

Evidence-based Practice Center Systematic Review Protocol

Project Title: Pharmacotherapy for Adults With Alcohol-Use Disorders in Outpatient Settings

I. Background and Objectives for the Systematic Review

Alcohol misuse, which includes the full spectrum from drinking above recommended limits (i.e., risky/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 use⁸) 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

Term	Definition
Risky or hazardous use	Consumption of alcohol above recommended daily, weekly, or per-occasion amounts. ² 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	A. A maladaptive pattern of alcohol-use leading to clinically significant impairment or distress, as manifested by one (or more) of the following, occurring within a 12-month period: <ul style="list-style-type: none"> (1) recurrent alcohol use resulting in a failure to fulfill major role obligations at work, school, or home (e.g., repeated absences or poor work performance related to alcohol use; alcohol-related absences, suspensions, or expulsions from school; neglect of children or household); (2) recurrent alcohol use in situations in which it is physically hazardous (e.g., driving an automobile or operating a machine when impaired); (3) recurrent alcohol-related legal problems (e.g., arrests for alcohol-related disorderly conduct); or (4) continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol (e.g., arguments with spouse about consequences of intoxication, physical fights). B. The symptoms have never met the criteria for alcohol dependence.
Alcohol dependence ¹¹ (alcoholism, alcohol addiction)	A maladaptive pattern of alcohol use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period: <ul style="list-style-type: none"> (1) tolerance, as defined by either of the following: <ul style="list-style-type: none"> (a) a need for markedly increased amounts of alcohol to achieve intoxication or desired effect or (b) markedly diminished effect with continued use of the same amount of alcohol; (2) withdrawal, as manifested by either of the following: <ul style="list-style-type: none"> (a) the characteristic withdrawal syndrome for alcohol or (b) alcohol (or a closely related drug) is taken to relieve or avoid withdrawal symptoms; (3) alcohol is often taken in larger amounts or over a longer period than was intended; (4) there is a persistent desire or unsuccessful efforts to cut down or control alcohol use; (5) a great deal of time is spent in activities necessary to obtain alcohol, use alcohol, or recover from its effects;

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

Term	Definition
Alcohol dependence ¹¹ (alcoholism, alcohol addiction) (continued)	(6) important social, occupational, or recreational activities are given up or reduced because of alcohol use; <i>or</i> (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 disorders (AUDs) include harmful use, alcohol abuse, and alcohol dependence;^{12,13} they are relatively common in developed countries.¹² Prevalence of AUDs is higher for men than for women, with estimates indicating a lifetime risk of more than 20 percent for men.^{12,14-16} Alcohol dependence has lifetime prevalence rates of about 17 percent for men and 8 percent for women.¹⁷

AUDs cause substantial morbidity and mortality—that is, threefold to fourfold increased rates of early mortality.¹⁸⁻²⁰ 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.^{12,21} 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.²² Acute alcohol-related harm can be the result of fires, drowning, falls, homicide, suicide, motor vehicle crashes, child maltreatment, and pedestrian injuries.²³ In addition, AUDs can complicate the assessment and treatment of other medical and psychiatric problems.¹²

AUDs 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.¹² Twenty to 30 percent of people with AUDs achieve long-term remission without any formal treatment.^{12,24,25}

Some studies indicate that less than 10 percent of those with AUDs are able to achieve long periods of nonproblematic drinking.²⁶⁻³⁰ Thus, the goal of treatment in the United States is typically abstinence, because of the belief that it is unlikely that those with AUDs can return to controlled, healthy alcohol use. However, controlled drinking and harm reduction are often goals of treatment in parts of Europe.^{12,29}

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 (disulfiram, naltrexone, acamprosate). Treatment may be delivered via intensive outpatient programs using group or individual counseling, alcoholism treatment centers, or other approaches.

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.³¹ 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.¹² However, the long-term efficacies of specific treatment approaches have not been systematically compared with one another in randomized trials, making interpretation and recommendations for specific interventions difficult.

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.³² These measures include significant increases in abstinent days or decreases in heavy drinking episodes, improved physical health, reductions in health care costs, and improvements in psychosocial functioning. Research using these nonabstinent outcomes provides additional evidence for the effectiveness of treatment for alcohol dependence. Miller et al. (2001)³¹ analyzed seven large multisite trials that tested the treatment approaches noted above. They found that whereas, in aggregate, about 25 percent of individuals maintained sobriety over 1 year, the remaining nonabstinent individuals showed substantial decreases in drinking days (from 63% pretreatment to 25% posttreatment) and a mean 57 percent decrease in drinks per drinking day.

Treatment outcomes can be affected by many factors, including the following: (1) AUDs are a heterogeneous group of disorders with considerable variability in outcome and prognosis; (2) comorbidities: multiple physical and emotional illnesses can influence treatment outcomes; (3) there are many forms of treatment, including multiple varieties of psychosocial interventions and several pharmacological interventions; and (4) patients have many pathways to treatment, ranging from voluntary care-seeking to legally mandated treatment. This complexity contributes to variance in treatment outcomes and lack of clarity about any particular best treatment. Nevertheless, many individuals with AUDs respond well to treatment.

Medications 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. Disulfiram can be an effective adjunct to psychosocial treatment for alcohol dependence, though its effectiveness requires a high degree of patient motivation and adherence, thereby limiting its overall usefulness. Since the 1990s two oral medications—naltrexone and acamprosate—and one long-acting intramuscular formulation of naltrexone have been approved by the 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.¹³ 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. Table 3 describes medications that have been used (off-label) or studied for treatment of AUDs.

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

Generic Drug Name	Mechanism	Dosing
Acamprosate	Thought to antagonize glutamatergic N-methyl-D-aspartate (NMDA) receptors and agonize gamma-aminobutyric acid (GABA) type A receptors	666 mg 3 times per day
Disulfiram	Inhibits aldehyde dehydrogenase (ALDH2), causing accumulation of acetaldehyde during alcohol consumption, which produces highly unpleasant symptoms	250 to 500 mg per day
Naltrexone	Opioid antagonist; competitively binds to opioid receptors and may block the effects of endogenous opioids	Oral: 50 to 100 mg per day Intramuscular injection: 380 mg per month

Table 3. Medications that have been used off-label or studied in double-blind randomized controlled trials for adults with alcohol-use disorders

Drug Class	Drug(s)
Alpha blockers	Prazosin
Anticonvulsants/mood stabilizers	Topiramate, valproate, lithium
Anxiolytics	Buspirone
Dopamine agonists	Bromocriptine
Gamma-aminobutyric acid (GABA)-B agonist	Baclofen
GABA analogue	Gabapentin
N-methyl-D-aspartate (NMDA) receptor antagonist	Memantine
Norepinephrine reuptake inhibitor	Viloxazine
Opioid receptor antagonist	Nalmefene
Second-generation (atypical) antipsychotics	Amisulpride, aripiprazole, olanzapine, quetiapine
Serotonin 5-HT ₃ receptor antagonist	Ondansetron
Serotonin-norepinephrine reuptake inhibitors	Atomoxetine
Selective serotonin reuptake inhibitors	Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline
Tricyclic antidepressants	Amitriptyline, desipramine, imipramine
Other antidepressants	Nefazodone
Smoking cessation aid	Varenicline

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.³³ The average effect sizes for these medications are considered low to moderate (from 0.11 to 0.16 for effects on abstinence or heavy drinking) when heterogeneous populations of patients with alcohol dependence are studied.³³

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 only 1 in 4 individuals with alcohol dependence receives treatment.¹⁷ Furthermore, of those patients who receive treatment, less than 1 in 10 receives medication as part of his or her treatment, which leads to a prescribing rate for the entire population of individuals with alcohol dependence of less than 1 in 100. 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.

The use of medications for alcohol dependence has had a very slow uptake into clinical practice, including primary care practices. Very low prescribing rates for these medications indicate that primary care providers are rarely using these medications. This suggests that primary care clinicians are uncertain about how and when to use them (or may not believe evidence supports the use of these medications).

O'Malley and O'Connor³⁴ recently reviewed the issues surrounding the use of medications for alcohol dependence in primary care settings. 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.³⁵

Existing Guidance

A 1999 Evidence Report for AHRQ examined the efficacy of disulfiram, opioid antagonists (naltrexone and nalmefene), acamprosate, serotonergic agents, and lithium in the treatment of alcohol dependence.³⁶ Naltrexone and acamprosate had the best evidence of efficacy, though the magnitude of effect was variable. Naltrexone and acamprosate were found to reduce drinking frequency and maintain abstinence, and naltrexone was found to reduce drinking quantity and prevent relapse (acamprosate trials did not measure the latter two outcomes). Included trials were mainly in substance abuse treatment settings, and cointerventions (e.g., counseling) were not described in much detail. Efficacy in primary care settings was unknown. Many additional trials have been published since that report was completed.

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.¹³ 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 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 to service users who have a goal of abstinence but for whom acamprosate and oral naltrexone are not suitable, or prefer disulfiram and understand the relative risks of taking the drug; and (3) to have specialist and competent staff administer pharmacological interventions. A network meta-analysis of relapse-rate reduction using acamprosate, naltrexone, and placebo favored acamprosate but yielded wide credible intervals, probably due to the inclusion of only three studies.

The Veterans Administration (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.³⁷⁻³⁹ 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. At least 9 systematic reviews and 26 trials have been published since the last search date of the VA guidelines (October 2007).

Rationale for an Evidence Review

The treatment of alcohol dependence and the use of medications in the treatment of alcohol dependence are associated with uncertainty and variation across providers and settings. Many clinicians and treatment programs do not use medications for alcohol dependence despite evidence of efficacy, little evidence of harms, and FDA approval. The low use of medications for alcohol dependence could contribute to unnecessary morbidity and mortality.

Since the 1999 AHRQ report on medications for alcohol dependence, many new trials have been published: 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 alcohol dependence. The need for a new and comprehensive comparative effectiveness review of medications for AUDs appears in order. Such a review will provide significant assistance to dissemination efforts to educate U.S. clinicians in the management of AUDs. The potential to improve the health and welfare of the U.S. population could be significant as well.

Other reasons for this review include the following: (1) intramuscular naltrexone (Vivitrol) is a fairly recently approved medication; (2) to include an assessment of studies using the medications in primary care settings, and to assess applicability of the evidence to primary care; (3) to assess whether some medications are more or less effective for adults with certain genetic polymorphisms (a literature that several Key Informants emphasized the need to synthesize and critique); and (4) to inform updates to clinical practice guidelines.

II. The Key Questions

The draft key questions (KQs) were posted on the EHC website for public comment from September 20 through October 18, 2012. No changes were made based on public review of the draft KQs, PICOTS (populations, interventions, comparators, outcomes, timing, and setting) and analytic framework. The only comments we received were attempts to provide answers to the questions rather than to provide input about the draft KQs, analytic framework, or PICOTS.

Key Question 1:

- a: Which medications are efficacious for improving consumption outcomes for adults with alcohol-use disorders in outpatient settings?
- b: How do medications for adults with alcohol-use disorders compare for improving consumption outcomes in outpatient settings?

Key Question 2:

- a: Which medications are efficacious for improving health outcomes for adults with alcohol-use disorders in outpatient settings?
- b: How do medications for adults with alcohol-use disorders compare for improving health outcomes in outpatient settings?

Key Question 3:

- a: What adverse effects are associated with medications for adults with alcohol-use disorders in outpatient settings?
- b: How do medications for adults with alcohol-use disorders compare for adverse effects in outpatient settings?

Key Question 4:

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

Key Question 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?

Key Question 6:

Are any of the medications more or less effective for adults with certain genetic polymorphisms (e.g., of the mu-opioid receptor gene [*OPRM1*]) compared with adults without such polymorphisms?

For the above KQs, the following PICOTS criteria apply:

- **Population(s)**
 - Adults (age 18 years or older) with alcohol-use disorders

- **Interventions**

- Pharmacotherapy for relapse prevention or pharmacotherapy combined with various co-interventions (including both FDA-approved drugs and those being used off label).
- Studies evaluating pharmacotherapy that utilized co-interventions with other treatments for AUDs (e.g., behavioral counseling, cognitive behavioral therapy, motivational enhancement therapy, psychosocial treatments, or self-help such as 12-step programs [e.g., Alcoholics Anonymous]) will be eligible for inclusion, as long as they meet other inclusion/exclusion criteria.
- Medications approved by the FDA for treatment of alcohol dependence
 - acamprostate
 - disulfiram
 - naltrexone
- Medications used off-label, or those under investigation
 - amitriptyline
 - aripiprazole
 - atomoxetine
 - baclofen
 - buspirone
 - citalopram
 - desipramine
 - escitalopram
 - fluoxetine
 - fluvoxamine
 - gabapentin
 - imipramine
 - nalmefene
 - olanzapine
 - ondansetron
 - paroxetine
 - prazosin
 - quetiapine
 - sertraline
 - topiramate
 - valproate
 - varenicline
 - viloaxine
- This review will not include pharmacotherapy for alcohol withdrawal.

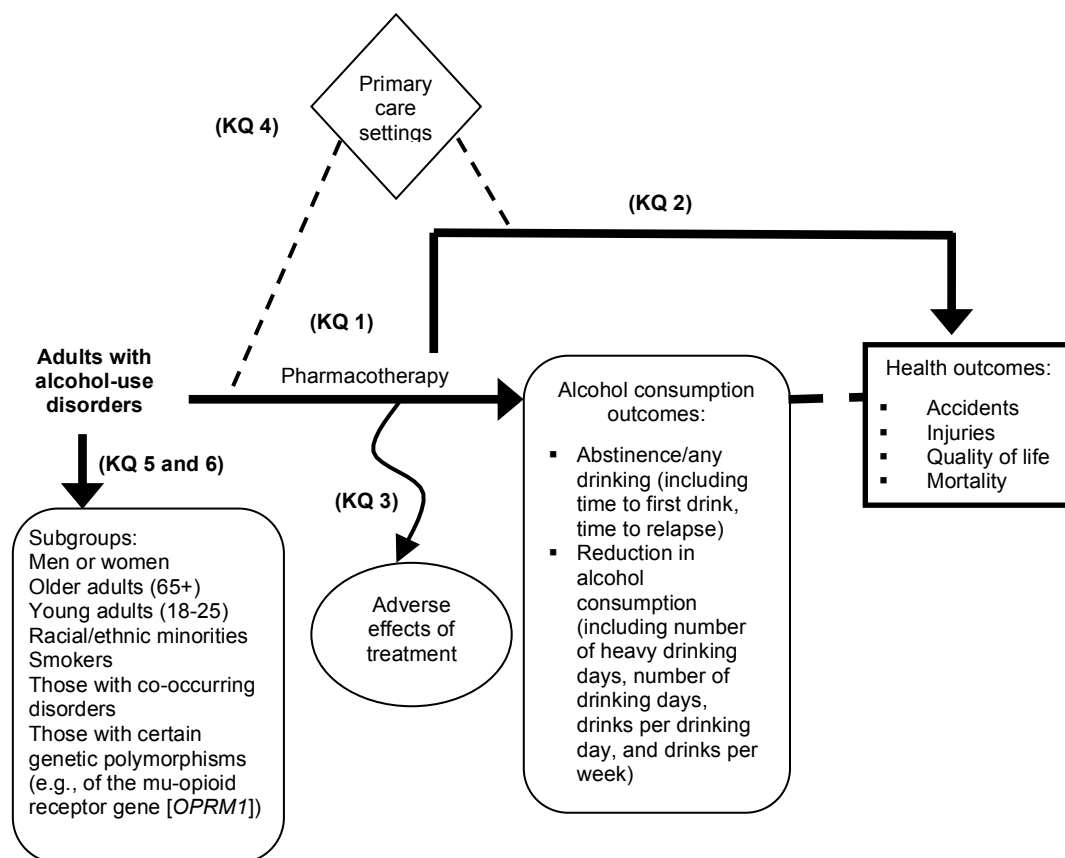


- **Comparators**
 - For KQs 1 through 5, studies must compare one of the medications listed above with placebo or another medication.
 - For KQ 6, studies must compare people who have a genetic polymorphism with people who do not have the polymorphism.
- **Outcomes**
 - Consumption outcomes
 - abstinence/any drinking
 - rates of continuous abstinence
 - percentage of days abstinent
 - time to first drink/lapse
 - time to heavy drinking/relapse
 - reduction in alcohol consumption
 - number of heavy drinking days
 - percent of subjects with no heavy drinking days
 - number of drinking days
 - drinks per drinking day
 - drinks per week
 - Health outcomes
 - accidents
 - injuries
 - 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
- **Timing**
 - Studies with at least 12 weeks of followup from the time of medication initiation.
- **Setting**
 - Outpatient health care (i.e., nonlaboratory) settings; KQ 4 applies to primary care settings only (i.e., internal medicine, family medicine, pediatrics, obstetrics/gynecology, or college and university health clinics).

III. Analytic Framework

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



IV. Methods

A. Criteria for Inclusion/Exclusion of Studies in the Review—Table 4 presents the inclusion/exclusion criteria for this review. We do not repeat all of the PICOTS information related to the inclusion/exclusion criteria.

Table 4. Inclusion/exclusion criteria

Category	Inclusion	Exclusion
Population	Adults (age 18 years or older) with alcohol-use disorders (as defined above in the Background section). For KQ 5, co-occurring disorders will include other mental health disorders (e.g., depression) and acute or chronic medical conditions (e.g., cirrhosis).	Children and adolescents under 18
Geography	No limits	
Time period	1970–present; searches to be updated after the draft report goes out for peer review	
Length of followup	At least 12 weeks	Less than 12 weeks
Settings	Outpatient health care (i.e., nonlaboratory) settings	All other settings; Laboratory settings; Inpatient settings
Interventions	As defined above in PICOTS	Pharmacotherapy for alcohol withdrawal; any drugs not listed in the PICOTS above; combinations of medications (e.g., studies randomizing subjects to naltrexone plus ondansetron vs. placebo).
Comparators	As defined above in PICOTS	No comparison; non-concordant historical controls.
Outcomes	As defined above in PICOTS	Craving; cue reactivity.
Publication language	English	All other languages [†]
Admissible evidence (study design and other criteria)	Original research; eligible study designs include the following: <ul style="list-style-type: none"> For all KQs, RCTs with masking of subjects and providers (i.e., double-blind). For KQ2b, we will also include head-to-head prospective cohort studies. For KQs 3 (focused on harms) and 5 (focused on subgroups), we will also include non-RCTs, open-label trials, secondary analyses or subgroup analyses from trials, prospective cohort studies, and case-control studies comparing two or more of the medications of interest. For KQ 6, we will also include secondary analyses or subgroup analyses from trials and prospective cohort studies comparing people with genetic polymorphisms with those without such polymorphisms. 	Case series Case reports Nonsystematic reviews Editorials Letters to the editor Articles rated as high risk of bias Studies with historical, rather than concurrent, control groups

[†] Because of limited time and resources, we will include only studies published in English.

Abbreviations: KQ = key question; PICOTS = populations, interventions, comparators, outcomes, timing, and setting; RCT = randomized controlled trial.

B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions—We will systematically search, review, and analyze the scientific evidence for each

KQ. The steps that we will take to accomplish the literature review are described below.

To identify articles relevant to each KQ, we will begin with a focused MEDLINE search on alcohol-use disorders by using a variety of terms, medical subject headings (MeSH), and major headings; and by limiting the search to English-language, adult (18 and older), and human-only studies. Relevant terms are listed in Table 5. We will also search the Cochrane Library, the Cochrane Central Trials Registry, the Cumulative Index to Nursing and Allied Health Literature, EMBASE, and PsycInfo by using analogous search terms. We will conduct quality checks to ensure that the known studies (i.e., studies included in the previous review on pharmacotherapy for alcohol-use disorders and those identified during Topic Refinement) are identified by the search. If they are not, we will revise and rerun our searches.

Table 5. PubMed literature search terms

Category	Search Terms
Population	"Alcohol-Related Disorders" [MeSH] OR "Alcoholism" [MeSH] OR "Alcohol Drinking" [MeSH] OR alcohol depend* OR alcohol misuse OR alcohol addiction* OR alcohol abuse OR problem drink* OR alcohol problem* OR "alcohol consumption" [All Fields] OR harmful alcohol* OR harmful drink* OR (drinking[tiab] OR drinker[tiab] OR drinkers[tiab]) AND alcohol[tiab]
Interventions	"Alcohol Deterrents" [MeSH] 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 varenicline OR viloxazine
Limits	Humans Adults English language Publication date from 1970 to [date of search]

We will *not* simply conduct one search starting from where the 1999 systematic review for AHRQ left off. Rather, because our review has some differences in scope (e.g., more included medications, questions about comparative effectiveness [KQs 1b, 2b, 3b], primary care [KQ 4], and genetic polymorphisms [KQ 6]), we will search the literature published since 1970. This search date was selected based on the earliest publications found during topic refinement, the earliest studies found in previous systematic reviews (which was from 1974), and expert opinion.

We will search the "gray literature" for unpublished studies relevant to this review and will include studies that meet all the inclusion criteria and contain enough methodological information for assessment of internal validity/quality.



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Gray literature sources will include ClinicalTrials.gov, the World Health Organization's International Clinical Trials Registry Platform, and pharmaceutical companies' scientific information packets (which will be requested by the Scientific Resource Center).

We reviewed our search strategy with the Technical Expert Panel (TEP) and did they did not have any recommendations to alter it. In addition, to attempt to avoid retrieval bias, we will manually search the reference lists of systematic reviews, landmark studies, and background articles on this topic to look for any relevant citations that might have been missed by electronic searches.

We will conduct an updated literature search (of the same databases searched initially) concurrent with the peer review process. Any literature suggested by Peer Reviewers or from the public will be investigated and, if appropriate, incorporated into the final review. Appropriateness will be determined by the same methods described above.

C. Data Abstraction and Data Management—All titles and abstracts identified through searches will be independently reviewed for eligibility against our inclusion/exclusion criteria by two trained members of the research team. Studies marked for possible inclusion by either reviewer will undergo a full-text review. For studies without adequate information to determine inclusion or exclusion, we will retrieve the full text and then make the determination. All results will be tracked in an EndNote[®] bibliographic database (Thomson Reuters, New York, NY).

We will retrieve and review the full text of all titles marked for possible inclusion during the title/abstract review phase. Each full-text article will be independently reviewed by two trained members of the team using the eligibility criteria described above. If both reviewers agree that a study does not meet the eligibility criteria, the study will be excluded. If the reviewers disagree, conflicts will be resolved by discussion and consensus or by consulting a third member of the review team. As described above, all results will be tracked in an EndNote database. We will record the reason that each excluded full-text publication did not satisfy the eligibility criteria so that we can later compile a comprehensive list of such studies.

For studies that meet our inclusion criteria, we will abstract important information into evidence tables. We will design data abstraction forms to gather pertinent information from each article, including characteristics of study populations (e.g., age, sex, race, ethnicity, and smoking status of enrolled populations; proportion with alcohol dependence and other AUDs; co-occurring disorders of enrolled populations; source of subject recruitment), interventions (e.g., dose and frequency of administration; type of provider prescribing the treatment; co-interventions), comparators, settings (e.g.,

primary care, substance abuse treatment settings), study designs, methods, and results. Trained reviewers will extract the relevant data from each included article into the evidence tables. All data abstractions will be reviewed for completeness and accuracy by a second member of the team.

D. Assessment of Methodological Risk of Bias of Individual Studies—To assess the risk of bias (i.e., internal validity) of studies, we will use predefined criteria based on the AHRQ *Methods Guide for Comparative Effectiveness Reviews*,⁴⁰ including questions to assess selection bias, confounding, performance bias, detection bias, and attrition bias (i.e., those about adequacy of randomization, allocation concealment, similarity of groups at baseline, masking, attrition, whether intention-to-treat analysis was used, method of handling dropouts and missing data, validity and reliability of outcome measures, and treatment fidelity). In general terms, results from a study assessed as having low risk of bias are considered to be valid. A study with moderate risk of bias is susceptible to some risk of bias but probably not enough to invalidate its results. A study assessed as high risk of bias has significant risk of bias (e.g., stemming from serious issues in design, conduct, or analysis) that may invalidate its results. We plan to exclude studies deemed high risk of bias from our main data synthesis and main analyses; we will include them only in sensitivity analyses.

Two independent reviewers will assess risk of bias for each study. Disagreements between the two reviewers will be resolved by discussion and consensus or by consulting a third member of the team.

E. Data Synthesis—If we find multiple similar studies for a comparison of interest, we will consider quantitative analysis (i.e., meta-analysis) of the data from those studies. To determine whether quantitative analyses are appropriate, we will assess the clinical and methodological heterogeneity of the studies under consideration following established guidance.⁴¹ We will do this by qualitatively assessing the PICOTS of the included studies, looking for similarities and differences. When quantitative syntheses are not appropriate (e.g., because of clinical heterogeneity, insufficient numbers of similar studies, or insufficiency or variation in outcome reporting), we will synthesize the data qualitatively.

For quantitative syntheses, we will use random-effects models to estimate pooled effects.⁴² For continuous outcomes (e.g., percentage of days abstinent) measured with the same scale, we will report the weighted mean difference (WMD) between intervention and control. If we combine multiple scales (e.g., different scales to measure quality of life) in one meta-analysis, we will use the standardized mean difference (SMD), Cohen's d. For binary outcomes (e.g., adverse events), we will calculate risk differences between groups or risk ratios (e.g., if mortality data are reported from studies with various

followup durations, we will base the analysis on number of deaths per person-year and report a risk ratio). For each meta-analysis, we will conduct sensitivity analyses by adding studies excluded for having high risk of bias. To assess statistical heterogeneity, we will calculate the chi-squared statistic and the I^2 statistic.^{43,44}

We plan to stratify analyses and/or perform subgroup analyses when possible and appropriate. Planned stratifications or categories for subgroup analyses include those listed for Key Question 5 as well as geographic location of studies (United States vs. all other countries).

If appropriate (based on our assessment of clinical and methodological heterogeneity, and availability of sufficient numbers of studies), we will conduct a network meta-analysis using Bayesian methods to compare the efficacy of medications. The analysis will include both head-to-head and placebo-controlled trials.

F. Grading the Strength of Evidence (SOE) for Individual Comparisons and Outcomes

We will grade the strength of evidence based on the guidance established for the Evidence-based Practice Center Program.⁴⁵ 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 other optional domains that may be relevant for some scenarios, such as a dose-response association, plausible confounding that would decrease the observed effect, strength of association (magnitude of effect), and publication bias.

Table 6 describes the grades of evidence that can be assigned. Grades reflect the strength of the body of evidence to answer KQs on the comparative effectiveness, efficacy, and harms of the interventions included in this review. Grades do not refer to the general efficacy or effectiveness of interventions. Two reviewers will assess each domain for each key outcome, and differences will be resolved by consensus.

We will grade the strength of evidence for alcohol-consumption measures, accidents, injuries, quality of life, and mortality.

Table 6. Definitions of the grades of overall strength of evidence⁴⁵

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.

G. Assessing Applicability—We will assess applicability of the evidence following guidance from the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.⁴⁶ We will use the PICOTS framework to explore factors that affect applicability. Some factors identified a priori that may limit the applicability of evidence include the following: age of enrolled populations; sex of enrolled populations (e.g., few women may be enrolled in the studies); race/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.

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VI. Definition of Terms

See Table 1.

VII. Summary of Protocol Amendments

In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale.

VIII. Review of Key Questions

For all EPC reviews, key questions were reviewed and refined as needed by the EPC with input from Key Informants and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed. In addition, the key questions were posted for public comment and finalized by the EPC after review of the comments.

IX. Key Informants

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 healthcare 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 TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts comprise a multi-disciplinary 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 health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design and/or 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 nor 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.

Technical Experts must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

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 of 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 CERs and Technical briefs, be published three months after the publication of the Evidence report.

Potential Reviewers must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Invited Peer

Reviewers may not have any financial conflict of interest greater than \$10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

XII. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than \$1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest which cumulatively total greater than \$1,000 will usually disqualify EPC core team investigators.

XIII. Role of the Funder

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