Comparative Effectiveness Review
Number 134

Effective Health Care Program

Pharmacotherapy for Adults With Alcohol-Use Disorders in Outpatient Settings

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]

Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

The full report and this summary are available at **www.effectivehealthcare.ahrq.gov/reports/final.cfm**.

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,

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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.

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

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 b-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?

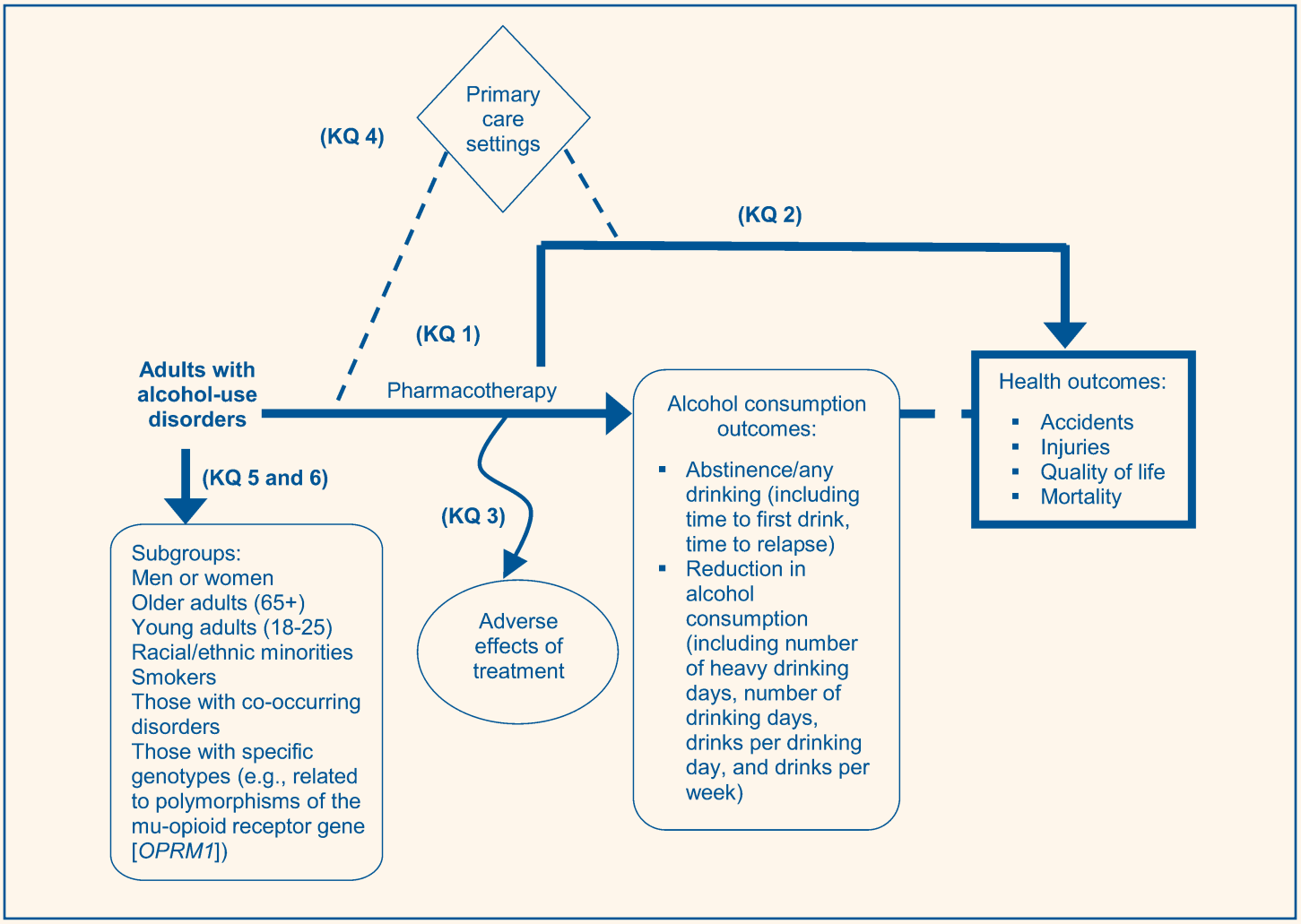
KQ 5: Are any of the medications more or less effective than other medications for men or women, older adults, young adults, racial or ethnic minorities, smokers, or those with co-occurring disorders?

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



Note: 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.

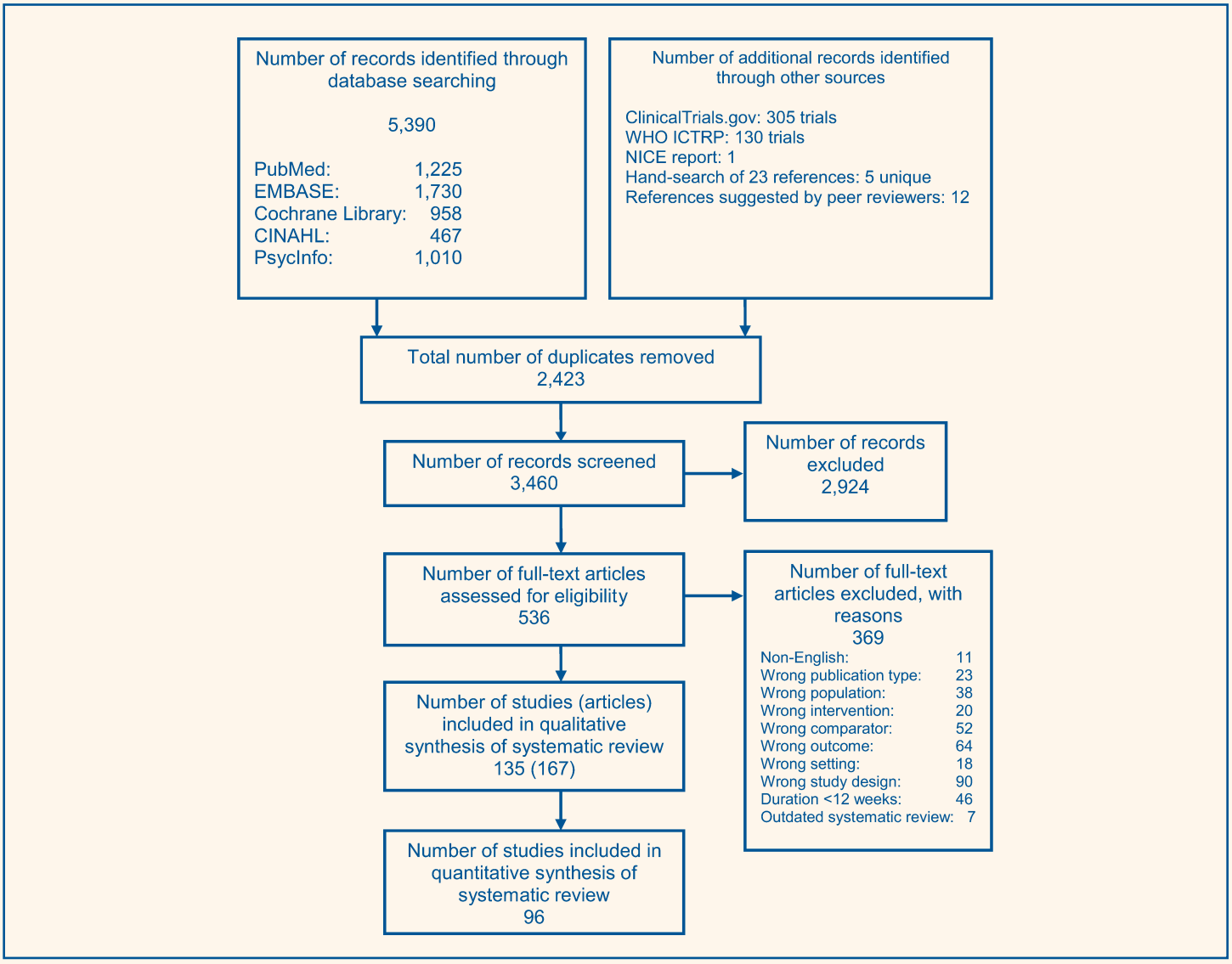
Applicability

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

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

Medication	Outcome	N Studies; N Subjects[a]	Results—Effect Size (95% CI)[b]	NNT[c]	Strength of Evidence
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.

Table E. Evidence gaps for future research by Key Question (continued)		
KQ	**Evidence Gap**	**Potential Future Research**
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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Full Report

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