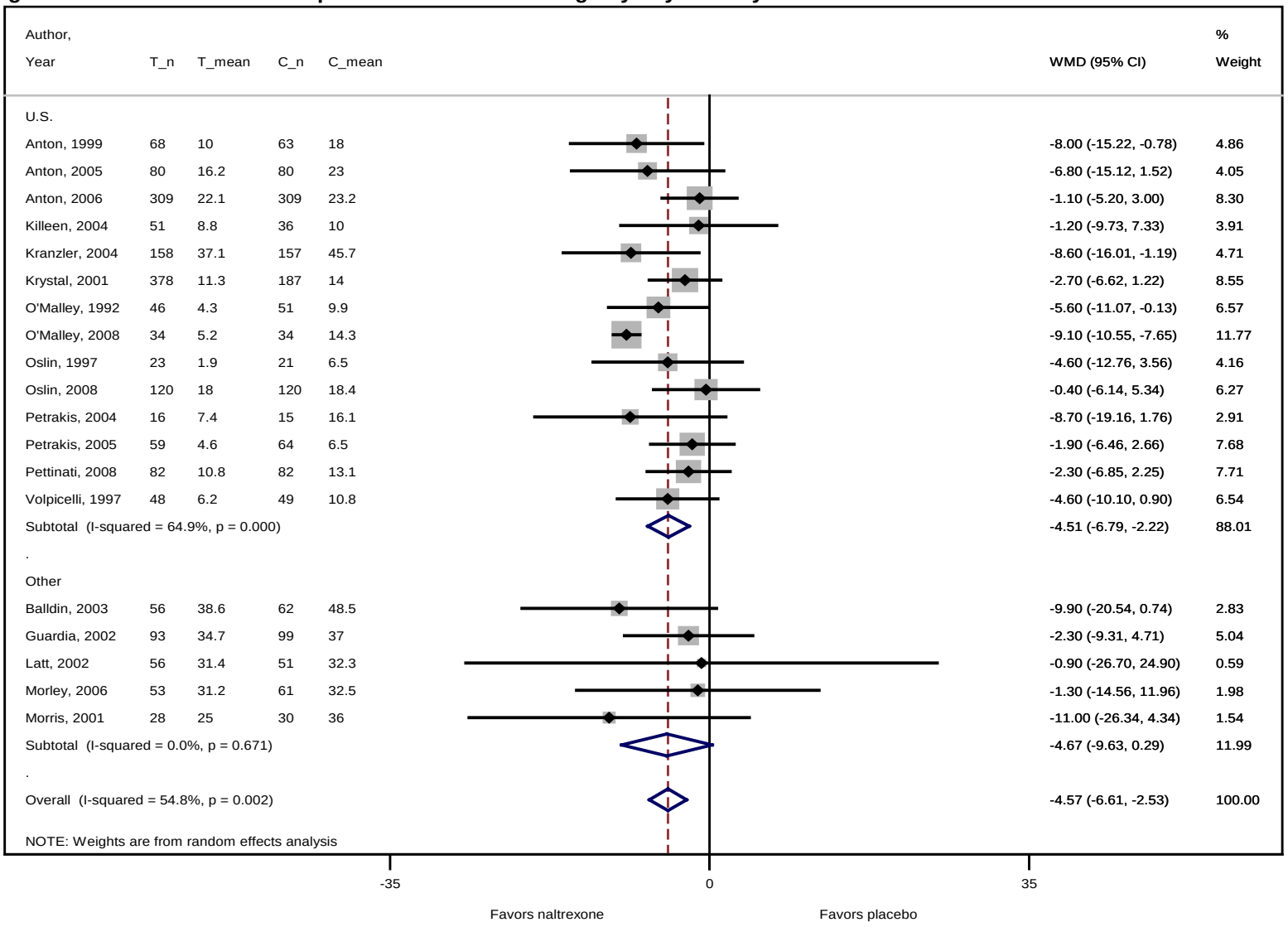


Figure F-30. Naltrexone versus placebo: Percent drinking days by duration of treatment

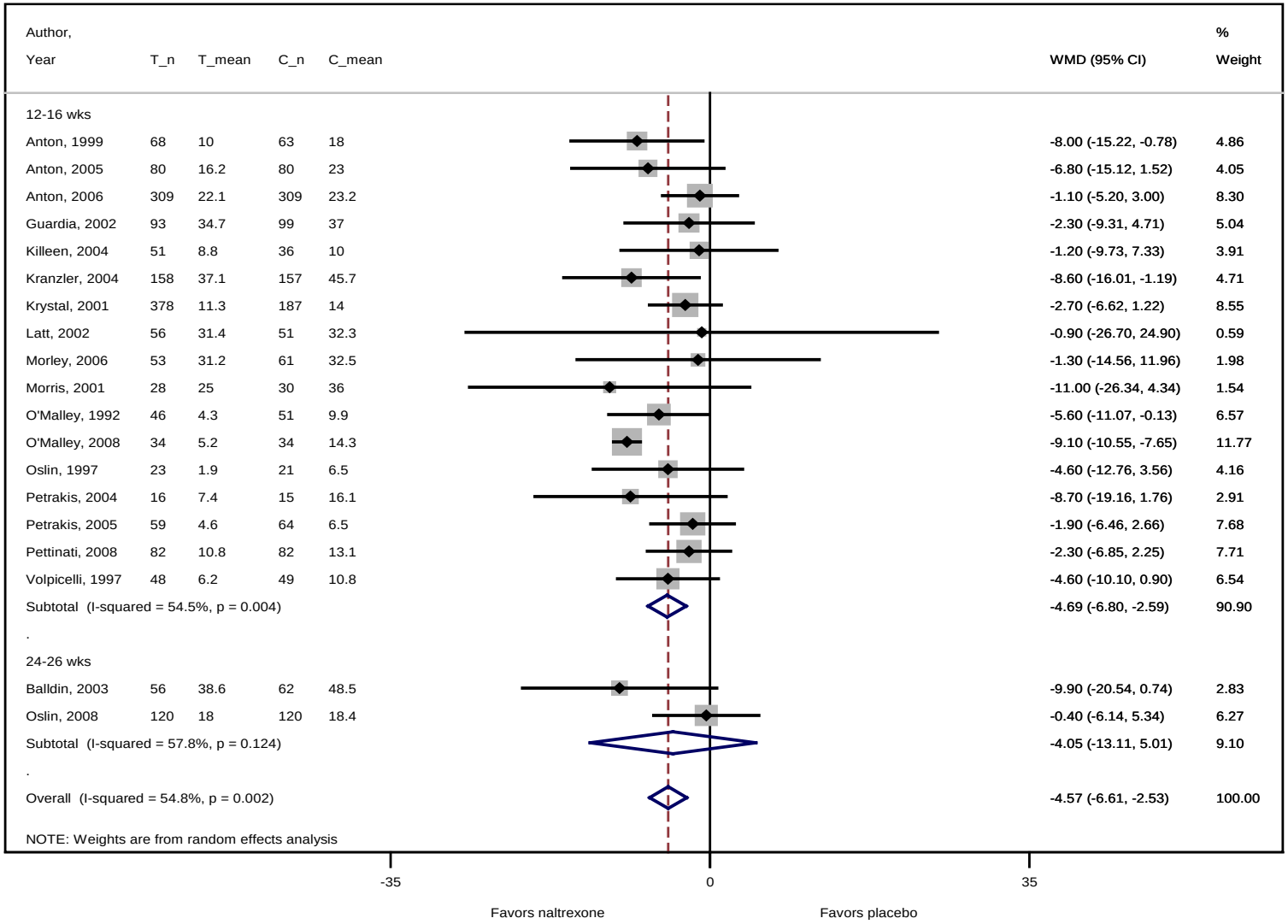
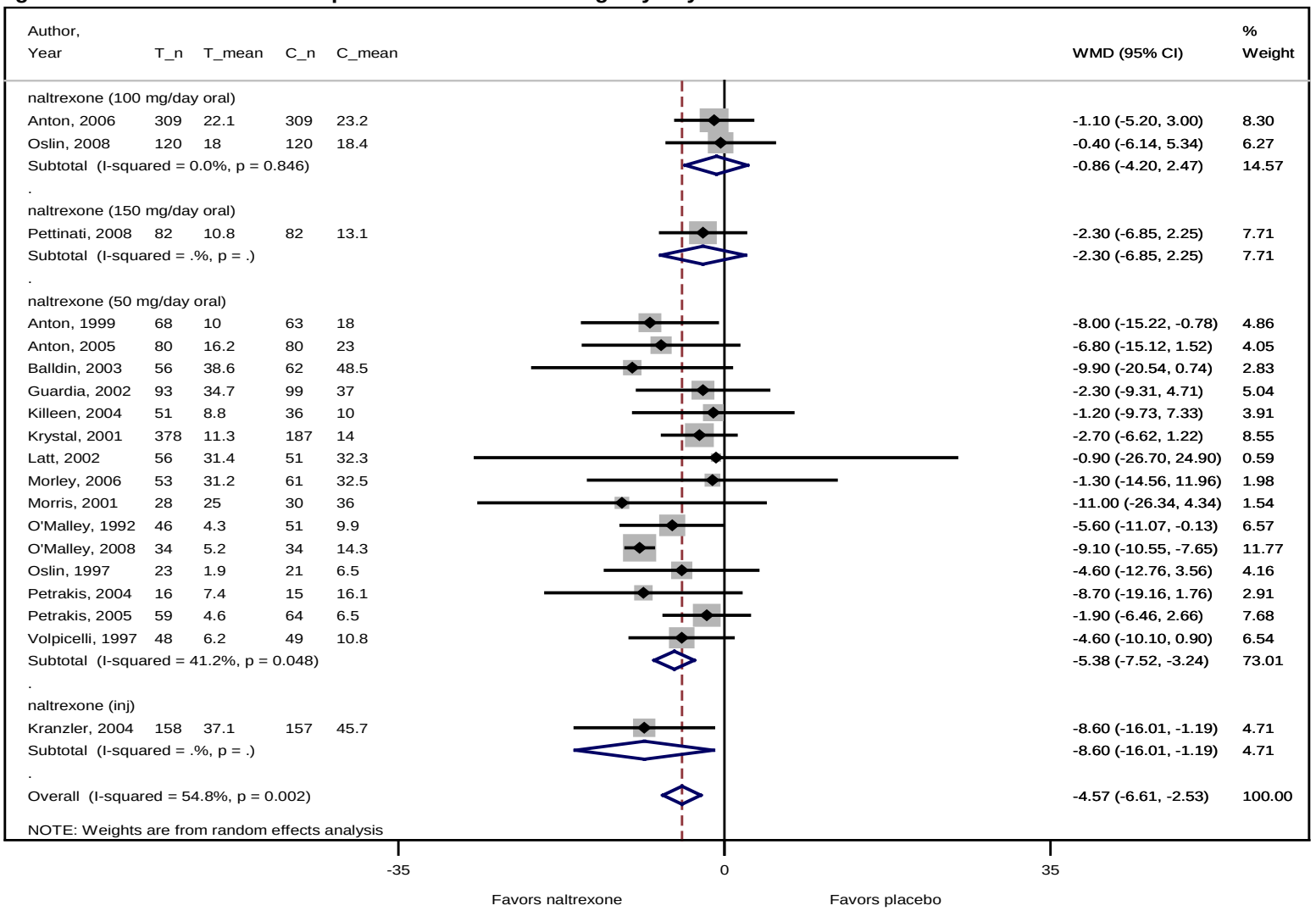


Figure F-31. Naltrexone versus placebo: Percent drinking days by naltrexone dose



Note: Dose for Oslin, 1997 represents an average of 50 mg.day; study participants received 100 mg two times per week and 150 mg one time per week.

Figure F-32. Naltrexone versus placebo: Percent drinking days by dual diagnosis (low/medium risk of bias)

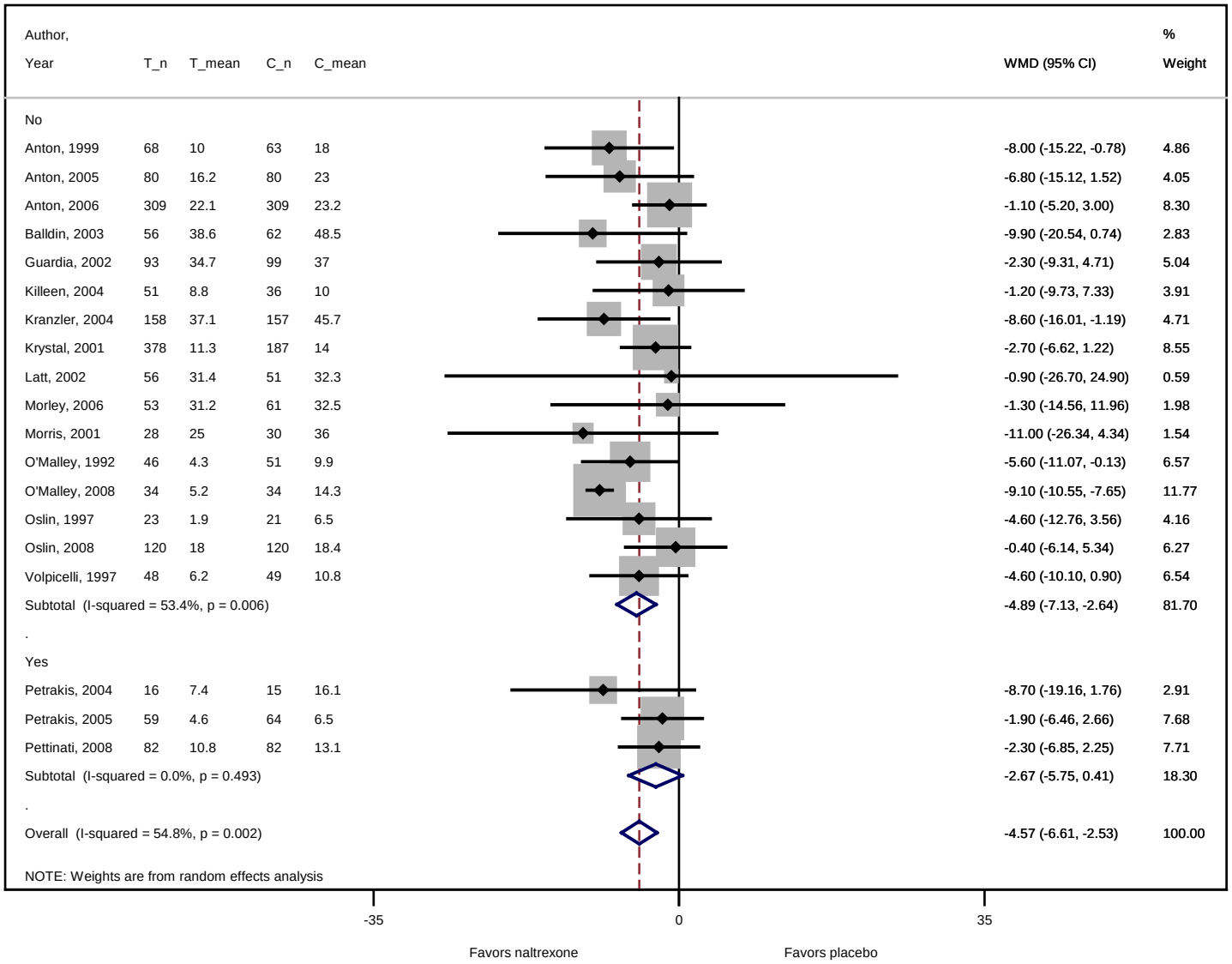


Figure F-33. Naltrexone versus placebo: Percent drinking days by dual diagnosis (all risk of bias)

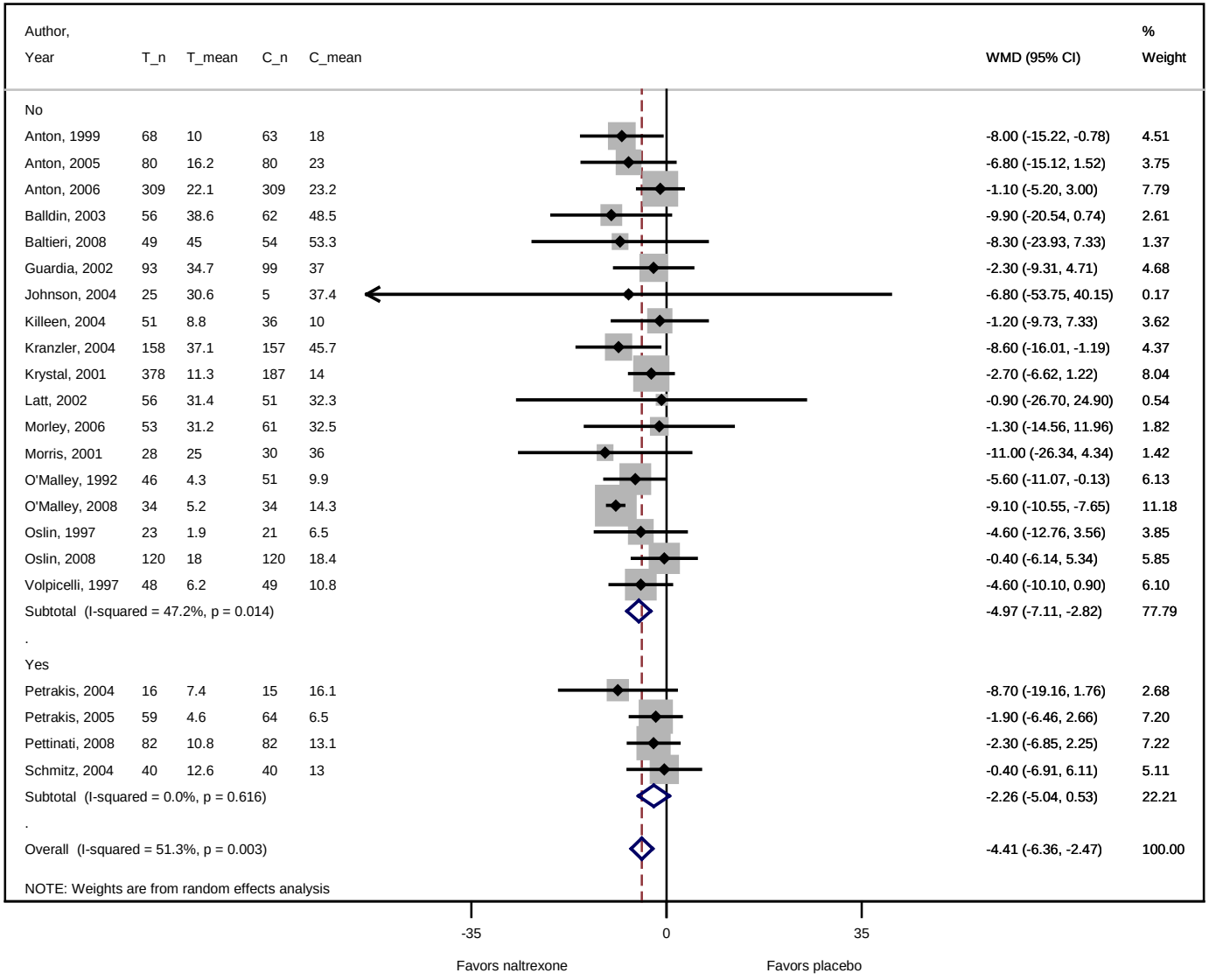


Figure F-34. Naltrexone versus placebo: Percent heavy drinking days by risk of bias

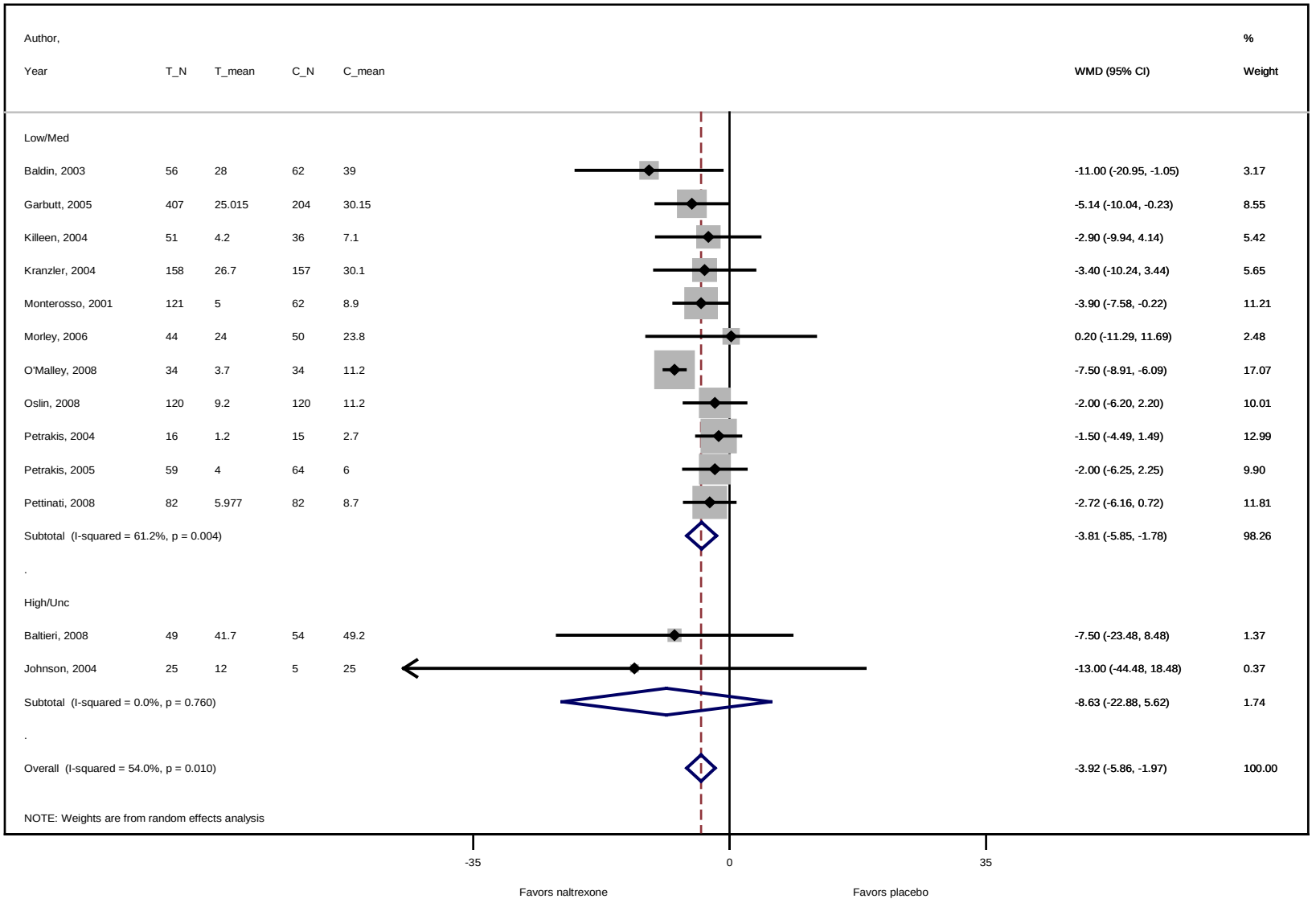


Figure F-35. Naltrexone versus placebo: Percent heavy drinking days by country

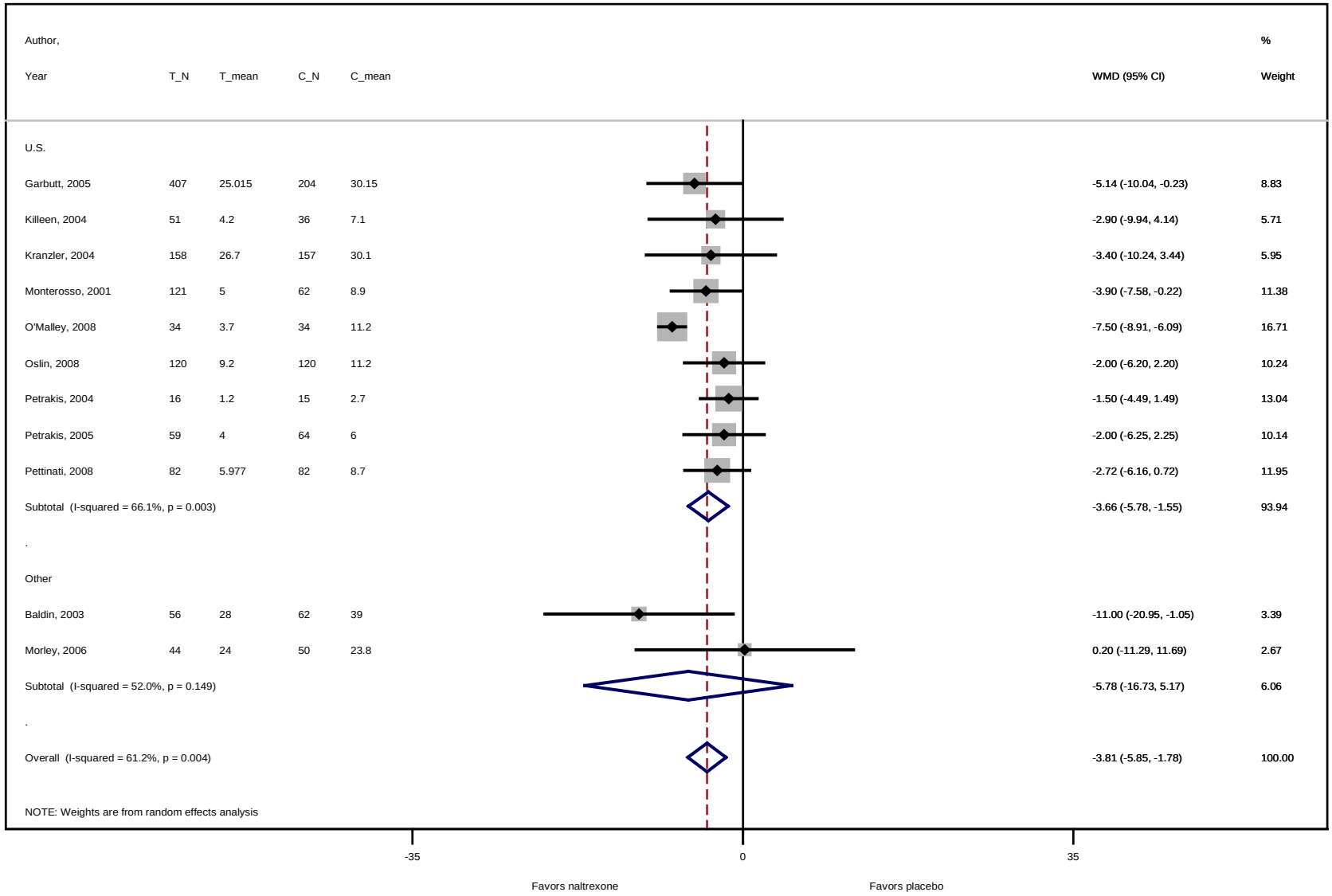


Figure F-36. Naltrexone versus placebo: Percent heavy drinking days by duration of treatment

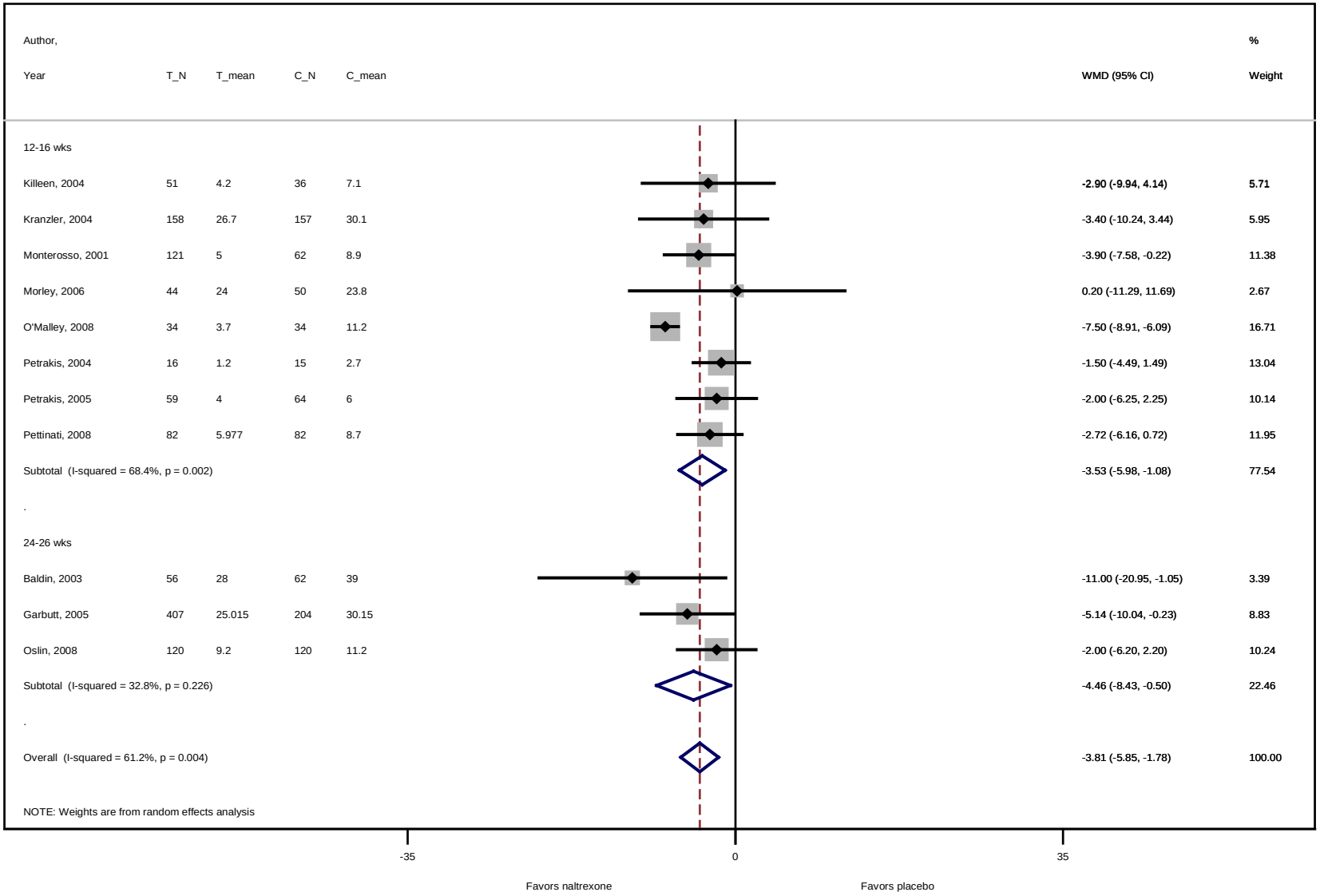


Figure F-37. Naltrexone versus placebo: Percent heavy drinking days by naltrexone dose

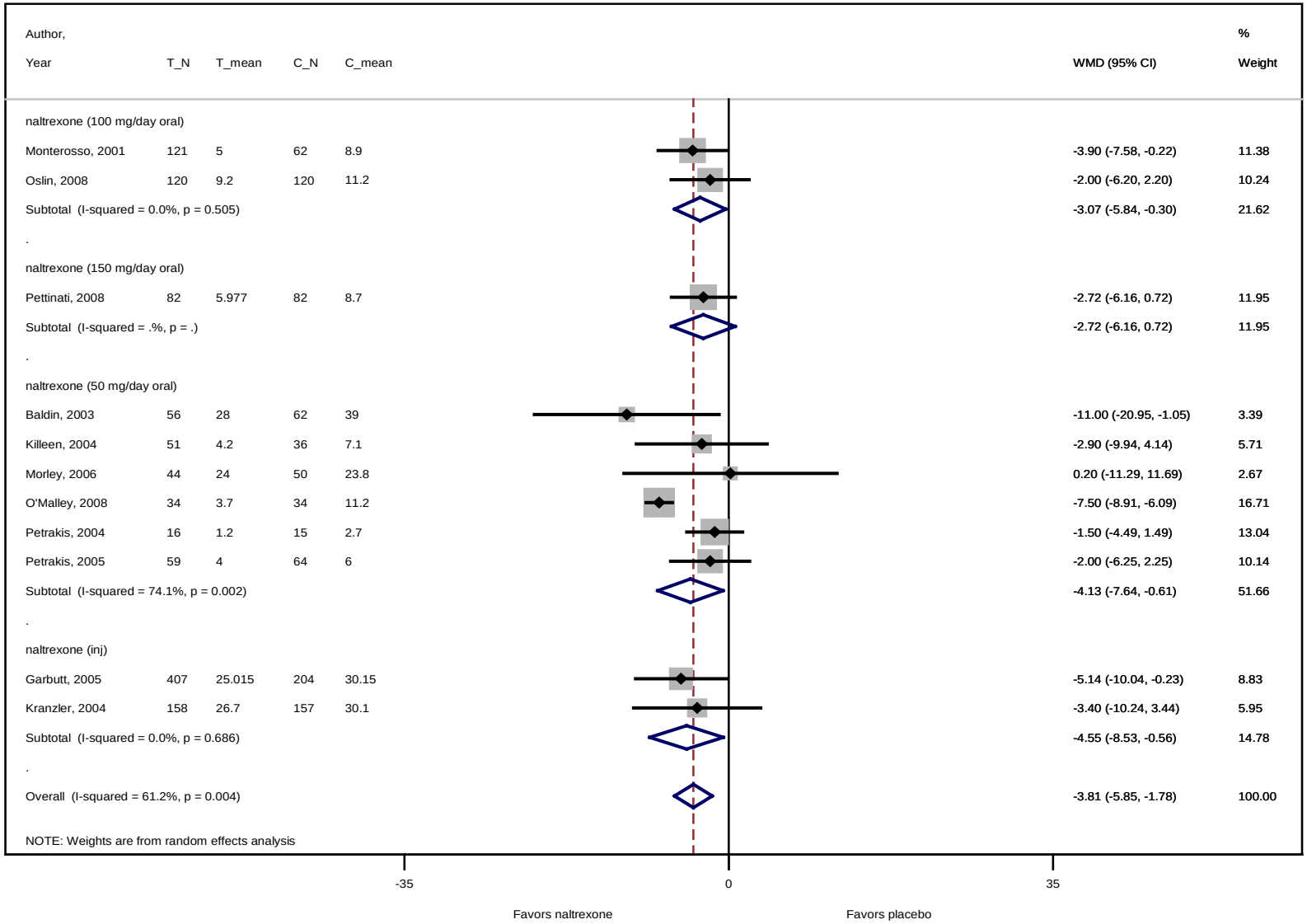


Figure F-38. Naltrexone versus placebo: Percent heavy drinking days by dual diagnosis (low/medium risk of bias)

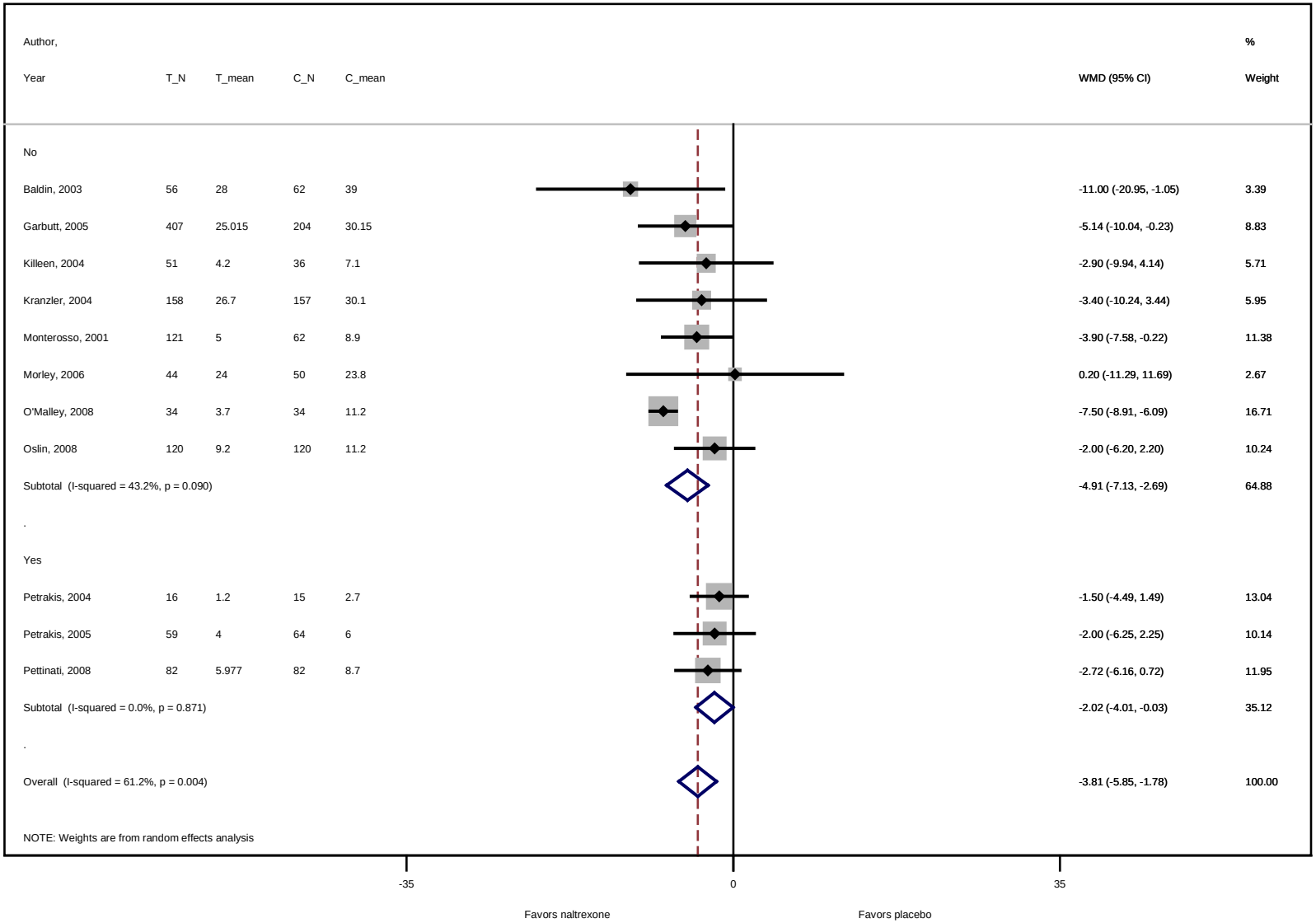


Figure F-39. Naltrexone versus placebo: Percent heavy drinking days by dual diagnosis (all risk of bias)

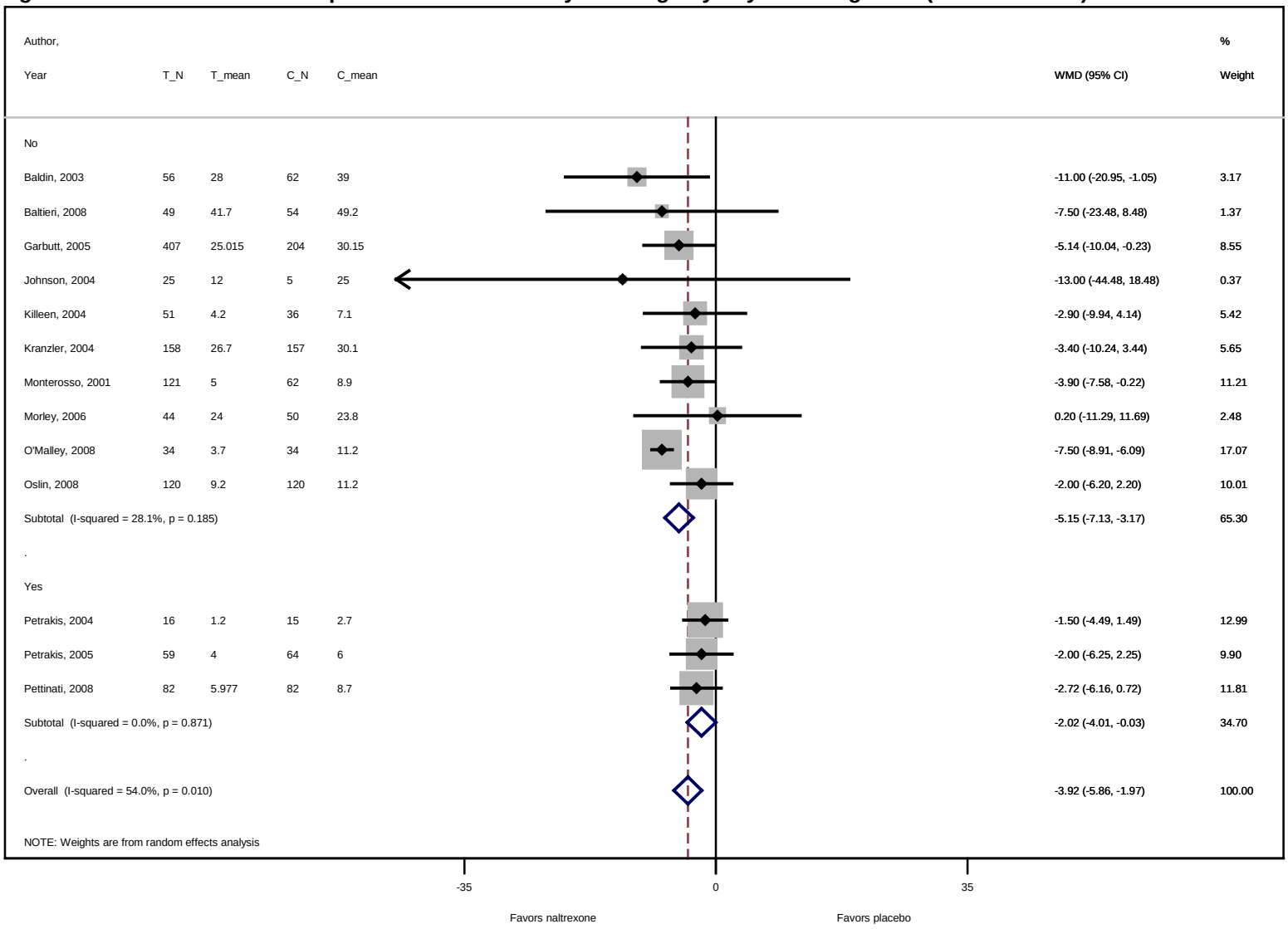
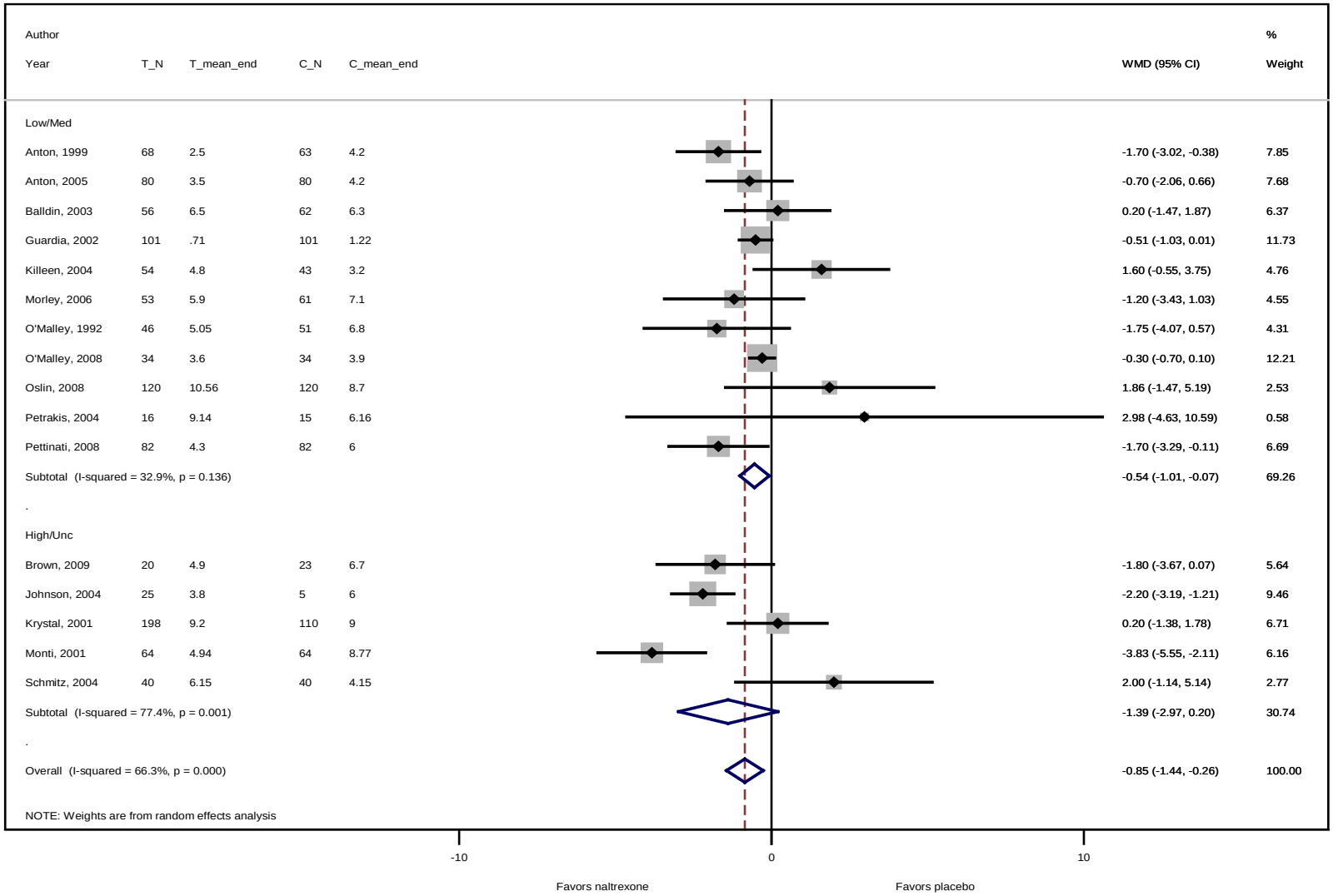


Figure F-40. Naltrexone versus placebo: Drinks per drinking day by risk of bias



Note: Monti, 2001 and Krystal, 2001 are rated High risk of bias for this outcome because of attrition

Figure F-41. Naltrexone versus placebo: Drinks per drinking day by country

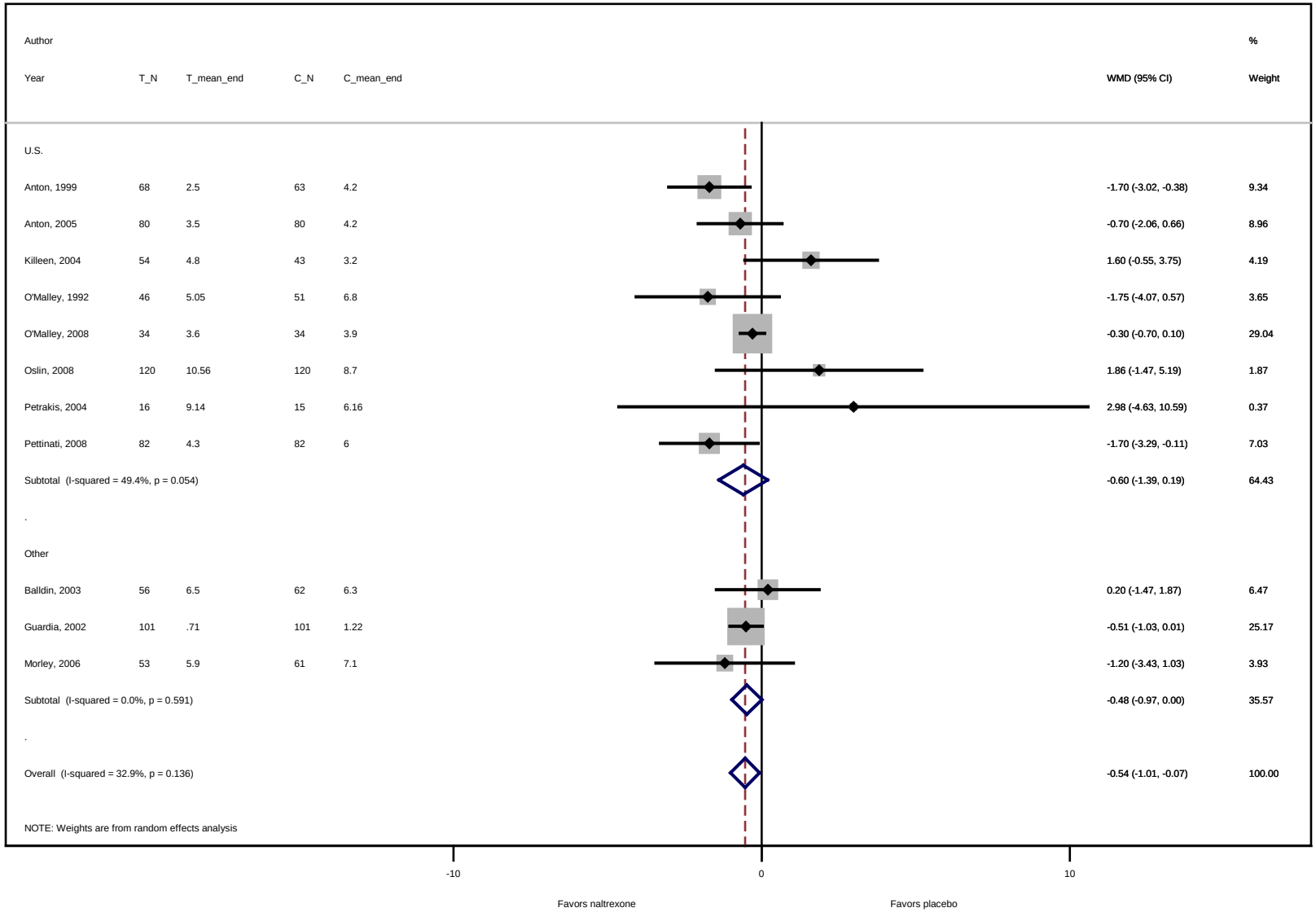


Figure F-42. Naltrexone versus placebo: Drinks per drinking day by duration of treatment

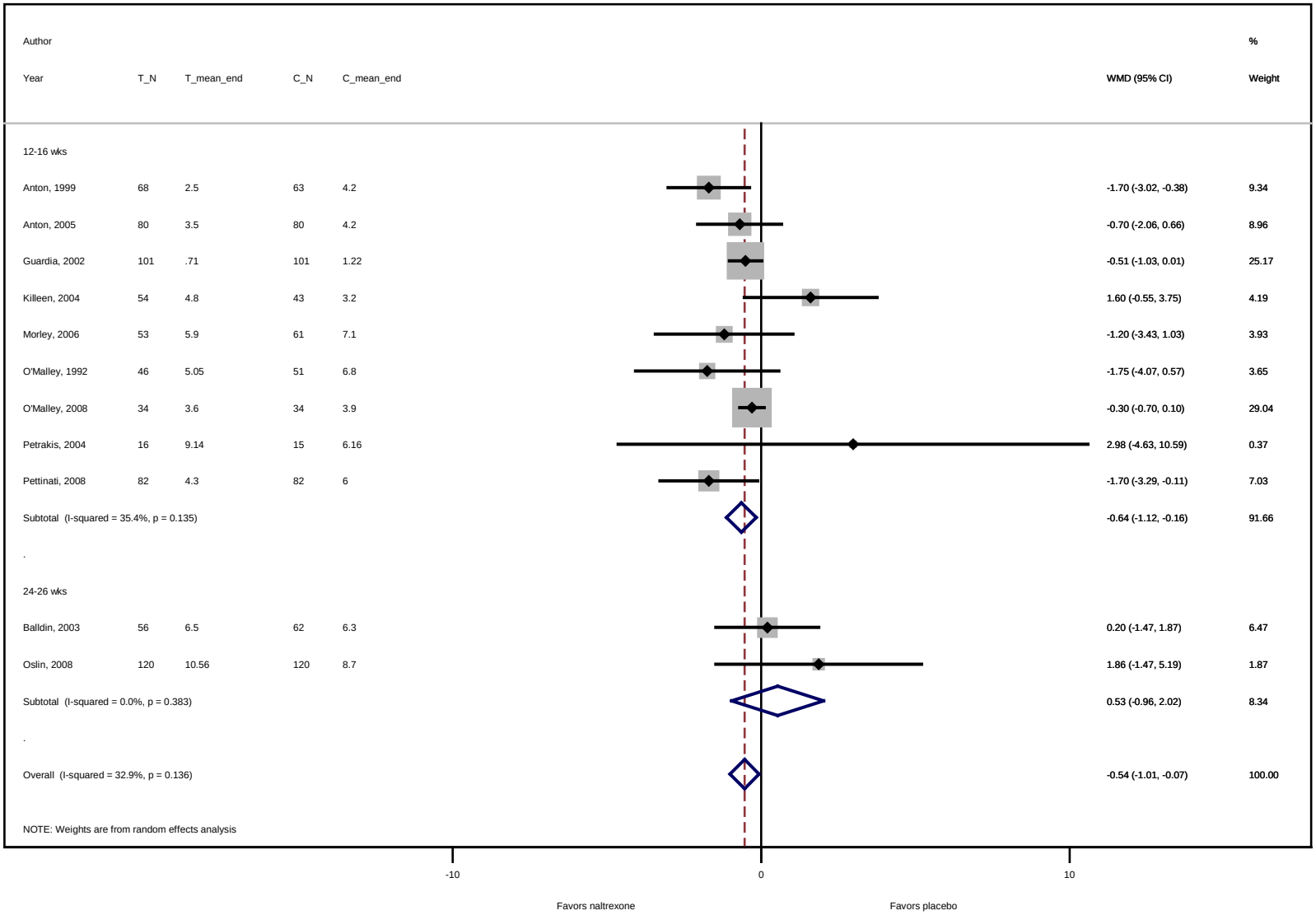


Figure F-43. Naltrexone versus placebo: Drinks per drinking day by naltrexone dose

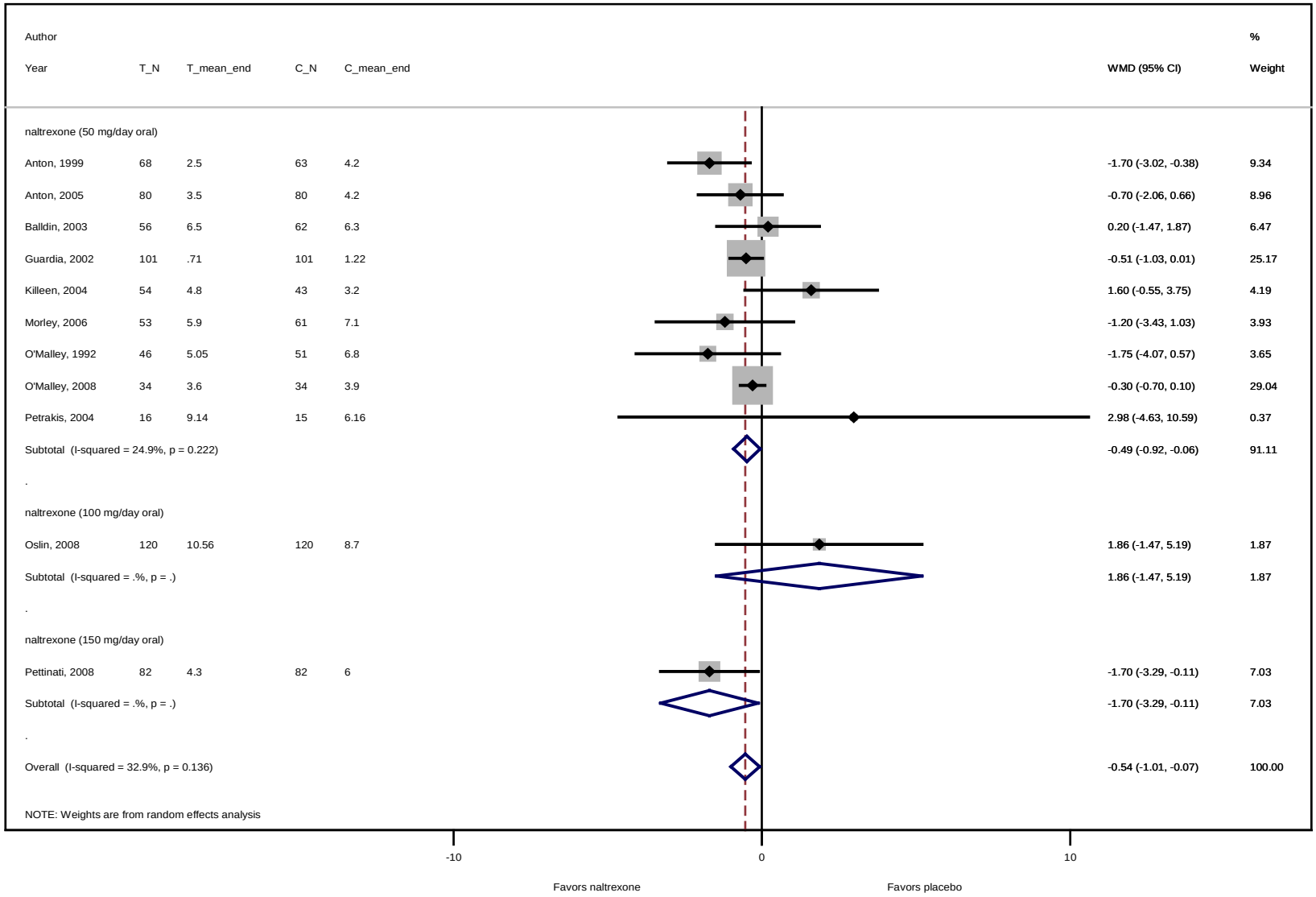


Figure F-44. Naltrexone versus placebo: Drinks per drinking day by dual diagnosis (low/medium risk of bias)

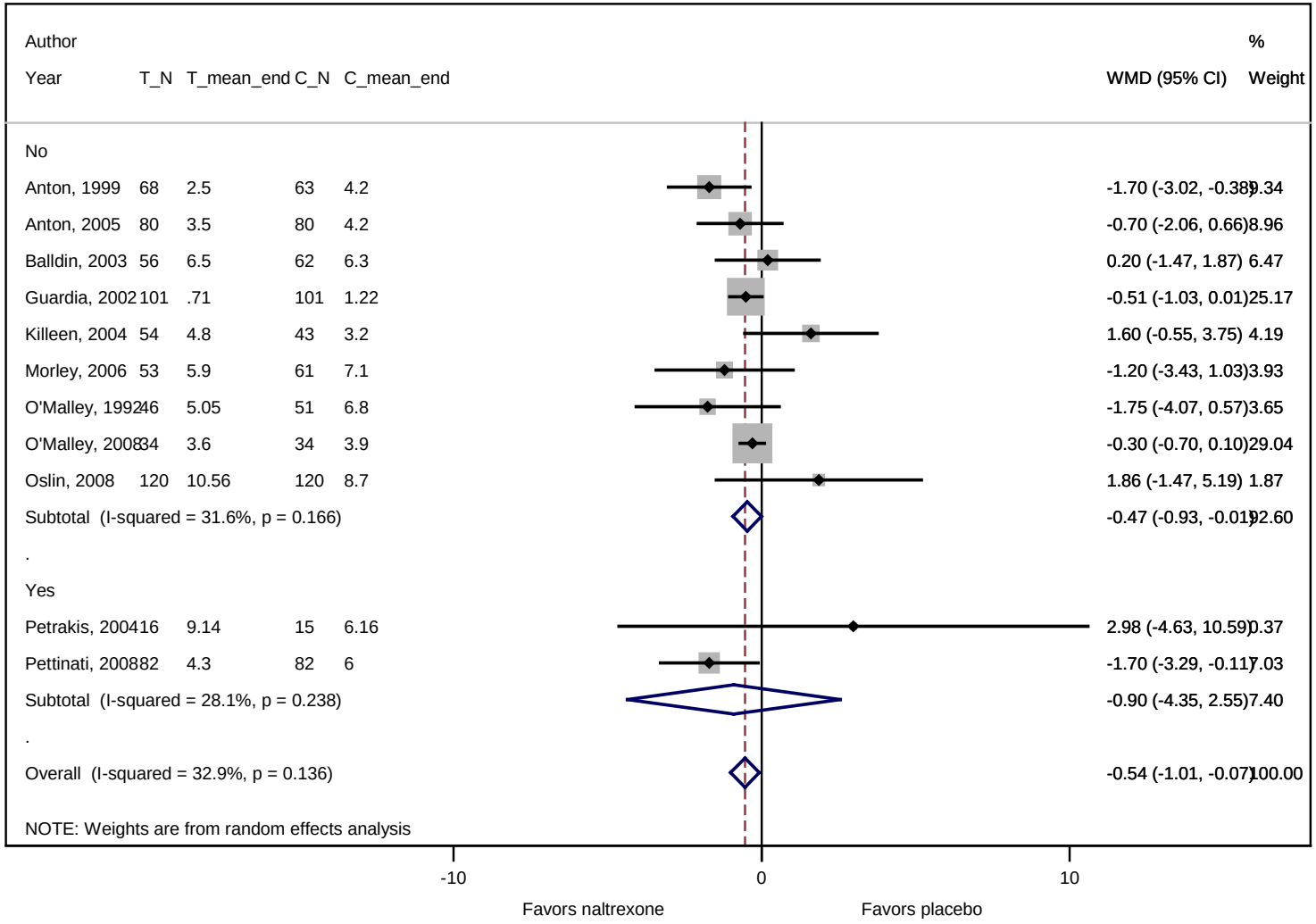


Figure F-45. Naltrexone versus placebo: Drinks per drinking day by dual diagnosis (all risk of bias)

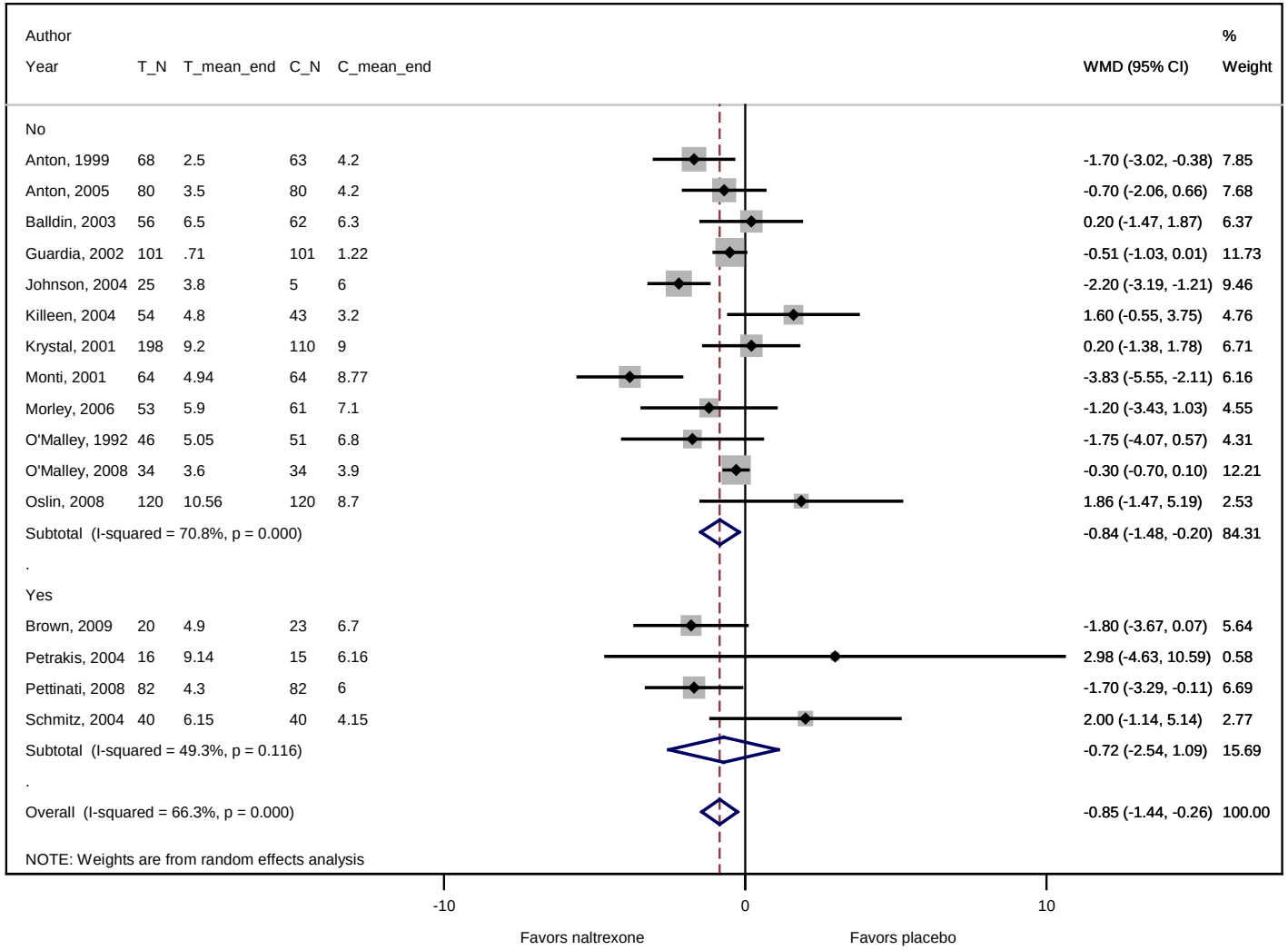


Figure F-46. Acamprosate versus naltrexone: Return to any drinking by risk of bias

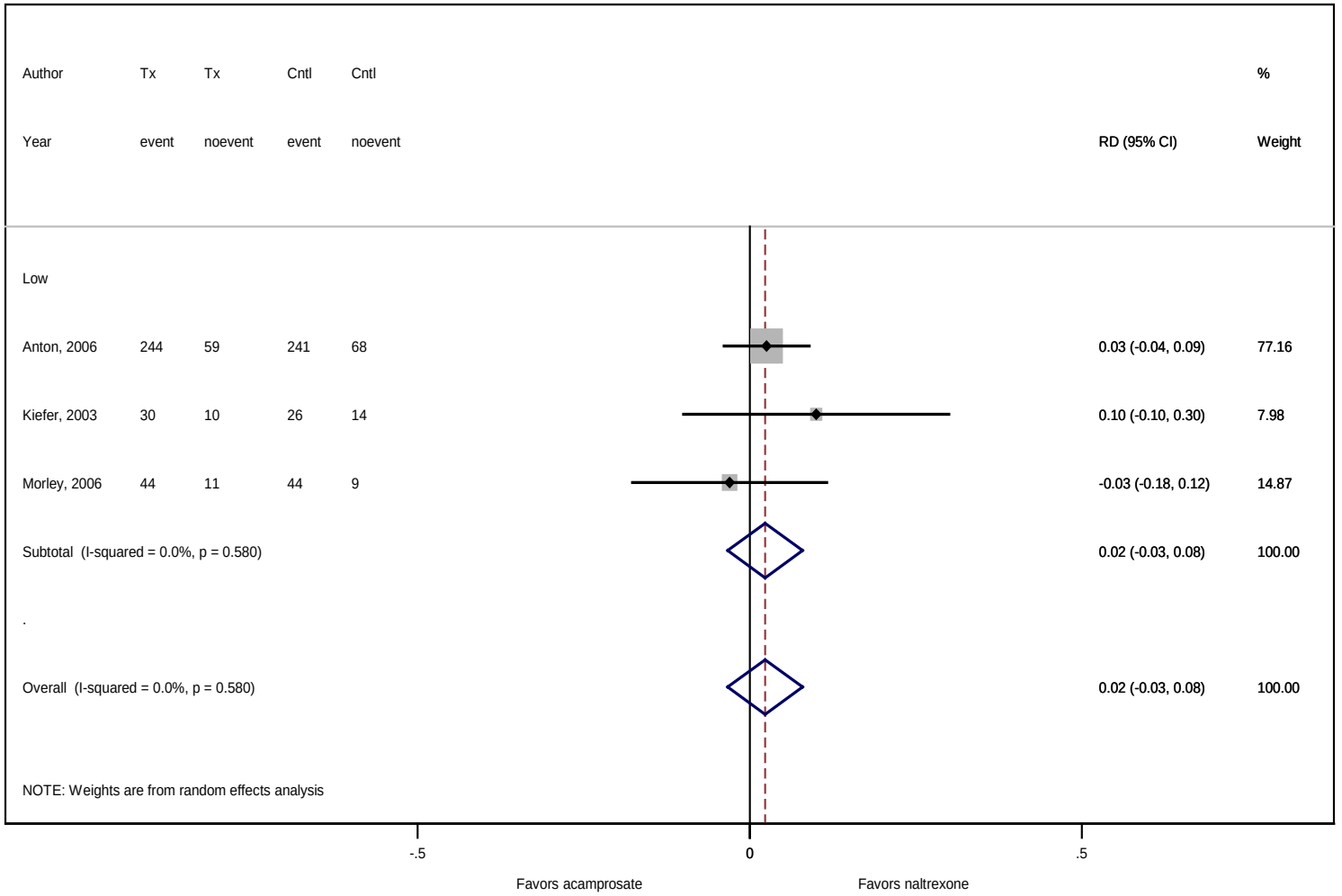


Figure F-47. Acamprosate versus naltrexone: Return to heavy drinking by risk of bias

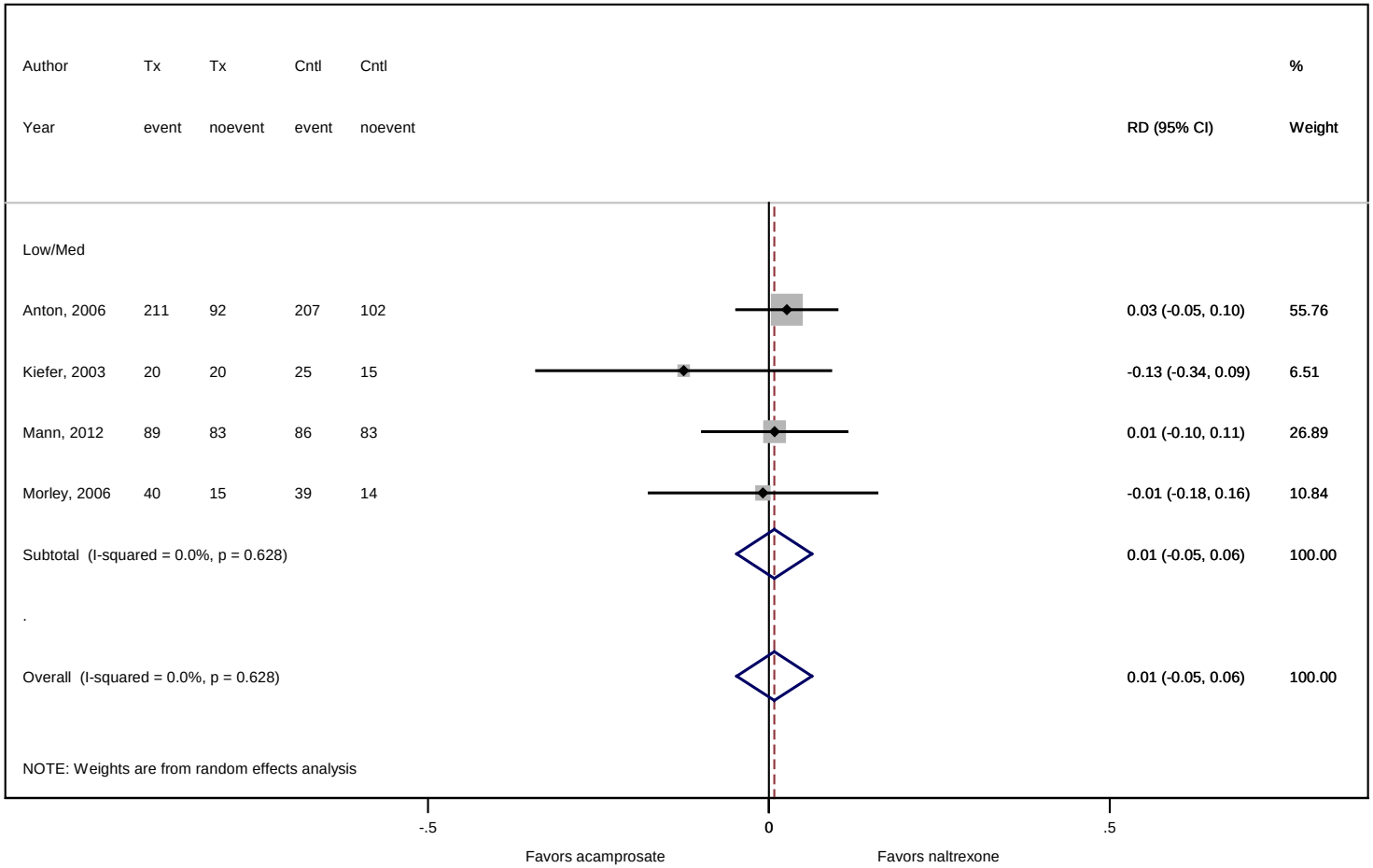


Figure F-48. Acamprosate versus naltrexone: Percent drinking days by risk of bias

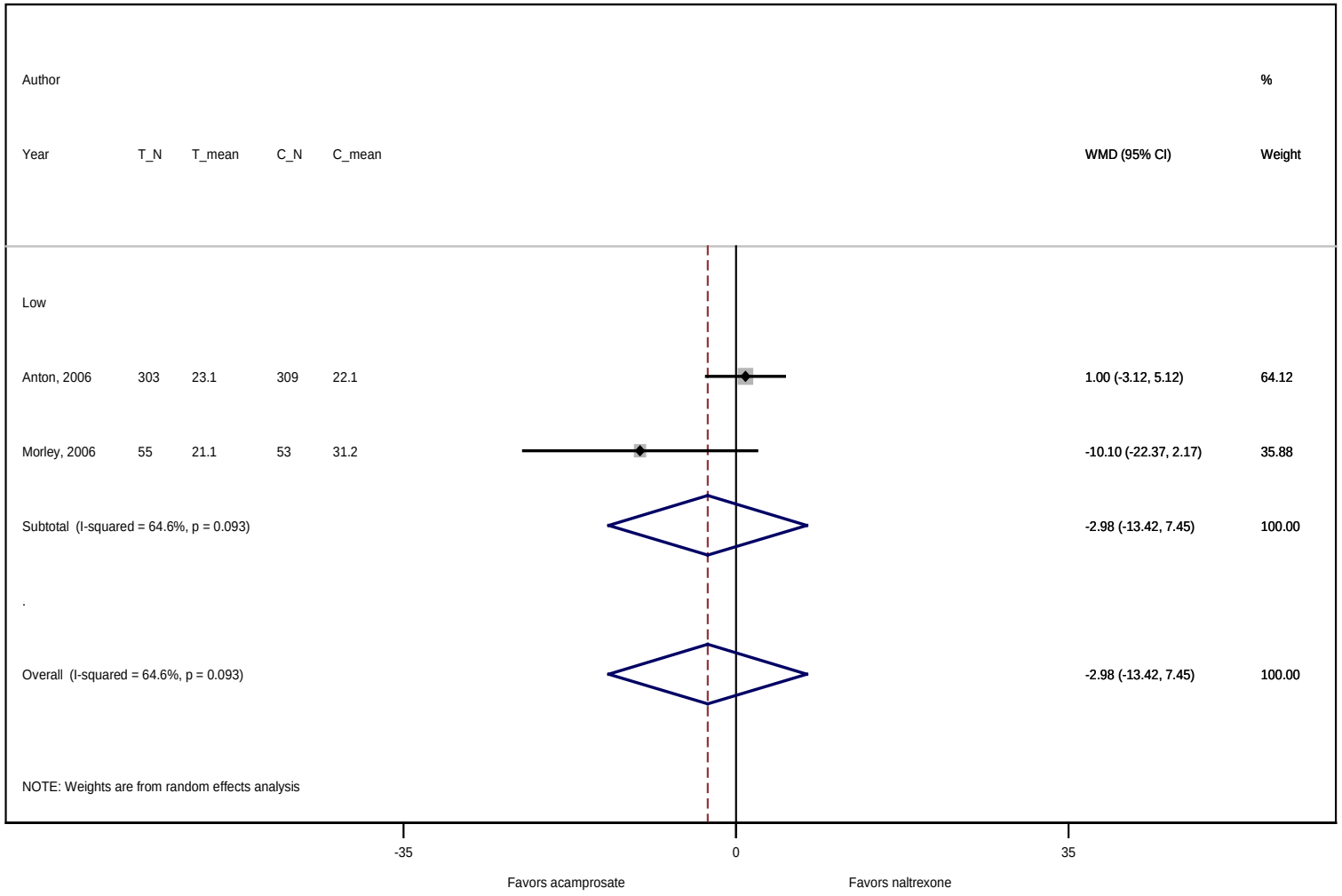


Figure F-49. Buspirone versus placebo: Return to any drinking by risk of bias

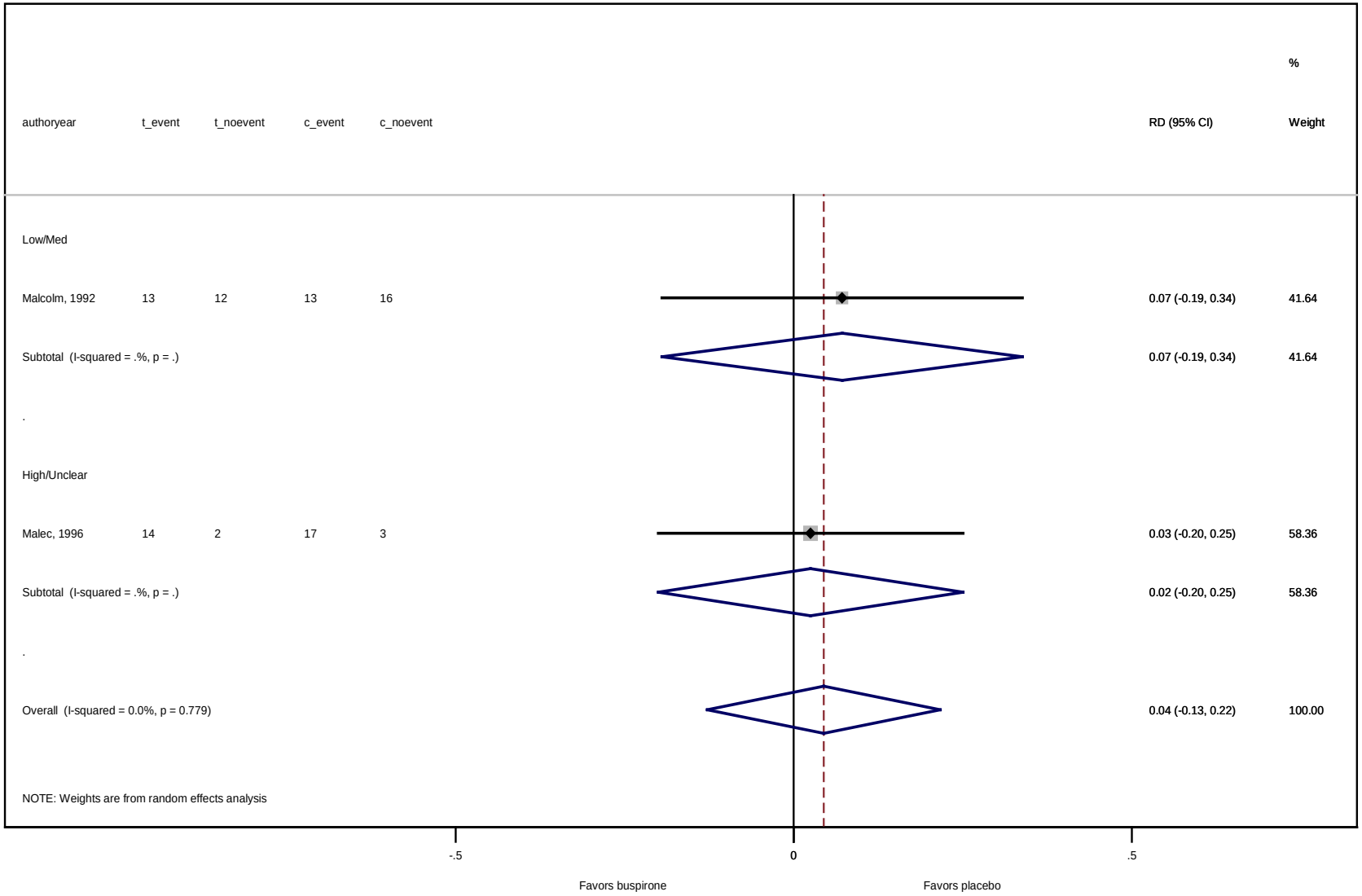


Figure F-50. Fluoxetine versus placebo: Return to any drinking by risk of bias

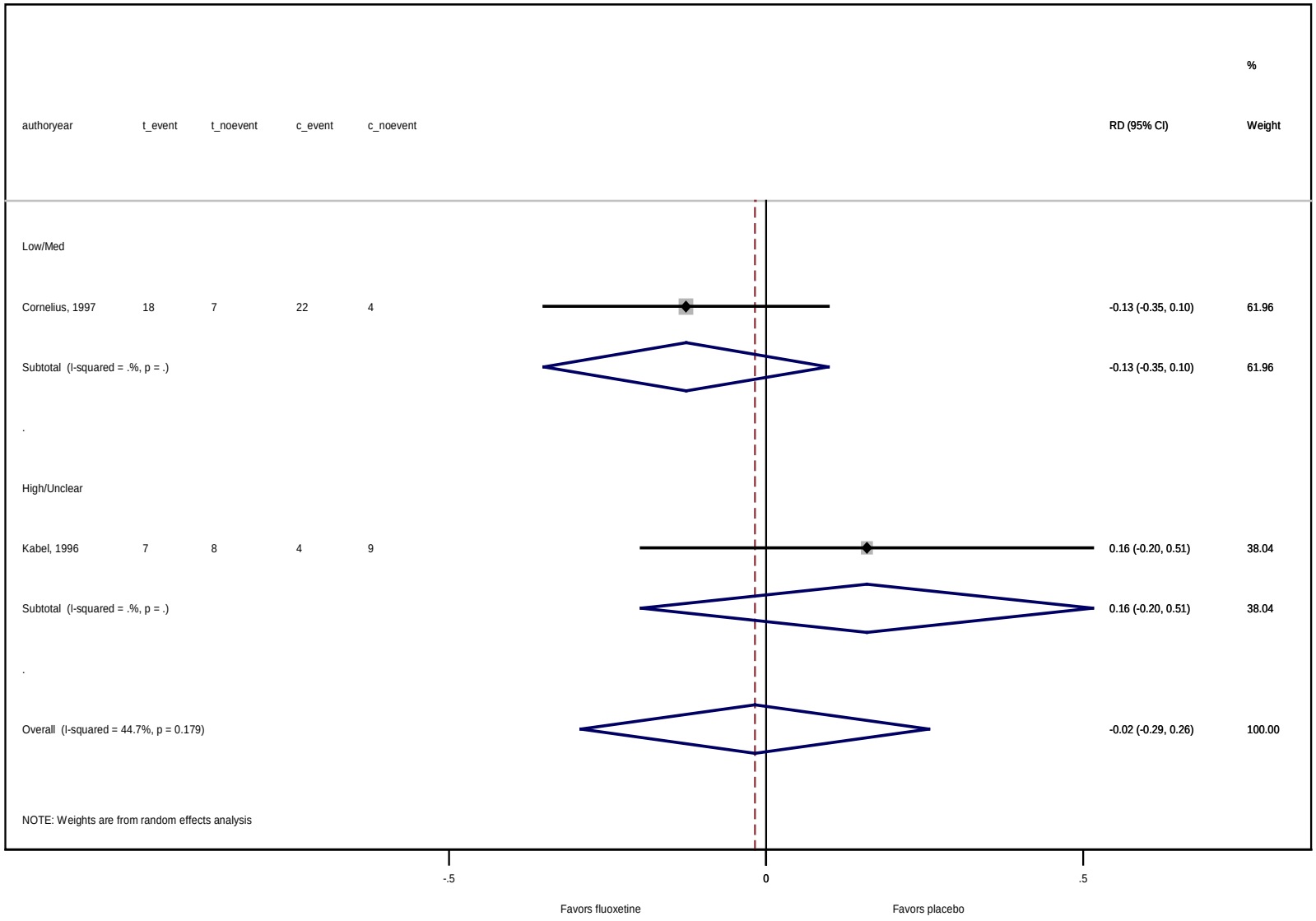


Figure F-51. Valproic acid versus placebo: Return to heavy drinking by risk of bias

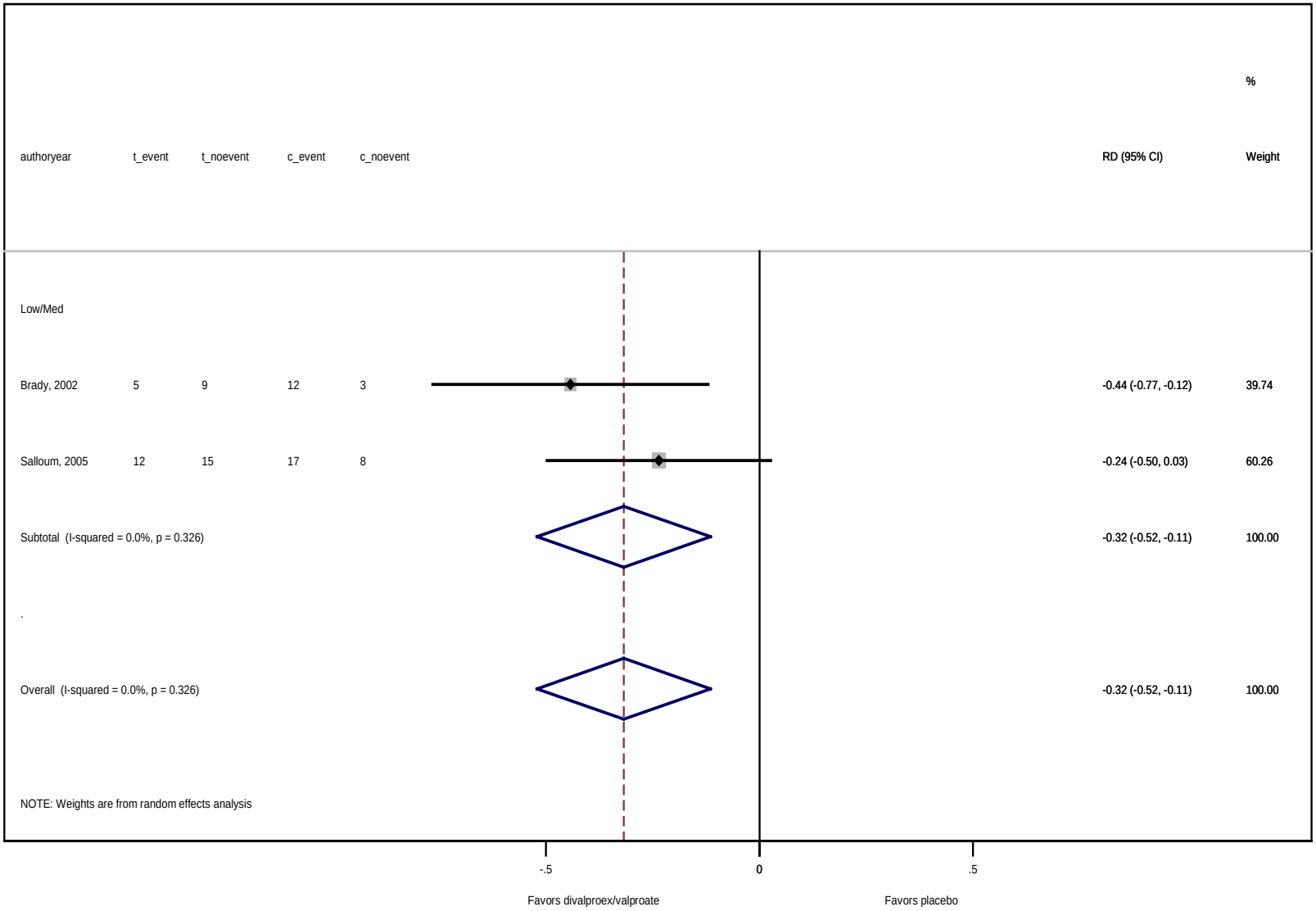


Figure F-52. Nalmefene versus placebo: Return to heavy drinking by risk of bias

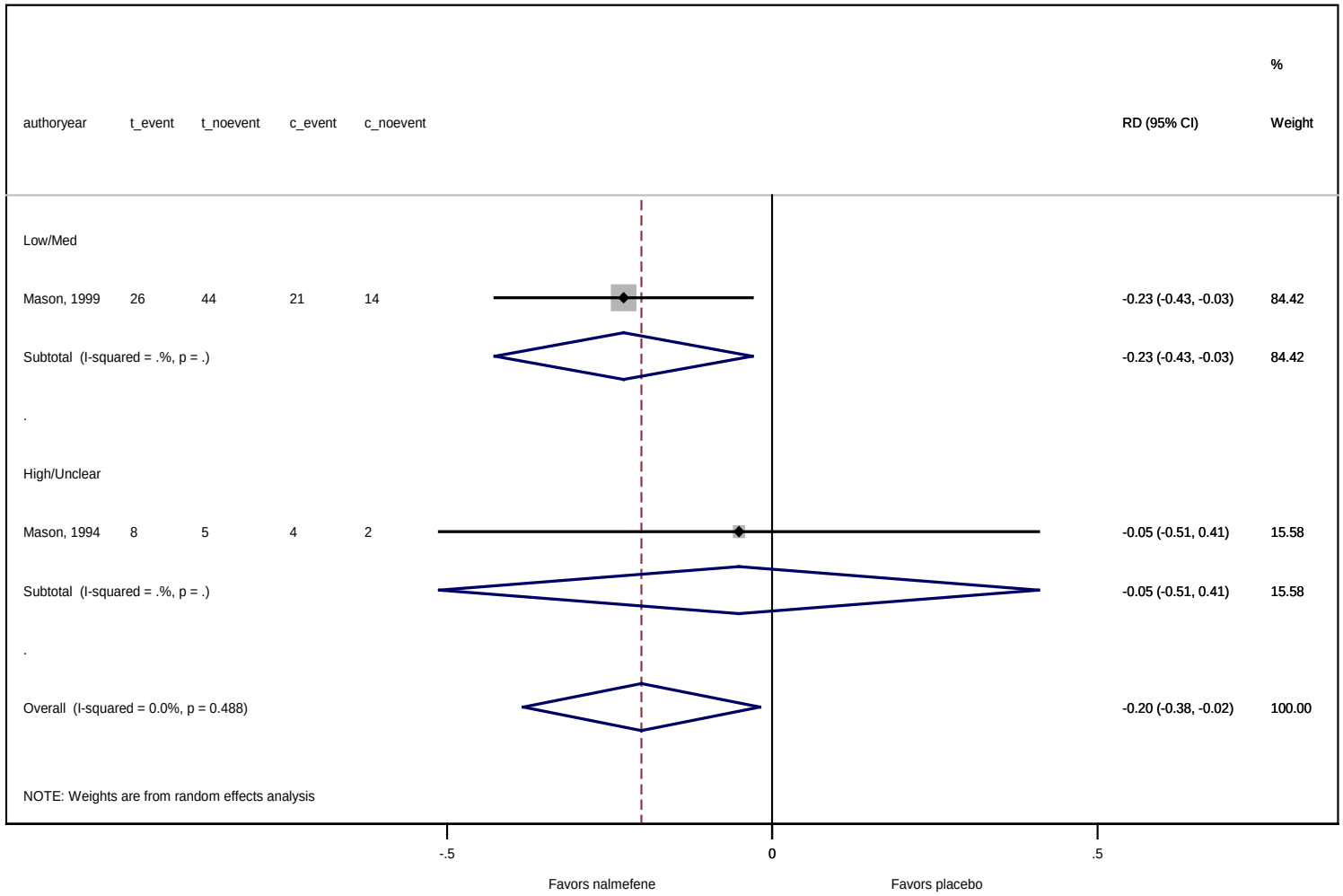


Figure F-53. Sertraline versus placebo: Return to heavy drinking by risk of bias

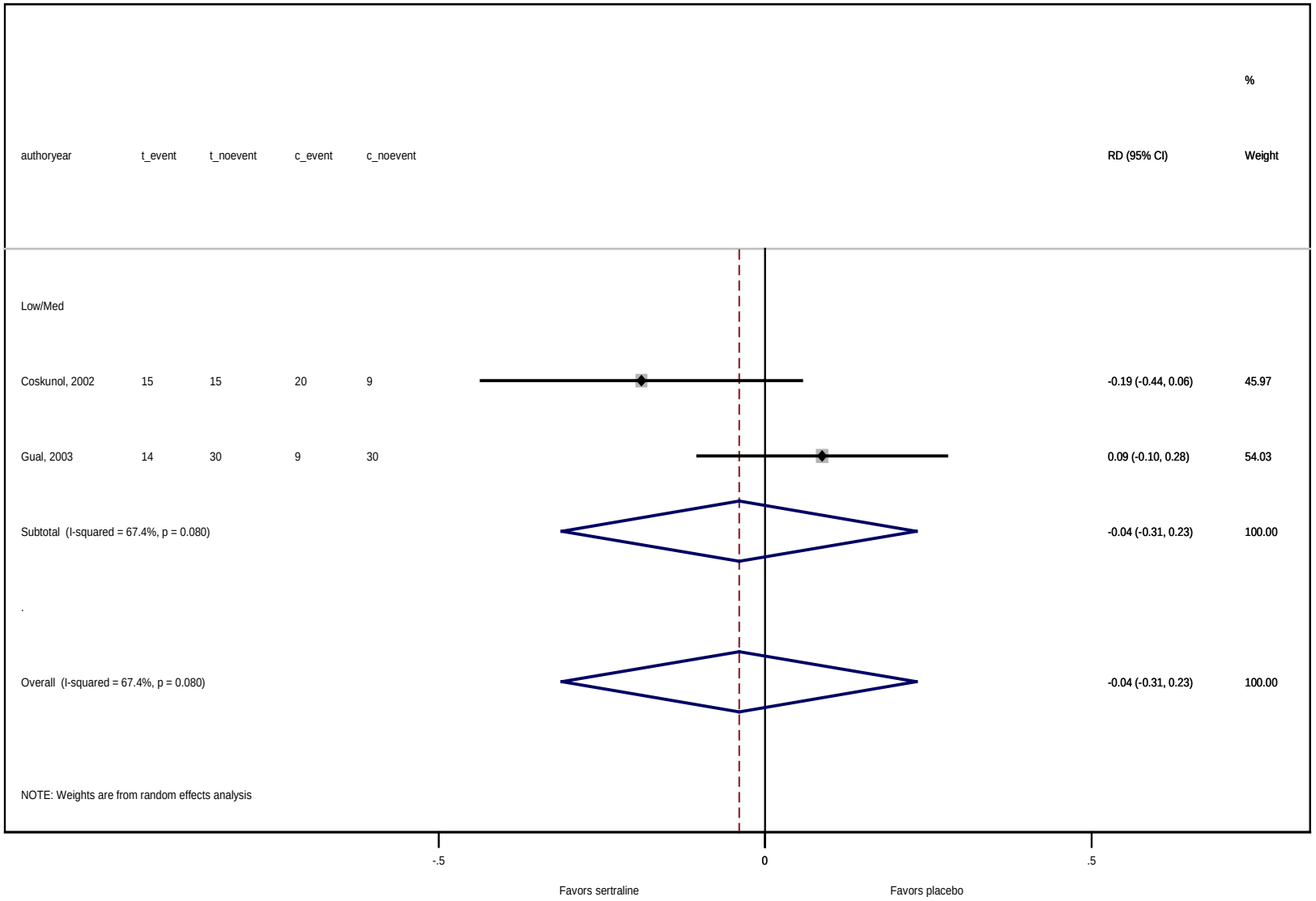


Figure F-54. Buspirone versus placebo: Percent drinking days by risk of bias

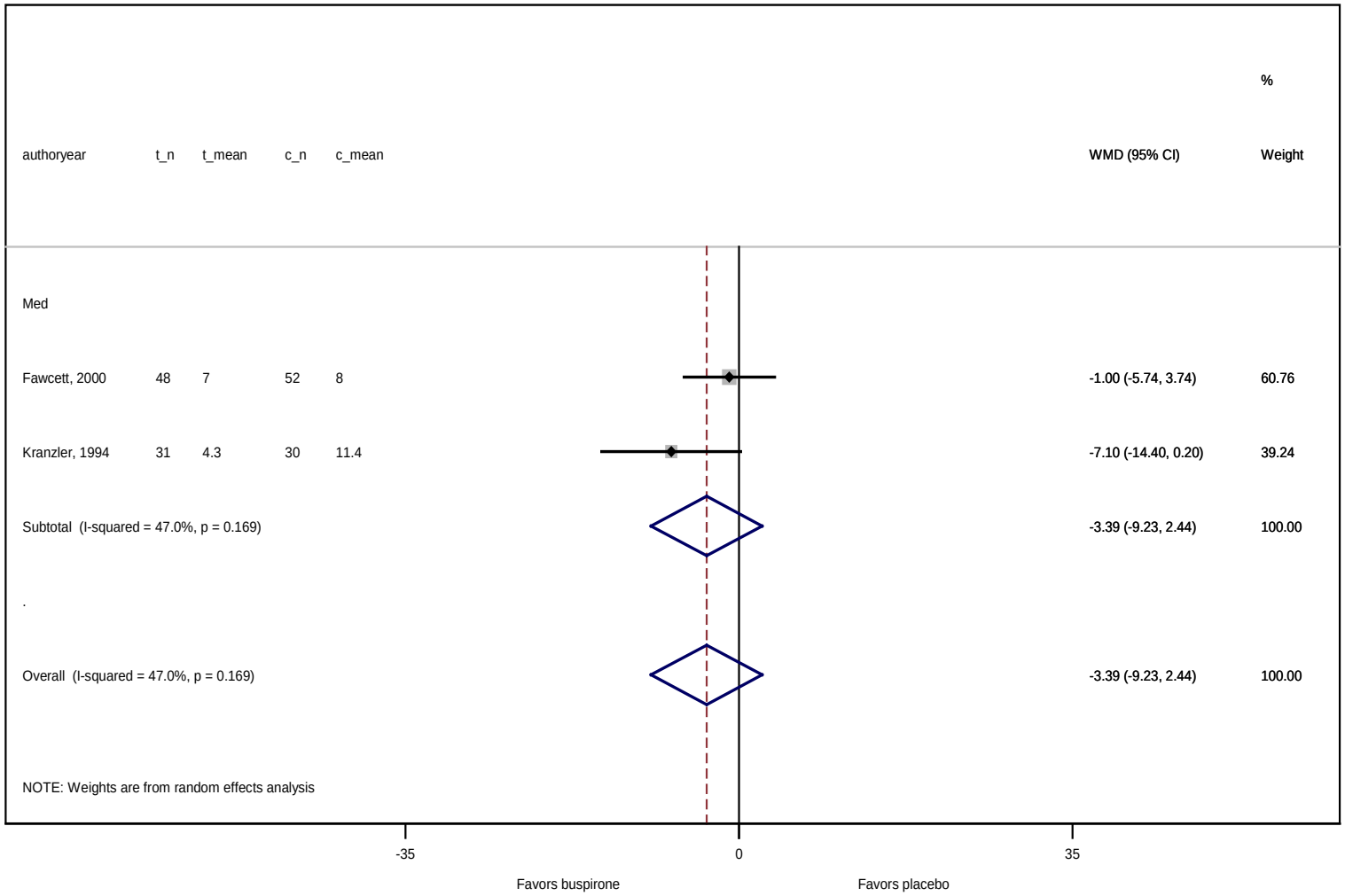


Figure F-55. Fluoxetine versus placebo: Percent drinking days by risk of bias

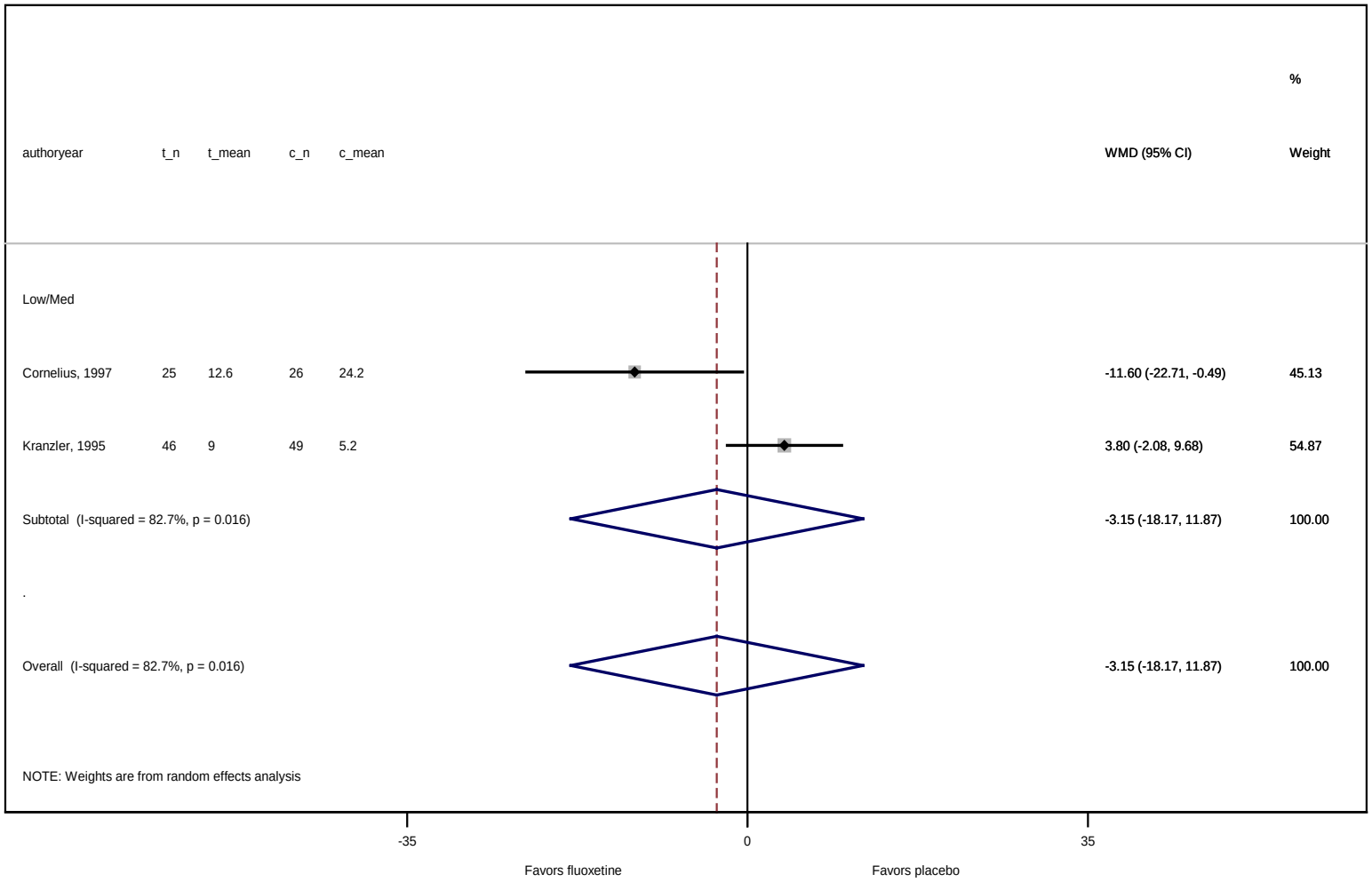


Figure F-56. Nalmefene versus placebo: Percent drinking days by risk of bias

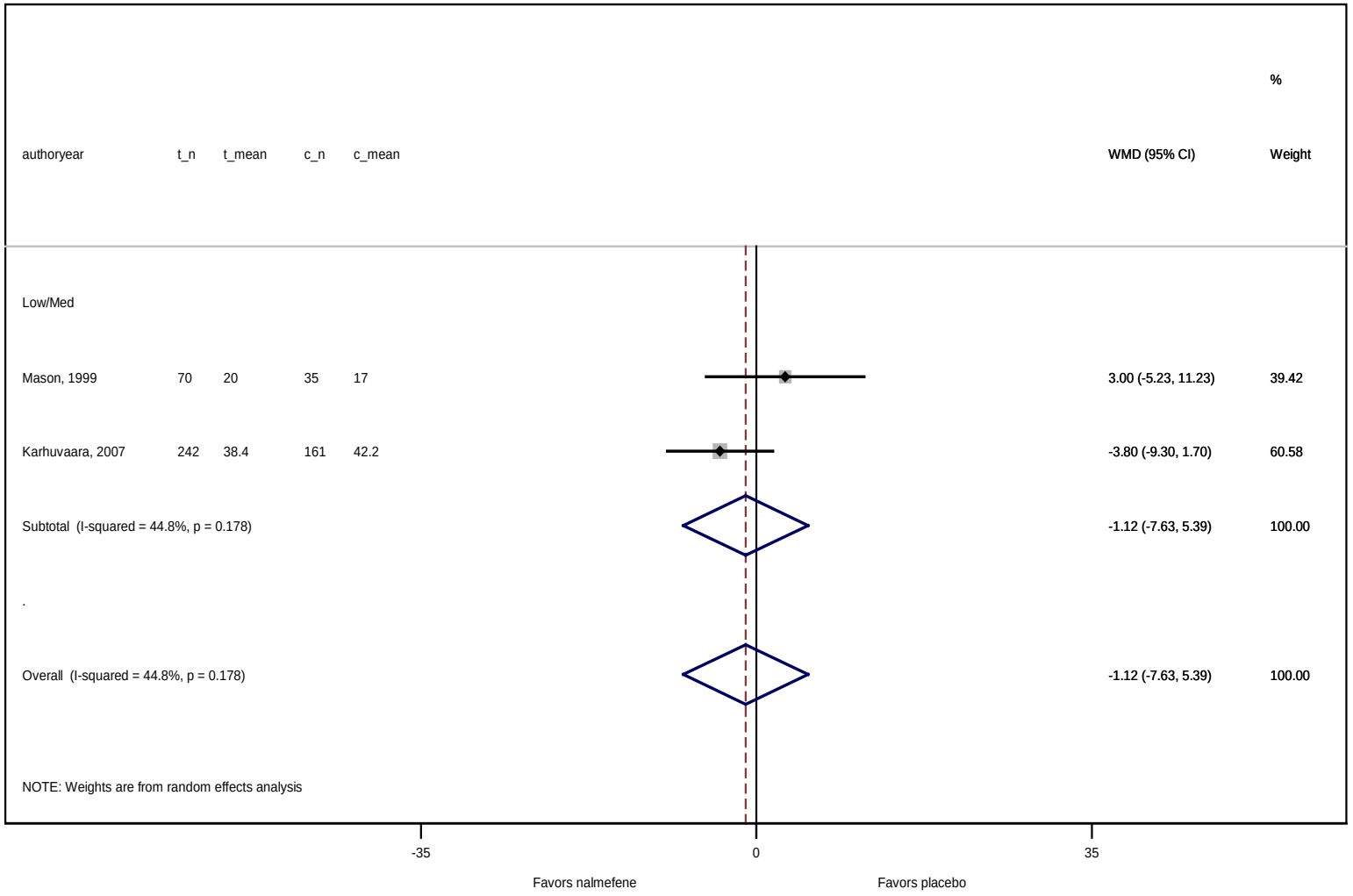


Figure F-57. Quetiapine versus placebo: Percent drinking days by risk of bias

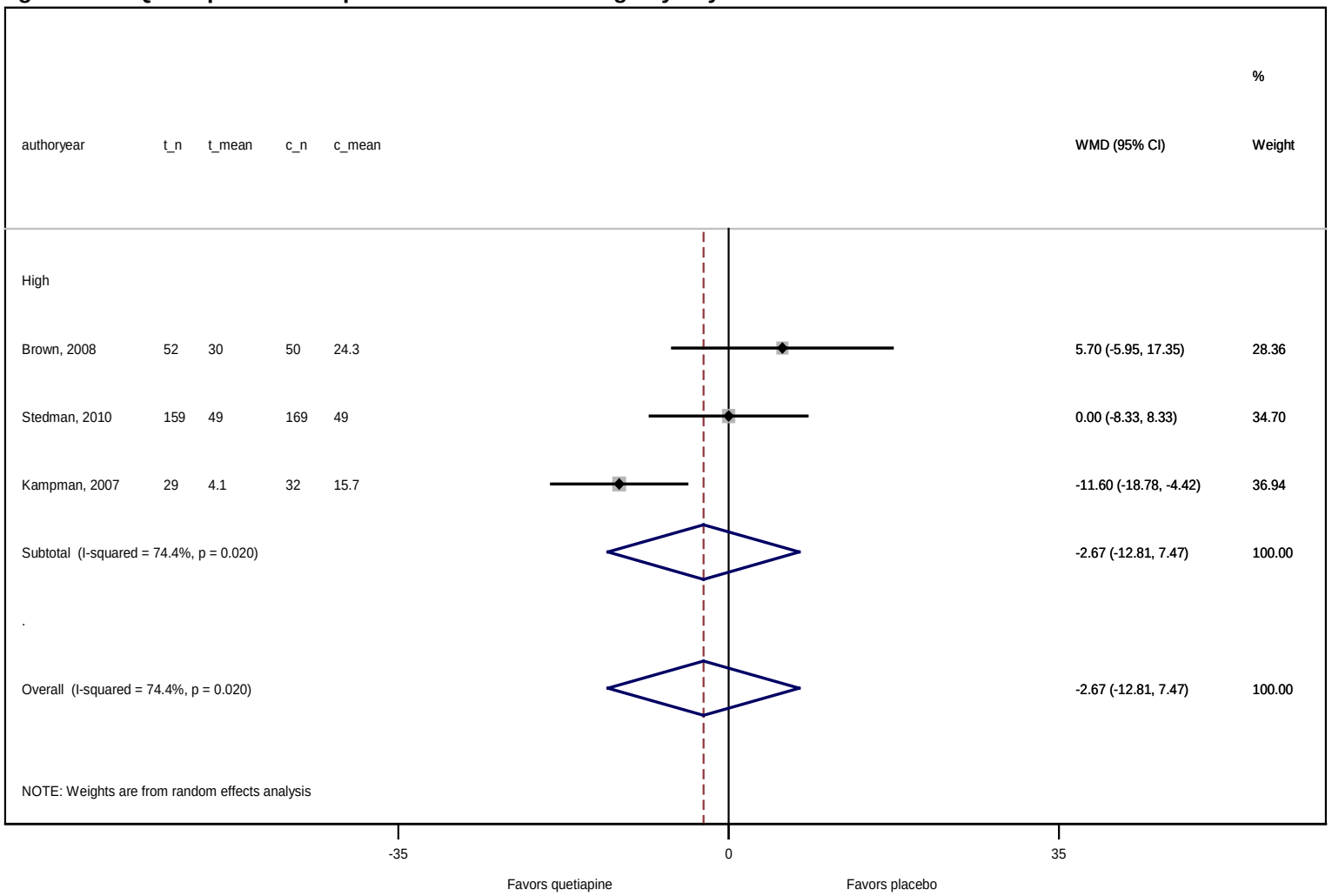


Figure F-58. Sertraline versus placebo: Percent drinking days by risk of bias

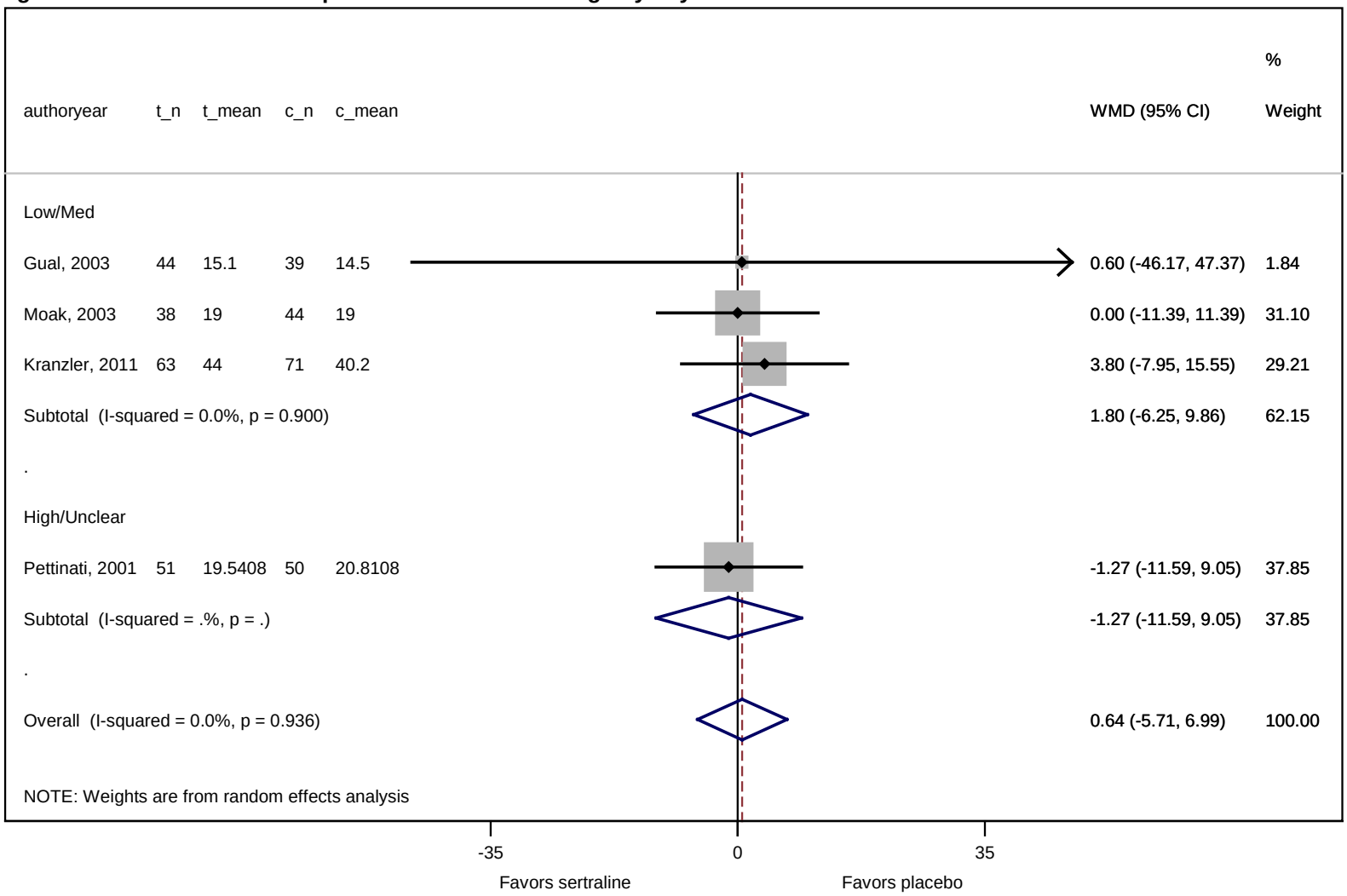


Figure F-59. Topiramate versus placebo: Percent drinking days by risk of bias

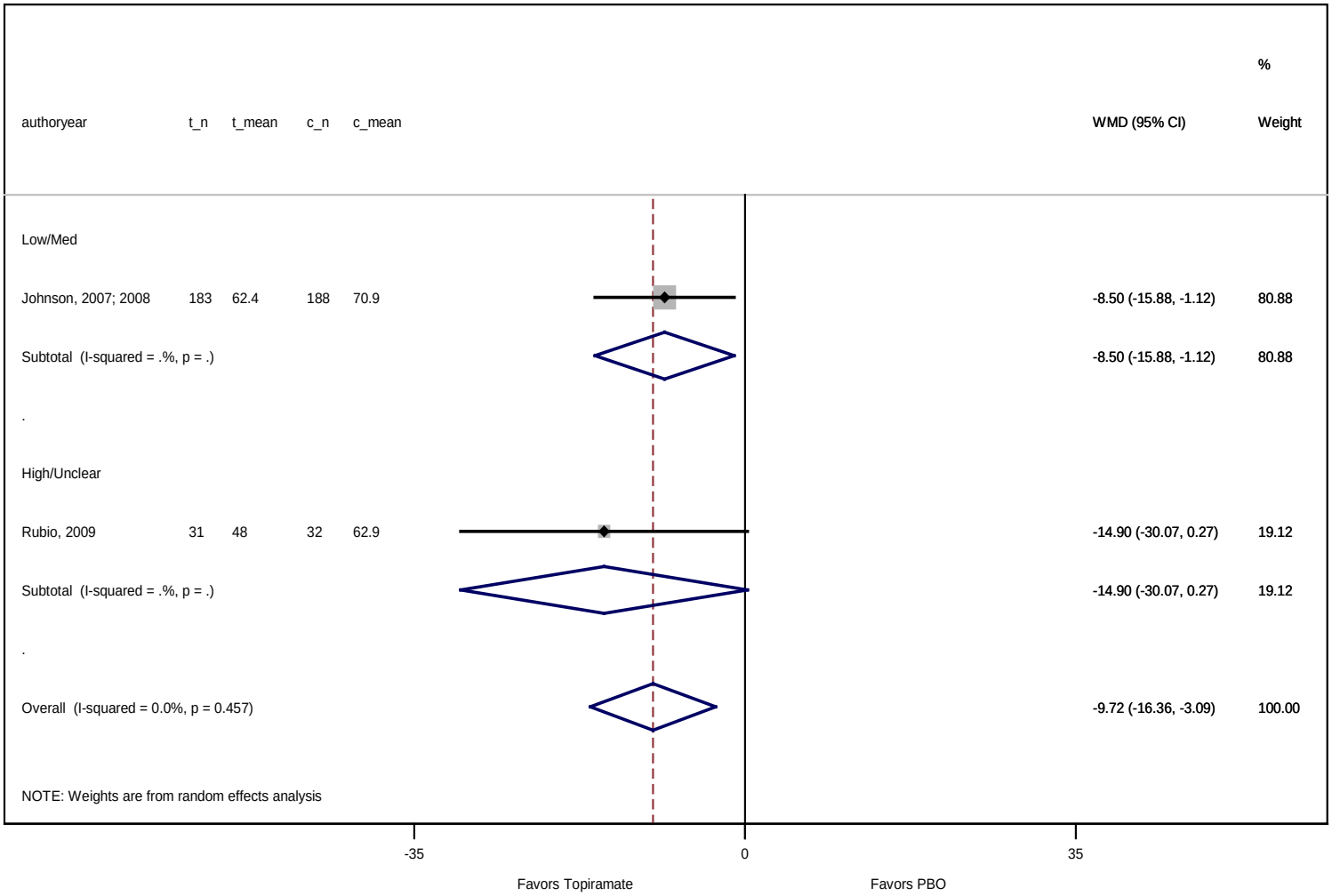


Figure F-60. Valproic acid versus placebo: Percent drinking days by risk of bias

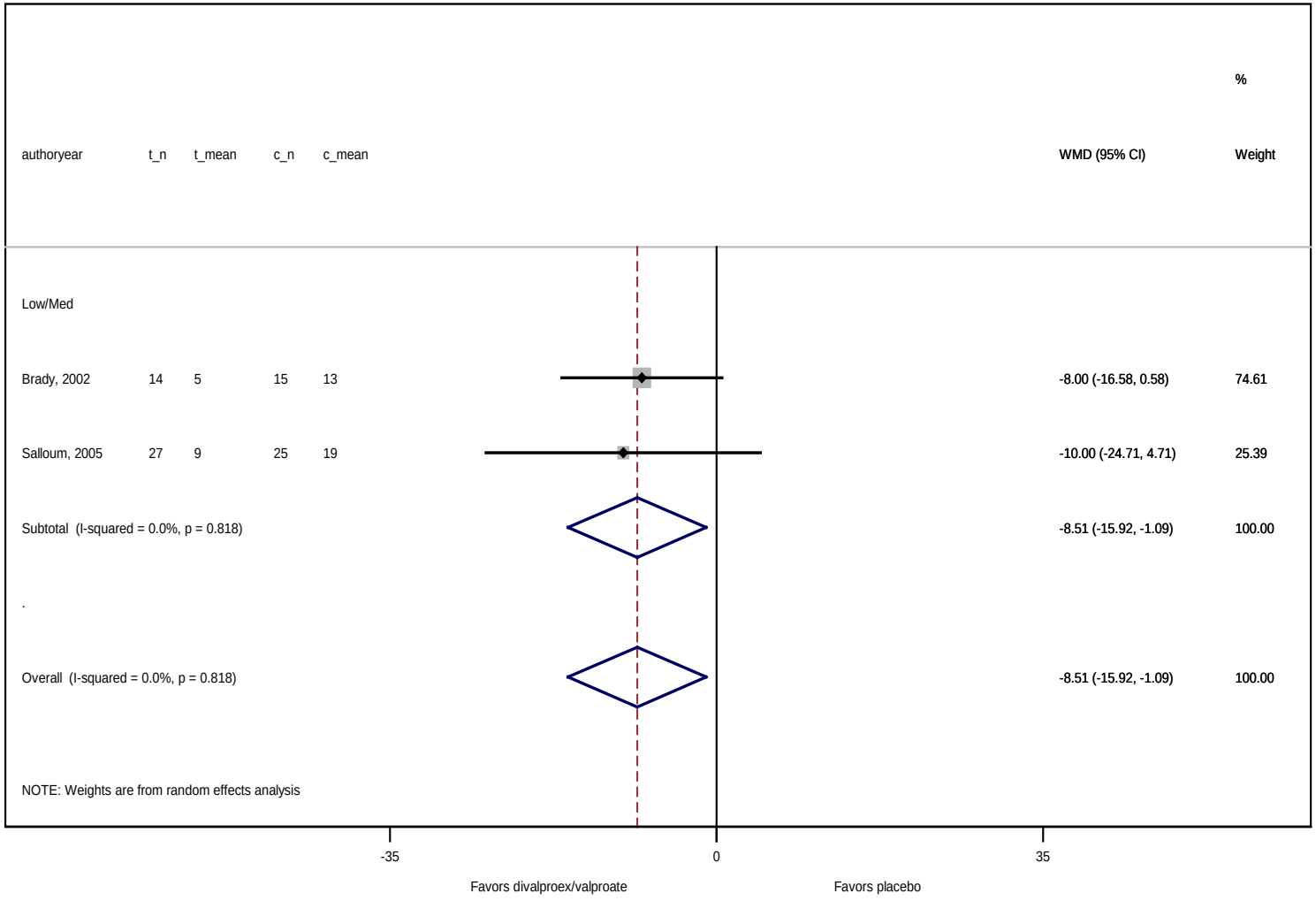


Figure F-61. Nalmefene versus placebo: Change in heavy drinking days over the past month by risk of bias; observed cases (OC) analysis

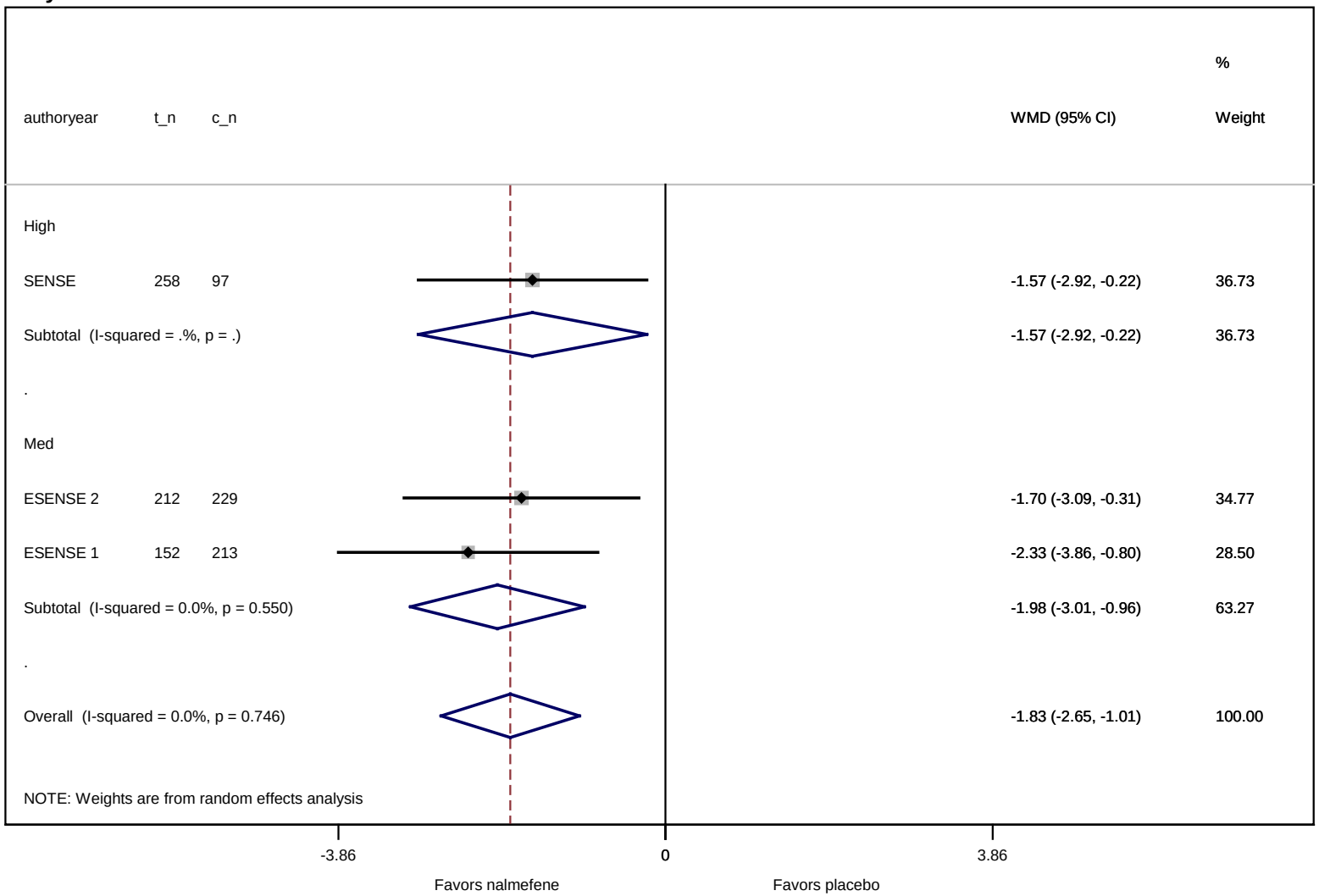


Figure F-62. Nalmefene versus placebo: Change in heavy drinking days over the past month by risk of bias; placebo mean imputation (PMI) analysis

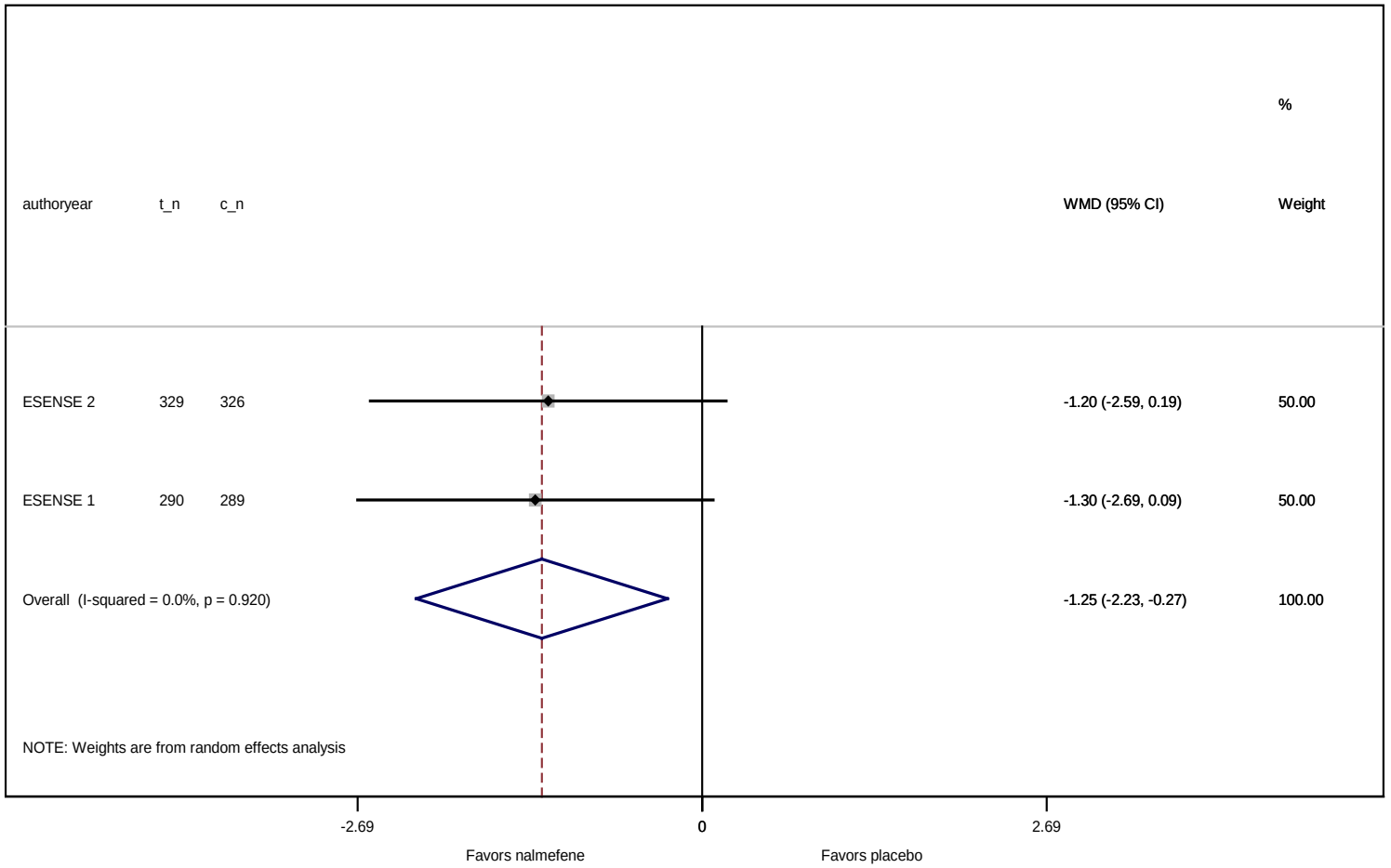


Figure F-63. Quetiapine versus placebo: Percent heavy drinking days by risk of bias

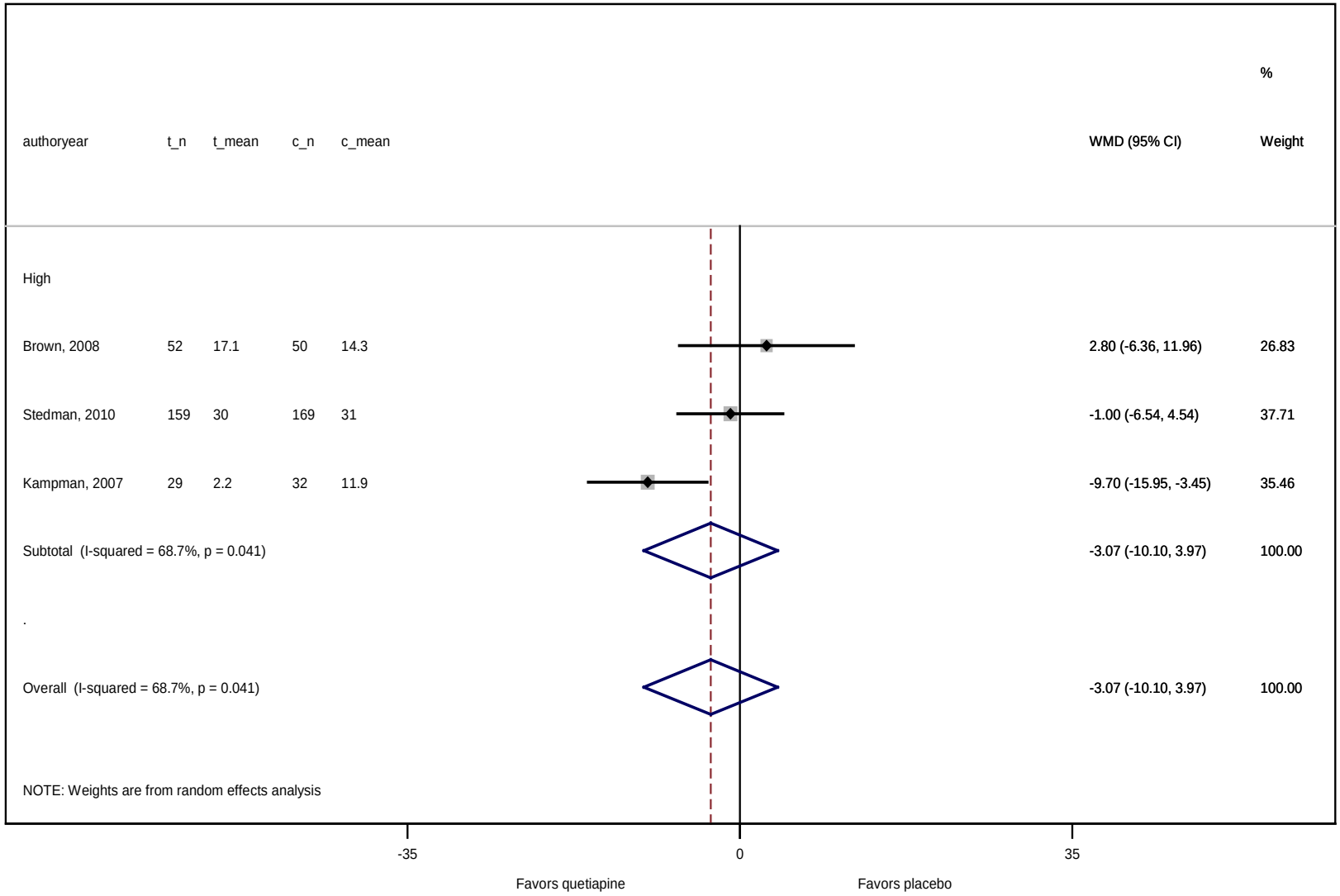


Figure F-64. Sertraline versus placebo: Percent heavy drinking days by risk of bias

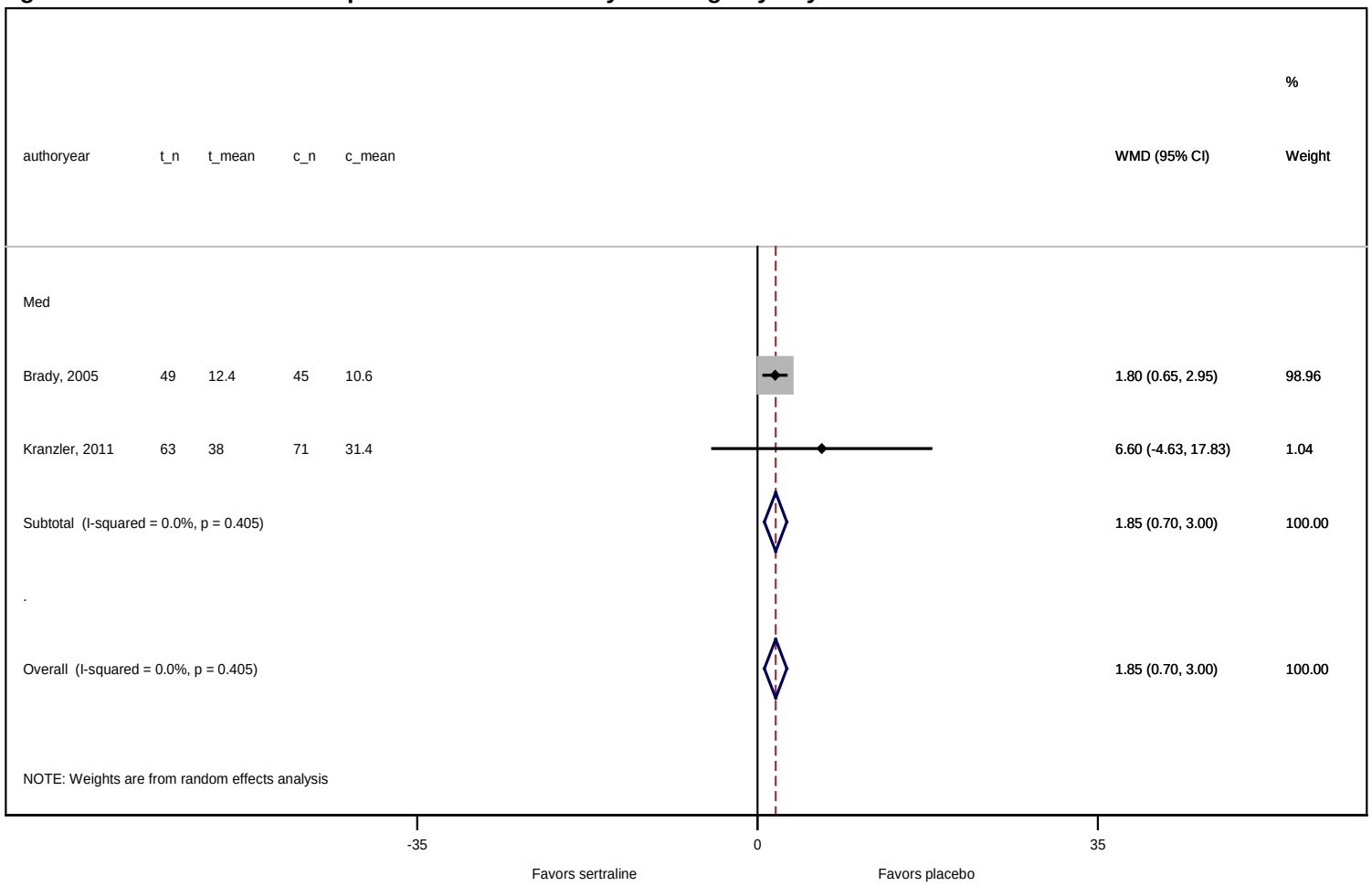


Figure F-65. Topiramate versus placebo: Percent heavy drinking days; low and medium risk of bias

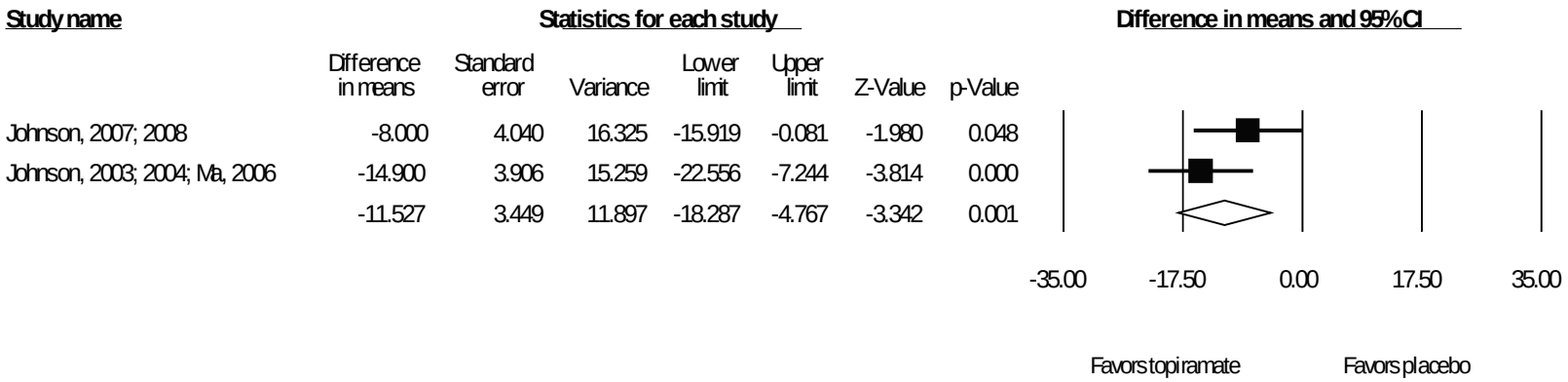


Figure F-66. Topiramate versus placebo: Percent heavy drinking days; sensitivity analysis

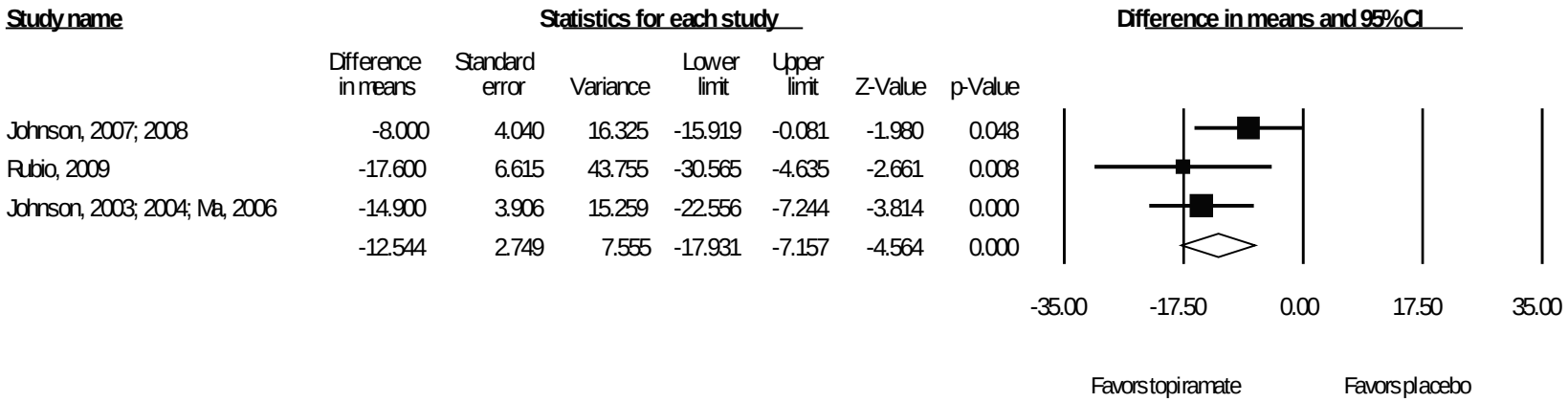


Figure F-67. Valproic acid versus placebo: Drinks per drinking day by risk of bias

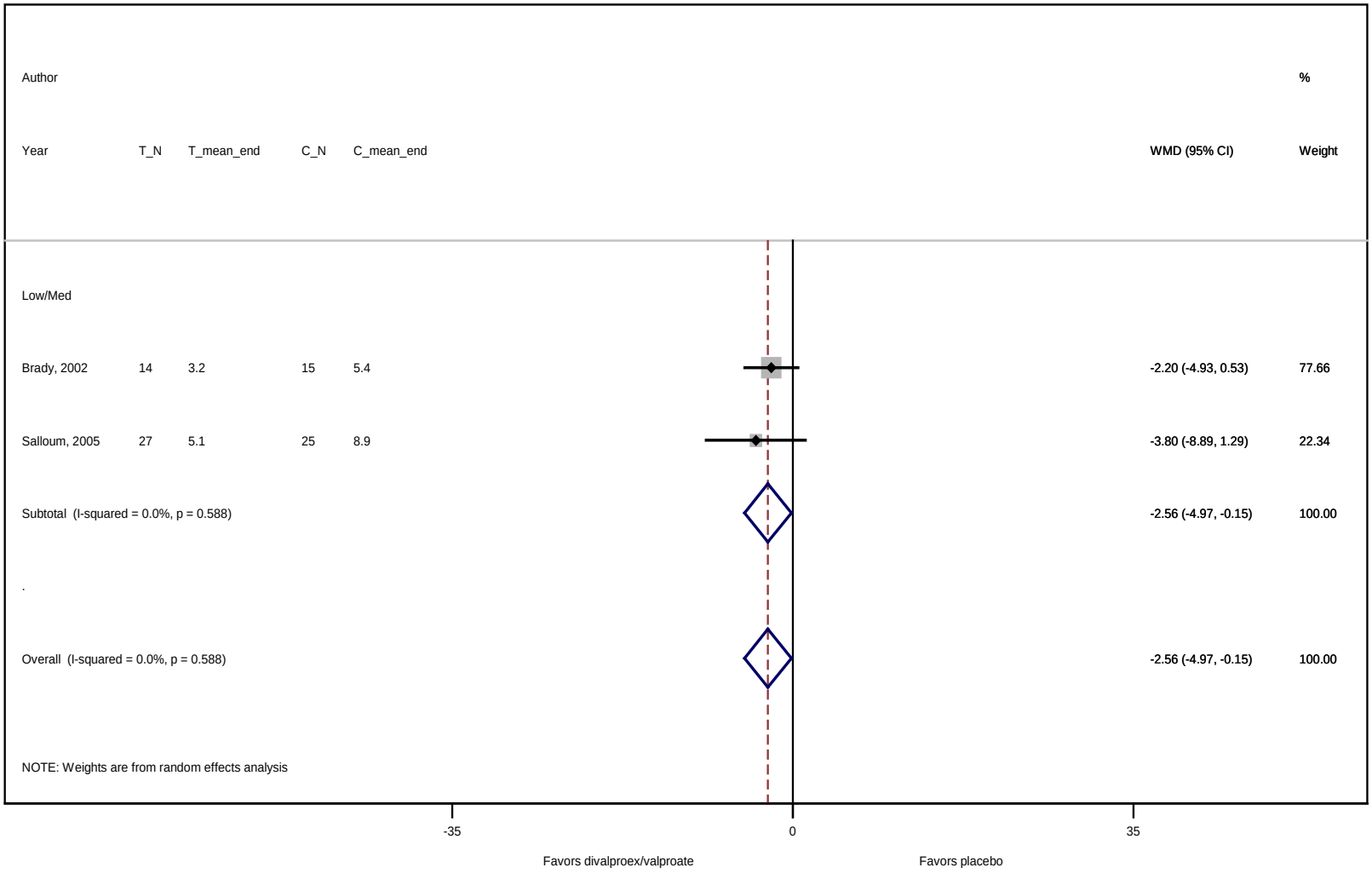


Figure F-68. Fluoxetine versus placebo: Drinks per drinking day by risk of bias

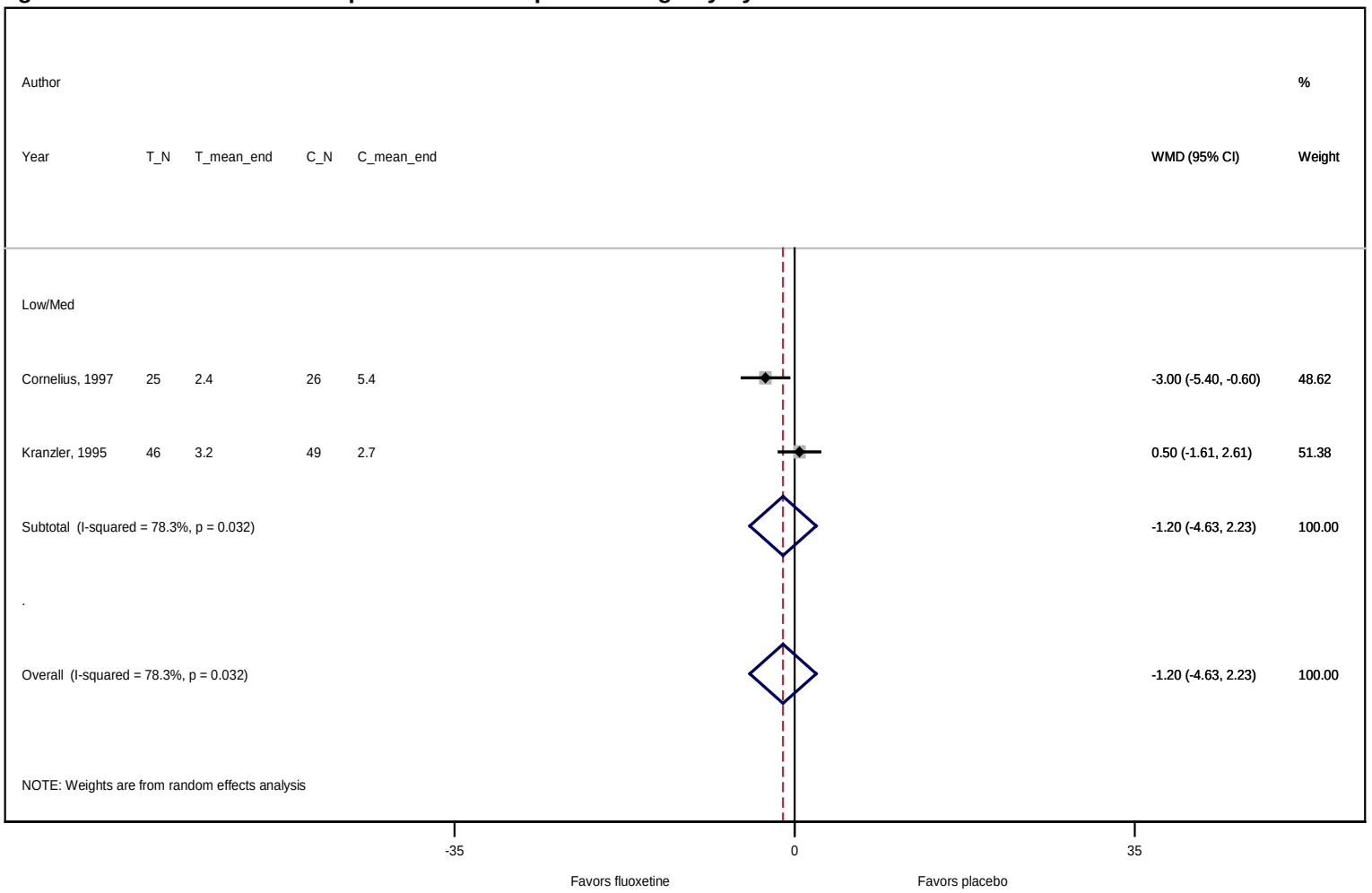


Figure F-69. Nalmefene versus placebo: Drinks per drinking day by risk of bias

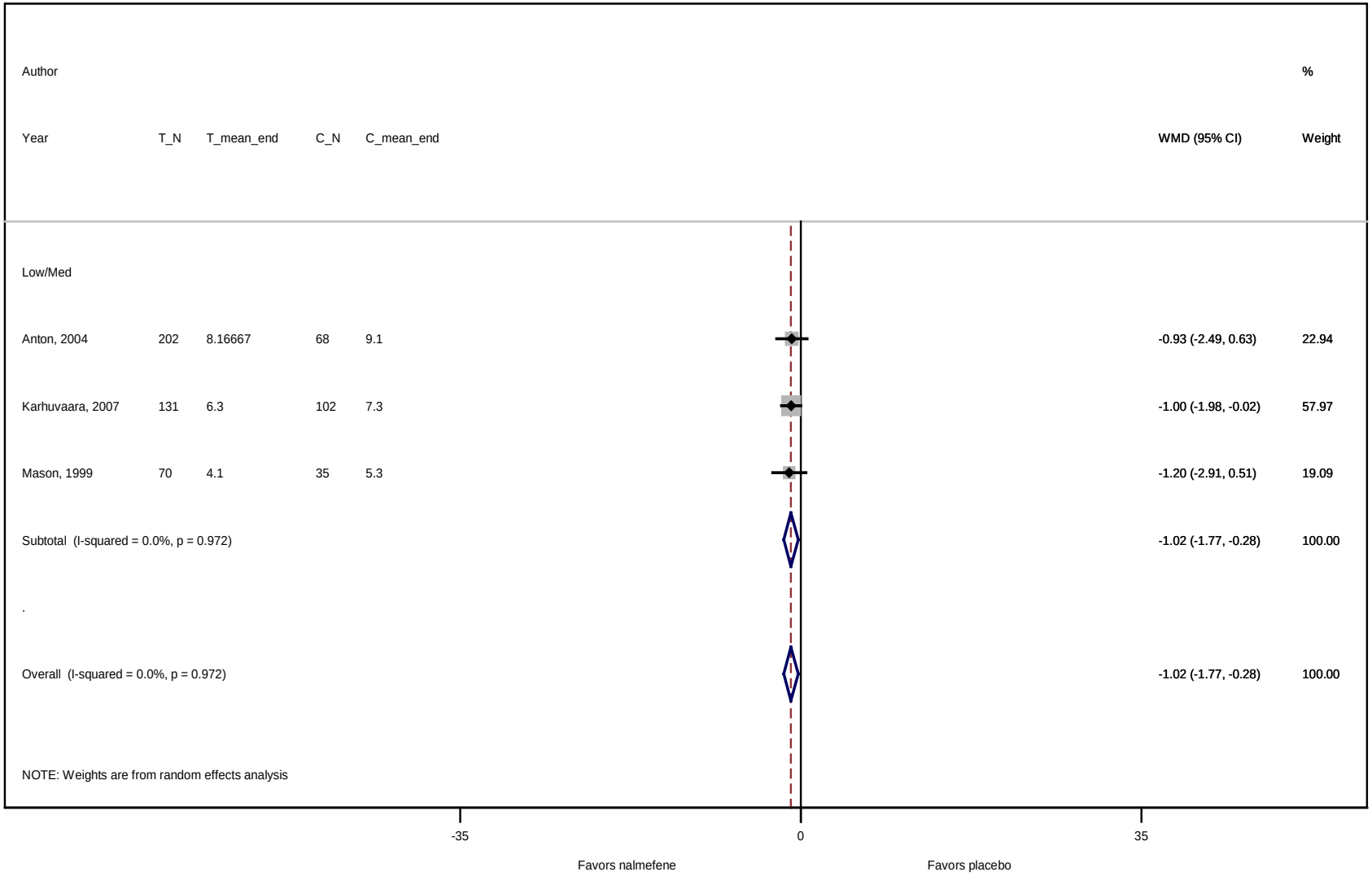


Figure F-70. Sertraline versus placebo: Drinks per drinking day by risk of bias

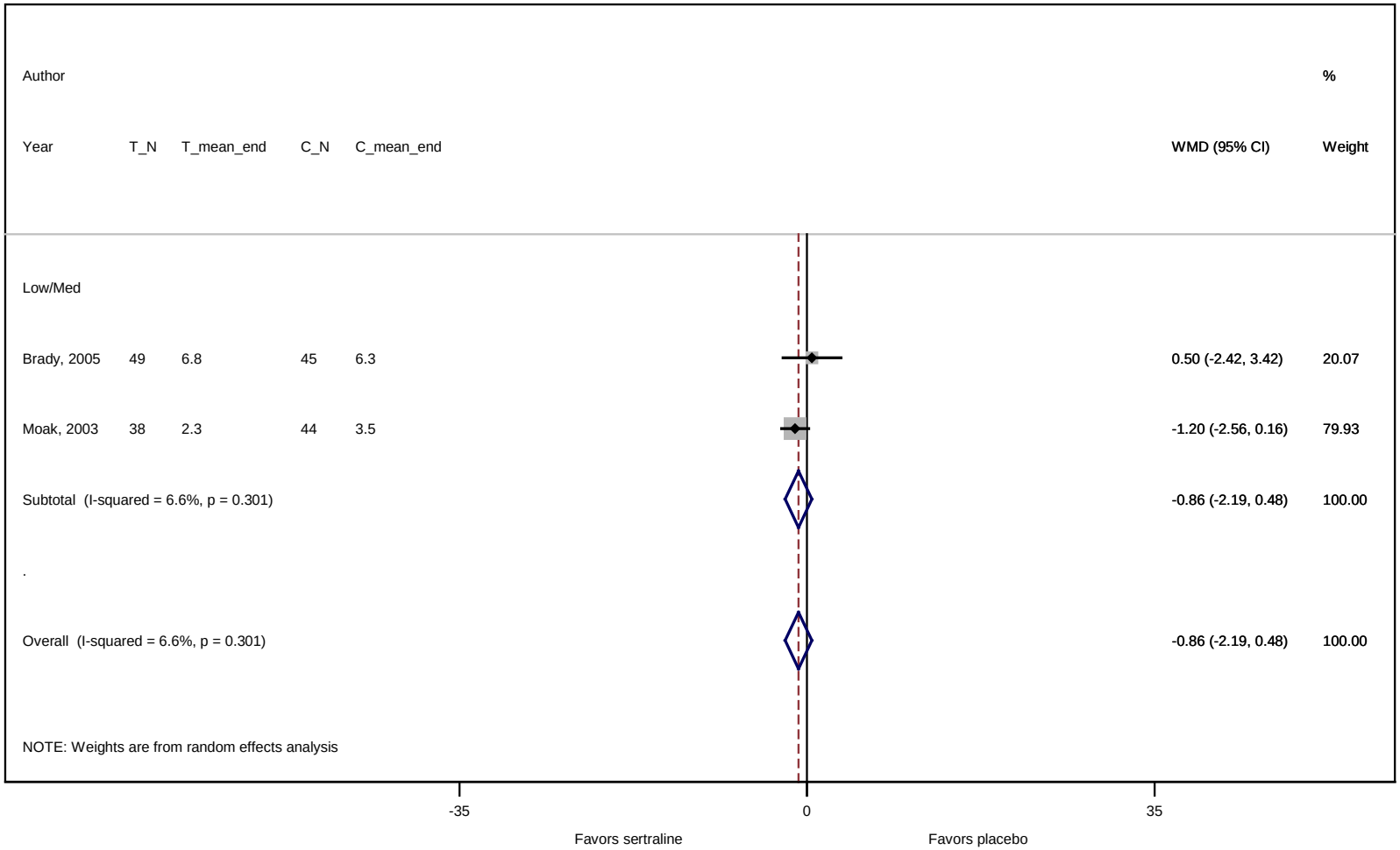
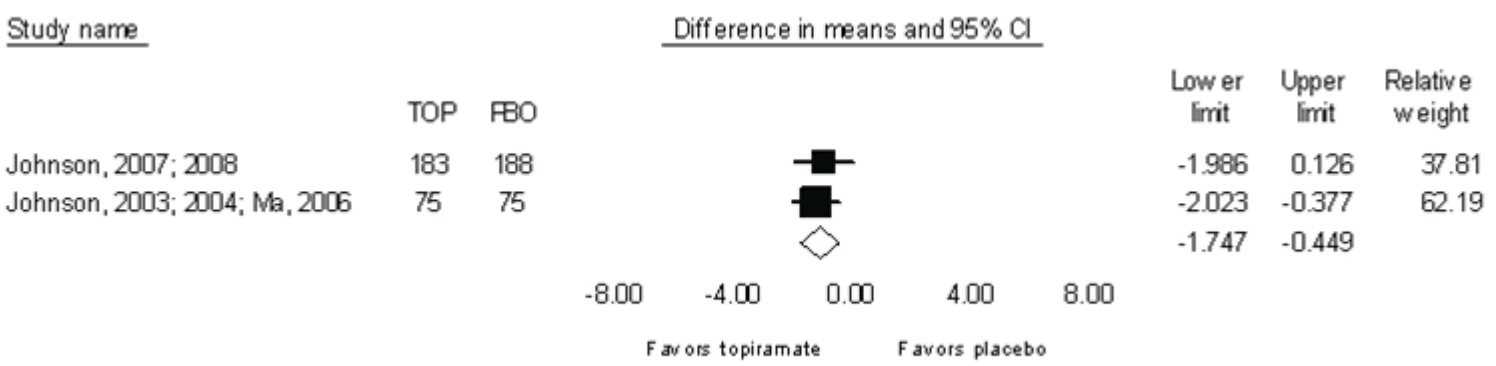


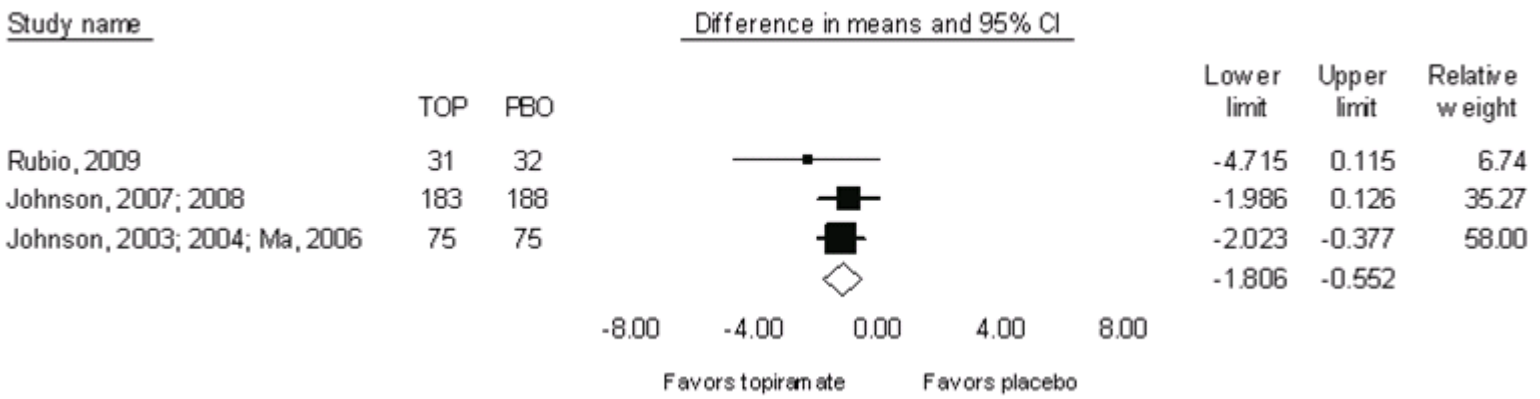
Figure F-71. Topiramate versus placebo: Drinks per drinking day, low/medium risk of bias studies



WMD: -1.098, 95% CI (-1.747 to -0.449)

Heterogeneity			
Q-value	df (Q)	P-value	I-squared
0.156202	1	0.692677	0

Figure F-72. Topiramate versus placebo: Drinks per drinking day, sensitivity analysis with high risk of bias study



WMD: -1.179, 95% CI (-1.806 to -0.552)

Heterogeneity			
Q-value	df (Q)	P-value	I-squared
1.043611	2	0.593448	0

Key Question 3 Meta-Analysis Results

We found insufficient data for all included medications to perform meta-analyses for the following harms: Glaucoma, Metabolic Acidosis, Palpitations

Figure F-73. Anxiety – Acamprosate versus placebo by risk of bias rating

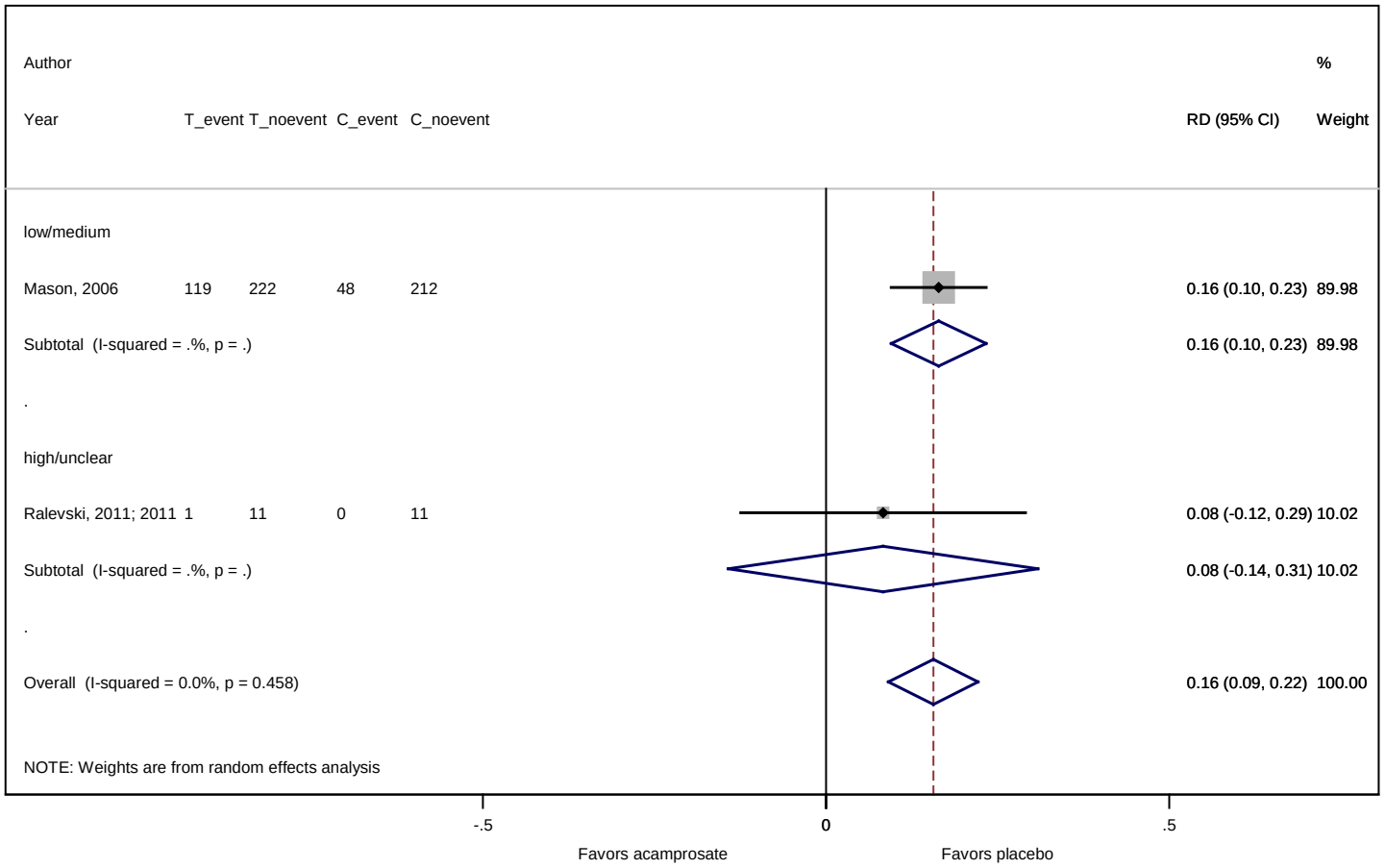


Figure F-74. Anxiety – Naltrexone versus placebo by risk of bias rating

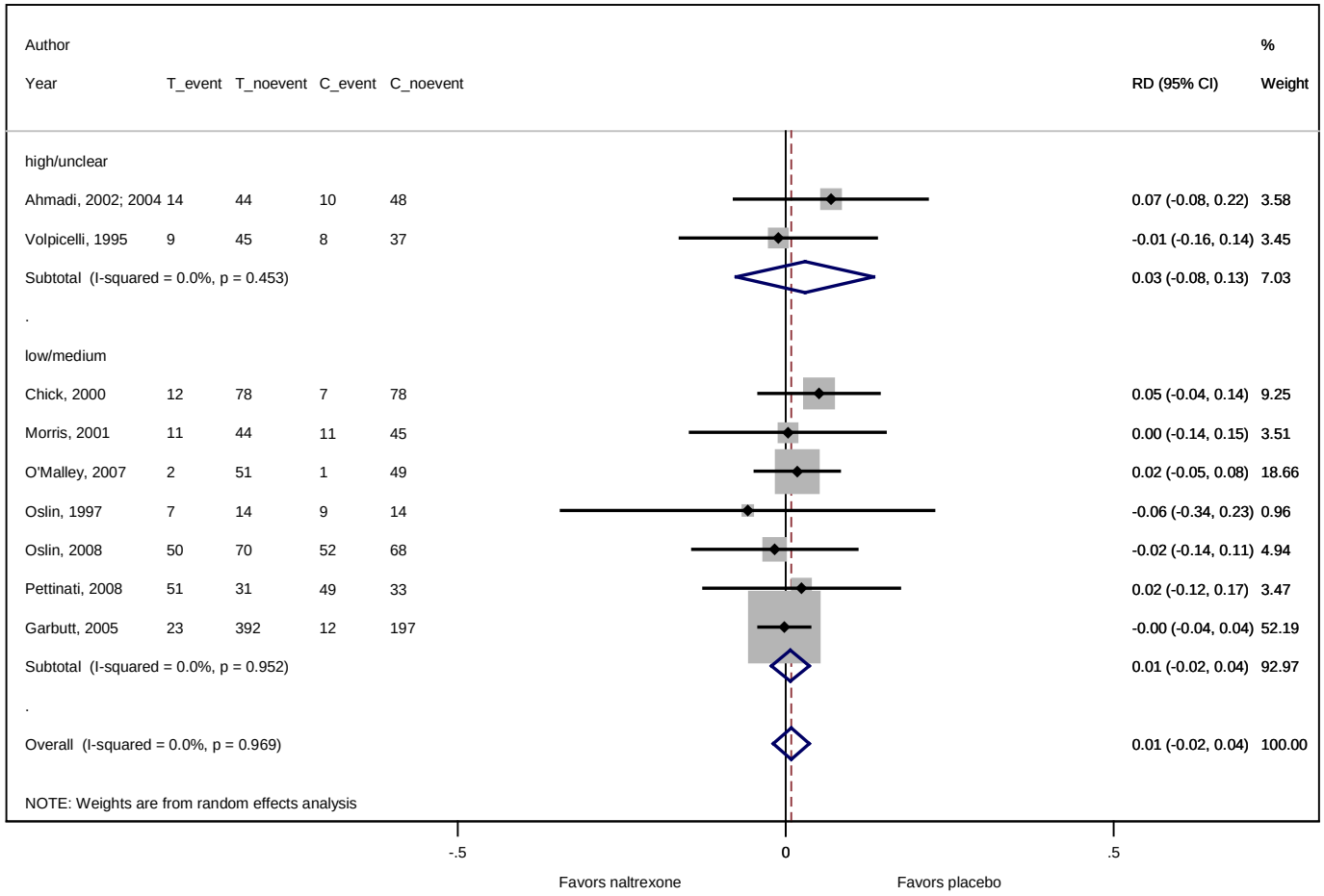


Figure F-75. Cognitive dysfunction – Nalmefene versus placebo by risk of bias rating

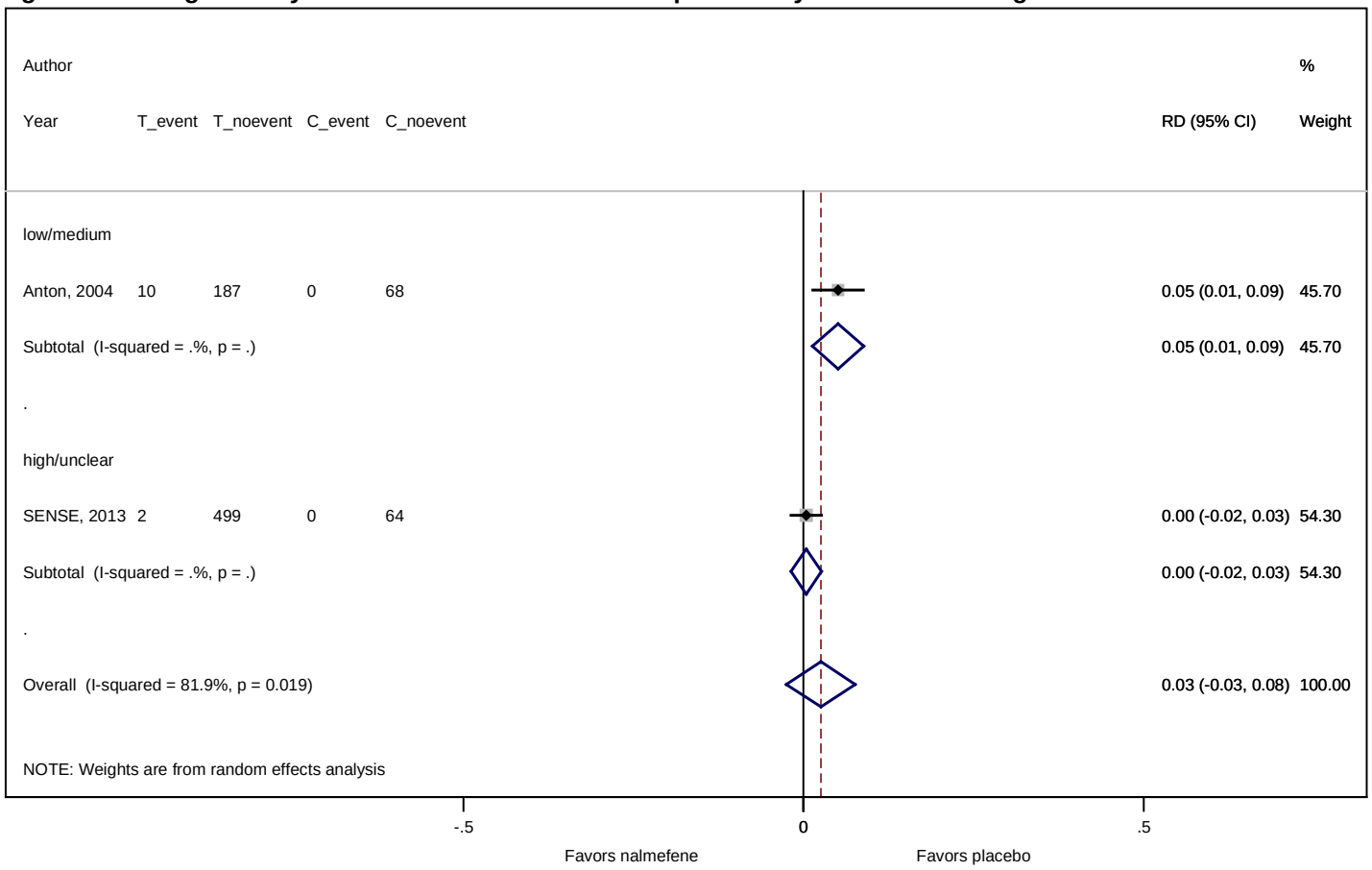
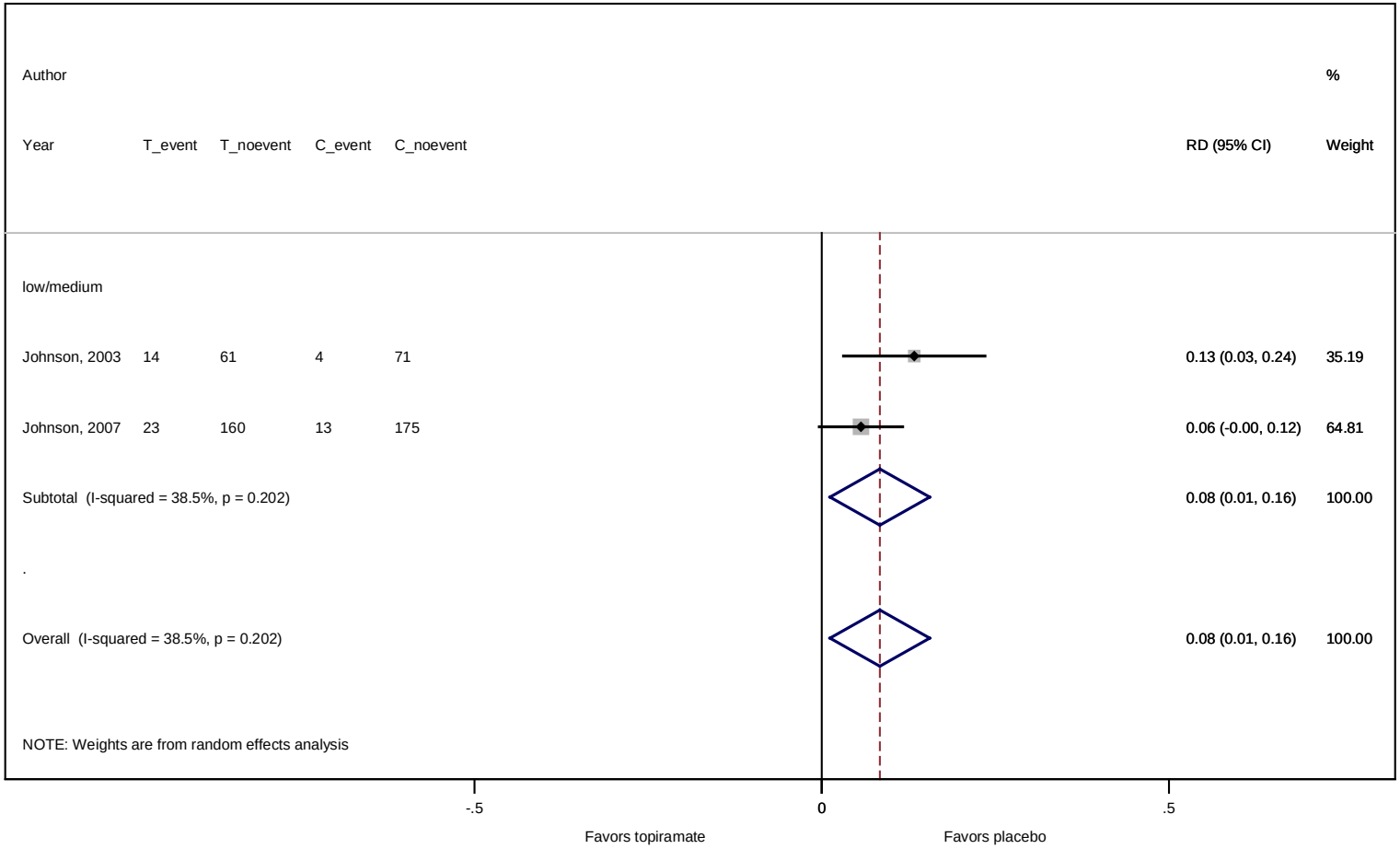


Figure F-76. Cognitive dysfunction – Topiramate versus placebo by risk of bias



* Note: Values from Johnson, 2007 are from data reported as “difficulty with memory;” the study also reported data for “difficulty with concentration,” which also favored placebo.

Figure F-77. Diarrhea – Acamprosate versus placebo by risk of bias rating

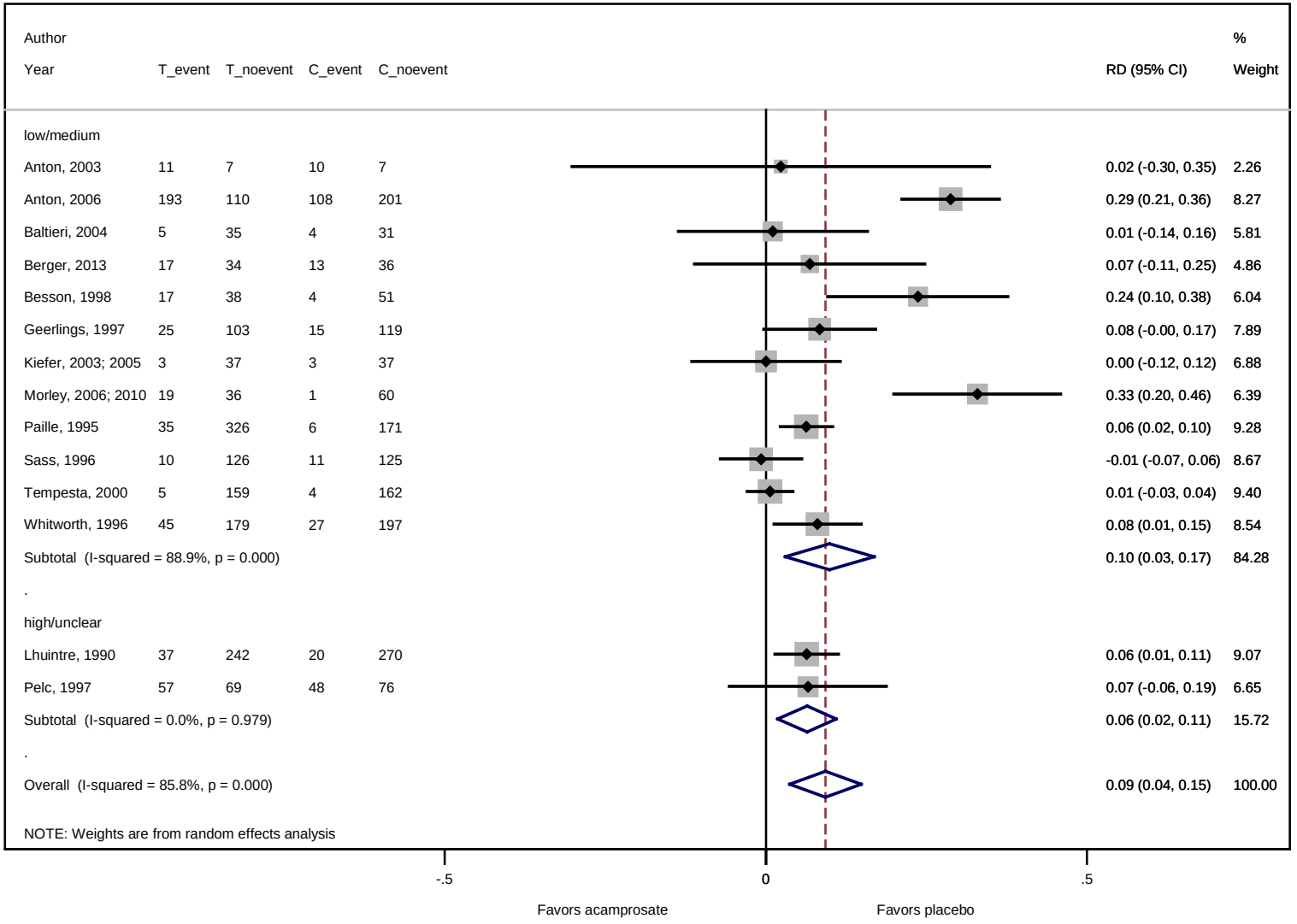


Figure F-78. Diarrhea – Naltrexone versus placebo by risk of bias rating

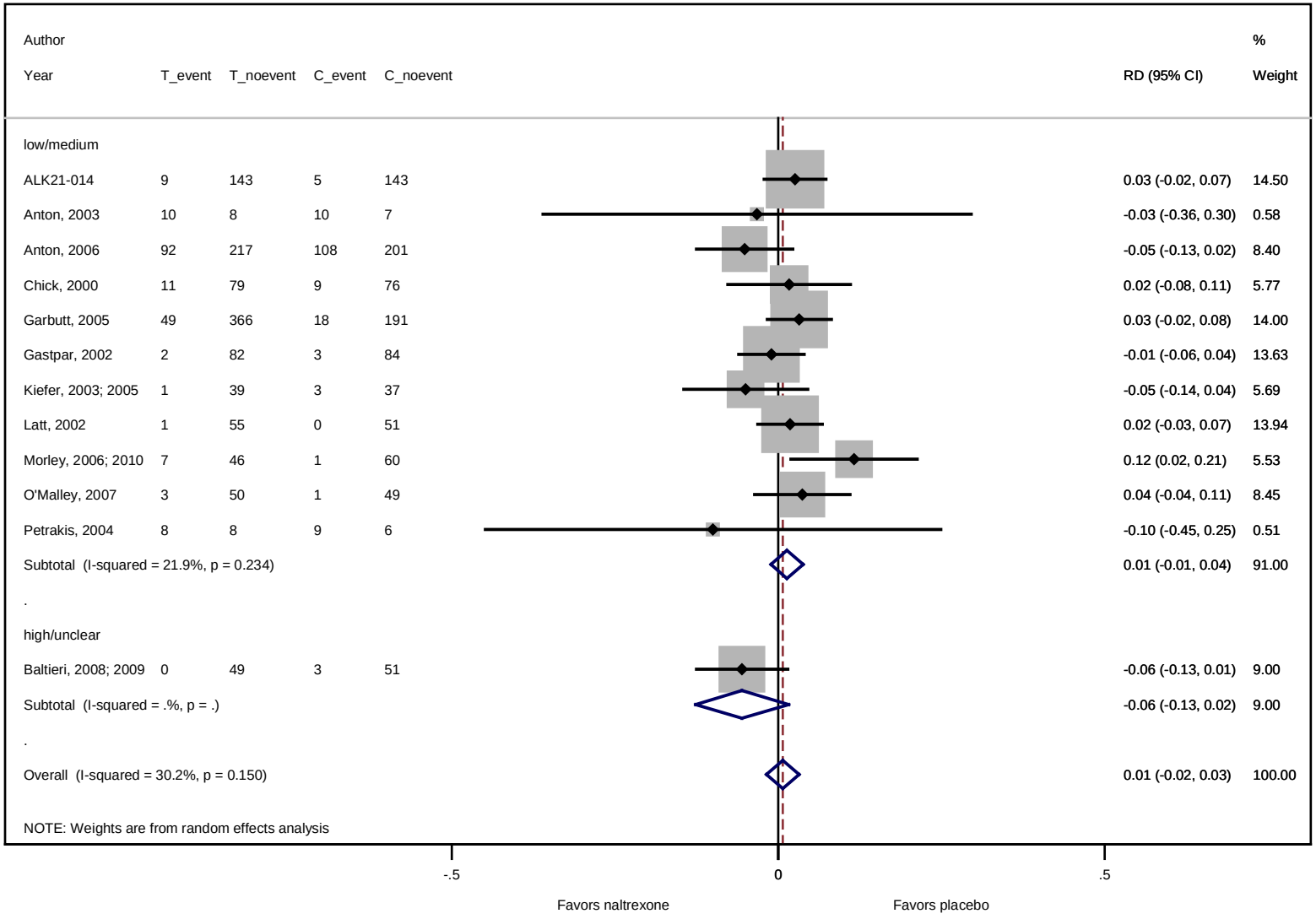


Figure F-79. Diarrhea – Acamprosate versus naltrexone by risk of bias rating

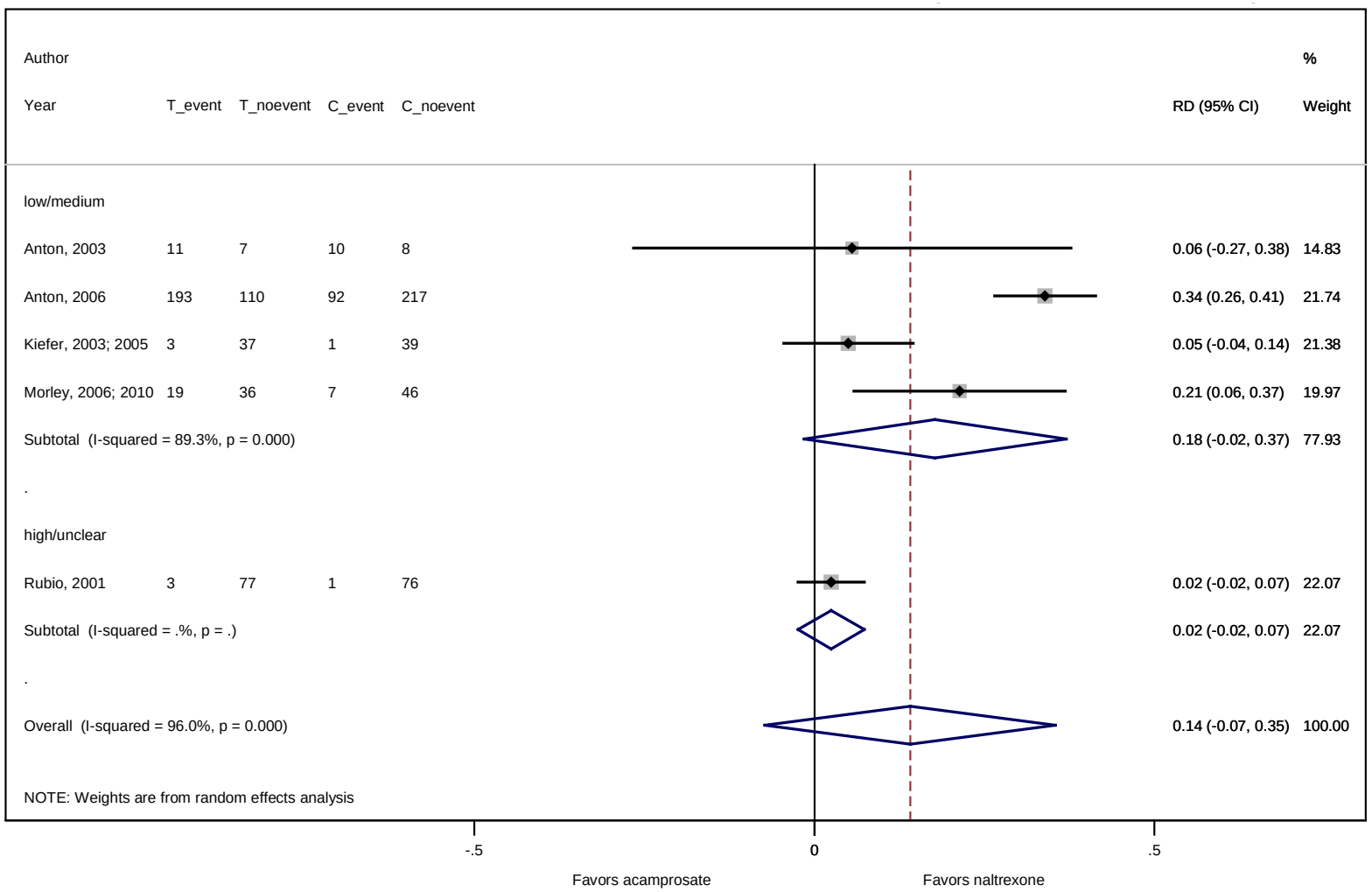


Figure F-80. Diarrhea – Nalmefene versus placebo by risk of bias rating

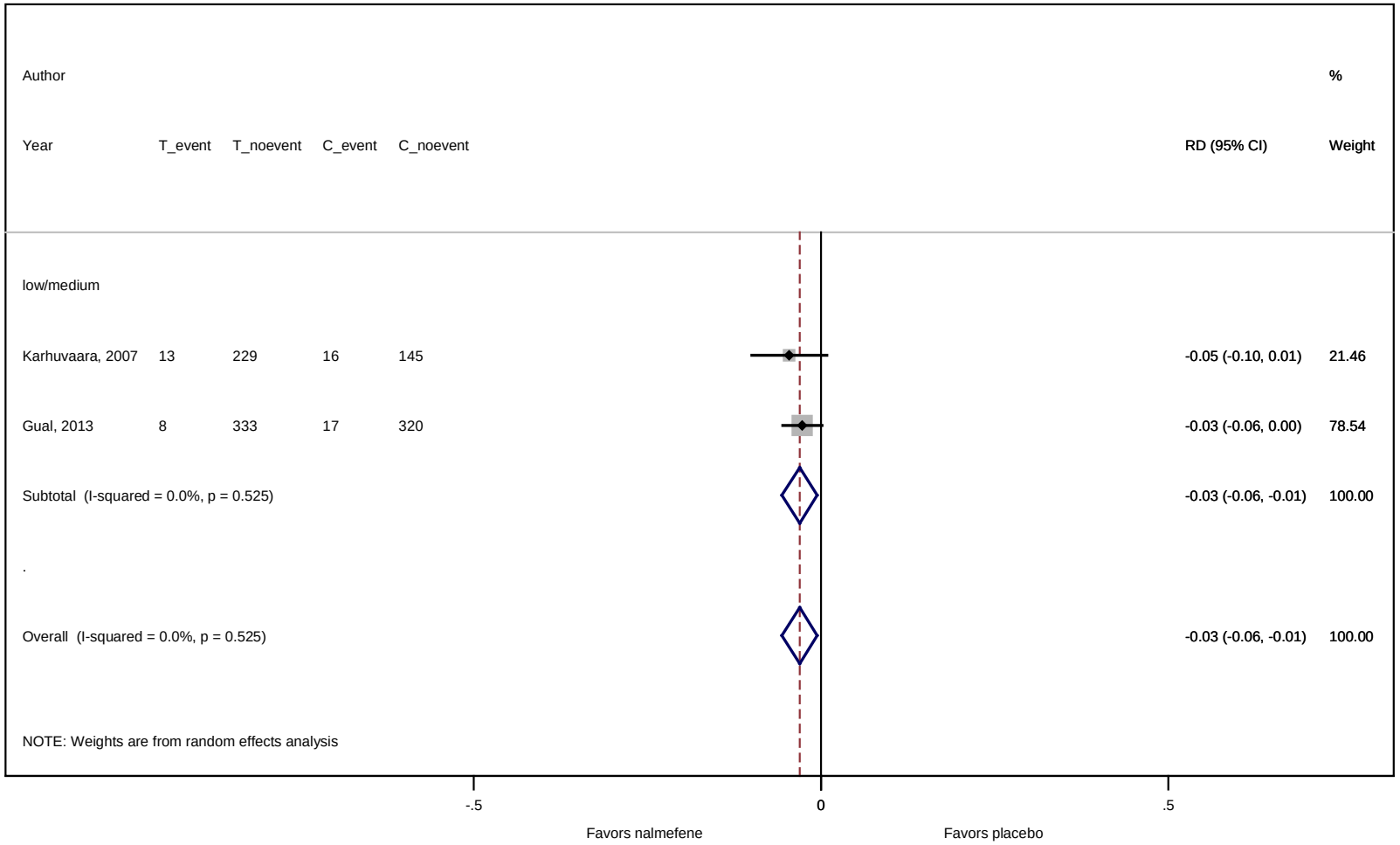


Figure F-81. Diarrhea – Topiramate compared with placebo by risk of bias rating

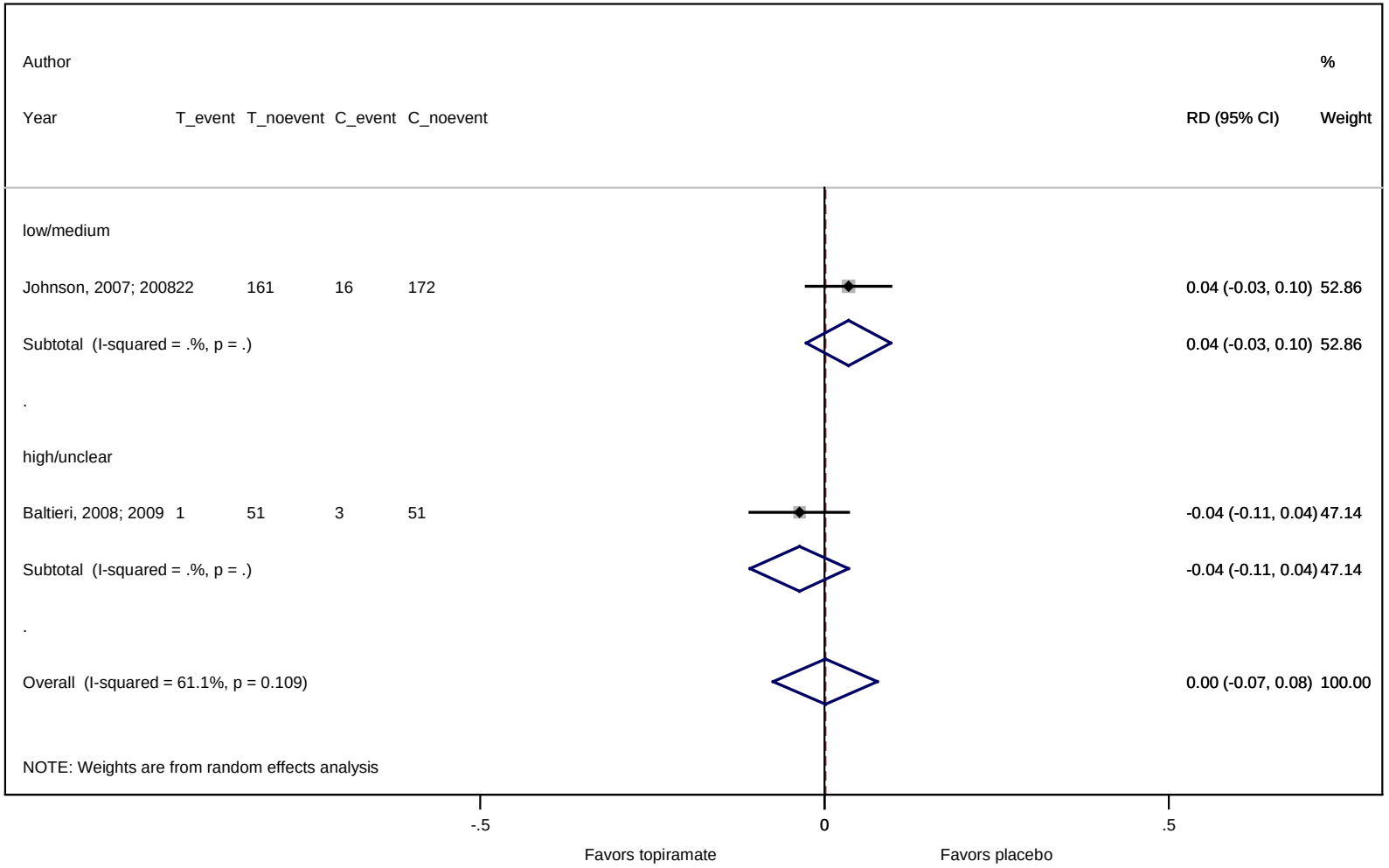


Figure F-82. Dizziness – Acamprosate versus placebo by risk of bias rating

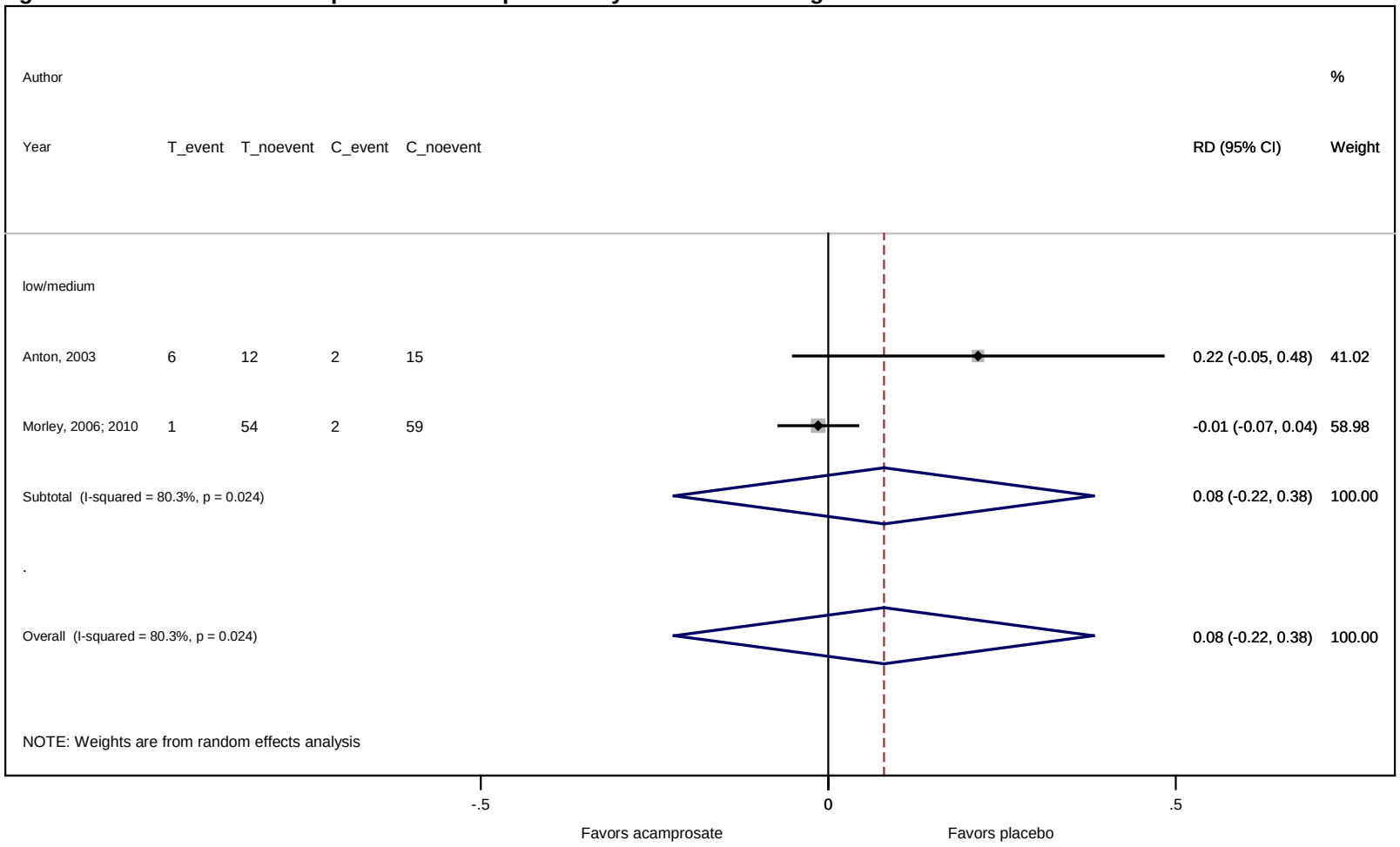


Figure F-83. Dizziness – Naltrexone versus placebo by risk of bias rating

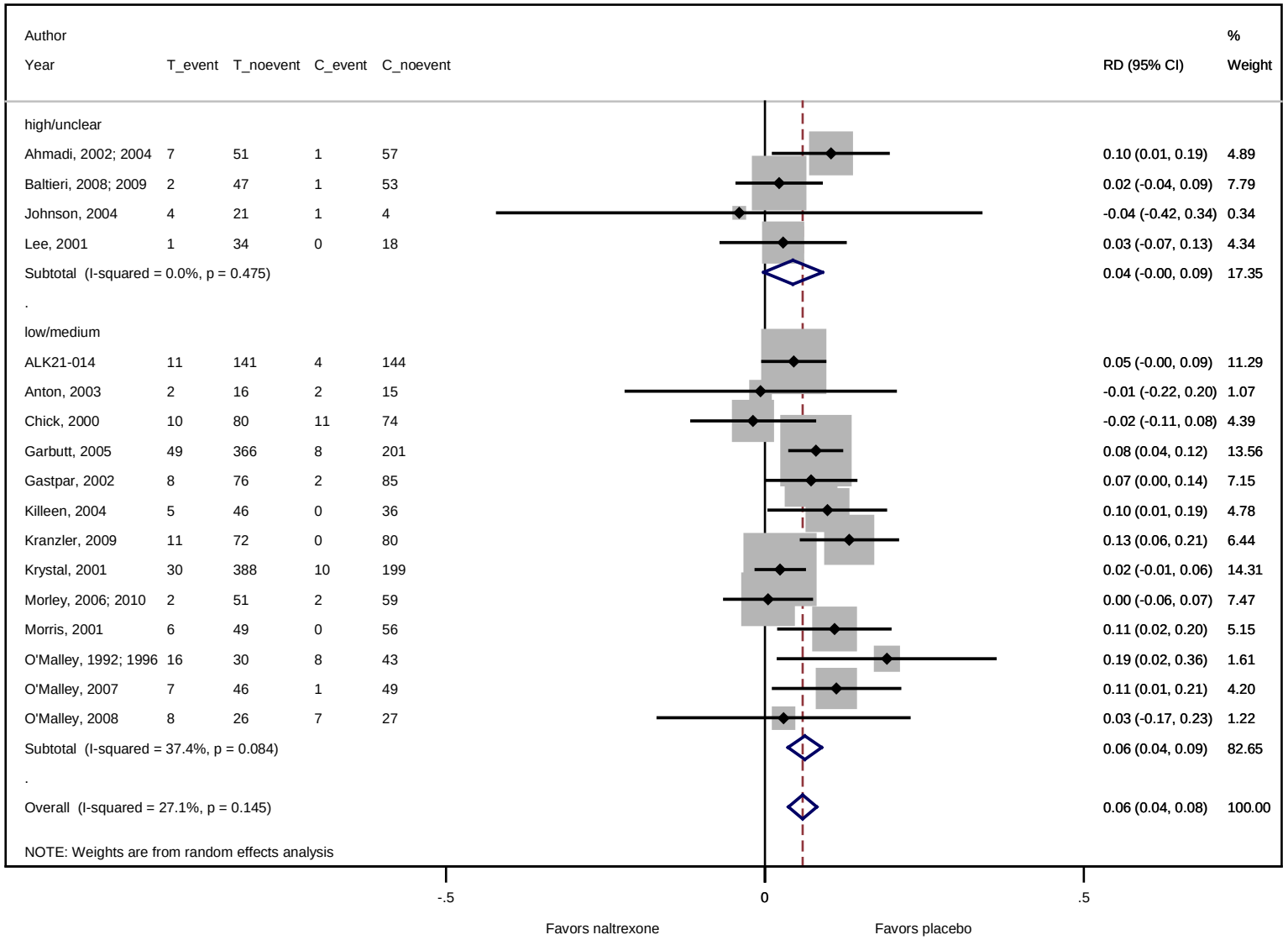


Figure F-84. Dizziness – Acamprosate versus naltrexone by risk of bias rating

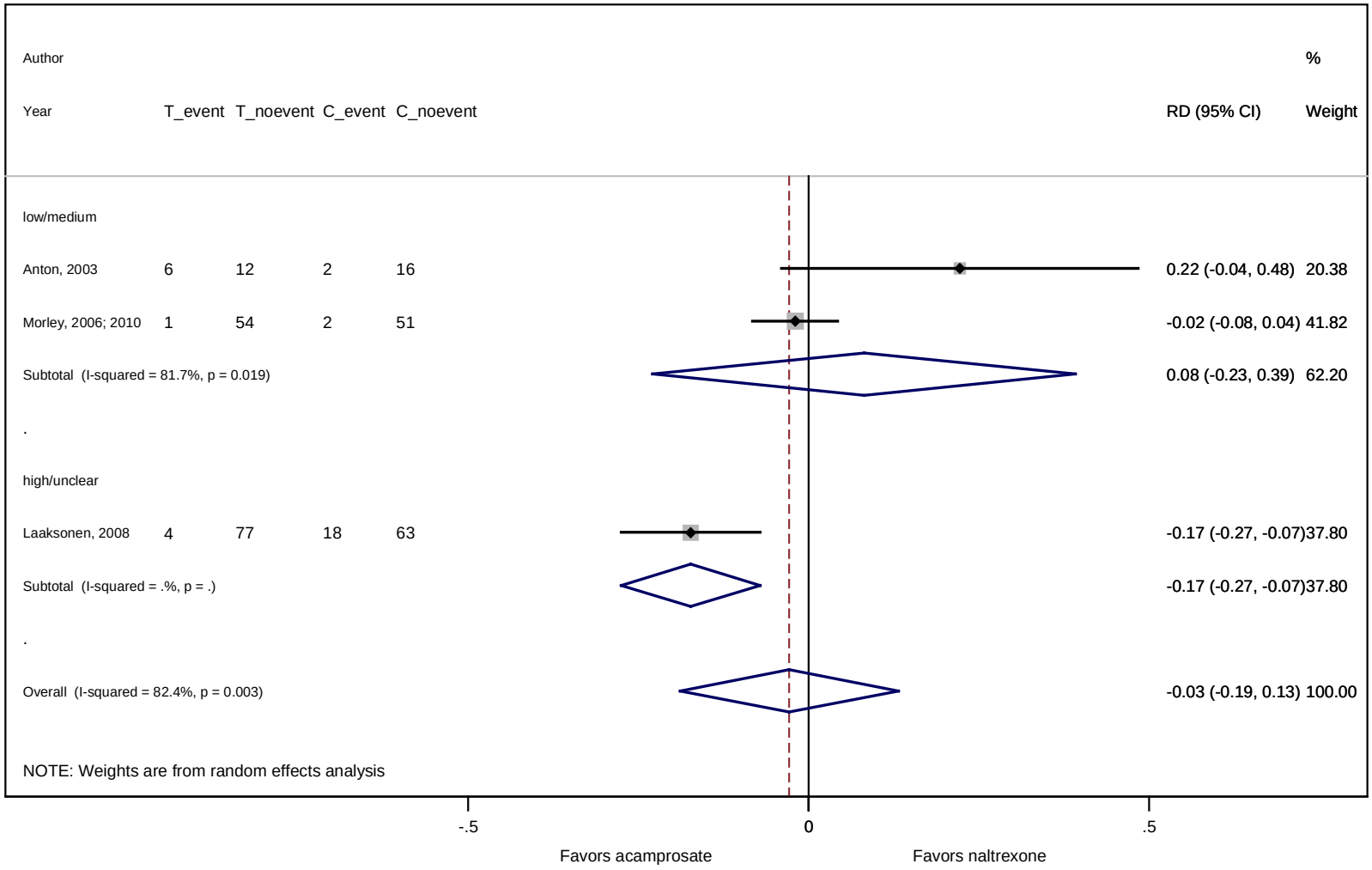


Figure F-85. Dizziness – Nalmefene versus placebo by risk of bias rating

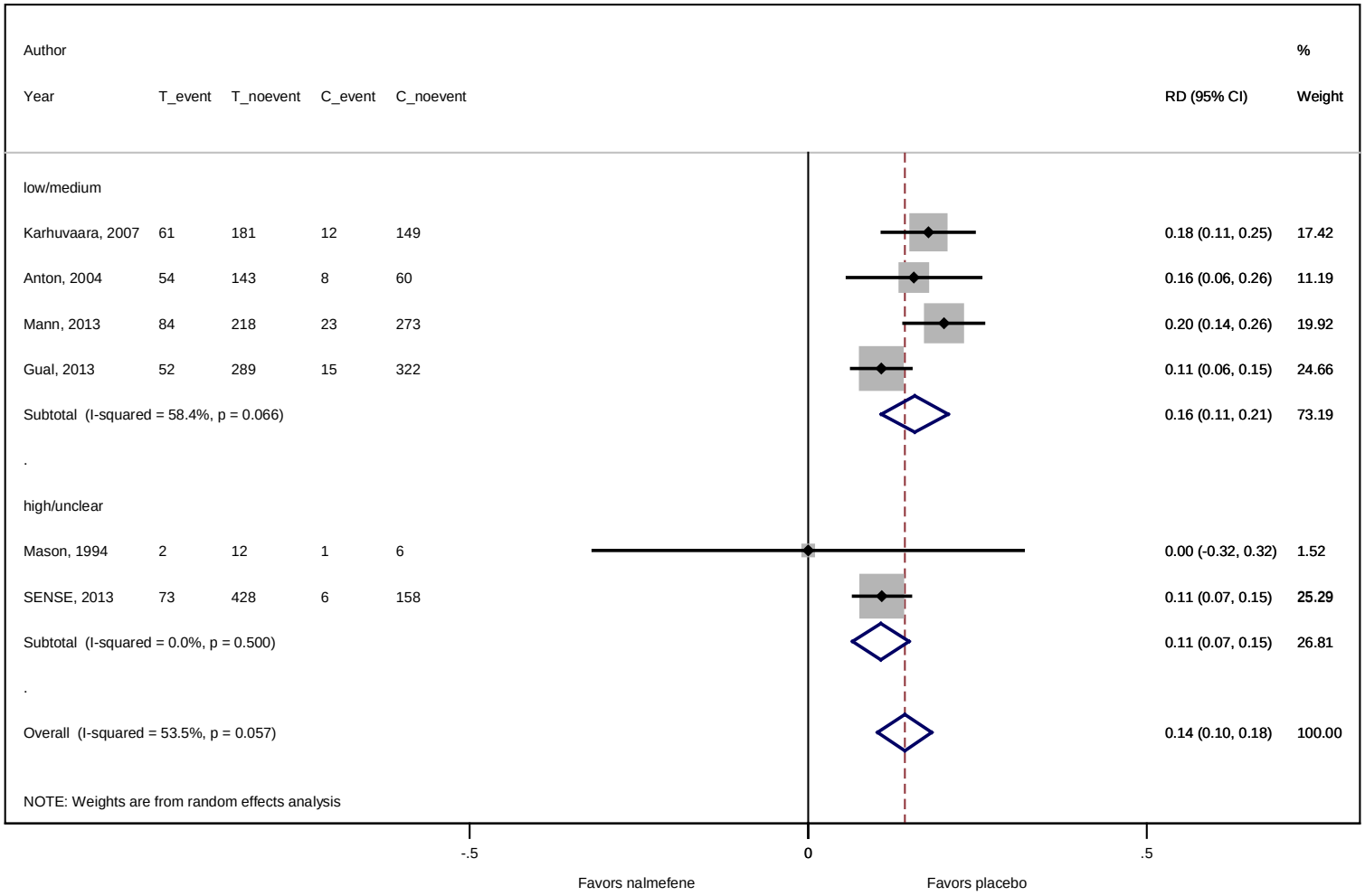


Figure F-86. Dizziness – Topiramate versus placebo by risk of bias rating

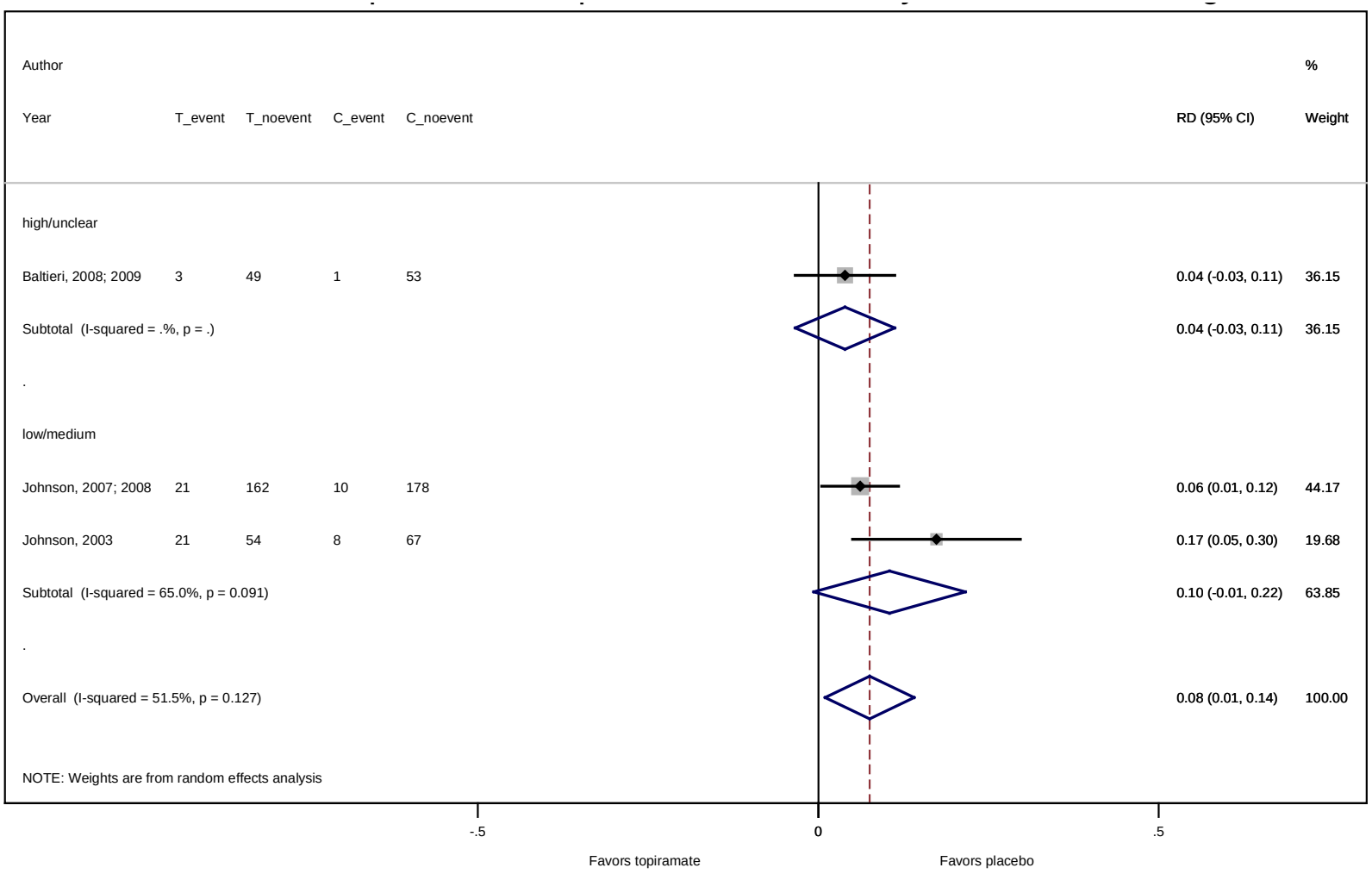


Figure F-87. Headache – Acamprosate versus placebo by risk of bias rating

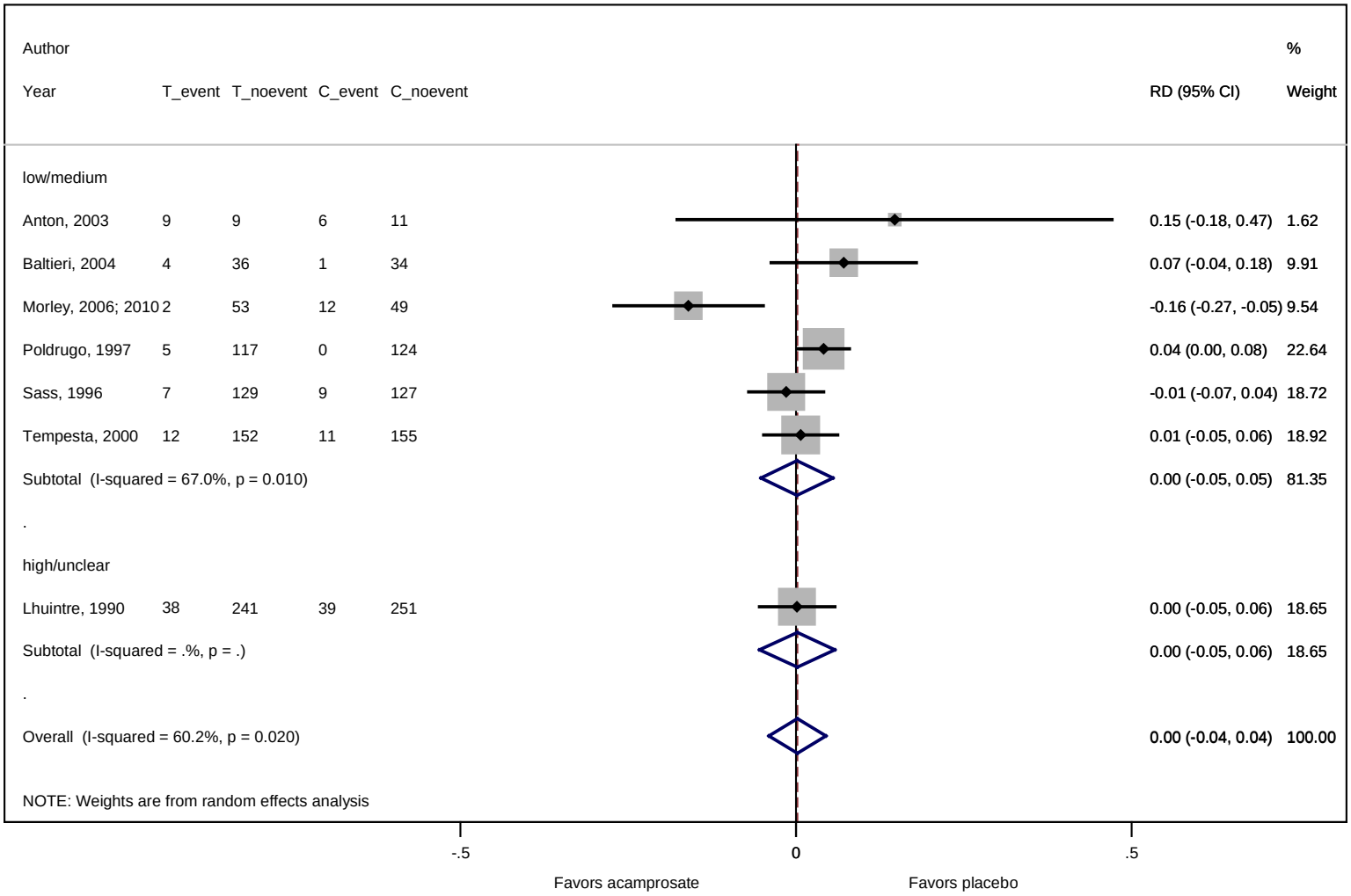


Figure F-88. Headache – Naltrexone versus placebo by risk of bias rating

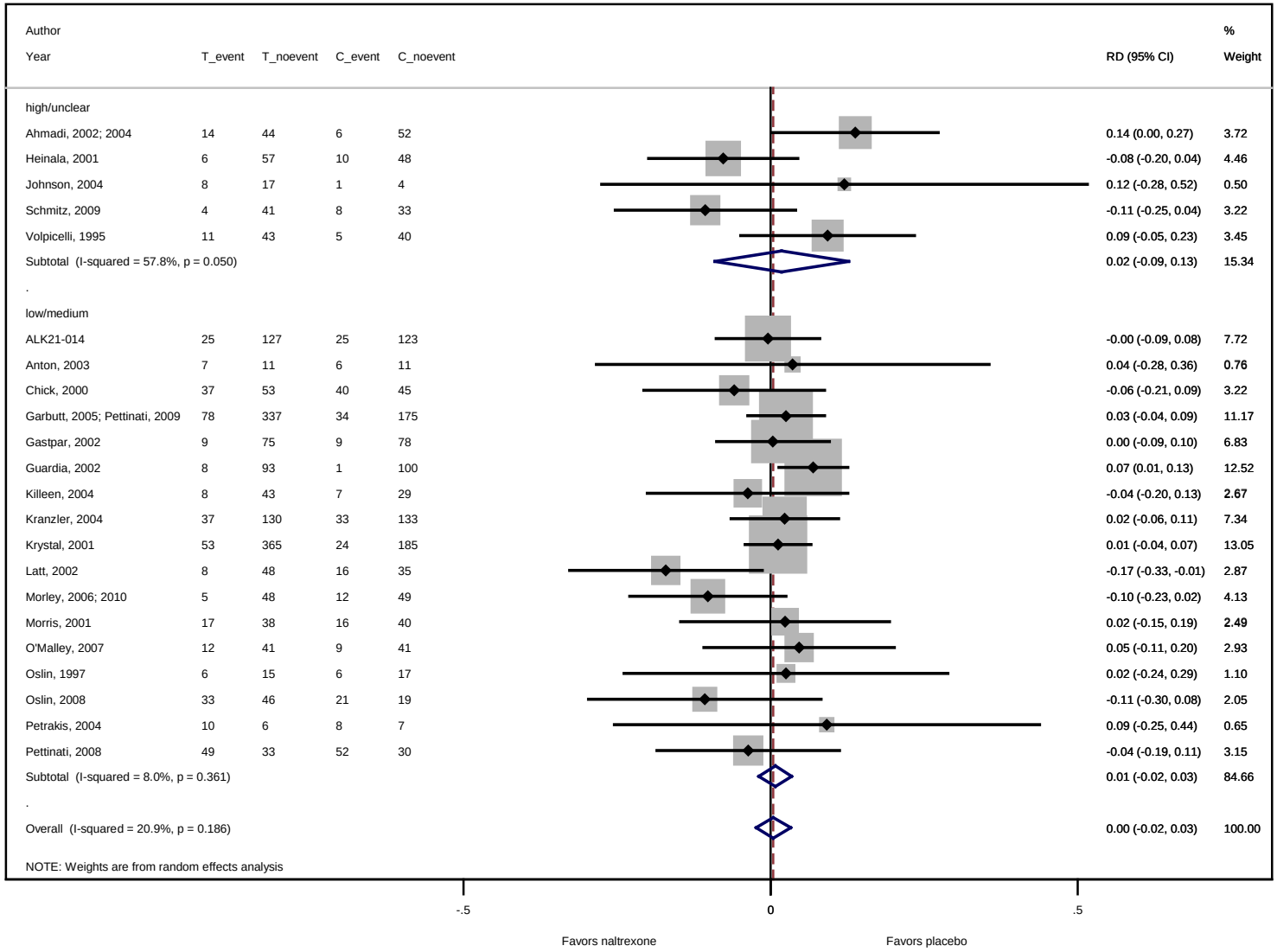


Figure F-89. Headache – Acamprosate versus naltrexone by risk of bias rating

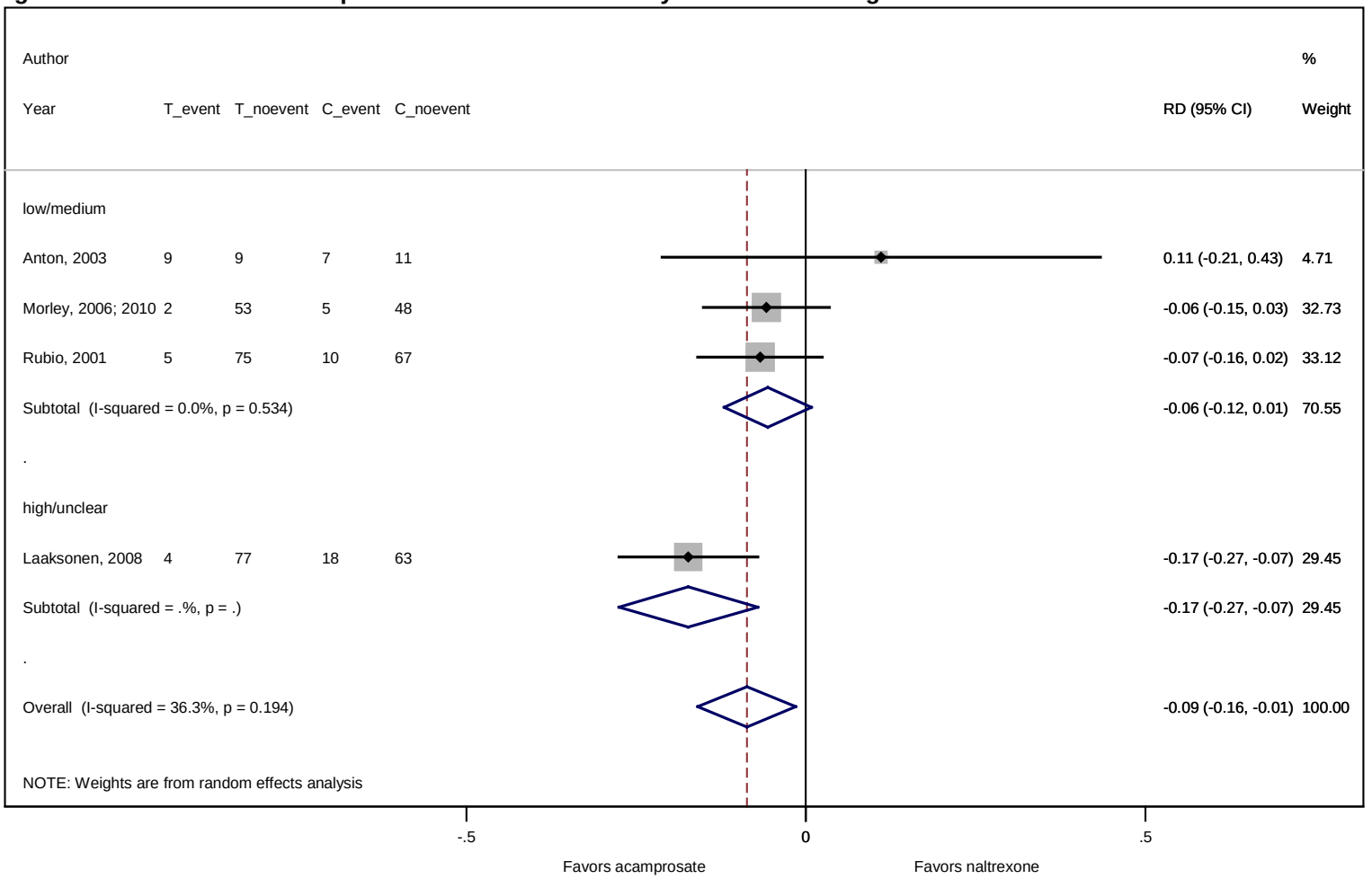


Figure F-90. Headache – Nalmefene versus placebo by risk of bias rating

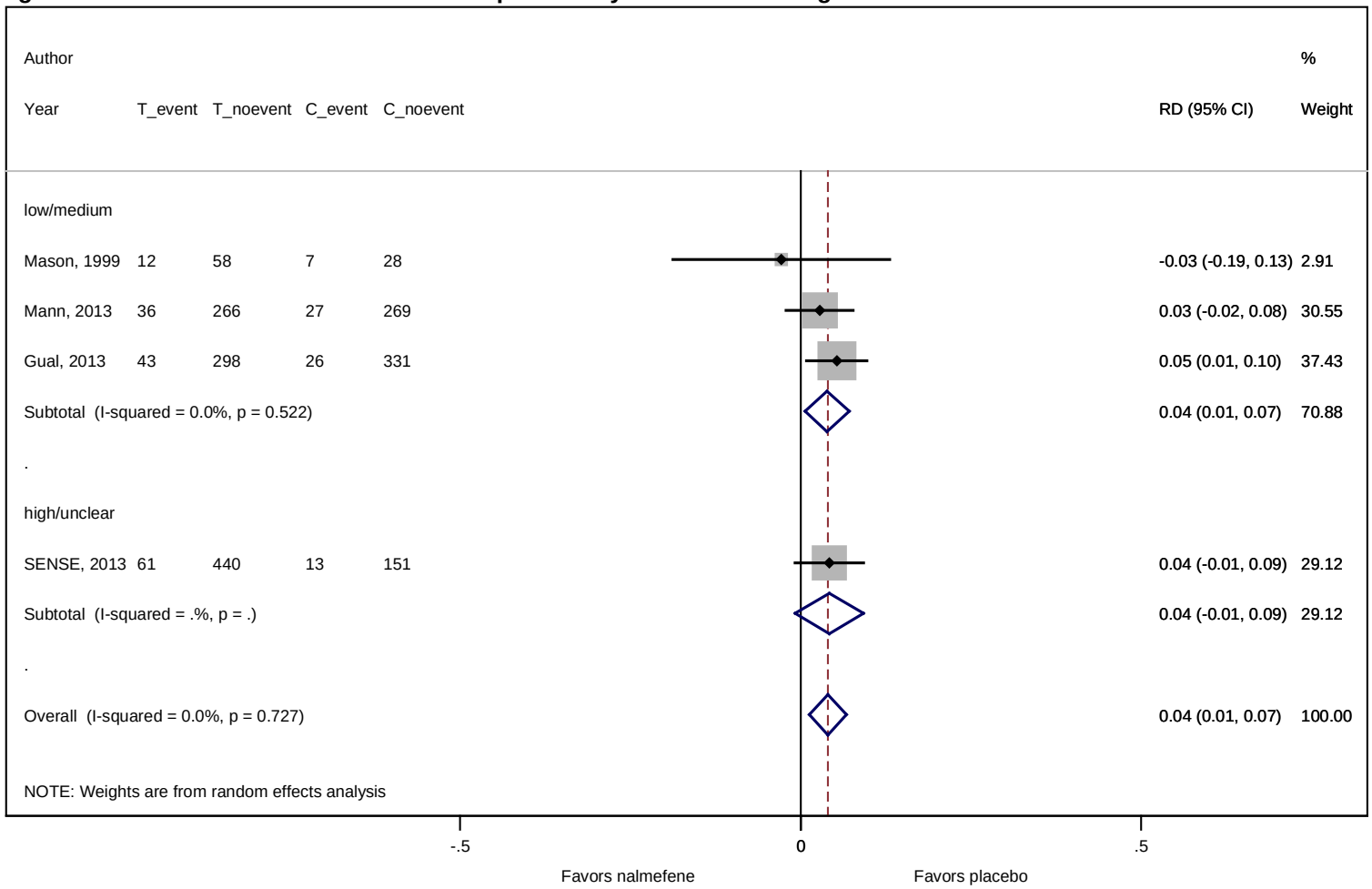


Figure F-91. Insomnia – Acamprosate versus placebo by risk of bias rating

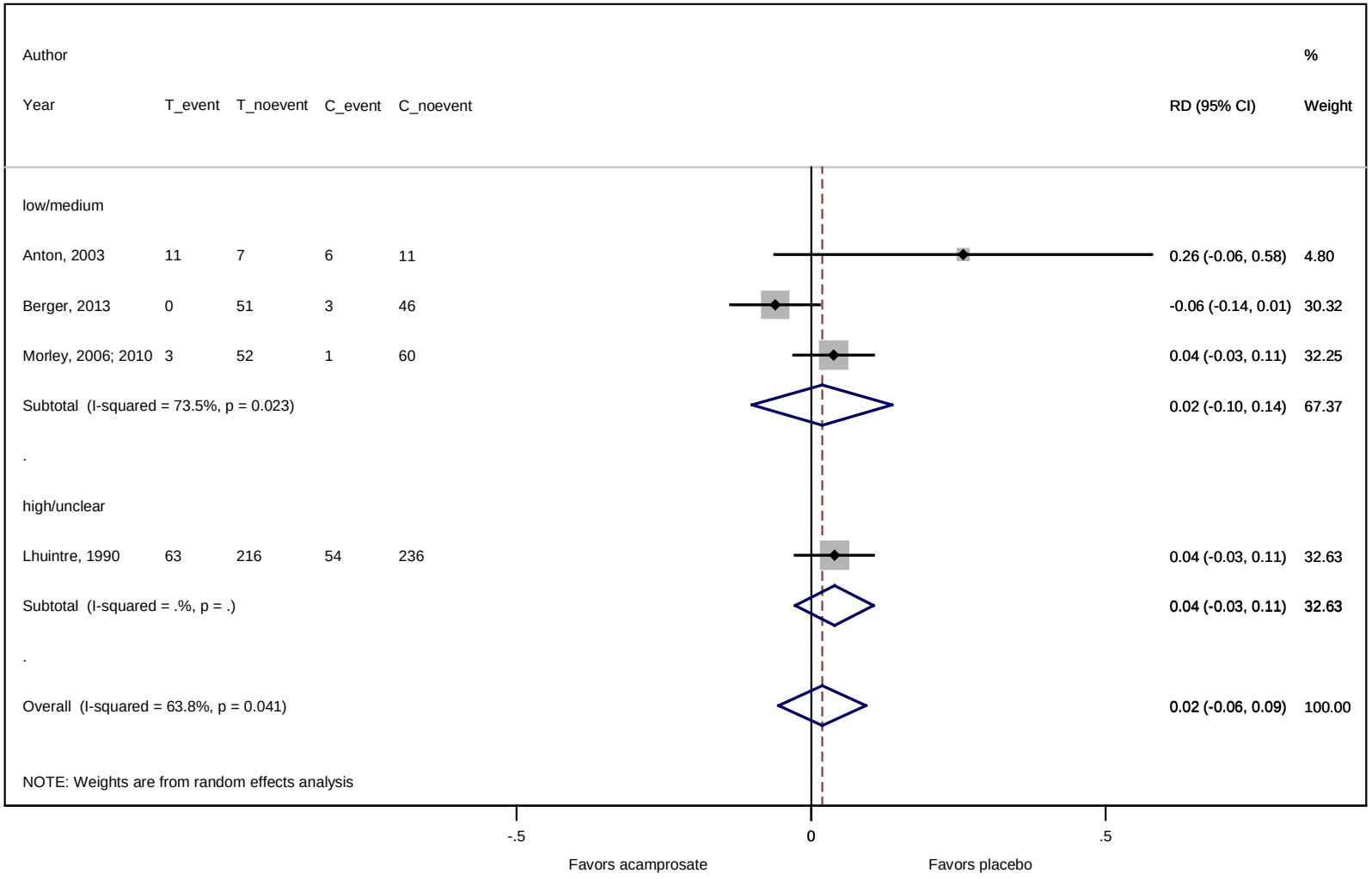


Figure F-92. Insomnia – Naltrexone versus placebo by risk of bias rating

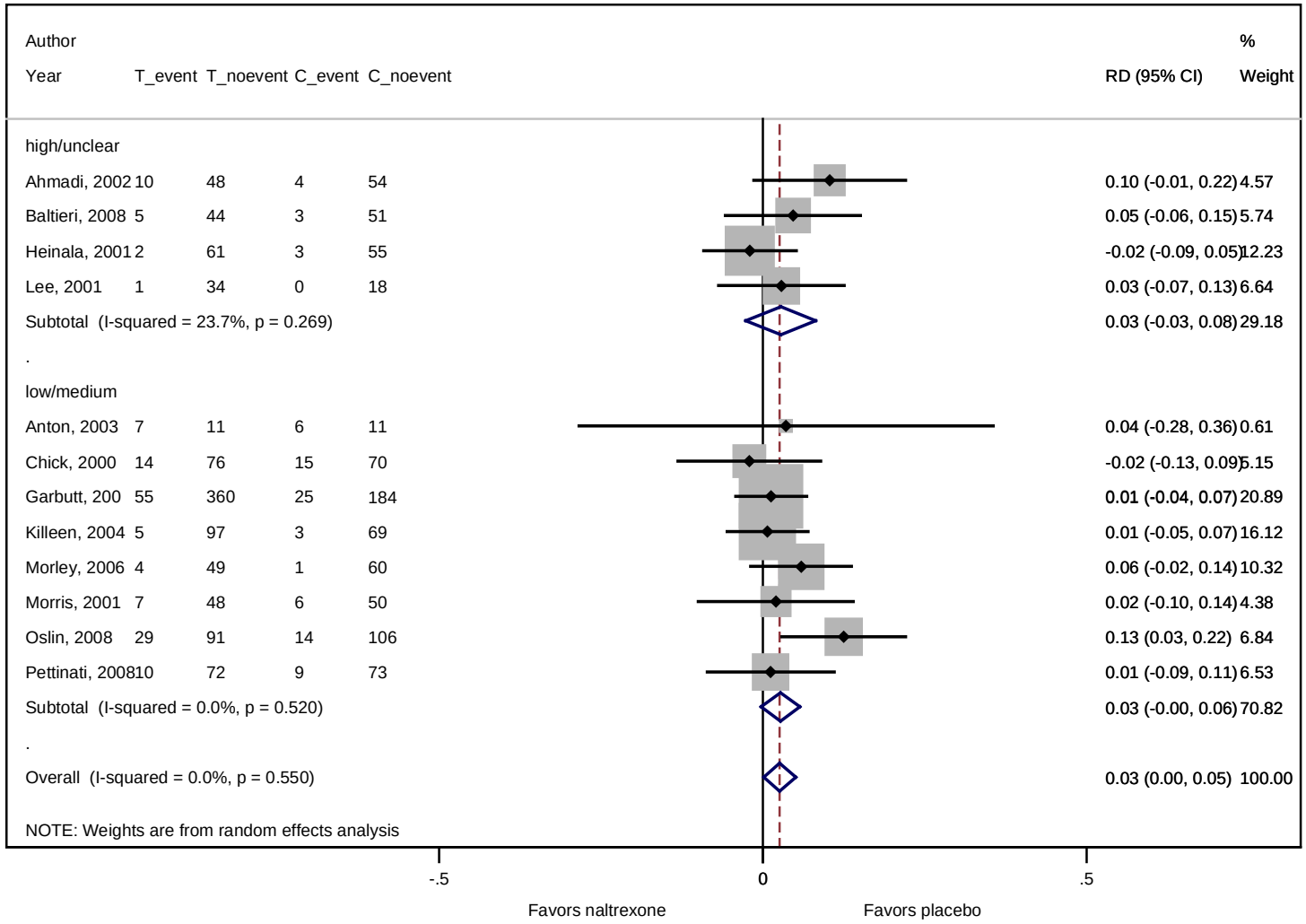


Figure F-93. Insomnia – Acamprosate versus naltrexone by risk of bias rating

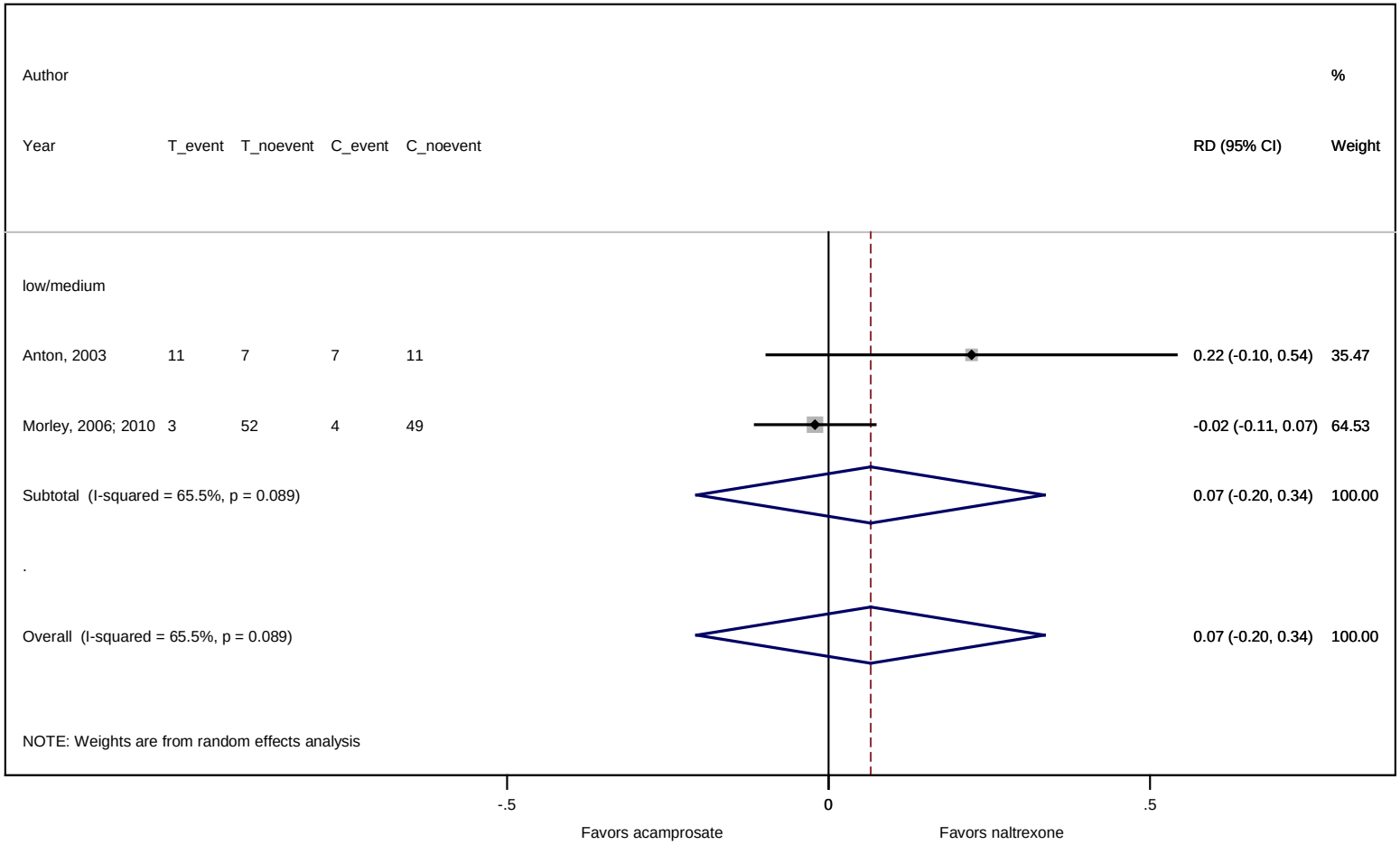


Figure F-94. Insomnia – Nalmefene versus placebo by risk of bias rating

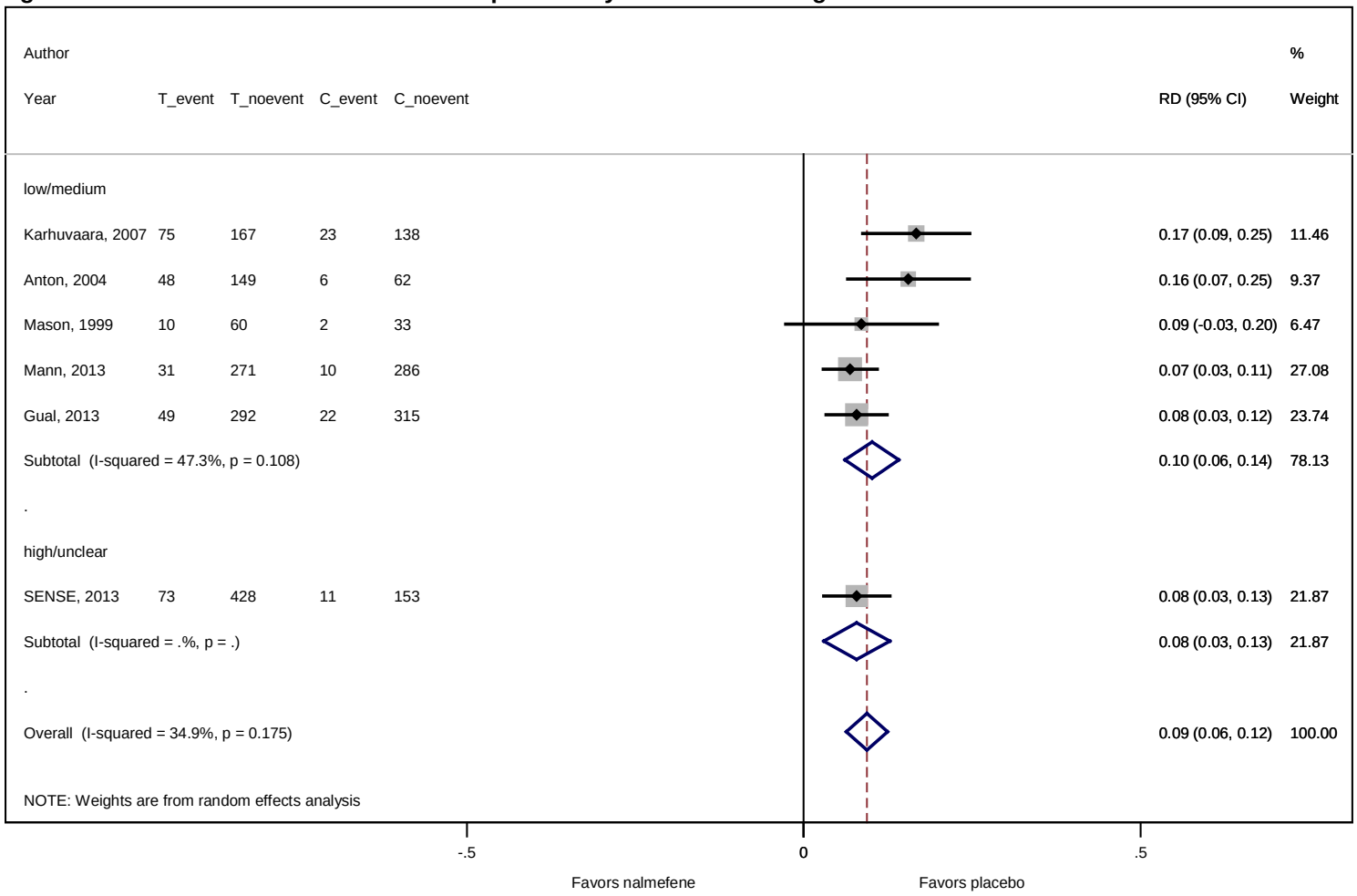


Figure F-95. Insomnia – Topiramate versus placebo by risk of bias rating

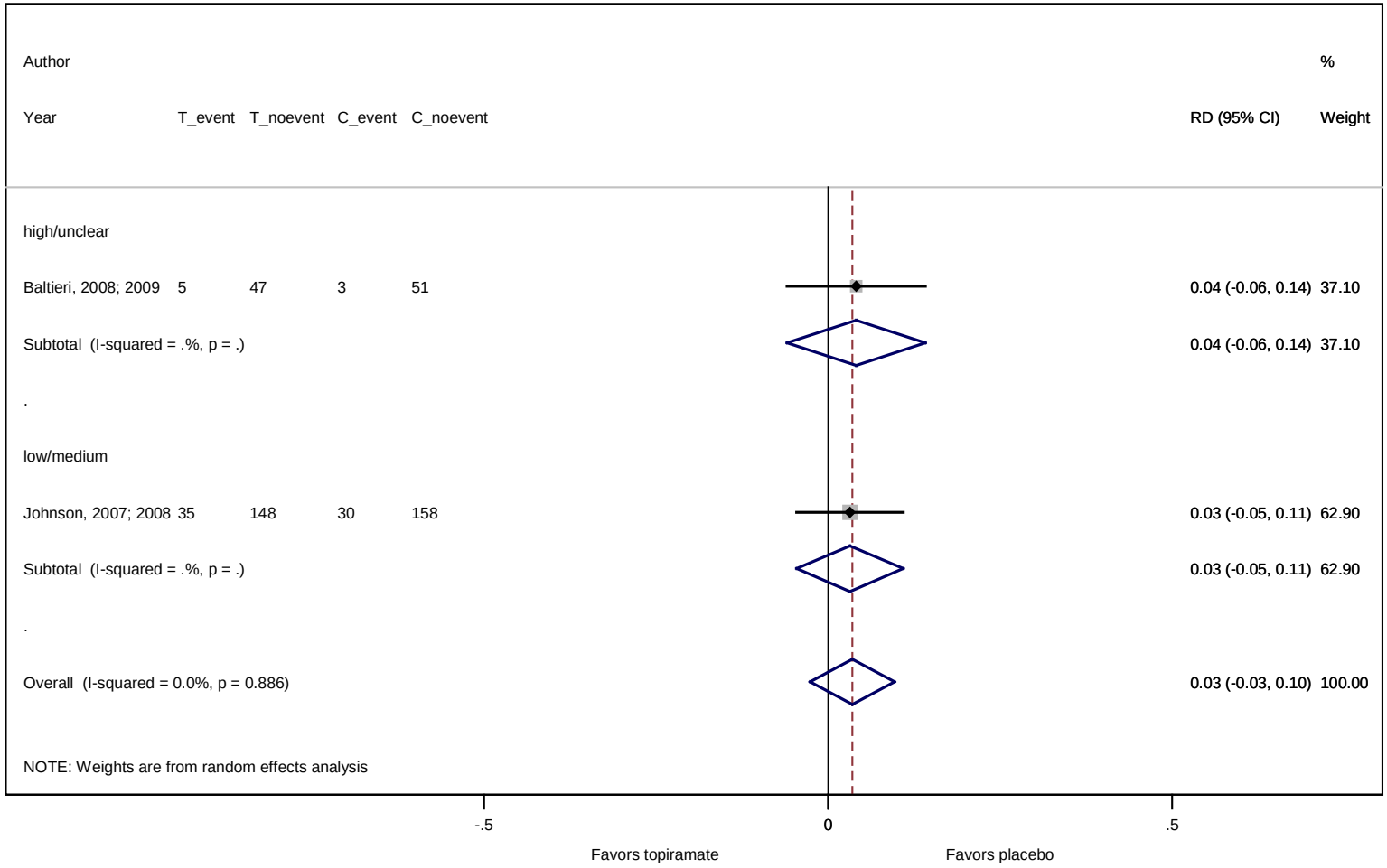


Figure F-96. Nausea – Acamprosate versus placebo by risk of bias rating

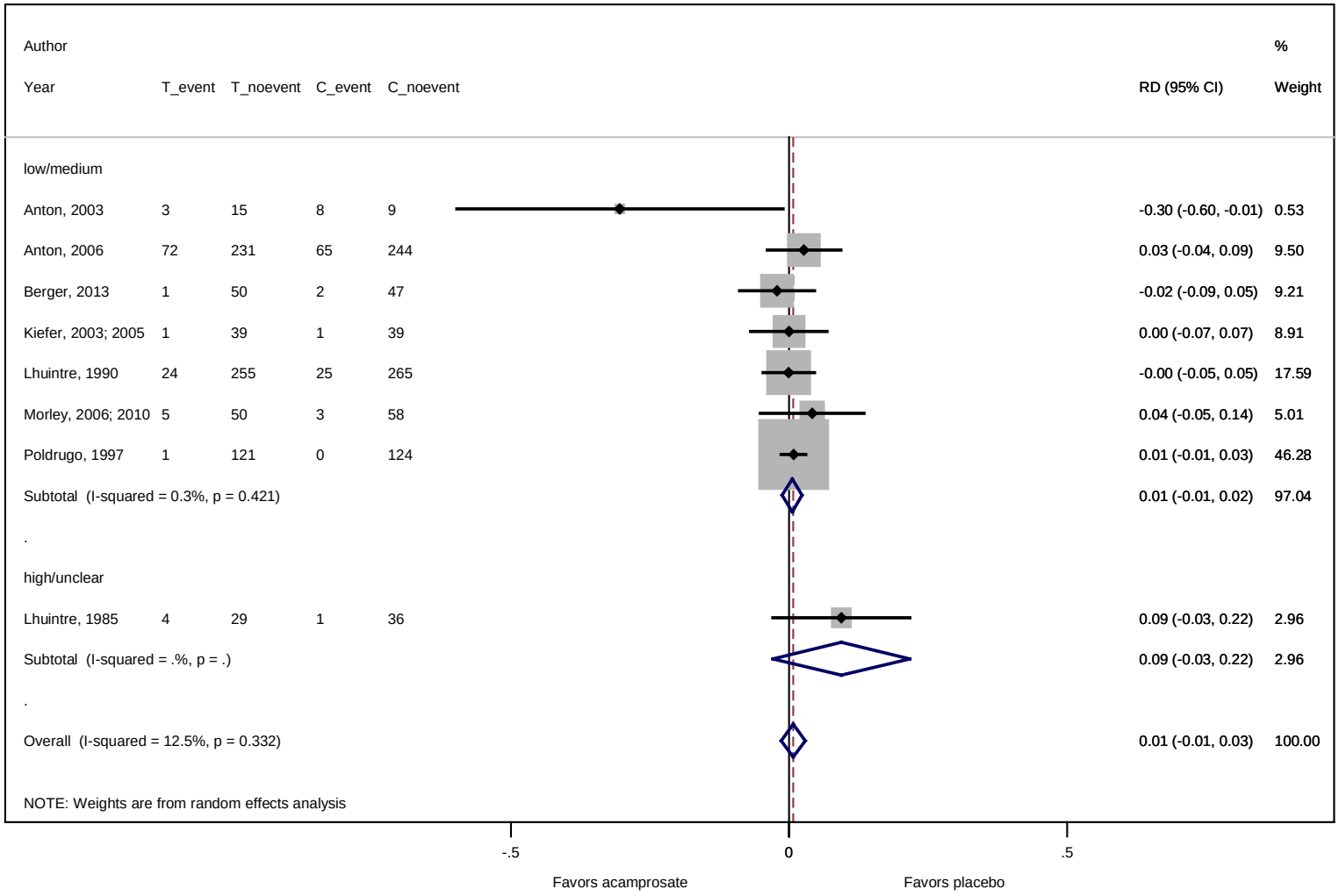
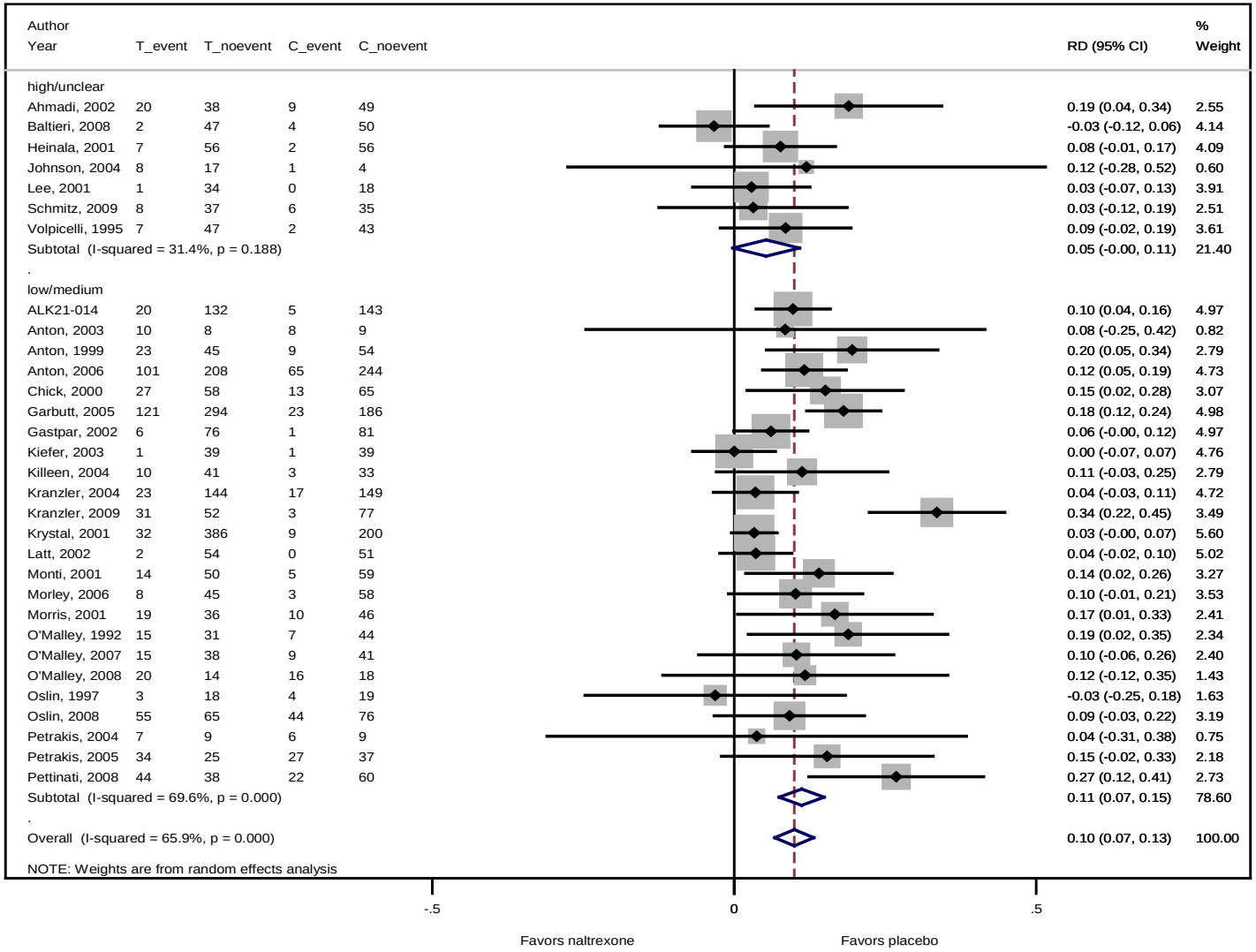


Figure F-97. Nausea – Naltrexone versus placebo by risk of bias rating



*Footnote: Kranzler, 2009 combines events reported by targeted and daily naltrexone and by targeted and daily placebo

Figure F-98. Nausea – Acamprosate versus naltrexone by risk of bias rating

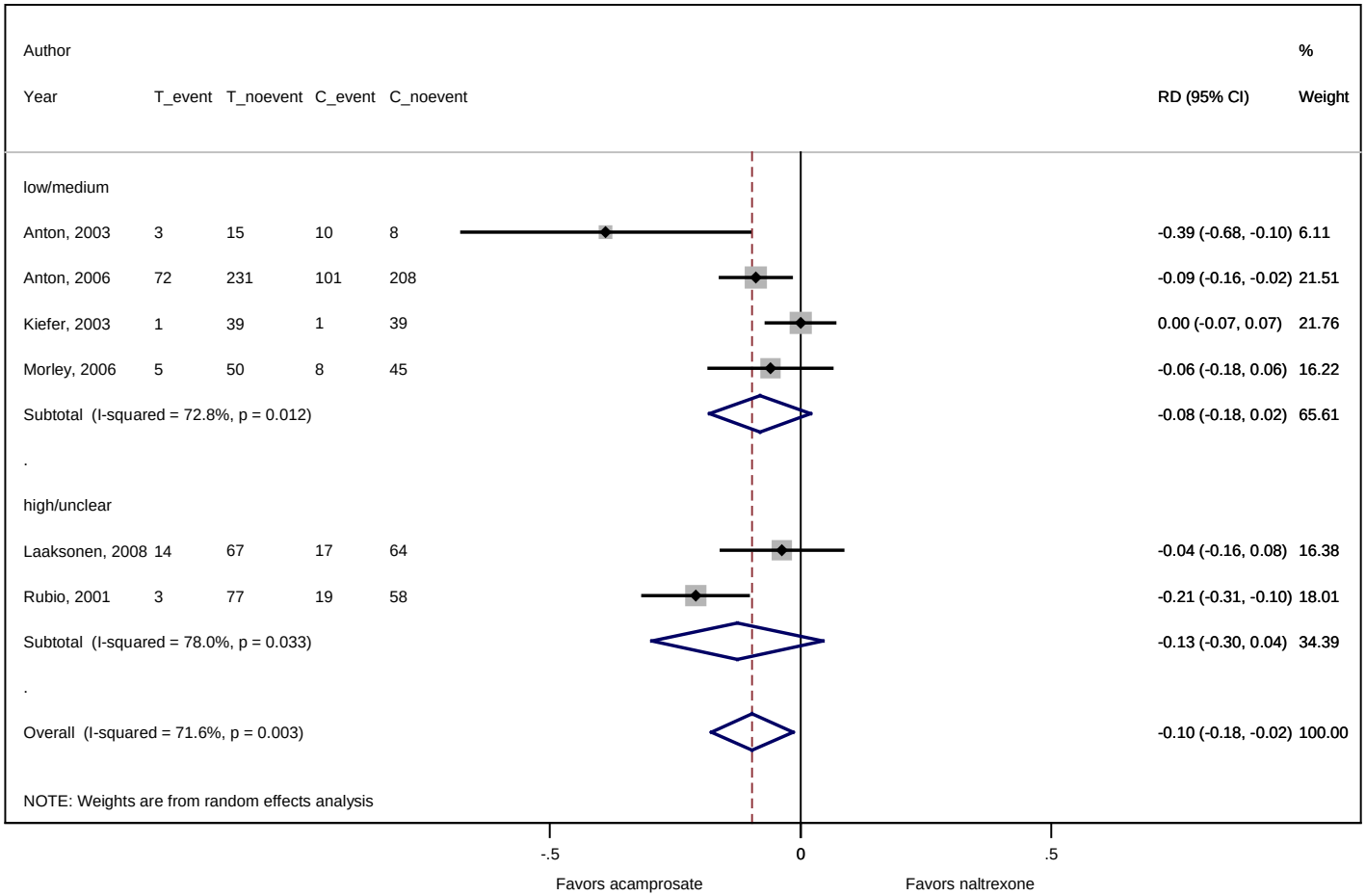


Figure F-99. Nausea – Nalmefene versus placebo by risk of bias rating

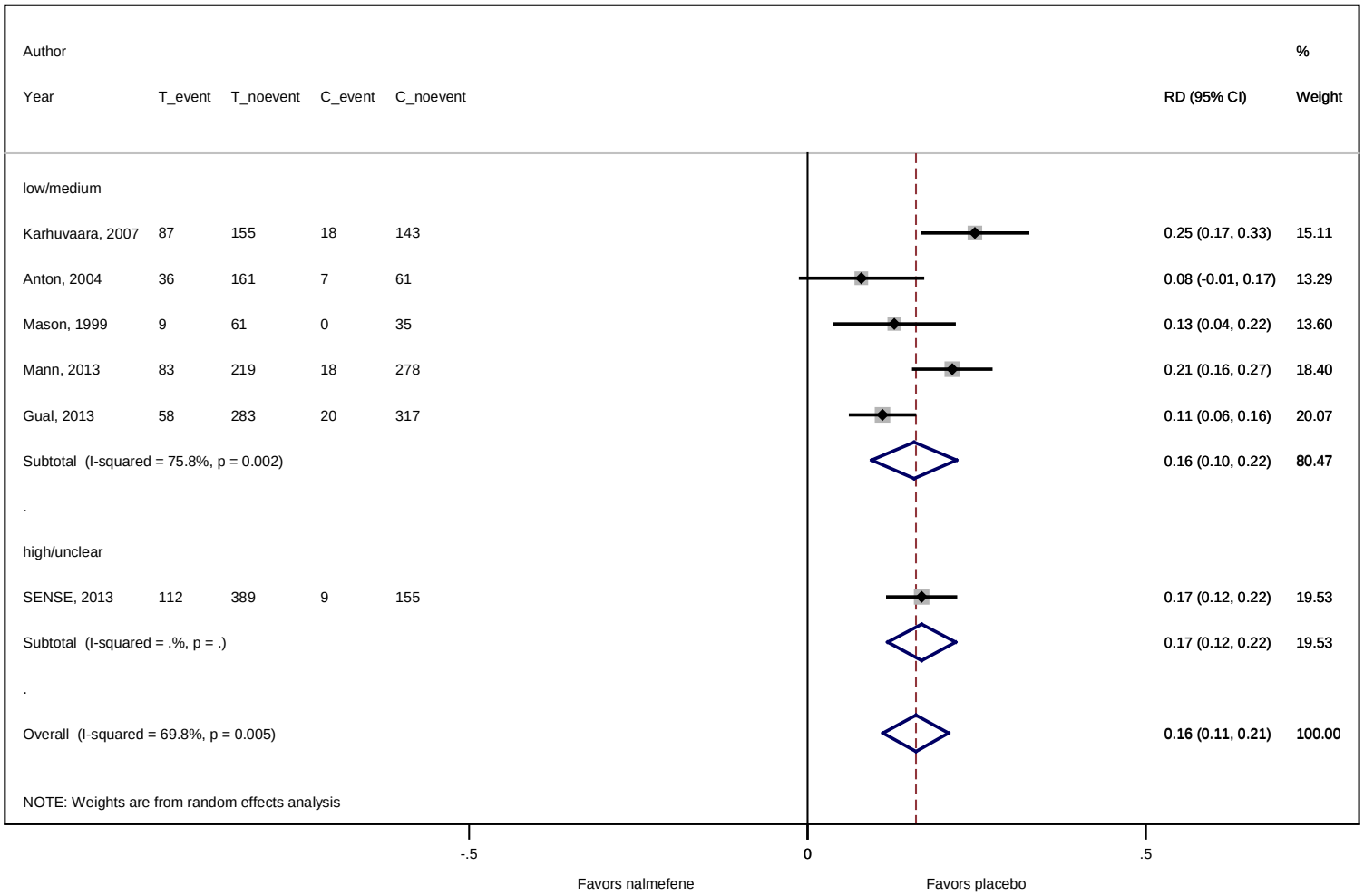


Figure F-100. Nausea – Topiramate versus placebo by risk of bias rating

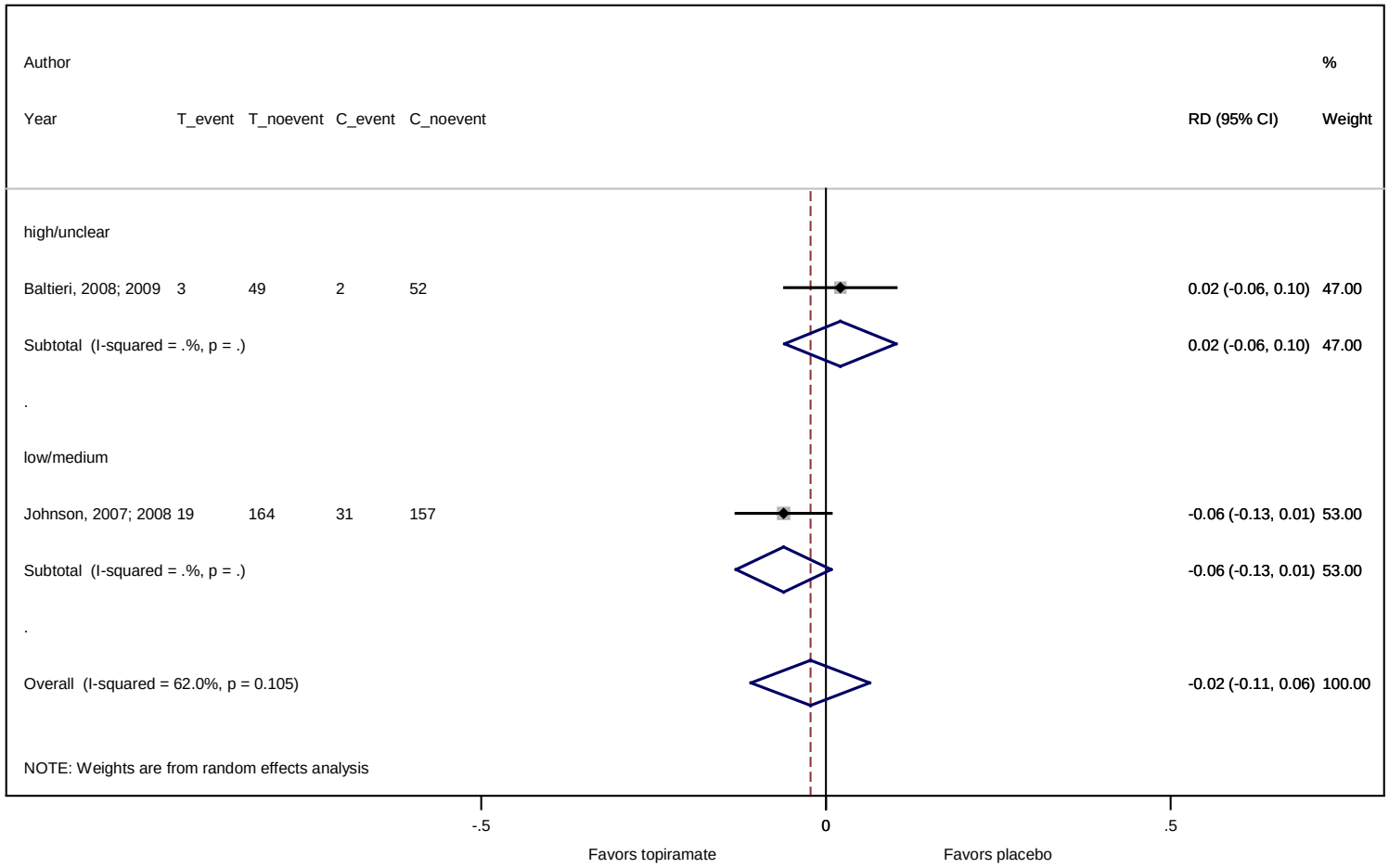


Figure F-101. Numbness – Acamprosate versus placebo by risk of bias rating

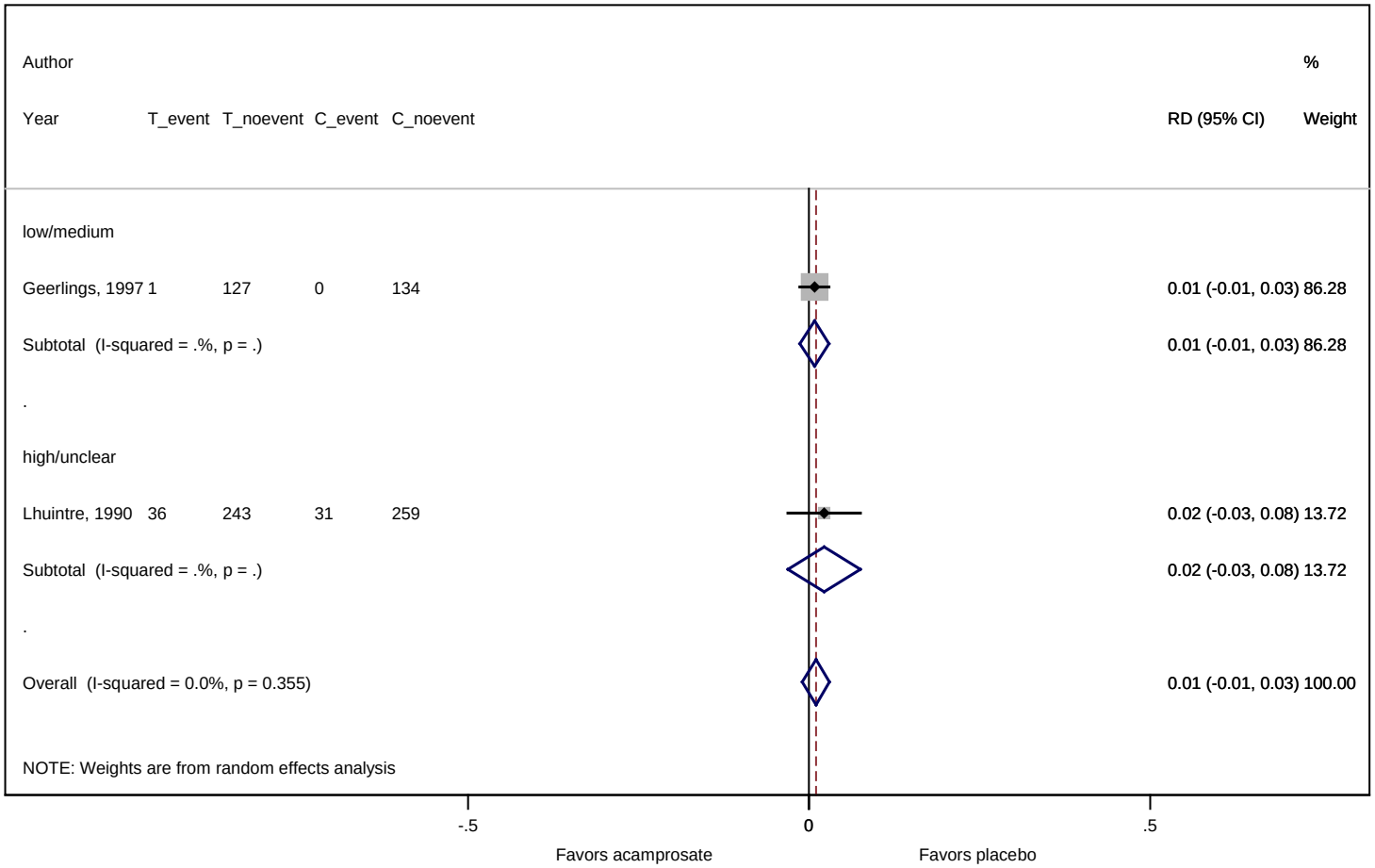


Figure F-102. Numbness – Naltrexone versus placebo by risk of bias rating

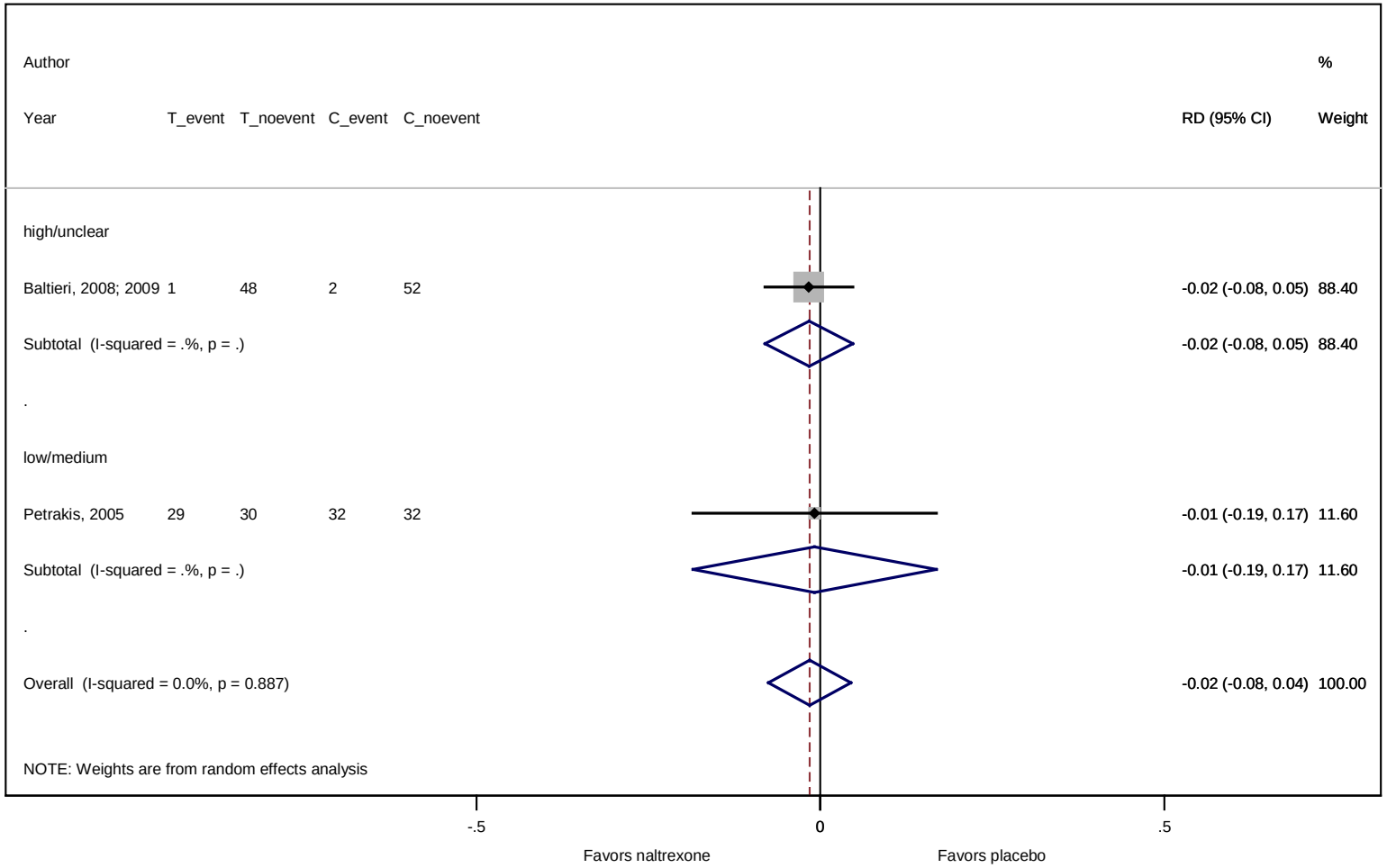


Figure F-103. Numbness – Topiramate versus placebo by risk of bias rating

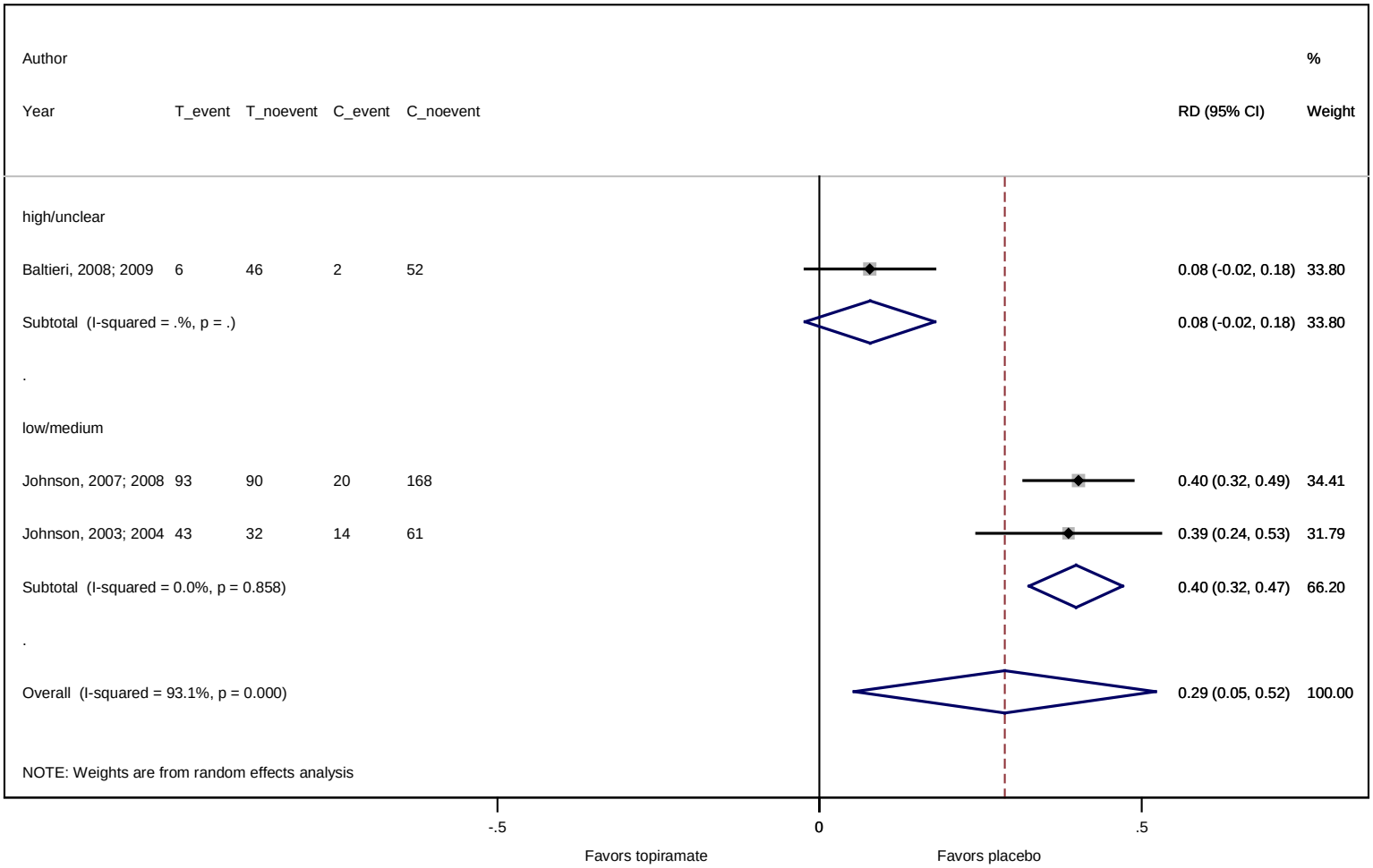


Figure F-104. Rash – Acamprosate versus placebo by risk of bias rating

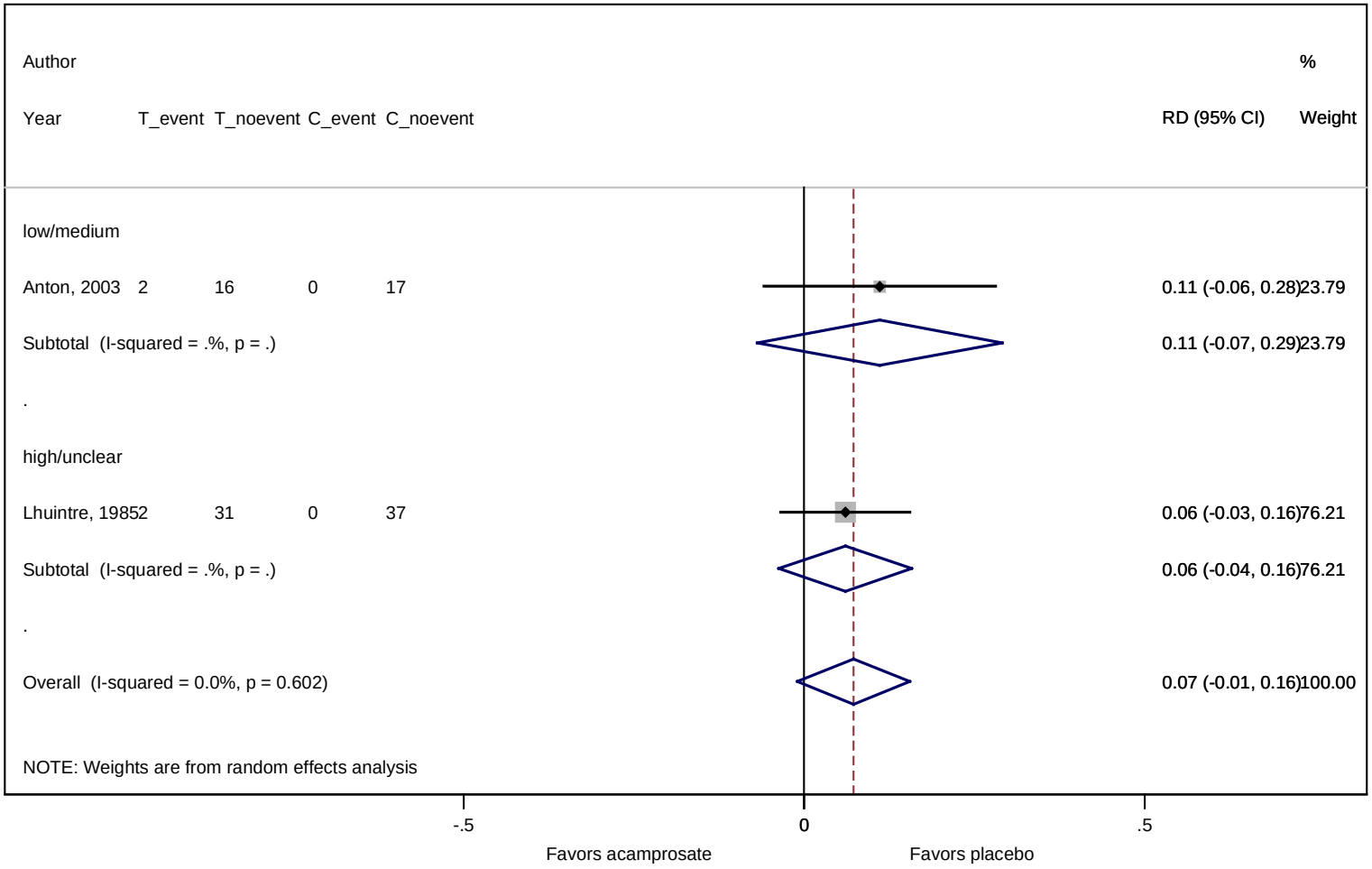


Figure F-105. Rash – Naltrexone versus placebo by risk of bias rating

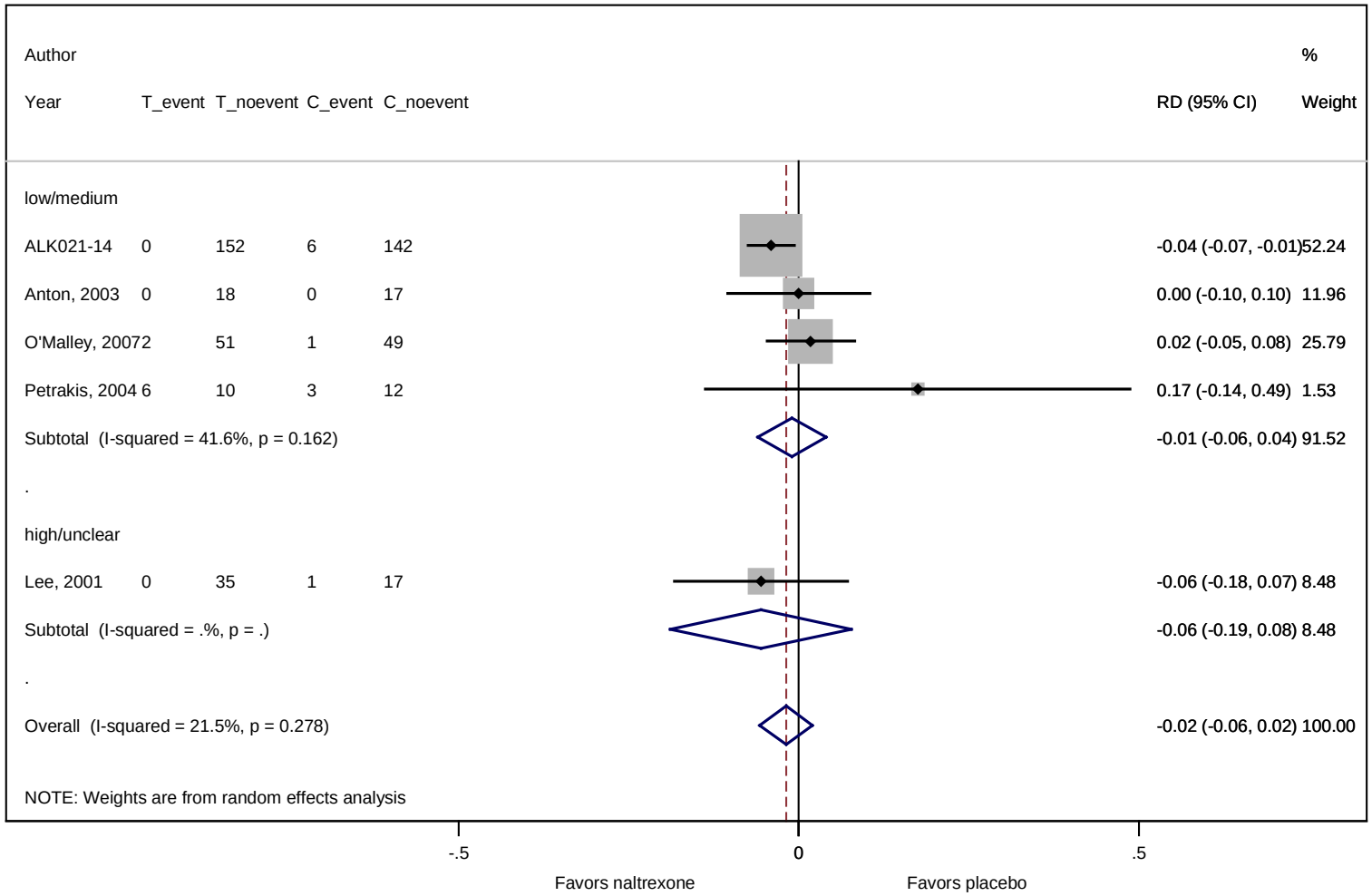


Figure F-106. Suicide attempts/suicidal ideation – Acamprosate versus placebo by risk of bias rating

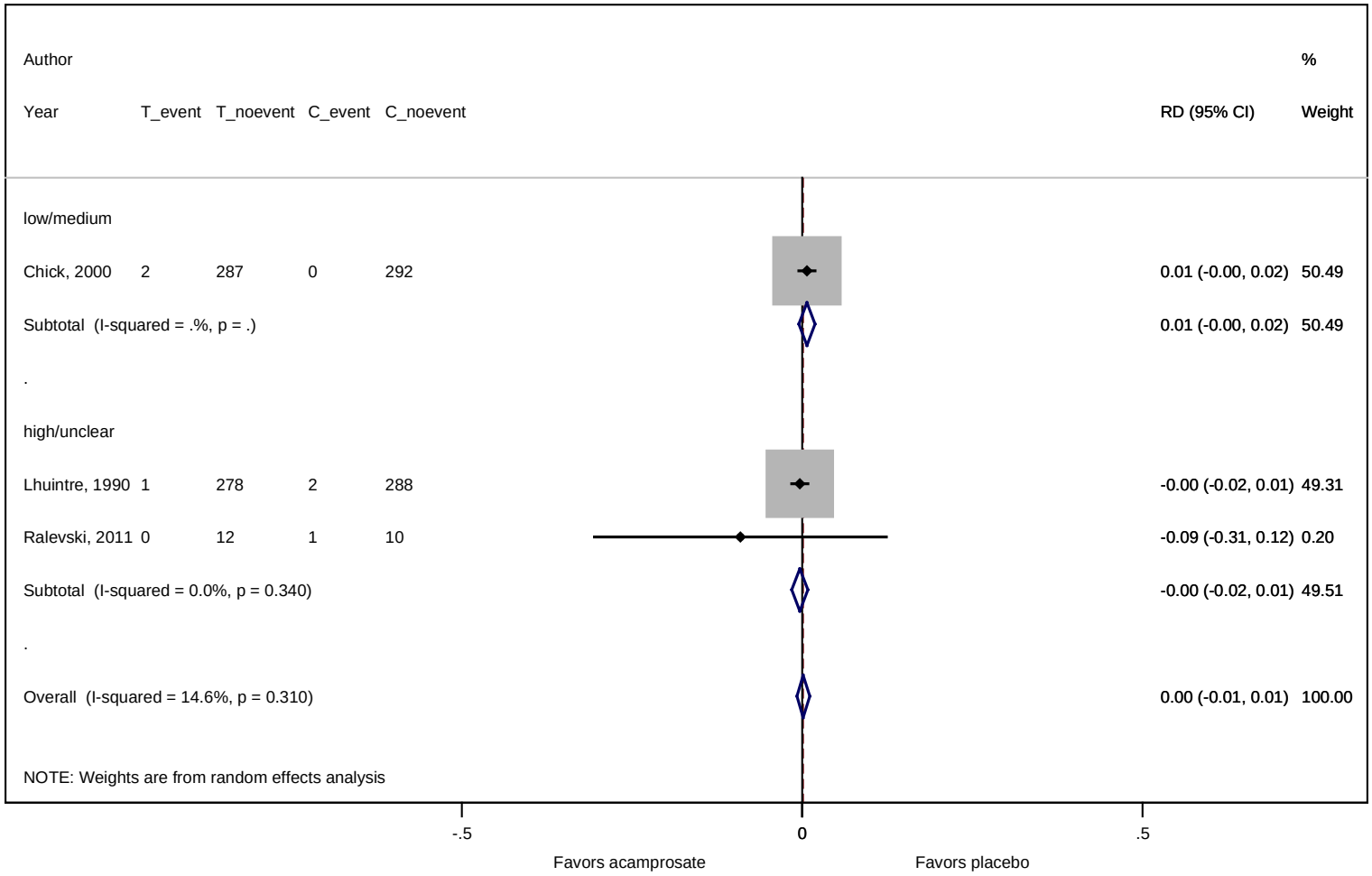


Figure F-107. Suicide attempts/suicidal ideation – Nalmefene versus placebo by risk of bias rating

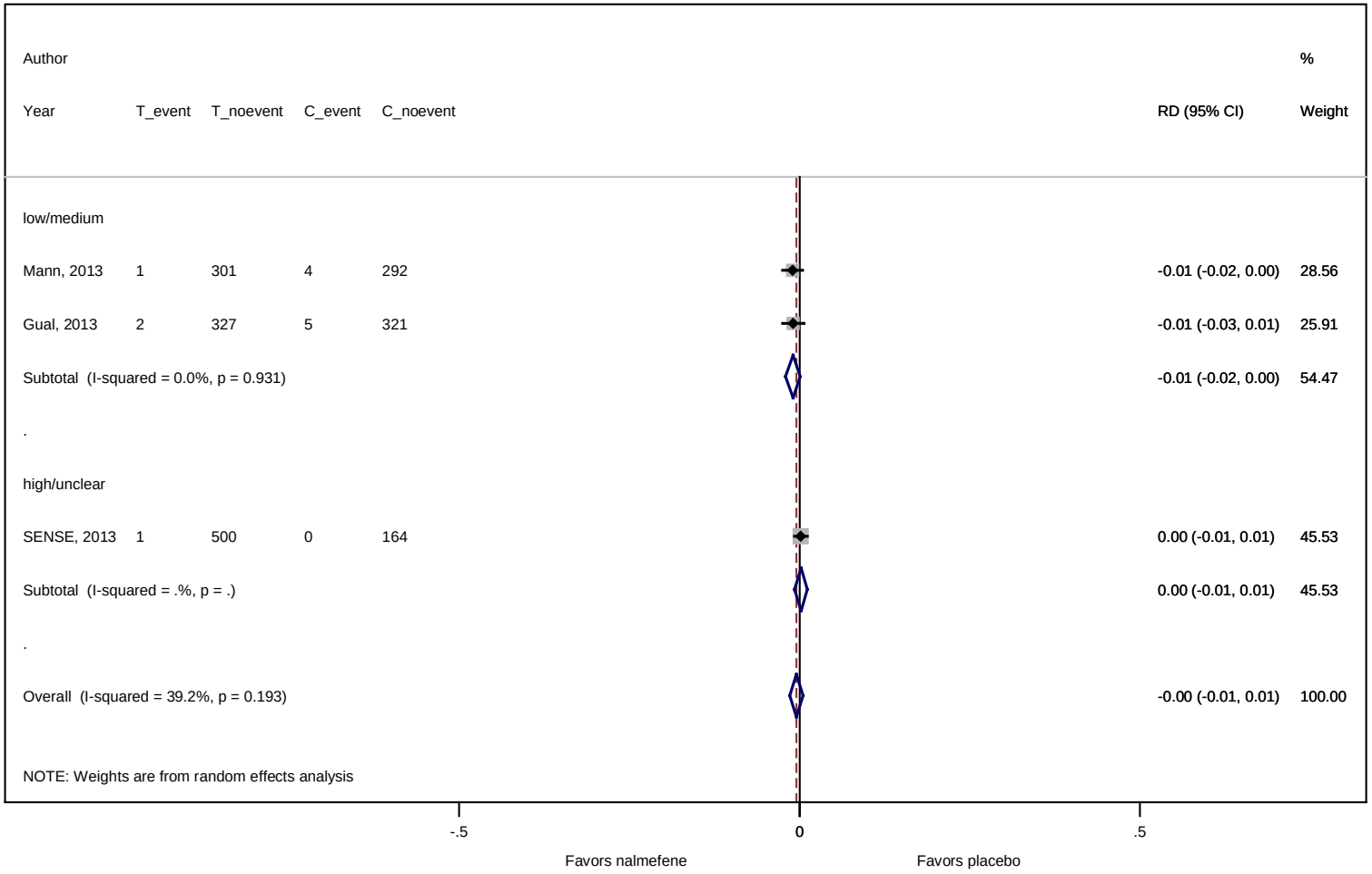


Figure F-108. Vision changes (blurred vision) – Naltrexone versus placebo by risk of bias rating

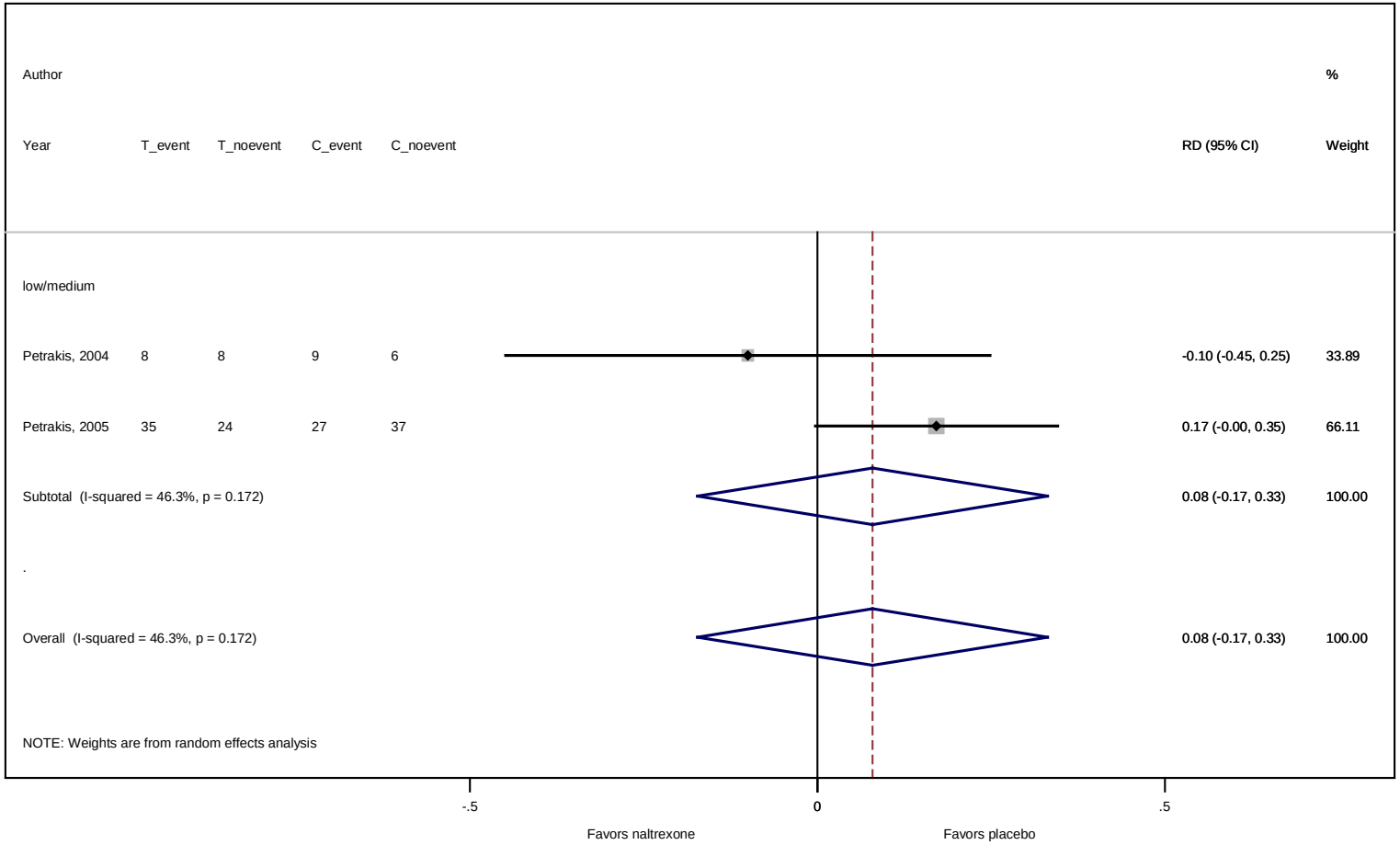


Figure F-109. Vomiting – Acamprosate versus placebo by risk of bias rating

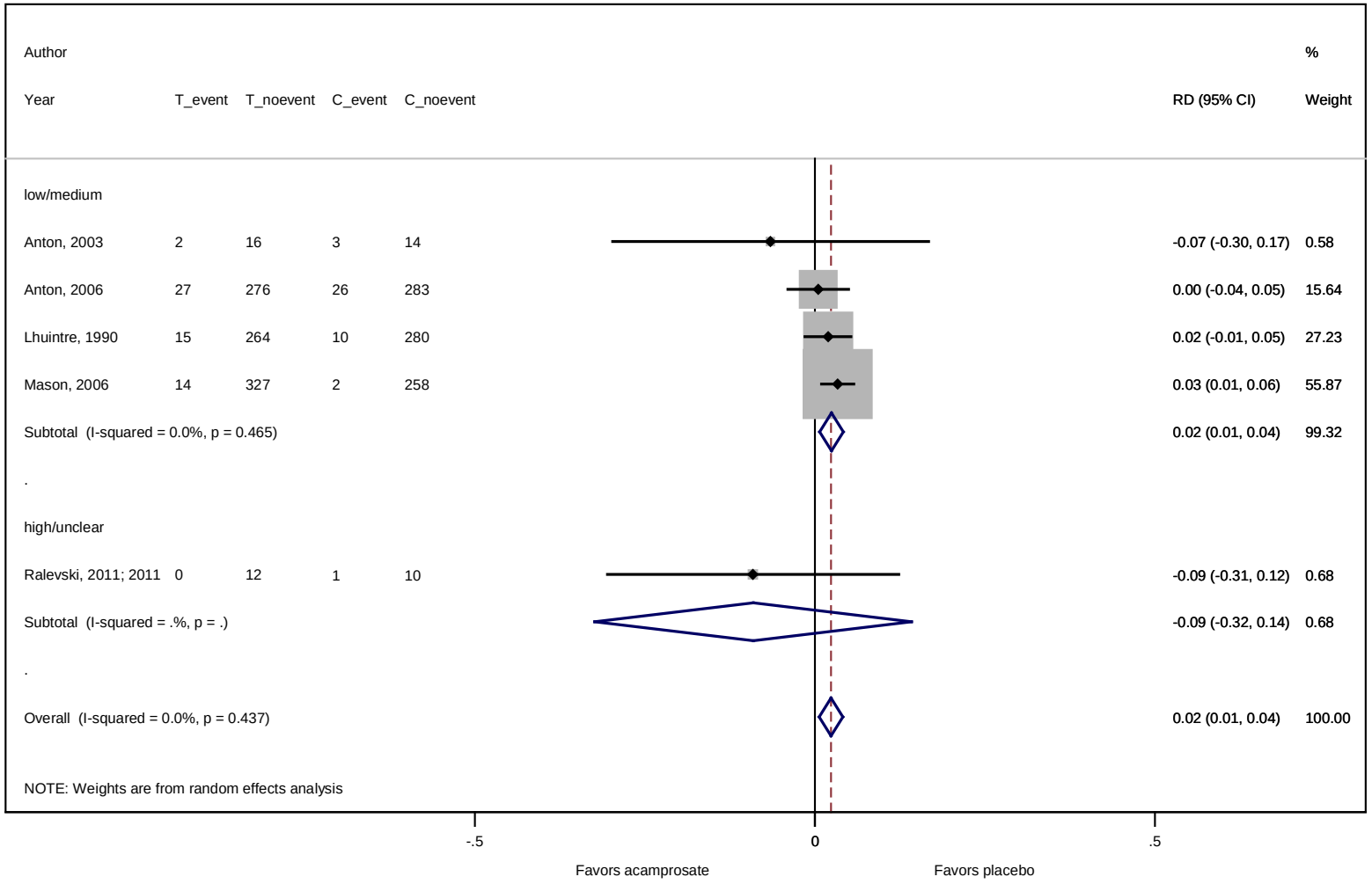


Figure F-110. Vomiting – Naltrexone versus placebo by risk of bias rating

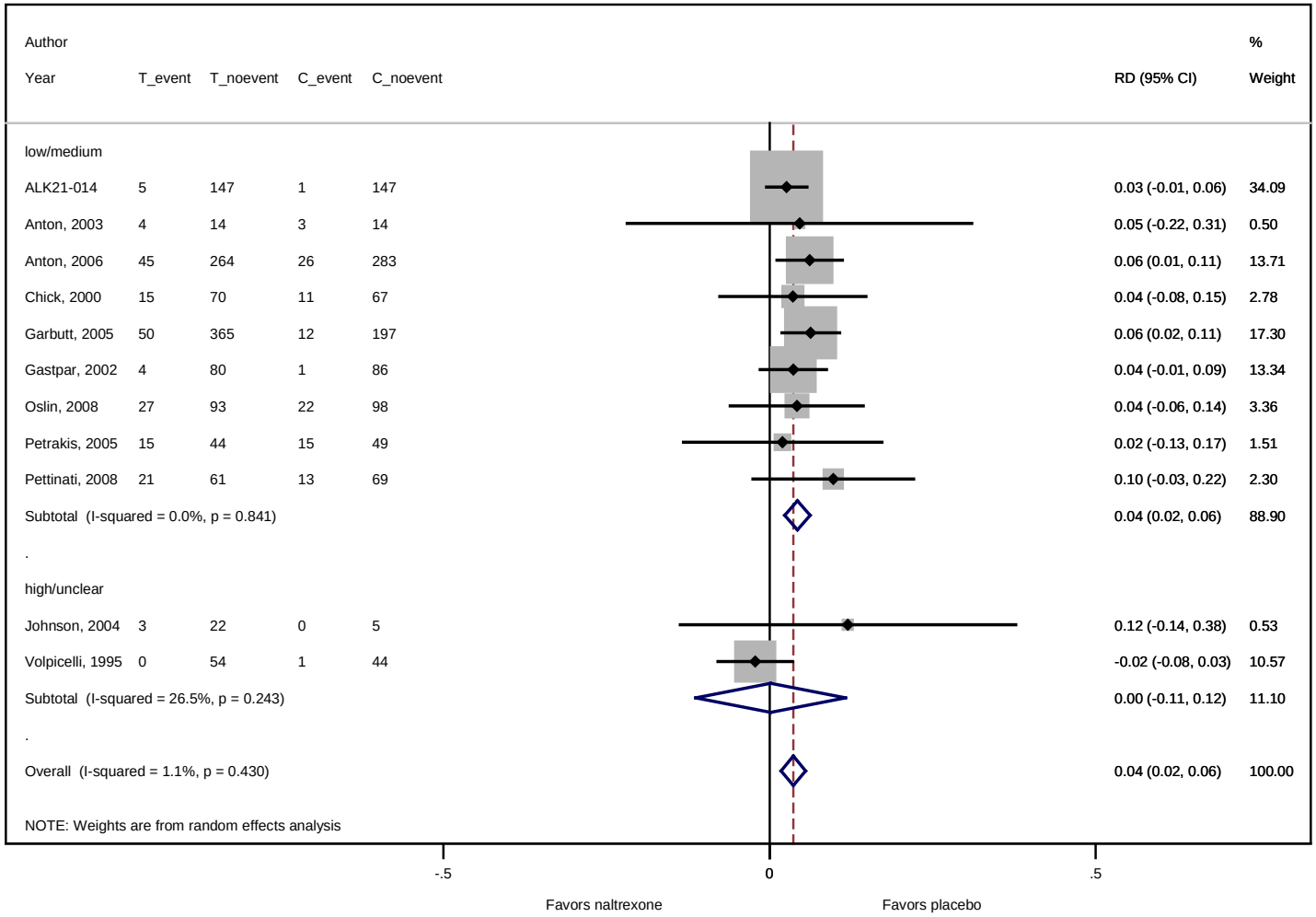


Figure F-111. Vomiting – Acamprosate versus naltrexone by risk of bias rating

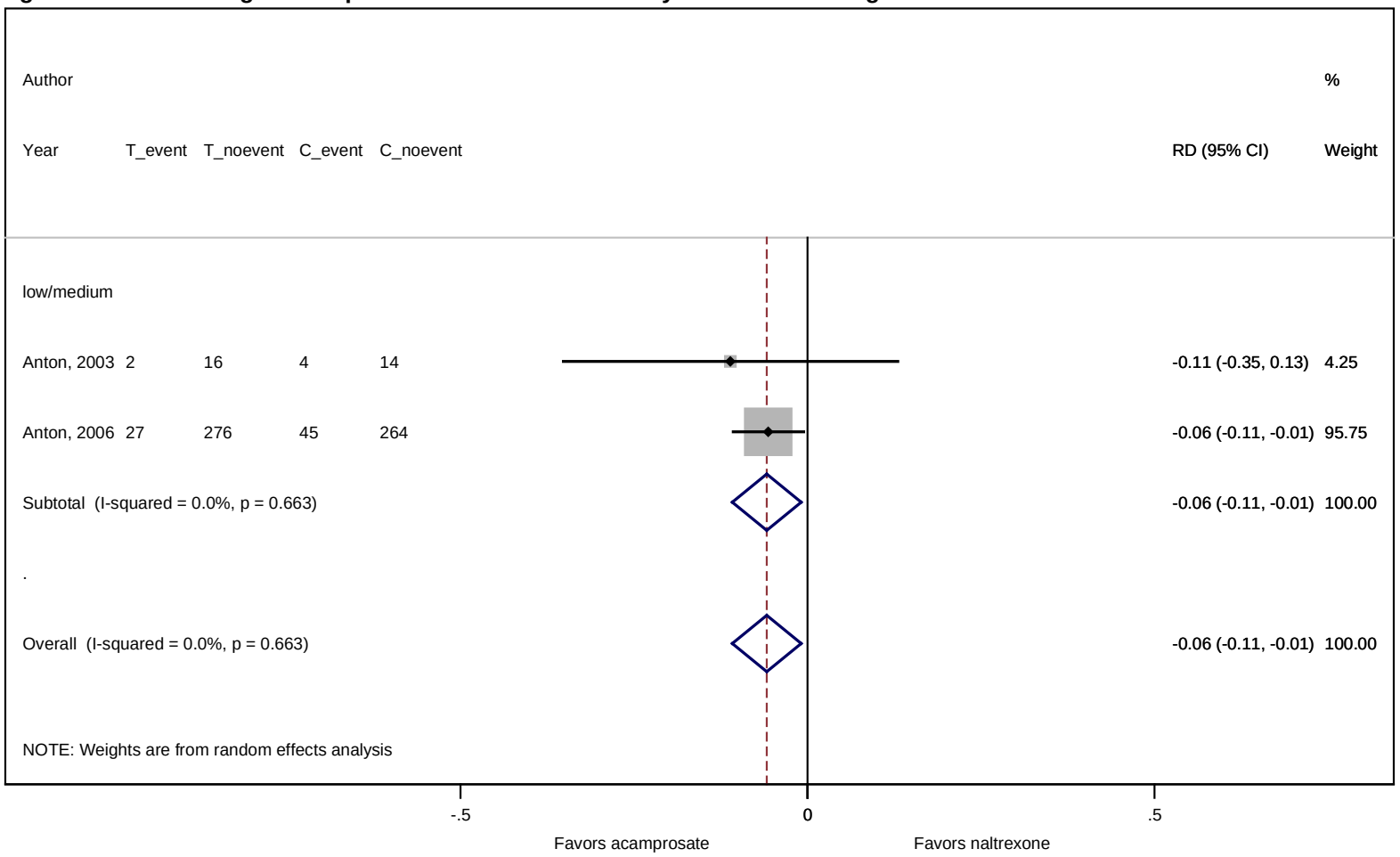


Figure F-112. Vomiting – Nalmefene versus placebo by risk of bias rating

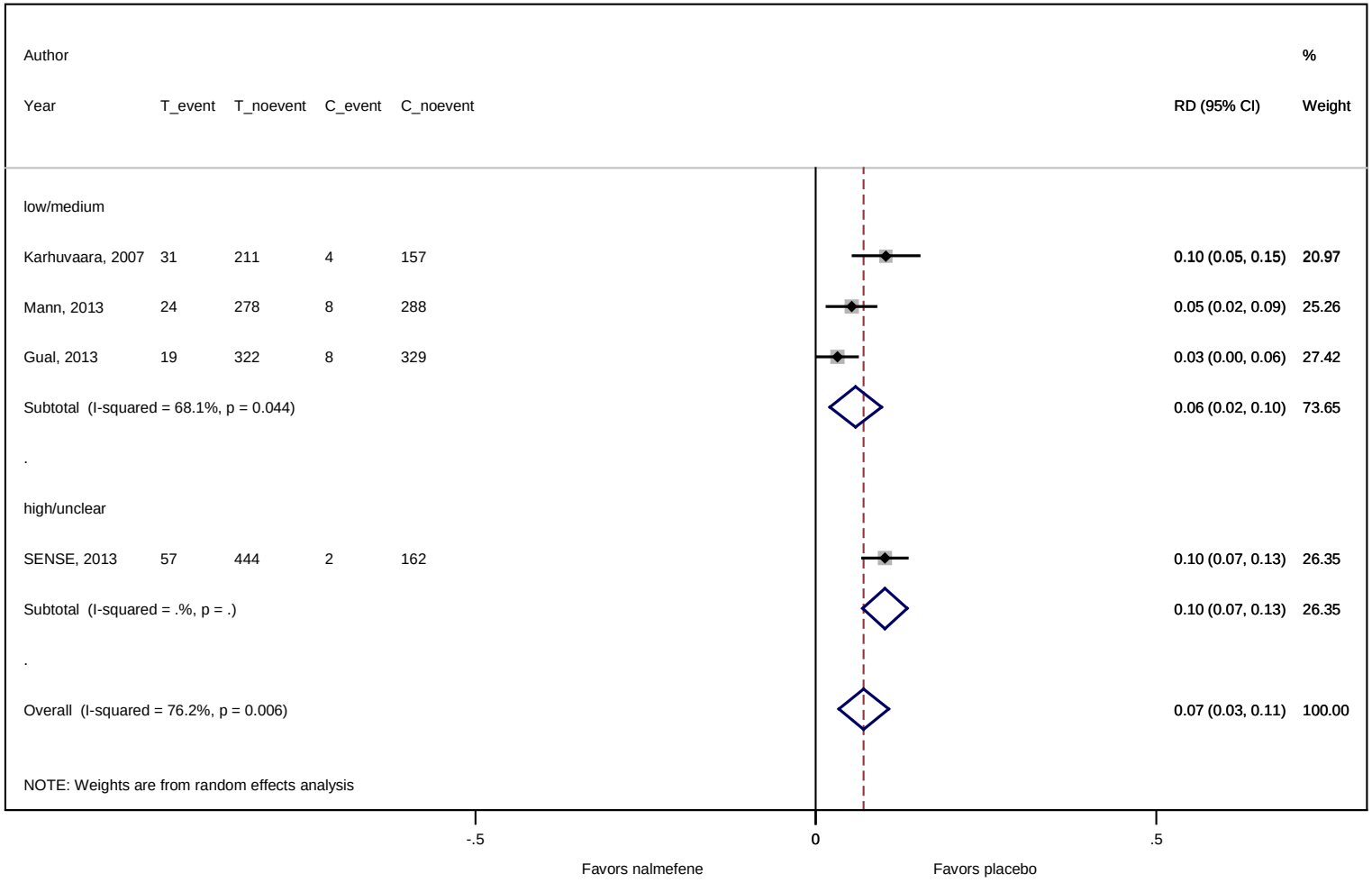


Figure F-113. Withdrawals due to adverse events – Acamprosate versus placebo by risk of bias rating

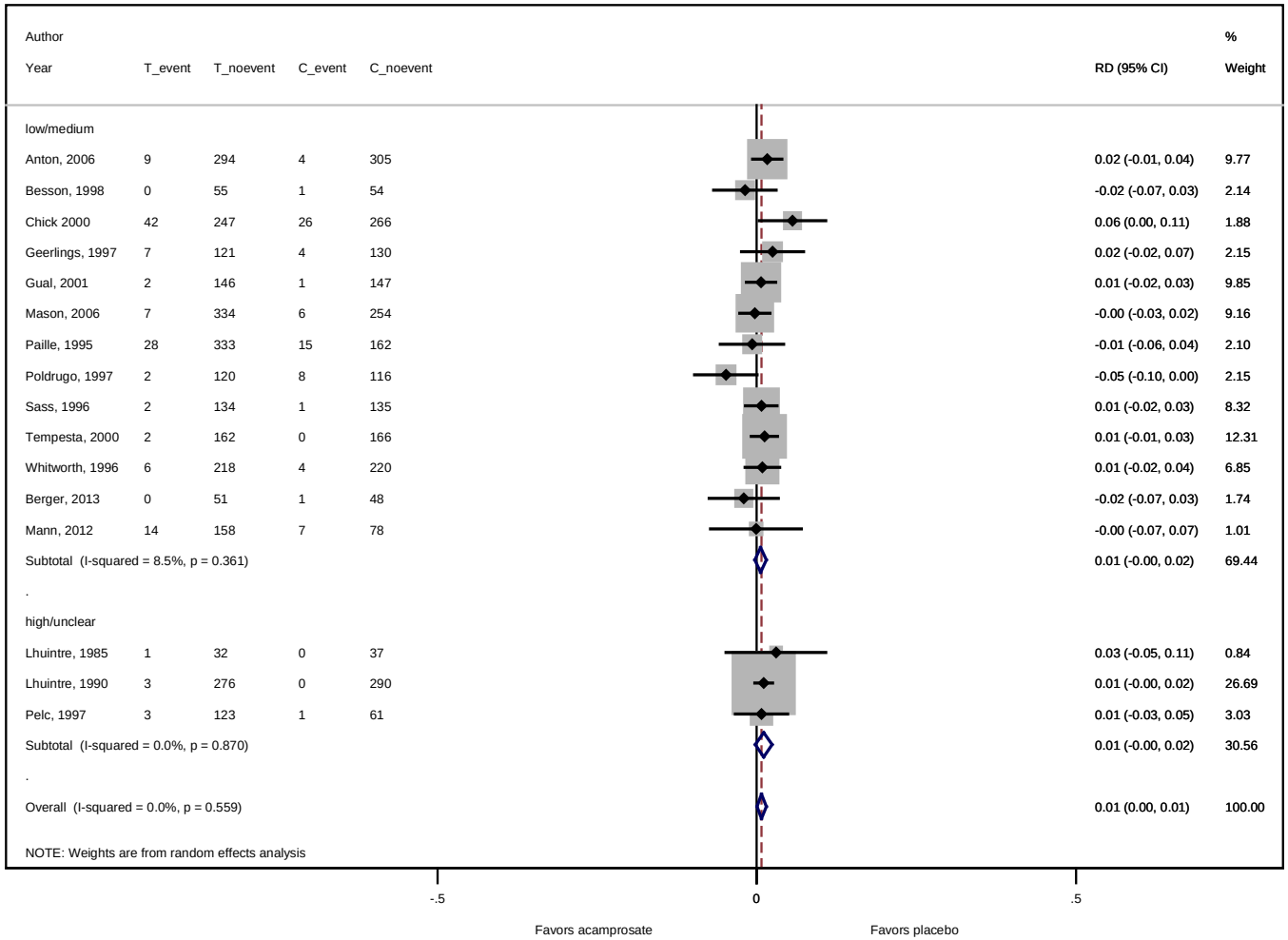


Figure F-114. Withdrawals due to adverse events – Naltrexone versus placebo by risk of bias rating

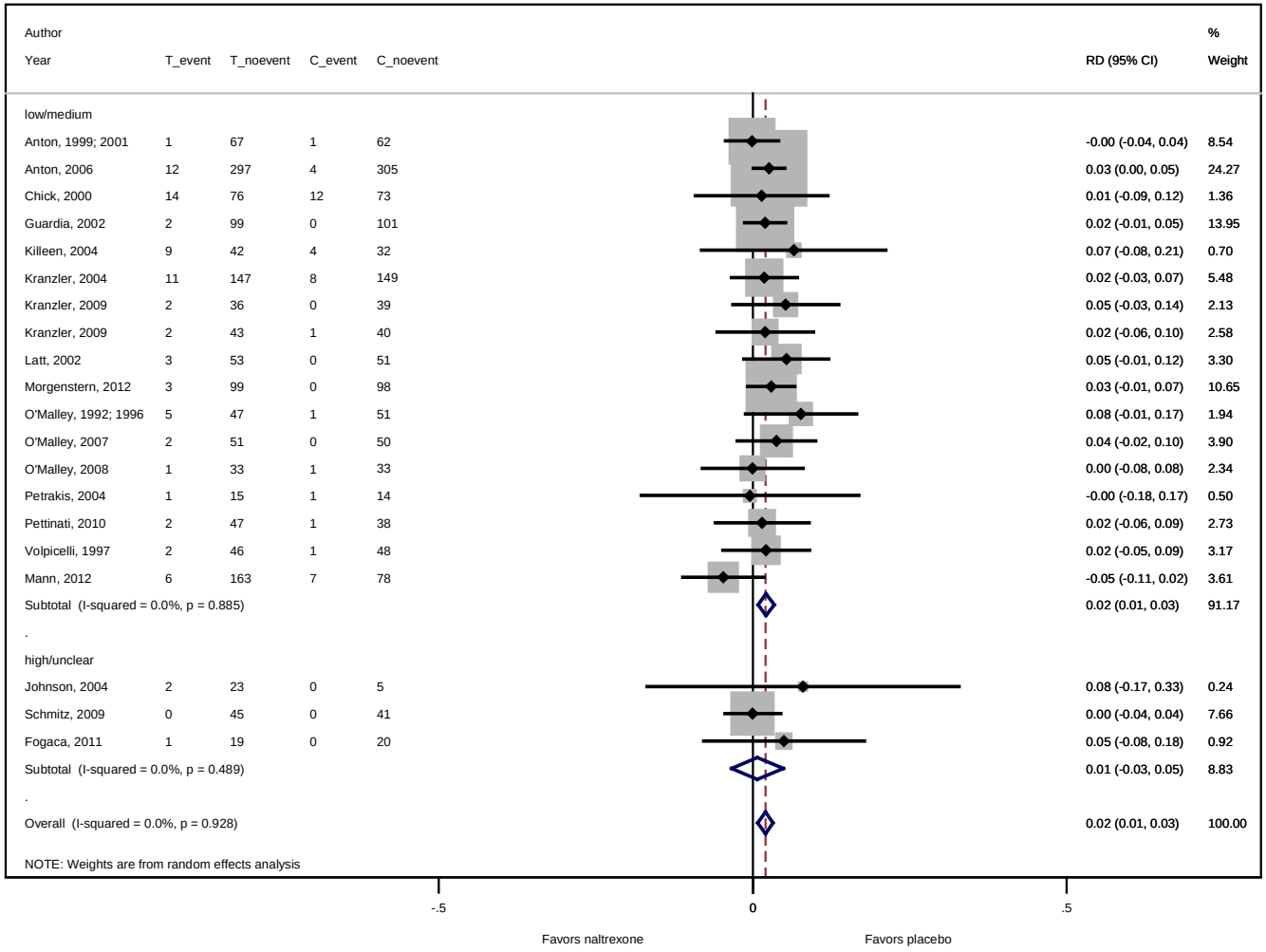


Figure F-115. Withdrawals due to adverse events – Acamprosate versus naltrexone by risk of bias rating

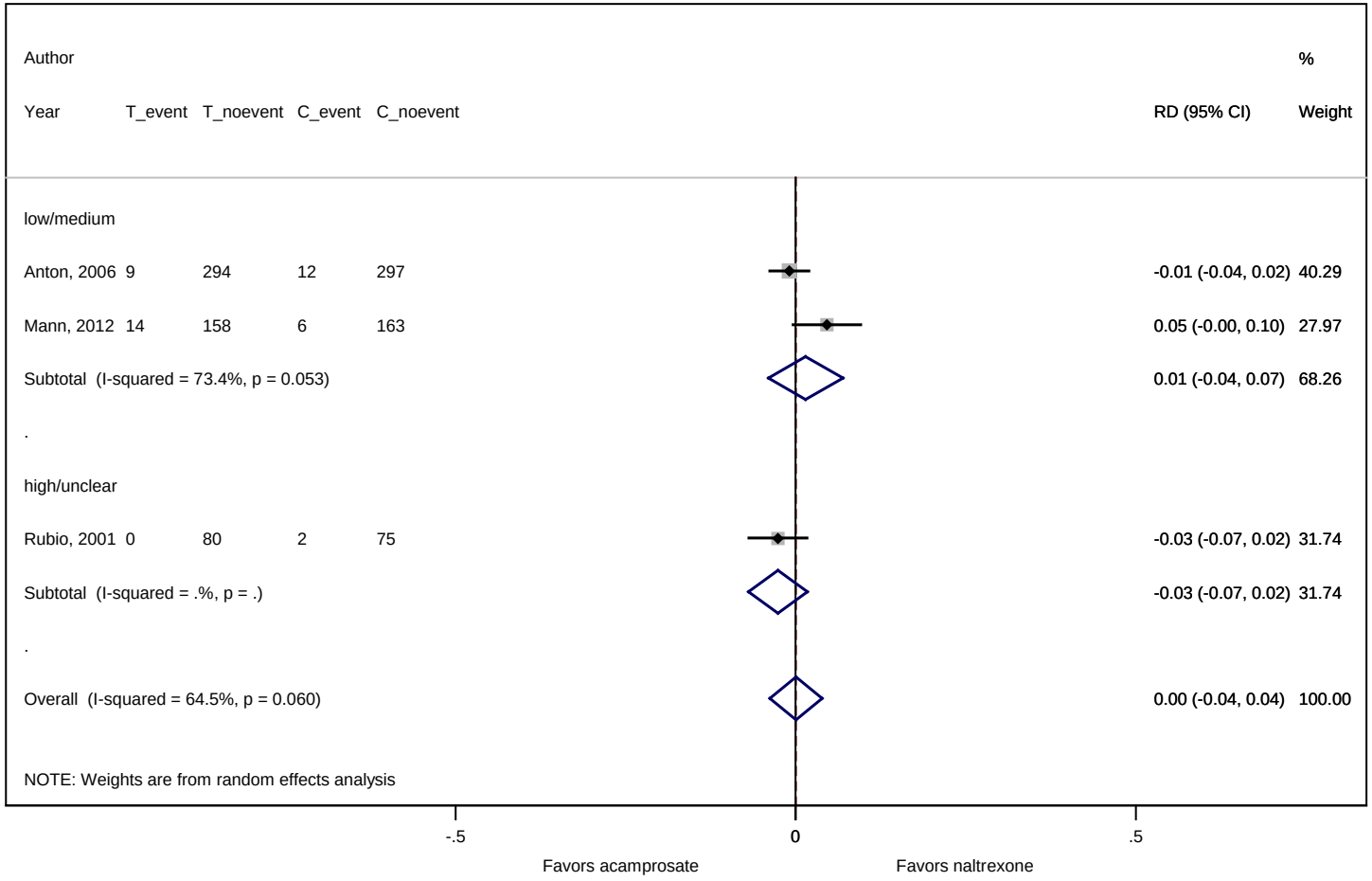


Figure F-116. Withdrawals due to adverse events – Nalmefene versus placebo by risk of bias rating

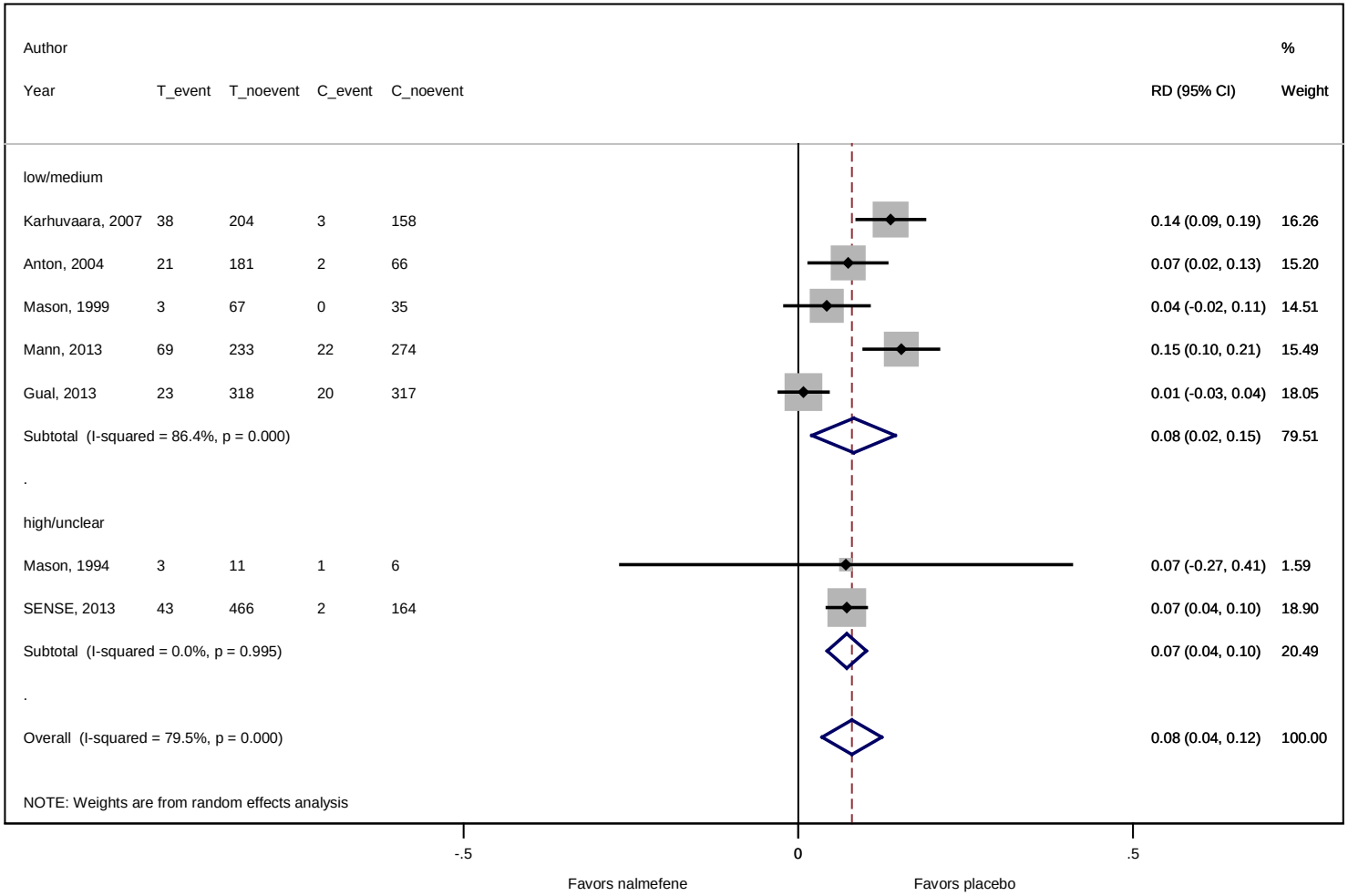
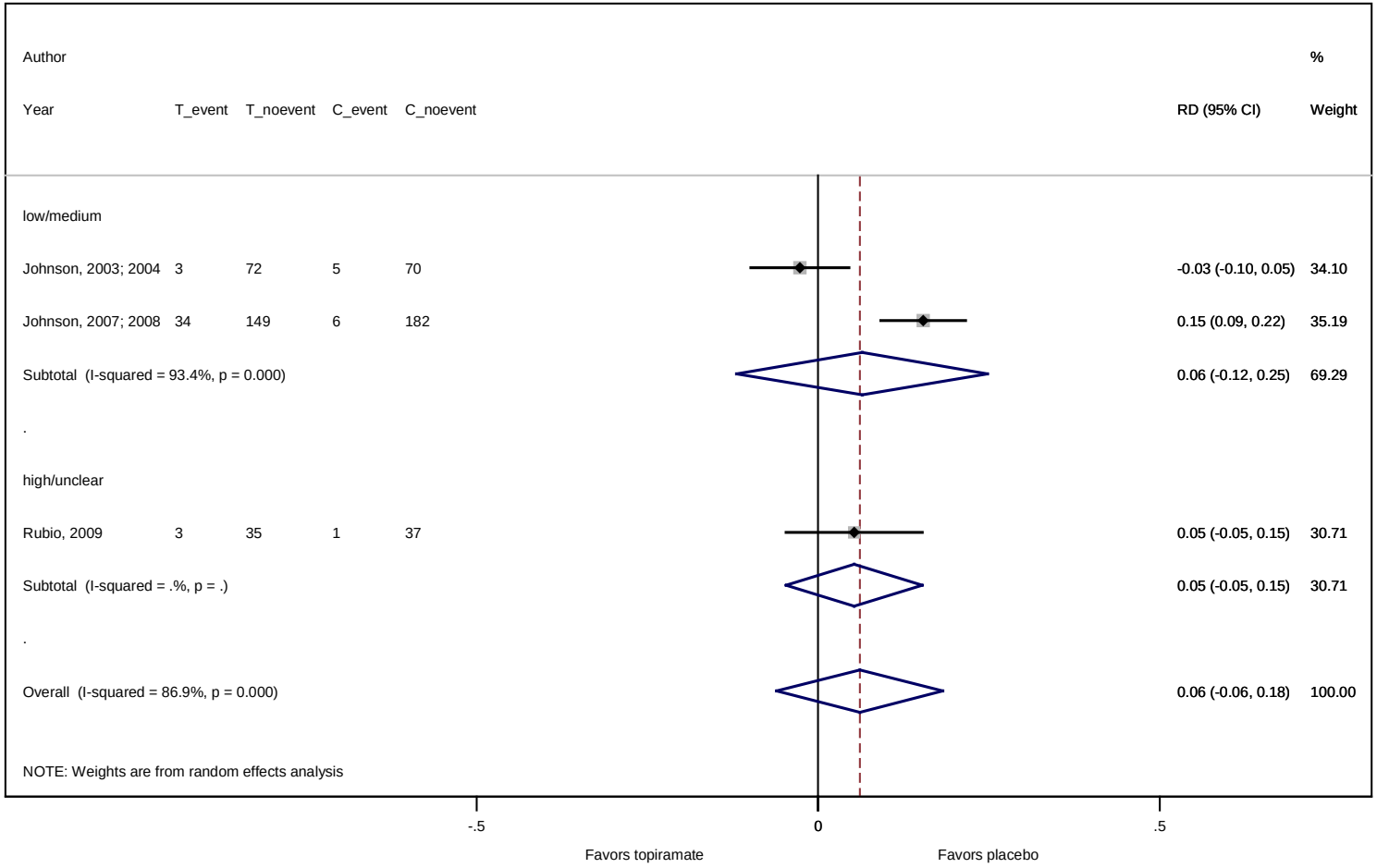


Figure F-117. Withdrawals due to adverse events – Topiramate versus placebo by risk of bias rating



Key Question 6 Meta-Analysis Results

Figure F-118. Return to any drinking: Naltrexone response by genotype, AA versus AG, GG by risk of bias rating

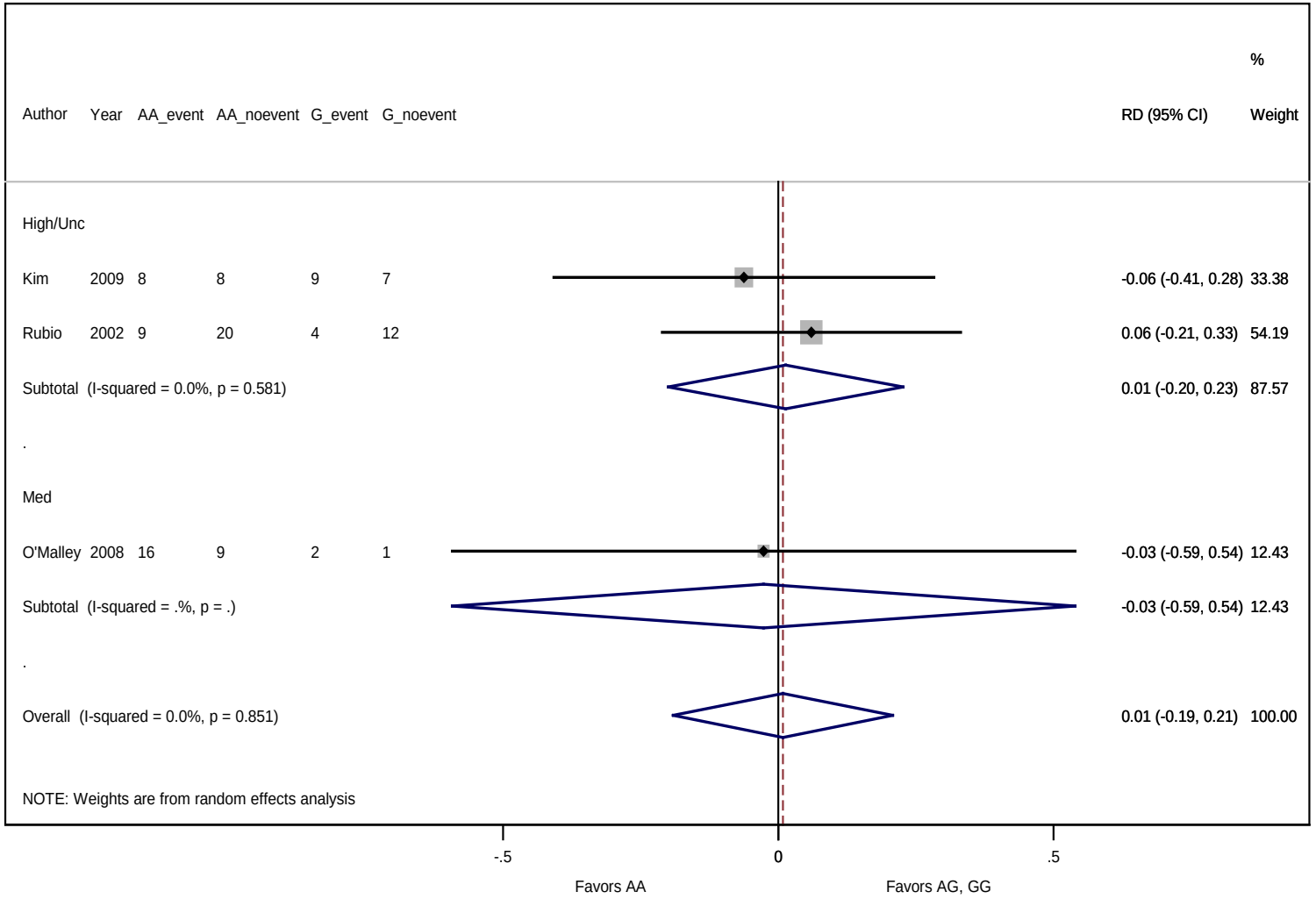
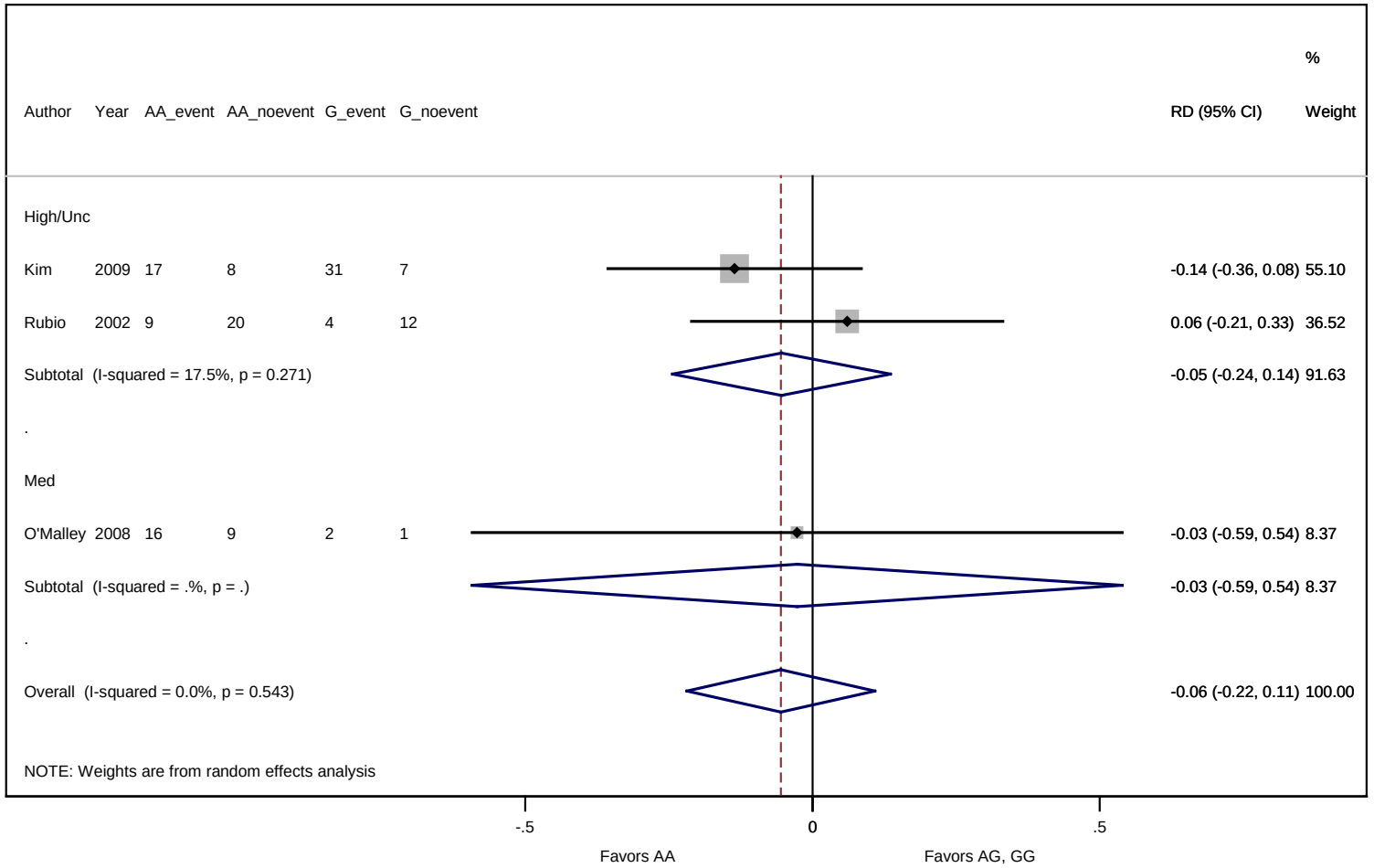


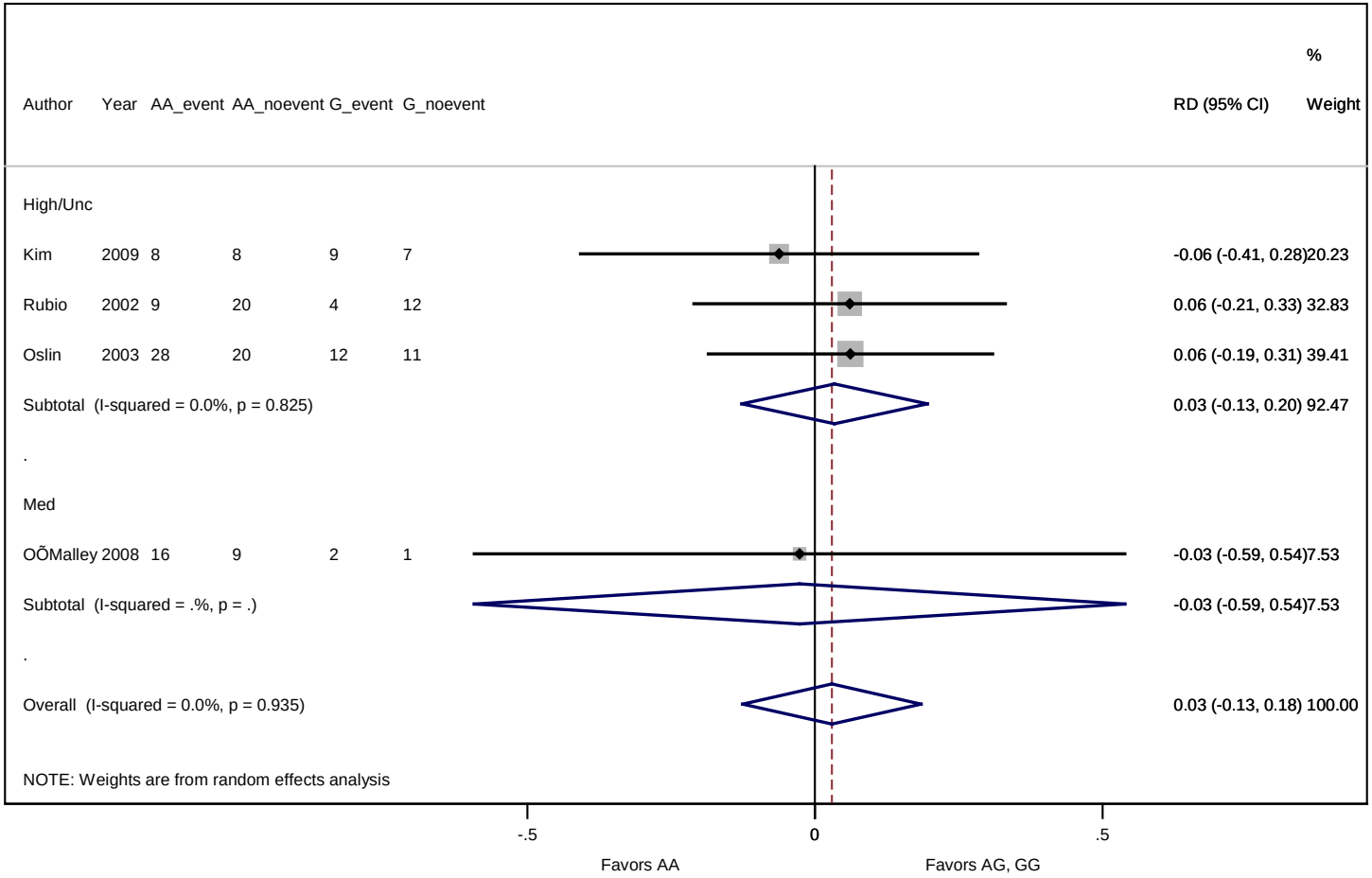
Figure F-119. Return to any drinking: Naltrexone response by genotype, AA versus AG, GG; Sensitivity Analysis I



Note: This SA is with imputing bad outcome (return to any drinking) for those dropped from Kim results that they reported.

Main analysis used Kim data reported by the article for the 32/63 who were adherent to NTX for 12 weeks; SA run with importing bad outcome for those lost (9 more for AA group and 22 more for the G carrier group)

Figure F-120. Return to any drinking: Naltrexone response by genotype, AA versus AG, GG; Sensitivity Analysis II



Note: Added Oslin 2003 (which did not meet inclusion criteria): Oslin 2003: Despite the main effect of genotype in the naltrexone-treated group, there was no medication by genotype interaction on relapse rates (OR 2.27 (95% CI: 0.44, 11.60, P 0.326). There was also no medication by genotype interaction for abstinence OR 0.89 (95% CI: 0.18, 4.38), P 0.889). Of note, there was a significant effect of naltrexone in reducing rates of relapse in the overall pooled sample even when genotype was included in the regression analysis (OR 2.42 (95% CI: 1.09, 5.39), p 0.030)

Figure F-121. Return to heavy drinking: Naltrexone response by genotype, AA versus AG, GG by risk of bias rating (RoB)

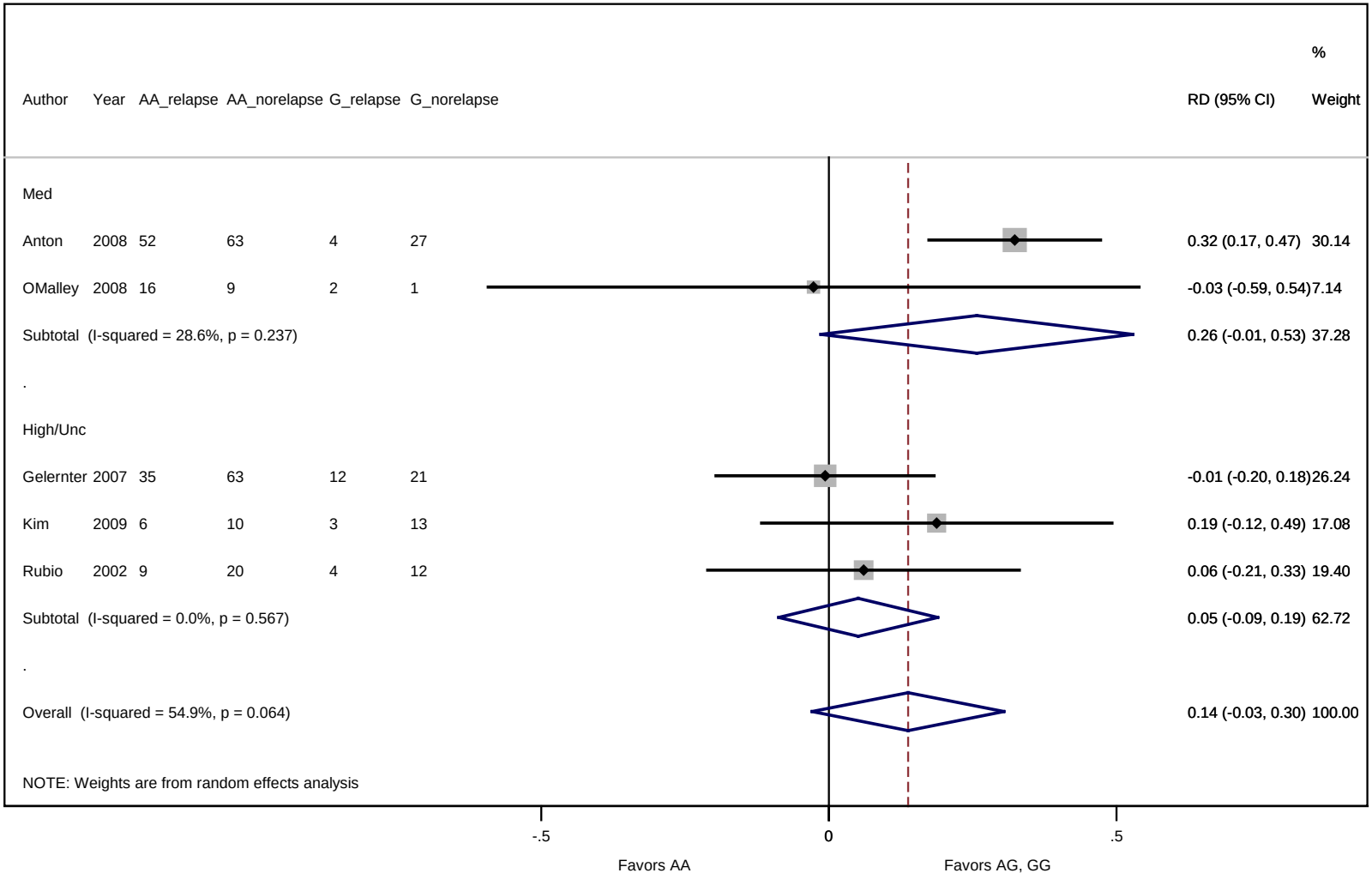
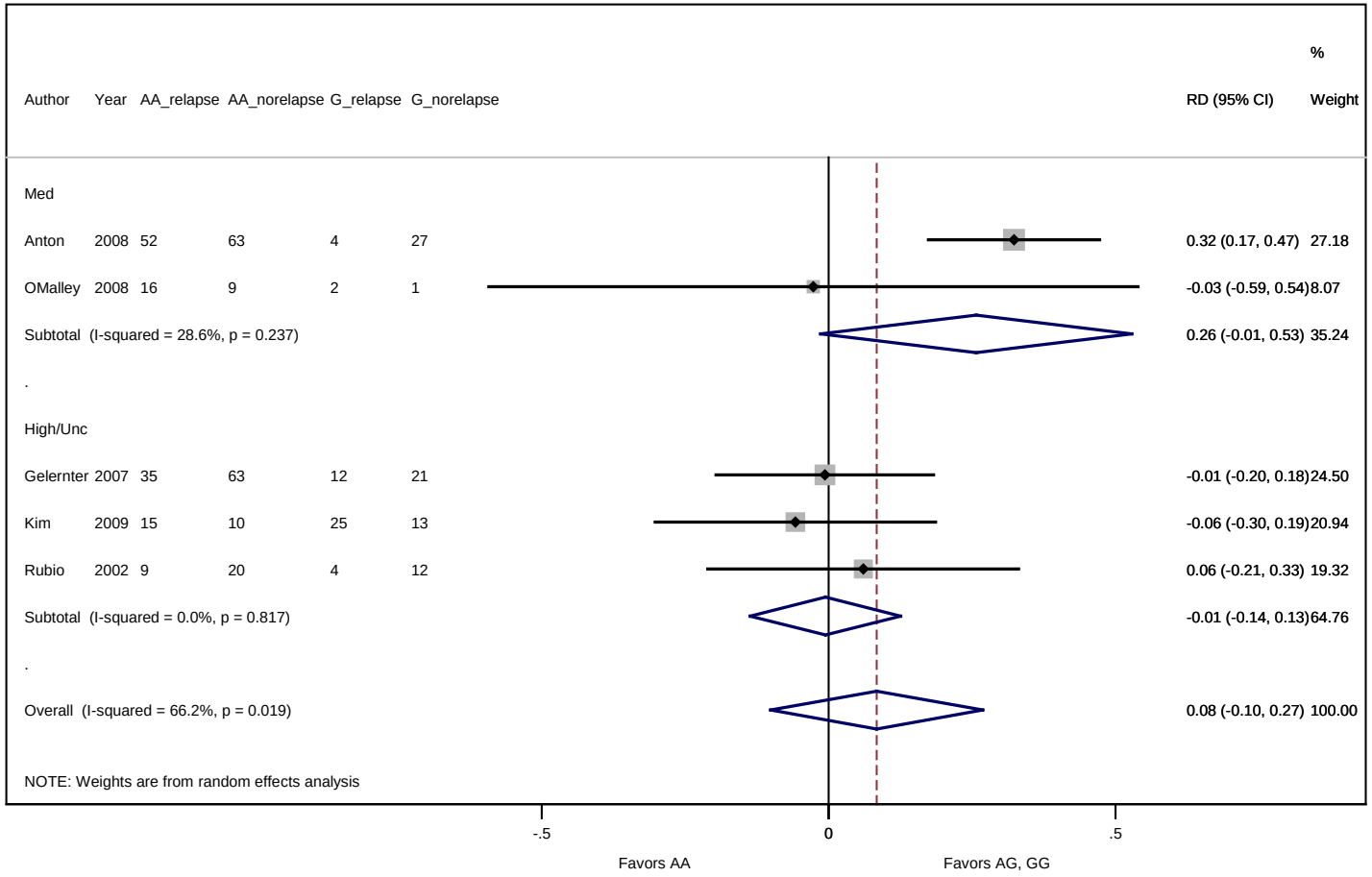
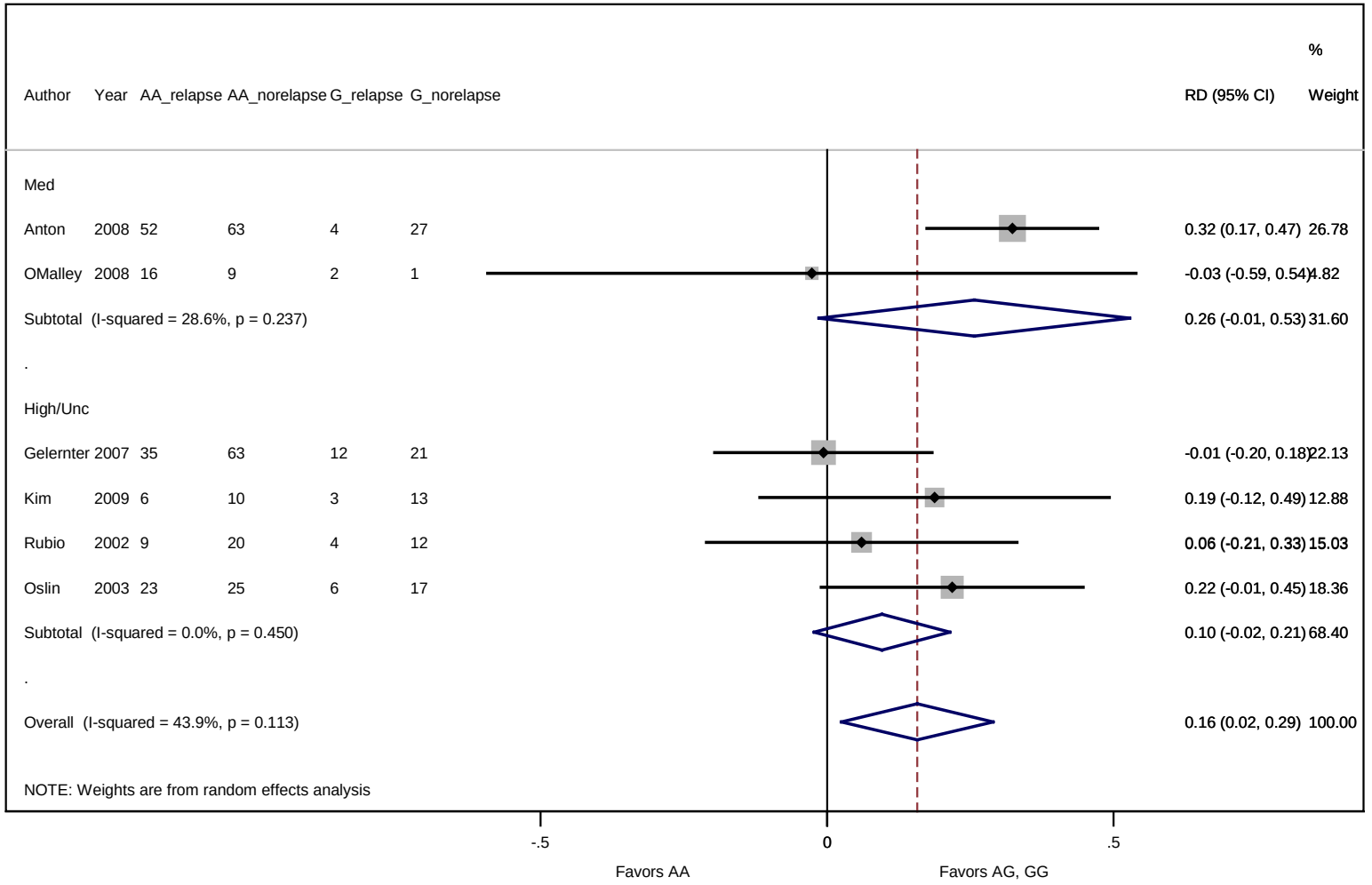


Figure F-122. Return to heavy drinking: Naltrexone response by genotype, AA versus AG, GG; Sensitivity Analysis I



Note: This sensitivity analysis done with imputing bad outcome for Kim, 2009 missing data

Figure F-123. Return to heavy drinking: Naltrexone response by genotype, AA versus AG, GG; Sensitivity Analysis II



Note: Added Oslin, 2003 (which did not meet inclusion criteria)

Appendix G. Additional Studies of Genetic Polymorphisms Meeting Inclusion Criteria but With Only One Study for a Drug-Polymorphism Pair

Characteristics of Trials

Table G-1 summarizes characteristics of the six included studies. Five were analyses of subjects from randomized controlled trials, and one was a prospective cohort study of patients taking disulfiram.[1] One of the trials compared naltrexone 50 mg/day with topiramate 50 to 400 mg/day;[2] one was a three-arm study that compared acamprosate 1,998 mg/day, naltrexone 50 mg/day and placebo;[3] the others were placebo-controlled trials of nalmefene 20 mg/day,[4] olanzapine 5 mg/day,[5] and sertraline 200 mg/day.[6] Duration of treatment ranged from 12 to 28 weeks; one trial also reported three- and six-month off-treatment follow-up data.[6] Two were conducted in the U.S.,[5,6] two in Germany,[1,3] and one each in Finland[4] and Spain.[2]

Mean age was very similar across studies, in the 40s. All patients met criteria for alcohol dependence. Enrollment of women and non-White subjects, when reported, was generally low. None of the studies reported information on smoking history at baseline. Two studies reported co-occurring psychiatric conditions: in one, 23 percent had a personality disorder,[2] and in the other, 26 percent had a concurrent drug use disorder.[6] Co-interventions in the studies included BRENDA, combined behavioral interventions, and coping skills therapy. One study was rated medium risk of bias;[6] the other five were rated high risk of bias.

In the three-arm study that compared acamprosate, naltrexone and placebo,[3] the rs13273672 polymorphism in the *GATA4* gene was associated with relapse. At the end of 90 days of treatment, fewer patients with AA genotype relapsed than patients with AG or GG (45.7 percent versus 53.9 percent versus 69.0 percent, p=0.0066). The polymorphism was associated with relapse for patients treated with acamprosate, but not for those who received naltrexone or placebo.

In the trial that compared sertraline with placebo, analyses examined the main and interaction effects with time of 3 factors—medication group, age of onset of alcohol dependence, and 5-*HTTLPR* genotype.[6] The study reported differential effects for S' carriers and for L' homozygotes, with no significant effects in S' carriers. Late-onset (>25 years of age) alcoholics with the L'L' genotype who received sertraline had fewer drinking days at 12 weeks than those who received placebo (p=0.007), but there was no treatment difference in heavy drinking days. Early-onset L'L' individuals who received sertraline had more drinking days and more heavy drinking days (p=0.002 and p=0.004, respectively) at 12 weeks than those who received placebo. At three months off-treatment, late onset L'L' patients who had received sertraline continued to have fewer drinking days compared with placebo-treated patients (p=0.027).

The prospective cohort study of disulfiram revealed no significant gene-treatment interaction for time to relapse or cumulative abstinence between genotype groups based on the SNP rs1611115 of the *DBH* gene.[1]

Table G-1. Characteristics of included studies that assessed the association between genetic polymorphisms and medication response

Author, Year	Arm Dose, mg/day (N)	Genotypes Assessed	Medication Duration (F-u)	Setting	Age Years	Percentage Non-White	Percentage Female	Cointervention(s)	Risk of Bias
Arias, 2008[4]	Nalmefene 20 (166) Placebo (106)	*OPRM* *OPRD* *OPRK*	28	Finland; Outpatient 15 sites	49 to 50	0	20	BRENDA 100%	High
Florez, 2008[2]	Topiramate 50-400 (45) Naltrexone 50 (45)	*DRD2* *DRD3* *HTR2A* *SLC6A*	26	Spain; Outpatient	46	0	13	NR	High
Hutchison, 2006[5]	Olanzapine 5 (33) Placebo (31)	*DRD4*	12	U.S.; Outpatient clinical research center	43 to 45	4 to 33	26 to 42	Brief structured psychosocial intervention 100%	High
Kiefer, 2011[3]	Acamprosate 1998 (147) Naltrexone 50 (148) Placebo (74)	*GATA4*	12	Germany; Unclear	45	NR	NR	Medical management (CBI) 100%	High
Kranzler, 2012[6]	Sertraline 200 intended, mean dose 169 (63) Placebo (71)	*5-HTTLPR*[a]	12 (26)	U.S.; Outpatient; university health center	48	8	19	CS 100%	Med
Mutschler, 2012[1]	Disulfiram NR (62)	*DBH*[b]	12	Germany; SA treatment, Outpatient	48	NR	32	CBI 100%	High

[a]5-HTTLPR is a polymorphism in the serotonin transporter gene. Variation at this locus includes higher-activity long (L) and lower-activity short (S) alleles.

[b] SNP tested was rs1611115, located in the promoter region of the DBH gene.

Notes: Age (y) is the mean age in years, unless otherwise stated

Abbreviations: CBI, combined behavioral intervention; CS, coping skills; DBH, dopamine beta-hydroxylase; DR, dopamine receptor; follow-up in weeks; HTR2A, serotonin 2A receptor; mg, milligrams; N = Number; NR, not reported; OPRD, δ-opioid receptor; OPRK, κ-opioid receptor; OPRM, μ-opioid receptor; prosp., prospective; SLC6A, dopamine transporter; SSGA, secondary or subgroup analysis of a randomized controlled trial; U.S., United States

References for Appendix G

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3. Kiefer F, Witt SH, Frank J, et al. Involvement of the atrial natriuretic peptide transcription factor GATA4 in alcohol dependence, relapse risk and treatment response to acamprosate. Pharmacogenomics J. 2011 Oct;11(5):368-74. PMID: 20585342.
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5. Hutchison KE, Ray L, Sandman E, et al. The effect of olanzapine on craving and alcohol consumption. Neuropsychopharmacology. 2006 Jun;31(6):1310-7. PMID: 16237394.
6. Kranzler HR, Armeli S, Tennen H. Post-treatment outcomes in a double-blind, randomized trial of sertraline for alcohol dependence. Alcohol Clin Exp Res. 2012 Apr;36(4):739-44. PMID: 21981418.