Evidence-based Practice Center Systematic Review Protocol

Project Title: *Pharmacotherapy for Adults With Alcohol-Use Disorders in Outpatient Settings: Systematic Review Update*

I. Background and Objectives for the Systematic Review Update

Alcohol consumption is the third leading preventable cause of death in the United States, accounting for 95,000 deaths annually.[1] Recently available data from the 2019 National Survey on Drug Use and Health suggest that more than 14.5 million Americans 12 years of age or older met Diagnostic and Statistical Manual of Mental Disorders version 5 (DSM-5) criteria for an alcohol-use disorder (AUD) in the past year.[2] Of those, only about 7 percent reported receiving treatment of any type, with 4 percent prescribed a U.S. Food and Drug Administration (FDA)-approved medication as part of treatment, despite evidence of effectiveness for some pharmacotherapies.[3]

Definitions of unhealthy alcohol use (sometimes previously referred to as alcohol misuse)[4] continue to evolve. Unhealthy alcohol use includes risky drinking (without AUD) to severe AUD. The current definition used for diagnosis of AUD is from the DSM-5.[5] The inclusion criteria for severity of misuse differ across studies, particularly as the definitions have evolved over time (Table 1). For the purposes of this report, we will extract definitions used by the included studies as noted in Table 1. We will carefully note definitions used in individual studies and will work to cross walk differing definitions to the DSM-V AUD diagnostic criteria; for example, current evidence is that DSM-IV alcohol dependence corresponds to DSM-AUD of at least moderate severity.[6-8]

In this protocol, we often use the term "AUD" to refer generically to an alcohol-use disorder that is severe enough to warrant pharmacotherapy, and we use "DSM-5 AUD" to refer to the specific DSM-5 disorder.

Table 1. Definitions of unhealthy alcohol use (sometimes previously referred to as alcohol misuse)

Term	Definition
Alcohol-use disorder (DSM-5)[5]	A maladaptive pattern of alcohol use leading to clinically significant impairment or distress, as manifested by two (or more) of the following, occurring within a 12-month period: Having times when the patient drank more or longer than intended. More than once wanted to cut down or stop, tried it, but could not. Spending a lot of time drinking or being sick/getting over the aftereffects of drinking. Wanting to drink so badly that they could not think of anything else. Found that drinking (or being sick from drinking) often interfered with taking care of home or family responsibilities, caused problems at work, or caused problems at school. Continuing to drink even though it was causing trouble with family and friends.

Term	Definition
Alcohol-use disorder (DSM-5)[5] **(continued)**	Giving up or cutting back on activities that were important or interesting in order to drink. More than once gotten into situations while or after drinking that increased the chances of getting hurt (e.g., driving, swimming, unsafe sexual behavior). Continued to drink even though it was causing depression or anxiety, other health problems, or memory blackouts. Having to drink much more than previously in order to get the desired effect or finding that the usual number of drinks had much less effect than previously. Experiencing the symptoms of withdrawal after the effects of alcohol were wearing off, such as trouble sleeping, shakiness, restlessness, nausea, sweating, racing heart, or seizure. Severity is determined based on the number of symptoms present: Mild: 2-3 symptoms Moderate: 4-5 symptoms Severe: 6 or more symptoms
Risky or hazardous use	Consumption of alcohol above recommended daily, weekly, or per-occasion amounts.[9] Consumption levels that increase the risk for health consequences.
Harmful use[10, 11]	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/social (e.g., depressive episodes secondary to drinking).
Alcohol abuse (from DSM-IV)[12]	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: (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 from DSM-IV[12] (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: (1) tolerance, as defined by either of the following: (a) a need for markedly increased amounts of alcohol to achieve intoxication or desired effect or (b) markedly diminished effect with continued use of the same amount of alcohol; (2) withdrawal, as manifested by either of the following: (a) the characteristic withdrawal syndrome for alcohol or (b) alcohol (or a closely related drug) is taken to relieve or avoid withdrawal symptoms; (3) alcohol is often taken in larger amounts or over a longer period than was intended;

Term	Definition
Alcohol dependence from DSM-IV[12] (alcoholism, alcohol addiction) **(continued)**	(4) there is a persistent desire or unsuccessful efforts to cut down or control alcohol use; (5) a great deal of time is spent in activities necessary to obtain alcohol, use alcohol, or recover from its effects; (6) important social, occupational, or recreational activities are given up or reduced because of alcohol use; *or* (7) alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by alcohol (e.g., continued drinking despite recognition that an ulcer was made worse by alcohol consumption).

DSM-5 = Diagnostic and Statistical Manual of Mental Disorders version 5, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders version 4

AUDs are relatively common in developed countries.[13, 14] Prevalence of AUDs is high with estimates indicating a lifetime risk of more than 20 percent, and men have more than twice the prevalence of lifetime AUD than women.[13, 15-17] Alcohol dependence, which includes those with more serious AUD, has lifetime prevalence rates of about 17 percent for men and 8 percent for women.[18]

AUDs cause substantial morbidity and mortality—that is, threefold to fourfold increased rates of early mortality.[19-21] 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.[13, 22] Excessive alcohol consumption is also a major factor in injury and violence, including sexual violence.[23] Alcohol-related harm can be the result of fires, drowning, falls, homicide, suicide, motor vehicle crashes, child maltreatment, and pedestrian injuries.[24, 25] In addition, AUDs can complicate the assessment and treatment of other medical and psychiatric problems.[13]

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 adopted. Treatment may be delivered via intensive outpatient programs using group or individual counseling, alcoholism treatment centers, or general outpatient care.

Regardless of treatment location, the goals of treatment can range from abstinence to achieving nonproblematic drinking. Although complete abstinence has been cited as a predominant goal in a substantial portion of the treatment literature, awareness has grown over the past 15 to 20 years that treatment may still be beneficial even if complete abstinence is not achieved. Some studies indicate that less than 10 percent of those with AUDs are able to achieve long periods of nonproblematic drinking.[26-30] As a result, research has used other outcomes to measure the effectiveness of treatment, which can be subsumed under the concept of harm reduction.[31] These measures include significant increases in abstinent days or decreases in heavy drinking episodes, improved physical health, reductions in healthcare costs, and improvements in psychosocial functioning. Research using these nonabstinent outcomes provides additional evidence for the effectiveness of treatment for AUD. Miller et al.[32] 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 outcomes and prognosis; (2) individuals may have co-occurring conditions and challenges, including multiple physical and emotional illnesses that can influence treatment outcomes; (3) there are many forms of treatment, including multiple varieties of psychosocial interventions and several pharmacological interventions; (4) patients have many pathways to treatment, ranging from voluntary care seeking to legally mandated treatment; and (5) patient motivation may differ on the basis of numerous constructs, including employment, family, legal, and social reasons. 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.[33]

Medications for Alcohol-Use Disorders

This review is focused on the effectiveness and role of pharmacotherapy for AUDs in the outpatient setting. Current use of pharmacotherapy is low, despite existing evidence of effectiveness. Medications for AUDs may hold an FDA indication for an alcohol-use condition, including dependence or AUD, or may be FDA approved for other indications but used off label to treat AUDs. This review covers the four medications with FDA indications for AUD, as well as several other medications that have been studied and are used in the United States.

From the 1950s until the early 1990s, the pharmacotherapy consisted only of disulfiram, which produces significant physical symptoms, such as nausea and tachycardia, within 12 hours of alcohol consumption. Anticipatory fear of this response may act as a deterrent to consuming alcohol. Disulfiram can be an effective adjunct to psychosocial treatment, 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 FDA for AUDs. These medications were originally approved for people with alcohol dependence, generally after a successful withdrawal from alcohol and together with psychological intervention.[14] Table 2 describes the medications available in the United States that are FDA approved for treatment of AUDs, their mechanism of action, and dosing. A small group of additional medications are used off label and have been studied for the treatment of AUD with some positive results. Table 3 describes the medications that have most commonly been used (off label) for AUD and will be included in this review.

Table 2. FDA-approved medications for treating adults with AUDs

Generic Drug Name	Mechanism	Dosing
Acamprosate	The exact mechanism of action is unclear but acamprosate is thought to antagonize glutamatergic N-methyl-D-aspartate receptors and lead to increased activation of the GABA type A receptors.[34-36]	666 mg 3 times per day
Disulfiram	A thiuram derivative which blocks the oxidation of alcohol at the acetaldehyde stage. When taken concomitantly with alcohol, there is an increase in serum acetaldehyde levels[37]	250 to 500 mg per day
Naltrexone oral	Acts as a competitive antagonist at opioid receptor sites, showing the highest affinity for Mu receptors. Endogenous opioids are involved in modulating the expression of alcohol's reinforcing effects. It also modifies the hypothalamic-pituitary-adrenal axis to suppress alcohol consumption[38]	50 to 100 mg per day
Naltrexone intramuscular injectable	Acts as a competitive antagonist at opioid receptor sites, showing the highest affinity for mu receptors. Endogenous opioids are involved in modulating the expression of alcohol's reinforcing effects. It also modifies the hypothalamic-pituitary-adrenal axis to suppress alcohol consumption[38]	380 mg per month

AUD = alcohol-use disorder; CNS = central nervous system; FDA = Food and Drug Administration, GABA =Gamma-Aminobutyric Acid.

Table 3. Medications most commonly used off label in the United States for adults with AUDs

Drug Class	Drug(s)
Anticonvulsants/mood stabilizers	Topiramate
GABA-B agonist	Baclofen
GABA analog	Gabapentin
Serotonin 5-HT3 receptor antagonist	Ondansetron

AUD = alcohol-use disorder; GABA = gamma-aminobutyric acid.

In clinical trials, the medications with an FDA indication have shown evidence for efficacy in enhancing abstinence, reducing relapse to heavy drinking, and reducing overall drinking behavior.[39]

As noted above, however, only about 7 percent of individuals who met criteria for an AUD reported receiving treatment of any type, with 4 percent prescribed a U.S. FDA-approved medication as part of treatment. Low prescribing rates are thus partly a function of low overall treatment rates. Nonetheless, very low prescribing rates for these medications indicate that primary care providers are likely rarely using these medications. Therefore, expanding awareness and access to this relatively new treatment modality to primary care has the potential to improve health outcomes and reduce the burden of this devastating illness.

O'Malley and O'Connor[40] reviewed the use of medications for AUD 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."(pg.109) 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.[40] 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.[41, 42]

Existing Guidance and Evidence Reviews

In 2011, the United Kingdom's National Institute for Clinical Excellence released a set of clinical guidelines on the identification and treatment of people with alcohol dependence and harmful alcohol use.[14] 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 those with 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.

In 2014, the Agency for Healthcare Research and Quality (AHRQ) Effective Healthcare Program (EHC) published a systematic review of pharmacologic treatment for AUDs, which is the basis for this update review.[33] The review included data from 135 studies, reported in 167 papers. Both acamprosate and naltrexone demonstrated effectiveness, with the number needed to treat (NNT) to prevent one person from returning to any drinking of 12 to 20, respectively. NNT for preventing one person from returning to heavy drinking was 20 for oral naltrexone at 50 mg per day. Injectable naltrexone was not associated with a benefit for return to any or heavy drinking, but there was a reduction in heavy drinking days, although the strength of the evidence was low. Because acamprosate did not show a benefit for the outcome of heavy drinking, no NNT was calculated for that outcome specifically. The use of disulfiram was not supported by the evidence, although there was weak evidence suggesting a benefit in some patients with excellent adherence, based on a subgroup analysis in one trial.

That review examined a number of medications used off label that are available in the United States and found moderate evidence at the time supporting the efficacy of topiramate. There was insufficient direct evidence to support benefits of pharmacologic treatment for improving health outcomes, rather than drinking outcomes.

The American Psychiatric Association (APA) (2018) recommends either naltrexone or acamprosate as first-line therapy for patients who have been diagnosed with moderate to severe AUD and who wish to reduce drinking or achieve abstinence.[43] Disulfiram, topiramate, and gabapentin may be second-line options depending on the patient's goals, co-occurring conditions, and intolerance or lack of response to first-line medications. The APA further recommends against the use of antidepressants or benzodiazepines for

treating AUD and further against pharmacological treatment during pregnancy or breastfeeding except in certain circumstances. Naltrexone may also be used to treat a patient with AUD and a co-occurring opioid use disorder if the patient wishes to abstain from opioid use or can do so for a clinically appropriate time before starting naltrexone treatment.

The Department of Veterans Affairs and Department of Defense published an updated guideline in 2021[44] that includes first-line recommendations for pharmacotherapy for patients with moderate to severe AUD. They include "strong" recommendations for the use of naltrexone or topiramate and "weak" recommendations for acamprosate and disulfiram, all of which should be offered in the outpatient setting and in combination with addiction-focused counseling.

Rationale for an Evidence Review Update

Pharmacotherapy is recommended by the APA, concomitant with behavioral intervention, and the American Association of Family Physicians has summarized pharmacologic treatment for AUD, based on the AHRQ EHC review.[43] Nonetheless, AUD is substantially undertreated, with fewer than 5 percent of individuals with AUD receiving pharmacotherapy. Reasons for lack of prescribing are likely multifactorial, including both patient and physician lack of awareness of the availability of pharmacotherapy and lack of confidence in the efficacy of such therapies.[45,46]

This is particularly concerning given the frequency and impact that AUD has on both mortality and morbidity and despite recommendations for treatment by the APA and other organizations as noted above. Furthermore, during the COVID-19 pandemic, researchers at RTI International found significant increases between February and April 2020 in overall (+29%), excessive (+20%), and binge (+21%) drinking, suggesting that the need for treatment has increased.[47]

Since the 2014 AHRQ report on medications for AUD, the literature has grown to a point that there is potential for new evidence to affect clinical decision making at a time with known increases in AUD. There are new studies for several relevant medications, more data on outcomes beyond abstinence, and more literature on the ability to treat AUD medically in the outpatient primary care setting. An updated review could lead to increased and more effective dissemination and has the potential to improve the health and welfare of the U.S. population.

Purpose of the Review

The purpose of this review is to integrate new evidence that can update the prior review on medical treatment for AUD with the goal of providing current data that are of use in decision making to guideline developers, clinicians, and patients.

II. The Key Questions

The Key Questions (KQs) for this update are the same questions that were addressed in the 2014 review with the exception of removing the prior KQ 6 on pharmacogenomics.

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

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

KQ 2a: Which medications are efficacious for improving health outcomes (including functioning and quality-of-life outcomes) for adults with alcohol-use disorders in outpatient settings?

KQ 2b: How do medications for adults with alcohol-use disorders compare for improving health outcomes (including functioning and quality-of-life outcomes) in outpatient settings?

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

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

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

KQ 5: Are any of the medications more or less effective than other medications for older adults, younger adults, smokers, or those with co-occurring disorders?

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. This includes
    - Medications approved by FDA for treating alcohol dependence:
      - acamprosate
      - disulfiram
      - naltrexone (oral or injectable)
    - Certain medications in use off label that are available in the United States:
      - baclofen
      - gabapentin
      - ondansetron
      - topiramate
      - prazosin
      - varenicline
  - Studies evaluating pharmacotherapy that used 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.
  - This review will not include pharmacotherapy for alcohol withdrawal.

- **Comparators**
  - Studies must compare one of the medications listed above with placebo or another eligible medication.

- **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
      - percentage 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

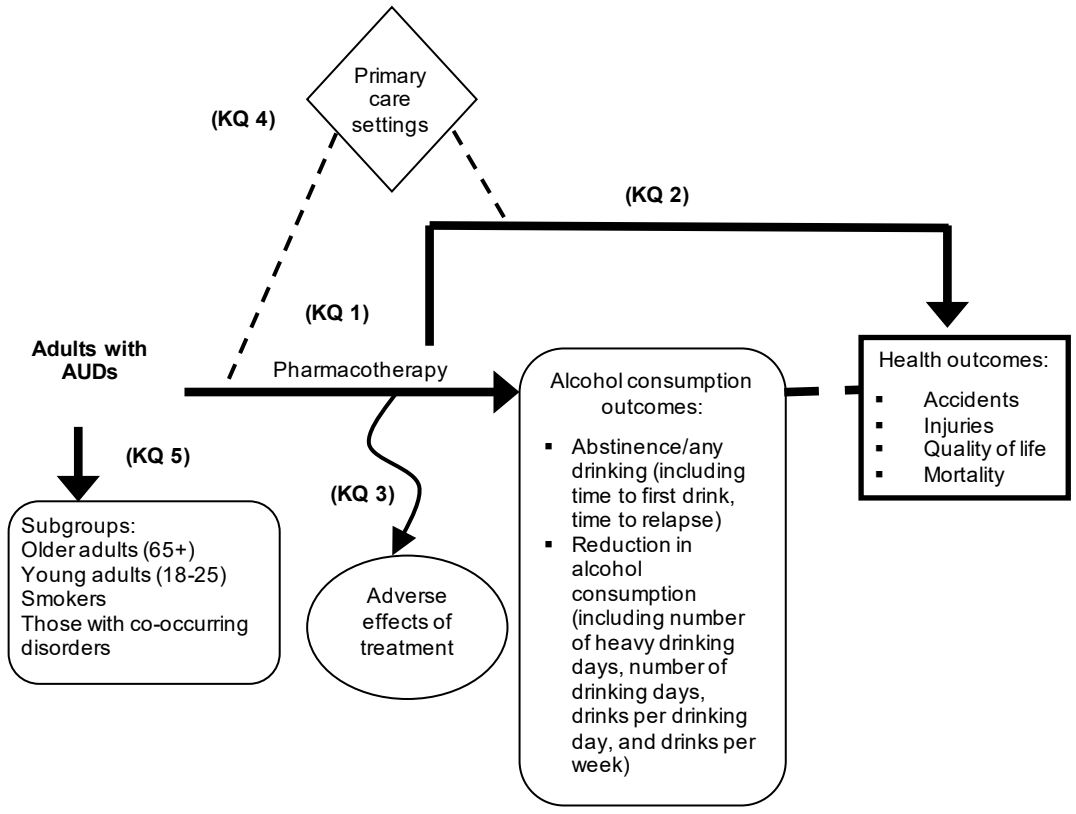
- tiredness
- weakness
- constipation

- **Timing**
  - Studies with at least 12 weeks of planned pharmacologic treatment and followup from the time of medication initiation

- **Setting**
  - Outpatient healthcare settings; KQ 4 applies to primary care settings only (i.e., internal medicine, family medicine, 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



AUD = alcohol-use disorders; KQ = Key Question.

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 AUDs (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 age 18 years
Geography	No limits	
Time period	6 months prior to date of the last update search for the previous review (10/11/2013) to the present; searches to be updated after the draft report goes out for peer review	
Length of followup	At least 12 weeks of planned treatment in an outpatient setting	Less than 12 weeks
Settings	Outpatient healthcare settings	All other 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; nonconcordant historical controls
Outcomes	As defined above in PICOTS	Craving; cue reactivity[a]
Publication language	English	All other languages[b]
Admissible evidence (study design and other criteria)	Original research; eligible study designs include the following: For all KQs, we will include RCTs with masking of subjects and providers (i.e., double blind). For KQ 2b, we will also include head-to-head prospective cohort studies. For KQ 3 (focused on harms), nonserious harms will be extracted from the efficacy RCTs; serious harms will be extracted from 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 in which at least 50 events are reported. For KQ 5 (focused on subgroups), we will include RCTs and secondary analyses or subgroup analyses from RCTs comparing two or more of the medications of interest.	Case series Case reports Nonsystematic reviews Editorials Letters to the editor Studies with historical, rather than concurrent, control groups

[a] We will exclude studies that only report craving and/or cue reactivity; we will include studies that report eligible outcomes in addition to craving and/or cue reactivity.

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

AUD = alcohol-use disorder; KQ = Key Question; PICOTS = populations, interventions, comparators, outcomes, timing, and setting; RCT = randomized controlled trial.

B. Literature Search Strategies to Identify 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 AUDs by using a variety of terms, including medical subject headings (MeSH) and by limiting the search to English-language, adult (18 years or older), and human-only studies. Relevant terms are listed in Table 5. We will also search PsycINFO, the Cochrane Library, the Cochrane Central Trials Registry, the Cumulative Index to Nursing and Allied Health Literature, and Embase (for primary studies only) using analogous search terms. The PubMed search strategy will be peer reviewed by another Evidence-based Practice Center (EPC) librarian, and any changes suggested will be considered by the team. We will conduct quality checks to ensure that the known studies (i.e., studies included in the previous review on pharmacotherapy for AUDs) 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 Alcoholics[Mesh] OR "Alcoholism"[Mesh] OR "Alcohol Drinking" [MeSH] OR "alcohol abuse" OR "alcohol addiction*" OR "alcohol consumption" OR "alcohol depend*" OR "alcohol misuse" OR "alcohol problem*" OR alcoholism OR "alcohol use disorder*"[tw] OR ((drinking[tiab] OR drinker[tiab] OR drinkers[tiab]) AND alcohol*[tiab]) OR "harmful alcohol*" OR "harmful drink*" OR "problem drink*"
Interventions	"Naltrexone"[Mesh] OR naltrexone OR ReVia OR Vivitrol OR Acamprosate[Mesh] OR acamprosate OR Campral OR Disulfiram[Mesh] OR disulfiram OR disulphiram OR Baclofen[Mesh] OR Baclofen OR "Baclofen S"[All Fields] OR Gabapentin[Mesh] OR Gabapentin OR Gabapentine OR "Gabapentin S"[All Fields] OR Ondansetron OR Topiramate[Mesh] OR Topiramate OR "Topiramate S"[All Fields]OR "Varenicline"[Mesh] OR Chantix[tw] OR "Prazosin"[Mesh] or prazosin[tw]
Limits	Humans Adults English language Publication date from 10/11/2013 to 3/14/2022

For our search, we will use the same general approach as the original 2014 AUD review but have specified the list of medications based on those that are in current clinical use in consultation with the Technical Expert Panel (TEP). For study design (for both effectiveness and harms) and target population, we will apply the same inclusion and exclusion criteria that were applied in the original review. Nonserious harms will be extracted from the efficacy RCTs; serious harms will be extracted from 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 in which at least 50 events are reported.

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. Gray literature sources will include ClinicalTrials.gov and the World Health Organization's International Clinical Trials Registry Platform.

We reviewed our search strategy with the TEP. 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. A Supplemental Evidence and Data (SEADs) notice will also be posted on the Effective Health Care (EHC) Program website for four weeks to receive supplemental evidence and data from the public.

We will conduct an updated literature search (of the same databases searched initially) concurrent with the peer and public 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. Additional details can be found in Appendix A.

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 Distiller SR and 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 Distiller SR. 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; alcohol use status at the time of intervention (e.g. currently drinking vs. abstinent)) as well as recorded information on craving if measured, interventions (e.g., dose and frequency of administration; type of provider prescribing the treatment; co-interventions), detailed information on comparators, settings (e.g., primary care, substance abuse treatment settings), study designs, methods, and results and funding source. Where available, we will specifically extract data on those symptoms that are noted in the DSM-IV definition of AUD. Length of followup will be extracted to assess the degree to which long-term outcomes are available. 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*,[48] 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 include studies of any risk-of-bias rating in our main data synthesis and main analyses; we will conduct sensitivity analyses that remove studies deemed high risk of bias.

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.[49] 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.[50] For continuous outcomes (e.g., percentage of days abstinent) measured with the same scale, we will report the weighted mean difference 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, and Hedge's g. 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 excluding studies with high risk of bias. To assess statistical heterogeneity, we will calculate the I^2 statistic.[51, 52]

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 KQ 5 and 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 for Individual Comparisons and Outcomes—We will grade the strength of evidence based on the guidance established for the EPC Program.[53] 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 evidence[53]

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*.[54] 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 who have less severe disorders and may be less applicable to patients with more severe forms of AUD.

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VI. Definition of Terms

See Table 1.

VII. Summary of Protocol Amendments

If we need to amend this protocol, we will give the date of each amendment, describe the change and give the rationale in this section.

VIII. Review of Key Questions

The KQs will be reviewed and refined as needed by the EPC with input from the TEP to assure that the questions are current, specific, and explicit about what information is being reviewed. Because this is an Update, the KQs were not posted for public comment.

IX. Technical Experts

Technical Experts comprise a multidisciplinary group of clinical, content, and methodologic experts who provide input in defining populations, interventions, comparisons, or outcomes as well as identifying particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as 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 $5,000 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.

X. 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 comparative effectiveness reviews and technical briefs, be published 3 months after the publication of the evidence report.

Potential reviewers must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than 50,000. Peer Reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

XI. 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 that cumulatively total greater than $1,000 will usually disqualify EPC core team investigators.

XII. Role of the Funder

This project was funded under Contract No. 75Q80120D00007 from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The Task Order Officer reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

XIII. Registration

This protocol will be registered in the international prospective register of systematic reviews (PROSPERO).

Appendix A. Literature Search Strategies

PubMed

Search number	Query
1	"Alcohol-Related Disorders"[Mesh] OR Alcoholics[Mesh] OR "Alcoholism"[Mesh] OR "Alcohol Drinking" [MeSH] OR "alcohol abuse" OR "alcohol addiction*" OR "alcohol consumption" OR "alcohol depend*" OR "alcohol misuse" OR "alcohol problem*" OR alcoholism OR "alcohol use disorder*"[tw] OR ((drinking[tiab] OR drinker[tiab] OR drinkers[tiab]) AND alcohol*[tiab]) OR "harmful alcohol*" OR "harmful drink*" OR "problem drink*"
2	"Naltrexone"[Mesh] OR naltrexone OR ReVia OR Vivitrol
3	#1 AND #2
4	Acamprosate[Mesh] OR acamprosate OR Campral OR Disulfiram[Mesh] OR disulfiram OR disulphiram
5	#1 AND #4
6	Baclofen[Mesh] OR Baclofen OR "Baclofen S"[All Fields] OR Gabapentin[Mesh] OR Gabapentin OR Gabapentine OR "Gabapentin S"[All Fields] OR Ondansetron[Mesh] OR Ondansetron OR Topiramate[Mesh] OR Topiramate OR "Topiramate S"[All Fields] OR "Varenicline"[Mesh] OR Chantix[tw] OR "Prazosin"[Mesh] or prazosin[tw]
7	#1 AND #6
8	#3 OR #5 OR #7
9	(#8 AND Humans[Mesh:NOEXP]) OR (#8 NOT Animals[Mesh:NOEXP])
10	Adult[Mesh] OR adult OR adults OR elderly
11	#9 AND #10
12	Infan* OR newborn* OR new-born* OR perinat* OR neonat* OR baby OR baby* OR babies OR toddler* OR minors OR minors* OR boy OR boys OR boyfriend OR boyhood OR girl* OR kid OR kids OR child OR child* OR children* OR schoolchild* OR schoolchild OR school child[tiab] OR school child*[tiab] OR adolescen* OR juvenil* OR youth* OR teen* OR under*age* OR pubescen* OR pediatrics[mh] OR pediatric* OR paediatric* OR peadiatric* OR school[tiab] OR school*[tiab] OR prematur* OR preterm*
13	#9 NOT #12
14	#11 OR #13
15	address[pt] OR "autobiography"[pt] OR "bibliography"[pt] OR "biography"[pt] OR "case report"[tw] OR "case reports"[tw] OR "case series"[tw] OR "comment"[pt] OR "comment on"[All Fields] OR congress[pt] OR "dictionary"[pt] OR "directory"[pt] OR "editorial"[pt] OR "festschrift"[pt] OR "historical article"[pt] OR "interview"[pt] OR lecture[pt] OR "legal case"[pt] OR "legislation"[pt] OR letter[pt] OR "news"[pt] OR "newspaper article"[pt] OR "patient education handout"[pt] OR "periodical index"[pt] OR rats[tw] OR cow[tw] OR cows[tw] OR

Search number	Query
	chicken[tw] OR chickens[tw] OR horse[tw] OR horses[tw] OR mice[tw] OR mouse[tw] OR bovine[tw] OR sheep OR ovine OR murine OR murinae
16	#14 NOT #15
17	("2013/10/11"[Date - Entry] : "3000"[Date - Entry]) OR ("2013/10/01"[Date - Publication] : "3000"[Date - Publication])
18	#16 AND #17 Filter: English
19	"Systematic Reviews as Topic"[Mesh] OR "systematic review"[subset] OR "systematic review"[ti] OR "meta-analysis"[pt] OR "meta-analysis"[ti] OR "systematic literature review"[ti] OR "this systematic review"[tw] OR ("systematic review"[tiab] AND review[pt]) OR "cochrane database syst rev"[ta] OR "umbrella review"[tiab] OR "meta-analysis"[tiab] OR "meta-analyses"[tiab] OR "meta-synthesis"[tiab] OR "meta-syntheses"[tiab]
20	#18 AND #19
21	randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]
22	#18 AND #21
23	"Case-Control Studies"[MeSH] OR "Cohort Studies"[MeSH] OR "Epidemiologic Studies"[MeSH] OR "Cross-Sectional Studies"[MeSH] OR "Organizational Case Studies"[MeSH] OR "Cross-Over Studies"[MeSH] OR "Follow-Up Studies"[MeSH] OR "Seroepidemiologic Studies"[MeSH] OR "Evaluation Studies"[Publication Type] OR "comparative study"[pt] OR "compared"[tw] OR "case control"[tw] OR "multivariate"[tw] OR (cohort[all] OR (control[all] AND study[all]) OR (control[tw] AND group*[tw]) OR epidemiologic studies[mh] OR program[tw] OR clinical trial[pt] OR comparative stud*[all] OR evaluation studies[all] OR statistics as topic[mh] OR survey*[tw] OR follow-up*[all] OR time factors[all] OR ci[tw]) NOT (review[pt] OR meta analysis[pt] OR consensus[mh] OR guideline[pt] OR history[sh])
24	#18 AND #23
25	#24 NOT #22

Cochrane Library (Wiley)

Search number	Query
1	[mh "Alcohol-Related Disorders"] OR [mh Alcoholics] OR [mh Alcoholism] OR [mh "Alcohol Drinking"] OR "alcohol abuse":ti,ab,kw OR ("alcohol":ti,ab,kw NEXT addiction*:ti,ab,kw) OR "alcohol consumption":ti,ab,kw OR ("alcohol":ti,ab,kw NEXT depend*:ti,ab,kw) OR "alcohol misuse":ti,ab,kw OR ("alcohol":ti,ab,kw NEXT problem*:ti,ab,kw) OR alcoholism:ti,ab,kw OR ("alcohol use":ti,ab,kw NEXT disorder*:ti,ab,kw) OR ((drinking:ti,ab OR drinker:ti,ab OR drinkers:ti,ab) AND alcohol*:ti,ab) OR ("harmful":ti,ab,kw NEXT alcohol*:ti,ab,kw) OR ("harmful":ti,ab,kw NEXT drink*:ti,ab,kw) OR ("problem":ti,ab,kw NEXT drink*:ti,ab,kw)
2	[mh Naltrexone] OR naltrexone OR ReVia OR Vivitrol
3	#1 AND #2
4	[mh Acamprosate] OR acamprosate OR Campral OR [mh Disulfiram] OR disulfiram OR disulphiram
5	#1 AND #4
6	[mh Baclofen] OR Baclofen OR "Baclofen S" OR [mh Gabapentin] OR Gabapentin OR Gabapentine OR "Gabapentin S" OR [mh Ondansetron] OR Ondansetron OR [mh Topiramate] OR Topiramate OR "Topiramate S" OR [mh "Varenicline"] OR Chantix:ti,ab,kw OR [mh "Prazosin"] or prazosin:ti,ab,kw
7	#1 AND #6
8	#3 OR #5 OR #7
9	[mh Adult] OR adult OR adults OR elderly
10	#8 AND #9
11	Infan* OR newborn* OR new-born* OR perinat* OR neonat* OR baby OR baby* OR babies OR toddler* OR minors OR minors* OR boy OR boys OR boyfriend OR boyhood OR girl* OR kid OR kids OR child OR child* OR children* OR schoolchild* OR schoolchild OR "school child":ti,ab OR ("school" NEXT child*):ti,ab OR adolescen* OR juvenil* OR youth* OR teen* OR under*age* OR pubescen* OR [mh pediatrics] OR pediatric* OR paediatric* OR peadiatric* OR school:ti,ab OR school*:ti,ab OR prematur* OR preterm*
12	#8 NOT #11
13	#10 OR #12
14	address:pt OR autobiography:pt OR bibliography:pt OR biography:pt OR "case report":ti,ab,kw OR "case reports":ti,ab,kw OR "case series":ti,ab,kw OR comment:pt OR "comment on" OR congress:pt OR dictionary:pt OR directory:pt OR editorial:pt OR festschrift:pt OR "historical article":pt OR interview:pt OR lecture:pt OR "legal case":pt OR legislation:pt OR letter:pt OR news:pt OR "newspaper article":pt OR "patient education handout":pt OR "periodical index":pt OR rats:ti,ab,kw OR cow:ti,ab,kw OR cows:ti,ab,kw OR chicken:ti,ab,kw OR chickens:ti,ab,kw OR horse:ti,ab,kw OR horses:ti,ab,kw OR mice:ti,ab,kw OR mouse:ti,ab,kw OR bovine:ti,ab,kw OR sheep OR ovine OR murine OR murinae
15	#13 NOT #14
16	#15 Limited to Date added to CENTRAL trials database (Custom range: October 11, 2013 to February 11, 2022; and limited to year first published 2013-2022)

Cumulative Index to Nursing and Allied Health (CINAHL Plus with Full Text, Ebsco)

#	Query	Limiters/Expanders
S1	(MH "Alcohol-Related Disorders"+) OR (MH Alcoholics+) OR (MH Alcoholism+) OR (MH "Alcohol Drinking"+) OR "alcohol abuse" OR "alcohol addiction*" OR "alcohol consumption" OR "alcohol depend*" OR "alcohol misuse" OR "alcohol problem*" OR alcoholism OR "alcohol use disorder*" OR (((TI drinking OR AB drinking) OR (TI drinker OR AB drinker) OR (TI drinkers OR AB drinkers)) AND (TI alcohol* OR AB alcohol*)) OR "harmful alcohol*" OR "harmful drink*" OR "problem drink*"	Expanders - Apply equivalent subjects Search modes - Find all my search terms
S2	(MH Naltrexone+) OR naltrexone OR ReVia OR Vivitrol	Expanders - Apply equivalent subjects Search modes - Find all my search terms
S3	S1 AND S2	Expanders - Apply equivalent subjects Search modes - Find all my search terms
S4	(MH Acamprosate+) OR acamprosate OR Campral OR (MH Disulfiram+) OR disulfiram OR disulphiram	Expanders - Apply equivalent subjects Search modes - Find all my search terms
S5	S1 AND S4	Expanders - Apply equivalent subjects Search modes - Find all my search terms
S6	(MH Baclofen+) OR Baclofen OR "Baclofen S" OR (MH Gabapentin+) OR Gabapentin OR Gabapentine OR "Gabapentin S" OR (MH Ondansetron+) OR Ondansetron OR (MH Topiramate+) OR Topiramate OR "Topiramate S" OR (MH "Varenicline") OR "chantix" OR (MH "Prazosin") OR "prazocin"	Expanders - Apply equivalent subjects Search modes - Find all my search terms
S7	S1 AND S6	Expanders - Apply equivalent subjects Search modes - Find all my search terms
S8	S3 OR S5 OR S7	Expanders - Apply equivalent subjects Search modes - Find all my search terms
S9	(MH Adult+) OR adult OR adults OR elderly	Expanders - Apply equivalent subjects

#	Query	Limiters/Expanders
		Search modes - Find all my search terms
S10	S8 AND S9	Expanders - Apply equivalent subjects Search modes - Find all my search terms
S11	Infan* OR newborn* OR new-born* OR perinat* OR neonat* OR baby OR baby* OR babies OR toddler* OR minors OR minors* OR boy OR boys OR boyfriend OR boyhood OR girl* OR kid OR kids OR child OR child* OR children* OR schoolchild* OR schoolchild OR (TI "school child" OR AB "school child") OR (TI "school child*" OR AB "school child*") OR adolescen* OR juvenil* OR youth* OR teen* OR under*age* OR pubescen* OR (MH pediatrics+) OR pediatric* OR paediatric* OR peadiatric* OR (TI school OR AB school) OR (TI school* OR AB school*) OR prematur* OR preterm*	Expanders - Apply equivalent subjects Search modes - Find all my search terms
S12	S8 NOT S11	Expanders - Apply equivalent subjects Search modes - Find all my search terms
S13	S10 OR S12	Expanders - Apply equivalent subjects Search modes - Find all my search terms
S14	PT address OR PT autobiography OR PT bibliography OR PT biography OR "case report" OR "case reports" OR "case series" OR PT comment OR "comment on" OR PT congress OR PT dictionary OR PT directory OR PT editorial OR PT festschrift OR PT "historical article" OR PT interview OR PT lecture OR PT "legal case" OR PT legislation OR PT letter OR PT news OR PT "newspaper article" OR PT "patient education handout" OR PT "periodical index" OR rats OR cow OR cows OR chicken OR chickens OR horse OR horses OR mice OR mouse OR bovine OR sheep OR ovine OR murine OR murinae	Expanders - Apply equivalent subjects Search modes - Find all my search terms
S15	S13 NOT S14	Expanders - Apply equivalent subjects Search modes - Find all my search terms
S16	S15	Limiters - Published Date: 20131001-20221231

#	Query	Limiters/Expanders
		Expanders - Apply equivalent subjects Search modes - Find all my search terms
S17	S16	Limiters - English Language Expanders - Apply equivalent subjects Search modes - Find all my search terms
S18	(MH "Systematic Reviews as Topic"+) OR SB "systematic review" OR TI "systematic review" OR PT meta-analysis OR TI meta-analysis OR TI "systematic literature review" OR "this systematic review" OR ((TI "systematic review" OR AB "systematic review") AND PT review) OR (SO "cochrane database syst rev" OR ST "cochrane database syst rev" OR IB "cochrane database syst rev") OR (TI "umbrella review" OR AB "umbrella review") OR (TI meta-analysis OR AB meta-analysis) OR (TI meta-analyses OR AB meta-analyses) OR (TI meta-synthesis OR AB meta-synthesis) OR (TI meta-syntheses OR AB meta-syntheses)	Limiters - English Language Expanders - Apply equivalent subjects Search modes - Find all my search terms
S19	S17 AND S18	Expanders - Apply equivalent subjects Search modes - Find all my search terms
S20	PT "randomized controlled trial" OR PT "controlled clinical trial" OR (TI randomized OR AB randomized) OR (TI placebo OR AB placebo) OR (MW "drug therapy") OR (TI randomly OR AB randomly) OR (TI trial OR AB trial) OR (TI groups OR AB groups)	Expanders - Apply equivalent subjects Search modes - Find all my search terms
S21	S17 AND S20	Expanders - Apply equivalent subjects Search modes - Find all my search terms
S22	(MH "Case-Control Studies"+) OR (MH "Cohort Studies"+) OR (MH "Epidemiologic Studies"+) OR (MH "Cross-Sectional Studies"+) OR (MH "Organizational Case Studies"+) OR (MH "Cross-Over Studies"+) OR (MH "Follow-Up Studies"+) OR (MH "Seroepidemiologic Studies"+) OR PT "Evaluation Studies" OR PT "comparative study" OR compared OR "case control" OR multivariate OR (cohort OR (control AND study) OR	Expanders - Apply equivalent subjects Search modes - Find all my search terms

#	Query	Limiters/Expanders
	(control AND group*) OR (MH "epidemiologic studies"+) OR program OR PT "clinical trial" OR "comparative stud*" OR "evaluation studies" OR (MH "statistics as topic"+) OR survey* OR follow-up* OR "time factors" OR ci) NOT (PT review OR PT "meta analysis" OR (MH consensus+) OR PT guideline OR MW "History")	
S23	S17 AND S22	Expanders - Apply equivalent subjects Search modes - Find all my search terms
S24	S23 NOT S21	Expanders - Apply equivalent subjects Search modes - Find all my search terms

Embase (Embase.com)

No	Query
#1	'alcohol-related disorders'/exp OR 'alcohol-related disorders' OR 'alcoholics'/exp OR 'alcoholics' OR 'alcohol drinking'/exp OR 'alcohol drinking' OR 'alcohol abuse'/exp OR 'alcohol abuse' OR 'alcohol addiction*' OR 'alcohol consumption'/exp OR 'alcohol consumption' OR 'alcohol depend*' OR 'alcohol misuse'/exp OR 'alcohol misuse' OR 'alcohol problem*' OR 'alcoholism'/exp OR 'alcoholism' OR 'alcohol use disorder*' OR ((drinking.tw. OR drinker.tw. OR drinkers.tw.) AND alcohol*.tw.) OR 'harmful alcohol*' OR 'harmful drink*' OR 'problem drink*'
#2	'naltrexone'/exp OR naltrexone OR revia OR vivitrol
#3	#1 AND #2
#4	'acamprosate'/exp OR acamprosate OR campral OR 'disulfiram'/exp OR disulfiram OR disulphiram
#5	#1 AND #4
#6	'baclofen'/exp OR baclofen OR 'baclofen s' OR 'gabapentin'/exp OR gabapentin OR gabapentine OR 'gabapentin s' OR 'ondansetron'/exp OR ondansetron OR 'topiramate'/exp OR topiramate OR 'topiramate s' OR 'varenicline'/exp OR varenicline OR chantix OR 'prazosin'/exp OR prazosin
#7	#1 AND #6
#8	#3 OR #5 OR #7
#9	#8 AND 'humans'/de OR (#8 NOT 'animals'/de)
#10	#9 AND ([adult]/lim OR [young adult]/lim OR [middle aged]/lim OR [aged]/lim OR [very elderly]/lim)
#11	infan* OR newborn* OR 'new born*' OR perinat* OR neonat* OR baby OR baby* OR babies OR toddler* OR minors OR minors* OR boy OR boys OR boyfriend OR boyhood OR girl* OR kid OR kids OR child OR child* OR children* OR schoolchild* OR schoolchild OR 'school child':ti,ab OR 'school child*':ti,ab OR adolescen* OR juvenil* OR youth* OR teen* OR under*age* OR pubescen* OR 'pediatrics'/exp OR pediatric* OR paediatric* OR peadiatric* OR school:ti,ab OR school*:ti,ab OR prematur* OR preterm*
#12	#9 NOT #11
#13	#10 OR #12
#14	#13 AND ('conference abstract'/it OR 'conference paper'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'short survey'/it)
#15	#13 NOT #14
#16	'case report' OR 'case reports' OR 'case series' OR term:it OR 'comment on' OR rats OR cow OR cows OR chicken OR chickens OR horse OR horses OR mice OR mouse OR bovine OR sheep OR ovine OR murine OR murinae
#17	#15 NOT #16
#18	#15 NOT #16 AND [english]/lim
#19	#15 NOT #16 AND [english]/lim AND [11-10-2013]/sd NOT [01-01-2023]/sd AND [2013-2022]/py
#20	'systematic review'/exp OR 'systematic review (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis (topic)'/exp OR 'systematic literature review':ti,ab OR 'this systematic

No	Query
	review':ti,ab OR 'umbrella review':ti,ab OR 'meta-analysis':ti,ab OR 'meta-analyses':ti,ab OR 'meta-synthesis':ti,ab OR 'meta-syntheses':ti,ab
#21	#19 AND #20
#22	'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'random allocation'/exp OR 'controlled trial'/exp OR 'control trial' OR (('control':ab,ti OR 'controlled':ab,ti) AND 'trial':ab,ti) OR 'drug therapy'/exp OR randomized:ti,ab OR placebo:ti,ab OR randomly:ti,ab OR trial:ti,ab OR groups:ti,ab
#23	#19 AND #22
#24	('case-control studies'/exp OR 'cohort studies'/exp OR 'epidemiologic studies'/exp OR 'cross-sectional studies'/exp OR 'organizational case studies'/exp OR 'cross-over studies'/exp OR 'follow-up studies'/exp OR 'seroepidemiologic studies'/exp OR 'evaluation study'/exp OR 'comparative study'/exp OR compared:ti,ab,kw OR 'case control':ti,ab,kw OR multivariate:ti,ab,kw OR cohort OR (control AND study) OR (control AND group*) OR program:ti,ab,kw OR 'clinical trial'/exp OR 'comparative stud*' OR 'evaluation studies' OR 'statistics as topic'/exp OR survey*:ti,ab,kw OR 'follow up*' OR 'time factors' OR ci:ti,ab,kw) NOT ('review'/exp OR 'meta analysis'/exp OR 'consensus'/exp OR 'guideline'/exp OR 'history'/exp)
#25	#19 AND #24
#26	#25 NOT #23

PsycINFO

#	Query	Limiters/Expanders
1	DE "Alcohol Abuse" OR DE "Alcohol Drinking Patterns" OR DE "Alcohol Use Disorder" OR DE "Alcoholism" OR “alcohol-related disorders” OR "alcohol abuse" OR "alcohol addiction" OR "alcohol consumption" OR "alcohol depend*" OR "alcohol misuse" OR "alcohol problem*" OR alcoholics OR alcoholism OR "alcohol use disorder* OR ((drinking OR drinker OR drinkers) AND alcohol*) OR “harmful alcohol*" OR "harmful drink*" OR "problem drink*"	Expanders - Apply equivalent subjects Search modes - Find all my search terms
2	Acamprosate OR Campral OR Disulfiram OR Disulfiram OR Disulphiram OR Baclofen OR Gabapentin OR Gabapentine OR Naltrexone OR Revia OR Vivitrol OR Ondansetron OR Topiramate OR Varenicline OR Chantix OR Prazosin	Expanders - Apply equivalent subjects Search modes - Find all my search terms
3	S1 AND S2	Expanders - Apply equivalent subjects Search modes - Find all my search terms
4	S3	Limiters - Published Date: 20131001-20221231; English; Language: English; Population Group: Human Expanders - Apply equivalent subjects Search modes - Find all my search terms
5	S4	Limiters - Age Groups: Adulthood (18 yrs & older), Aged (65 yrs & older), Very Old (85 yrs & older) Expanders - Apply equivalent subjects Search modes - Find all my search terms
6	Infan* OR newborn* OR new-born* OR perinat* OR neonat* OR baby OR baby* OR babies OR toddler* OR minors OR minors* OR boy OR boys OR boyfriend OR boyhood OR girl* OR kid OR kids OR child OR child* OR children* OR schoolchild* OR schoolchild OR school child[tiab] OR school child*[tiab] OR adolescen* OR juvenil* OR youth* OR teen* OR under*age* OR pubescen* OR pediatrics[mh] OR pediatric* OR paediatric* OR peadiatric* OR school[tiab] OR school*[tiab] OR prematur* OR preterm*	Expanders - Apply equivalent subjects Search modes - Find all my search terms
7	S4 NOT S6	Expanders - Apply equivalent subjects Search modes - Find all my search terms

#	Query	Limiters/Expanders
8	S5 OR S7	Expanders - Apply equivalent subjects Search modes - Find all my search terms
9	DE "Autobiography" OR DE "Biography" OR DE "Case Report" OR DE "Newspapers" (DE "Biography" OR DE "Newspapers" OR TX "comment on" OR TW "case report*" OR TX "case series" OR TX congress OR TX dictionary OR TX directory OR TX editorial OR TX festschrift OR TX "legal case" OR TX legislation OR TX "patient education handout" OR TX "periodical index" OR TX rats OR TX cow OR TX cows OR TX chicken OR TX chickens OR TX horse OR TX horses OR TX mice OR TX mouse OR TX bovine OR TX sheep OR TX ovine OR TX murine OR TX murinae	Expanders - Apply equivalent subjects Search modes - Find all my search terms
10	S8 NOT S9	Expanders - Apply equivalent subjects Search modes - Find all my search terms
11	S10	Limiters - Methodology: - Systematic Review, META ANALYSIS, METASYNTHESIS Expanders - Apply equivalent subjects Search modes - Find all my search terms
12	DE "Randomized Controlled Trials" OR DE "Randomized Clinical Trials") OR “controlled clinical trial” OR TI (randomized OR placebo OR "drug therapy" OR randomly OR trial OR groups) OR AB ("controlled clinical trial" OR randomized OR placebo OR "drug therapy" OR randomly OR trial OR groups)	Expanders - Apply equivalent subjects Search modes - Find all my search terms
13	S10 AND S12	Expanders - Apply equivalent subjects Search modes - Find all my search terms
14	"Case-Control Studies" OR DE “Cohort Analysis” OR "Epidemiologic Study” OR "Cross-Sectional Study" OR "Organizational Case Study" OR "Cross-Over Study” OR "Follow-Up Study" OR "Seroepidemiologic Study"[MeSH] OR "Evaluation Study" OR "comparative study" OR "compared" OR "case control" OR "multivariate" OR (cohort OR (control AND study) OR (control AND group*) OR program OR DE "Clinical Trials" OR “comparative stud*” OR survey* OR “follow-up*” OR “time factors”) NOT (DE “Literature Review” OR DE "Meta Analysis")	Expanders - Apply equivalent subjects Search modes - Find all my search terms
15	S10 AND S14	Expanders - Apply equivalent subjects Search modes - Find all my search terms

Gray Literature Searches

ClinicalTrials.gov

Condition or disease box:
(“Alcohol-Related Disorders” OR “Alcoholism” OR “Alcohol Drinking” OR alcohol depend* OR "alcohol misuse" OR alcohol addiction* OR "alcohol abuse" OR problem drink* OR alcohol problem* OR “alcohol consumption” OR harmful alcohol* OR harmful drink* OR (drinking OR drinker OR drinkers) AND alcohol*)

Intervention/treatment box:
(Naltrexone OR ReVia OR Vivitrol OR acamprosate OR Campral OR disulfiram OR baclofen OR “baclofen s” OR gabapentin OR gabapentine OR “gabapentin s” OR ondansetron OR topiramate OR “topiramate s” OR Chantix OR Varenicline OR Prazosin)

Checked boxes for Adult and Older Adult.

Together in Expert Search box:

AREA[ConditionSearch] (“Alcohol-Related Disorders” OR “Alcoholism” OR “Alcohol Drinking” OR alcohol depend* OR EXPAND[Concept] "alcohol misuse" OR alcohol addiction* OR EXPAND[Concept] "alcohol abuse" OR problem drink* OR alcohol problem* OR “alcohol consumption” OR harmful alcohol* OR harmful drink* OR (drinking OR drinker OR drinkers) AND alcohol*) AND AREA[InterventionSearch] (Naltrexone OR ReVia OR Vivitrol OR acamprosate OR Campral OR disulfiram OR baclofen OR “baclofen s” OR gabapentin OR gabapentine OR “gabapentin s” OR ondansetron OR topiramate OR “topiramate s”) AND AREA[StdAge] EXPAND[Term] COVER[FullMatch] ("Adult" OR "Older Adult") AND AREA[LastUpdatePostDate] EXPAND[Term] RANGE[11/13/2013, 02/14/2022]

WHO International Clinical Trials Registry Platform (ICTRP), 2-14-2022

Condition box:
Alcohol* OR Drink*

Intervention box:
Naltrexone OR ReVia OR Vivitrol OR acamprosate OR Campral OR disulfiram OR baclofen OR baclofen s OR gabapentin OR gabapentine OR gabapentin s OR ondansetron OR topiramate OR topiramate s Chantix OR Varenicline OR Prazosin

Limited to:
Did not check box to look for trials in children.
Recruitment status: ALL
Date of Registration is between: 13/11/2013 and 14/02/2022 (November 13 2013 – February 14, 2022)